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**27 HSKIKI**

VELI LOŠINJ  
2021

**27<sup>th</sup> CROATIAN MEETING  
OF CHEMISTS AND CHEMICAL ENGINEERS**

WITH INTERNATIONAL PARTICIPATION • 5<sup>th</sup> SYMPOSIUM "VLADIMIR PRELOG"  
5-8 OCTOBER 2021 • VELI LOŠINJ, HOTEL PUNTA, CROATIA

**BOOK OF ABSTRACTS**



27<sup>th</sup> CROATIAN MEETING OF CHEMISTS AND CHEMICAL ENGINEERS  
27. HRVATSKI SKUP KEMIČARA I KEMIJSKIH INŽENJERA  
5–8 October 2021, Veli Lošinj, Croatia

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**27<sup>th</sup> Croatian Meeting of Chemists and Chemical Engineers**

with international participation

**5<sup>th</sup> Symposium Vladimir Prelog**

5 – 8 October 2021

Veli Lošinj, Vitality Hotel Punta, Croatia

**BOOK OF ABSTRACTS**

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## FOREWORD

The 27<sup>th</sup> Croatian Meeting of Chemists and Chemical Engineers (27HSKIKI) is organized by the *Croatian Chemical Society* and the *Croatian Society of Chemical Engineers* in a small yet enticing Croatian town Veli Lošinj, placed on island Lošinj from 5 to 8 October 2021.

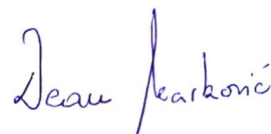
The meeting has traditionally been organized jointly by the Croatian Chemical Society and the Croatian Society of Chemical Engineers on a biannual basis (from 1969). It gathers 400 – 500 chemists and chemical engineers from Croatia and neighboring countries that, coming from academia and industry, contribute to the Meeting with posters and oral presentations. The official language of the Meeting is English.

The meeting is organised in the format of sections: chemistry, materials and nanotechnology, environment protection and sustainable development, chemical engineering and biotechnology, industry and entrepreneurship, and education (in English and Croatian)

Croatian Meetings of Chemists and Chemical Engineers have a long history of hosting distinguished scientists as plenary lecturers. During last fifty years we were honored by talks given by many Nobel laureates, like V. Prelog, R. Huber, J.-M. Lehn, R. Ernst, A. Yonath and D. Shechtman as well as many other world known scientist, such as P. W. Atkins, G. Baldi, B. Delmon, B. Feringa, J. R. Flower, G. F. Froment, L. Riekert, D. W. T. Rippin, E. U. Schlunder, K. Schugerl, K. B. Wiberg, M. Zlokarnik and many others. Our distinguished plenary lecturers were also R. Darton, R. Gani and J. M. Le Lann.

The full-length papers of scientific contributions presented at the Meeting will be gladly considered for the publication in the following journals: *Croatica Chemica Acta*, *Chemical and Biochemical Engineering Quarterly* and *Food Technology and Biotechnology*.

In addition to the scientific program, the enchanting town Veli Lošinj will ensure our guests and participants to enjoy the beauties of typical Primorje's sceneries of north coastal Croatian island Lošinj. Veli Lošinj, the real pearl of Mediterranean, is located on the Adriatic coast only 50 km from Rijeka airport and in close vicinity are airports of Zagreb, Trieste and Pula.

A handwritten signature in blue ink that reads 'Dean Marković'.

**Dean Marković**

*Chair of the Scientific and  
Organizing Committee*



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## CONTENTS

### PLENARY LECTURES

<b>Chris Meier</b> <i>Viral polymerases as intervention targets using nucleoside triphosphate prodrugs</i> .....	2
<b>David Bogle</b> <i>Process systems engineering – a perspective looking forward</i> .....	3
<b>Zoltan K. Nagy</b> <i>Quality-by-control (QBC) approaches for process intensification in advanced pharmaceutical manufacturing and discovery</i> .....	4
<b>Ante Jukić</b> <i>Nanostructured and functional materials and additives based on poly(alkyl methacrylates)</i> .....	5
<b>Ana-Sunčana Smith</b> <i>Multiscale simulations of reactive interfaces</i> .....	6
<b>Pierangelo Metrangolo</b> <i>A journey through the world of halogen bonding</i> .....	7
<b>Ben L. Feringa</b> <i>Dynamic molecular systems from switches to motors</i> .....	8

### INVITED LECTURES

<b>Josip Požar</b> <i>The solvent effect on the host-guest complexation equilibria; the good and the bad</i> .....	10
<b>Mato Knez</b> <i>Atomic layer processing: a toolbox for fabricating functional hybrid materials</i> .....	11
<b>Srećko Gajović</b> <i>Treating mouse as a stroke patient - can molecular changes in the living mouse brain be visible?</i> .....	12
<b>Milan Nikolić</b> <i>Molekule ljubavi na satu kemije</i> .....	13
<b>Krunoslav Žižek</b> <i>Orally disintegrating tablets and mini-tablets containing solid dispersion – dosage forms for better patient compliance and enhanced oral absorption of drug</i> .....	14
<b>Dörte Rother</b> <i>Synthetic enzyme cascades – from set-up to sustainable process chains</i> .....	15
<b>Višnja Stepanić, Davor Oršolić, Tomislav Šmuc</b> <i>(Re)purposing starts virtually by predictive machine-learning models</i> .....	16
<b>Davor Kovačević</b> <i>Polyelectrolyte multilayers: from fundamental studies to biomedical applications</i> .....	17
<b>Māris Turks, Irina Novosjolova, Ērika Bizdēna</b> <i>Substitution and ring opening of fused pyrimidines using their activation by azido and triazolyl groups</i> .....	18
<b>Lucija Peterlin Mašič</b> <i>New multitargeting antibiotics against antimicrobial resistance</i> .....	19
<b>Vladimir Stilinović, Luka Fotović, Nikola Bedeković</b> <i>Halogenated aromatic cations as halogen bond donors</i> .....	20
<b>Pawel Dydio</b> <i>Cooperative Dual-Catalytic Transition Metal Systems for Selective Functionalization of Less Reactive Sites</i> .....	21

Dajana Kučić Grgić, Martina Miloloža, Kristina Bule, Viktorija Prevarić, Matija Cvetnić, Šime Ukić, Vesna Ocelić Bulatović, Marinko Markić, Tomislav Bolanča <i>Bioremediation as a promising strategy for microplastics removal by bacteria Bacillus cereus and Pseudomonas alcaligenes</i> .....	22
Françoise Colobert <i>Atropisomerism: a gate to modern drugs</i> .....	23
Grégory Genta-Jouve <i>Numerical methods in Natural Products Chemistry</i> .....	24
Matija Gredičak <i>Construction of tetrasubstituted centers of chirality in isoindolinones via Brønsted acid catalysis</i> .....	25
Đani Škalamera <i>Development of structurally defined saponin-based vaccine adjuvants</i> .....	26
Ivana Panžić, Vilko Mandić, Michael Wurmshuber, Daniel Kiener <i>Advanced in-situ electron microscopy analysis of the nanostructured semiconducting zincite thin-films</i> .....	27
Ana Mornar, Biljana Nigović, Daniela Amidžić Klarić, Edvin Brusač, Mario-Livio Jeličić <i>Current trends in the analysis of products labelled as botanical food supplements</i> .....	28
Emil Dražević <i>Opportunities and Challenges of Electrochemical Synthesis of Ammonia</i> .....	29
<b>SECTION LECTURES</b>	
Krešimir Molčanov, Valentina Milašinović, Biserka Kojić-Prodić <i>Two-electron multicentric bonding (pancake bonding) between semiquinone radicals</i> .....	30
Mateja Pisačić, Marijana Đaković <i>Crystalline coordination polymers on the move</i> .....	31
Andrea Usenik, Leon Poljanić, Doroteja Radonić, Katarina Pičuljan, Željka Car, Vesna Petrović Peroković, Josip Požar <i>Shining a light on hydrophobically driven complexation: the bittersweet story behind fluorescent mannoconjugates</i> .....	32
Mateja Toma, Lana Petrincec, Valerije Vrček <i>Ferrocenoyl-nucleobases. The chemistry in dark and in light</i> .....	33
Jelena Isailović, Kristijan Vidović, Samo B. Hočevar <i>Electrochemical sensors for gaseous hydrogen peroxide</i> .....	34
Edvin Brusač, Mario-Livio Jeličić, Daniela Amidžić Klarić, Biljana Nigović, Ana Mornar <i>Ebay and supplements don't mix: determination of andrographolides, boswellic acids, curcuminoids and piperine in products available locally and online</i> .....	35
Floren Radovanović-Perić, Vilko Mandić, Dragana Vuk, Ivana Panžić, Thomas Rath <i>Small molecule based photoabsorbers for application in photovoltaic devices</i> .....	36
Oksana Yurkevich, Iva Šarić, Evgeny Modin, Mladen Petravić, Mato Knez <i>Vapor phase approach for synthesis of smart hybrid materials</i> .....	37
Karina Ashurbekova, Kristina Ashurbekova, Arbresha Muriqi, Borja Alonso-Lerma, Iva Šarić, Leire Barandiaran, Evgeny Modin, Mladen Petravić, Raul Perez-Jimenez, Michael Nolan, Mato Knez <i>Antibacterial biomimetic metallochitin thin films grown by molecular layer deposition</i> .....	39
Karen J. Ardila-Fierro, José G. Hernández <i>Mechanistic study of the mechanochemical acetate-assisted C–H activation with [CpRhCl<sub>2</sub>]<sub>2</sub></i> .....	40
Barbara Štimac Tumara, Muhamed Sućeska <i>Calibration of pressure-based reaction rate law used for numerical modelling of non-ideal ANFO explosives</i> ....	41
Filip Vranješević, Maria Kolympadi Markovic, Valerije Vrček, Dean Marković <i>Cyclic carbamate formation through transition metal-catalyzed CO<sub>2</sub> capture</i> .....	42



<b>Antun Barišić, Sanja Škulj, Zoe Jelić Matošević, Branimir Bertoša</b> <i>Computational study of the glycosylated HRP enzyme used in pathogen detection</i> .....	43
<b>Iva Zonjić, Lidija Marija Tumir, Filip Šupljika, Ivo Crnolatac, Livio Racané, Sanja Tomić, Marijana Radić Stojković</b> <i>Recognition of DNA:RNA hybrid and triplex structures by a series of benzothiazole ligands</i> .....	44
<b>Sara Matić, Filip Šupljika, Mihaela Matovina, Sanja Tomić</b> <i>Effect of cancer mutations on DPP III – KEAP1 binding</i> .....	45
<b>Renata Ruić Funčić, Lovro Dujić, Mislav Maldini</b> <i>Černobil i online istraživačka, grupna nastava</i> .....	46
<b>Silvija Krnić, Kristina Kristek</b> <i>Kemijska ravnoteža u obrnutoj učionici kemije</i> .....	48
<b>Dražen Crnčec</b> <i>Usvajanje odgojno-obrazovnih ishoda kemije u osnovnoj školi kroz međupredmetnu temu “Održivi razvoj” na primjeru poučne staze “Svetomartinska Mura”</i> .....	49
<b>Monika Pavić, Maja Jurić-Babaja</b> <i>Pokus u filmu</i> .....	50
<b>Mirta Malčić, Suzana Lovrić</b> <i>Usavršavanje učitelja kemije i biologije kroz županijska stručna vijeća</i> .....	51
<b>Mirjana Cvetković-Kižlin, Nataša Kletečki</b> <i>Primjena eTwining projekta u nastavi kemije i biologije</i> .....	52
<b>Domagoj Vrsaljko, Petra Ivanković, Katarina Jozinović, Iva Katalinić Paić, Laura Keran, Ines Pehar, Luka Posavac, Domagoj Prlić, Gracia Vukorepa, Ivan Karlo Cingesar</b> <i>3D-printed equipment for chemical processing industries</i> .....	53
<b>Rajna Koren, Manuel Martinović, Patrik Nikolić, Ivica Odorčić, Lucija Ostojić, David Visentin, Katarina Vrbnjak, Vedran Miletić, Željko M. Svedružić</b> <i>Supercomputers as microscopes for the 21<sup>st</sup> century: substrate channeling, epigenetic regulation, and molecular basis of alzheimer's disease</i> .....	54
<b>Želimir Kurtanjek</b> <i>Causality analysis in chemistry and chemical engineering</i> .....	56
<b>Marina Šekutor, Jasna Alić, Roman Messner, Florian Lackner, Wolfgang E. Ernst</b> <i>The role of london dispersion in the formation of diamantane clusters inside helium nanodroplets</i> .....	57
<b>Ivan Kodrin, Petar Šutalo, Barbara Panić, Ivana Biljan</b> <i>Computational study of nitrogen-containing covalent organic polymers</i> .....	58
<b>Josip Draženović, Tomislav Rožić, Nađa Došlić, Nikola Basarić</b> <i>Excited state intramolecular proton transfer from nitrogen to carbon atom in aminobiphenyls</i> .....	59
<b>Tana Tandarić, Alja Prah, Jernej Stare, Janez Mavri, Robert Vianello</b> <i>Computational investigation of the mechanism of the irreversible inhibition of the monoamine oxidase B enzyme</i> .....	60
<b>Dejan Oспенica, Anita Bosak, Ana Matošević, Katarina Komatović, Nikola Maraković</b> <i>4-aminoquinolines, a privileged pharmacophore - from antimalarials to inhibition of cholinesterase</i> .....	61
<b>Valentina Rep, Silvana Raić-Malić</b> <i>Amidino-substituted benzazoles: promising antitrypanosomal and cytostatic agents</i> .....	62
<b>Gordana Peh nec Pavlović</b> <i>Cooperation of professional associations of the Croatian Chamber of Economy with Science in the function of raising the competitiveness of the economy</i> .....	63

<b>Sanja Renka, Mallaurie Foucaud, Teodoro Klaser, Petr Kalenda, Petr Mošner, Andrea Moguš-Milanković, Ana Šantić</b> <i>Effect of controlled crystallization on the ionic and electronic conductivity in phosphate glasses</i> .....	64
<b>Ivana Vinković Vrček, Željko Debeljak, Emerik Galić, Nikša Drinković, Nazende Günday-Türelı, Emre Türelı, Vedran Micek, Nikolina Kalčec, Dario Mandić, Dunja Gorup, Marija Ćurlin</b> <i>Design of nanocarriers to reduce systemic toxicity of antitumor agents: doxorubicin case study</i> .....	66
<b>Ivan Pucko, Mislav Mišetić, Marko Racar, Fabio Faraguna</b> <i>Synthesis of maleic based polymeric additives and their influence on the low-temperature properties of diesel and biodiesel fuel</i> .....	67
<b>Klara Perović, Hrvoje Kušić, Marin Kovačić, Ana Lončarić Božić, Marijana Kraljić Roković</b> <i>Investigation of correlation between different sacrificial agents and photoelectrochemical properties of TiO<sub>2</sub>-based catalysts for H<sub>2</sub> generation</i> .....	68
<b>Mario Bohač, Tihana Čižmar, Vedran Kojić, Krunoslav Juraić, Ivana Grčić, Andreja Gajović</b> <i>Novel low-cost synthesis of transparent BaTiO<sub>3</sub>-TiO<sub>2</sub> nanotube heterostructures for photocatalysis</i> .....	69
<b>Daniło Bertagna Silva, Gianluigi Buttiglieri, Bruna Babić, Goran Smoljanić, Danijela Ašperger, Sandra Babić</b> <i>Design of experiments for photolytic and photocatalytic degradation of 5 pharmaceuticals in water</i> .....	71
<b>Ranka Godec, Martina Šilović Hujjić, Ivana Jakovljević, Zdravka Sever Štrukil, Suzana Sopčić</b> <i>Mass concentrations of carbon pollutants at a typical street canyon location</i> .....	73
<b>Irina Pucić, Vlado Cuculić, Željko Kwokal</b> <i>DSC analysis of submillimeter microplastics from Adriatic sea</i> .....	74
<b>Mia Gotovuša, Mihovil Medić, Iva Žuvić, Marko Racar, Jelena Parlov-Vuković, Marija Tirić Unetić, Lucija Konjević, Fabio Faraguna</b> <i>Influence of reaction parameters on the synthesis of fatty acid propyl, isoamyl and octyl esters and their application properties in blends with mineral diesel</i> .....	75
<b>Gordana Šelo, Ana-Marija Dukarić, Ana Bucić-Kojić, Marina Tišma, Mirela Planinić</b> <i>Recovery of bioactive phenolic compounds from biologically treated grape pomace by ten filamentous fungi</i> .....	76
<b>Nevena Milčić, Martina Sudar, Zvezdana Findrik Blažević, Maja Majerić Elenkov</b> <i>Solvent tolerance of halohydrin dehalogenases</i> .....	77
<b>Anđela Zeko-Pivač, Anja Bošnjaković, Mirela Planinić, Ana Bucić-Kojić, Marina Tišma</b> <i>Production of hydrolytic and lignolytic enzymes during cultivation of <i>Trametes versicolor</i> on brewer's spent grain</i> .....	78
<b>Marijana Đaković</b> <i>Can mechanical responses of flexible crystals be controlled and deliberately delivered?</i> .....	79
<b>Marijana Jurić, Lidija Kanižaj, Sanja Burazer, Krešimir Molčanov, Ana Šantić, Sanja Renka, Jasminka Popović, Dario Barišić, Damir Pajić</b> <i>Homo- and heterometallic oxalato-bridged coordination polymers: structural, magnetic and electrical properties</i> .....	80
<b>Lidija Androš Dubraja, Marko Dunatov, Andreas Puškarić</b> <i>Molecular ferroelectrics based on bicyclic amine cations and chlorocobaltate(II) anions</i> .....	81
<b>Lidija Kanižaj, Pavla Šenjog, Damir Pajić, Luka Pavić, Krešimir Molčanov, Marijana Jurić</b> <i>Magnetic and electrical features of 1D and 3D oxalate-bridged coordination polymers</i> .....	82
<b>Nataša Burić, Marina Šekutor</b> <i>Preparation and characterization of diamondoid esters</i> .....	83
<b>Melita Lončarić, Martina Jakovljević Kovač, Mario Komar, Maja Molnar</b> <i>Synthesis of coumarin, rhodanine and thiazolidinedione derivatives in deep eutectic solvents via Knoevenagel condensation</i> .....	84

<b>Ivo Piantanida, Ksenija Božinović, Dragomira Majhen, Goutam Kumar Kole, Todd B. Marder, Marta Koščak</b>	
<i>2- and 2,7-substituted pyridine pyrenes derivatives and their DNA/RNA interactions .....</i>	85
<b>Magdalena Kralj, Sara Krivačić, Petar Kassal, Antonio Supina, Željka Boček, Ivan Halasz</b>	
<i>Avenue to facile medium-scale production of graphene quantum dots and graphene nanosheets.....</i>	86
<b>Ana Alebić-Juretić, Boris Mifka</b>	
<i>Airborne desert dust in the northern Adriatic area (Croatia): different sources .....</i>	87
<b>Sarah Mateša, Irena Ciglencčki</b>	
<i>Application of the electrochemical method for monitoring polysulfides (S<sub>x</sub>) in marine euxinic environment (Rogoznica lake, Croatia).....</i>	88
<b>Mario Špadina, Atda Selmani, Bertrand Siboulet, Davor Kovačević, Goran Dražić, Jean-Francois Dufreche, Klemen Bohinc</b>	
<i>Revising solute adsorption models in the case of loose TiO<sub>2</sub> nanotubes surfaces.....</i>	89
<b>Iva Rezić</b>	
<i>Investigation of allergenic metals on fashion accessories and decorative metallized yarns .....</i>	91
<b>Luka Pavić, Stjepko Fazinić, Hüseyin Ertap, Mevlüt Karabulut, Andrea Moguš-Milanković, Ana Šantić</b>	
<i>Model-free scaling of conductivity spectra: insight into electrical transport in iron phosphate-based glasses ....</i>	92
<b>POSTERS</b>	
<b>Chemistry</b>	
<b>Maša Buljac, Ivana Škugor Rončević, Nives Vladislavić, Marijo Buzuk</b>	
<i>Electrochemical behavior of natural reducers on carbon nanomaterials: a contribution to the optimization of electroanalytical methods.....</i>	94
<b>Ivana Škugor Rončević, Nives Vladislavić, Boris-Marko Kukovec, Marijo Buzuk, Maša Buljac</b>	
<i>Transition metal coordination polymers: synthesis, spectroscopic and electrochemical studies .....</i>	96
<b>Ivana Vrca, Vedrana Čikeš Čulić, Ivica Blažević, Tea Bilušić</b>	
<i>The influence of the black mustard sample preparation method on chemical composition, antiproliferative and proapoptotic effects .....</i>	97
<b>Dajana Gašo-Sokač, Valentina Bušić, Maja Molnar</b>	
<i>An eco-friendly preparations of izonicotinamide quaternary salts in deep eutectic solvents.....</i>	99
<b>Robert Kerep, Tino Šeba, Tin Weitner, Mario Gabričević</b>	
<i>Evaluation of thermodynamic parameters between antidepressant imipramine and human <math>\alpha</math>1-acid glycoprotein by isothermal titration calorimetry.....</i>	100
<b>Kristinka Vinković, Danijela Ašperger, Bruna Babić, Gabrijela Priščan</b>	
<i>Determination of pseudoestrogenic compounds in thermochromic printing ink .....</i>	101
<b>Josip Radić, Marija Bralić, Maša Buljac, Marina Šola</b>	
<i>Potentiometric response characteristics of carbon paste electrode for maprotiline determination.....</i>	102
<b>Antonela Ninčević Grassino, Sara Spalj, Tomislav Bosiljkov</b>	
<i>Evaluation of pectin biofilms with incorporated phenolic extracts of “karoma” spent espresso coffee grounds .....</i>	103
<b>Antonela Ninčević Grassino, Sara Spalj, Iva Sušić, Marina Šango</b>	
<i>Microwave-assisted extraction of polyphenols from coffee (green and roasted) and its by-products (silver skin and spent coffee ground) .....</i>	104
<b>Armands Sebris, Kaspars Traskovskis, Irina Novosjolova, Māris Turks</b>	
<i>Synthesis and photophysical properties of purine-carbazole donor acceptor systems.....</i>	105

<b>Dawid Zielinski, Andrea Szepecht, Paulina Hinc, Marcin Smiglak</b> <i>DABCO-based ionic liquids as active latent curing agents in thermosets developed with conventional and biobased epoxy resins.....</i>	106
<b>Gabrijel Zubčić, Sofia Shkunnikova, Davor Šakić</b> <i>From aminyl radicals to cations; mechanism switch in Hofmann-Löffler-Freytag-like reactions.....</i>	107
<b>Mirza Bojić, Martin Kondža, Željko Maleš</b> <i>Acacetin, apigenin, chrysin and pinocembrin cause irreversible CYP3A4 inhibition by heme destruction .....</i>	108
<b>Luka Krstulović, Marijana Jukić, Teuta Opačak-Bernardi, Miroslav Bajić, Ljubica Glavaš-Obrovac</b> <i>Synthesis and antitumor activity of novel 7-chloro-4-aminoquinoline-benzimidazoles.....</i>	109
<b>Mateja Belovari, Davor Nestić, Dragomira Majhen, Zoran Džolić</b> <i>Triazolylpyrene-derived pseudopeptides: fluorescence properties, cell-imaging and antiproliferative activity..</i>	110
<b>Domagoj Šubarić, Drago Bešlo, Ivana Majić, Dejan Agić, Melita Lončarić, Maja Molnar, Vesna Rastija</b> <i>Coumarine derivatives as potential acetylcholinesterase inhibitors .....</i>	111
<b>Andris Jeminejs, Svetlana Marija Goliškina, Irina Novosjolova, Ērika Bizdēna</b> <i>Azide-tetrazole tautomeric equilibrium controlled synthesis of inverted tetrazolo[1,5-a/c]quinazolines.....</i>	112
<b>Maja Karnaš, Domagoj Šubarić, Vesna Rastija, Dejan Agić, Ivana Majić, Mario Komar, Harshad Brahmbhatt, Maja Molnar</b> <i>Fluorinated pyrazoline derivatives as acetylcholinesterase inhibitors .....</i>	113
<b>Mirela Samardžić, Karlo Bubnjar, László Kiss, Aleksandar Széchenyi, Mateja Budetić</b> <i>Characterization of the new potentiometric sensor for thiabendazole determination.....</i>	114
<b>Mateja Budetić, Karlo Bubnjar, László Kiss, Aleksandar Széchenyi, Sanja Petrušić, Mirela Samardžić</b> <i>Optimization of the membrane of the potentiometric sensor for thiabendazole determination.....</i>	115
<b>Vesna Rastija, Karolina Vrandečić, Jasenka Čosić, Gabriella Kanižai Šarić, Maja Karnaš, Mario Komar, Maja Molnar</b> <i>Biological activities coumarinyl Schiff bases related to plant protection: deeper insight into the mechanism of action .....</i>	116
<b>Mirza Bojić, Goran Benković, Željko Maleš</b> <i>Oxidative metabolism of sakuranetin in humans.....</i>	117
<b>Tihana Marić, Maja Friščić, Igor Jerković, Željko Maleš</b> <i>Application of HS-SPME/GC-MS for characterisation of volatile compounds of <i>Sideritis romana</i> L. and <i>Sideritis montana</i> L. From Croatia .....</i>	118
<b>Agņija Ritere, Andris Jeminejs, Irina Novosjolova, Ērika Bizdēna, Māris Turks</b> <i>The functionalization of purine scaffold with selenium nucleophiles.....</i>	119
<b>Krista Gulbe, Jevgeņija Lugiņina, Edijs Jansons, Artis Kinēns, Māris Turks</b> <i>Metal-free sulfur dioxide-assisted glycosylation with glycosyl fluorides .....</i>	120
<b>Petra Stanić, Krešimir Molčanov</b> <i>Diverse stacking of tcnq radical anions in different salts with organic cations.....</i>	121
<b>Sandra Jurić</b> <i>Solvolytic behaviour of some ferrocenylphenylmethyl-4-methoxypyridinium cations in various solvents.....</i>	122
<b>Kristaps Leškovskis, Anatoly Mishnev, Irina Novosjolova, Māris Turks</b> <i>Aromatic substitution of azido-pyridopyrimidines and study of their azide-tetrazole equilibrium .....</i>	123
<b>Valentina Milašinović, Krešimir Molčanov, Boris A. Zakharov, Elena V. Boldyreva, Nikita E. Bogdanov</b> <i>Multicentre bonding of semiquinone radicals under variable temperature and high pressure conditions.....</i>	124
<b>Ankica Sekovanić, Zorana Kljaković-Gašpić, Tatjana Orct, Davor Zanella, Jasna Jurasović, Dora Šebešćen, Elena Klasiček</b> <i>Content of metal(oid)s in the muscle and liver of european eel (<i>Anguilla anguilla</i> L.) From the Raša river .....</i>	125



<b>Marija Terzić, Pavo Živković, Jelena Bijelić, Dalibor Tatar, Milenko Korica, Elvira Kovač-Andrić</b> <i>Ultrasound-assisted green synthesis and characterization of Ni/histidine MOF.....</i>	126
<b>Gordana Pavlović, Robert Katava, Danijela Drčić</b> <i>Preparation and characterization of Co(II) complex with 1H-benzimidazole-2-methanol.....</i>	127
<b>Silvia-Maria Franov, Davor Kovačević, Tajana Begović, Jasmina Jukić</b> <i>Stability and aggregation kinetics of TiO<sub>2</sub> nanoparticles.....</i>	128
<b>Renato Tomaš, Filip Burnić, Zdzislaw Kinart, Aleksandar Tot, Snežana Papović, Teona Teodora Borović, Milan Vraneš</b> <i>Volumetric properties of some imidazolium chloride ionic liquids in butan-1-ol at different temperatures .....</i>	129
<b>Livio Racané, Ivo Zlatar, Nataša Perin, Maja Cindrić, Vedrana Radovanović, Mihailo Banjanac, Kristina Butković, Suresh Shanmugam, Marijana Radić Stojković, Karmen Brajša, Marijana Hranjec</b> <i>Biological activity of benzimidazole and benzothiazole 2,5-disubstituted furane derivatives.....</i>	130
<b>Vinko Nemec, Dominik Cinčić</b> <i>The sulfur atom as a halogen bond acceptor in cocrystals of tetrahydro-4H-thiopyran-4-one and its derivatives .....</i>	131
<b>Toni Kujundžić, Vesna Rastija, Maja Karnaš, Mato Drenjančević, Vladimir Jukić, Florian Schwander</b> <i>Effects of defoliation treatments of grape variety babica on volatile compounds content in wine .....</i>	132
<b>Ana Lozančić, Lidija Kanižaj, Krešimir Molčanov, Ana Šantić, Marijana Jurić</b> <i>Characterization of the complexes prepared using building block tris(oxalato)chromate containing different alkyl ammonium cations .....</i>	133
<b>Juraj Nikolić, Tin Klačić, Davor Kovačević</b> <i>Determination of influential parameters for chitosan adsorption on silica surface.....</i>	134
<b>Milena Mlakić, Ilijana Odak, Stanislava Talić, Ivan Faraho, Martina Bosnar, Danijela Barić, Irena Škorić</b> <i>Synthesis, photochemistry and biological activity of new 1,2,3-triazolostilbenes. An experimental and computational study .....</i>	135
<b>Snežana Miljanić, Virna Zavidić, Adriana Kenđel</b> <i>Revealing DNA interactions with Hoechst 33258 by surface-enhanced raman spectroscopy.....</i>	136
<b>Goran Poje, Ivana Perković, Jana Held, Zrinka Rajić</b> <i>Antiplasmodial activity of triazole-type harmiquins .....</i>	137
<b>Karlo Sović, Zlatan Spahić, Ines Primožič, Tomica Hrenar</b> <i>Conformational analysis of 1N,3N-substituted imidazole 2-aldoximes .....</i>	138
<b>Nea Baus Topić, Dominik Cinčić</b> <i>Thermochromic imines as halogen bond donors in crystal engineering of multi-component crystals .....</i>	139
<b>Marijana Pocrnić, Nives Galić</b> <i>Inclusion complexes of meloxicam and selected cyclodextrins in solution and in the solid state.....</i>	140
<b>Aleksandra Šimanović, Antonija Ožegović, Irena Dokli, Andreja Lesac</b> <i>The effect of mesogenic core on liquid-crystalline behaviour .....</i>	141
<b>Antonija Ožegović, Aleksandra Šimanović, Irena Dokli, Andreja Lesac</b> <i>Influence of the spacer length on mesogenic properties of chiral liquid crystal dimers .....</i>	142
<b>Anja Beč, Lucija Žonja, Marijana Hranjec, Kristina Starčević, Leentje Persoons, Dirk Daelemans</b> <i>Synthesis and biological activity of novel amidino-substituted benzimidazoles and benzothiazoles.....</i>	143
<b>Dragana Mutavdžić Pavlović, Kristina Tolić, Tatjana Gazivoda Kraljević, Marijana Hranjec, Livio Racané, Marijana Pocrnić, Nives Galić, Mislav Runje</b> <i>Stability of amidino substituted benzothiazole derivatives with antitumor activity .....</i>	144
<b>Ida Boček, Robert Vianello, Marijana Hranjec</b> <i>Novel iminocoumarin derived imidazo[4,5-b]pyridines as potential pH sensors.....</i>	145

<b>Barbara Panić, Marina Koprivnjak, Tomislav Marić, Ivana Biljan</b> <i>Study of the growth process of nitrosobenzene adlayers on gold surface</i> .....	146
<b>Katarina Lisac, Sara Marijan, Dominik Cinčić</b> <i>Cocrystallization of cobalt(II) and nickel(II) complexes with perhalogenated halogen bond donors</i> .....	147
<b>Kristina Pršir, Ivana Murković Steinberg, Svjetlana Krištafor</b> <i>Synthesis and optical sensing properties of novel 1,2,3-triazolyl-benzothiazoles</i> .....	148
<b>Kristina Pršir, Mislav Matić, Marlena Grbić, Gerhard J. Mohr, Svjetlana Krištafor, Ivana Murković Steinberg</b> <i>Novel naphthalimide-based “on-off” fluorescent probes for detecting Hg<sup>2+</sup> and Cu<sup>2+</sup> ions</i> .....	149
<b>Martina Piškorić, Leon Sačar, Andrijana Meščić Macan, Silvana Raić-Malić</b> <i>Synthesis of new purine and pyrimidine 1,1'-disubstituted ferrocene conjugates using mechanochemistry</i> .....	150
<b>Danijela Bakarić, Darija Domazet Jurašin, Zlatko Brkljača, Petra Maleš</b> <i>Ion influence on pretransition of multilamellar phosphatidylcholine liposomes</i> .....	151
<b>Matilda Šprung, Doris Crnčević, Renata Odžak</b> <i>Antimicrobial activity of quaternary ammonium compounds derived from pyridinium-4-aldoxime</i> .....	152
<b>Karla Jagić, Marija Dvorščak, Darija Klinčić</b> <i>Extraction of polybrominated diphenyl ethers from human milk samples</i> .....	153
<b>Lidija Posavec, Filip Kučas, Vinko Nemec, Dominik Cinčić</b> <i>2,2'-bipyridine derivatives as halogen bond acceptors in multicomponent crystals</i> .....	154
<b>Ana Mikelić, Ines Primožič, Tomica Hrenar</b> <i>Molecular docking study of quinuclidine derivatives against cholinesterases using machine learning</i> .....	155
<b>Ani Radonić, Marina Zekić, Zvonimir Marijanović, Ljilja Žilić</b> <i>Analysis of sulfur-containing volatile compounds from two wild-growing brassicaceae plants by HS-SPME/GC-MS</i> .....	156
<b>Dejan Agić, Domagoj Šubarić, Maja Karnaš, Mario Komar, Zrinka Karačić, Sanja Tomić, Drago Bešlo, Vesna Rastija, Maja Molnar</b> <i>Interactions of human dipeptidyl peptidase III with coumarinyl Schiff bases</i> .....	157
<b>Lucija Ptiček, Petra Grbčić, Sandra Kraljević Pavelić, Martin C. Taylor, John M. Kelly, Silvana Raić-Malić, Livio Racané</b> <i>Synthesis and biological activity of bis-6-amidino-benzazoles linked through aliphatic unit</i> .....	158
<b>Toni Grgurić, Manuel Petroselli, Corrado Bacchiocchi, Massimo Cametti, Zoran Džolić, Mario Cetina</b> <i>Anion-templated assembly of biphenyl-bis-urea receptor</i> .....	159
<b>Olivera Politeo, Kristina Kardum, Mirko Ruščić</b> <i>Chemical profile and enzyme inhibition potential of water extracts from Centaurea plants</i> .....	160
<b>Anđela Buljan, Paola Sinković, Marin Roje</b> <i>Synthesis and enantioseparation of (±)-marinoaziridine precursors</i> .....	161
<b>Tin Klačić, Klemen Bohinc, Davor Kovačević</b> <i>Controlling the properties of poly(allylamine hydrochloride)/poly(acrylic acid) ultrathin multilayer films by varying the supporting anion</i> .....	162
<b>Adriana Kenđel, Petra Hudika, Snežana Miljanić, Ivo Piantanida, Enrique García-España</b> <i>Surface-enhanced raman study of the interactions between pyrene derivative of polyamine and double-stranded polynucleotides</i> .....	163
<b>Adriana Kenđel, Izabela Đurasović, Snežana Miljanić</b> <i>Silver and gold colloids as substrates for SERS study of methylene blue and rhodamine B</i> .....	164
<b>Marija Bakija, Berislav Perić, Srećko I. Kirin</b> <i>Synthesis and characterization of oxazoline amino acid bioconjugates</i> .....	165

<b>Robert Ostrički, Leentje Persoon, Els Vanstreels, Dirk Daelemans, Tatjana Gazivoda Kraljević</b> <i>Synthesis, structural characterization and antitumor evaluation of novel 1,2,3-triazole derivatives of benzoxazole</i> .....	166
<b>Vladislavs Kroškins, Jevgeņija Lugiņina, Kristiāns Jankovičs, Māris Turks</b> <i>C-H activation of lupane type triterpenoids</i> .....	167
<b>Vesna Sokol, Boris-Marko Kukovec</b> <i>Thermodynamics of association reaction of rubidium bromide in 2-methylpropan-2-ol + water mixture with an alcohol mass fraction of 0.80</i> .....	168
<b>Ivana Škugor Rončević, Nives Vladislavić, Nabanita Chatterjee, Vesna Sokol, Clive L. Oliver, Boris-Marko Kukovec</b> <i>Structural and electrochemical studies of cobalt(II) and nickel(II) coordination polymers with 6-hydroxynicotinate and 4,4'-bipyridine</i> .....	169
<b>Mladen Borovina, Mateja Pisačić, Ana Husinec, Valentina Badurina, Marijana Đaković</b> <i>Mechanical properties of copper(II) and cadmium(II) halides equipped with 3-nitropyridine ligands</i> .....	170
<b>Karla Korade, Mateja Prpić, Dragutin Hasenay, Danijel Namjesnik, Tajana Begović</b> <i>Surface reactions in aqueous solutions of insoluble oxides (TiO<sub>2</sub>) and poorly soluble oxides (SiO<sub>2</sub>)</i> .....	171
<b>Gordan Horvat</b> <i>Simultaneous regression analysis of titration data obtained by several analytical methods</i> .....	172
<b>Gordan Horvat, Ivan Petters, Ivana Jakuš, Nikolina Vidović, Nikola Cindro, Giovanna Speranza, Vladislav Tomišić</b> <i>Anion binding properties of two pentameric homocyclopeptides in acetonitrile and methanol</i> .....	173
<b>Igor Picek, Blaženka Foretić, Dijana Žilić, Ana Šantić, Jasminka Popović</b> <i>The reversible electron transfer within hydrochromic charge-transfer material containing pyridinium oxime and hexacyanoferrate(II) ions</i> .....	174
<b>Zrinko Jurić, Aleksandar Mandić, Tatjana Šumanovac, Marina Šekutor, Đani Škalamera</b> <i>Preparation and conformational analysis of 1,1'-biadamantane and its derivatives</i> .....	175
<b>Michael Ramek, Jelena Pejić, Jasmina Sabolović</b> <i>Density functional structure prediction of neutral physiological copper(II) compounds with L-cysteine and L-histidine</i> .....	176
<b>Silvio Jakopec, Natalija Pantaloni Juraj, Anamaria Brozović, Berislav Perić, Srećko I. Kirin, Silvana Raić-Malić</b> <i>Transition metal complexes of dipicolylamine, iminodiacetamide and bis-triazole derivatives</i> .....	177
<b>Suresh Shanmugam, Marijana Radić Stojković, Silvija Maračić, Silvana Raić-Malić</b> <i>DNA and RNA binding studies of novel amidine- and amidoxime-substituted heterocycles</i> .....	178
<b>Anja Rakas, Sara Prenc, Silvana Raić-Malić, Tatjana Gazivoda Kraljević</b> <i>Synthesis of novel 1,2,3-triazolyl benzoxazole derivatives using deep eutectic solvents</i> .....	179
<b>Ivana Sokol, Anja Rakas, Leentje Persoons, Els Vanstreels, Dirk Daelemans, Silvana Raić-Malić, Tatjana Gazivoda Kraljević</b> <i>Synthesis and antitumor evaluations of novel 2-aryl substituted benzimidazole derivatives</i> .....	180
<b>Siniša Habazin, Dražen Mlinarević, Marta Balog, Ana Bardak, Robert Gaspar, Kálmán Ferenc Szűcs, Sandor G. Vari, Frano Vučković, Gordan Lauc, Mislav Novokmet, Marija Heffer</b> <i>Changes in rat immunoglobulin g n-glycosylation are associated with chronic stress</i> .....	181
<b>Željka Car, Vesna Petrović Peroković, Monika Kovačević, Rosana Ribić, Lidija Barišić</b> <i>Optimization of synthetic route to ferrocene esters of desmuramyl dipeptides</i> .....	182
<b>Matija Modrušan, Renato Tomaš, Lucija Glazer, Nikola Cindro, Katarina Leko, Vladislav Tomišić</b> <i>Thermodynamics of complexation of alkali and alkaline earth metal cations by a phenanthridine-based calix[4]arene glycoconjugate</i> .....	183

<b>Alen Bjelopetrović, Stipe Lukin, Dajana Barišić, Mario Pajić, Manda Ćurić</b> <i>Mechanistic insight into solid-state C–H bond activation in azobenzene by palladium(II) chloride</i> .....	184
<b>Dajana Barišić, Ivan Halasz, Alen Bjelopetrović, Darko Babić, Manda Ćurić</b> <i>Mechanistic study of mechanochemical regioselective halogenation of aromatic C–H bond with Pd catalysts</i> .....	185
<b>Luka Fotović, Nikola Bedeković, Vladimir Stilinović</b> <i>N-(4-halogenobenzyl)-(3-halogeno)pyridinium cations as halogen bond donors</i> .....	186
<b>Mario Pajić, Dajana Barišić, Alen Bjelopetrović, Marina Juribašić Kulcsár, Manda Ćurić</b> <i>Solid-state Suzuki-miyaura Cross-Coupling Reactions catalyzed by dimeric monopalladated azobenzenes</i> .....	187
<b>Nikolina Filipović, Berislav Marković, Željko Debeljak, Katarina Mišković Špoljarić</b> <i>Application of MALDI-TOF-MSI method on 3D cell models</i> .....	188
<b>Iwona Wójcik, Thomas Sénard, Erik L. de Graaf, George M. C. Janssen, Arnoud H. de Ru, Gillian Dekkers, Yassene Mohammed, Peter A. van Veelen, Manfred Wuhrer, Gestur Vidardsson, David Falck</b> <i>Site-specific glycosylation mapping of endogenous fc gamma receptor iiib derived from neutrophils</i> .....	189
<b>Kristina Pavić, Goran Poje, Maja Beus, Zrinka Rajić</b> <i>Antiproliferative activity of novel harmirins</i> .....	190
<b>Lorena Kordić, Sanja Matečić Mušanić</b> <i>Application of ternary phase diagrams in development of solution co-crystallization process</i> .....	191
<b>Hrvoje Rimac, Marina Marinović, Zrinka Rajić</b> <i>A QSAR study of amide-type harmicines as potential antimalarials</i> .....	192
<b>Matea Dragoš, Monica Vidotto, Nadica Maltar-Strmečki</b> <i>OSL study on irradiated and non-irradiated dried tomatoes as ingredient in the mediterranean diet</i> .....	193
<b>Ante Bubić, Zoran Štefanić, Branimir Bertoša, Ivana Leščić Ašler</b> <i>Adenylosuccinate synthetase from Helicobacter pylori: characterization of active site using x-ray diffraction and molecular dynamics simulations</i> .....	194
<b>Dario Matulja, Petra Grbčić, Sandra Kraljević Pavelić, Dean Marković</b> <i>Antiproliferative properties of synthetic granulatamide B and its structural analogues</i> .....	195
<b>David Klarić, Nives Galić</b> <i>High-resolution mass spectrometry characterization of cinnarizine – <math>\beta</math>-cyclodextrin inclusion complexes</i> .....	196
<b>Lucija Hok, Hrvoje Rimac, Janez Mavri, Robert Vianello</b> <i>Covid-19 infection and neurodegeneration: a potential link revealed by computational simulations</i> .....	197
<b>Lucija Vujević, Bahar Karadeniz, Dijana Žilić, Krunoslav Užarević, Marina Kveder</b> <i>Magnetic properties of MOF-525 and PCN-223 doped with copper (II) ions studied by EPR spectroscopy</i> .....	198
<b>Luka Barešić, Zoran Glasovac, Davor Margetić</b> <i>Cocatalytic activity in aldol reaction of a novel thiourea- and guanidinium-oxanorbornanes</i> .....	199
<b>Ana Amić, Dejan Milenković</b> <i>Free radical scavenging potency of 5-hydroxyferulic acid</i> .....	200
<b>Ana Amić, Jasmina M. Dimitrić Marković, Zoran Marković, Dejan Milenković, Žiko Milanović, Marko Antonijević, Denisa Mastifák Cagardová</b> <i>Lox inhibition and iron chelation by ferulic acid – a theoretical approach</i> .....	201
<b>Andrea Dandić, Željka Car, Vesna Petrović Peroković</b> <i>Novel para N-aryl substituted 3-hydroxypyridin-4-ones and their adamantyl derivatives</i> .....	202
<b>Antonia Matić, Zrinka Karačić, Gordan Horvat, Antonija Tomić, Hrvoje Brkić, Sanja Tomić</b> <i>Dipeptidyl peptidase III inhibition tests by metal dications</i> .....	203



<b>Anamarija Briš, Yasujiro Murata, Yoshifumi Hashikawa, Davor Margetić</b> <i>Computational study of reactivity of guanidine substituted sym-tetrazines in cycloaddition reactions</i> .....	205
<b>Goran Poje, Jana Held, Zrinka Rajić</b> <i>Cytotoxicity of harmiquines, hybrids based on harmine and chloroquine scaffolds</i> .....	206
<b>Ina Erceg, Suzana Šegota, Maja Dutour Sikirić</b> <i>The kinetics of bovine serum albumin adsorption onto CaP/TiO<sub>2</sub> nanocomposites</i> .....	207
<b>Ivan Marić, Anđela Pustak, Marijan Gotić, Tanja Jurkin</b> <i>A gamma irradiation method for the synthesis of iron oxide/gold nanostructures</i> .....	209
<b>Ivana Drventić, Ana Kroflić</b> <i>A method for fast analysis of pahs and nitro-pahs in ambient particulate matter</i> .....	210
<b>Ivona Čipor, Josip Moharić, Leo Frkanec</b> <i>Novel supramolecular nanocomposite hydrogels for biomedical applications</i> .....	211
<b>Iva Pukleš, Nikola Sakač, Brunislav Matasović, Marija Jakić, Marija Jozanović</b> <i>Rapid and simple microfluidic methods for detection of bioactive compounds in complex samples</i> .....	212
<b>Nika Gazdek, Karmen Radošević, Lucija Horvat, Ruža Frkanec, Leo Frkanec</b> <i>Design and synthesis of new supramolecular nano-structured materials based on peptide hydrogelator Ac-L-Phe-L-Phe-L-Ala-NH<sub>2</sub> and embedded liposomes</i> .....	213
<b>Pavo Živković, Martina Medvidović Kosanović, Aleksandar Sečenji</b> <i>Anodic pretreatment of carbon graphene paste modified screen printed electrode for enhancing the electrochemical sensing characteristics</i> .....	214
<b>Pavo Živković, Robert Petrić, Aleksandar Sečenji</b> <i>Preparation and characterization of chitosan hydrogel-based optical sensor for total antioxidant capacity determination</i> .....	215
<b>Marija Paurević, Aleksandra Maršavelski, Milenko Korica, Rosana Ribić</b> <i>Adamantane-containing desmuramyl peptides: synthesis and structural insight into NOD2 binding</i> .....	216
<b>Tomislav Friganović, Davor Šakić, Tin Weitner</b> <i>Inner filter effect corrections for protein fluorescence measurements in microplates using variable z-focus position</i> .....	217
<b>Đurđa D. Krstić, Petar M. Ristivojević, Uroš M. Gašić, Milica M. Fotirić Akšić, Dušanka M. Milojković-Opsenica, Jelena Đ. Trifković</b> <i>Phenolic profile as a tool for the authenticity assesment of cultivated berry seeds</i> .....	218
<b>Filip Andrić, Petar Ristivojević, Dušanka Milojković-Opsenica, Jelena Trifković, Gertrud Morlock</b> <i>Fast detection of apricot juice frauds by pumpkin juice based on planar chromatography, image analysis and chemometrics</i> .....	220
<b>Glorija Medak, Josip Bronić, Andreas Puškarić, Nina Popov</b> <i>Effect of metal cations on zeolite acidity</i> .....	222
<b>Jasmina Lapić, Ivana Kuzman, Mateja Toma, Valerije Vrčec, Senka Djaković</b> <i>Effect of C-5 substituent on the regioselectivity of N-ferrocenylation of uracil</i> .....	223
<b>Lu Turković, Natan Koraj, Tajana Silovski, Andrijana Ščavničar, Mila Lovrić, Biljana Nigović, Miranda Sertić</b> <i>Development of a novel dispersive liquid-liquid microextraction method for the simultaneous analysis of six anticancer drugs in human plasma</i> .....	224
<b>Marija Jozanović, Nikola Sakač, Dubravka Madunić-Čačić, Tajana Koščak, Iva Pukleš, Nikolina Sermek, Dean Marković</b> <i>Surfactant sensor based on 1,3-dihexadecyl-1h-benzo[d]imidazol-3-ium for anionic surfactants in industrial wastewaters</i> .....	225

<b>Martina Gudelj, Sunčica Srzentić, Perica Bošković</b> <i>Thermodynamic properties of surfactant benzylododecyldimethylammonium bromide in binary mixture of propane-1,2-diol and water .....</i>	226
<b>Mateja Toma, Lana Petrinc, Valerije Vrčak</b> <i>Light induced decomposition of ferrocenoyl-nucleobases.....</i>	227
<b>Matija Modrušan, Toni Divjak, Nikolina Vidović, Nikola Cindro, Giovanna Speranza, Gordan Horvat, Vladislav Tomišić</b> <i>Anion binding affinities of linear penta-homopeptides in solution .....</i>	228
<b>Mirna Mandarić, Nikol Bebić, Edi Topić, Višnja Vrdoljak</b> <i>Construction of 1D zig-zag chain coordination polymers utilising (iso)nicotinoyl hydrazonato ligands and dioxomolybdenum core.....</i>	229
<b>Petar M. Ristivojević, Mihajlo Jakanovski, Filip Andrić, Dušanka M. Milojković-Opsenica, Jelena Đ. Trifković</b> <i>Natural deep eutectic solvent as extraction media for the main phenolic compounds from Rubi idaei leaves .....</i>	230
<b>Sanja Škulj, Antun Barišić, Zoe Jelić Matošević, Branimir Bertoša</b> <i>Influence of N-glycosylation on horseradish peroxidase stabilization .....</i>	232
<b>Danijela Mihelec, Mia Bušljeta, Željka Car, Vesna Petrović Peroković, Rosana Ribić</b> <i>Synthesis of new amphiphilic triazole derivatives of mannosylated desmuramyl dipeptide .....</i>	233
<b>Zrinka Karačić, Filip Šupljika, Ana Tomašić Paić, Lidija Brkljačić, Sanja Tomić</b> <i>Role of dipeptidyl peptidase III in pain regulation through cleavage of neuropeptides.....</i>	234
<b>Aleksandra Dramićanin, Filip Andrić, Mirjana Pešić, Aleksandar Kostić, Danijel Milinčić, Nebojša Momirović, Dušanka Milojković-Opsenica</b> <i>Effects of agricultural production systems on protein profiles of four different varieties of potato tubers .....</i>	235
<b>Iva Markuš, Andrea Usenik, Katarina Pičuljan, Marija Alešković, Marina Šekutor, Josip Požar</b> <i>Diamantane alcohols and hydrophobic cavities: the perfect pair also in non-aqueous solution? .....</i>	236
<b>Marija Cvetnić, Nikola Cindro, Nikola Bregović, Vladislav Tomišić</b> <i>Calix[4]arenes bearing urea moieties - investigation of supramolecular behaviour.....</i>	237
<b>Morana Drušković, Dražen Vouk, Danica Maljković, Mario Šiljeg</b> <i>Electrocoagulation and electrochemical advanced oxidation processes in oily wastewater treatment.....</i>	238
<b>Valentina Rep, Rebeka Štulić, Hana Čipčić Paljetak, Mario Matijašić, Mihaela Perić, Silvana Raić-Malić</b> <i>Synthesis and antibacterial activity of novel amidino substituted benzothiazoles and benzimidazoles.....</i>	239
<b>Ivo Piantanida, Goutam Kumar Kole, Todd B. Marder, Marta Koščak</b> <i>Interactions of methyl viologens of bis-(4'-ethynylpyridyl)arenes with DNA/RNA and their biological activity .....</i>	240
<b>Filip Vranješević, Maria Kolypadi Markovic, Valerije Vrčak, Dean Marković</b> <i>Cyclic carbamate formation through transition metal-catalyzed CO<sub>2</sub> capture .....</i>	241
<b>Darko Vušak, Dubravka Matković-Čalogović, Biserka Prugovečki</b> <i>Synthesis and crystal structure analysis of 3D zinc metal-organic frameworks involving amino acidates.....</i>	242
<b>Dinko Šoić, Toma Keser, Mislav Novokmet, Gordan Lauc, Olga Gornik</b> <i>High-throughput enrichment of complement C3 protein from human plasma using lectin affinity matrix.....</i>	243
<b>Dušanka M. Milojković-Opsenica, Anđelka M. Rosić, Đurđa D. Krstić, Jelena Đ. Trifković, Tomislav B. Tosti, Sandra B. Šegan</b> <i>Development and validation of hptlc method for determination of sugar profiles of honey and its syrup adulterants.....</i>	244

<b>Zvonimir Jažo, Ena Ivić, Ivana Drventić, Danica Bajić, Marko Vučemilo, Tea Dujmović, Ljilja Žilić, Mateo Glumac</b> <i>Isolation and chemical analysis of Immortelle essential oil.....</i>	246
<b>Gregor Talajić, Ivana Brekalo, Edi Topić, Nikola Cindro, Krunoslav Užarević</b> <i>Cyclobutanetetramino acid derived homochiral metal-organic frameworks.....</i>	247
<b>Irena Ivanišević, Josipa Kahlina, Stjepan Milardović</b> <i>Fabrication of all-solid-state ammonium selective electrode on a paper substrate.....</i>	248
<b>Jelena Trifković, Marko Jović, Vukosava Živković Radovanović, Filip Andrić, Petar Ristivojević, Dušanka Milojković-Opsenica</b> <i>Statistical analysis based green planar chromatographic methodology for quality control of food supplements: case study on Origanum vulgare.....</i>	249
<b>Jevgenija Lugiņina, Martin Linden, Māris Bazulis, Viktors Kumpiņš, Anatoly Mishnev, Siegfried R. Waldvogel, Māris Turks</b> <i>Application of betulin-derived nitrile oxides in the construction of cytostatic lupane-type triterpenoid-isoxazole conjugates.....</i>	251
<b>Leo Štefan, Ana Čikoš, Robert Vianello, Ivica Đilović, Miljenko Dumić</b> <i>Reactivity and thermal behaviour of 7-methyl-2H,3H,7H-imidazo[2,1-b]thiazol-4-ium chloride.....</i>	252
<b>Maja Krstić Ristivojević, Bojana Filipčev, Marija Bodroža-Solarov, Tanja Ćirković Veličković</b> <i>Bioaccessibility of phytic acids and total phenolic content in grain of plant amaranthus cruentus upon simulated gastrointestinal digestion.....</i>	253
<b>Maria Kolymjadi Markovic, Filip Vranješević, Tomislav Pavlešić, Gabriela Ambrožić, Valerije Vrček, Dean Marković</b> <i>Experimental and computational approach to catalyzed domino reactions between propargyl alcohols and CO<sub>2</sub>.....</i>	255
<b>Mario-Livio Jeličić, Edvin Brusač, Daniela Amidžić Klarić, Biljana Nigović, Ana Mornar</b> <i>Spectroscopy and statistics - a powerful combination for drug compatibility evaluation.....</i>	256
<b>Marta Razum, Luka Pavić, Tihana Čižmar, Andreja Gajović, Damir Pajić, Ana Šantić</b> <i>Polaronic conductivity in vanadium phosphate glasses and the effect of molybdenum oxide addition.....</i>	257
<b>Marzena Łazarczyk, Karolina Kędra-Królik, Tajana Begović, Piotr Zarzycki</b> <i>Magnesium decreases the electrical double layer (EDL) forces between carbonate particles.....</i>	259
<b>Monika Kovačević, Jasna Mrvčić, Mojca Čakić Semenčić, Sunčica Roca, Jana Perica, Klara Širić, Lidija Barišić</b> <i>Synthesis, conformational analysis and preliminary biological evaluation of conjugates of ferrocene and hydrophobic amino acids.....</i>	260
<b>Nikola Bedeković, Luka Fotović, Vladimir Stilinović, Dominik Cinić</b> <i>Preservation of pyridone homosynthon in halogen-bonded cocrystals.....</i>	261
<b>Nina Popov, Mira Ristić, Svetozar Musić, Stjepko Krehula</b> <i>Influence of various metal cations on the formation and properties of α-Fe<sub>2</sub>O<sub>3</sub> (hematite) nanorods.....</i>	262
<b>Ozana Mišura, Marijana Đaković</b> <i>Co-crystals of Cd(II) coordination polymers with simple organic compounds.....</i>	263
<b>Petar Šutalo, Barbara Panić, Ivana Biljan, Ivan Kodrin</b> <i>Nitrogen-containing covalent organic polymers: synthesis, characterization and computational study.....</i>	264
<b>Robert Junior Kolman, Emina Mehić, Maja Majerić Elenkov, Irena Dokli</b> <i>Synthesis and biocatalysis of propargylic epoxides.....</i>	265
<b>Rūdolfs Bejaunieks, Mikus Puriņš, Viktors Kumpiņš, Māris Turks</b> <i>Exploration of Various Electrophile-Induced Transformations of Propargyl Silanes.....</i>	266

<b>Stipe Lukin, Tomislav Stolar, Ivor Lončarić, Igor Milanović, Nikola Biliškov, Marco di Michiel, Tomislav Friščić, Ivan Halasz</b> <i>Ion metathesis and double salt formation in the solid state</i> .....	267
<b>Tino Šeba, Robert Kerep, Mario Gabričević</b> <i>Separation of the native and desialylated human alpha-1-acid glycoprotein sialoforms using low-pressure pH gradient ion-exchange chromatography</i> .....	268
<b>Valentina Borko, Tomislav Friganović, Tin Weitner</b> <i>The effect of oxalate on the thermodynamic parameters for the binding of iron to human serum transferrin</i> .....	269
<b>Zlatan Spahić, Alen Martinko, Tomica Hrenar, Ines Primožič</b> <i>Synthesis and characterization of novel hybrid carbamates</i> .....	270
<b>Petar Štrbac, Davor Margetić</b> <i>Synthesis and exploration of 1,3-dipolar cycloaddition reactions of guanidine azides</i> .....	271
<b>Zoe Jelić Matošević, Mislav Brajković, Rui P. P. Neves, Pedro Alexandrino Fernandes, Branimir Bertoša</b> <i>Computational studies of the Mycobacterium tuberculosis transcriptional repressor MntR</i> .....	272
<b>Akmaral Kussayeva, Zoran Glasovac, Davor Margetić</b> <i>The endo and exo transition states for the diels-alder reaction between vinyl carbodiimides with N-alkyl imine</i> .....	273
<b>Ivana Landeka, Dominik Cinčić</b> <i>Cocrystallization of dasatinib with perfluorinated iodo- and bromobenzenes</i> .....	274
<b>Katarina Leko, Andrea Usenik, Robert Vianello, Lucija Hok, Vladislav Tomišić</b> <i>Thermodynamic and structural studies of complexation reactions of phenanthridine-based calix[4]arene derivative with alkaline earth metal cations</i> .....	275
<b>Tea Babić, Katarina Leko, Andrea Usenik, Matija Modrušan, Nikola Jakupec, Erik Uran, Vladislav Tomišić</b> <i>Complexation of transition metal cations by a lower-rim phenanthridine calix[4]arene derivatives</i> .....	276
<b>Helena Butkiewicz, Sandra Kosiorek, Volodymyr Sashuk, Oksana Danylyuk</b> <i>Structural studies on the host-guest complexes of carboxylated pillar[5]arene with amidine and guanidine drugs</i> .....	277
<b>Danijel Namjesnik, Jozefina Katić, Tin Klačić, Tajana Begović</b> <i>Properties of spontaneously and electrochemically formed Ti/TiO<sub>2</sub> layers in sodium chloride solution</i> .....	278
<b>Đani Škalamera, Ivan Logožar</b> <i>Isolation and derivatization of saponin from quillaja saponaria tree bark for the synthesis of a conjugate with desmuramyl dipeptide</i> .....	279
<b>Ivan Duka, Tihana Marić, Hrvoje Rimac, Željko Maleš, Mirza Bojić, Božena Mitić, Dario Hruševar, Ana-Marija Domijan</b> <i>HPLC method for quantification of naphthoquinones in plant extracts</i> .....	280
<b>Dario Matulja, Karlo Šurlina, Petra Grbčić, Sandra Kraljević Pavelić, Dean Marković</b> <i>Bioprospecting of the Adriatic sea Tunicate, Phallusia mammillata</i> .....	282
<b>Željka Soldin, Mateja Pisačić, Karla Zozoli, Marijana Đaković</b> <i>Elastically deformable crystals of Cd(II) coordination polymers</i> .....	284
<b>Karolina Kędra, Tajana Begović, Marzena Łazarczyk, Danijel Namjesnik, Piotr Zarzycki</b> <i>Electrochemical insights into spatial complexity of hematite - dicarboxylate interactions at the interface</i> .....	285
<b>Karla Akrap, Dario Kremer, Mirko Ruščić, Marija Nazlić, Valerija Dunkić</b> <i>Comparison of the composition of free volatile compounds of the species Veronica chamaedrys L. isolated by hydrodistillation and microwave extraction</i> .....	286

## Education

<b>Anita Belančić, Tatjana Jaćimović, Nataša Kletečki</b> <i>5<sup>th</sup> grade chemistry? Kemija u petom razredu?</i> .....	288
<b>Martina Šeler Namjesnik, Martin Buljubašić</b> <i>Photocatalytic degradation of essential oils – a school project</i> .....	289
<b>Nikolina Penić, Draginja Mrvoš-Sermek</b> <i>Valence – basic chemical concept Valencija – temeljni kemijski pojam</i> .....	290

## Industry and entrepreneurship

<b>Julija Jurić, Wendy M. Kohrt, Domagoj Kifer, Kathleen M. Gavin, Marija Pezer, Peter A. Nigrovic, Gordan Lauc</b> <i>Effects of estradiol on biological age measured by the glycan age index</i> .....	291
<b>Filip Čerepinko, Katarina Jozinović, Ana Juričić, Suzana Kralj, Anabela Ljubić, Kristina Povijač, Emanuel Tomljenović, Veronika Žlabravec</b> <i>Smart laboratory fume hood – student project</i> .....	292

## Chemical engineering and biotechnology

<b>Monika Šabić Runjavec, Marija Vuković Domanovac, Ernest Meštrović</b> <i>Bioengineering approach for bioremediation of pharmaceutical wastewater</i> .....	293
<b>Goran Lukač, Marijana Marcelja, Igor Dejanović</b> <i>Application of the relative gain array in the control system design of thermally coupled distillation sequences</i> .....	294
<b>Marina Duplančić, Ivana Elizabeta Zelić, Vjeran Gomzi, Vesna Tomašić, Dejana Carić, Dijana Žilić</b> <i>Photodegradation of neonicotinoids on a TiO<sub>2</sub>-based photocatalysts - efficiency of reactive oxygen species</i> .....	295
<b>Filip Car, Vesna Tomašić, Domagoj Vrsaljko</b> <i>Emerging monolithic catalysts for the catalytic oxidation of aromatic volatile organic compounds</i> .....	296
<b>Sabino Sepčić, Patrizia Janković, Daniela Kalafatović</b> <i>Design of linear and cyclic peptides for ester hydrolysis</i> .....	297
<b>Dino Skendrović, Ivana Bukarica, Ana Vrsalović Presečki</b> <i>Activation agent optimization in aldolase immobilization on mesoporous silica</i> .....	298
<b>Kristina Zagajski Kučan, Marko Rogošić</b> <i>Choline chloride: propylene glycol (1:4) deep eutectic solvent for extractive gasoline purification</i> .....	299
<b>Emina Mehić, Zvezdana Findrik Blažević, Maja Majerić Elenkov</b> <i>Biocatalytic scope of halohydrin dehalogenase from Mycobacterium sp. GP1 (HheB2) and mutant HheB2-T120A</i> .....	300
<b>Ivana Čevid, Nevena Milčić, Maja Majerić Elenkov, Zvezdana Findrik Blažević</b> <i>Validation of kinetic model of halohydrin dehalogenase-catalysed synthesis of (R)-epichlorohydrin</i> .....	302
<b>Vanja Kosar, Tea Kapustić, Tina Podreka, Ivana Elizabeta Zelić, Vesna Tomašić</b> <i>Removal of acetamiprid over TiO<sub>2</sub>/perlite photocatalyst</i> .....	303
<b>Viktorija Prevarić, Kristina Bule, Martina Miloloža, Dajana Kučić Grgić, Matija Cvetnić, Marinko Markić, Šime Ukić, Tomislav Bolanča</b> <i>Dibutyl phthalate degradation by advanced oxidation processes</i> .....	304
<b>Ivan Karlo Cingesar, Viktorija Katušić, Katarina Jozinović, Domagoj Vrsaljko</b> <i>Channel surface modification of 3D printed droplet generators</i> .....	305
<b>Angela Kapitanović, Helena Otmačić Ćurković</b> <i>Artificially obtained sulphate-carbonate patina on bronze substrates - preparation and characterization</i> .....	306



<b>Ines Šoljić, Ivana Šoić, Sanja Martinez</b> <i>Applicability of the paste electrolyte cell for in situ electrochemical testing the surface protection of bronze...</i>	307
<b>Marija Lukić, Domagoj Vrsaljko</b> <i>Optimization of polymeric millireactors produced by additive manufacturing .....</i>	308
<b>Marijan-Pere Marković, Ivan Karlo Cingesar, Petar Kassal, Domagoj Vrsaljko</b> <i>Design and production of a millireactor system with a pH-sensitive coating.....</i>	309
<b>Valentina Šimatović, Josip Sacher, Jasna Prlić Kardum</b> <i>Influence of antisolvent addition on crystallization kinetics and granulometric properties of fosanprenavir calcium .....</i>	310
<b>Miće Jakić, Sanja Perinović Jozić, Laura Ključec, Ivana Bandić</b> <i>the effect of hot melt extrusion on the thermal properties of post-consumer PET bottles.....</i>	311
<b>Olivera Galović, Slavica Mikić, Manuela Grčević, Marija Paurević, Martina Šrajec Gajdošik, Zlata Kralik</b> <i>Fatty acid determination in hens feed mixture .....</i>	312
<b>Petra Marin, Denis Vadlja, Nevena Milčić, Zvezdana Findrik Blažević, Maja Majerić Elenkov</b> <i>Lyophilization conditions for the stabilization of halohydrin dehalogenases .....</i>	313
<b>Marko Babić, Goran Mauša, Željko Svedružić, Daniela Kalafatović</b> <i>Theoretical evaluation of enzyme active sites and catalytic peptides involved in ester hydrolysis.....</i>	314
<b>Ivan Vrbanić, Igor Kultan, Ozren Wittine, Eugen Marčević, Nenad Bolf</b> <i>Razvoj simulacije procesa izmjene topline u cijevnom reaktoru.....</i>	316
<b>Karla Dubaić, Nina Popović, Ivan Sušan, Sofija Ivković, Anja Kovač, Zdravka Knežević, Maša Safundžić Kučuk, Leo Štefan</b> <i>Preformulation approach for the development of preservative free steroid-based formulation.....</i>	317
<b>Matea Gavran, Hrvoje Dorić, Nenad Bolf</b> <i>Development of the calibration model for real-time measurement of glycine concentration in glycine-water system using ANN .....</i>	318
<b>Anja Šimić, Zvonimir Jažo, Antonija Parčina, Klaudija Gusić, Samela Selimović, Samira Huseinović, Sanida Bektić, Vedrana Čikeš Čulić, Olivera Politeo</b> <i>Cytotoxic activity of the common juniper essential oil.....</i>	319
<b>Zvonimir Jažo, Antonija Parčina, Ena Ivić, Sanida Bektić, Vedrana Čikeš Čulić, Mila Radan</b> <i>Cytotoxic activity of laurel essential oil.....</i>	320
<b>Maja Levak Zorinc, Lucija Horvat, Ruža Frkanec, Nadica Ivošević DeNardis</b> <i>Algae-derived plasma membrane carriers .....</i>	321
<b>Adriana Lepur, Iva Bebek, Marina Markeš, Anita Šporec, Kristijan Milaković</b> <i>Monitoring and control of critical parameters in fermentation processes by HPLC and Raman spectroscopy ..</i>	322
<b>Vedran Petrić, Zoran Mandić</b> <i>Three electrode electrochemical investigation of different salt/solvent electrolyte combinations in a symmetrical carbon/carbon double layer supercapacitor.....</i>	323
<b>Nikola Rimac, Željka Ujević Andrijić, Vladimir Cvjetović</b> <i>Fouling detection in industrial heat exchanger using recurrent LSTM neural network model.....</i>	324
<b>Jasna Prlić Kardum, Anamarija Mitar, Marijana Zovko Končić</b> <i>Optimizing the extraction of polyphenols from plantain leaves.....</i>	326
<b>Kristina Bule, Viktorija Prevarić, Matija Cvetnić, Šime Ukić, Tomislav Bolanča, Martina Miloloža, Dajana Kučić Grgić, Marinko Markić, Dora Matijašec</b> <i>Degradation of polyethylene and polypropylene microplastics by advanced oxidation processes.....</i>	327

## Environment protection and sustainable development

<b>Anđelina Bubalo, Dražen Vouk, Danica Maljković, Tomislav Bolanča</b> <i>Gasification of sewage sludge as a sustainable circular economy perspective</i> .....	328
<b>Bruna Babić, Silvia Morović, Krešimir Košutić, Danijela Ašperger</b> <i>Photolysis of N-nitrosodipropylamine, mebendazole and clothianidin in drinking water</i> .....	329
<b>Silvia Morović, Brunna Babić, Danijela Ašperger, Krešimir Košutić</b> <i>Removal of N-nitrosodipropylamine, mebendazole and clothianidin from drinking water by reverse osmosis</i> .	330
<b>Marin Popović, Tayebah Sharifi, Marin Kovačić, Marijana Kraljić Roković, Hrvoje Kušić, Urška Lavrenčić Štangar, Ana Lončarić Božić</b> <i>Enhancement of solar driven degradation of Ciprofloxacin by photodeposited Fe onto iso-type homojunction BiVO<sub>4</sub> surface</i> .....	331
<b>Suzana Sopčić, Gordana Pehnc</b> <i>Determination of carbohydrates in atmospheric particulate matter by high-performance anion-exchange chromatography with pulsed amperometric detection</i> .....	332
<b>Ivana Jakovljević, Zdravka Sever Štrukil, Ivan Bešlić, Gordana Pehnc</b> <i>Spatial distribution of polycyclic aromatic hydrocarbons in the air of Zagreb during winter</i> .....	333
<b>Nives Novosel, Damir Kasum, Petar Žutinić, Tarzan Legović, Nadica Ivošević DeNardis</b> <i>Algal motility as an indicator of environmental stress</i> .....	334
<b>Brunislav Matasović, Tatjana Radanović, Elvira Kovač-Andrić</b> <i>Tropospheric photo-smog pollution in Dubrovnik from 2015 to 2017</i> .....	335
<b>Martina Miloloža, Kristina Bule, Lucija Anzulović, Amadea Badurina-Petričević, Ivana Jazbišek, Paula Patrčević, Viktorija Prevarić, Matija Cvetnić, Šime Ukić, Tomislav Bolanča, Marinko Markić, Vesna Ocelić Bulatović, Dajana Kučić Grgić</b> <i>Bioremediation of water polluted with PS and PVC microplastics by bacteria Bacillus cereus and Pseudomonas alcaligenes</i> .....	336
<b>Antonija Tomić, Matija Cvetnić, Hrvoje Kušić, Marin Kovačić, Ana Lončarić Božić</b> <i>Predictive quantitative structure–property relationship (QSPR) and response surface modeling for adsorption processes of contaminants of emerging concern in water onto TiO<sub>2</sub></i> .....	337
<b>Luka Mesek, Sara Pršić, Blanka Krčelić, Petra Brajenić, Martina Miloloža, Dajana Kučić Grgić, Vesna Ocelić Bulatović</b> <i>Impact of light pollution</i> .....	338
<b>Zdravka Sever Štrukil, Ivana Jakovljević, Gordana Pehnc</b> <i>Trends of polycyclic aromatic hydrocarbons in PM<sub>10</sub> particle fraction in Zagreb from 2016 to 2020</i> .....	339
<b>Kristina Tolić, Dragana Mutavdžić Pavlović, Matija Cvetnić, Igor Jajčinović</b> <i>Photocatalytic behavior of anticancer drugs: kinetic study and toxicity assessment</i> .....	340
<b>Niki Simonović, Marija Marguš, Mathieu Dutour-Sikirić, Irena Ciglencečki</b> <i>Dynamics of organic matter in rogoznica lake as an indication of global change</i> .....	341
<b>Stefani Tonković, Marin Kovačić, Zlata Hrnjak-Murgić, Ana Lončarić Božić</b> <i>Combined thermal - and UV - degradation of polyethylene terephthalate - characterization of aged material</i>	343
<b>Gabriella Kanižai Šarić, Ana Marojević, Maja Karnaš, Maja Molnar, Ivana Majić, Vesna Rastija</b> <i>Inhibition of Bacillus subtilis growth by fluorinated pyrazole derivatives</i> .....	344
<b>Marko Rukavina, Marija Lukić, Marijana Serdar</b> <i>Application of red mud in geopolymers technology</i> .....	345
<b>Marija Kuštro, Leo Bolješić, Dubravka Tavra, Dora Brdek, Martina Miloloža, Kristina Bule, Viktorija Prevarić, Matija Cvetnić, Šime Ukić, Tomislav Bolanča, Vesna Ocelić Bulatović, Dajana Kučić Grgić</b> <i>Comparison of toxicity tests for microplastic using freshwater microalgae Chlorella sp. and Scenedesmus sp.</i> .....	347

Mirna Habuda-Stanić, Huiyu Dong, Antonija Kristek Janković <i>Structural characterisation of modified bioadsorbents</i> .....	348
Kristijan Vidović, Samo Hočevar, Irena Ciglencečki-Jušić <i>A new approach for studying adsorption processes on solid electrodes in seawater conditions</i> .....	349
Karla Plenča, Andrea Opačak, Sara Cvetković, Matija Cvetnić, Ana Lončarić Božić, Zvonimir Matusinović, Hrvoje Kušić <i>Laboratory pyrolysis of biomass: gas product analysis</i> .....	351
Andrea Opačak, Karla Plenča, Sara Cvetković, Matija Cvetnić, Tomislav Bolanča, Ana Lončarić Božić, Zvonimir Matusinović, Hrvoje Kušić <i>Optimization of biomass pyrolyzation on laboratory pyrolysis system</i> .....	352
Irena Ciglencečki, Ivica Vilibić, Jelena Dautović, Niki Simonović, Vjeročka Vojvodić, Božena Čosović, Petra Zemunik, Natalija Dunić, Hrvoje Mihanović <i>Long-term (30 years) study of dissolved organic matter in the northern Adriatic sea; an indication of global changes and the bios variations</i> .....	353
Marko Racar, Mia Gotovuša, Ivan Pucko, Fabio Faraguna <i>Synthesis of fatty acid octyl esters combined with glycerol extraction and reuse of acid catalyst</i> .....	355
Valentina Gluščić, Mirjana Čačković, Gordana Pehnc, Ivan Bešlić <i>Content of ionic compounds in the ambient fine particulate matter fraction</i> .....	356
Iva Šimić, Gordana Mendaš, Gordana Pehnc, Andrea Milinković, Sanja Frka <i>Different performances of a bulk collector for the determination of PAHs and PCBs in total deposited matter</i> .....	357
<b>Materials and nanotechnology</b>	
Irena Ivanišević, Sara Krivačić, Iva Gudan Pavlović, Stjepan Milardović, Petar Kassal <i>Amphiphilic silver nanoparticles for inkjet printed electronics on flexible plastic substrates</i> .....	358
Iva Rezić, Mislav Majdak, Lela Martinaga, Maja Somogyi Škoc, Vanja Ljoljić Bilić, Ivan Kosalec <i>Development and characterization of antibacterial coating with nanoparticles active against MRSA and MSSA</i> .....	359
Andreja Žužić, Jelena Macan <i>Permanganometric determination of oxygen nonstoichiometry in manganites</i> .....	360
Jelena Bijelić, Manisha Sahu, Sugato Hajra, Dong Ik Oh, Hoe Joon Kim, Igor Djerdj <i>Triple perovskite-based triboelectric nanogenerator: a facile method of energy harvesting and self-powered information generator</i> .....	361
Dalibor Tatar, Pascal Cop, Ruben Maile, Yu Sun, Omeir Khalid, Patrick Esch, Sven Heiles, Herbert Over, Bernd M. Smarsly, Igor Djerdj <i>Impact of aliovalent/isovalent ions (Gd, Zr, Pr, and Tb) on the catalytic stability of mesoporous ceria in the HCl oxidation reaction</i> .....	362
Marija Tkalčević, Jordi Sancho Parramon, Matej Bubaš, Goran Dražić, Peter Nadazdy, Sigrid Bernstorff, Maja Mičetić <i>Magnetron sputtering deposition of 3D networks of nanopores in alumina</i> .....	363
Mateja Piljić, Maja Somogyi Škoc, Iva Rezić <i>Preparation and characterization of silica-Nigella sativa L. hybrid materials</i> .....	365
Ivana Periša, Marija Tkalčević, Lovro Basioli, Mile Ivanda, Sigrid Bernstorff, Maja Mičetić <i>Magnetron sputtering deposition of core/shell Ge/Al quantum dot lattices in amorphous Al<sub>2</sub>O<sub>3</sub> matrix</i> .....	366
Marko Robić, Mira Ristić, Stjepko Krehula, Svetozar Musić <i>Synthesis and properties of electrospun fibres in the system Er<sub>2</sub>O<sub>3</sub>-Fe<sub>2</sub>O<sub>3</sub></i> .....	367
Igor Jajčinović, Sara Pršić, Kristina Tolić, Vedrana Špada, Ivan Brnardić <i>Aging of photocatalysts TiO<sub>2</sub>, TiO<sub>2</sub> / multiwall carbon nanotubes and TiO<sub>2</sub> / graphene oxide in air</i> .....	368

<b>Matej Ercegović, Filip Brleković, Jelena Macan, Juraj Šipušić</b> <i>Improvement of acoustic and fire resistant properties of wood-wool cement composite panel .....</i>	369
<b>Francis M. dela Rosa, Tayebah Sharifi, Marin Kovačić, Marijana Kraljić Roković, Hrvoje Kušić, Urška Lavrenčić Štangar, Ana Lončarić Božić</b> <i>Solothermal synthesis, characterization and photocatalytic properties of TiO<sub>2</sub>/Fe<sub>2</sub>O<sub>3</sub> nanocomposites .....</i>	370
<b>Sara Krivačić, Magdalena Kralj, Irena Ivanišević, Ivan Halasz, Petar Kassal</b> <i>Inkjet printable conductive inks based on melamine intercalated graphene nanosheets .....</i>	371
<b>Lucija Fiket, Patricia Žagar, Anamarija Horvat, Lana Brkić, Marin Božičević, Denis Sačer, Roko Blažic, Zvonimir Katančić</b> <i>Synthesis of stretchable and self-healable conductive polymer based on poly(3,4-ethylenedioxythiophene) .....</i>	372
<b>Katarina Marušić, Helena Mijić, Irina Pucić, Branka Mihaljević</b> <i>Polymer nanocoatings crosslinked by <math>\gamma</math>-rays .....</i>	373
<b>Katarina Marušić, Nives Matijaković, Helena Pišonić, Branka Mihaljević</b> <i>Application of radiation technology for preservation of cultural heritage made of leather .....</i>	374
<b>Marin Božičević, Magdalena Vujasinović, Lucija Fiket, Denis Sačer, Roko Blažic, Ana Čikoš, Zvonimir Katančić</b> <i>Investigation of the conditions for the synthesis of poly(3,4-ethylenedioxythiophene) ATRP macroinitiator .....</i>	375
<b>Ana Peršić, Nina Popov, Stjepko Krehula, Ljerka Kratočil Krehula</b> <i>The influence of UV ageing on the properties of low density polyethylene/hematite composites .....</i>	376
<b>Edi Radin, Goran Dražić, Goran Štefanić, Anđela Pustak, Tanja Jurkin, Ivan Marić, Matea Raić, Nikola Baran, Marijan Gotić</b> <i>Solid state dispersions of platinum in the SnO<sub>2</sub> nanomaterials .....</i>	377
<b>Edi Radin, Goran Dražić, Goran Štefanić, Anđela Pustak, Tanja Jurkin, Ivan Marić, Matea Raić, Nikola Baran, Marijan Gotić</b> <i>Mechanochemical synthesis and characterisation of Pt-Fe<sub>2</sub>O<sub>3</sub> nanomaterials .....</i>	378
<b>Nikolina Janton, Gordana Matijašić</b> <i>Preparation and characterization of celecoxib and cheese whey granules .....</i>	379
<b>Nikolina Kalčec, Valerije Vrčec, Barbara Pem, Lucija Božičević, Ivana Vinković Vrčec</b> <i>NMR study of interaction of L-dopa and dopamine with gold nanoparticles .....</i>	380
<b>Gabrijela Radić, Klara Perović, Hrvoje Kušić, Marijana Kraljić Roković</b> <i>Ascorbic acid influence on the photoelectrochemical response of TiO<sub>2</sub> and SnS<sub>2</sub> .....</i>	381
<b>Katarina Mužina, Antonela Čugalj, Katarina Marija Drmić, Stanislav Kurajica</b> <i>Combustion synthesis of copper-doped cerium aluminate .....</i>	382
<b>Ivana Katarina Ivković, Stanislav Kurajica, Gordana Matijašić, Marina Duplančić</b> <i>The comparison of advanced synthesis methods for ceria nanoparticles doped with manganese .....</i>	383
<b>Monica Vidotto, Ina Erceg, Timor Grego, Shaan Chamaray, Tatjana Antonić Jelić, Marie Lasgorceix, Anne Leriche, Božana Čolović, Maja Dutour Sikirić, Nadica Maltar-Strmečki</b> <i>Thermal stability of gamma radiation induced radicals in ion-substituted hydroxyapatites .....</i>	384
<b>Matea Raić, Lara Mikac, Mile Ivanda</b> <i>Novel honeycomb silicon structure as potential anode material for Li-ion cells .....</i>	385
<b>Vedran Kojić, Mario Boháč, Krešimir Salamon, Gracin, Davor, Krunoslav Juraić, Andreja Gajović</b> <i>Improved optical and electrical properties of formamidinium lead iodide perovskite films on ZnO nanorods with polyvinylpyrrolidone additive .....</i>	386
<b>Arijeta Baftić, Ivana Panžić, Donata Jambriško, Ivana Capan, Luka Pavić, Vilko Mandić</b> <i>Nanostructured SnO<sub>2</sub> thin-films for solar cells .....</i>	387
<b>Irena Krešić, Matko Erceg, Nataša Stipanelov Vrandečić, Sanja Perinović Jozić</b> <i>Preparation and characterization of poly(ethylene oxide)/cloisite 20a nanocomposites .....</i>	388

<b>Maria Kolympadi Markovic, Robert Peter, Ivana Jelovica Badovinac, Iva Šarić, Marko Perčić, Rafaela Radičić, Dean Marković, Mato Knez, Gabriela Ambrožić</b> <i>Preparation of ZnO/organosilane/ZnO hybrid thin films via atomic layer deposition (ALD) and solution surface modification</i> .....	389
<b>Marko Dunatov, Andreas Puškarić, Luka Pavić, Lidija Androš Dubraja</b> <i>Structural and dielectric studies of bis(oxalato)chromium(III) complexes with azabicyclic cations</i> .....	390
<b>Antoneta Tomljenović, Juro Živičnjak, Veronika Stamać</b> <i>Usage durability of knitwear made of man-made artificial fibers from cellulose</i> .....	391
<b>Juro Živičnjak, Ivan Mihaljević, Zenun Skenderi, Antoneta Tomljenović</b> <i>Comfort of socks made of innovative cellulose materials</i> .....	392
<b>Sanja Perinović Jozić, Ivan Bajan, Miće Jakić, Branka Andričić</b> <i>Preparation of poly(ethylene oxide) film with variation of drying temperature</i> .....	393
<b>Ruža Frkanec, Ilija Brzić, Nikolina Kalčec, Ivana Vinković Vršek, Lucija Horvat, Tihana Kurtović, Leo Frkanec</b> <i>Towards nanobiosensor for coronavirus (Covid-19) detection: conjugation of monoclonal anti-SARS-Cov-2 antibodies to gold nanoparticles</i> .....	394
<b>Berislav Marković, Dalibor Tatar, Aleksandar Miletić, Ákos Kukovecz, Igor Djerdj</b> <i>Synthesis of 1,2-diketones from aldehyde using novel ceria-zirconia high-entropy oxides as actual catalysts</i> .....	395
<b>Josipa Bilić, Manuel Širola, Vedrana Špada, Neven Peko</b> <i>Analyses on chemical and mechanical stripping of coatings on metal plate mock-ups</i> .....	396
<b>Kamran Syed, Hrvoje Gebavi, Davor Ristić, Eduard Ilobet, Mile Ivanda</b> <i>Gas Sensors on Flexible Polyimide, Rigid Alumina and Silicon Substrate for the Nitrogen dioxide (NO<sub>2</sub>) and Ammonia (NH<sub>3</sub>) Gas Detection</i> .....	398
<b>Sara García-Ballesteros, Josipa Papac, Ana M. Amat, Hrvoje Kušić</b> <i>Environmental aspect of photocatalysis for the degradation of oxytetracycline in water: N-S-TiO<sub>2</sub> vs TiO<sub>2</sub></i> .....	400
<b>WORKSHOPS</b>	
<b>Education</b>	
<b>Vlatka Husetović, Marijana Bastić</b> <i>Vertikalna povezanost kurikulumskih sadržaja kemije i prirode od ishoda na razini aktivnosti preko pokusa do vrednovanja</i> .....	405
<b>Martina Kalac</b> <i>Radionica aromaterapije u OŠ Maria Martinolića</i> .....	406
<b>Milan Nikolić, Olgica Martinis</b> <i>Pokusi i ishodi u nastavi kemije</i> .....	407
<b>Helena Peter Jelenčić, Olgica Martinis</b> <i>Analiza inicijalne provjere znanja iz kemije u srednjoj školi</i> .....	408
<b>Industry and entrepreneurship</b>	
<b>Ernest Meštrović</b> <i>Entrepreneurial skills – workshop</i> .....	409
<b>Spiridion Brusina Medal Lecture</b>	
<b>Tomislav Friščić</b> <i>Spiridion Brusina Medal Lecture: Solvent-free Notes on Natural Sciences [Predavanje povodom medalje Spiridion Brusina: naravoslovne crtice bez otapala]</i> .....	410
<b>INDEX</b> .....	412





27<sup>th</sup> CROATIAN MEETING OF CHEMISTS AND CHEMICAL ENGINEERS  
27. HRVATSKI SKUP KEMIČARA I KEMIJSKIH INŽENJERA  
5–8 October 2021, Veli Lošinj, Croatia

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# PLENARY LECTURES

## VIRAL POLYMERASES AS INTERVENTION TARGETS USING NUCLEOSIDE TRIPHOSPHATE PRODRUGS

Chris Meier

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Over the last decades a variety of nucleoside analogues were clinically used in antiviral chemotherapy. However, often the antiviral potency of the nucleoside analogues is limited due to the lack of intracellular phosphorylation into the triphosphorylated forms by cellular kinases. This problem cannot be solved by using the phosphorylated nucleosides due to their high polarity. To overcome this hurdle lipophilic precursors of nucleotides, which are able to pass the cell membrane and deliver the nucleotides intracellularly (*pronucleotides*) were developed, e.g. nucleoside mono- (*cycloSal*-system) and nucleoside diphosphate prodrug approaches (*DiPP*-approach) and finally nucleoside triphosphate (NTP) prodrugs. In our work, d4TTP prodrugs with different aliphatic masking units have been synthesized via two different routes based on phosphoramidite or *H*-phosphonate chemistry. Our triphosphate delivery system is comprised of enzymatically cleavable masking groups (acyloxybenzyl-moieties) which are attached to the  $\gamma$ -phosphate group. Chemical hydrolysis and esterase studies, enzymatic cleavage in CEM/O cell extract, primer extension assays, PCR assays, whole-cell incubations and antiviral HIV tests will be discussed which proved the successful delivery of NTPs. This *TriPP*Pro-concept will open up unknown possibilities not only in Medicinal Chemistry but also in Chemical Biology.<sup>[1,2]</sup> Next, a prodrug approach in which the  $\gamma$ -phosphate of NTPs is modified by two different groups was developed. One of these groups represents a cleavable acyloxybenzyl masking group while the second group is a non-cleavable alkyl residue. Such compounds showed a very high stability towards dephosphorylation as compared to d4TTP in cell extract studies. In antiviral assays, these compounds were highly potent against HIV-1 and HIV-2 in thymidine kinase-deficient CD4<sup>+</sup> T-cells (CEM/TK<sup>-</sup>). Primer extension assays using HIV's reverse transcriptase and different cellular human DNA-polymerases showed that the new compounds act as a substrate for RT but were found to be non-substrates for cellular DNA-polymerases  $\beta$  and  $\gamma$ .

These prodrug systems were developed for combating HIV-replication but were also applied to inhibition of Influenza infections.

Moreover, the interaction of a selected nucleoside triphosphate of the SARS-CoV-2-polymerase will be discussed.<sup>[3]</sup>

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## **PROCESS SYSTEMS ENGINEERING – A PERSPECTIVE LOOKING FORWARD**

David Bogle

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The lecture will address the way that Process Systems Engineering is enabling the digital revolution in the Process Industries to achieve 'Smart Process Manufacturing'. Process Systems Engineering is the branch of Chemical Engineering developing and utilising computational tools and techniques for design, operation and management for the process industries: chemical, refining, pharmaceutical and other industrial sectors where chemical change occurs. Much algorithmic research and practice has already been achieved to enable Smart Process Manufacturing but there are technical challenges to obtain designs and operating strategies that are robust when there is considerable uncertainty and variation in operating conditions, particularly for greater agility in response to customer and societal needs. The significant amounts of data that are generated are underused which remains a challenge for researchers. The lecture will highlight some of the technical challenges and end by focusing on a few research areas where progress is needed.

## **QUALITY-BY-CONTROL (QBC) APPROACHES FOR PROCESS INTENSIFICATION IN ADVANCED PHARMACEUTICAL MANUFACTURING AND DISCOVERY**

Zoltan K. Nagy

Davidson School of Chemical Engineering, Purdue University

The advent of process analytical technologies (PAT) more than two decades ago has brought the applications of advanced control of pharmaceutical manufacturing processes in the realm of possibility. The role of advanced feedback control concepts in improving the performance of batch processes, as well as enabling technologies in the paradigm shift from batch to continuous manufacturing will be corroborated. Examples how advanced control can be used for process intensification and the improved production of pharmaceutical particulates will be provided, with application to both continuous drug substance and drug product manufacturing. Examples will include advanced control approaches for the integrated crystallization and wet mill system and the spatial control in continuous oscillatory flow crystallization platforms using spherical crystallization as a process intensification approach to simultaneously control critical quality attributes of particulate products, including size and shape distribution, purity and polymorphic form. We will illustrate how these advanced model-based control approaches allow to achieve a desired trade-off between manufacturability and bioavailability in advanced pharmaceutical manufacturing. The application of a systematic quality-by-control (QbC) framework for the design of hierarchical control systems for continuous tablet production via direct compaction will also be described. The distributed manufacturing of pharmaceuticals using miniaturised pharmaceutical manufacturing (MiniPharm) platforms will be described that exploits the information from high throughput reaction screening approaches based on DESI and MS technologies and uses a reconfigurable plug-and-play platform of reactors and separators for continuous API production integrated with drop-wise additive manufacturing platform (DAMP), which can provide a novel intensified process route for rapid and reactive personalized dosage manufacturing of final formulated products suitable for direct delivery. The talk will also describe the enabling role of feedback control in the development of a rapid reaction screening platform that can be used for the optimization of reaction conditions and the discovery of new reaction pathways or new active molecules for drug discovery. The talk intends to provide motivating examples of the next stage of innovation in advanced pharmaceutical manufacturing, illustrating the potential benefits of process systems engineering concepts and the new quality-by-control (QbC) framework in improving product quality and process efficiency while reducing costs and time-to-market.

## **NANOSTRUCTURED AND FUNCTIONAL MATERIALS AND ADDITIVES BASED ON POLY(ALKYL METHACRYLATES)**

Ante Jukić

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Polymeric materials based on alkyl methacrylates are usually manufactured by the free radical copolymerization, which in relation to other polymerization mechanisms allows their relatively simple functionalization. This is especially valid for the monomers of similar copolymerization reactivity ratios such as functional methacrylates with amino or hydroxy groups. In this case, it is facilitated to obtain products of the desired properties, and the copolymerization itself is considered pseudo-ideal. When the copolymerization reactivities of comonomers are different or unknown with respect to methacrylate monomers, they need to be determined experimentally using various copolymerization models and equations. This results in wide possibilities of changing the polymer composition and structure with a direct impact on the application properties. Here, several examples will be presented of how by changing the composition and structure of copolymers based on alkyl methacrylate, a significant improvement of the target properties was achieved or how the introduction of new ones enabled further applications. The first group of examples includes the functionalization of methacrylate additives of lubricating oils and oil nanofluids which improve viscosity, lubricity, thermal and shear stability, and dispersive properties. The second group of examples illustrates the development of nanostructured polymethacrylate materials where miscibility and compatibility are achieved either by chemical functionalization of nanofillers (carbon nanotubes) or by chemical functionalization of the polymer matrix.



## MULTISCALE SIMULATIONS OF REACTIVE INTERFACES

Ana-Sunčana Smith

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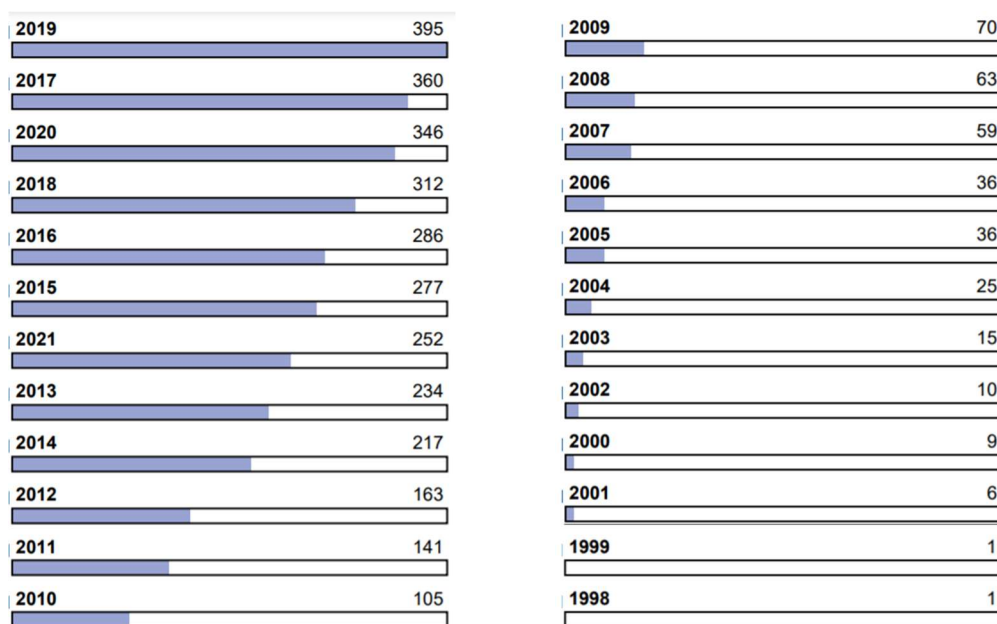
Numerous biological and technological processes depend on the reactivity on the molecular scale, which is ultimately reflected in a response on the scale of the system. For example, a catalytic reaction rate of a occurring on a liquid interface is coupled to the mesoscopic properties of that interface. The latter change as the reaction proceeds due to the solubility of reactants and the reaction itself. This is reflected in changes of interface content, viscosity, structuring and temperature, resulting in a feedback into reaction rate and reactant transport coefficients, overall affecting the efficiency of the system. Predicting the latter is a major issue due this coupling of a multitude of relevant time and length scales. However, it is necessary to address these problems to aid with the optimization of the system design. In my presentation, I will discuss some strategies in multiscale modeling, from the molecular to the mesoscopic level focusing on modeling supported ionic liquid phase catalysis.

## A JOURNEY THROUGH THE WORLD OF HALOGEN BONDING

Pierangelo Metrangolo<sup>a-e</sup>

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In recent years, halogen bonding has grown from a scientific curiosity to one of the most interesting noncovalent interactions for constructing supramolecular assemblies (Figure 1) [1]. According to the recently proposed IUPAC provisional recommendation [2], “A halogen bond occurs when there is evidence of a net attractive interaction between an electrophilic region associated with a halogen atom in a molecular entity and a nucleophilic region in another, or the same, molecular entity”. This definition acknowledges the qualitative analogy between halogen bonding and the ubiquitous hydrogen bonding. In this lecture, I will survey my 20 years of research, starting from small molecule crystal engineering and arriving to the relevant implications of *in-vivo* halogenation mechanisms [3].



**Figure 1.** Numbers of papers published in the last 20 years reporting the wording *Halogen Bonding* (source SciFinder 29/07/2021).

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## DYNAMIC MOLECULAR SYSTEMS FROM SWITCHES TO MOTORS

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The fascinating molecular motors and machines that sustain life offer a great source of inspiration to the molecular explorer at the nanoscale. Among the major challenges ahead in the design of complex artificial molecular systems is the control over dynamic functions and responsive far-from-equilibrium behaviour. Chemical systems ultimately require integration of structure, organization and function of multi-component dynamic molecular assemblies at different hierarchical levels. A major goal is to achieve and exploit translational and rotary motion.

In this presentation the focus is on the dynamics of functional molecular systems as well as triggering and assembly processes. We design motors in which molecular motion is coupled to specific functions. For instance, molecular switches allow for information storage systems, control of biological systems like protein channels are key to precision pharmaceuticals as demonstrated in Photopharmacology. Responsive behavior will be illustrated in self-assembly and responsive materials with a focus on cooperative action, amplification along multiple length scales and 2D and 3D organized systems. This allows the design of responsive polymers, liquid crystal materials and artificial muscles. The design, synthesis and functioning of rotary molecular motors and machines will also be presented with a prospect toward future dynamic molecular systems and responsive materials

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# INVITED LECTURES

## THE SOLVENT EFFECT ON THE HOST-GUEST COMPLEXATION EQUILIBRIA; THE GOOD AND THE BAD

Josip Požar

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The lecture will cover the most important aspects of the solvent effect on thermodynamics of the complexation reactions involving calixarenes, cyclodextrins, and cucurbiturils as hosts and alkali-metal cations as well as non-polar species as guests. The rationalization of the medium influence on the binding properties of investigated macrocycles will rely on the thermodynamic data (complex stability constants, reaction and dissolution Gibbs energies, enthalpies and entropies) and the structural insights (NMR and computational methods). In addition, standard thermodynamic parameters of the reactants and the products transfer among the solvents will be discussed.

A range of phenomena, from specific<sup>[1,2]</sup> and selective<sup>[2]</sup> solute-solvent interactions to the temperature-dependent hydration of hydrophobic guests in water<sup>[3]</sup> will be presented. The trends regarding solvation of host and guest with respect to their size and structure will be revealed and their influence on the complexation thermodynamics pointed out. The potential for solvophobicity driven hosting of non-polar species in organic solvents will be also addressed.<sup>[3]</sup>

The results of thermodynamic studies of host-guest reactions in different media clearly indicate how remarkable and complex the often underappreciated solvent influence on the binding ability of investigated macrocycles can be. They also provide a basis for targeted design of the efficient supramolecular receptors.<sup>[4]</sup>

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## ATOMIC LAYER PROCESSING: A TOOLBOX FOR FABRICATING FUNCTIONAL HYBRID MATERIALS

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Atomic layer deposition (ALD) has become the method-of-choice for solving many technical issues that occurred on the way towards designing current and future electronics. Serious effort has been invested in order to optimize the materials, processes and processing instrumentation, which eventually resulted in the success story of this processing technique.

The ALD process can be seen from various perspectives. On the one hand, it allows controlled deposition of thin films on a variety of substrates and in this way enables a modification of a given functionality of a surface or even introduction of a new functionality. On the other hand, it may be seen as a chemical reactor that allows precise dosing of a chemical, allowing for chemical interaction and modification of the substrate. Considering both points of view, the process opens large variation possibilities for a design of novel functional materials for emerging applications and devices. Among those functional materials hybrid materials play an increasingly important role. Hybrid materials are in most cases blends of inorganic and organic materials and are considered to be key for the next generation of materials research. The main goal while fabricating such materials is to bridge the worlds of polymers and ceramics, ideally uniting the most desirable properties within a singular material. Furthermore, in a well performing hybrid material the individual components will add value to their counterpart in a synergistic way.

In this talk, some approaches will be discussed that show great promise for establishing ALD as the method-of-choice for innovation in technological fields beyond the microelectronics industry. In an adapted processing mode, the ALD processing technology also allows infusing metals into polymeric substrates, which leads to novel material blends that cannot easily be obtained in other ways. In either of those cases the chemical or physical properties of the initial substrate are improved, or new functionalities added. With some showcases, this talk will discuss approaches towards non-traditional application of ALD to fabricate novel materials with great promise in energy storage, catalysis, personal protection, or flexible electronics.

## TREATING MOUSE AS A STROKE PATIENT - CAN MOLECULAR CHANGES IN THE LIVING MOUSE BRAIN BE VISIBLE?

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The stroke represents a major health problem, however for ischemic stroke the current therapies are oriented only to recanalization strategies or supportive care in the dedicated stroke centers. The preclinical in vivo stroke models are crucial in design of novel therapeutic approaches, however from many promising candidates, none proved to be beneficial for the patients in the clinical settings.

To upgrade the insight in the ischemic stroke damage and subsequent repair we have created a platform aimed to monitor living mice after temporary (30 min) occlusion of middle cerebral artery (i.e. tMCAO) at multiple time points for 28 days. The brain morphology was analyzed by high field (7T) magnetic resonance imaging (MRI), and molecular events by bioluminescence imaging (BLI) of transgenic animals bearing a luciferase reporter. The functional outcomes were evaluated by scoring of the neurological status.

The beauty of chemistry used in this in vivo paradigm is that the luciferin, being a substrate of the luciferase and providing for the measurable light production in the living mouse brain, can be chemically modified, i.e. “caged”. The caged luciferins are not available to luciferase and need to be “released” from the “cage” when cleaved by endogenous mouse enzymes, e.g. caspase 3 or 7, and after cleavage the “free” luciferin is available for the chemical light-producing reaction.

Here we present the innovative use of caged DEVD-luciferin to address the caspase activity in the mouse brain, corresponding to the apoptosis after ischemic stroke. Two different transgenic animals were used, Gap43-luc, expressed only in neurons engaged in the repair and CAG-luc, with ubiquitous promoter where luciferase is expressed in all tissues. This allowed to address the levels of post-stroke repair in the living mouse, as well as the extent of post-stroke apoptosis. The methodology was used to compare the modified neuroinflammation of Tlr2-deficient animals to their wild type counterparts, and it could distinguish them with ease, although the effect combines apoptosis with other currently elusive molecular pathways.

**Acknowledgments.** The study was supported by the Croatian Science Foundation project RepairStroke IP-06-2016-1892, and by the European Union through the European Regional Development Fund, under Grant Agreement No. KK.01.1.1.07.0071, project “Sinergy of molecular markers and multimodal in vivo imaging during preclinical assessment of the consequences of the ischemic stroke (SineMozak)”, under grant agreement No. KK.01.1.1.04.0085, project “Genomic engineering and gene regulation in cell lines and model organisms by CRISPR/Cas9 technology – CasMouse”, and as the Scientific Centre of Excellence for Basic, Clinical and Translational Neuroscience under Grant Agreement No. KK.01.1.1.01.0007, project “Experimental and clinical research of hypoxic-ischemic damage in perinatal and adult brain”. Multimodal imaging was done at Laboratory for Regenerative Neuroscience - GlowLab, University of Zagreb School of Medicine.

## "LJUBI, LJUBI, AL' GLAVU NE GUBI": MOLEKULE LJUBAVI NA SATU KEMIJE

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Volimo se hvaliti da se bavimo centralnom (dakle, iznimno važnom) znanosti. U praksi je kemija jedan od (naj)manje omiljenih predmeta, praćena ne tako laskavim opaskama: "opet mućkaš nešto smrdljivo i opasno", ili "stroj ne može oprati mrlje od tvojih kemikalija". Pandemija SARS-CoV-2 istisnula je nastavu iz učionica i promijenila tradicionalne oblike podučavanja, što nastavnicima dodatno otežava obradu složenih (bio)kemijskih pojmova i fenomena. Kako dodatno zainteresirati učenike za "čudesni svijet hemije"? Odabirom sadržaja bliskih učenicima iz vlastitog iskustva!? Jedan takav, svima dobro poznat, je fenomen ljubavi. Tko nije voleo, oplakivao zbog neuzvrćene ljubavi, inspirirao se pogledima, dodirima i porukama voljene osobe? Kakve se hemijske promjene dešavaju u tijelu u "ludim godinama"? Kako približiti učenicima te procese i povezati ih s drugim nastavnim sadržajima? Moj je zadatak pokušati odgovoriti na ova pitanja. Upoznajmo skupa Kupidona, gospođu energiju, kralja i kraljicu, gladijatora, Romea, krotitelja lavova i belog viteza u ljubavi.

# ORALLY DISINTEGRATING TABLETS AND MINI-TABLETS CONTAINING SOLID DISPERSION – DOSAGE FORMS FOR BETTER PATIENT COMPLIANCE AND ENHANCED ORAL ABSORPTION OF DRUG

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Oral absorption is still the gold standard for drug delivery despite the new trends in the development of complex therapeutic agents. This is mainly due to the patient preference for solid dosage forms, convenience of administration, accuracy of dosing, and crucially to the safety of the patients. Recently, pharmaceutical industry is dealing with development and production of novel, and a more effective dosage forms for oral absorption of already existing drugs. Such, somewhat different, drug products are very promising since their formulation flexibility for the manufacturers, therapeutic effects and clinical benefits to many patient groups. This presentation will reveal our vision to use chemical engineering methodology (Figure 1) to design different, and a more effective dosage forms for better patient compliance and enhanced oral absorption of particular drug.

The ideal drug candidate for this, we believe, is lurasidone hydrochloride, an atypical anti-psychotic API with low aqueous solubility and consequently poor gastrointestinal absorption and low bioavailability. For the purpose of drug solubility enhancement, solid dispersions of a drug in matrices of hydrophilic polymers were prepared by various process technologies (Figure 1) and properly characterized by analytics that could explain physically the enhanced dissolution properties. Orally disintegrating tablets (ODTs) and orally disintegrating mini-tablets (ODMTs) were successfully prepared using solid dispersions of a drug, *in-situ* fluidized bed melt granulation and traditional tableting. Our intention here will be to present how our methodology and formulation carried are effectively used to improve drug solubility, to affect on release kinetics, and how to enhance oral absorption and overall therapeutic effect of drug.

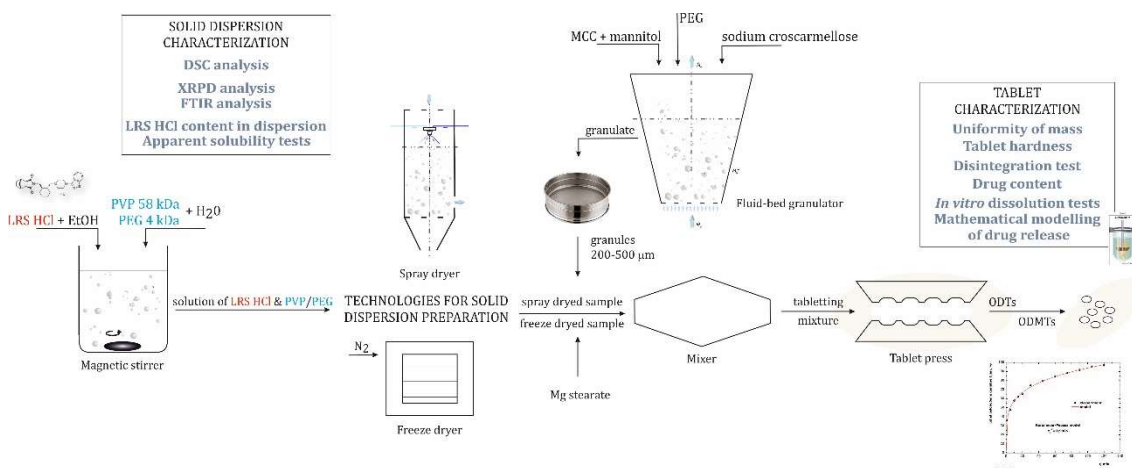
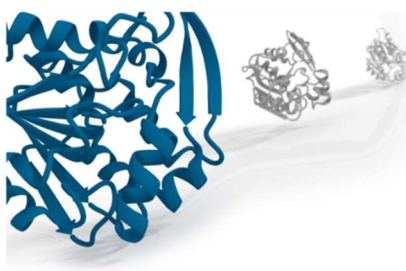


Figure 1. Schematic of research methodology.

## SYNTHETIC ENZYME CASCADES – FROM SET-UP TO SUSTAINABLE PROCESS CHAINS

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Enzymatic multi-step reactions offer significant potential to yield fine-chemicals, chiral building blocks and active pharmaceutical ingredients with excellent stereoselectivities. But the access to economically feasible product concentrations can be a challenge. This challenge can be met using an integrated engineering approach that includes enzyme engineering, reaction optimisation and optimal process design. Examples of synthetic enzyme

casca des for the production of pharmaceutically active ingredients meeting selectivities >98 % and product concentrations >50 g/L will be presented.

By the flexible combination of enzymes with varying substrate specificities and stereo/regioselectivities, the access to whole product platforms is possible. Combining (*R*)- and (*S*)-selective transaminases and carbonylases in a modular way, all four stereoisomers of e.g. amino alcohols like nor(pseudo)ephedrine,<sup>[1]</sup> methoxamine or metamino<sup>[2]</sup> are gained from differently substituted starting aldehydes. On top, tetrahydroisoquinolines (THIQ) containing three chiral centres can be synthesised by an additional cyclisation step. This step is either catalysed by a norcoclaurine synthase or simply by phosphate giving stereocomplementary products.<sup>[2]</sup> This example shows the power of hybrid systems, where optimal catalysts are selected, no matter from which origin they are. Since recently, we also combine enzymes and chemical catalysts with (living) microbial cell factories in process chains. In this way, renewable raw materials are converted into valuable chiral compounds in a sustainable way. The entire process chain, including downstream processing, is evaluated in terms of ecological and economic efficiency.<sup>[3,4]</sup> When high product titres in (multi-step) biocatalysis and easy downstream processing is targeted, the use of unconventional reaction conditions, like microaqueous reaction systems using green solvents, can be very beneficial.<sup>[3,5]</sup>

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## (RE)PURPOSING STARTS VIRTUALLY BY PREDICTIVE MACHINE-LEARNING MODELS

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The cheapest, fastest and efficient way to find active compounds for biological targets, novel biological activities for compounds “in shelves” or to reveal targets for discovered natural products, is to test compounds virtually by using proper *in silico* approaches and/or models at the beginning. The predictive machine learning (ML) model developed for specific (bio)activity can be applied for prioritizing assays for *in vitro* testing of compounds and their (re)purposing. The two ML models which may shed light on potential biological activities for compounds, will be presented. They have been developed by using publicly available datasets and are incorporated within virtual modular platforms for detecting potential phytotoxic molecules and kinase inhibitors.

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## POLYELECTROLYTE MULTILAYERS: FROM FUNDAMENTAL STUDIES TO BIOMEDICAL APPLICATIONS

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Polyelectrolyte multilayers (PEMs) are surface coatings created by alternating deposition of positively and negatively charged polyelectrolytes (polycations and polyanions) on a solid surface. PEM build-up strongly depends on applied experimental conditions (*e.g.* ionic strength, supporting electrolyte type, pH and concentration). The goal of our research was finding the answers to fundamental questions concerning the PEM build-up.<sup>[1]</sup> We examined the influence of various experimental conditions on PEM formation and compared the PEM properties with the properties of corresponding polyelectrolyte complexes in solution.<sup>[2]</sup> Furthermore, the possibility of PEM biomedical application was explored, with the emphasis on prevention of bacterial adhesion to various surfaces.<sup>[3–5]</sup> In recent years we have developed new successful strategies for designing soft nano materials whose properties can be finely adjusted according to application requirements.

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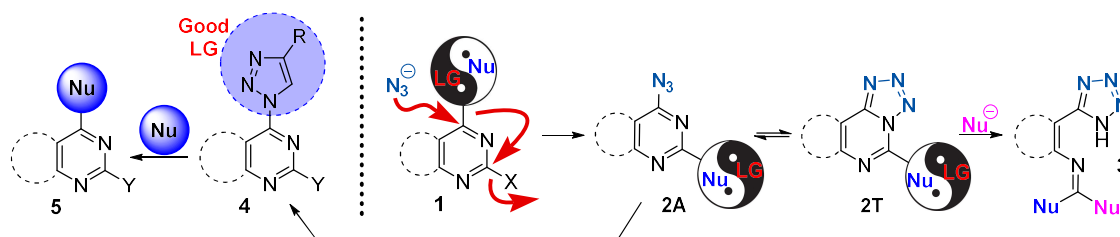
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## SUBSTITUTION AND RING OPENING OF FUSED PYRIMIDINES USING THEIR ACTIVATION BY AZIDO AND TRIAZOLYL GROUPS

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We have developed synthesis of 2,6-bis-triazolyl-purine derivatives **4** (Y = 1,2,3-triazole) and demonstrated their application in  $S_NAr$  reactions by substituting C(6) position of purine with a broad range of *N*-, *S*-, *Se*-, *C*-, *O*-, and *P*-nucleophiles (Scheme 1).<sup>[1]</sup> 2,6-Bis-triazolyl-purine derivatives **4** and their  $S_NAr$  products **5** are fluorescent and this has led to development of ion sensing, cell imaging systems and applications in materials science.<sup>[2]</sup> On the other hand, azido-substituted fused pyrimidines of type **2** exhibit azide-tetrazole tautomerism, which was instrumental to develop novel substitution methodologies (nucleophile-nucleofuge dance) around the cycle<sup>[3]</sup> and also pyrimidine ring opening reactions leading to compounds of type **3**.<sup>[4]</sup>



Scheme 1.

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## NEW MULTITARGETING ANTIBIOTICS AGAINST ANTIMICROBIAL RESISTANCE

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There is an urgent need for new therapies and new antibiotics to treat deadly infections caused by so-called ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) which are often resistant to available antibiotics. Antimicrobial resistance is becoming an increasingly urgent public health threat in both clinical and community settings. One promising strategy to address this rapid evolution of resistance is the design of antimicrobial compounds that equipotently inhibit two bacterial targets. The rationale for this approach is that the development of resistance to multitargeting antibiotics would require the simultaneous occurrence of multiple specific mutations at both targets, which is extremely rare.

We have developed a new structural class of multitargeting antibiotics against two well-established molecular targets with innovative approaches to potent and safe multitargeting antibiotics with limited resistance. We targeted the antibacterial activity of the new molecules against ESKAPE pathogens to address an unmet medical need, with a target product profile of methicillin-resistant (MRSA), vancomycin-intermediate (VISA) *Staphylococcus aureus* and *Acinetobacter baumannii* clinical isolates.

## HALOGENATED AROMATIC CATIONS AS HALOGEN BOND DONORS

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The key feature which enables halogen atoms to act as Lewis acids in order to form halogen bonds, is presence of an area of depleted electron density ( $\sigma$ -hole).<sup>[1]</sup> Most common strategies for the design of halogen bond donors thus rely on using the most polarisable halogens (I and Br) as donor atoms, bonded to electron-withdrawing molecular residues. This is usually achieved by addition of substituents on the hydrocarbon skeleton (most commonly fluorine, as in perfluorinated iodo and bromo-hydrocarbons<sup>[2]</sup>), or binding the halogen to an electronegative heteroatom (e.g. nitrogen in halogenoimines<sup>[3]</sup>). There is, however, another approach for ensuring a large positive electrostatic potential on the halogen atom: making the halogen atom a part of a positively charged species.<sup>[4]</sup>

Here we will present a systematic study of both the possibilities and the limitations of using halogenopyridinium (**X-Py**) cations as halogen bond donors. For this purpose, we have selected mono-halogenated pyridine derivatives (*o*-, *m*- and *p*-; chloro, bromo and iodo), both as protonated and as *N*-methylated pyridinium cations. While both protonation and *N*-methylation of halogenopyridines lead to a considerable increase in the electrostatic potential of the halogen  $\sigma$ -hole, **X-Py** cations have not shown to be superior to the commonly used neutral halogen bond donors. A closer inspection of the distribution of the charge, demonstrates that the halogen  $\sigma$ -hole is generally not the most positive site on the surface of the cation. In spite of this, cations derived from iodo- and even bromopyridines form halogen bonds with remarkable consistency, which makes them reliable halogen bond donors for synthesis of halogen bonded materials.

**Acknowledgements.** This research was supported by the Croatian Science Foundation through grant No. IP-2019-04-1868.

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# COOPERATIVE DUAL-CATALYTIC TRANSITION METAL SYSTEMS FOR SELECTIVE FUNCTIONALIZATION OF LESS REACTIVE SITES

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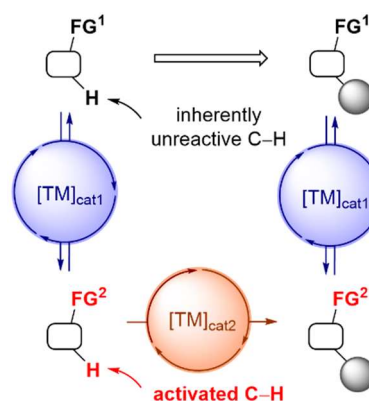
Here I will present our studies dedicated to the development of dual-catalytic system that enable selective functionalization reactions of substrates at their typically unreactive sites, such as ubiquitous unactivated C-H bonds.<sup>[1]</sup> Our strategy rests on merging a metal-catalyzed reversible reaction and a metal-catalyzed functionalization reaction (Figure 1).<sup>[2]</sup> Such reactions occur directly under mild conditions without the pre-activation steps and without the use of highly reactive reagents. For instance, we demonstrated the transient and reversible oxidation of an alcohol group by catalytic Ru-complexes enables direct arylation of the otherwise unreactive  $\beta$ -C-H bond of aliphatic alcohols by a Pd-catalyst, and direct  $\gamma$ -regio- and enantioselective hydroarylation of the C=C double bond of allylic alcohols by a Rh-catalyst. Due to the mild reagents and conditions of both the reversible reaction and the functionalization reaction, the devised methodologies are general and compatible with a broad scope of substrates, including natural product-like molecules. These studies highlight the potential of the multi-catalytic approach to address challenging transformations to circumvent multi-step procedures and use of highly reactive reagents in organic synthesis.

Our current efforts in the exploration of the full potential of the approach will be further discussed.

**Acknowledgements.** We thank the University of Strasbourg, the European Research Council (ERC Starting Grant 'Reverse&Cat'), the French National Research Agency through the IdEx Unistra framework, and the Frontier Research in Chemistry Foundation through the LabEx Chemistry of Complex Systems framework for generous financial support of our research program.

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**Figure 1.** A cooperative dual-catalytic system combining reversible activation and functionalization reactions.

## BIOREMEDIATION AS A PROMISING STRATEGY FOR MICROPLASTICS REMOVAL BY BACTERIA *Bacillus cereus* AND *Pseudomonas alcaligenes*

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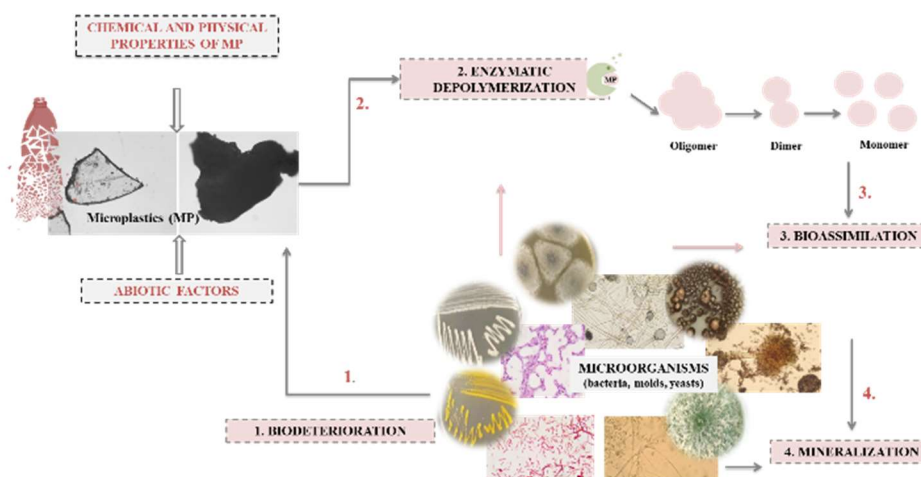
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Microplastics (MPs) attract ever-increasing attention due to environmental concerns. MPs were defined as plastic particles <5 mm in size, which can be formed from the degradation of larger plastic consumer products and the production of plastic debris in industrial processes. These particles are mostly made from polyethylene (PE), polypropylene (PP), polystyrene (PS), polyethylene terephthalate (PET) and polyvinyl chloride (PVC). Bioremediation has been highlighted as a promising tool for removal MPs from water. Bioremediation is a cost-effective treatment that involves degradation of pollutants by microorganisms. In this study, bioremediation of water polluted with MPs, PS and PVC, by bacterium *Bacillus cereus* and *Pseudomonas alcaligenes* were investigated. The results show that *Bacillus cereus* degraded PS and PVC better than *Pseudomonas alcaligenes*, and PS better than PVC.



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## ATROPISOMERISM: A GATE TO MODERN DRUGS

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Chirality is an intriguing feature of nature and many natural, biologically active compounds are stereogenic. Indeed, the unique tridimensional structure of chiral compounds frequently accounts for specific interactions with active sites of enzymes allowing highly selective therapeutic actions. Such a tridimensionality may arise from the presence of not only chiral stereocenters but also axial chirality, corresponding to a hindered rotation around an axis. Indeed, an analysis of 1900 small molecules drugs in the USD FDA Drug Bank (FDA: Food and Drug Administration) reveals that approximately 15% of FDA-approved scaffolds contain one or more atropisomeric axis and additional 10% of molecules are “proatropisomeric”. Even more markedly, the prevalence of atropisomeric compounds has been expanding drastically since 2011 and over the last years almost one of out three FDA-approved small molecules contains axial chirality element and additional 16% are proatropisomeric.

Currently, the axial chirality (ie. atropoisomerism) generally concerns C–C bonds, as in case of biaryl and hetero-biaryl compounds. In contrast, the axial chirality arising from a restricted rotation around a C–N bond is clearly underdeveloped.

With regard to the vivid interest on the C–C and C–N axially chiral compounds, we designed new asymmetric strategies to build-up such compounds.

## NUMERICAL METHODS IN NATURAL PRODUCTS CHEMISTRY

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In this presentation we will focus on how numerical methods have been increasingly applied to the natural products field in the last decade. Focusing on the identification of compounds from both marine and terrestrial organisms, we will describe the actual road of a modern natural product chemist from raw material sampling to structure elucidation, from the Mediterranean Sea to the Amazon Reef.

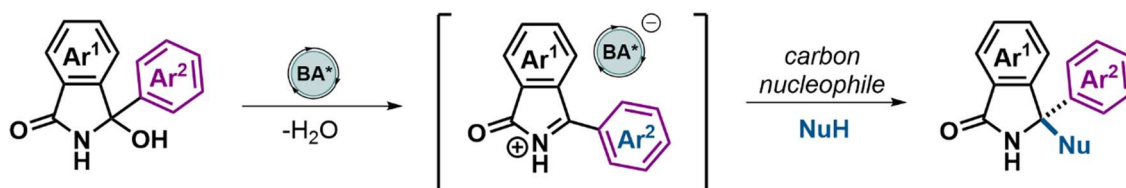
## CONSTRUCTION OF TETRASUBSTITUTED CENTERS OF CHIRALITY IN ISOINDOLINONES VIA BRØNSTED ACID CATALYSIS

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Isoindolinones have attracted much attention among synthetic chemists, as they are integral structural parts of a number of natural products and biologically active compounds. In most cases, only a single enantiomer is effective, or has a better activity profile than the other. Consequently, the synthesis of these structural motifs and the natural products that contain them has been the subject of much elegant and effective research. The most straightforward way to functionalize isoindolinones includes transformations of easily accessible 3-hydroxyisoindolinone precursors. Their ability to form highly reactive species under mild conditions renders them as an attractive substrates in various catalytic reactions.

The overview of our recent achievements in the construction of isoindolinone derivatives comprising tetrasubstituted centers of chirality will be presented. The focus will be given on chiral Brønsted acid-catalyzed additions of aromatic and non-aromatic carbon nucleophiles to *in situ* generated isoindolinone-derived ketimines for the construction of titled compounds. Generally, the transformations proceed smoothly and the corresponding products are isolated predominantly in high yields and enantioselectivities.



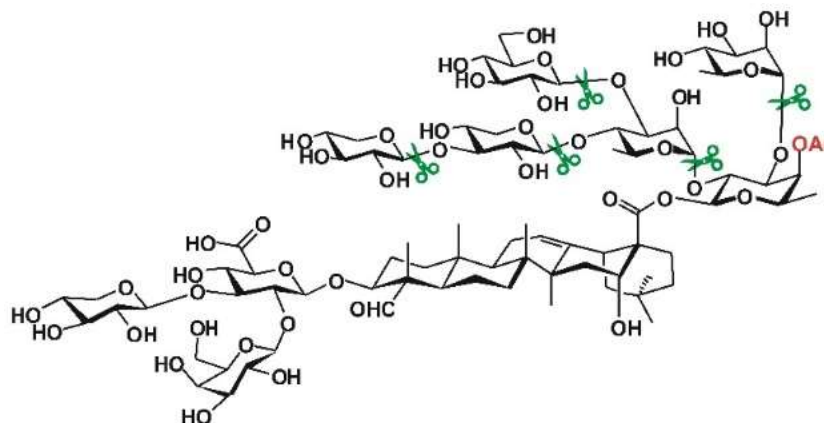
## DEVELOPMENT OF STRUCTURALLY DEFINED SAPONIN-BASED VACCINE ADJUVANTS

Đani Škalamera

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Adjuvants are substances that enhance the immunogenicity of a vaccine in order to achieve strong and durable immune responses to specific antigens. Immunoadjuvants isolated from the *Quillaja saponaria* Molina tree bark are very promising candidates in the development of synthetic structurally defined vaccine adjuvants. The lead compound from this series, QS-21, is one of the most potent adjuvants known to date. After being studied in over 100 clinical trials, it is finally approved for human use (herpes zoster vaccine Shingrix<sup>®</sup>, GSK). Many clinical trials of QS-21 in vaccines against infectious diseases and cancer are currently on the way. However, *Quillaja* saponins (QS) have inherent drawbacks which restrain their wider use, such as: chemical instability, limited supply, laborious purification process and dose-limiting toxicity.<sup>[1]</sup> Therefore, there is a need for the development of structurally defined, homogeneous and simplified QS saponin-based adjuvants with improved chemical stability and synthetic accessibility. Chemical synthesis is currently the only viable way to access structurally defined QS analogs in a sufficient amount for adjuvant screenings and potential application in clinics.

The lecture will focus on the recent progress in the design, synthesis, and immunological evaluations of new QS analogs based on the structures of natural QS-7 and QS-17/18 *Quillaja* saponins.<sup>[2]</sup>



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## ADVANCED IN-SITU ELECTRON MICROSCOPY ANALYSIS OF THE NANOSTRUCTURED SEMICONDUCTING ZINCITE THIN-FILMS

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Zincite semiconductors show high electron mobility and large exciton binding energy.<sup>[1]</sup> Recently it was shown zincite films can be prepared in low-dimensional configurations. Overcoming challenges of describing such films reveals just how much such 1D configuration can be desirable for boosting materials physical properties such as the charge transfer efficiency. Synthetic wise, powerful physical deposition techniques often require demanding conditions while some chemical processing can enable large-scale fabrication at mild temperatures, such as such chemical bath route for growth of well-aligned zincite nanorods.<sup>[2]</sup> For characterisation purpose, conventional methods struggle to fully reveal the investigated material, whereas a more detailed insight in some material characteristics, particularly in the nanoscale regime, asks for a more sophisticated approach.

Here we synthesised 1D nanostructured zincite thin-films on different substrates. We show their structure-performance behaviour with advanced imaging techniques. Specifically, we focus on the in-situ micromechanical experiments with advanced analysis techniques (such as nanoindentation) under various conditions during scanning electron microscopy (in situ SEM). The course of characterisation was assisted by focused ion beam (FIB) based material preparation and structuring as well as digital image correlation techniques to observe, describe and understand the occurrence of local deformations and generally microstructural evolution. We were able to conduct a miniaturised fracture testing within the electron microscope and nanoindenter. Results were utilised to qualify and quantify the materials resistance to mechanical failure such as undesirable cracking events dependant on the chosen synthesis parameters. The mitigation of such events should enable major development role of the nanoscale optoelectronic devices especially on conductive flexible substrates beneficial for high performance photovoltaics.

**Acknowledgements.** The financial support by the projects PZS-2019-02-1555 PV-WALL and UIP-2019-04-2367 SLIPPERY SLOPE from the Croatian Science Foundation is gratefully acknowledged.

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## CURRENT TRENDS IN THE ANALYSIS OF PRODUCTS LABELLED AS BOTANICAL FOOD SUPPLEMENTS

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Herbal food supplements are derived from natural substances for improved quality of consumer's life. Even though herbal medicines have been present for centuries, there is little consensus from country to country on the definition, usage, terminology, or even requirements for their quality control. Despite regulations to improve the botanical food supplements marketplace, many challenges remain; as a result, the quality of products easily accessible to consumers can be highly variable.

Analytical methods that allow rapid and reliable testing of dietary supplements for the presence of bioactive substances, synthetic drugs and chemical contaminants are needed. Chromatographic and spectroscopic techniques have become primary tools in this endeavor.

Thus, the development of state-of-the-art analytical methods to explore issues involving dietary supplements is an objective of research of the scientific group of Department of Pharmaceutical Analysis.

A new fast-screening direct injection mass spectrometric method for identification of various pharmacologically active ingredients in food supplements will be presented. Several reliable analytical methods using hyphenated technique liquid chromatography–mass spectrometry for determination of bioactive ingredients as well as contaminants were developed. Dramatic variation from manufacturer's claims as well as high batch-to-batch variation was found in many products. Gas chromatography and atomic absorption spectrometry were used for determination of volatile ingredients and metal contaminants in almost 100 samples used for various conditions in adult and pediatric patients. High amount of ethanol found in products for young children is of particular concern. Metal content in the investigated phytoestrogen-containing dietary supplements was below the international established limits for heavy metals, except Pb content in one capsule.

Bioavailability is a key step in ensuring efficacy of pharmacologically active biosubstances. Only by understanding the mechanisms of absorption and distribution of bioactive ingredients of dietary supplements, can their bioavailability be enhanced and thus the potential for greater health benefits be realized. For this purpose, biomimetic chromatography using stationary phases with immobilized phospholipids and proteins was implemented in our research.

Advantages and drawbacks of analytical procedures developed by our research group will be critically discussed.

**Acknowledgements.** This work has been supported by the Croatian Science Foundation under the grant numbers HRZZ-UIP-2017-05-3949 and HRZZ-DOK-2018-01-9047.



## OPPORTUNITIES AND CHALLENGES OF ELECTROCHEMICAL SYNTHESIS OF AMMONIA

Emil Dražević

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Renewable energy sources are today considered a main solution to decarbonize the power sector. However, the production of electrical energy from renewables is rarely matched with the consumption. Ideally, renewable electrical energy can be stored and used when winds is not blowing and sun is not shining. Among many different energy storage technologies, storing electrical energy in chemical bonds appears as an obvious choice of long-term energy storage. First choice is H<sub>2</sub> production using an electrolyser; however H<sub>2</sub> has low volumetric energy density and is difficult to transport. Ammonia on the other hand (NH<sub>3</sub>) appears as a good candidate for the long-term storage because it has a much higher volumetric energy density and it is much easier to transport and store energy in the form of ammonia. Today almost all ammonia is produced in Haber-Bosch process, which can be completely electrified using off-the-shelf technologies. However, if an alternative to the high-pressures (i.e. 100-300 bar) and temperature conventional Haber-Bosch process arises, such process would be relevant for smaller, decentralized scales. Electrochemical synthesis of NH<sub>3</sub> is a process that can activate nitrogen at room temperatures, using protons and electrons instead of heat. This talk introduces electrochemical ammonia synthesis, the main advantages and challenges associated with the process and a recent theoretical paper that revealed three new metal catalysts that might aid to cracking the selectivity code.

**Acknowledgements:** The talk has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101022738.

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27<sup>th</sup> CROATIAN MEETING OF CHEMISTS AND CHEMICAL ENGINEERS  
27. HRVATSKI SKUP KEMIČARA I KEMIJSKIH INŽENJERA  
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# SECTION LECTURES

## TWO-ELECTRON MULTICENTRIC BONDING (PANCAKE BONDING) BETWEEN SEMIQUINONE RADICALS

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Stacking of planar organic radicals with short interplanar separation ( $< 3.1 \text{ \AA}$ ) involves coupling of spins and a significant covalent contribution to total interaction energy. This type of weak non-localised covalent bonding is called 'pancake bonding'.<sup>[1,2]</sup>

Our studies of pancake bonding using X-ray charge density involves four salts of tetrachlorosemiquinone<sup>[3,4]</sup> and 5,6-dichloro-2,3-dicyano radical anions.<sup>[5]</sup> For the first time we have experimentally confirmed their partial covalent character. Experimentally determined AIM-criteria for pancake bonding involve a presence of a (3,+3) critical point (i.e. a local minimum of electron density) between the rings, and presence of multiple (3,-1) (i.e. bonding) critical points with electron density close to  $0.1 \text{ e \AA}^{-3}$ .<sup>[1,2]</sup> Also, the crystals are diamagnetic (stacks of pancake-bonded dimers and trimers) or antiferromagnetic (stacks of equidistant radicals) due to coupled spins in the neighbouring radicals. Recently we have extended charge density studies to high temperatures and high pressure using Transferrable Aspheric Atom Model (TAAM) refinement. The first results show increase of covalent nature of pancake bonding with pressure.<sup>[6]</sup>

**Acknowledgements.** Financial support by the Croatian Science Foundation, grant IP-2019-04-4674 is gratefully acknowledged.

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## CRYSTALLINE COORDINATION POLYMERS ON THE MOVE

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The newly discovered fascinating ability of molecular crystals to mimic the behaviour of biological systems, i.e., capability of crystalline material to respond with a mechanical motion to a variety of thermal, light, or mechanical stimuli, while retaining its crystallinity, has attracted the attention of a wide scientific audience.<sup>[1]</sup> The long-range ordered crystal structure that enables fast and efficient energy transfer, combined with mechanical flexibility qualifies such materials as a great candidates for utilization in emerging technologies.<sup>[2]</sup> However, the structural features that allow molecular crystals, either organic or metal-organic compounds, to respond flexibly are not yet perspicuous.

Recently, we have reported that crystalline coordination polymers of cadmium(II) show surprisingly wide spectrum of diverse mechanical responses, which were governed by introduced fine structural changes.<sup>[3,4]</sup> To further examine structure-property correlation and get closer to unravelling the intricacies of structural factors that enable crystals of coordination polymers to respond flexibly upon application of mechanical force, with a desired nature and extent of bending motion, we opted for another family of Cd(II) coordination polymers. We focus on pyridine-based ligands decorated with the amide moiety, while keeping all the other molecular features constant. The mechanical behavior of selected crystalline polymers was quantified through custom designed experiments, commented from a structural point of view, and compared with similar mechanically responsive metal-containing systems.

**Acknowledgements.** This work has been fully supported by the Croatian Science Foundation under project „From form to function: Mechanically flexible crystalline materials with controllable responses“ (IP-2019-04-1242).

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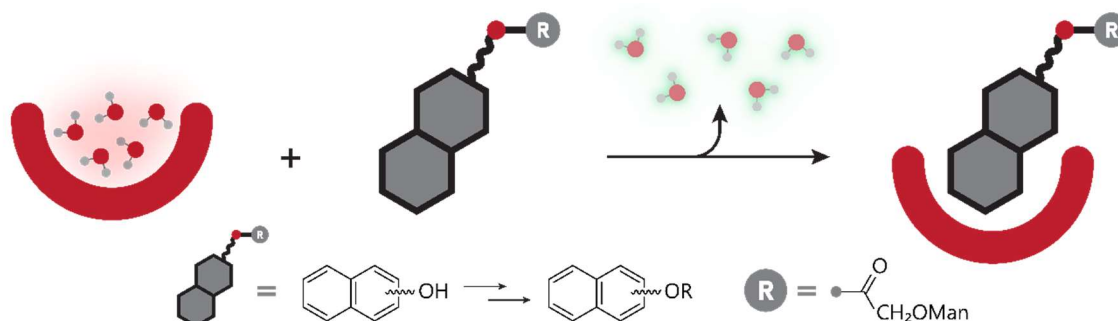
## SHINING A LIGHT ON HYDROPHOBICALLY DRIVEN COMPLEXATION: THE BITTERSWEET STORY BEHIND FLUORESCENT MANNOCONJUGATES

Andrea Usenik,\* Leon Poljanić, Doroteja Radonić, Katarina Pičuljan, Željka Car, Vesna Petrović Peroković, Josip Požar

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Regioisomeric mannoconjugates of naphthyl alcohols were synthesized by coupling of protected mannopyranose and corresponding esters of bromoacetic acid with 1- and 2-naphthyl moieties (Figure 1). Their complexation and the complexation of corresponding nonfunctionalized alcohols with cyclodextrins ( $\alpha$ -,  $\beta$ - and  $\gamma$ -) and cucurbit[7]uril was explored by means of isothermal titration calorimetry, spectrophotometry, fluorimetry and NMR spectroscopy. The complexation of 2-naphthol with cucurbit[7]uril was thermodynamically most favorable. A pronounced temperature dependence of  $\Delta_r H^\circ$  and  $\Delta_r S^\circ$ , resulting in an almost complete enthalpy-entropy compensation was observed for some of the examined host-guest systems. In these cases, the complexation thermodynamics was in line with the classical rationale of the hydrophobic effect at lower temperatures, and the non-classical explanation at higher ones.<sup>[1,2]</sup> The results of  $^1\text{H}$  NMR titrations and ROESY experiments were in agreement with the results obtained by other experimental methods and have revealed an interesting difference in complex formation kinetics among the investigated host molecules.



**Figure 1.** Schematic representation of the complexation process and guest structures.

**Acknowledgements.** This research was fully supported by the Croatian Science Foundation (project MacroSol; IP-2019-04-9560)

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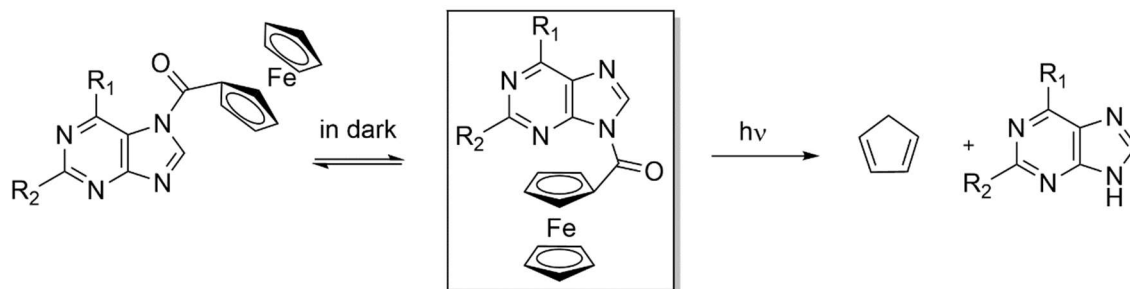
## FERROCENOYL-NUCLEOBASES. THE CHEMISTRY IN DARK AND IN LIGHT

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Organometallic nucleobase derivatives correspond to a new generation of conjugates in which metallocenes are linked to the basic structural elements of heredity. Due to their electrophoric and bioactive properties, they are of use in (bio)analytical and medicinal chemistry.<sup>[1]</sup> The first ferrocenoyl-purines (Figure) were prepared in our laboratory.<sup>[2]</sup> We observed that these compounds are sensitive to light. When exposed to UV or visible light, the photochemical degradation occurs in solution, with cyclopentadiene and free nucleobase released from the starting structure. In the absence of light, on the contrary, these compounds are very stable, and no decomposition was observed. In polar organic solvents, however, they undergo N7/N9 isomerization until dynamic equilibrium is reached. This transacylation yields a reaction mixture in which both regioisomers are present and no other transformation was noticed for weeks.



**Acknowledgements.** Thanks go to Croatian Science Foundation (project IP-2016-06-1137).

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## ELECTROCHEMICAL SENSORS FOR GASEOUS HYDROGEN PEROXIDE

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During the past few decades, considerable attention has been given to hydrogen peroxide, as an omnipresent analyte, particularly in clinical studies/diagnostics, biology, environmental protection, atmospheric studies, homeland security as well as different ways of its detection. Various methods have been developed for the detection of hydrogen peroxide, such as electrochemical methods,<sup>[1]</sup> high-performance liquid chromatography,<sup>[2]</sup> titrimetry,<sup>[3]</sup> spectroscopy,<sup>[4]</sup> chemiluminescence,<sup>[5]</sup> and others.<sup>[6,7]</sup> Favorable sensitivity and selectivity are evidently achieved by most of these techniques; however, a high pricing, restricted portability, and often relatively complex sample preparation pose a challenge that still needs to be addressed. In addition, the detection of gaseous hydrogen peroxide brings further complications connected to the sensor's sensitivity, instability of hydrogen peroxide, and sampling protocols. From this aspect, electrochemistry certainly offers several attractive advantages, such as portable and inexpensive instrumentation, simple or even no sample pretreatment, direct on-site detection followed immediately after analyte sampling/accumulation, excellent sensitivity, and numerous possibilities for various electrochemical sensing schemes, together with sensor miniaturization.

In this work, we will present the preparation and characterization of a novel sensor(s) for sensitive on-site detection of gaseous hydrogen peroxide. We will discuss their advantages and drawbacks together with potential application scenarios for indoor/outdoor H<sub>2</sub>O<sub>2</sub> monitoring. Finally, we will demonstrate the operation of such sensors in the real environment.

**Acknowledgements.** This research received financial support from the Slovenian Research Agency's Young Researchers Programme (grant agreement No. 52020) and the fundamental research programme Analytics and Chemical Characterization of Materials and Processes (P1-0034).

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## EBAY AND SUPPLEMENTS DON'T MIX: DETERMINATION OF ANDROGRAPHOLIDES, BOSWELIC ACIDS, CURCUMINOIDS AND PIPERINE IN PRODUCTS AVAILABLE LOCALLY AND ONLINE

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Active substance content is one of the essential parameters of any preparation, as it often governs both efficacy and safety of the overall product. It is well known herbal products are not subjected to such rigorous control as conventional pharmaceuticals, so their quality can drastically differ. Therefore, the goal of this work was to assess the active substance content of turmeric, green chiretta and Indian frankincense-based products available locally and online. As these products are often comprised of two or more stated herbal constituents, a universal HPLC-DAD method for determination of three curcuminoids, piperine (curcuminoid bioavailability enhancer), three andrographolides and six boswellic acids was developed and validated for the first time. Sonication extraction step was optimized using three-factorial Box-Behnken design, while the optimal parameters were extraction solvent of 81.5% (V/V) ethanol/water, sonication time of 30 min and extraction temperature of 60 °C (model desirability 0.927). The method was validated according to ICH guidelines, with selectivity (evaluated using standard addition method) and robustness of the method (evaluated using Plackett-Burman design) being paid special attention to. In total, 54 samples (19 raw material and 35 herbal preparation) were analyzed. Drastic differences in declared content of herbal preparations (1.4 to 176.8%) were observed. Regarding raw material, two online-marketed samples showed suspiciously high amounts of curcuminoids, pointing to possible adulteration. Overall, most online-marketed products showed either very little active substances (39% of Internet-bought preparation samples showed less than 20% declared content, implying no efficacy) or substantially higher amounts which could potentially cause adverse effects (one sample containing andrographolides) or lead to an interaction with concomitantly used drugs (one sample containing piperine). In conclusion, consumers should purchase dietary supplements and similar products from certified manufacturers in local pharmacies and refrain from buying them online.

**Acknowledgements.** This work has been supported by the Croatian Science Foundation under the grant numbers HRZZ-UIP-2017-05-3949 and HRZZ-DOK-2018-01-9047.

## SMALL MOLECULE BASED PHOTOABSORBERS FOR APPLICATION IN PHOTOVOLTAIC DEVICES

Floren Radovanović-Perić,<sup>a,\*</sup> Vilko Mandić,<sup>a</sup> Dragana Vuk,<sup>a</sup> Ivana Panžić,<sup>a</sup> Thomas Rath<sup>b</sup>

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Recently, organic photovoltaic devices have received increased attention due to combination of their comparatively simple and cost effective processing and ability to derive low weight, flexible thin-film solar cells. The process of electron-hole pair generation and its extraction toward the electrodes is essential to achieve high performance for all photovoltaic devices and can be influenced by a number of common approaches, such as tuning the bandgap of the photoactive material i.e. broadening the HOMO/LUMO levels (deepening the HOMO levels of the donor material), as well as optimization of the deposition geometry i.e. tailoring the optimal film morphology through molecular interactions to achieve high charge carrier transfer. The latest is of particular interest for small photoactive organic molecules, such as squaraine (SQ) dyes and their derivatives, as they show great preference in supramolecular assembly based on molecular design when deposited into thin-films [1]. SQ photoactive layers (donor materials) used in solar cells are generally mixed with acceptor materials, such as fullerene or their derivatives (e.g. PCBM) into bulk heterojunction layers such approach may widen the absorption spectra [2]. In this study, an optimal synthesis route and film deposition parameters were determined by mixing of several SQ based materials with a number of commercial acceptor materials in various ratios and subsequent depositions. The samples were characterized through SEM and AFM to examine film morphology and UV/Vis spectroscopy to determine the absorption spectra. Furthermore, GIXRD measurements revealed the crystalline constituent layers of the prepared cells and suggested possible presence of any superstructural organisation. We correlated the nature and number of substituents linked onto the SQ base to some degree of functional performance of the synthesized films and thereof assembled photovoltaic devices.

**Acknowledgements.** The financial support by the projects UIP-2019-04-2367 SLIPPERY SLOPE and PZS-2019-02-1555 PV-WALL of the Croatian Science Foundation is gratefully acknowledged.

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## VAPOR PHASE APPROACH FOR SYNTHESIS OF SMART HYBRID MATERIALS

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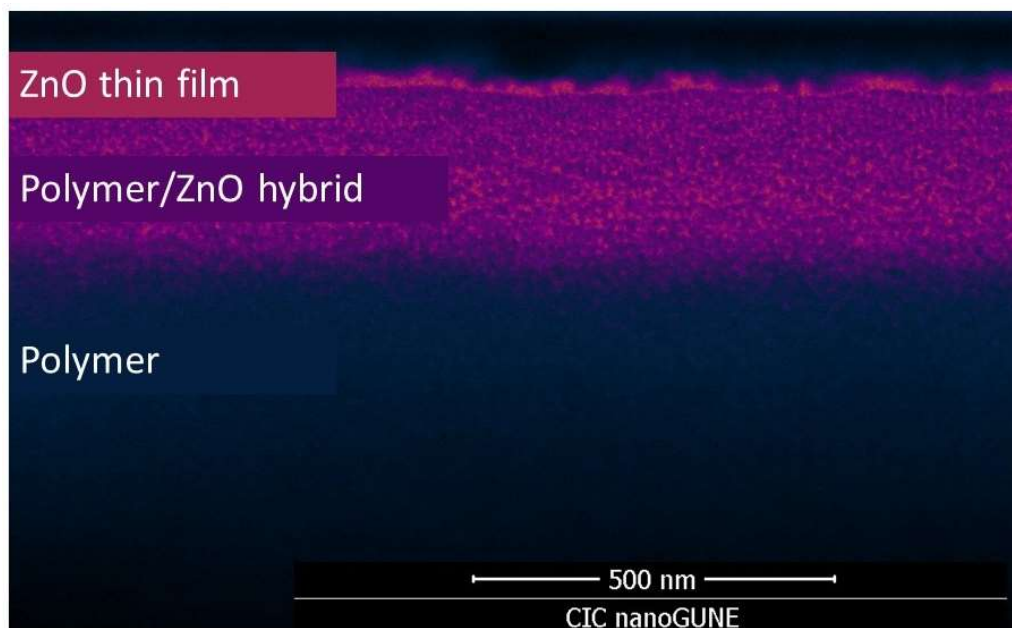
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The ambitious goal of material science is to develop smart materials which combine few different functionalities. Latest advances in technology demand lightweight, flexible and conductive materials for flexible electronic devices, which placed polymer-based structures into the focus of the researcher's attention. However, electrical circuits in flexible electronic devices are inorganic and they are also subjected to bending or stretching whilst device usage. Constant mechanical stress leads to wearing of the inorganic structures, thus causing underperformance of the devices or even their failure. Self-healing materials may answer this technological demand.

To impart the above-described properties into one material, the conductivity of inorganics should be coupled with the flexibility and transparency of the organics. Such modification of the polymers is possible by vapor phase infiltration (VPI).<sup>[1]</sup> VPI is distinguished from atomic layer deposition owing to the prolonged exposure of substrates to gaseous precursors. In the case of soft polymeric substrates, precursors can diffuse into the free volume of a polymer and react with available functional sites or get physically trapped. Such a process leads to simultaneous growth of inorganic clusters in the bulk of the polymer and an inorganic film on its surface. Subsurface inorganic nanoclusters in a polymeric matrix form a hybrid layer with altering density and a smooth transition from the bulk of the polymer to the inorganic thin film (Figure 1). This gradient layer can compensate mechanical stress and suppress crack formation upon bending, thus preventing the loss of electrical conductivity upon bending, folding, or stretching.

In this work, we developed a VPI process of zinc and indium oxides by exposure of polymers to alternating pulses of diethyl zinc and water, and trimethylindium and hydrogen peroxide precursors, respectively. We investigated in detail the chemical structure of the obtained hybrids by X-ray photoelectron spectroscopy (XPS), electron diffraction, transmission electron microscopy (TEM), and energy-dispersive X-ray spectroscopy (EDX). The electrical performance was tested by measuring the sheet resistance of the ParyleneC/In<sub>2</sub>O<sub>3</sub> hybrid upon multiple bending over a radius of 5,5 mm. The self-healing ability of these nanocomposites will be discussed.



**Figure 1.** Scanning electron microscopy (SEM) image of focused ion beam (FIB) cross-section of polymer infiltrated with diethyl zinc and water by VPI.

**Acknowledgements.** This work is funded by the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement №765378.

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## ANTIBACTERIAL BIOMIMETIC METALLOCHITIN THIN FILMS GROWN BY MOLECULAR LAYER DEPOSITION

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Natural chitin and chitinoid materials have outstanding physical and biological properties, which inspired the process development for biomimetic chitinoid organic and hybrid organic-inorganic thin films by applying Molecular Layer Deposition (MLD) presented in this work.

Here, we present a new class of organic–inorganic hybrid polymers called "metallo-saccharides", based on sugar-type precursors. For a controlled MLD growth, the hexosamine monosaccharide N-Acetyl-D-mannosamine (ManNAc) was coupled with trimethylaluminum (TMA) repetitively in a cyclic manner for the growth of the hybrid organic-inorganic alumochitin thin films.

The self-limiting behavior of the surface reactions and the growth rate were determined by in-situ quartz crystal microbalance (QCM) and X-ray reflectivity (XRR) studies. The QCM measurements revealed a linear mass increase with the number of MLD cycles, and the film growth rate of  $\sim 20$  ng/cm<sup>2</sup>/cycle at 115 °C. XRR studies showed a growth rate of  $\sim 1.3$  Å/cycle and a constant density of  $\sim 2.5$  g/cm<sup>3</sup>. The chemical structures of the coatings were studied with ex-situ X-ray photoelectron spectroscopy (XPS) and attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR). Characterization of the film structure, morphology, and conformality were performed by High-resolution transmission electron microscopy (HR-TEM), showing uniform and conformal alumochitin films around ZrO<sub>2</sub> nanoparticles (NPs).

The chemical interaction between ManNAc and TMA, and the possibility of hybrid alumochitin film formation were modeled by density functional theory (DFT). The computed interaction energies between TMA and ManNAc are negative, meaning that there's a strong interaction between these precursors. Theoretical modeling revealed that the proposed reaction mechanism for ManNAc and TMA MLD process is energetically favorable.

The evaluation of the antimicrobial activity of alumochitin thin film against Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli*) bacteria was assessed. Bacteria attachment and proliferation on glass substrates, covered with MLD film were analyzed by confocal microscopy. Both bacteria grow and proliferate on the crystalline nanocellulose and aluminosilazane films, used as a positive control. While neither *Staphylococcus aureus*, nor *E. coli* bacteria attached to the surface of the alumochitin film. These results show a great antimicrobial activity of alumochitin MLD film against gram-positive and gram-negative bacteria, as well as its enormous application potential as bioactive surfaces.

**Acknowledgements.** This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 765378.

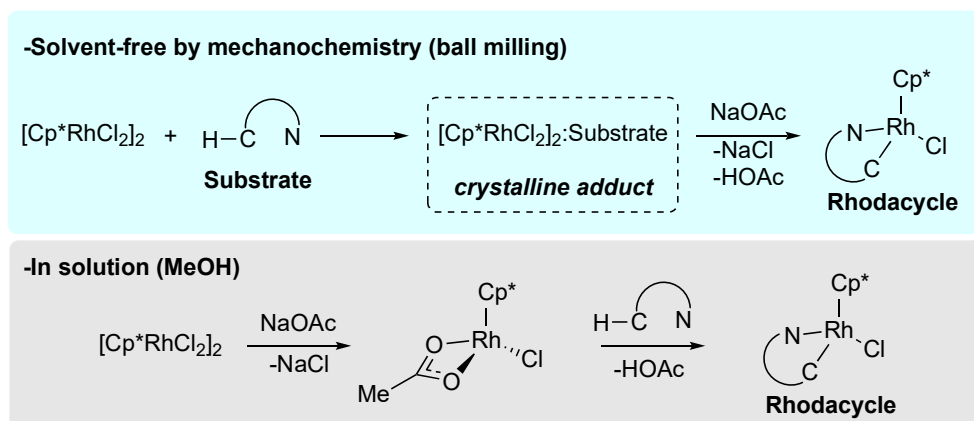
## MECHANISTIC STUDY OF THE MECHANOCHEMICAL ACETATE-ASSISTED C–H ACTIVATION WITH $[\text{Cp}^*\text{RhCl}_2]_2$

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The use of mechanochemistry to carry out solventless metal-catalyzed C–H functionalizations through the formation of metallacycles is gaining ground in chemical synthesis. [1] However, until now, little is known about the mechanistic steps leading to the C–H activation under mechanochemical conditions. In this work, we studied the mechanochemical formation of rhodacycles by ball milling N-substrates and  $[\text{Cp}^*\text{RhCl}_2]_2$  in the presence of NaOAc. Ex-situ analysis of the mechanochemical reactions revealed the formation of unusual crystalline intermediates between the substrates and the rhodium dimer prior to the C–H activation step (Scheme; top). This sequence of events differs from the generally accepted steps in solution in which cleavage of  $[\text{Cp}^*\text{RhCl}_2]_2$  is initiated by acetate ions (Scheme; bottom). [2]



**Scheme.** Cyclorhodation by mechanochemistry (top) and in solution (bottom).

The results of this investigation clarify some of the fundamental aspects of mechanochemical cyclorhodations and are expected to help in the design of better catalysts and processes for mechanochemical metal-catalyzed C–H functionalizations.

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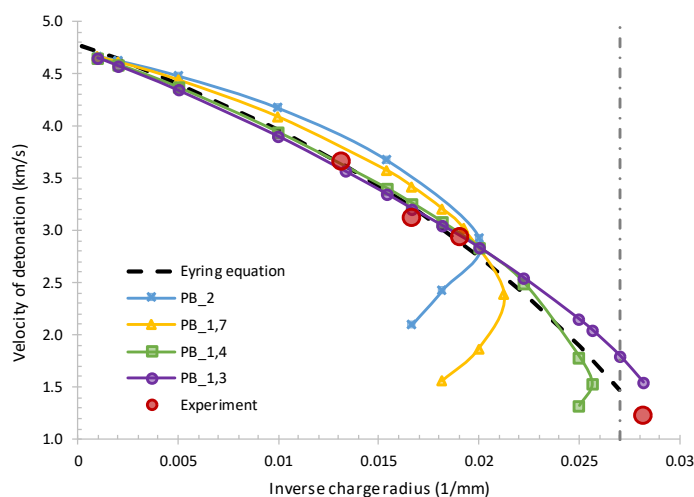
# CALIBRATION OF PRESSURE-BASED REACTION RATE LAW USED FOR NUMERICAL MODELLING OF NON-IDEAL ANFO EXPLOSIVES

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Commercial explosives based on ammonium nitrate, such as ANFO, are widely used in the mining industry and are classical examples of non-ideal high explosives. Detonation of such explosives is characterized by a strong dependence of detonation parameters on charge diameter, density of explosives, presence and characteristics of confinement, as well as incomplete consumption of explosive at the sonic point. For numerical modelling of detonation of ANFO explosive, we used a non-ideal detonation model based on Wood-Kirkwood detonation theory<sup>[1]</sup> coupled with thermochemical code EXPLO5, supplemented with reaction rate law, radial expansion of detonation products and equations of state of unreacted explosive and detonation products.<sup>[2]</sup>

In this work we have calibrated kinetic parameters in single-step pressure-based reaction rate model, based on experimental detonation velocity data measured on a range of explosive charge radii. It was shown that single-step pressure-based reaction rate model, with pressure exponent 1,3 the best reproduces experimental detonation velocity-charge radius curve. Thus calibrated reaction rate law may be used to predict temporal and spatial distribution of flow parameters in the chemical reaction zone, which contributes better understanding of processes occurring in the reaction zone.



**Figure 1.** Velocity of detonation vs. inverse charge radius of ANFO explosive for calibrated pressure-based reaction rate laws

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## CYCLIC CARBAMATE FORMATION THROUGH TRANSITION METAL-CATALYZED CO<sub>2</sub> CAPTURE

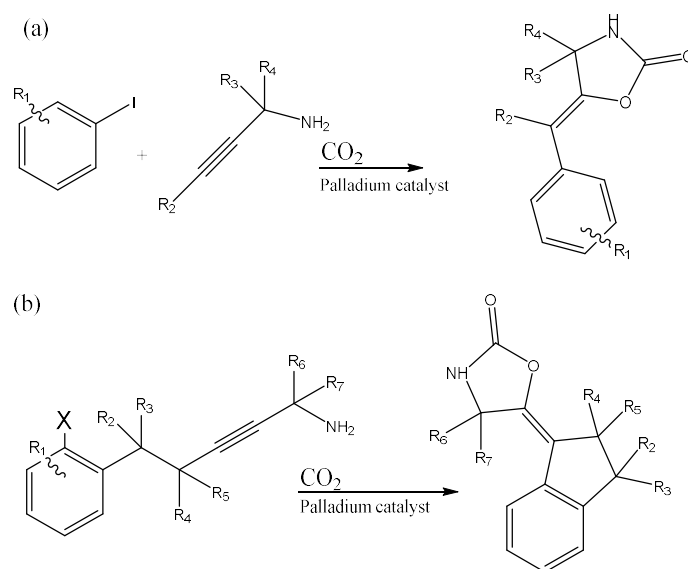
Filip Vranješević,<sup>a</sup> Maria Kolypadi Markovic,<sup>a</sup> Valerije Vrček,<sup>b</sup> Dean Marković<sup>a,\*</sup>

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The optimization of reaction substrates and conditions using *in silico* methods represents the future of organic synthesis. We have evaluated potential substrates for a novel Pd-catalyzed CO<sub>2</sub> capture reaction (Figure 1b) using QM analysis of reaction thermodynamics (with B3LYP/B2PLYP functionals) and selected several amines that appeared promising.



**Figure 1.** (a) The type of reaction reported by Nevado<sup>[1]</sup> that forms carbamates with a tetrasubstituted alkene from CO<sub>2</sub> using a Pd catalyst; (b) Our (intramolecular) version of this cascade reaction.

These substrates have been synthesized and are currently being tested for CO<sub>2</sub> capture under a range of experimental conditions and catalysts. A similar reaction has been reported by Nevado's group in 2016.<sup>[1]</sup> However, if successful, our intramolecular cascade reaction will enable us to produce a complex cyclic carbamate motif in one step using a simple reaction under mild conditions and a very cheap, environmentally friendly reactant (CO<sub>2</sub>). In addition, the mechanism of this reaction will be studied to further optimize the reaction conditions *in silico*. Finally, as cyclic carbamate moieties are often present in many small molecule therapeutics (e.g. Efavirenz and Linezolid), the products of this reaction will be tested for anti-cancer and antibacterial activity.

**Acknowledgements.** This project is funded by the Croatian Foundation for Science (HRZZ-IP-2019-04-8846).

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## COMPUTATIONAL STUDY OF THE GLYCOSYLATED HRP ENZYME USED IN PATHOGEN DETECTION

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The main objective of the MARILIA project is to develop a novel pathogen detection concept for water samples. Powerful tools for detecting protein-protein interactions (PPI), created between a pathogen and a protein detector, can be developed by using protein-fragment complementation assays (PCA).<sup>[1]</sup> A new type of PCA has been recently developed by Martell and associates<sup>[2]</sup> based on the horseradish peroxidase (HRP). The HRP enzyme PCA has numerous advantages, such as: functioning in extracellular environments, generating spatially restricted fluorescent signal, etc. However, hyperglycosylation can present a significant hurdle when expressing recombinant HRP in yeast cells.<sup>[3]</sup>

Using Molecular Dynamics (MD) simulations the effect of glycans on the availability of the surface groups, including the HIS-tag groups needed for the purification process, were investigated. The results of MD simulations show strong influence of the glycan on the overall stability of the HRP enzyme, but also indicate some critical drawbacks in availability of the surface groups that present possible targets for the attachment of the linker that is necessary for PCA design. Different forms of the HRP enzyme, that are used in the HRP PCA, have been simulated.

Additionally, the influence of the mutations introduced by Martell and associates<sup>[2]</sup> was also studied by MD simulations. Key mutations that cause significant structural and dynamical changes in the HRP enzyme were identified.

**Acknowledgements.** This research was supported by the European Union's Horizon 2020 research and innovation program under grant agreement No 952110

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## RECOGNITION OF DNA:RNA HYBRID AND TRIPLEX STRUCTURES BY A SERIES OF BENZOTHAZOLE LIGANDS

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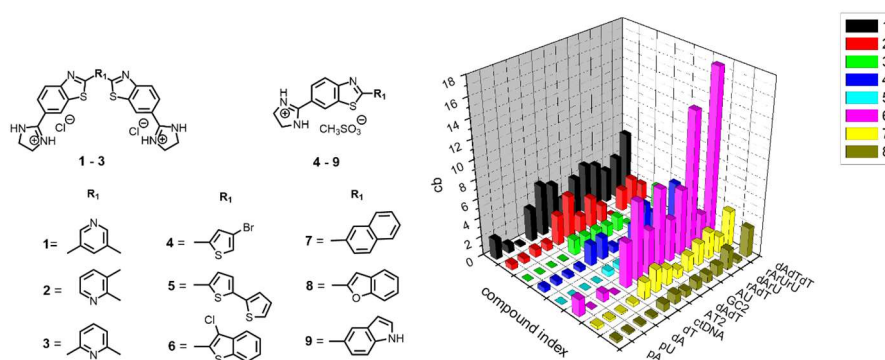
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DNA:RNA hybrids and triplexes are formed as intermediate structures during many biologically important processes such as DNA replication, transcription, telomere replication and modulation of structure and/or function of specific genes (antigenic strategy for gene regulation).<sup>[1,2,3,4]</sup> Interactions of an array of nucleic acid structures with a small series of benzothiazole ligands (**1-9**) were screened by competition dialysis assay (Figure 1). The main aim of this study was detection of benzothiazole structures with preferential binding to DNA:RNA hybrids and ATT triplex in regard to regular (non-hybrid) DNA and RNA duplexes and single-stranded forms. Complexes of nucleic acids and benzothiazoles, screened by this method, were then characterised by UV/Vis, fluorescence, circular dichroism (CD) spectroscopy, isothermal titration calorimetry and Compounds **1** and **6** showed the highest affinities toward 13 nucleic acid structures while **5**, despite lower affinities, yielded higher selectivity among studied compounds. While both **6** and **1** exerted high binding affinities toward ATT, the latter showed stronger binding to rAdT hybrid whereas the former preferred dArU hybrid. Modes of binding to ATT triplex, dArU and rAdT hybrids were determined via CD spectroscopy.



**Figure 1.** a) Structures of benzothiazole derivatives. b) Summary of competition dialysis results with eight compounds binding to 13 nucleic acid structures and sequences (**cb** = compound concentration in  $\mu\text{M}$ ); sodium cacodylate buffer,  $I = 0.05 \text{ mol dm}^{-3}$ ,  $\text{pH}=7$ , + 1 mM EDTA.

**Acknowledgements.** We thank Croatian Science Foundation for the financial support within the project: „DNARNAHyB-MolBio“(HrZZ No. IP-2018-01-4694).

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## EFFECT OF CANCER MUTATIONS ON DPP III – KEAP1 BINDING

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The NRF2-KEAP1 signaling pathway plays a critical role in regulating the antioxidative stress response in cells.<sup>[1]</sup> KEAP1 acts as the main cellular sensor of oxidative stress and as a repressor of the transcription factor NRF2, which is responsible for the transcription of antioxidant response element genes (ARE). Therefore, the release of NRF2 from KEAP1 and its translocation to the nucleus promote cell survival. However, this pathway is often deregulated in cancer cells, which may lead to chemotherapy resistance.<sup>[2]</sup> It has been reported that under oxidative stress conditions, dipeptidyl peptidase III (DPP III) can also bind competitively to KEAP1 and induce the release of NRF2.<sup>[3]</sup> This interaction occurs mainly between the ETGE binding motif in the flexible loop of DPP III and the Kelch domain of KEAP1. Mutations of DPP III found in cancer tissues and reported in the cBioPortal for Cancer Genomics were selected to investigate their potential to induce structural and functional changes in DPP III. We were particularly interested in identifying mutations that affect binding between DPP III and KEAP1 and potentially modulate oxidative stress response and chemotherapy resistance in cancer cells. In this study, we combined different experimental and computational approaches and identified several highly relevant mutations for DPP III – KEAP1 binding.<sup>[4]</sup>

**Acknowledgements.** We acknowledge funding by the Croatian Science Foundation within the Project 'Biological relevance of dipeptidyl peptidase III and its impact on human health' (IP-2018-01-2936).

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## ČERNOBIL I ONLINE ISTRAŽIVAČKA, GRUPNA NASTAVA

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Od ožujka do kraja svibnja 2020. godine učenici trećeg razreda prirodoslovno-matematičke Gimnazije Franje Petrića, inspirirani serijom Černobil, istraživali su radioaktivnost povezanu s dobivanjem električne energije, medicinom, materijalima i poljoprivredom. Kako se nastava provodila na daljinu, preko platforme Teams, nastavnica je imala ulogu moderatora, a učenici su, podijeljeni u grupe, postavljali pitanja i hipoteze, postavili istraživački plan, pronalazili izvore podataka, skupljali i analizirali materijale, pisali izvješće <sup>[1]</sup>, recenzirali radove ostalih grupa te na kraju napravili samoprocjenu istraživačkog rada i svoj doprinos grupnom radu <sup>[2]</sup>.

Kao izvor podataka poslužile su najviše web stranice, no i enciklopedije, medicinski priručnici, razgovori s građanima Pripjata u Ukrajini, te svojim roditeljima i generacijom svojih roditelja koji su doživjeli černobilsku katastrofu. Jedna od aktivnosti u istraživanju je bilo i anketno istraživanje <sup>[3]</sup> iskustva osoba koje su doživjele posljedice Černobilske nesreće u Hrvatskoj kako bi se učenici upoznali s prošlošću iz prve ruke te s anketom kao znanstvenom metodom istraživanja. Svi učenici su sudjelovali u stvaranju baze pitanja za anketu, nakon čega je dvoje učenika izabralo relevantna pitanja te sastavilo anketni upitnik. Dvojica učenika, suautori ovog članka, analizirali su rezultate te napisali izvješće. Anketa je provedena tijekom travnja 2020. godine.

Tijekom istraživačkog rada postavilo se i pitanje usporedbe černobilske katastrofe s pandemijom COVID-19. Jedan od zaključaka rada jest da se utjecaj černobilske katastrofe na ljude može uspoređivati sa sličnim katastrofama svjetskih ili kontinentalnih razmjera. Zbog toga je u zaključku rada predloženo više istraživanja: opsežnije istraživanje o utjecaju černobilske katastrofe na ljude s odabranim pitanjima, poboljšanim uzorkom ispitanika te *sestrinsko* istraživanje iste tematike u odnosu na pandemiju COVID-19 koja je prisutna od 2020., ističući razlike u dostupnosti informacija i mjere zaštite za građane u odnosu na situaciju koja prijeti javnom zdravlju te izaziva strah i paniku među građanima.

Prednosti online istraživačke nastave koja se provodi u skupinama su brojne. Kao najvažnija ističe se samostalnost u radu, učenju i pisanju rada. Samostalnost u nastavi na daljinu je puno izraženija nego u nastavi u živo, jer su kontakti nastavnik-učenik svedeni na minimum [4]. Samostalnost u radu povećava odgovornost za rezultate učenja, time i stres kod učenika. Stresni učinci povećane odgovornosti smanjeni su grupnim radom zbog podijele posla, ali i međusobne suradnje učenika u analizi materijala i izrade krajnjeg izvješća rada. Ipak, svaki učenik mogao je razvijati sposobnost uočavanja bitnog, kritičkog razmišljanja, identificiranja istraživačkih pitanja koja je moguće testirati, nasuprot informativnih pitanja, provedbe istraživanja, mjerenja i prikupljanja podataka, upotrebu odgovarajućih metoda za opis, sumiranje i analiziranje podataka, razmatranje alternativnih objašnjenja te komuniciranje metoda, rezultata i predviđanja. Prednost grupnog rada u nastavi na daljinu za nastavnika jest ušteda vremena prilikom izmjena informacija i vrednovanja učenika.

Izvođenje online istraživačke, grupne nastave ima i nedostataka. U nastavi na daljinu, kao što je već poznato, nedostaje živa riječ, rasprava, diskusija. Učenicima je nedostajala izmjena informacija uživo, *licem u lice* – između njih samih unutar skupine. Komunicirali su pomoću različitih servisa za komunikaciju, platformi za videokonferencije ili platforme Teams. Digitalna komunikacija, svedena samo na verbalno izražavanje te mogućnost da se uključe kad god mogu

ili žele, usporavala je i rasplinjavala međusobno dogovaranje i rad na istraživanju. Također, nedostatak razgovora uživo između učenika i nastavnice usporavao je proces istraživanja i smanjio kvalitetu uputa ili objašnjenja.

Učenici ističu kao problem literaturu koja je najčešće bila *prestručna* ili je bila napisana na engleskom jeziku kojeg nisu uvijek znali dobro prevesti. Naglašenije nego u nastavi uživo, prisutan je bio i uobičajeni problem izvođenja nastave u skupinama učenika – nemogućnost precizne procjene pojedinačnog doprinosa učenika istraživačkom radu i grupnoj suradnji.

**Ključne riječi:** nastava na daljinu, istraživačka nastava, grupni rad, Černobil, anketa, kemija, radioaktivnost

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## KEMIJSKA RAVNOTEŽA U OBRNUTOJ UČIONICI KEMIJE

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Mnogi kemiju smatraju teškim predmetom, kako za učenje tako i za poučavanje. Ispravno tumačenje kemijskih pojmova umijeće je učitelja i nastavnika kemije s obzirom na apstraktne stručne pojmove koje valja približiti učenicima. Nastavniku kemije svakako je u interesu pronaći načine da učenicima pomognu u razumijevanju kemijskih koncepata i da nauče interpretirati kemijske pojave koristeći kemijsku terminologiju. U ovom izlaganju cilj nam je predstaviti sudionicima obradu nastavne teme *Kemijska ravnoteža* u sklopu koncepta *Promjene i procesi*<sup>[1]</sup> primjenom metode obrnute učionice.<sup>[2]</sup> Učenici se već prije dolaska na sat upoznaju s nastavnim materijalom na temu *Kemijske ravnoteže*, kako bi se vrijeme na satu koristilo za razgovor o nejasnoćama s kojima su se susreli prolazeći kroz nastavni materijal prije sata, produbljivanje znanja kroz izvođenje pokusa i diskusiju. Ova metoda usmjerena je na učenika tako što potiče njihovu autonomiju i samostalnost u rješavanju problema. Aktivnosti na satu prožete su problemskim zadatkom u kojem učenici trebaju predložiti tijek kao i očekivane rezultate pokusa u kojem se ispituje utjecaj promjene koncentracije na kemijsku ravnotežu u otopini kalijeva tiocijanata i željezova(III) nitrata. Učenici kroz pokus opažaju nastale promjene te ih tumače na temelju spoznaja o principima uspostave kemijske ravnoteže. Ovakvim načinom poučavanja učenici su zaposleni aktivnostima koje zahtijevaju njihovu međusobnu suradnju, a nastavnik dobiva ulogu mentora koji potiče učenike na samostalno i samoregulirano učenje, postavlja im pitanja usmjeravajući ih na bitne segmente u svrhu ostvarivanja zadanih ishoda. Na kraju sata učenici izlažu svoje rezultate i iznose zaključke do kojih su došli. Korištenjem metode obrnute učionice potičemo učenike da budu samostalni i odgovorni za svoje rezultate, razvijamo njihove organizacijske vještine i vještine timskoga rada s naglaskom na razvoj istraživačkog duha i kritičkog promišljanja.

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## USVAJANJE ODGOJNO-OBRAZOVNIH ISHODA KEMIJE U OSNOVNOJ ŠKOLI KROZ MEĐUPREDMETNU TEMU “ODRŽIVI RAZVOJ” NA PRIMJERU POUČNE STAZE “SVETOMARTINSKA MURA”

Dražen Crnčec

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Usvajanje odgojno-obrazovnih ishoda nastavnog predmeta Kemija primarni je zadatak poučavanja kemije u osnovnoj školi. Temeljem novog kurikulumu nastavnog predmeta Kemija za osnovne škole utvrđena su četiri makrokoncepta (Tvari, Promjene i procesi, Energija te Prirodnoznanstveni pristup).<sup>[1]</sup> Kurikularnom reformom uvedena je i međupredmetna tema Održivi razvoj određena trima domenama (Povezanost, Djelovanje i Dobrobit).<sup>[2]</sup> Cilj ovog rada je analizirati mogućnosti povezivanja makrokonceptata kurikulumu kemije s domenama međupredmetnog kurikulumu Održivi razvoj kroz poučavanje i učenje (nastavni proces) na primjeru u objektivne stvarnosti – poučnoj stazi Svetomartinska Mura. Poučna staza Svetomartinska Mura rezultat je nastojanja lokalne zajednice i škole da se održivo očuva prostor, te se, među ostalim, omogući jedna od najvažnijih funkcija takvog prostora – edukacija. Prije analize povezanosti kurikulumu provedena je izvanučionička nastava kemije učenika Osnovne škole Sveti Martin na Muri. Rezultati analize na razini trećeg odgojno – obrazovnog ciklusa unutar triju domena međupredmetnog kurikulumu “Održivi razvoj” (ODR A.3.1, A.3.2, A.3.2, B.3.1, B.3.2, C.3.1, C.3.2)<sup>[2]</sup> koreliraju sa predviđenim odgojno-obrazovnim ishodima kurikulumu kemije u osnovnoj školi (KEM OŠ A.7.1, A.7.3, A.8.3, B.7.1, B.8.1, C.7.3, D.7.1, D.7.3, D.8.1, D.8.3).<sup>[1]</sup>

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## POKUS U FILMU

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Ovim radom želja nam je prikazati rad na satima kemije i informatike u novonastalim uvjetima nazvanim „Novo normalno“. Tijekom prošle školske godine, kada je nastava bila provođena dio po modulu A i dio po modelu C, od nas nastavnika i naših učenika tražena je prilagodba novonastalim uvjetima. U tim uvjetima smo učenje, kako samostalno tako i suradničko, organizirali u virtualnom okruženju. Nastavu kemije prilagodili smo novim uvjetima sa smanjenim kontaktom među učenicima poštujući sve predložene epidemiološke mjere. Pokus je važan u nastavi kemije kako bi sadržaji koji se usvajaju bili bolji. Nakon obrade u svrhu ponavljanja učenici su izvodili pokuse u svom domu te su snimke provedenih pokusa slali nastavnicima. Učenici su imali zadatak napraviti film o pokusu koji su radili. Film je trebao sadržavati zadane dijelove te biti napravljen prema zadanim kriterijima iz informatike i kemije. Film su mogli izraditi u programu za obradu videa po želji. Tijekom ovog procesa vodili smo računa o ostvarivanju zadanih ishoda za nastavu kemije i informatike, a tako i ostvarenju među predmetnih tema. Tijekom izlaganja u obliku ppt prezentacije bit će prikazan i dio učeničkih ostvarenja.

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### Aplikacije za izradu filma:

Android: *Inshot* (mobitel, tablet)

Windows: *Fotografije*, *Windows Movie Maker* (računalno)

## USAVRŠAVANJE UČITELJA KEMIJE I BIOLOGIJE KROZ ŽUPANIJSKA STRUČNA VIJEĆA

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Stručno usavršavanje je obavezan dio zaduženja učitelja i nastavnika. Važan oblik stručnog usavršavanja provodi se na ŽSV-ima.

U ovom izlaganju predstaviti ćemo jedan primjer dobre prakse pod nazivom: Stručno usavršavanje **učitelja kemije i biologije** uz primjenu videozapisa nastave te ćemo prikazati i terensku nastavu koju smo proveli kao prvo ŽSV-e u ovoj školskoj godini.

Cilj projekta Stručno usavršavanje učitelja kemije i biologije uz primjenu videozapisa nastave je osmisлити kvalitetan model stručnog usavršavanja učitelja kemije i biologije, koji može doprinijeti boljim rezultatima učenja hrvatskih učenika.

Cilj terenske nastave je povezati procese iz svakodnevnog života s ishodima u nastavi kemije i biologije u osnovnoj i srednjoj školi. Terensku nastavu smo proveli u mjestu Pleternica gdje smo posjetili Interpretacijski centar Terra Panonica te hidroelektranu na rijeci Orljavi.

U skolpu rada ŽSV-a učitelji redovito ispunjavaju evaluacijske upitnike pomoću kojih mi voditeljice dobijemo povratnu informaciju o radu našeg ŽSV-a.

Rezultate i statističku obradu rezultata možete pogledati na sljedećoj poveznici: <http://bitly.ws/gs8H>

Tijekom nastave na daljinu redovito smo održavale stručne skupove s temama o digitalnim alatima i primjerima dobre prakse iz nastave.

**Usavršavanje na ŽSV-a od izuzetne je važnosti jer su takva vijeća, s voditeljima u aktivnoj ulozi, poveznica učitelja i nastavnika s AZOO-om.**

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## PRIMJENA ETWINING PROJEKTA U NASTAVI KEMIJE I BIOLOGIJE

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U radu je prikazana primjena analize rezultata provedenog eTwining projekta<sup>[1]</sup> u nastavi kemije i biologije. Tijekom 2019. uključili smo se s učenicima koji pohađaju dodatnu nastavu kemije i biologije u međunarodni eTwining project “Interesting science for kids”, a realiziran je do kraja školske godine 2020./2021. Učenici su tijekom izvođenja dodatne nastave kemije izvodili pokuse na temu *Staničnog disanja* i svoje rezultate prikazali ostalim sudionicima projekta. Izdvojeni pokusi izvedeni su tijekom redovne nastave kemije pri obradi tema *Što je kemija?*, *Svojstva i vrste tvari*, *Smjese tvari*, *Tvari u prirodi*, te nastavi biologije pri obradi tema *Osnovna obilježja živih bića i organiziranost u prirodi*, *Prijenos tvari kroz organizam*, *Disanje živih bića*. Pokusi su provedeni u tri od šest razredna odjela sedmog razreda. naše škole. Pomoću digitalnih alata<sup>[2]</sup> ispitana je usvojenost ishoda poučavanja u svih šest razrednih odjela. Uočili smo kako učenici radom na projektima razvijaju kompetencije komunikacije na materinskom jeziku, komunikacije na stranim jezicima, matematičke kompetencije i osnovne kompetencije u znanosti i tehnologiji, digitalne kompetencije, uče kako učiti, društvene građanske kompetencije, smisao za inicijativu i poduzetništvo.<sup>[3]</sup> Rezultati projekta pokazali su i kako su učenici radom na eTwinning projektu usvojili specifične vještine korištenja znanja i metoda (vještine izvođenja eksperimenata, bilježenja rezultata i opažanja i donošenja zaključaka) koje im pomažu u objašnjavanju prirodnih zakonitosti.

In this work the application of e-Twining projects<sup>[1]</sup> in chemistry and biology teaching will be presente. During 2019., we joined, with students who attend additional classes in chemistry and biology, in the international e-Twining project *Interesting science for kids*, and it was realized by the school year 2020./2021. In additional chemistry classes, students performed experiments on the topic of *Cellular Respiration* and presented their results to other project participants. Those experiments were performed in chemistry class during the processing of the topic *What is chemistry?*, *Properties and types of substances*, *Mixtures of substances*, *Substances in nature* and in biology classes through topics *Basic characteristics of living beings and organization in nature*, *Transfer of substances through the body*, *Respiration of living beings*. The experiments were conducted in three of the six 7<sup>th</sup> grades in our school. The adoption of outcomes in all six classrooms was examined using digital tools.<sup>[2]</sup> We noticed that students working on projects develop communication skills in their mother tongue, communication in foreign languages, in science and technology, digital competences, learn how to learn, social and civic competences, a sense of initiative and entrepreneurship.<sup>[3]</sup>

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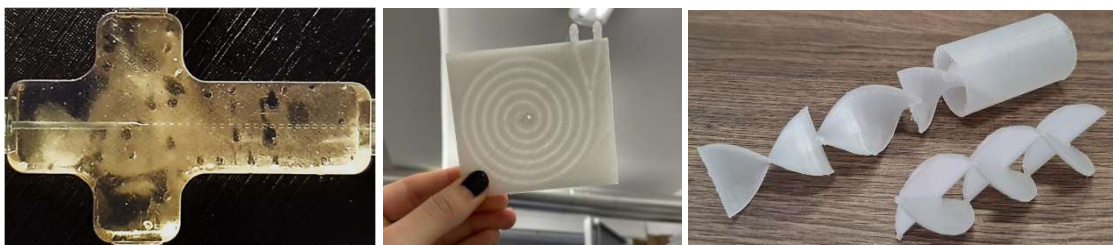
## 3D-PRINTED EQUIPMENT FOR CHEMICAL PROCESSING INDUSTRIES

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The talk will present the advances of additive manufacturing in chemical engineering and the research conducted by students of the Faculty of Chemical Engineering and Technology in this field.

Three independent researches will be presented. The first investigated the possibility of using 3D-printing technologies to fabricate droplet generators capable of producing stable dispersions with well-defined particle sizes by modifying the operating conditions and channel surface properties. In the second, an inertial microfluidic separator was fabricated in which a two-phase mixture of water and three different powders is separated by hydrodynamic forces occurring in the channels. Quartz sand, baby powder and nano calcium carbonate were used for this purpose. The aim of the third investigation was to prepare a functional filament of cycloolefin copolymer (COC) and PETG with the addition of fillers  $\text{TiO}_2$  and carbon nanotubes (CNT). The addition of the fillers changes the physicochemical properties of the polymer and gives the material photocatalytic properties. In this work,  $\text{TiO}_2$  and CNT were added to COC and PETG in different ratios and the mechanical properties of the as-prepared composites were determined. The produced polymer composites were used for 3D-printing of static mixers.



**Figure 1.** 3D printed devices for chemical processing industry fabricated in our laboratory. From left to right: droplet generator, microfluidic inertial separator and two types of static mixers.

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## SUPERCOMPUTERS AS MICROSCOPES FOR THE 21<sup>ST</sup> CENTURY: SUBSTRATE CHANNELING, EPIGENETIC REGULATION, AND MOLECULAR BASIS OF ALZHEIMER`S DISEASE

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**Background:** Drug-design and the related pathogenic events are complex molecular processes that depend on the power of supercomputers for visualization and quantitative analysis. We use a combination of computational studies and wet laboratory measurements, to evaluate, strengthen, and expand our insights in molecular mechanisms.

**Methods:** Supramolecular organization in physiological and pathogenic conditions is analyzed using multiscale molecular dynamic calculations.<sup>[4]</sup> Supramolecular complexes have included protein-protein interaction,<sup>[4]</sup> protein-DNA interaction,<sup>[1]</sup> and protein-membrane interactions.<sup>[3]</sup> *In silico* high-throughput screenings with compounds from commercial databases, are used as the initial fast and cheap approach for the development of drug-candidates [2].<sup>[2]</sup> QM/MM protocols are used for the design and optimization of mechanism based-inhibitors of enzyme activity.<sup>[1]</sup>

### Results:

1. *Inhibitors and activators of DNA methylation and epigenetic regulation.*<sup>[1]</sup> Transition-state analogs of human DNA methyltransferases are designed as potential drugs that act as mechanism-based inhibitors.<sup>[1]</sup> The analogs are prepared with 68 structural modifications using insights from wet laboratory studies and from MD and MM/QM protocols.<sup>[1]</sup> High-throughput *in silico* screenings of 200 thousand compounds from commercial databases, have been used as the fastest and cheapest initial strategy, for development of twenty specific inhibitors of different human DNA methyltransferases, Dnmt1 and Dnmt3.<sup>[1,2]</sup> Steered molecular dynamics studies of protein-DNA interaction showed that a decrease in DNA stability can lead to activation of DNA methyltransferases. The insights are used in for the development of activators of DNA methylation.

2. *Molecular basis of Alzheimer's disease: novel diagnostic protocols and drug design strategies.* Wet laboratory experiments and multiscale molecular dynamic studies showed that the saturation of membrane-embedded protease gamma-secretase with its amyloid substrate can trigger pathogenic protein aggregation in Alzheimer s disease.<sup>[3]</sup> We found that the main candidate-drugs, such as semagacestat and avagacestat have failed, because multiple drug molecules can bind simultaneously to the target enzyme.<sup>[3]</sup> Binding of the drugs to multiple sites leads to competition between enzyme activation and inhibition. Thus, the drugs can facilitate



development of the disease, by decreasing the catalytic capacity of the target enzyme, just as the disease-causing mutations.<sup>[3]</sup>

3. *Supramolecular organization and substrate channeling.*<sup>[4]</sup> Numerical integration of catalytic rates showed that the chances for substrate channeling depend on the overlap between the *off*-rates for donor-enzyme-substrate complex and donor-enzyme-acceptor-enzyme complex. Thus, the manipulations with the enzyme-substrate *off*-rates can be used in metabolic engineering protocols. Multiscale molecular dynamics studies showed that NADH dehydrogenases GAPDH and LDH can form channeling complex only under limiting NAD(H) concentrations.<sup>[4]</sup> NAD(H) channeling between the two enzymes is an extension of NAD(H) channeling between the subunits in each tetramer.<sup>[4]</sup> The channeling paths for negatively charged substrates are defined as patches of positive electric fields on the protein surface.<sup>[4]</sup> Substrate channeling complex is also observed in amyloid metabolism between beta and gamma-secretase, as part of pathogenic processes in Alzheimer's disease.

Conclusions: Supercomputers will have the same impact on progress in biomedical sciences as microscopes had in the last 200 years. We use computational methods at three different levels. Cell physiology and pathophysiology can be described at the level of supramolecular interactions.<sup>[4]</sup> The insights into molecular physiology and pathophysiology can be used for the development of mechanism-based drugs,<sup>[1]</sup> or for design of high-throughput *in silico* screening protocols.<sup>[2]</sup> In the parallel process, numerical integrations and rate constants for different steps in the catalytic cycle can be used for the design, optimization, and interpretation of mechanistic studies of enzyme activity.<sup>[3,4]</sup>

**Acknowledgements.** This work has been supported by the Center for Advanced Computing and Modelling, University of Rijeka, and calculations performed on supercomputer BURA founded in part by Ministry of Science, Education and Sports of the Republic of Croatia under the project Research Infrastructure for Campus-based Laboratories at the University of Rijeka, number RC.2.2.06-0001. Project has been co-funded from the European Fund for Regional Development (ERDF).

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## CAUSALITY ANALYSIS IN CHEMISTRY AND CHEMICAL ENGINEERING

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Application of BigData in chemistry and chemical engineering is due to access of high throughput instruments and data fusion of omics in chemistry and bioinformatics. Availability of Big Data enables development of AI models for investigation of pattern classification, pattern association and prediction. However, most of AI models are applied as effective agnostic (“black box”) predictors and usually do not contribute to new scientific knowledge. AI models do not provide causality due to confounding of model variables, which are commonly highly correlated, and lead to back door noncausal associations and colliders of common effects. In the last decades developed is mathematical theory of causality and algorithmic computer analysis for testing and discovery of causality.<sup>[1,2]</sup> It is based on Bayesian integration of prior structural knowledge and experimental evidence (data). Causality analysis of variable  $x$  follows three methodological steps: prediction, doing  $do(x)$ , and counterfactual estimation. Confounding of causality is removed by  $d$ -separation algorithm producing adjustment of the structural knowledge network. The  $do(x)$  operator estimates causality on population level, while counterfactual causality is “out of box” on sample level and is algorithmic basis for scientific discovery. Here are presented two cases: causality analysis of industrial waste water treatment plant (WTP) and causality of peptides molecular descriptors for of biological activity. The WTP is a two stage process with pretreatment, primary and secondary settler, and biological reactor. The plant is monitored daily during two years with 38 physical and chemical parameters. Determined are population level causalities between parameters of input flows of row water and the plant global output performances. The second example is aimed for scientific discovery of causality between peptide molecular descriptors and their cell level activity. Tested are 1800 descriptors for 100 peptides with each up to 50 aminoacids. Prior to causality analysis the descriptors are regularized and PC algorithm is applied for generation of the corresponding directed acyclic graph (DAG). Potential discoveries are predicted by counterfactual analysis.

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## THE ROLE OF LONDON DISPERSION IN THE FORMATION OF DIAMANTANE CLUSTERS INSIDE HELIUM NANODROPLETS

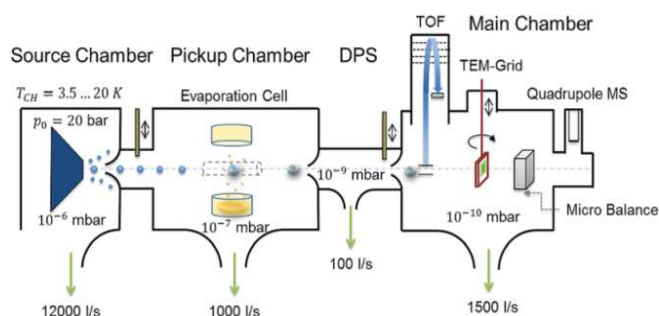
Marina Šekutor,<sup>a,\*</sup> Jasna Alić,<sup>a</sup> Roman Messner,<sup>b</sup> Florian Lackner,<sup>b</sup> Wolfgang E. Ernst<sup>b</sup>

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Helium nanodroplets (HNDs) are unique hosts for the study of weak interactions between molecules since helium has very low polarizability and becomes superfluid at low pressures and near-zero Kelvin temperatures, thus making it an ideal medium for trapping weakly binding van der Waals complexes.<sup>[1,2]</sup> For our study we chose diamantane molecules that are bulky and rich in C–H bonds because they can readily engage in London dispersion (LD) intermolecular interactions with each other. When HNDs were doped with diamantane molecules, we observed spontaneous cluster conglomeration and the formed clusters were analyzed by time-of-flight mass spectrometry (Figure 1).<sup>[3]</sup> We also successfully identified and characterized magic number clusters, distinct cluster sizes with large abundances. The experimental findings were supported by meta-dynamics simulations and subsequent DFT computations in order to further analyze the observed cluster structures. The obtained interaction energies were attributed to LD attraction and we could therefore quantitatively demonstrate that dispersion interactions indeed dominate molecule packing in these diamantane assemblies.



**Figure 1.** Experimental setup used for HNDs generation and diamantane cluster synthesis.[2,3]

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# COMPUTATIONAL STUDY OF NITROGEN-CONTAINING COVALENT ORGANIC POLYMERS

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Emissions of greenhouse gases have a global impact by contributing to climate change. New materials capable of facile CO<sub>2</sub> capture have to be developed and porous materials are very promising candidates for the gas storage due to their low densities and high internal surface areas. Among different crystalline metal-organic (MOFs) and covalent-organic frameworks (COFs), many covalent-organic polymers (COPs), although lacking crystallinity thus making their pore size less uniform, show very similar behaviour toward binding of gases.<sup>[1,2]</sup>

We have synthesized and characterized a series of new azo-bridged COPs by condensation reactions between 1,3,5-tris(4-nitrophenyl)benzene and various aromatic diamino compounds acting as linkers between central units. A computational analysis was performed to give a better insight into selective binding properties of CO<sub>2</sub>/N<sub>2</sub> and core functionalities of new azo-bridged COPs. In addition, a detailed conformational search was carried on (a) core functionalities like trifunctionalized pyridine, triazine and amine; (b) linkers of variable length including biphenyl and those in which two phenyl rings were separated by one and two methylene groups, oxygen, sulphur, carbonyl and (c) different types of nitrogen-nitrogen linkages (azo, azoxy and azodioxy) connecting two phenyls. Binding energies were calculated to estimate the selectivity of different structural fragments toward selective binding of CO<sub>2</sub> and N<sub>2</sub>. Although, the model is simple in comparison with the whole system, all the investigated fragments show a greater selectivity toward CO<sub>2</sub> over N<sub>2</sub>. The calculated binding energy values may serve as a rough guideline for the design of better nitrogen-based COPs for the selective binding of CO<sub>2</sub>.

**Acknowledgements.** This work has been fully supported by Croatian Science Foundation under the project IP-2020-02-4467.

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## EXCITED STATE INTRAMOLECULAR PROTON TRANSFER FROM NITROGEN TO CARBON ATOM IN AMINOBIPHENYLS

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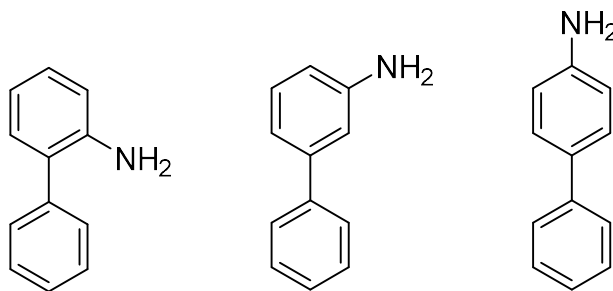
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Excited-state intramolecular proton transfer (ESIPT) is a fundamental photochemical reaction that has been intensively investigated due to numerous applications in sensing technologies and material science.<sup>[1]</sup> ESIPT takes place in molecules bearing proton donor and acceptor groups in close proximity, whose acidity and basicity are enhanced upon excitation. Furthermore, example of ESIPT between the phenolic OH and the adjacent carbon atom have been well documented.<sup>[2]</sup> However, examples where amino functional group acts as a photoacid are scarce.

Here we report on the investigation of ESIPT reactivity in *o*-, *m*- and *p*-aminobiphenyl derivatives (Figure 1). The process was investigated by irradiations in D<sub>2</sub>O-CH<sub>3</sub>CN whereupon the regiospecific deuterium incorporation took place and indirectly pointed to the ESIPT reaction mechanism. Properties of the excited states leading to the ESIPT were investigated by steady-state and time-resolved fluorescence, and we determined the p*K*<sub>a</sub> values of the molecules in the ground and the first singlet excited state by UV-vis and fluorescence titrations. To corroborate the experimental findings, the computations have been performed using the Algebraic Diagrammatic Construction to second order (ADC(2) method,<sup>[3]</sup> which completely unraveled the reaction mechanism and observed ESIPT photochemical pathways.



**Figure 1.** Structures of the investigated aminobiphenyl derivatives.

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# COMPUTATIONAL INVESTIGATION OF THE MECHANISM OF THE IRREVERSIBLE INHIBITION OF THE MONOAMINE OXIDASE B ENZYME

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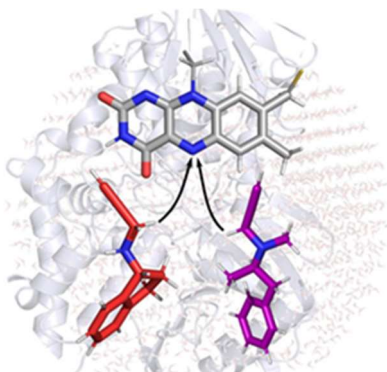
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Monoamine oxidase B (MAO B) is a flavoenzyme<sup>[1]</sup> responsible for the regulation of levels exogenic and endogenic amine in the human body, including amine neurotransmitters in the brain, which is why it represents a crucial pharmacological target for treating Parkinson's and Alzheimer's diseases. This computational investigation elucidates the mechanism of the irreversible MAO B inhibition with clinical propargylamine inhibitors, rasagiline and selegiline,<sup>[2]</sup> and their derivatives desmethyl-selegiline and methyl-rasagiline. The quantum-chemical analysis within the cluster model showed that this reaction proceeds in three steps, with the rate-limiting abstraction of the inhibitor's  $\alpha$ -methylene H<sup>-</sup> anion by FAD in the first step.<sup>[3]</sup>



The obtained results are in excellent agreement with experimental observations. The proposed mechanism is further characterized by the Empirical Valence Bond approach on the entire enzyme structure, whereas molecular dynamics simulations identified residues crucial for the binding. The offered insight provides important guidelines for the development of new and more effective MAO B inhibitors.<sup>[4]</sup>

**Acknowledgements.** We thank the University of Zagreb Computing Centre (SRCE) for granting computational resources on the ISABELLA cluster.

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## 4-AMINOQUINOLINES, A PRIVILEGED PHARMACOPHORE - FROM ANTIMALARIALS TO INHIBITION OF CHOLINESTERASE -

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Quinoline heterocycle is one of the few privileged scaffold<sup>[1,2]</sup> that express a broad spectrum of biological activity. 4-Aminoquinolines (4-AQ), an important sub-group of quinoline family, was primarily boosted in the middle of the 20<sup>th</sup> century as replacement of quinine, and were the first-line defenders for the treatment of malaria for decades. However, discover that 4-AQ based compounds exhibit wide biological activity that influenced many biochemical processes,<sup>[3,4]</sup> placed this pharmacophore in the centre of drug repurposing programs.<sup>[5]</sup>

Although it is known that quinoline influenced degradation of Alzheimer  $\beta$ /A4 amyloid precursor protein<sup>[6]</sup> and that inhibits human erythrocyte membrane AChE, just recently more detailed investigation of 4-AQ as potentially active agents are reported. As part of our broader research in this field,<sup>[7]</sup> we investigate 4-AQ as reversible inhibitors of AChE and BChE. We synthesized a series of derivatives that differs in the structure of diamino alkyl- or aryl-side chain and substitution on the terminal amino group. Starting from the corresponding 4-chloroquinoline and using different alkyl- or aryl-diamines corresponding 4-aminoquinolines were obtained. Further modifications of terminal amino-group produced final derivatives that were examined as inhibitors of cholinesterase's activity. We found that length of the side chain, conformation flexibility and substitution of aryl-group influenced the inhibitory capacity of AChE and BChE and selectivity as well. Other details will be discussed.

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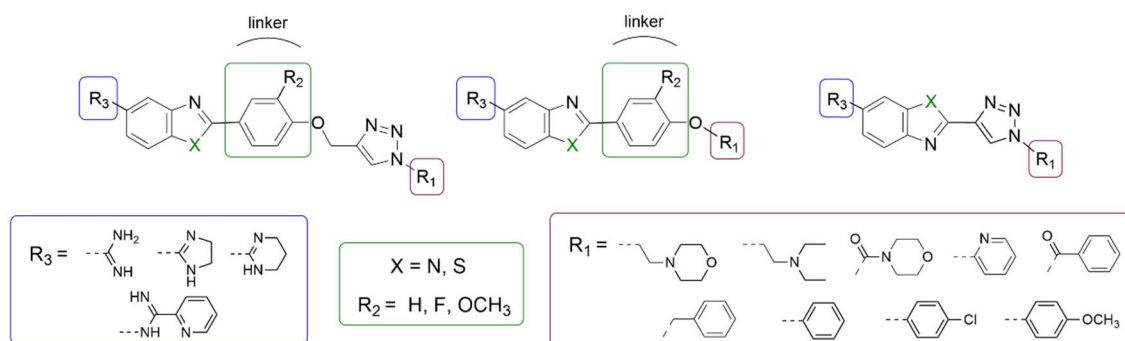
## AMIDINO-SUBSTITUTED BENZAZOLES: PROMISING ANTITRYPANOSOMAL AND CYTOSTATIC AGENTS

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Cancer, an uncontrolled, rapid and pathological proliferation of cells, is the second leading cause of death, with more than 18 million cases worldwide annually. On the other hand, human African trypanosomiasis (HAT) is a life-threatening, neglected tropical disease, with around 60 million people at risk in 36 sub-Saharan African countries. The current drugs used to treat HAT, are toxic and not always effective due to the appearance of drug-resistance.<sup>[1,2]</sup> In continuation of our scientific research based on the development of aromatic amidines as DNA-binding ligands, cytostatic and antitrypanosomal agents,<sup>[2–5]</sup> we have designed and synthesized novel amidino-substituted benzazole derivatives. Design of novel amidino derivatives was focused on diversification of three regions of target molecules: type of amidino substituent on left-hand side and type of aromatic and aliphatic substituents on right-hand side of a molecule, as well as central heterocycle from benzimidazole to benzothiazole to modulate biological properties.



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## **COOPERATION OF PROFESSIONAL ASSOCIATIONS OF THE CROATIAN CHAMBER OF ECONOMY WITH SCIENCE IN THE FUNCTION OF RAISING THE COMPETITIVENESS OF THE ECONOMY**

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The new EU legislation, Green Deal and low-carbon strategy, the new European Industrial Strategy, Chemical Sustainable Strategy as well as the new Action Plan for Circular Economy present great challenge to industry which ask for changes. Major changes to the industry is going towards digital, green and the sustainable economy. The accomplishment of this challenging task should be tackled in collaboration with the scientific community, which should help further develop the industry and help make it sustainable and competitive in the European and global market. The Croatian Chamber of Economy and professional associations which are active there are willing and able to assist between two interested party and to help our industry to become more competitive and sustainable.

## EFFECT OF CONTROLLED CRYSTALLIZATION ON THE IONIC AND ELECTRONIC CONDUCTIVITY IN PHOSPHATE GLASSES

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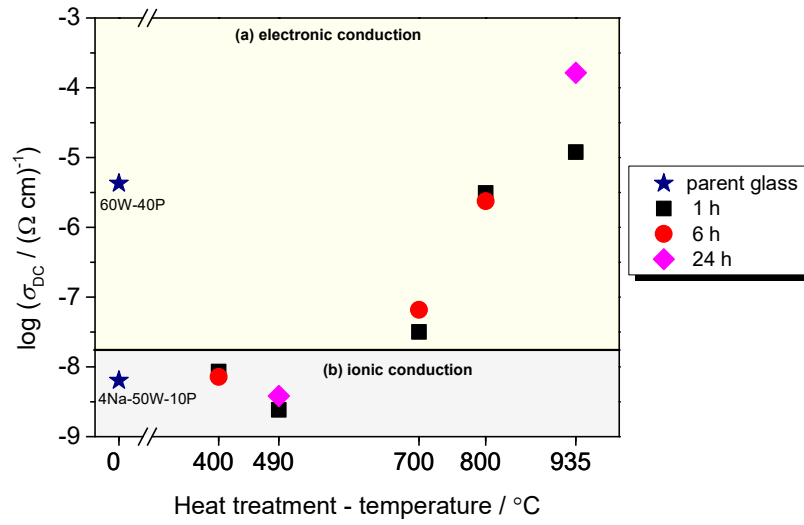
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Glass-ceramics are advanced functional materials that contain crystalline phase(s) embedded in a glass matrix. Their electrical properties can be modified by tuning the nature and amount of phase(s) that crystallize in the glass upon the heat-treatment. This study shows how crystallization influences the mobility of electrons (polarons) and sodium ions in binary  $\text{WO}_3\text{-P}_2\text{O}_5$  and  $\text{Na}_2\text{O-WO}_3\text{-P}_2\text{O}_5$  glasses, respectively.

The parent  $60\text{WO}_3\text{-}40\text{P}_2\text{O}_5$  and  $40\text{Na}_2\text{O-}50\text{WO}_3\text{-}10\text{P}_2\text{O}_5$  (in mol%) glasses were prepared by conventional melt-quenching technique and were subsequently heat-treated at temperatures above their glass transition temperature and at their crystallization temperature (700 °C, 800 °C and 935 °C for  $60\text{WO}_3\text{-}40\text{P}_2\text{O}_5$  glass and 400 °C and 490 °C for  $40\text{Na}_2\text{O-}50\text{WO}_3\text{-}10\text{P}_2\text{O}_5$  glass) for various times (from 1 to 24 hours). The electrical properties of prepared glass-ceramics were investigated by impedance spectroscopy in a wide frequency (0.01 Hz – 1 MHz) and temperature (-30 °C – 250 °C) range while structural properties were evaluated by X-ray powder diffraction (XRPD) and SEM-EDS analysis. In the case of  $60\text{WO}_3\text{-}40\text{P}_2\text{O}_5$  glass, heat-treatments from 700 °C to 935 °C induced evolution of structure from amorphous to the structures with dominant  $\text{W}_2\text{O}_3(\text{PO}_4)_2$  and minor  $\text{WO}_3$  crystalline phases. The electrical conductivity of amorphous sample prepared at 700 °C decreased in comparison to the parent glass due to the rearrangement of the glass network upon heating which accompanies breaking of the bonds in the tungsten clusters which consequently impedes transport of polarons. Nevertheless, with further increase in heat-treatment time and temperature a significant rise in conductivity was observed as a consequence of crystallization of conductive  $\text{W}_2\text{O}_3(\text{PO}_4)_2$  and  $\text{WO}_3$  phases. The highest conductivity was obtained for glass-ceramic prepared at 935 °C for 24h where rapid electron transport occurs through  $\text{WO}_3$  crystallites (Figure 1). On the other hand,  $40\text{Na}_2\text{O-}50\text{WO}_3\text{-}10\text{P}_2\text{O}_5$  sample heat-treated at 400 °C remained amorphous with similar ionic conductivity as the parent glass, whereas treatment at 490 °C resulted in partially crystallized sample with slightly lower conductivity (Figure 1). Here, the glass-ceramic was found to contain  $\text{Na}_2\text{W}_2\text{O}_7$  crystallites embedded in amorphous glassy matrix. In the crystalline  $\text{Na}_2\text{W}_2\text{O}_7$  phase, sodium ions move between interstitial positions of corner-sharing  $\text{WO}_6$  octahedral and  $\text{WO}_4$  tetrahedral due to which their mobility is slower and hence overall ionic conductivity of the glass-ceramic lower. Therefore, in contrast to the electronically conductive binary tungsten-phosphate glass in which the crystallization produces a significant increase in conductivity, the crystallization processes in sodium tungsten-phosphate glass have a negative effect on the mobility of sodium ions causing a decrease in ionic conductivity in glass-ceramics.



**Figure 1.** (a) electronic conductivity in 60WO<sub>3</sub>-40P<sub>2</sub>O<sub>5</sub> parent glass and prepared glass-ceramics and (b) ionic conductivity in 40Na<sub>2</sub>O-50WO<sub>3</sub>-10P<sub>2</sub>O<sub>5</sub> parent glasses and prepared glass-ceramics as a function of heat-treatment time and temperature.

## DESIGN OF NANOCARRIERS TO REDUCE SYSTEMIC TOXICITY OF ANTITUMOR AGENTS: DOXORUBICIN CASE STUDY

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The application of nanoparticles (NPs) has enormous potential for increasing the efficiency of drug and gene delivery, while decreasing the unwanted toxic effects, especially in developing antitumor drugs.<sup>[1,2]</sup> One of the very effective agent against a wide range of malignancies is doxorubicin (DOX) that is also characterized by low selectivity leading to severe side effects, like cardiotoxicity that limit its long-term use and prevents optimal benefits for the patient.<sup>[3]</sup> This study evaluated the metabolic alterations in liver, kidney and heart of animals induced by innovative DOX nanoformulation compared to conventional and liposomal formulation that are already in clinical use. Imaging mass spectrometry (IMS) was used to simultaneously record the intensities of numerous m/z signals that correspond to different metabolites' contents in tissue sections. Metabolites and pathways associated with the administration of different DOX pharmaceutical formulations were compared to the metabolic alterations described in the literature. Obtained results indicated the value of nanotechnology to open up opportunities for the development of safe and efficient drug nanoformulations.

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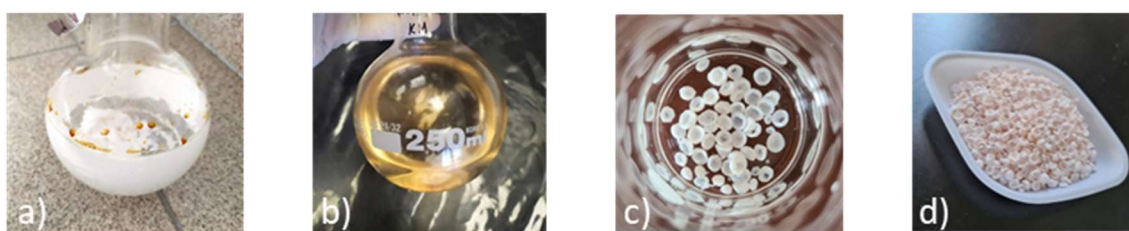
## SYNTHESIS OF MALEIC BASED POLYMERIC ADDITIVES AND THEIR INFLUENCE ON THE LOW-TEMPERATURE PROPERTIES OF DIESEL AND BIODIESEL FUEL

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Fuel properties change significantly with temperature, so at low temperatures diesel and biodiesel/diesel blends tend to form paraffin waxes, which can clog the supply channels and completely block the operation of the motor. Even though many different fuel additives have been developed, which meet the current requirements for use, this issue cannot be considered resolved and more demanding requirements are expected in the coming period. In our work, six different polymeric additives based on maleic anhydride were synthesized by radical polymerization and their influence on the low-temperature properties of diesel and biodiesel fuels was examined. The polymers were synthesized in different molar ratios of starting monomers - maleic anhydride (MA) and vinyl acetate (VA) in molar ratios MA/VA = 50/50 and 80/20. The functionalization of the polymer molecules was done with three different alcohols in which the anhydride ring was opened, and the alkyl chain of the alcohol was attached to the polymer. By using different alcohols, the influence of alkyl chain length of alcohols on the solubility of the polymer additive in the fuel and the properties of the added fuel was evaluated. The purity of the polymer additives was monitored by Fourier-transform infrared spectroscopy (FTIR) and proton nuclear magnetic resonance (<sup>1</sup>H NMR) spectroscopy. Molecular weight distribution and molecular weight averages of prepared additives were determined with gel permeation chromatography (GPC) and the thermal properties of MAVA additives and their mixtures with fuels were examined by differential scanning calorimetry (DSC). Standard tests for low-temperature properties performed according to ASTM D 5950 for the pour point (PP) and EN 115 for the cold filter plugging point (CFPP) have shown that PP improved up to 21 °C in diesel and up to 3 °C in biodiesel.



**Figure 1.** Purification process of MAVA copolymers: -a) evaporated product after synthesis, b) product dissolved in THF, c) precipitation with hexane and d) pure MAVA

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## INVESTIGATION OF CORRELATION BETWEEN DIFFERENT SACRIFICIAL AGENTS AND PHOTOELECTROCHEMICAL PROPERTIES OF TiO<sub>2</sub>-BASED CATALYSTS FOR H<sub>2</sub> GENERATION

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The limited supply of nonrenewable energy sources requires the use of alternative fuels, such as hydrogen (H<sub>2</sub>). One of the ambitious ways to obtain it is photocatalysis, which uses a semiconductor material(s) and sunlight or artificial light to split water and produce H<sub>2</sub>. The most studied material, TiO<sub>2</sub>, cannot be activated by visible light, so it is of critical interest to combine it with visible light responsive photocatalytic materials, such as sulfide-based as well as carbon-based materials to decrease the band-gap and reduce the high charge recombination rate.

Since the splitting of pure water is a low efficiency process, higher H<sub>2</sub> production efficiencies should be achieved by enriching the water with various electron donors that act as sacrificial agents and consume holes to prevent the charge carrier recombination. In this work, the effect of different volume ratios (5-20 vol%) of sacrificial agents (methanol, ethanol, ethylene glycol, and triethanolamine) on the photoelectrochemical properties of the as-prepared TiO<sub>2</sub>/SnS<sub>2</sub>/GO-RGO nanocomposite with different GO-RGO contents was systematically investigated.

The electrochemical performance of the fabricated working electrodes was analyzed by linear sweep voltammetry, electrochemical impedance spectroscopy, Mott-Schottky analysis and open circuit potential (OCP) measurements. The experimental application of the listed techniques allowed the calculation of the electron lifetime, charge recombination rate, flat band potential (E<sub>FB</sub>) and visible light response of the tested components. Considering the obtained values, triethanolamine (TEOA) in high volume fraction (more than 10 %) was found to be the most suitable for the use in H<sub>2</sub> production. Omitting the electron donors used has a great impact on reducing the photocatalyst efficiency. Regardless of the sacrificial agents used, the presence of GO-RGO in all tested materials enabled more efficient charge separation with lower charge carrier recombination compared to the pure components.

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## NOVEL LOW-COST SYNTHESIS OF TRANSPARENT BaTiO<sub>3</sub>-TiO<sub>2</sub> NANOTUBE HETEROSTRUCTURES FOR PHOTOCATALYSIS

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Titanium (IV) oxide, a semiconducting metal oxide praised by the scientific community for its chemical and mechanical stability and non-toxicity, has found its way into a vast array of uses ranging from pigments, food additives, ceramics, cosmetics, self-cleaning surfaces, batteries, photocatalysis, photovoltaics, sensors etc.<sup>[1]</sup> The implementation of TiO<sub>2</sub> in photocatalysis has been extensively researched, especially nanostructured TiO<sub>2</sub>, that has almost completely shifted the scientific focus off of bulk TiO<sub>2</sub> because of the large increase in its specific surface, in other words surface to volume ratio. Consequently, nanostructuring TiO<sub>2</sub> results in increased numbers of photo-induced reactions, light absorption, photogenerated carrier density, photoreduction<sup>[2]</sup> and facilitates increased contact of the material with its surroundings.<sup>[3]</sup>

To further improve photocatalysis, different nanomaterial modifications can be used e.g. doping, and surface modifications like bilayer or heterostructure formation. Heterostructure formation on TiO<sub>2</sub> has been thoroughly researched and ranges from expensive variants involving noble metals like Au,<sup>[4]</sup> Ag<sup>[5]</sup> or Pt,<sup>[6]</sup> and much cheaper alternatives like Cu<sup>[7]</sup> or metal oxides like CuO<sup>[8]</sup> and ZnO.<sup>[9]</sup> Another interesting alternative to expensive noble metals is a perovskite semiconductor: barium titanate, BaTiO<sub>3</sub> (BTO), a synthetic material usually used in electronic components, but recently there have been shown promising results regarding heterostructures with TiO<sub>2</sub>, precisely in perovskite solar cells,<sup>[10]</sup> relative humidity sensors<sup>[11]</sup> and photocatalysis<sup>[12]</sup> showcasing the sheer versatility of this material.

In this presentation we will show the preparation steps in a novel, low-cost and simple method of synthesizing BTO-TiO<sub>2</sub> heterostructures and the results of the photocatalytic degradation of diclofenac under UV/Vis irradiation. Transparent TiO<sub>2</sub> nanotube arrays were prepared by anodizing magnetron sputtered Ti thin films on conductive FTO covered glass and the BTO layers were prepared by spin coating Ba(OH)<sub>2</sub> solutions on top of nanotubes and annealed to promote Ba<sup>2+</sup> and TiO<sub>2</sub> interactions. The structural properties of the samples were investigated using X-ray diffraction (XRD), scanning electron microscopy (SEM) and energy dispersive X-ray spectroscopy (EDS).

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## DESIGN OF EXPERIMENTS FOR PHOTOLYTIC AND PHOTOCATALYTIC DEGRADATION OF 5 PHARMACEUTICALS IN WATER

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Pharmaceuticals and their degradation by-products are ubiquitous in water bodies, particularly in the effluent of wastewater treatment plants, but also in the environment.<sup>[1]</sup> Studies show that, even in small quantities, these substances can cause adverse acute and chronic effects in aquatic life and humans.<sup>[2]</sup>

A great number of works have been investigating parameters which influence kinetic rates of pollutant degradation using UV-LEDs but there is a lack of literature evaluating proper photoreactor design and its impact on reaction rates. In this study, a full factorial Design of Experiments (DoE) approach was used to investigate the simultaneous degradation of 5 different pharmaceuticals in water by photolysis and photocatalysis. An initial solution containing 2 mg/L of each compound (ciprofloxacin, trimethoprim, sulfamethoxazole, venlafaxine hydrochloride, and desvenlafaxine) was illuminated with a lab-scale UV-LED photoreactor (150 mL) for 1 hour. The significance of 4 independent categorical variables (table 1) and their combined effect on each compound's rate of degradation and the effluent Total Organic Carbon (TOC) and toxicity by *Vibrio fischeri* was analysed.

**Table 1.** Independent DoE variables

Independent coded variables	-1	+1
Matrix (A)	MQ water	Tap water
LEDs wavelength (B)	274 nm (UVC)	365 nm (UVA)
Catalyst presence (C)	No	Yes
Duty Cycle (D)	0.50	1.00 (continuous)

The results show that every compound was degraded differently in each of the treatments. Anyway, the effect BC (combining the LED wavelength and catalyst presence) was relevant to all of them. The degradation was enhanced either with UVA in the presence of the catalyst or with UVC in the absence of the catalyst. This can be explained by the light screening effect of the catalyst,<sup>[3]</sup> which hinders the photolytic degradation route when UVC is used. For longer wavelengths, in the case of UVA, the screening effect was smaller. Additionally, only ciprofloxacin was degraded by UVA photolysis alone, so the radical production routes created by the catalyst led to a faster degradation. The matrix factor (A in table 1) was the most prominent regarding TOC abatement. This highlights the importance of adequate pretreatments to optimize light-based processes and avoid light screening and radical scavenging related to the

effluent matrix and content.<sup>[4]</sup> The *Vibrio fischeri* toxicity evaluation showed that lower wavelengths (UVC) helped reducing the toxicity of the initial solution, but attention should be paid to the fact that experiments with UVA generally increased the toxicity levels. This can be explained by the formation of degradation by-products. Many reports in the literature concerning the chosen pharmaceuticals, in fact, call the attention to the formation of toxic substances after the treatment.<sup>[5,6,7]</sup>

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## MASS CONCENTRATIONS OF CARBON POLLUTANTS AT A TYPICAL STREET CANYON LOCATION

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Narrow city streets engulfed by tall buildings are favourable to a general effect of a “canyon” in which pollution accumulates strongly on a relatively small area because of weak or inexistent ventilation. The most important anthropogenic sources of primary particulate matter in cities are exhaust and non-exhaust emissions from road traffic as well as incomplete fuel combustion (diesel and gasoline) but they can also originate from resuspension from street surfaces. PM<sub>1</sub> (particulate matter with an aerodynamic diameter under 1 μm) mass concentration and its chemical composition depend strongly on meteorological factors (i.e., low ambient temperatures, temperature inversions), traffic, as well as street geometry. Especially in a canyon type street, the exhausts of motor vehicles accumulate and harm travellers, which are directly exposed to the atmosphere. Long and short-term exposure to ambient air pollution can trigger acute, chronic illness (cardiovascular diseases and asthma) or infectious diseases, preterm birth, earlier mortality and adverse neuropsychological effects. The aim of this study was to determine and compare levels of elemental carbon (EC), organic carbon (OC), total carbon (TC), water soluble OC (WSOC), polycyclic aromatic hydrocarbons (PAHs) and levoglucosan (LVG) mass concentrations and black smoke index (IBS) in PM<sub>1</sub> particles between the colder (January-March) and warmer (April-June) part of the year at one street canyon location in the centre of Zagreb during 2019.

Daily samples of airborne particles were collected on pre-fired quartz fibre filters from January to June 2019. PM<sub>1</sub> mass concentrations were determined gravimetrically. Samples were analysed for OC, TC, WSOC and EC with thermal/optical transmittance method (TOT) using a EUSAAR\_2 protocol, PAHs with high performance liquid chromatograph (HPLC) with a fluorescence detector and time programmed changes in excitation and emission, levoglucosan with high-performance anion-exchange chromatography with pulsed amperometric detection (HPAEC-PAD) while IBS was determined with the Smokestain reflectometer EEL43M.

Preliminary measurements showed seasonal variations of mass concentrations for carbon species in PM<sub>1</sub>. The higher concentrations were observed during the cold periods of the year, while lower concentrations were recorded during the warmer period. Data analysis indicate that carbon content in particulate matter may be influenced by traffic and traffic jams due to the increased number of traffic lights and vehicles standing with engines running. The reducing particle concentration could be due to vehicles standing more than moving and raised less dust from the road itself. Therefore, a lower temperature during wintertime favours the condensation of organic compounds onto pre-existing particles and higher OC mass concentrations and OC content in PM<sub>1</sub>.

**Acknowledgements.** These measurements were conducted within the internal scientific project “Organic content of PM<sub>1</sub> particle fraction” funded by the Institute for Medical Research and Occupational Health (PI: R. Godec).

## DSC ANALYSIS OF SUBMILLIMETER MICROPLASTICS FROM ADRIATIC SEA

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Microplastics (MP) is a widespread pollutant that originates from plastic debris accumulating in the environment. It mostly ends up in the ocean and other bodies of water. There it may become a vehicle for transport of various substances including toxic trace metals. By definition MP consists of particles that are less than 5 mm in length,<sup>[1]</sup> but a great part is of submillimeter dimensions. While larger MP particles can be easily analyzed by various common techniques, submillimeter ones are difficult to handle and separate, making even qualitative analysis challenging.

MP constituents are mostly semicrystalline polymers<sup>[1]</sup> like polyethylene, (LDPE and HDPE), polypropylene, (PP), poly(ethylene terephthalate), (PET), polystyrene (PS), poly(vinyl chloride), (PVC) and polyamide (PA). Differential scanning calorimetry (DSC) is a fast and relatively simple method of thermal analysis routinely used for polymer identification. If melting and/or crystallization (transformation) temperatures and heats are known quantitative analysis is relatively simple. MP polymer transformation temperatures differ sufficiently so qualitative analysis is relatively straightforward even for mixed polymers. However, even for virgin polymers the heats are not a single value but a range<sup>[2]</sup> that can be further extended by a number of factors. In case of MP environmental degradation changes transformation heats to an unknown extent.

The studied marine MP samples were collected in Stupica Mala bay at Žirje island. The goal of the presented study was to assess how much reliable information can be acquired on submillimeter fraction of MP (250 μm - 1 mm) by DSC. Larger MP particles collected in the same area and treated in the same manner were used as references along with virgin polymers. The peak temperatures in DSC thermograms revealed that the studied MP consists exclusively of polyolefines, (LDPE, HDPE and PP) and their blends. Since the measured samples contained MP particles of various composition some peak overlapping could not be avoided what made full quantification unreliable. Still, semiquantitative results were acceptable.

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## INFLUENCE OF REACTION PARAMETERS ON THE SYNTHESIS OF FATTY ACID PROPYL, ISOAMYL AND OCTYL ESTERS AND THEIR APPLICATION PROPERTIES IN BLENDS WITH MINERAL DIESEL

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Biodiesel is a renewable fuel obtained via transesterification reaction from triglycerides (vegetable oils or animal fats) and alcohol with a catalyst. Therefore, the structure of biodiesel, as well as its properties, depends on the structure of fatty acids and alcohols it derives from.<sup>[1]</sup> Here, fatty acid propyl, isoamyl and octyl esters were synthesized from different feedstocks (sunflower oil, rapeseed oil, animal fat) and corresponding alcohols (propanol, isoamyl alcohol and octanol) with KOH as the catalyst. Furthermore, the reaction parameters that influence the biodiesel conversion (reaction temperature, time, molar ratio of the reactants and weight fraction of the catalyst) were also investigated, analyzed and optimized. The results showed that the biodiesel conversion largely depends on two parameters – molar ratio of the reactants and the weight fraction of the catalyst. In addition, different biodiesel-diesel mixtures were prepared to assess the influence biodiesel has on the application properties of mineral diesel, e.g. density, viscosity, cold filter plugging point and lubricity. For instance, lubricity results showed a reduction in wear scar diameter with the increase of fatty acid propyl esters in these biodiesel-diesel blends. Finally, it was concluded that biodiesel, no matter what its origin was, could serve as an appropriate substitute to mineral diesel, up to 10 vol%.

**Acknowledgements.** This research was conducted within the Project of the Croatian Science Foundation Development of functional biofuels and (bio)additives and characterization of blends with mineral fuels (FunBioFA, UIP-2019-04-5242).

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## RECOVERY OF BIOACTIVE PHENOLIC COMPOUNDS FROM BIOLOGICALLY TREATED GRAPE POMACE BY TEN FILAMENTOUS FUNGI

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Grape pomace (GP), a by-product of the wine industry, was used as a substrate for the production of value-added products through the cultivation of the following filamentous fungi under solid-state fermentation conditions: *Trametes versicolor* TV6 (TV6), *Trametes versicolor* TV8 (TV8), *Trametes versicolor* AG613 (TV AG613), *Trametes gibbosa* (TG), *Phanerochaete chrysosporium* (PC), *Ceriporiopsis subvermispora* (CS), *Pleurotus eryngii* (PLERI), *Ganoderma lucidum* (GL), *Ganoderma resinaceum* (GR) and *Humicola grisea* (HG). Screening of the individual phenolic compound profiles was performed before and after biological treatment during 15 days.

The aim was to investigate the influence of biological treatment on the recovery of hydroxybenzoic acids, hydroxycinnamic acids, flavan-3-ols, flavonols, procyanidins and stilbene from GP. The results showed that from the above groups of phenolic compounds, the following individual phenolic compounds stood out with increasing extractability after biological treatment: ellagic acid (EA), *o*-coumaric acid (*o*-CoA), galocatechin gallate (GCG), kaempferol (KA), procyanidin B1 (PB1) and resveratrol (RES), whose concentrations in the untreated initial sample were 34.65 µg/g<sub>db</sub>, 4.43 µg/g<sub>db</sub>, 291.57 µg/g<sub>db</sub>, 10.22 µg/g<sub>db</sub>, 304.27 µg/g<sub>db</sub> and 46.07 µg/g<sub>db</sub>, respectively. The concentrations of EA and *o*-CoA after biological treatment with CS and TV AG613 were 303.72 µg/g<sub>db</sub> and 33.36 µg/g<sub>db</sub> (*t* = 15 d), while the concentrations of GCG, KA, PB1 and RES were 1064.70 µg/g<sub>db</sub>, 45.25 µg/g<sub>db</sub>, 633.16 µg/g<sub>db</sub> and 69.65 µg/g<sub>db</sub> after biological treatment with PLERI (*t* = 10 d for GCG and KA, *t* = 2 d for PB1, *t* = 5 d for RES).

**Acknowledgements.** This work was supported by the European Regional Development Fund (ERDF) [Grant KK.01.1.1.04.0107].

## SOLVENT TOLERANCE OF HALOHYDRIN DEHALOGENASES

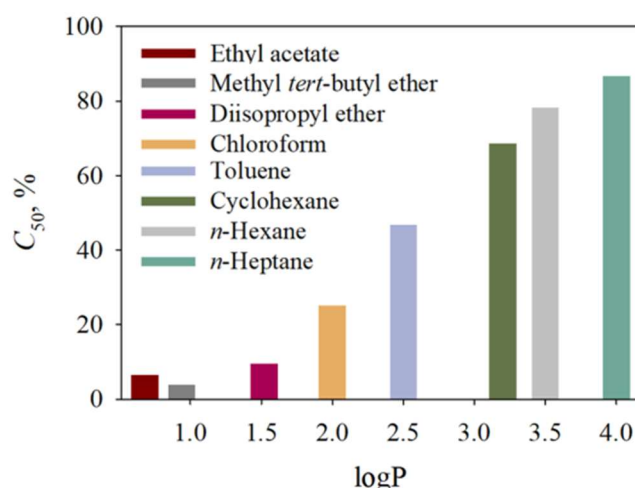
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Halohydrin dehalogenases (HHDHs, EC 4.5.1.-) are compelling candidates for industrial applications due to their selectivity and diversity, but poor substrate solubility and hydrolytic instability in aqueous medium make these biotransformations limited and unfavourable.<sup>[1]</sup> The introduction of organic solvents (OSs) into the reaction medium may minimize these effects, but at the same time decrease enzyme activity and stability. Activity of HheC from *Agrobacterium radiobacter* AD1 was determined in the presence of a wide OSs range. Correlation between OSs logP values and concentrations of half-inactivation ( $C_{50}$ ) was observed for water-immiscible solvents (Figure 1).<sup>[2]</sup> Additionally, activity during incubation with selected OSs was monitored during 72 h for HheC and thermostable variant ISM-4.<sup>[3]</sup> Results obtained reveal that ISM-4 variant is a robust and powerful ally for synthesis in more harsh conditions and a promising candidate for further experimentation in the direction of industrial implementations.



**Figure 1.** Dependence of  $C_{50}$  on logP for water-immiscible solvents.

**Acknowledgements.** This work was financially supported by the Croatian Science Foundation (HrZZ, IP-2018-01-4493).

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## PRODUCTION OF HYDROLYTIC AND LIGNOLYTIC ENZYMES DURING CULTIVATION OF *Trametes versicolor* ON BREWER'S SPENT GRAIN

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Brewer's spent grain (BSG) is a by-product of the brewing industry produced in large quantities worldwide. It plays an important role in the circular bioeconomy based on innovative solutions for waste utilization in the new production cycles.

In this work, BSG was used as a substrate for the production of hydrolytic enzymes (xylanase, invertase,  $\beta$ -glucosidase, cellulase) and lignolytic enzymes (laccase, manganese peroxidase, lignin peroxidase) by fungal solid-state fermentation by *Trametes versicolor*. Fermentation was carried out for 15 days and enzyme activities were measured daily.

*T. versicolor* proved to be a good producer of xylanase (V.A. = 514 U/mL,  $t$  = 15 d), invertase (V.A. = 225 U/mL,  $t$  = 10 d) and  $\beta$ -glucosidase (V.A. = 4.4 U/mL,  $t$  = 12 d), while low activities of cellulase were detected (V.A. = 0.079 FPU/mL,  $t$  = 10 d). The highest activities of laccase (V.A. = 174 U/L) and manganese peroxidase (V.A. = 140 U/L) were detected after the 10<sup>th</sup> day of fermentation, while lignin peroxidase activity was below the measurability limit. Chemical analysis of the BSG after treatment shows its high potential for application in food and feed industry, biogas production or production of value-added products (lactic acid, xylitol, ferulic acid, *p*-coumaric acid, poly-3-hidroxybutyrate, natural red pigment, ascorbic acid, citric acid, volatile fatty acid, cordycepin).

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## CAN MECHANICAL RESPONSES OF FLEXIBLE CRYSTALS BE CONTROLLED AND DELIBERATELY DELIVERED?

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The ability of molecular crystals to respond to external stimuli through a variety of mechanical responses has recently started to attract attention of a wider scientific community due to their potential application in emerging technologies. But to be in a position to implement mechanically responsive materials in smart devices a precise control of their responses is needed, and for that purpose a deep understanding of underlying principles leading to a targeted response is a necessity. Despite a growing number of literature reports, the rationale behind the flexible responses has not yet been quite understood.

With this in mind, we opted for a systematic approach, and focused on crystalline 1-D coordination polymers as those emerged as ideal model systems for exploring structural prerequisites for delivery of a specific mechanical output due to the preorganization of their molecular subunits. In this contribution, a number of families of 1-D coordination polymers displaying a whole spectrum of mechanical responses will be presented and mechanical outputs rationalized against the key structural features. In addition, several custom-made experiments that allowed a distinction between finely separated mechanical events will be demonstrated and complemented with a number of the state-of-the-art techniques for characterization and quantification of flexible responses.<sup>[1–3]</sup>

**Acknowledgements.** This work has been fully supported by the Croatian Science Foundation under project „From form to function: Mechanically flexible crystalline materials with controllable responses“ (IP-2019-04-1242).

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## HOMO- AND HETEROMETALLIC OXALATO-BRIDGED COORDINATION POLYMERS: STRUCTURAL, MAGNETIC AND ELECTRICAL PROPERTIES

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Coordination polymers are extensively studied due to a large variety of topologies and structures giving rise to a plethora of physical and chemical properties, which are often related to their intrinsic porous character and rich host-guest chemistry, making them archetypes of multifunctional molecular materials. The oxalate group,  $C_2O_4^{2-}$ , due to its various coordination modes towards the metal centres as well as its ability to mediate magnetic interactions between paramagnetic metal ions, certainly represents an excellent tailoring tool as evidenced by large number of oxalate-based transition-metal species of different nuclearity, connectivity and dimensionality. Furthermore, these systems are mostly negatively charged and therefore can be combined with functional molecular cations in order to afford complex salts combining cooperative magnetism with a second property of interest.

Proton conductivity is recently regarded as a new functionality of the coordination polymers. The simplest method to introduce proton carriers is to include counterion such as hydronium ( $H_3O^+$ ), ammonium [ $NH_4^+$ ,  $(CH_3)_2NH_2^+$ ,...] or anion ( $SO_4^{2-}$ ), resulting in the charged compounds. The counterions form the H-bonding with the guest water or the framework, representing the continuous H-bond network with efficient proton conduction.

In our research we focus on structural properties of novel homo- and heterometallic oxalate-bridged coordination polymers reflected on their magnetic and electrical behaviours: one-dimensional exhibiting antiferromagnetic spin chains of the host anions  $[Fe^{III}Cl_2(C_2O_4)]_n^{n-}$ , whereas the alkyl ammonium counterions [ $(C_2H_5)(CH_3)_2NH^+$  or  $(C_2H_5)_2(CH_3)NH^+$ ] and the guest molecules give rise to high room-temperature proton conductivity, and two polymorphs containing two-dimensional honeycomb layers  $[Fe^{II}_2(C_2O_4)_3]_n^{2n-}$ , which are bridged by paramagnetic  $[Cu(H_2O)(terpy)]^{2+}$  cations (terpy = 2,2':6',2''-terpyridine), ultimately giving three-dimensional network showing long-range magnetic order and strong dependence of electrical conductivity on the relative humidity revealing proton conduction mechanism.

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## MOLECULAR FERROELECTRICS BASED ON BICYCLIC AMINE CATIONS AND CHLOROCOBALTATE(II) ANIONS

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Solid–solid phase transition compounds with electric, magnetic, and thermally switchable states usually provide an effective strategy for the design of functional materials such as ferroelectric materials, nonlinear-optical switches, and switchable dielectric devices. Among these properties, ferroelectric behaviour is particularly desirable because it is possible to switch rapidly between different states by an external electric field. The most widely used materials for ferroelectric applications are mainly pure inorganic oxides such as BaTiO<sub>3</sub>, LiNbO<sub>3</sub>, and PbZr<sub>1-x</sub>Ti<sub>x</sub>O<sub>3</sub>, due to their superior electric properties, high thermal stability and phase transition temperature. Recent studies have shown that ferroelectric metal-organic molecule based materials are a promising candidates to replace the predominant lead-based ferroelectrics.<sup>[1,2]</sup> The strategy in design of molecular ferroelectrics frequently relies on rotating polar globular ionic molecules, such as 1-azabicyclo[2.2.2]octane (ABCO), as they can be readily reoriented in response to an applied electric field and induce ferroelectric polarization. In attempt to prepare new molecular ferroelectric systems different bicyclic amine cations, including simple derivatives of globular ABCO molecule (O-ABCO = 1-azabicyclo[2.2.2]octan-3-one; COOH-OH-ABCO = 3-hydroxy-1-azabicyclo[2.2.2]octane-3-carboxylic acid) and more complex chiral natural alkaloids with ABCO fragment (Q= quinine; Cnd = cinchonidine) have been used in reactions with chlorocobaltate(II) anions. A series of complexes of the formula ACoCl<sub>3</sub> (A = O-ABCO, COOH-OH-ABCO, Q, Cnd) has been prepared. By using the combined techniques of variable-temperature powder X-ray structural analyses, differential scanning calorimetry, impedance spectroscopy, and polarization-voltage measurements, we revealed exciting structural and electric properties in this series of compounds.

**Acknowledgements.** Financial support from the Croatian Science Foundation (UIP-2019-04-7433) is gratefully acknowledged.

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## MAGNETIC AND ELECTRICAL FEATURES OF 1D AND 3D OXALATE-BRIDGED COORDINATION POLYMERS

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The design and synthesis of new materials with targeted physical properties represents an operative area of research for materials scientists. The combination of magnetic oxalate-based coordination polymers with organic/inorganic functional cations provides a suitable approach for designing hybrid magnetic materials exhibiting multifunctional properties. The oxalate moiety,  $C_2O_4^{2-}$ , acts as a linker between metal centers, with various possibilities of coordination to metal centers yielding open structures with dimensionalities ranging from 0 to 3. A property of oxalate ions that has been of specific interest is their ability to mediate electronic effects between paramagnetic metal ions. Proton conductivity is a new performance of the coordination polymers since they could provide required proton-conducting pathways, mostly by introducing (i) the guest molecules and counterions or acids into the voids, creating complicated hydrogen-bonded networks; (ii) other functional groups which can improve the acidity and hydrophilicity of the organic ligands and thus form an efficient proton transport pathway.

Three novel oxalate-bridged coordination polymers have been synthesized using  $[Cr(C_2O_4)_3]^{3-}$  as building block: 1D homometallic  $\{[Mn(bpy)(C_2O_4)] \cdot 1.5H_2O\}_n$  (**1**) (bpy = 2,2'-bipyridine) and heterodimetallic  $\{[CrCu_3(bpy)_3(CH_3OH)(H_2O)(C_2O_4)_4][Cu(bpy)Cr(C_2O_4)_3] \cdot CH_2Cl_2 \cdot CH_3OH \cdot H_2O\}_n$  (**2**), as well as 3D heterotrimetallic  $\{[CaCr_2Cu_2(phen)_4(C_2O_4)_6] \cdot 4CH_3CN \cdot 2H_2O\}_n$  (**3**) (1,10-phenanthroline), and their structural diversity is reflected on magnetic and electrical properties which have been studied. The Mn-chains of **1** are antiferromagnetic; **2** shows the existence of antiferromagnetic oxalate-bridged  $Cu^{2+}$  dimers, which are independent from the oxalate-bridged  $Cu^{2+}$  and  $Cr^{3+}$  ions interacting ferromagnetically; **3** displays dimeric behavior, with  $Cu^{2+}$  and  $Cr^{3+}$  ions coupled ferromagnetically. Further, polymers **1** and **3** exhibit lower electrical conductivity at RT in comparison to compound **2**.<sup>[1]</sup>

**Acknowledgements.** This work has been supported by the Croatian Science Foundation under the project IP-2019-04-5742.

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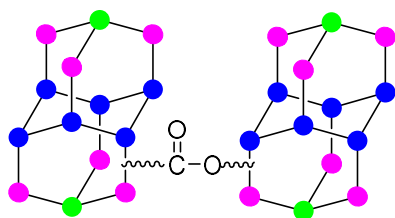
## PREPARATION AND CHARACTERIZATION OF DIAMONDROID ESTERS

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Diamondoids are cage-shaped hydrocarbons that have a spatial arrangement of their carbon atoms resembling the diamond crystal lattice. Diamondoids possess terminal hydrogen atoms suitable for derivatization and they can therefore be efficiently functionalized since their CH and CH<sub>2</sub> cage positions differ markedly in their reactivity. Thus, functionalized diamondoids find application in medicine, material science, nanotechnology, supramolecular chemistry, *etc.* [1,2]



**Figure 1.** Schematic representation of the prepared diamondoid esters

It has also been shown that these bulky, non-polar organic molecules create self-organized structures when deposited on metal surfaces due to London dispersion interactions. [3,4] Herein we present a new series of diamondoid esters that we prepared with a future goal of their application in nanomaterial design. More specifically, the prepared compounds will be deposited on various carrier surfaces to explore the relationship between structure and self-organization. Such monolayers will be analyzed using scanning tunneling microscopy and computational tools.

**Acknowledgements.** This project was supported by the Croatian Science Foundation (UIP-2017-05-9653).

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# SYNTHESIS OF COUMARIN, RHODANINE AND THIAZOLIDINEDIONE DERIVATIVES IN DEEP EUTECTIC SOLVENTS VIA KNOEVENAGEL CONDENSATION

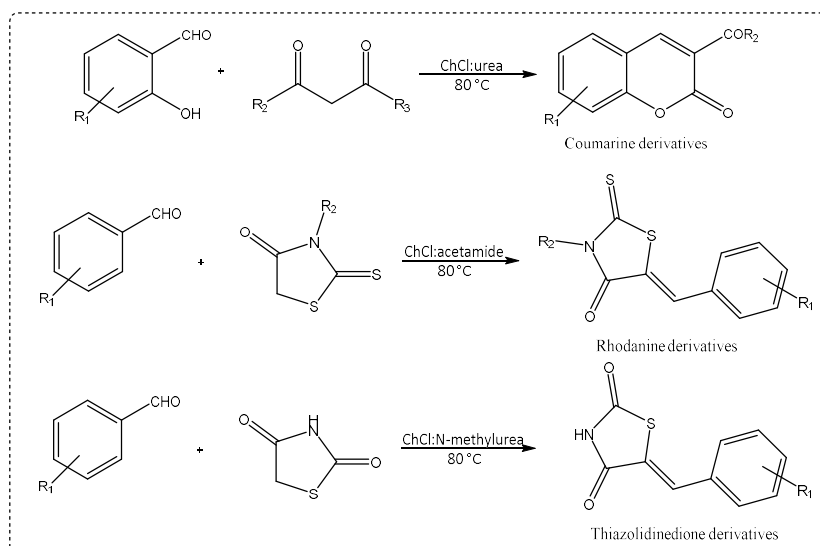
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Environmental pollution has led to the development of numerous methods in organic synthesis that are considered as green and environmental friendly. The application of deep eutectic solvents (DESs) in organic synthesis is considered a green method due to avoidance of organic solvents and toxic catalysts. Recently, DESs, due to their properties (thermal stability, low vapor pressure, biodegradability, nonflammability and component for their preparation are very cheap and easily available), are increasingly replacing conventional solvents. Many compounds are synthesized for the purposes of the pharmaceutical, food and many others industries.

In this work three groups of compounds are synthesized, namely coumarins, rhodanines and thiazolidinediones. All compounds are synthesized in DESs *via* Knoevenagel condensation. Initially, model reaction was performed in 20 various DESs at 80 °C in order to find the best reaction media for each compound group. DESs are based on choline chloride (ChCl) as hydrogen bond acceptor and 20 other components in role of hydrogen bond donors. According to the highest yields obtained, it turned out that ChCl:urea, ChCl:acetamide and ChCl:*N*-methylurea are the best reaction medias for synthesis of coumarine, rhodanine and thiazolidinedione derivatives, respectively. Coumarine, rhodanine and thiazolidinedione derivatives (**Scheme 1**) were successfully synthesized and isolated. Coumarins are obtained in the yields from 6 to 98 %. The yields of synthesized rhodanine and thiazolidinedione derivatives were in the range 51–99 % and 21–90 %, respectively.



**Scheme 1.** Synthesis of coumarin, rhodanine and thiazolidinedione derivatives via Knoevenagel condensation

**Acknowledgements.** This work has been supported in part by Croatian Science Foundation under the project “Green Technologies in Synthesis of Heterocyclic Compounds” (UIP-2017-05-6593).

## 2- AND 2,7-SUBSTITUTED PYRIDINE PYRENES DERIVATIVES AND THEIR DNA/RNA INTERACTIONS

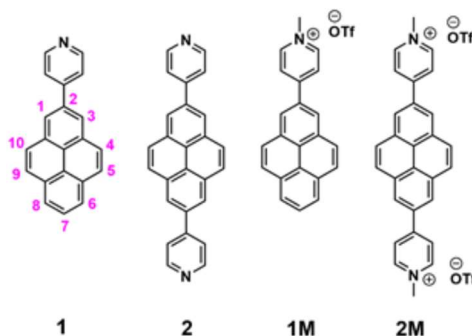
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Pyrene is one of the most frequently studied fluorophore due to its environmental emission sensitivity and tendency to excimers and exciplexes formation.<sup>[1]</sup> 1-, 3-, 6- and 8-substituted pyrenes are already well known, while 2- and 7-substituted ones are less researched while possessing very interesting photophysical properties. Planar structure of pyrene allows “aromatic stacking” with nucleobases, also intercalation between DNA/RNA basepairs<sup>[2]</sup> and possibility of groove binding.<sup>[3]</sup> Our preliminary studies indicated strong interactions of cationic analogues (**1M** and **2M**) with *ct*-DNA,<sup>[4]</sup> mainly based on intercalation. Only the monocation **1M** showed a pronounced fluorescent selectivity between various DNAs and RNAs, in contrast to the less selective **2M**. Neutral, monopyridine analogue **1** binds to DNA upon protonation at *pH* 5 (biorelevant because of tumor tissues acidity), with increase in pyrene excimer emission. Biological studies on the lung tumor cell line (A549) indicated for **1**, **1M**, and **2M** a significant increase in cytotoxicity upon illumination, which was explained by the singlet oxygen generation and the consequent intense action of ROS species. New compounds with an intense fluorescent response and photo-induced bioactivity are promising candidates for new theranostic agents.<sup>[5]</sup>



**Scheme 1.** Structures of studied of 2- and 2,7-substituted pyridine pyrenes.

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## AVENUE TO FACILE MEDIUM-SCALE PRODUCTION OF GRAPHENE QUANTUM DOTS AND GRAPHENE NANOSHEETS

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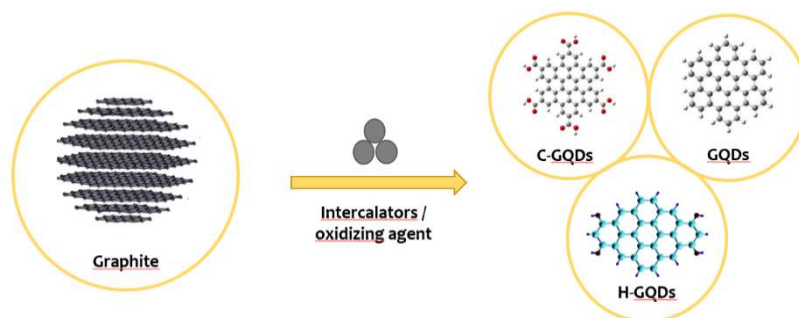
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Graphene quantum dots (GQDs) and graphene nanosheets (GNs) have attracted significant attention for a wide range of applications due to their unique physicochemical properties. Numerous top-down and bottom-up methods for GQDs/GNs have been reported, however they are limited to the small-scale preparation and necessity for the use of harsh solvents, complicated synthetic processes and long reaction time.<sup>[2]</sup> Mechanochemistry is emerging as an environmentally benign alternative for medium and large-scale graphene production, fulfilling principles of Green Chemistry.<sup>[3]</sup> Herein we describe several different routes for a single and few layer GQDs and GNs medium-scale production and its potential application in printable conductive inks.



**Acknowledgements.** This work was supported by the Ministry of Environment and Energy, the Ministry of Science and Education, the Environmental Protection and Energy Efficiency Fund and the Croatian Science Foundation under the project “New Materials for Energy Storage”, in the total amount of 1,962,100 HRK and by the Centre of Excellence for Advanced Materials and Sensing Devices, a project financed by the European Union through the European Regional Development Fund - the Competitiveness and Cohesion Operational Programme (KK.01.1.1.01.0001)

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## AIRBORNE DESERT DUST IN THE NORTHERN ADRIATIC AREA (CROATIA): DIFFERENT SOURCES

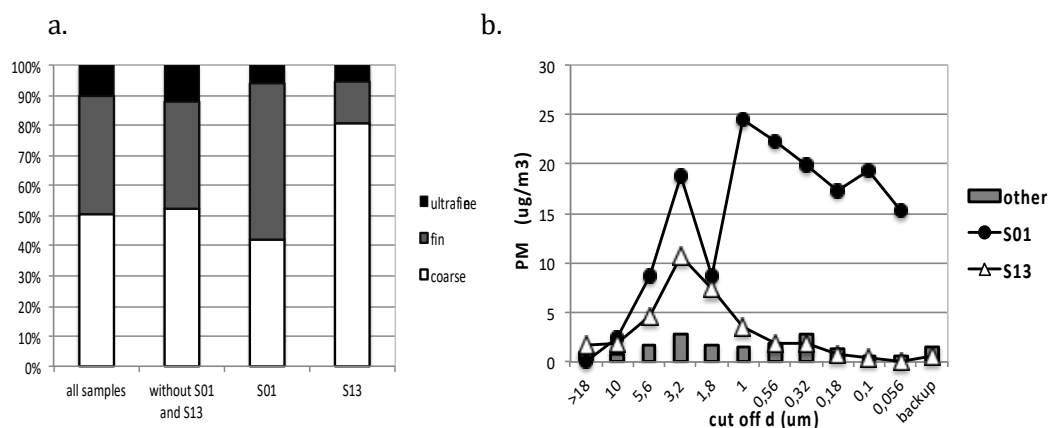
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During the project ECOMOBILITY, whose aim was to estimate the impact of ship traffic on air quality in Rijeka,<sup>[1]</sup> two particular weekly samples were collected, during the first and the thirteen week of sampling, i.e. S01 and S13, respectively. Both samples have similarities regarding species characteristic for desert dust contribution, but HySplit analyses excluded Saharan desert to be the source of the S01 sample. Unlike Saharan dust, this sample had high contribution of fine and ultrafine particles (>50 % and 9.8 %, respectively), as well as secondary inorganic (sulphates, ammonium) and organic (water soluble organic compounds- WSOC) aerosols.



**Figure 1.** a. Contribution of coarse, fine and ultrafine fractions to PM; b. fractional profiles of S01, S13 and other samples. S01 shows big difference in fine and ultrafine fractions

Detailed synoptic situation and HySplit backward trajectories pointed out Syrian desert as the source of this sample. Although the Saharan dust episodes, mostly in precipitation, are well known in the Northern Adriatic area, this is the first time to indicate Syrian desert as a source of airborne particulates. This assumption was confirmed with chemical species characteristic for Syrian desert, i.e. higher content of potassium from K- feldspar and phosphates.

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## APPLICATION OF THE ELECTROCHEMICAL METHOD FOR MONITORING POLYSULFIDES ( $S_x^{2-}$ ) IN MARINE EUXINIC ENVIRONMENT (ROGOZNICA LAKE, CROATIA)

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Rogoznica Lake (RL) is small and shallow naturally eutrophicated marine lake, situated on the eastern Adriatic coast in Croatia (43°32' N, 15° 58' E). The main characteristic of the RL is seasonally stratified water column into the upper oxic and lower anoxic layers.<sup>[1]</sup> Due to intense sulfate reduction, the anoxic layer is rich in dissolved  $HS^-$  (up to 5 mM).<sup>[1]</sup> At the oxic-anoxia boundary, a pinkish colored chemocline develops seasonally, and it is characterized by a dense population of purple phototrophic sulfur bacteria (PSB).<sup>[2]</sup> PSB are known to store sulfur  $S(0)$  intracellularly, which by cell lysis would be released in water, and under euxinic conditions solubilized by  $HS^-$  in nucleophilic polysulfides,  $S_x^{2-}$ .  $S_x^{2-}$  play important role in trace metal, C and S biogeochemical cycles.

Due to large range of reduced sulfur species (RSS:  $S^{2-}$ ,  $HS^-$ ,  $S^0$ ,  $S_x^{2-}$ ,  $RSH$ ) concentrations (nM – mM) in the RL water column, this environment is an ideal site for testing and development of methodology for RSS characterization and speciation.<sup>[1,3,4 and references therein]</sup>

The direct determination of  $S_x^{2-}$  in samples containing other RSS remains a challenge; partly because many of the S species are thermodynamically unstable. In this work, for the first time in natural samples, differential pulse voltammetry (DPV) was used for direct determination of  $S_x^{2-}$  in the euxinic aqueous environment (RL). In this approach an adsorption phenomenon associated with  $S_x^{2-}$  or a product of its cathodic reaction with the Hg electrode created a characteristic current minimum at -1.0 V (vs. Ag/AgCl), which magnitude is proportional to the concentration of  $S(0)$  existing in the form of polysulfidic sulfur.<sup>[5]</sup> In our case, well defined DPV peaks were recorded for model  $K_2S_x$  solution. The same approach, and obtained calibration, demonstrated presence of  $S_x^{2-}$  in the RL water column, below the chemocline (up to 0.1 mM polysulfide S (0)). Additionally, in the studied samples, total RSS concentration was measured by cyclic voltammetry (CV),<sup>[1-4]</sup> while sampled DC polarography (SDC) at the Hg electrode revealed a ratio between anodic and cathodic currents, i.e. the ratio between sulfide and  $S(0)$  presence in the molecule of  $S_x^{2-}$ .<sup>[2,4]</sup>

Concentrations of  $S_x^{2-}$ , as well as total RSS, varied seasonally depending on redox conditions in the lake. However, position of oxic-anoxia boundary (chemocline position), light intensity, and  $HS^-$  concentration greatly influence on  $S_x^{2-}$  distribution and concentration within the RL water column.

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## REVISING SOLUTE ADSORPTION MODELS IN THE CASE OF LOOSE TiO<sub>2</sub> NANOTUBES SURFACES

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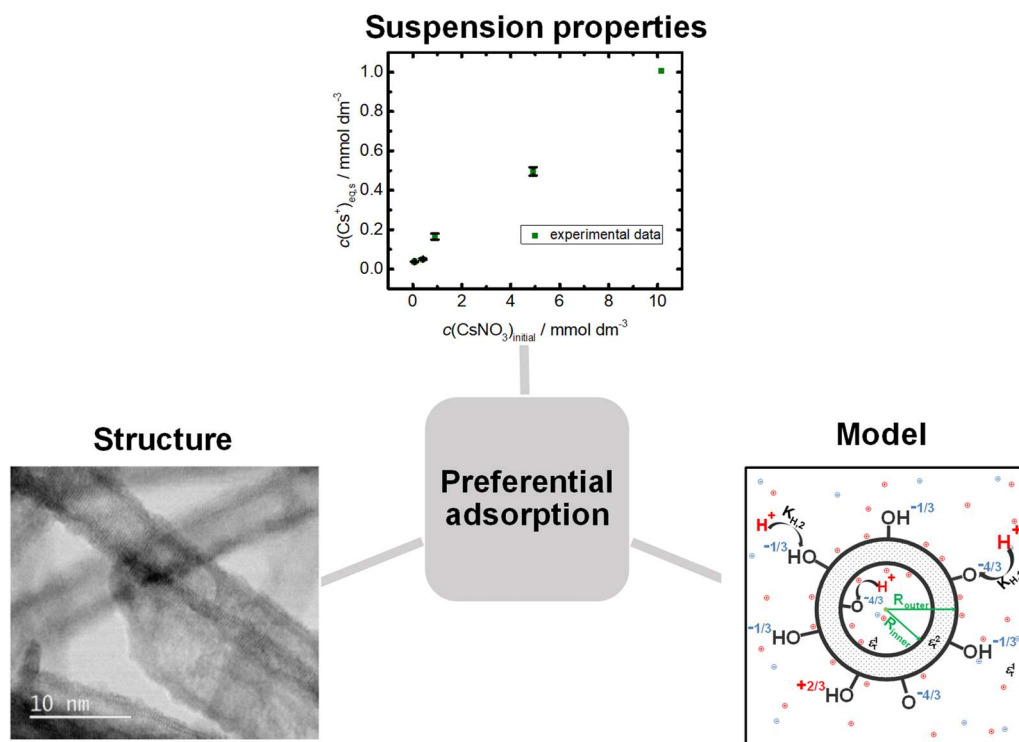
Due to their high specific surface and pH-tunability, loose TiO<sub>2</sub> nanotubes (NTs) are emphasized as suitable candidates for applications in the decontamination or catalysis in thousands of papers per year.<sup>[1–2]</sup> Nevertheless, the general mechanism of the solute adsorption, that underlies the efficiency of these applications, in most cases of loose nanotubular structures is not rationalized. Usual macroscopic models are applied that provide no real insight into processes at nanoscale. It is not obvious on which exposed surface the adsorption process occurs, and what is the extent of coupling of the effect of both surfaces. As a result the relative preferential affinity of the solute between the inner or the outer NTs surfaces exposed to the liquid medium requires further study and adsorption models need revising.<sup>[3]</sup>

We address this question by investigating the case of the preferential adsorption of monovalent Cs<sup>+</sup> cations onto loose TiO<sub>2</sub> NTs in aqueous solutions, at the range of pH and bulk CsNO<sub>3</sub> concentration. To probe the adsorption/charge relation, we conducted a complementary set of experimental techniques that probe the overall adsorption efficiency, equilibrium properties of the NTs suspension, and the stereological estimation of Cs<sup>+</sup> concentration in post-adsorption dried solid sample. Furthermore, we used the classical density functional theory, to calculate the difference in adsorption between inner and outer surfaces, as well as the charge of NTs for various system compositions.<sup>[3]</sup> Effects of specific Cs<sup>+</sup> binding, as well as the effect of the polydispersity of NTs radii were accounted for. We used the model that can interpret potentiometric titrations of the suspension, but also to rationalize Cs<sup>+</sup> adsorption, and compare to experimentally derived efficiency.

Since each of the aforementioned techniques probes a distinct thermodynamic state of the system, the individually obtained ‘adsorption’ properties seldom match quantitatively, and only the trend can be established. In this integrated approach, we tried to explain the origin of quantitative differences between different techniques.

**Keywords:** nanotubes, adsorption, modelling, surface, preferential





**Figure 1.** Overview of the approach used to probe the difference in Cs<sup>+</sup> binding between inner and outer TiO<sub>2</sub> nanotubes surfaces.

**Acknowledgements:** M. Š. acknowledges Slovenia Research agency for support through project CEA NC-0020.

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## INVESTIGATION OF ALLERGENIC METALS ON FASHION ACCESSORIES AND DECORATIVE METALLIZED YARNS

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The majority of everyday fashion accessories contain metals, although some of them (Ni, Cr, Co) may cause allergies. Due to the corrosion process which occurs in the sweat, metal ions can cause allergic reactions during direct and prolonged contact with the skin. Nickel, originating from different sources such as metalized yarns, jewelry or buttons, represents the most common cause of contact allergic dermatitis.<sup>[1]</sup> For example, 20 % of female population and about 6 % of male population was allergic to nickel,<sup>[2]</sup> but after adopting new regulative during the last 10 years, this number reduced to 15-17% of women, and 1-3% of man population. Some researchers presume that the trigger for such discrepancies between the genders is the nickel jewelry which induces the contact allergic dermatitis in women population.

Therefore, the aim of this research was to estimate the possible risk of allergies resulting from the direct skin exposure to fashion accessories. Different items (buttons, metalized yarns and coins) were characterized by chromatographic, spectroscopic and microscopic methods.<sup>[3–5]</sup> Combination of ICP-OES, SEM-EDX, TLC, and FTIR provided information on samples constitution, morphology, topology and chemical composition. In addition, the samples were tested for metal leaching: in order to obtain information on the amounts of metals released by their daily usage, extraction experiments of metalized items were performed applying an artificial acidic sweat solution at 30°C during different time extraction periods. After the extraction, the mass of the metals released (Cu, Fe, Ni and Zn) were quantified by inductively coupled plasma - optical emission spectrometry (ICP-OES). The mass rate of Ni extracted per area much exceeded the permissible values according to the European Norm (from 50 to 110 times). This indicates that nickel containing fashion accessories may represent a serious health hazard, especially to sensitive people and should be used with a special attention.

**Acknowledgements.** The presentation compares recent results to previous research and collaboration with many great professors and colleagues,<sup>[1–5]</sup> for which the author is grateful; especially to prof. Ilse Steffan and her team from the Institute of Analytical Chemistry, University of Vienna, Austria, and prof. Lidija Ćurković and her colleagues from the Faculty of mechanical engineering and naval architecture, University of Zagreb. This work was financially partially supported by the Croatian Science Foundation, project IP-2019-04-1381 under the title „Antibacterial coating for biodegradable medicine materials ABBAMEDICA“.

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## MODEL-FREE SCALING OF CONDUCTIVITY SPECTRA: INSIGHT INTO ELECTRICAL TRANSPORT IN IRON PHOSPHATE-BASED GLASSES

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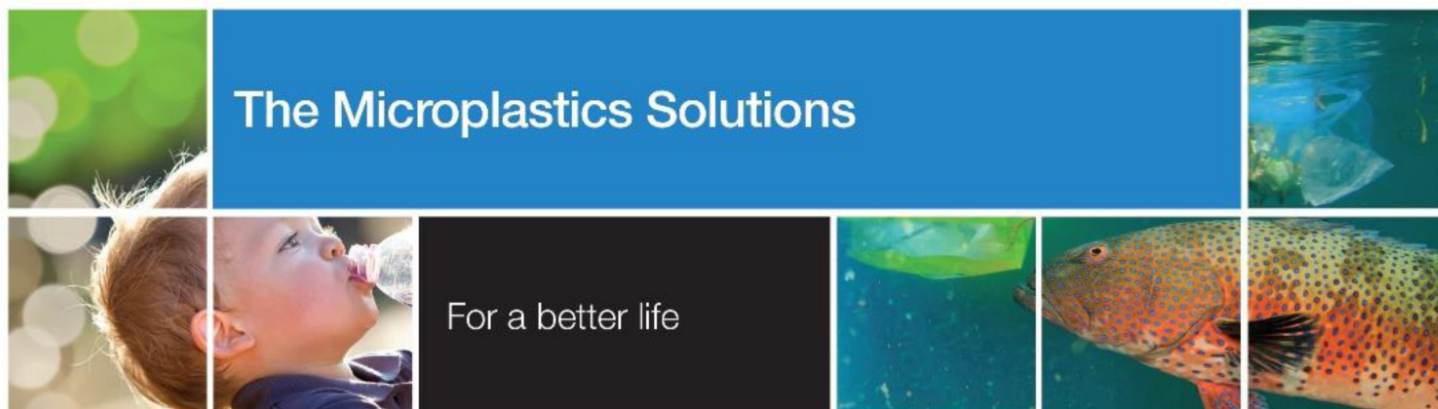
Iron phosphate-based glasses (IPG) belong to a family of electronically conducting amorphous materials. A small polaron hopping conduction mechanism is observed owing to the presence of transition metal ions, e.g. iron, in more than one valence state. These materials are of great scientific interest due to their potential application as electrode materials for batteries, electronic circuit elements, electrical switching devices, etc. Here, we report on the impact of the additional glass-forming oxide on the polaronic transport in binary IPG glasses. The electrical transport properties and correlation to glass structure in  $B_2O_3$ – $Fe_2O_3$ – $P_2O_5$  system are studied by Solid-State Impedance Spectroscopy (SSIS) in a wide frequency and temperature range.<sup>[1]</sup>

Electrical transport in these glasses shows a strong dependence on the polaron number density determined by the overall  $Fe_2O_3$  content and the fraction of  $Fe^{2+}$  ions. While the analysis of DC conductivity and its temperature dependence gives important information on the long-range transport of charge carriers in glasses, features of the frequency-dependent conductivity provide insights into the processes of their localized motions. The DC conductivity trend is found to be unimpaired to the amount of gradually added second glass-former,  $B_2O_3$ . However, a detailed study of the scaling properties of the conductivity spectra reveals that structural changes induced by its addition up to 17.7 mol %, notably impact frequency-dependent conductivity. In this respect, we apply two relatively simple yet very insightful scaling procedures, namely Summerfield and Sidebottom scaling. Obtained results provide new valuable information on the influence of  $B_2O_3$ , as a second glass-former, and resulting mixed glass network, on the formation of polarons and their dynamics.

**Acknowledgements.** This work is supported by the Croatian Science Foundation, POLAR-ION-GLASS project IP-2018–01–5425.

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## ELECTROCHEMICAL BEHAVIOR OF NATURAL REDUCERS ON CARBON NANOMATERIALS: A CONTRIBUTION TO THE OPTIMIZATION OF ELECTROANALYTICAL METHODS

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Nowadays, the determination of polyphenols has become an important target due to their biological activities and the role of their importance for food and beverages quality.<sup>[1]</sup> As electrochemically active compounds, the behaviour of polyphenols can be easily electrochemically monitored.<sup>[2,3]</sup> This can be useful in the evaluation of the mechanism involved in the stability, their reducing activity and other aspects of their redox behaviour.

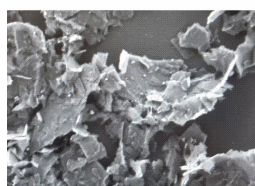
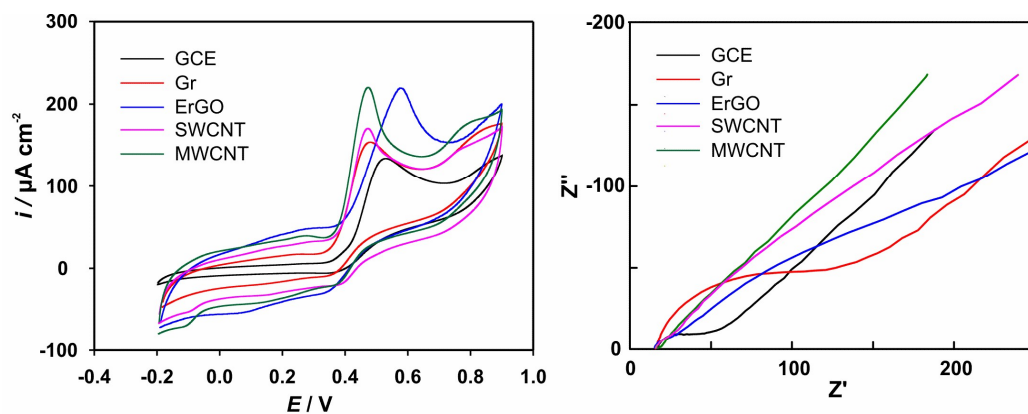
Many articles, related to polyphenols electrochemical behaviour on carbon nanomaterials modified electrodes,<sup>[4,5]</sup> can be found, sometimes controversial results have been published. This is not surprising since polyphenols redox behaviour depends not only on the chemical structure of polyphenols but also on factors such as kind of used carbon nanomaterials, mechanism of the reaction, pH, support solution, time, presence of oxygen, the concentration of polyphenols, etc.

Therefore, it is necessary to consolidate information of the electrochemical behaviour of polyphenols depending on various factors. As a part of the large study of the electrochemical behaviour of polyphenols (non-flavanoids and flavanoids), here we present results of the investigation related to the electrochemical behaviour of gallic acid and quercetine onto glassy carbon electrode (GCE), modified with different carbon nanomaterials (CNM) such as graphene, electrochemically reduced graphene oxide, single-walled carbon nanotubes and multi-walled carbon nanotubes.

Results obtained by cyclic voltammetry and electrochemical impedance spectroscopy revealed significant differences in electrochemical kinetic parameters depending on used CNM and its morphology (characterization was performed by scanning electronic microscopy) as well as used support solutions and their composition. Also, parameters obtained with various CNM, at different pH, can be promising for selectivity improvement, as well as in establishing a method of determination.

Obtained results offer valuable information useful for the investigators focused on the development of electrochemical sensors for determination of the polyphenols, which can include further modification of the electrodes with various organic or inorganic mediators, various composite materials, etc.

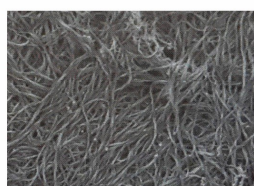




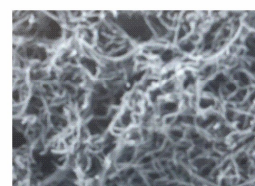
graphene (Gr)



reduced graphene oxide (ErGO)



single-walled carbon nanotubes (SWCNT)



multi-walled carbon nanotubes (MWCNT)

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## TRANSITION METAL COORDINATION POLYMERS: SYNTHESIS, SPECTROSCOPIC AND ELECTROCHEMICAL STUDIES

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Metal-organic frameworks (MOFs) attract increasing interest due to their intriguing structural characteristics as well as desired performances, including sensor technology, luminescence, ion exchange, catalytic properties, etc. Carefully selected organic ligands with certain features, such as multidentate and rigid ligands with multi-proton acceptor or donor sites, might be utilized as versatile linkers, being useful in constructing and tailoring coordination polymers with desirable properties. Metal coordination polymers of suitable organic ligands potentially allow the variation and control of redox properties.

Herein, we present the synthesis, IR spectra and electrochemical characterization of metal coordination polymers with hydroxynicotinic acids.

**Keywords:** Transition metal, Coordination polymers, Hydroxynicotinic acids, Spectral properties, Electrochemical behavior

**Acknowledgments.** Izradu ovog rada potpomogla je Zaklada Hrvatske akademije znanosti i umjetnosti.



## THE INFLUENCE OF THE BLACK MUSTARD SAMPLE PREPARATION METHOD ON CHEMICAL COMPOSITION, ANTIPROLIFERATIVE AND PROAPOPTOTIC EFFECTS

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Black mustard (*Brassica nigra* L.) is a plant that belongs to *Brassicaceae* family and contains glucosinolates which in contact with the enzyme myrosinase usually decompose into isothiocyanates which give mustard its flavour.<sup>[1]</sup> The most researched degradation products of glucosinolates are isothiocyanates, which are generally known to be the most biologically active,<sup>[2]</sup> but in the presence of epithiospecifier protein (ESP), epithionitriles and nitriles may be formed.<sup>[3,4]</sup> Isothiocyanates and their metabolites help reduce the risk of developing various types of cancer such as lung, liver, esophagus, stomach, small and large intestine.<sup>[5]</sup> Degradation products of glucosinolates may exert their antitumor properties via few different mechanisms that include the immediate detoxification of carcinogens such as the prevention of the formation of carcinogen-induced DNA-adducts.<sup>[6]</sup>

The aim of this study was: to determine the influence of the sample preparation method on the chemical composition of black mustard seeds volatile isolates obtained by microwave-assisted distillation (MAD), microwave hydrodiffusion and gravity (MHG), and Clevenger hydrodistillation.

Also, the aim of the study was to determine the antiproliferative activity of volatile isolates against two tumor cell lines (breast cancer cell line MDA-MB-231, and bladder cancer cell line TCCSUP) by MTT assay and its proapoptotic effects determined by flow cytometry.

GC-MS analysis showed that but-3-enyl isothiocyanate is a main component in *Brassica nigra* L. after Clevenger hydrodistillation (80.58%). After MAD and MHG, the main component in that two isolates is 4,5-epithio-pentanenitrile (50.70%, and 59.93%). After 72 h, MHG volatile isolate from *B. nigra* showed high antiproliferative activity (9,06 µg/mL) against human breast cancer cell line MDA-MB-231. The best antiproliferative activity of *B. nigra* MHG volatile isolate against human bladder cancer cell line TCCSUP was after 48 h and 72 h (58.95 and 27.21 µg/mL).

**Acknowledgments.** This work has been fully supported by the Croatian Science Foundation within the project "Plants as a source of bioactive sulfur compounds and their ability to hyperaccumulate metals", HRZZ-IP-2016-06-1316.

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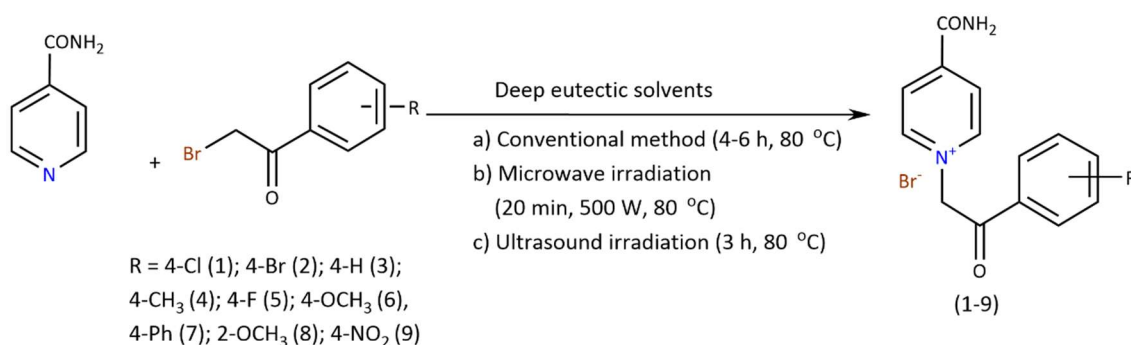
## AN ECO-FRIENDLY PREPARATIONS OF IZONICOTINAMIDE QUATERNARY SALTS IN DEEP EUTECTIC SOLVENTS

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Deep eutectic solvents (DES) are liquids composed of two or three safe, inexpensive components, often interconnected by noncovalent hydrogen bonds which produce eutectic mixture whose melting point is lower than that of each component. No data in literature have been found on the quaternization reaction in DES. The use of DES have several advantages: they are environmentally benign and biodegradable, easy for purification and simple for preparation. An environmentally sustainable method for preparing quaternary salts of izonicotinamide and substituted 2-bromoacetophenones was demonstrated here using choline chloride-based DES. The quaternization reaction was carried out by three synthetic approaches: conventional method, microwave and ultrasonic irradiation. Results showed that the high reaction yields, the easy environment-friendly solvents and short reaction times are in agreement with principles of green chemistry, making microwave method as a new approach for preparation of quaternary salts in DES.



**Figure 1.** The quaternization reaction of izonicotinamide with substituted 2-bromoacetophenones in deep eutectic solvents by three different methods

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## EVALUATION OF THERMODYNAMIC PARAMETERS BETWEEN ANTIDEPRESSANT IMIPRAMINE AND HUMAN $\alpha$ 1-ACID GLYCOPROTEIN BY ISOTHERMAL TITRATION CALORIMETRY

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Binding of drugs to proteins influence their pharmacokinetic and pharmacodynamics action. In the blood, the drug is distributed in the body in the free form or bound to plasma protein.  $\alpha$ 1-acid glycoprotein (AGP, also known as orosomucoid) is an important plasma protein involved in the binding and transport of many drugs, particularly basic one.<sup>[1]</sup> This research uses sensitive and modern isothermal titration calorimetry (ITC) technique for characterization of microscopic thermodynamic parameters that trigger the binding of drugs to AGP.<sup>[2]</sup> ITC is a convenient and widely used experimental technique to directly measure released or absorbed heat during association processes such as protein-drug interaction and to quantitatively measure the binding affinity. The binding of basic drug imipramine displayed an exothermically driven binding interaction with AGP. Binding energy were guided by a combination of favorable (negative) enthalpy ( $\Delta_r H = -11.2$  kcal/mol) and favorable (positive) entropy ( $\Delta_r S = 4.62$  kcal/molK) contribution to the Gibbs free energy ( $\Delta_r G = -6.57$  kcal/mol) with dissociation constant ( $K_D = 23.7$   $\mu$ M). Enthalpy change is an important step in understanding the driving forces that characterize the protein-drug interaction information very much needed in the drug discovery process.

**Acknowledgments.** This work was fully supported by the Croatian Science Foundation under the project number IP-2016-06-3672.

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## DETERMINATION OF PSEUDOESTROGENIC COMPOUNDS IN THERMOCHROMIC PRINTING INK

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The use of thermochromic ink is growing daily, but they contain pseudoestrogenic compounds that have a harmful effect on the human health. Common pseudoestrogenic compounds found in thermochromic ink are bisphenol A and benzophenone. Bisphenol A has a role of the colour developer and benzophenone is used as a photo-initiator in the UV-curing ink. Since they are registered as harmful and their use is limited, manufacturers are using new compounds whose use is not limited yet but also have a pseudoestrogenic effect. Therefore, the main goal of this study is to develop and validate an appropriate chromatographic method for monitoring 4,4'-(4-methylpentane-2,2-diyl)diphenol in various ink samples.<sup>[1,2]</sup>

Validated parameters were specificity, selectivity, linearity, precision, accuracy, quantitation limit and detection limit. Following validation, eleven samples of thermochromic ink were analyzed and 4,4'-(4-methylpentane-2,2-diyl)diphenol was found in nine of them. The mass fractions of 4,4'-(4-methylpentane-2,2-diyl)diphenol in the samples ranged from 0.12 % to 0.90 %. These results indicate that thermochromic ink that do not contain bisphenol A as a developer can contain a significant amount of bisphenol A related pseudoestrogenic compound. So, it could be concluded that thermochromic ink without bisphenol A may also present a health risk in the use of thermochromic ink for human but also for environment.

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## POTENTIOMETRIC RESPONSE CHARACTERISTICS OF CARBON PASTE ELECTRODE FOR MAPROTILINE DETERMINATION

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In this paper, for the first time, carbon paste electrodes (CPE) were prepared for potentiometric quantitative determination of maprotiline, a second generation antidepressant.<sup>[1]</sup> A series of pastes of different composition and ratios of components were prepared. Dibutyl phthalate, dioctyl phthalate, 2-nitrophenyl octyl ether, bis(2-ethylhexyl) adipate and tris(2-ethylhexyl) phosphate were used as binders, whereas sodium tetraphenylborate, phosphotungstic acid, phosphomolybdic acid and ammonium reineckate were used as precipitating reagents to synthesize the ion association complexes (IAC).

A 2.0 mm diameter Teflon holder made in laboratory,<sup>[2]</sup> significantly reduced the consumption of paste components, since a lot of measurements could have been performed with 150 mg of paste, which was enough to examine all analytical parameters. Response characteristics of all electrodes were tested in 0.015 M acetate buffer solution (pH = 4.5) at room conditions.

Unmodified CPEs showed no significant linearity, while some of CPEs with incorporated IAC and salt exhibited near-Nernstian slope over the linear dynamic range of  $1.0 \times 10^{-6}$  –  $1.0 \times 10^{-2}$  mol L<sup>-1</sup> of maprotiline concentration.

Some of the prepared CPEs showed better preliminary response characteristics than the response characteristics of PVC electrodes previously reported.<sup>[3]</sup>

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## EVALUATION OF PECTIN BIOFILMS WITH INCORPORATED PHENOLIC EXTRACTS OF “KAROMA” SPENT ESPRESSO COFFEE GROUNDS

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Coffee is one of the most consumed beverages in the world. Due to huge coffee production and consumption, the large amounts of by-products are generated. For instance, the spent coffee grounds (SCGs) are particularly fine, solid residues gained during the preparation of coffee brew from roasted and grounded coffee with hot water or steam. After brew consumptions, the remained residues are usually discarded into the environment. However, the SCG is the bio-substrate of the high biotechnological and food values due to ample chemical composition based on cellulose, hemicellulose, polysaccharides, proteins, polyphenols, and minerals.

Considering the facts that SCG presented inexpensive, un-utilized biomass with ample chemical composition, in this study is showed the concept of SCG exploitation for phenols extraction with its subsequent incorporation into pectin base biofilms. The phenols were extracted from SCG by microwave-assisted extraction at  $t = 5$  min,  $T = 50$  °C and  $\varphi$  (ethanol) = 50 %. The obtained 50 % phenolic extracts were utilized for preparation of 5, 10 and 20 % (v/v) water extracts in which the 1 and 2 % pectin powder was dissolved. After addition of glycerol (50 and 70 %, v/v) and calcium chloride (2 %, v/v) the biofilms produced by casting method were evaluated in terms of their physical and mechanical properties.

As results revealed the SCG extracts are successfully used for preparation of functional biofilms, and which combination of pectin, glycerol and phenolic extracts will be further use depends mostly on biofilms implementation. For instance, the biofilms with SCR extracts are darker than control, and consequently influenced on their appearance and acceptability by the consumer. The best mechanical properties in terms of tensile strength, elongation at the break, and Young modulus showed the biofilms prepared by 1 % pectin, 50 % glycerol and 2 % CaCl<sub>2</sub> with addition of 10 and 20 % of phenolic extracts.



## MICROWAVE-ASSISTED EXTRACTION OF POLYPHENOLS FROM COFFEE (GREEN AND ROASTED) AND ITS BY-PRODUCTS (SILVER SKIN AND SPENT COFFEE GROUND)

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Coffee is the most important food commodity worldwide. Its economic importance is mainly due to an infusion prepared from the roasted and grounded coffee beans. Concerning the large production of coffee, as well as coffee consumption, the significant amounts of by-products are generated. In many cases the wasted fractions of coffees, such as silver skin (SS) and spent coffee ground (SCG) are not properly handled, and thus presented the highly pollutant biomasses for the environment. On the other hand, their ample chemical composition made both substrates as valuable resources for isolation of various compounds. In that connection, the present work shows the possibility of exploiting them as low-cost sources for polyphenols isolation.

The SS and SCG obtained by roasting of green coffee, and by the treatment of roasted and grounded coffee powder with hot water to obtain brew were extracted by microwave (MAE), at  $T = 50$  and  $70$  °C,  $t = 5$  and  $15$  min, and  $\varphi$  (ethanol) =  $50$  and  $70$  %. With the aim to evaluate the recovery of polyphenols from SS and SCG, the extraction was also done on green and roasted coffees.

The results obtained by UV/Vis spectrophotometry show that mass fractions of phenols decreased from roasted ( $57.79$ - $70.98$  mg/g) and green ( $48.48$ - $56.64$  mg/g) coffees to SCG ( $8.63$ - $12.95$  mg/kg) and SS ( $7.23$ - $9.32$  mg/g) residues, depending on used extraction parameters. The extraction done by refluxing for 2 h revealed the similar trend as MAE, i.e. espresso coffee ( $69.1$ - $71.1$  mg/g) > green coffee ( $46.8$ - $47.5$  mg/g) > SS ( $11.7$ - $13.1$  mg/g) > SCG ( $10.8$ - $12.1$  mg/g). Although the lower quantities of phenols were found in SS and SCG in comparison with espresso and green coffees, these by-products are still valuable, considering the facts that they are natural, inexpensive sources for their isolation. In addition, the results showed that not only the time, but also the temperature and solvent influence on phenols yields from these biomasses. For instance, the  $50$  °C and  $50$  % ethanol, and  $70$  °C and  $70$  % ethanol provided the best recovery of phenols from them. Thus, using mentioned parameters with minimal expenditure of time (5 min) it is possible to provides numerous extractions from SS and SCG by-products.

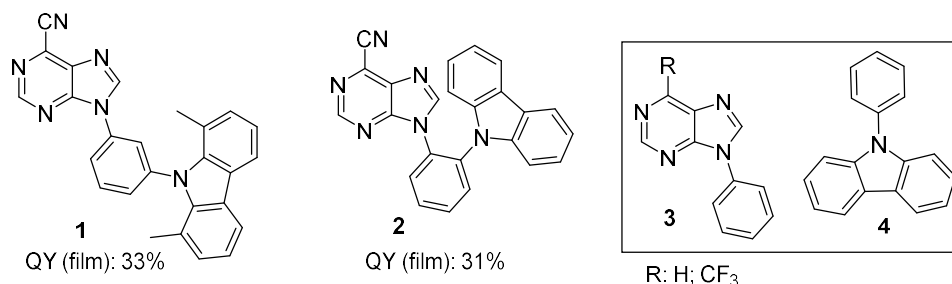
## SYNTHESIS AND PHOTOPHYSICAL PROPERTIES OF PURINE-CARBAZOLE DONOR ACCEPTOR SYSTEMS

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Earlier we reported the synthesis and photophysical properties of fluorescent 1,2,3-triazole-purine conjugates<sup>[1]</sup> and 2-azolympurine derivatives.<sup>[2]</sup> This work was followed up by a synthesis and an investigation of purine derivatives containing carbazole moiety, later to study their potential use in OLEDs.<sup>[3]</sup> We have modified purine structures to achieve optimal emission properties. The highest performing structure **1** is modified with methyl groups, which introduce steric hinderance and reduce rotation. An alternative structure **2** is prepared with purine and carbazole moieties connected through an *o*-substituted benzene ring, which changes torsion angles between cycles as well as reduces possible rotation. Different 6-substituted purines **3** are prepared for using in mixture with **4** as exciplex systems, which utilize disconnected donor and acceptor molecules for emission.



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## DABCO-BASED IONIC LIQUIDS AS ACTIVE LATENT CURING AGENTS IN THERMOSETS DEVELOPED WITH CONVENTIONAL AND BIOBASED EPOXY RESINS

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Epoxy-based composite materials make up a vast group of the entire composite industry. The multitude of applications of these materials has led to the development of many technologies of their production and the variety of raw materials: resins themselves, hardeners and, finally, structural frameworks - fabrics, fillings and others. On the other hand, there are issues related to the raw material production process itself. They are often technologies that generate harmful by-products or use toxic substrates. There are numerous reports on the production of new fully natural epoxy resins or other raw materials.<sup>[1,2]</sup>

One of the most interesting alternatives to classic curing initiators in epoxy compositions may be ionic liquids (ILs) - especially in the case of thermosets. Ionic liquids, as compounds consists of a cation and an anion, which mostly remain liquid at room temperature, can initiate the epoxide polymerization process both by cationic and anionic pathway.<sup>[3,4]</sup> Moreover, for the curing process to start, it is necessary to supply energy in the form of heat, which will initiate the decomposition of the ionic liquid into the active curing species. Curing process could be designed and adjusted into various technologies of composite production.

This study presents the synthesis of a large group of ionic liquids based on the DABCO (1,4 diazabicyclo[2.2.2]octane) cation, which were used to prepare prototype epoxy systems based on classic and bio epoxy resins. Both materials were characterized and compared. Curing process itself was analyzed using differential scanning calorimetry (DSC). Moreover, attempts have been made to produce fibrous composites based on natural fabrics with the best tested epoxy combinations.

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## FROM AMINYL RADICALS TO CATIONS; MECHANISM SWITCH IN HOFMANN-LÖFFLER-FREYTAG-LIKE REACTIONS

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C-H functionalization methods are often used in late-stage functionalization synthesis in the pharmaceutical industry. Inside the “reaction toolbox of C-H functionalization” are amination reactions that combine remote C(sp<sup>3</sup>)-H bond activation at otherwise unfunctionalized positions with C-N bond formation in a synthetically attractive fashion.<sup>[1]</sup> A traditional reaction in this class is the Hofmann-Löffler-Freytag (HLF) reaction.<sup>[2]</sup> This reaction utilizes N-centered radicals, generated via heat or light from N-halogen homolytical bond breaking. After intramolecular 1,5-HAT step, a  $\delta$ -C-centered radical is formed, which is then subsequently functionalized. In this process stereo-information is not conserved. Recently, an ionic mechanism is proposed involving nitrenium cations.<sup>[3]</sup> Heterolytically cleaved N-halogen bond produces nitrenium cation, that rearranges to carbocation with concerted nucleophilic attack that prevents loss of stereo-information. Substrates carrying a chiral benzylic position and a halogen activated nitrogen atom were transformed with full retention of configuration, which makes a radical mechanism less likely. Also, unlike many radical reactions, this transformation is promoted neither by light nor heat. In this work comparison between relative stabilities of radical species involved in typical HLF type of reactions, with relative stabilities of cationic species involved in this alternative ionic pathway will be discussed. Differentiation between pathways may suggest conditions needed to steer reactions through mechanisms that may (or may not) retain stereochemical information.

**Acknowledgments.** This work was supported by the Croatian Science Foundation through installation grant “LIGHT-N-RING” UIP 2020-02-4857.

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## ACACETIN, APIGENIN, CHRYSIN AND PINOCEMBRIN CAUSE IRREVERSIBLE CYP3A4 INHIBITION BY HEME DESTRUCTION

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Flavonoids are ubiquitous plant compounds consumed in everyday diet through fruits and vegetables. Cytochrome P450 enzymes are hemoproteins, involved in the metabolism of drugs and lipophilic xenobiotics. Most registered active pharmaceutical ingredients are substrates of CYP3A4 enzyme. It has previously been reported that acacetin, apigenin, chrysin and pinocembrin irreversibly inhibit CYP3A4 enzyme. The objective of this study was to determine if inhibition is achieved through heme destruction. For this purpose, hemochromopyridine test was used.

Hemochromopyridine test is based on the formation of heme iron complex with pyridine. Complex is yellow colored and can be measured spectrophotometrically. Heme concentration was measured after incubation of flavonoids with CYP3A4 baculosomes containing NADP reductase and cytochrome b5. Reaction was initiated with the addition of coenzyme NADPH. Heme concentration was determined after 30 minutes of incubation and was expressed as percentage to the control that did not contain an inhibitor.

The residual heme concentration after incubation with acacetin, apigenin, chrysin, and pinocembrin was 49%, 45%, 5%, 25%, respectively. Heme destruction can also be caused by the reactive oxygen species that are generated in the nonproductive cytochrome P450 cycle. To eliminate this possibility flavonoids incubations were repeated with the addition of superoxide dismutase and catalase. No significant change was observed in residual heme concentration when compared to incubation without superoxide dismutase and catalase.

It can be concluded that inhibition of cytochrome P450 by the analyzed flavonoids is mediated by heme destruction. Further analysis is needed to determine possible heme adducts and reactive flavonoid intermediaries responsible for the destruction.

## SYNTHESIS AND ANTITUMOR ACTIVITY OF NOVEL 7-CHLORO-4-AMINOQUINOLINE-BENZIMIDAZOLES

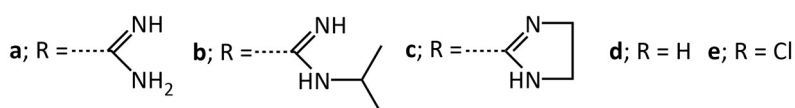
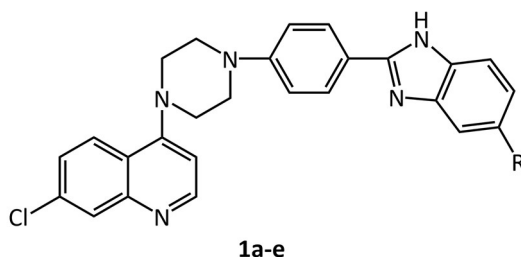
Luka Krstulović,<sup>a,\*</sup> Marijana Jukić,<sup>b</sup> Teuta Opačak-Bernardi,<sup>b</sup> Miroslav Bajić,<sup>a</sup>  
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In our ongoing efforts<sup>[1]</sup> to design novel antitumor hybrid molecules, novel derivatives of 7-chloro-4-aminoquinoline-benzimidazole have been synthesized, and their antiproliferative activity against tumor cell lines was investigated. All tested compounds showed antiproliferative effects against leukemia and lymphoma cell lines. Strongest activity was observed for compound **1d** which also showed no cytotoxic effect on normal cell lines.



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## TRIAZOLYPYRENE-DERIVED PSEUDOPEPTIDES: FLUORESCENCE PROPERTIES, CELL-IMAGING AND ANTIPROLIFERATIVE ACTIVITY

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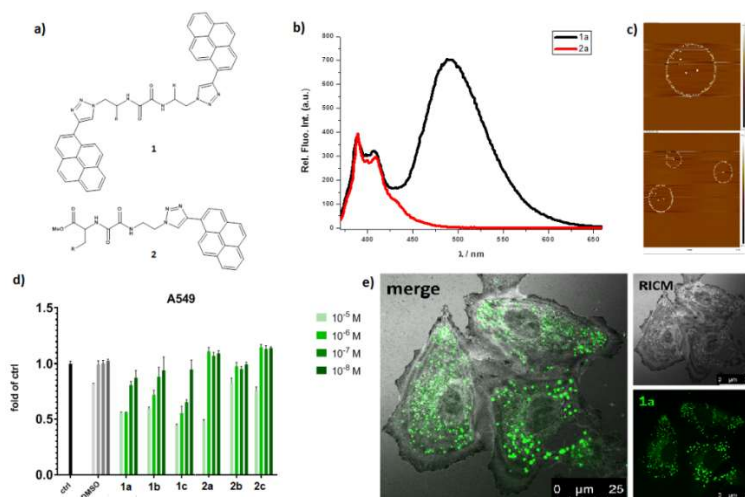
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Polyaromatic chromophores are one of the most studied groups of the chemosensor molecules due to their fluorescence properties. Pyrene is one of the most useful fluorogenic units due to its high detection sensitivity and its ability to form an excimer. Changes to the intensity of fluorescence emission confirm the formation of self assembled complex.<sup>[1]</sup> Due to their many interesting fluorescence properties, pyrene and its derivatives are of considerable interest for the development of sensors and diagnostic tools.<sup>[2]</sup>

A series of mono- (**2a-c**) and bis-1,2,3-triazolepyrene-appended (**1a-c**) retropeptides were designed and prepared in excellent yields *via* the standard copper-catalysed azide-alkyne cycloaddition (CuAAC). Their photophysical properties and morphology were fully investigated by UV-visible and fluorescence spectroscopy as well as AFM. The bis-1,2,3-triazole (**1a-c**) derivatives were prone to self-assemble into fluorescent nanoparticles in aqueous media.

*In vitro* antiproliferative activities of the novel 1,2,3-triazoles were evaluated against two human cancer cell lines, including A549 and RD cell lines, *via* the MTT assay.

The novel mono- (**2a-c**) and bis-1,2,3-triazoles (**1a-c**) developed in this work can ideally be utilised as potent candidates for pharmaceutical applications.



**Figure 1.** (a) general structures of novel triazolypyrene-derived retropeptides, (b) the fluorescence emission spectrum of **1a** and **2a** ( $R_a$  = iso-butyl) in DMSO, (c) AFM image of **1a**-nanoaggregates on mica, (d) MTT assay of pyrene compounds ( $R_a$  = iso-butyl,  $R_b$  = phenyltosylate,  $R_c$  = phenyl) on A549 cells and (e) confocal image of intracellular signal distribution of compound **1a** in A549 cells (RICM = reflection interference contrast microscopy)

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## COUMARINE DERIVATIVES AS POTENTIAL ACETYLCHOLINESTERASE INHIBITORS

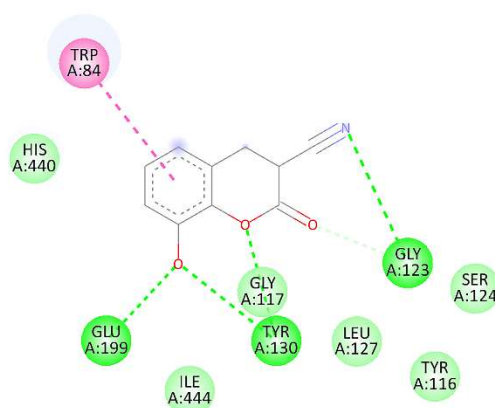
Domagoj Šubarić,<sup>a,\*</sup> Drago Bešlo,<sup>a</sup> Ivana Majić,<sup>a</sup> Dejan Agić,<sup>a</sup> Melita Lončarić,<sup>b</sup>  
Maja Molnar,<sup>b</sup> Vesna Rastija<sup>a</sup>

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Acetylcholinesterase inhibitors have been highly regarded as potential drugs for Alzheimer's disease treatment. Inhibitory properties of AChE inhibitors show great potential as active compounds in plant protection treatments, functioning as pesticides. 38 newly synthesized coumarin derivatives have been tested as potential acetylcholinesterase inhibitors by utilizing the Ellman protocol. The experiment was conducted on a 96-well microplate UV-Vis reader at a wavelength of 412 nm. Ligand-receptor interactions were observed by molecular docking. Inhibition activity results of the 38 compounds were compared to the obtained results of nematicidal activity study against two species of naturally occurring beneficial soil nematodes: *Heterorhabditis bacteriophora* and *Steinernema feltiae*. The highest inhibition activity against acetylcholinesterase was obtained by compound **19** (3-cyano-8-hydroxycoumarin) (78.21 % inhibition). The same compound has shown a very small percentage of mortality of nematodes: *H. bacteriophora* (20.75 %) and *S. feltiae* (11.25 %). The main interactions with amino acid residues in the binding site of acetylcholinesterase (pdb: 1eve) of compound **19** consist of conventional hydrogen bond (green); van der Waals (light green); and  $\pi$ -alkyl interactions (purple) (Figure 1).



**Figure 1.** The main interactions of compound **19** in binding site of acetylcholinesterase.

**Acknowledgments.** Croatian Science Foundation - the project UIP-2017-05-6593

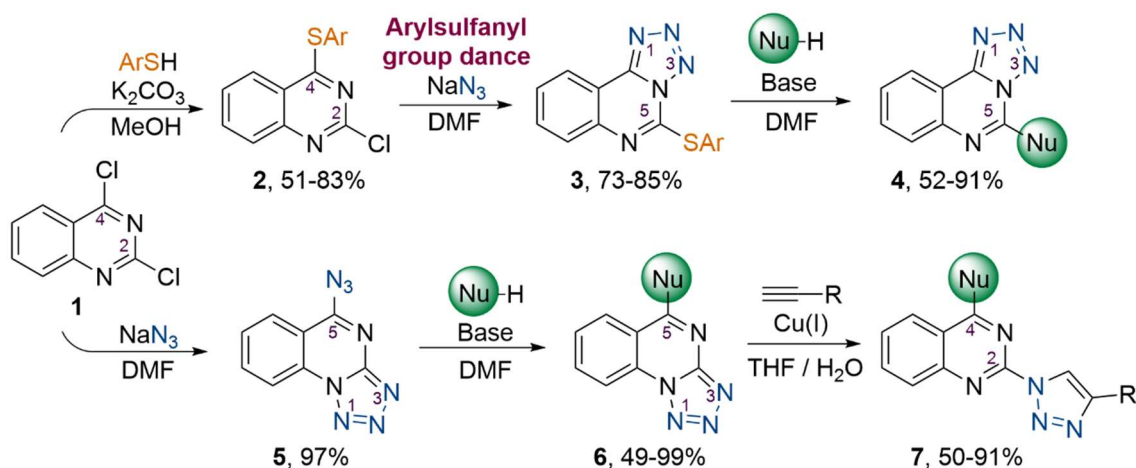
## AZIDE-TETRAZOLE TAUTOMERIC EQUILIBRIUM CONTROLLED SYNTHESIS OF INVERTED TETRAZOLO[1,5-A/C]QUINAZOLINES

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Quinazoline core is an example of privileged molecular scaffolds, which has already been proven as an effective tool in the treatment of different types of cancer.<sup>[1]</sup> We report unorthodox arylsulfanyl group dance around quinazoline core, leading to a variety of 5-substituted tetrazolo[1,5-c]quinazolines **3** and **4**.<sup>[2]</sup> On the other hand, inverted 5-substituted tetrazolo[1,5-*a*]quinazolines **6** can be obtained via regioselective  $S_NAr$  reaction of tautomerically locked 2,4-diazidoquinazoline **5**.



2-/4-Azidoquinazoline derivatives exist in azide-tetrazole tautomeric equilibrium that is affected by temperature, solvent polarity, pH and substituent electron effects. The ratio of tautomers can be controlled to achieve favourable regioselectivity of further transformations, such as  $S_NAr$ , CuAAC and Staudinger reactions.

**Acknowledgments.** This work was supported by the Latvian Council of Science grant No LZP-2020/1-0348.

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## FLUORINATED PYRAZOLINE DERIVATIVES AS ACETYLCHOLINESTERASE INHIBITORS

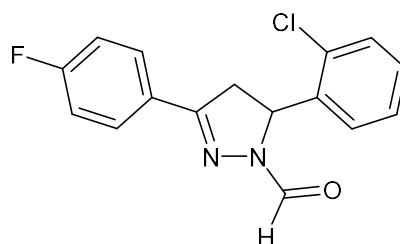
Maja Karnoš,<sup>a,\*</sup> Domagoj Šubarić,<sup>a</sup> Vesna Rastija,<sup>a</sup> Dejan Agić,<sup>a</sup> Ivana Majić,<sup>a</sup> Mario Komar,<sup>b</sup>  
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Acetylcholinesterase (AChE) is an enzyme responsible for the metabolism of acetylcholine (ACh), the neurotransmitter controlling motor activities in nematodes. Inhibition of AChE results in accumulation of ACh at neuromuscular junctions and leads to paralysis, which makes AChE a good target enzyme for the control of parasitic nematodes. AChE inhibitors used to control parasitic nematodes are mainly organophosphates and carbamates, however, due to their toxicity, they have been withdrawn or have restricted usage.<sup>[1]</sup> Halogenated pyrazoline derivatives exhibit various biological activities, among them antibacterial, antifungal, and antimicrobial.<sup>[2]</sup> A series of fluorinated pyrazolines was chosen for the investigation of possible AChE inhibition, using Ellman's protocol modified for microplate reader. All tested compounds exhibited moderate to good inhibitory effect against AChE at 50  $\mu$ M concentration, with compound **9** (Fig. 1) having the highest inhibition of 79.5 %. A molecular docking study was performed to gain insight into the binding interaction of compound **9** with AChE (PDB: 2c5g). Results show that compound **9** interacts with amino acid residues located in the peripheral active site of AChE, blocking the narrow passage to the catalytic site. The effect of fluorinated pyrazolines was also tested on two entomopathogenic nematodes, *Heterorhabditis bacteriophora*, and *Steinernema feltiae*. Entomopathogenic nematodes are beneficial nematodes used in insect pest management programs because of their resilience to pesticide exposure.<sup>[3]</sup> Since these nematodes mostly have been unaffected by tested compounds, it indicates their potential use as plant protection agents.



**Figure 1.** Chemical structure of compound **9**

**Acknowledgments.** Croatian Science Foundation the project “Green Technologies in Synthesis of Heterocyclic Compounds” (UIP-2017-05-6593)

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## CHARACTERIZATION OF THE NEW POTENTIOMETRIC SENSOR FOR THIABENDAZOLE DETERMINATION

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Thiabendazole (THIA) is a broad-spectrum anthelmintic and antifungal agent commonly used as a post-harvest fungicide in fruits and vegetables.<sup>[1]</sup> Due to the exposure to THIA through the diet, and its potential toxicity, it is necessary to develop simple, fast, selective and accurate methods for THIA determination. Potentiometric sensors could be suitable for that purpose.<sup>[2]</sup>

The new potentiometric sensor for THIA determination with sensor material based on ionic pair of THIA and 5-sulfosalicylate, dibutyl sebacate (DS) as plasticizer and polyvinyl chloride was characterized. Response characteristics, dynamic response, influence of pH and interferences were determined using direct potentiometry.

**Acknowledgments.** This study is supported by the European Structural and Investment Funds grant for the Croatian National Scientific Center of Excellence for Personalized Health Care, Josip Juraj Strossmayer University of Osijek (grant #KK.01.1.1.01.0010).

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## OPTIMIZATION OF THE MEMBRANE OF THE POTENTIOMETRIC SENSOR FOR THIABENDAZOLE DETERMINATION

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Thiabendazole (THIA) is systemic fungicide that has a broad spectrum of application.<sup>[1]</sup> Due to its possible residues on crops and harmful effects at higher levels, it should be determined and monitored in samples of fruits, vegetables, soil and water.<sup>[2]</sup> Ion-selective electrodes (ISEs), as simple and fast potentiometric sensors, could be a good alternative to commonly used methods for THIA determination such as high-performance liquid chromatography (HPLC), spectrofluorimetry and surface-enhanced Raman spectroscopy (SERS). The membrane, as a most important part of the ISE, responsible for its selectivity, can be optimized with the aim of developing sensor with better properties.

The new sensor material for THIA determination was prepared using ionic pair of THIA cation and the 5-sulfosalicylate anion. The sensor material was incorporated in liquid type of ISE membrane. For optimization of the membrane of the potentiometric sensor for THIA determination, six different plasticizers and the content of the sensor material in the membrane (1%, 3% and 5%) were varied. The optimal plasticizer and sensor material content were chosen due to the best response characteristics measured using direct potentiometry.

**Acknowledgments.** This study is supported by the European Structural and Investment Funds grant for the Croatian National Scientific Center of Excellence for Personalized Health Care, Josip Juraj Strossmayer University of Osijek (grant #KK.01.1.1.01.0010).

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## BIOLOGICAL ACTIVITIES COUMARINYL SCHIFF BASES RELATED TO PLANT PROTECTION: DEEPER INSIGHT INTO THE MECHANISM OF ACTION

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Coumarins, secondary plant metabolites<sup>[1]</sup> and their derivatives demonstrated a wide range of biological activities on different organisms (invertebrate pests, pathogenic fungus and other microorganisms and weeds). The aim was to study the inhibitory effects of coumarinyl schiff bases on the on the four cultures of plant pathogenic fungi (*Macrophomina phaseolina*, *Sclerotinia sclerotiorum*, *Fusarium oxysporum* f. sp. *lycopersici*, *F. culmorum*), as well as against two beneficial soil of bacteria (*Bacillus mycoides* and *Bradyrhizobium japonicum*). The radial growth of the fungal colonies was measured 48 h after inoculation. Coumarin derivatives were most effective were against *M. phaseolina*, but were not harmful against beneficial bacteria. The most effective compound against *M. phaseolina* was 4-bromophenyl-1-*p*-tolyl-1H-pyrazol derivatives of 2-((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)acetohydrazide (**4**) (71.51 % inhibition). In order to determine the possible mechanism of action of coumarin derivatives against pathogenic fungi, molecular docking study has been performed on three enzymes responsible for the fungal growth: demethylase (pdb ID: 5eah); chitinase (pdb ID: 4txe); transferase (pdb ID: 2p6g); and the three plant cell wall-degrading enzymes: endoglucanase I (pdb ID: 2ovw); proteinase K (pdb ID: 2pwb) [53]; pectinase (pdb ID: 1czf). Analyzed coumarin derivatives are promising candidates for developing plant protection products that could be safe for the environment, human health, and non-target organisms.

**Acknowledgments.** EU project, grant number KK.01.1.1.01.0005, Biodiversity and Molecular Plant Breeding; Croatian Science Foundation the project “Green Technologies in Synthesis of Heterocyclic Compounds” (UIP-2017-05-6593)

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## OXIDATIVE METABOLISM OF SAKURANETIN IN HUMANS

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Sakuranetin is natural plant polyphenol that has shown antiviral, anti-inflammatory, antiprotozoal, antimicrobial, antidiabetic and anticancer properties. In human body it is primarily susceptible to oxidative reactions mediated by cytochrome P450 enzymes. The objective of this study was to determine types of oxidative reactions in the metabolism of sakuranetin mediated by aforementioned enzymes.

Human liver microsomes (HLM) were used as source of enzymes. Metabolism was monitored by liquid chromatography coupled with mass spectrometry (electrospray ionization, time of flight detection) for metabolites determination and diode array detector for quantification. Specific cytochrome P450 enzymes involved in metabolism of sakuranetin were determined using specific inhibitors of each liver cytochrome P450.

In HLM incubations, demethylation at position 7 of the A ring produces naringenin (mass loss of 14.016). Naringenin was further susceptible to aromatic hydroxylation at the position 3' of the B ring, producing eriodictyol (mass increase of 15.995). A third product of sakuranetin metabolism was formed by aromatic hydroxylation at the position 3' of the B ring, producing 5,3',4'-trihydroxy-7-methoxyflavonone.

Kinetic parameters were determined for the combined reaction sakuranetin → naringenin → eriodictyol catalyzed by cytochromes P450 using the human liver microsomes as a source of enzyme. Rate constant was  $3.1 \pm 0.3 \text{ pM min}^{-1} \text{ pM}^{-1}$  and  $K_m$  value was  $152 \pm 31 \text{ }\mu\text{M}$  corresponding to the efficiency constant of  $(0.020 \pm 0.005) \times 10^6 \text{ M}^{-1} \text{ min}^{-1}$ .

Based on the inhibitions with a specific cytochrome P450 enzyme, CYP2C9 and CYP2E1 were determined to be the most significant enzymes involved in metabolism of sakuranetin.



## APPLICATION OF HS-SPME/GC-MS FOR CHARACTERISATION OF VOLATILE COMPOUNDS OF *Sideritis romana* L. AND *Sideritis montana* L. FROM CROATIA

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*Sideritis* L. (Lamiaceae) is a genus of plants abundant in the Mediterranean region that are traditionally used as remedies for respiratory, gastrointestinal, urogenital and other disorders, and for wound-healing,<sup>[1–3]</sup> although their chemical composition and different pharmacological activities are yet to be fully enlightened. In this study, volatile organic compounds (VOCs) of dried aerial parts of four populations of *Sideritis romana* L. and two populations of *S. montana* L. from Croatia extracted by headspace solid-phase microextraction (HS-SPME) using the divinylbenzene/carboxene/polydimethylsiloxane (DVB/CAR/PDMS) and the polydimethylsiloxane/divinylbenzene (PDMS/DVB) coated fiber were analyzed by gas chromatography-mass spectrometry. In total, 70 and 56 VOCs were determined using the DVB/CAR/PDMS and the PDMS/DVB coated fibre, respectively. Sesquiterpene hydrocarbons, followed by monoterpene hydrocarbons, were the most dominant groups of VOCs for all investigated populations except for the population of *S. romana* from Morinjski zaljev using both fibre types. Bicyclogermacrene and germacrene D were observed as the main VOCs of *S. romana* and *S. montana*, respectively. Other dominant compounds of both species differed due to the type of fibre that has been applied, with sesquiterpene hydrocarbons being more represented using the PDMS/DVB fibre in comparison with the DVB/CAR/PDMS fibre, by which more oxygenated monoterpenes were extracted.

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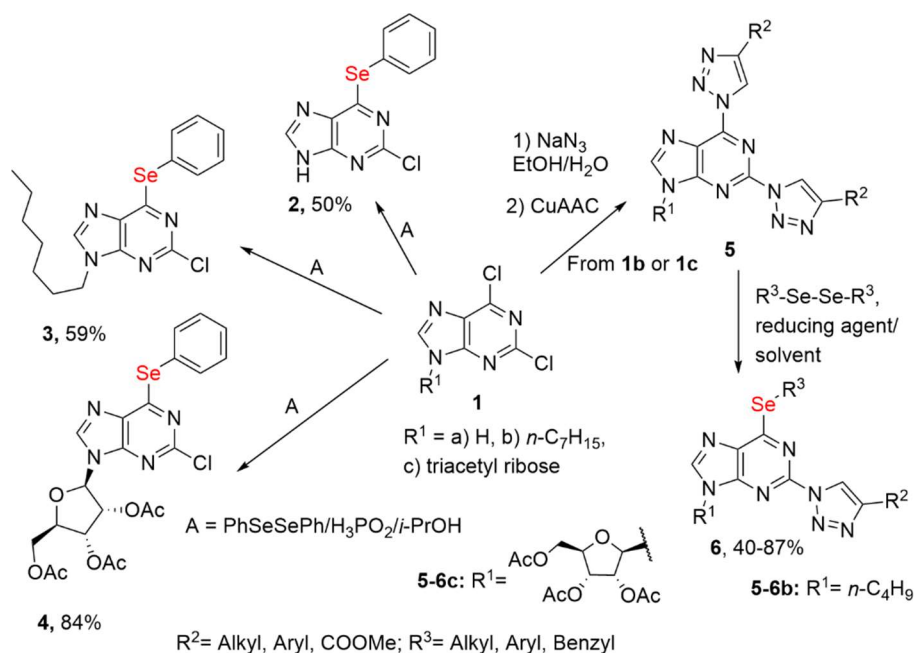
## THE FUNCTIONALIZATION OF PURINE SCAFFOLD WITH SELENIUM NUCLEOPHILES

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The importance of modified purine bases and purine nucleosides in medicine, biochemistry and biology is well recognized. On the other hand, the interest in the organoselenium compounds has increased in the last two decades due to their various biological activities. The combination of purine scaffold with selenium moieties can lead to the compounds with interesting properties.<sup>[1]</sup> Here we report the synthesis of 2-chloro-6-selanylpurine (**2-4**) and 2-triazolyl-6-selanylpurine (**6**) derivatives.



Earlier we demonstrated that 1,2,3-triazole moiety at C(6) position of purine is a good leaving group in S<sub>N</sub>Ar reactions with *N*, *S*, *O*, *C* and *P*-nucleophiles.<sup>[2]</sup> In this study we extended the range of nucleophiles with selenols. The synthetic routes to 6-selanyl-2-triazolylpurine nucleosides and 2-chloro-6-selanylpurines will be discussed.

**Acknowledgments.** This work was supported by the Latvian Council of Science grant No LZP-2020/1-0348.

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## METAL-FREE SULFUR DIOXIDE-ASSISTED GLYCOSYLATION WITH GLYCOSYL FLUORIDES

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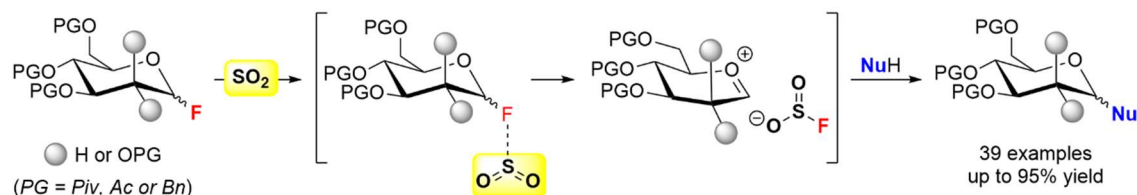
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Liquid SO<sub>2</sub> is a polar solvent that possesses Lewis acid properties. It is known to facilitate Lewis acid promoted and/or carbenium ion mediated chemical transformations.<sup>[1]</sup> Apart from that, SO<sub>2</sub> has an affinity towards fluoride ion that leads to covalent bonding in the form of relatively stable fluorosulfite anion (FSO<sub>2</sub><sup>-</sup>).<sup>[2]</sup>

Based on the aforementioned physico-chemical properties of SO<sub>2</sub>, we have developed sulfur dioxide-assisted glycosylation with glycosyl fluorides as glycosyl donors in liquid SO<sub>2</sub> without an external promoter.<sup>[3]</sup> The novel synthetic method was demonstrated with variously protected mannosyl and glucosyl fluorides, and series of *O*-, *S*- and *C*-glycosides were obtained in moderate to excellent yields. The α/β-selectivity of glycosylation was proposed to be substrate-controlled presenting thermodynamic equilibrium. The formation of fluorosulfite species during the glycosylation in the presence of SO<sub>2</sub> was proved by both <sup>19</sup>F NMR spectroscopy and DFT calculations.



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## DIVERSE STACKING OF TCNQ RADICAL ANIONS IN DIFFERENT SALTS WITH ORGANIC CATIONS

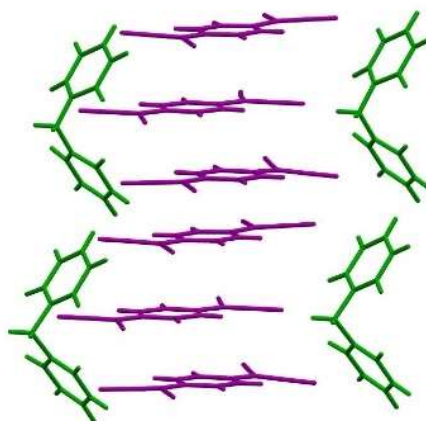
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$\pi$ -stacking is a well-known type of intermolecular interaction which occurs usually between aromatic rings, and is considered mostly as a weak interaction. However, recent studies in crystal engineering show that energy of some  $\pi$ - $\pi$  contacts may be comparable to stronger intermolecular interactions such as hydrogen bonding. Therefore,  $\pi$ -stacking has become an interesting and important field in supramolecular chemistry and it has a big role in design of functional materials such as optoelectronics, magnetic and conductive molecular materials.<sup>[1,2]</sup>

Herein we report studies on stacking of 7,7,8,8-tetracyanoquinodimethane (TCNQ) radical anions on its 8 salts with organic cations: tetrazolium, 2-amino-5-metil-*N*-methylpyridinium, *N*-ethyl-2-methylpyridinium, 1,4-dimethyl-DABCO cation, 2-chloro-*N*-methylpyridinium, 2-amino-pyridinium, *N,N*-dipyridylmethanium and phenyltrimethylammonium cations. In studied compounds stacking interactions are predominant with interplanar separations between TCNQ rings of 3,0–3,3 Å. Besides that, in some salts N–H $\cdots$ N and C–H $\cdots$ N hydrogen bonds are present. TCNQ moieties form stacks of dimers or trimers with alternating shorter and longer separation between TCNQ rings or stacks in columns with equidistant separations (Figure 1). Formal charges of TCNQ moieties in these salts are  $-1/2$ ,  $-2/3$  and  $-4/5$ .



**Figure 1** Stacking of TCNQ radical anions in salt with *N,N*-dipyridyl methanium cation.

**Acknowledgments.** The work was financed by the Croatian Science Foundation, grant no. IP-2019-04-4674.

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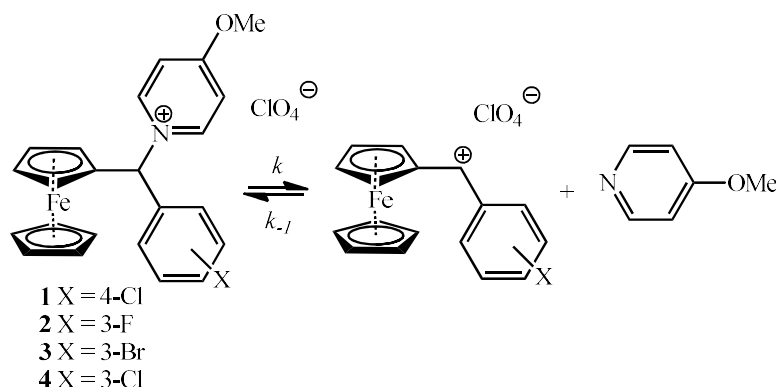
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## SOLVOLYTIC BEHAVIOUR OF SOME FERROCENYLPHENYLMETHYL-4-METHOXPYRIDINIUM CATIONS IN VARIOUS SOLVENTS

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The nucleofugalities of 4-methoxypyridine (4-OMePy) in pure and aqueous solvents have been derived from the  $S_N1$  solvolysis rate constants of the corresponding ferrocenylphenylmethyl-4-methoxypyridinium salts **1-4** (Scheme 1) by applying the linear free energy relationship (LFER) equation,  $\log k (25^\circ\text{C}) = s_f(N_f + E_f)$ .<sup>[1]</sup> In this equation  $k$  is a first order rate constant for  $S_N1$  reaction,  $s_f$  (slope of the  $\log k/E_f$  correlation line) and  $N_f$  (nucleofugality, negative intercept on the abscissa of the  $\log k/E_f$  correlation line) are nucleofuge specific parameters, while  $E_f$  is the electrofugality parameter of the corresponding ferrocenylphenylmethyl cations determined earlier.<sup>[2]</sup>



**Scheme 1.** Solvolysis of X-substituted ferrocenylphenylmethyl-4-methoxypyridinium perchlorates **1-4**.

In more polar solvents, pyridinium ions are more stabilized by solvation in the reactant ground state than in the corresponding transition state<sup>[3]</sup> and the reactivity (nucleofugality,  $N_f$ ) of 4-OMePy decrease with increasing solvent polarity. Due to strong electron-donor effect of the ferrocenyl group, it seems that 4-OMePy is somewhat better leaving group if the substrate is benzhydryl-4-methoxypyridinium salts than if it is ferrocenylphenylmethyl-4-methoxypyridinium salts. The electron-withdrawing substituents on the 4 position of pyridine ring increase the rate of heterolysis step of pyridinium salts and  $N_f$  value of substituted pyridine decreasing in order  $N_f(4\text{-ClPy}) > N_f(\text{Py}) > N_f(4\text{-MePy}) > N_f(4\text{-OMePy})$  in all examined solvents.

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## AROMATIC SUBSTITUTION OF AZIDO-PYRIDOPYRIMIDINES AND STUDY OF THEIR AZIDE-TETRAZOLE EQUILIBRIUM

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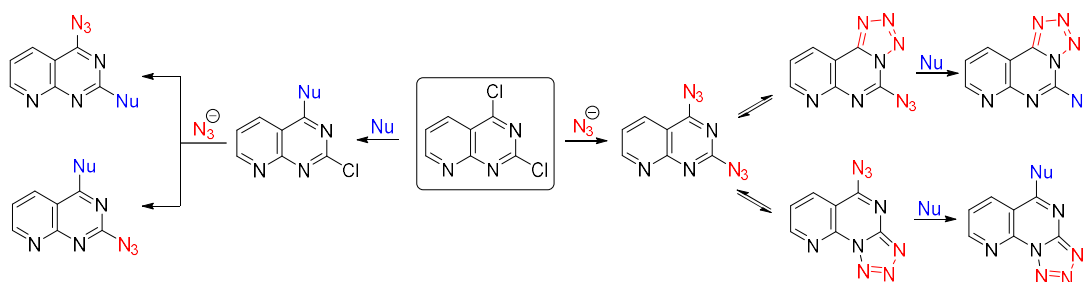
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Pyrimidine is essential building block of nucleic acids. Pyrimidine based drugs show a wide spectrum of biological activities, such as antiviral, antimicrobial and anticancer.<sup>[1]</sup> Therefore modifications of pyrimidine moiety and new synthesis methods toward modified pyrimidines are continuously developing.

Our group has previously discussed azido group mediated aromatic substitution rearrangements in purines and quinazolines and the importance of azido-tetrazolo equilibrium in diazidopurine.<sup>[2]</sup> Herein we extend our research to pyrido[2,3-*d*]pyrimidines.  $S_NAr$  regioselectivity patterns of the latter *via* different substitution routes (**Scheme 1**) have been explored. Also dynamic azido-tetrazolo equilibrium in various organic solvents is studied in detail and solid state tautomer forms are determined by single crystal x-ray spectroscopy.



**Scheme 1.**  $S_NAr$  substitution pattern of azido-pyridopyrimidines

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## MULTICENTRE BONDING OF SEMIQUINONE RADICALS UNDER VARIABLE TEMPERATURE AND HIGH PRESSURE CONDITIONS

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The dominant intermolecular interaction in crystals of organic radicals is  $\pi$ -stacking, which involves some of the closest interplanar and intermolecular C-C contacts ( $< 3 \text{ \AA}$ ).<sup>[1–2]</sup> Quantum chemical models indicate a considerable covalent component in the total interaction, and this type of weak multicentre covalent bonding has been dubbed ‘pancake bonding’.<sup>[3]</sup> Physical properties of crystals, such as magnetism and electric conductivity, are defined by stacking, so its in-depth study is important for understanding and designing radical-based molecular materials with targeted properties. Three types of stacks of planar radicals are known: (1) stacks of ‘pancake-bonded’ dimers, separated by weaker stacking contacts, (2) stacks of equidistant radicals with long-range ordering and (3) stacks of ‘pancake-bonded’ trimers of partially charged radicals.<sup>[1–2]</sup>

The first combined variable-temperature (90 – 400 K) and high-pressure (0.1 MPa – 6.0 GPa) single-crystal X-ray diffraction study of multicentre bonding (‘pancake bonding’) between planar semiquinone radicals revealed their behavior under a broad range of conditions. The dimension of a unit-cell, volume and distances between ring planes increased with increasing temperature. High pressure caused the phase transitions and decreased interplanar separations, indicating increased covalent contribution as compared to multicentre bonding at ambient pressure.

**Acknowledgments.** The work was financed by the Croatian Science Foundation, grant no. IP-2019-04-4674.

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## CONTENT OF METAL(OID)S IN THE MUSCLE AND LIVER OF EUROPEAN EEL (*Anguilla anguilla* L.) FROM THE RAŠA RIVER

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The drainage area of the Raša River (Istria, Croatia) is a geologically, hydrologically and pedologically interesting area, especially due to the vicinity of the abandoned Raša coal mines. In the past, this coal was used by local households, factories and thermal power plants, which resulted in the pollution of the surrounding environment with inorganic and organic pollutants. Although a large amount of coal and other terrigenous material rich with inorganic elements was deposited in the Raša Bay and the Raša River estuary, a special natural habitat for many animal species, the elements profile in the biota of the Raša River is yet to be investigated. European eels are a suitable environmental pollution indicator, often used for screening toxic substances, including metals, due to specific physiological features (life cycle), bioaccumulation capacity (long-living animals), feeding and habitat ecology (benthic species).

The aim of the study was to determine the content of metal(oid)s (Na, Mg, K, Ca, Fe, Cu, Zn, Se, Mn, Mo, V, Cr, Co, Ni, Tl, Sr, U, Ag, As, Cd, Hg, and Pb) in samples of muscle and liver of E. eels from the Raša River. Eels were collected at two sites: upstream near the Podpićan settlement (site 1) and 6 km upstream of the Raša River estuary (site 2), during June and July of 2020. Total length (TL) and body weight (BW) were measured, and samples of dorsal muscle and liver were taken. Element concentrations were determined by inductively coupled plasma – mass spectrometry (ICP-MS).

There were significant differences between sites. Eels caught at site 2 had higher levels of Ni, Cu and Sr in muscle, and of Mn and U in liver than eels caught on site 1. Furthermore, the eels caught on site 2 had higher levels of V, Cr, Mo, Cd, Tl and Ag in muscle and liver, and lower levels of Hg in muscle, and Mg and Ca in liver than at site 1. Negative correlations with TL and BW were found for Na, Mg, K, Ca, Mn, Mo, Sr and Tl in muscle, and Mg, K, Ca, Sr and Tl in liver, while positive correlations with TL and BW were found only in liver for Fe, Cu, Zn, Se, Cd and Pb.

The content of metal(oid)s in E. eels from the Raša River was similar or lower than the values reported in other European regions. This pointed to the good status of the Raša river ecosystem with regard to inorganic elements.

**Acknowledgments.** The study was funded by Croatian Science Foundation grant HRZZ-IP-2016-06-1998, METALORIGINS.

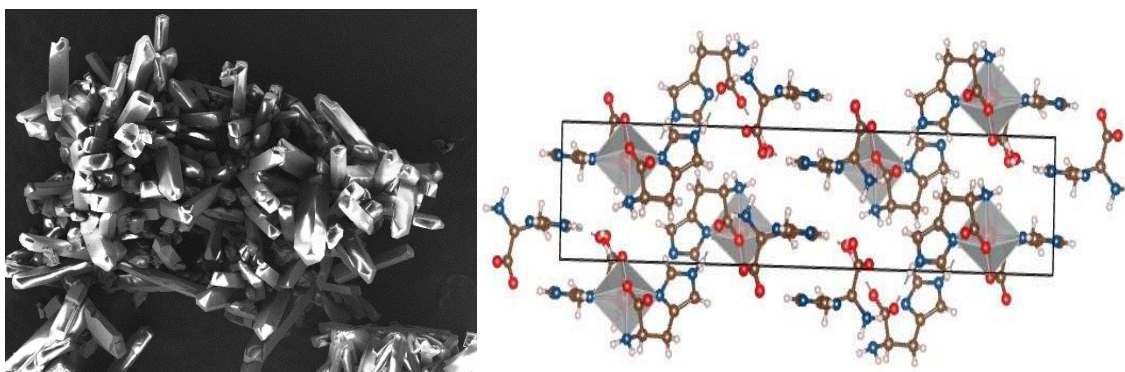
## ULTRASOUND-ASSISTED GREEN SYNTHESIS AND CHARACTERIZATION OF Ni/HISTIDINE MOF

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Metal organic frameworks (MOFs) are porous 3D networks which are assembled from organic ligands as linkers between metal cations. They are considered as promising materials for a variety of applications because of their fine tunable and uniform pore size.<sup>[1]</sup> Here we report ultrasound-assisted synthesis of Nickel(II)/histidine MOF and its structural, morphological and compositional characterization. Ultrasound-assisted synthesis is simple, environmental-friendly and most of all cost-effective method in which nickel acetate is decomposed with ultrasonic cavitation in basic water solution of histidine.<sup>[2]</sup> Synthesized compound is further structurally characterized by powder X-ray diffraction (PXRD), morphologically investigated by scanning electron microscopy (SEM), while chemical composition has been determined by X-ray photoelectron spectroscopy (XPS).



**Figure 1.** SEM image (left) and crystal structure visualization (right) of synthesized Ni/histidine MOF.

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## PREPARATION AND CHARACTERIZATION OF Co(II) COMPLEX WITH 1H-BENZIMIDAZOLE-2-METHANOL

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Complex, tetrakis(1*H*-benzimidazole-2-yl)methanol-*N*<sup>2</sup>,*O*<sup>3</sup>-di-chlorobico(II) chloride, [Co<sub>2</sub>Cl<sub>2</sub>(HL)<sub>4</sub>]Cl<sub>2</sub>; HL = 1*H*-benzimidazole-2-methanol) (Figure 1.) formed by the reaction of the cobalt(II) chloride hexahydrate and the ligand by heating to reflux in a propanol, was characterized by the infrared spectroscopy, thermogravimetric analysis and single-crystal X-ray diffraction. Infrared spectroscopy indicated the coordination of ligand in the neutral form on Co (II) ion. Ligand 1*H*-benzimidazole-2-methanol is commercially available substance which has the coordination potential in sight of endocyclic basic nitrogen atom and hydroxyl groups. The crystal and molecular structure of ligand is known.<sup>[1]</sup> Interest in this ligand arises from its two chemical functional groups, the imidazole ring and the hydroxymethyl group, which are often encountered in the active sites of some enzymes. Organic dyes from the class of benzimidazoles are also well known. Due to versatile coordination capacities, the ligand is considered to investigate metal-assembly phenomenons and also to explore the coordination chemistry of (1*H*-benzimidazol-2-yl)-methanol-like ligands class with eco-friendly metals due to the possible versatile application.

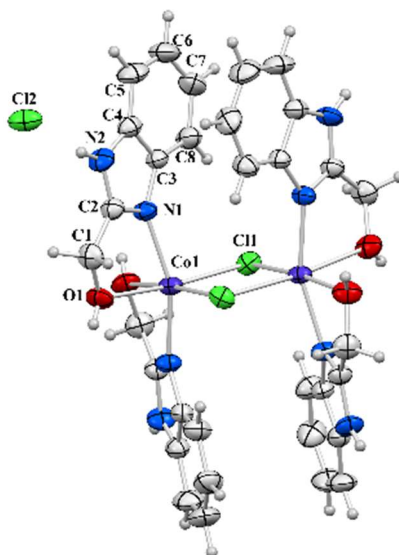


Figure 1. ORTEP view of the molecular structure of the complex

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## STABILITY AND AGGREGATION KINETICS OF TiO<sub>2</sub> NANOPARTICLES

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Wide range of possibilities for application of nanoparticles, from industry, cosmetics, pharmacy to environmental engineering, has resulted in large increase in necessary fundamental investigations.<sup>[1]</sup> Special interest exists for exploring nanoparticle stability in variety of experimental conditions (especially of those close to environmental) and understanding their possible toxicity.<sup>[2,3]</sup> Here, we investigated TiO<sub>2</sub> nanoparticle properties by dynamic and electrophoretic light scattering. Special emphasis we put on the preparation of stable suspensions and, in some critical experimental conditions, we performed the aggregation kinetics experiments.<sup>[4,5]</sup> We investigated the influence of pH, concentration and salt type on the stability of nanoparticles. Also, we explored the influence of two added polyelectrolytes as potential stabilizers<sup>[6]</sup> which could improve nanoparticle stability, i.e. resistance to aggregation with change of pH or addition of monovalent salts. The results showed that there is no significant aggregation of nanoparticles at low ionic strengths in the pH range around isoelectric point when the polyelectrolyte, either polycation (poly(diallyldimethylammonium)) or polyanion (poly(styrenesulfonate)), was present. Also, the higher concentration of added salt at constant pH values was necessary for the aggregation in the presence of polyelectrolyte compared to polyelectrolyte free case. There was also noted difference between polycation- and polyanion-modified particles. In the presence of polycation the aggregation started at significantly lower concentration than in the presence of polyanion.

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## VOLUMETRIC PROPERTIES OF SOME IMIDAZOLIUM CHLORIDE IONIC LIQUIDS IN BUTAN-1-OL AT DIFFERENT TEMPERATURES

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The volumetric properties of butan-1-ol mixtures with various ionic liquids (1-methylimidazolium chloride; 1,3-dimethylimidazolium chloride; 1-ethyl-3-methylimidazolium chloride, 1-butyl-3-methylimidazolium chloride, and 1-hexyl-3-methylimidazolium chloride) were determined by measuring densities at various temperatures  $T = (278.15, 283.15, 288.15, 293.15, 298.15, 303.15, 308.15, \text{ and } 313.15) \text{ K}$ , and up to molality of ionic liquids of  $0.1 \text{ mol} \cdot \text{kg}^{-1}$ . From obtained experimental data, the apparent molar volumes and standard partial molar volumes were derived.<sup>[1,2]</sup> By applying Masson's equation the apparent molar volumes at infinite dilution and interaction coefficients were calculated for each ionic liquid + butan-1-ol mixture.<sup>[3]</sup> The results are discussed in terms of ion-ion and ion-solvent interactions as well as from the point of structure-making or structure-breaking tendency of researched ionic liquids.<sup>[1,4]</sup>

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## BIOLOGICAL ACTIVITY OF BENZIMIDAZOLE AND BENZOTHIAZOLE 2,5-DISUBSTITUTED FURANE DERIVATIVES

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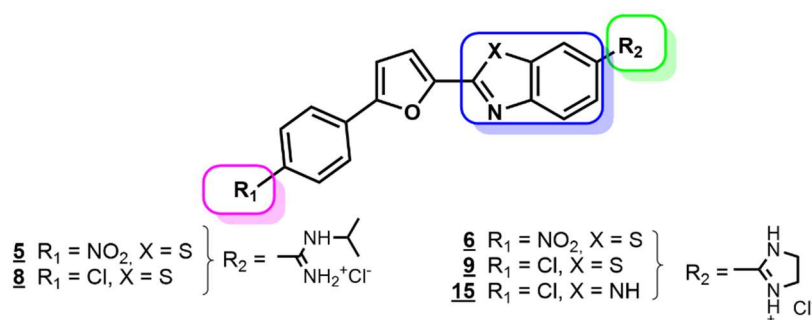
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Among all known nitrogen heterocycles, benzimidazole and benzothiazole moieties have been recognized as important and well-known constituents of biologically important molecules in medicinal and pharmaceutical chemistry.<sup>[1,2]</sup> Due to their wide range of biological activities, these heterocycles are still unavoidable structural motifs in the rational design of novel drugs.

Newly designed and synthesized cyano, amidino and acrylonitrile 2,5-disubstituted furane derivatives with either benzimidazole/benzothiazole nuclei have been evaluated for antitumor and antimicrobial activity, as well as for their interaction with ct-DNA. Compounds **5**, **6**, **8**, **9** and **15** showed high potential antitumor activity on three human lung cancer cell lines and high activity against *S. cerevisiae* as a eukaryotic model organism. DNA study showed that all compounds dominantly bind inside the minor groove of AT-rich DNA.



**Figure 1.** The structures of newly prepared benzimidazole and benzothiazole derivatives

**Acknowledgments.** This work was funded by the Croatian Science Foundation (projects IP-2018-01-4379 and IP-2018-01-4694).

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# THE SULFUR ATOM AS A HALOGEN BOND ACCEPTOR IN COCRYSTALS OF TETRAHYDRO-4H-THIOPYRAN-4-ONE AND ITS DERIVATIVES

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In the field of crystal engineering by using halogen bonds, sulfur is significantly less studied as an acceptor species relative to the oxygen or nitrogen atoms.<sup>[1]</sup> An interesting approach in the past two decades was the utilization of the  $sp^3$  hybridized sulfur atoms in 1,4-dithiane, 1,4-thioxane and thiomorpholine as halogen bond acceptors, whether in binary cocrystals<sup>[2]</sup> or metal complex adduct cocrystals.<sup>[3]</sup>

In order to further study  $sp^3$  hybridized sulfur as a halogen bond acceptor, we have selected tetrahydro-4H-thiopyran-4-one (**tpyr**), and building blocks derived from it, **tpyram** and **tpyraem**, which are obtained by reacting it with 4-aminomorpholine (**am**) or 4-(2-aminoethyl)morpholine (**aem**), respectively. All three compounds were then cocrystallized with a series of perhalogenated benzenes: 1,4-diiodotetrafluorobenzene, 1,3-diiodotetrafluorobenzene, 1,2-diiodotetrafluorobenzene, iodopentafluorobenzene, 1,3,5-triiodotrifluorobenzene and 1,4-dibromotetrafluorobenzene, resulting in the formation of 9 new products. Out of these, single crystals were obtained for 7 new products, and they were structurally characterized by X-ray diffraction. Halogen...sulfur halogen bonds were formed in 5 out of the 7 cases, the sulfur atom competing for halogen bonding not only with the carbonyl or morpholinyl fragment oxygen atoms, but also with the morpholinyl and imine nitrogen atoms.

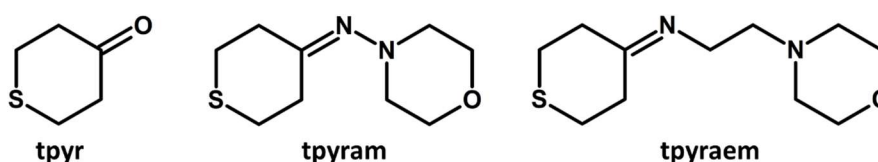


Figure 1. Sulfur-containing halogen bond acceptors used in this study.

**Acknowledgments.** Croatian Science Foundation (IP-2019-04-1868).

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## EFFECTS OF DEFOLIATION TREATMENTS OF GRAPE VARIETY BABICA ON VOLATILE COMPOUNDS CONTENT IN WINE

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Wine flavour and aroma are derived from large range of volatile compounds (e.g. esters, aldehydes, ketones, alcohols, terpenes, etc.) and their interactions. The outcome of defoliation on wine volatiles profile was associated with many factors: vegetation period, levels and zones of treatment; as well as time and weather conditions during harvest.<sup>[1]</sup>

The objective of this two years study (2017 and 2018) was to determine the effects of defoliation on grape variety Babica in condition of warm Mediterranean climate (wine-growing region Dalmatia, Croatia). Defoliation was performed before blooming (BLR), and at the end of veraison (VerLR), observing the concentrations ( $\mu\text{g/L}$ ) several groups of volatile compounds: monoterpenes; monoterpenols; aromatic esters and aromatic alcohols; aliphatic alcohols; aliphatic esters; aldehydes; and ketones. Volatile compounds were analysed using gas chromatograph (GC) coupled to a mass spectrophotometric (MS) detector along with stir bar sorptive extraction with polydimethylsiloxane phase. Identification of the separated compounds was performed by retention indices and MS spectra compared with mass spectral database. Comparisons of volatile compounds concentrations between different treatments, and between years, were made using analysis of variance (one-way ANOVA) with the least significant different (LSD) test used to examine the means at the  $p = 0.05$  level. The two most abundant volatiles found in wines is 2-methyl-1-butanol and 3-methyl-1-butanol (average concentrations (175.58 and 295.03  $\mu\text{g/L}$ , respectively). Treatments of defoliation significantly increased the concentrations for 2-hydroxy-propanoic acid-ethyl ester and octanoic acid ethyl ester, especially by VerLR, but only in the 2017 year.

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## CHARACTERIZATION OF THE COMPLEXES PREPARED USING BUILDING BLOCK TRIS(OXALATO)CHROMATE CONTAINING DIFFERENT ALKYL AMMONIUM CATIONS

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In the field of molecular magnetism, the oxalate group,  $C_2O_4^{2-}$ , has been demonstrated to be one of the most versatile ligands used in the preparation of the magnetic materials. Due to its various coordination modes towards the metal centres as well as its ability to mediate magnetic interactions between paramagnetic metal ions, a large number of oxalate-based transition-metal species of different nuclearity, connectivity and dimensionality have been synthesized and characterized, many of them having tunable magnetic frameworks<sup>[1]</sup>

Furthermore, oxalate-bridged crystalline coordination polymers have been studied as hydrated proton-conductive systems owing to their high crystallinity and high stability for water. Generally, the existence of hydrated protons is required to achieve high proton conductivity of solids at ambient temperature. The studies of proton conduction in coordination polymers mainly include two kinds of situations: one is that under the anhydrous condition, it mainly relies on the inherent water molecules or other minor molecules containing protons and hydrogen-bond network in the structures to carry out the proton transfer; another one is that under the aqueous condition, the external  $H_2O$  units play a vital function on the proton transmission.<sup>[2]</sup>

To achieve our final goal – exploration of the complexes containing noteworthy structural, magnetic and electrical features, two novel homo- and heterometallic oxalate-based systems have been synthesized and characterized using tris(oxalato)chromate,  $A_3[Cr^{III}(C_2O_4)_3]$  [ $A = (C_2H_5)_2(CH_3)NH^+$  or  $(C_2H_5)(CH_3)_2NH^+$ ], as ligands towards second transition metal ion ( $Mn^{II}$  or  $Cu^{II}$ ):  $\{[NH(CH_3)(C_2H_5)_2][Cr(bpy)(\mu-C_2O_4)_2MnCl_2]\}_n$  (**1**; bpy = 2,2'-bipyridine) and  $[NH(CH_3)_2(C_2H_5)][Cr(H_2O)(C_2O_4)_2]$  (**2**).

**Acknowledgments.** This work has been funded by the Croatian Science Foundation under Project No. IP-2019-04-5742.

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## DETERMINATION OF INFLUENTIAL PARAMETERS FOR CHITOSAN ADSORPTION ON SILICA SURFACE

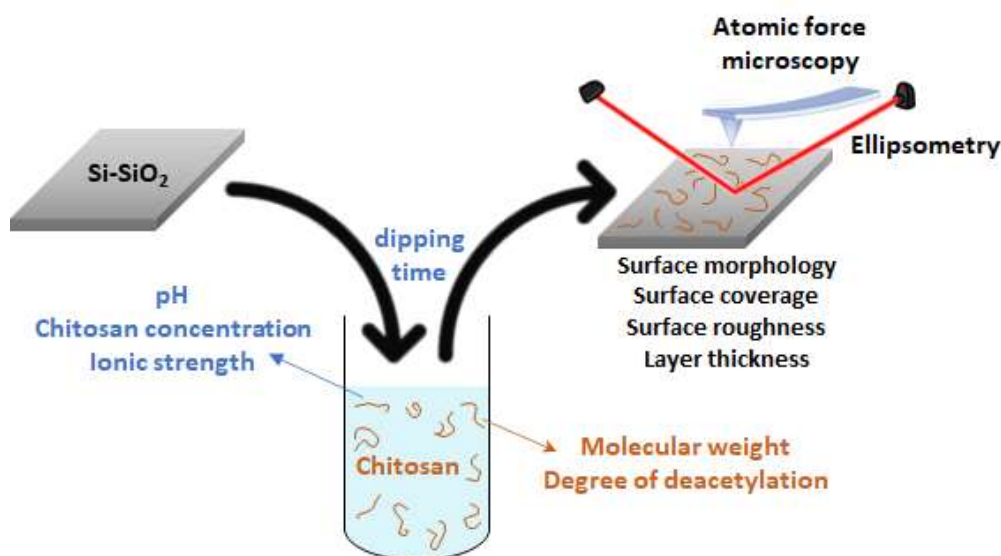
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Chitosan, a deacetylated derivative of chitin, is a biopolymer composed of two kinds of common saccharides, D-glucosamine and N-acetyl-D-glucosamine. The uniqueness of chitosan lies in its polycationic nature in acidic solutions. Due to its biocompatibility, anti-bacterial/fungal properties, non-toxicity and ease of adaptability to different forms (layers, film, capsules), its main applications are in agriculture, food processing and biotechnology.

In this work, we prepared chitosan monolayers on Si-SiO<sub>2</sub> substrates using dipping technique starting from chitosan with different molecular weights. Layer properties not only depend on both molecular weight and degree of acetylation of chitosan itself but also on the experimental parameters like solution pH, ionic strength, chitosan concentration and dipping time. Characterization of prepared monolayers was done using ellipsometry and atomic force microscopy (AFM). Ellipsometry was used as a screening method for layer thickness, while AFM was used to image the Si-SiO<sub>2</sub> surface, accurately determine layer roughness and thickness and to determine surface coverage with the chitosan layer.



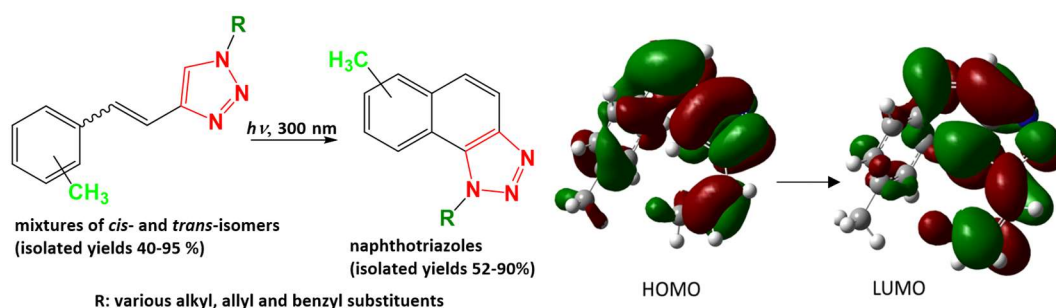
**Acknowledgments.** The research was financially supported by HRZZ under the project APPLPEMS (IPS-2020-01-6126).

## SYNTHESIS, PHOTOCHEMISTRY AND BIOLOGICAL ACTIVITY OF NEW 1,2,3-TRIAZOLOSTILBENES. AN EXPERIMENTAL AND COMPUTATIONAL STUDY

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Triazoles present an important class of heterocyclic compounds exhibiting a wide range of pharmacological activities<sup>[1]</sup> New 1,2,3-triazolostilbenes were synthesized and photochemically transformed to electrocyclization products in high yields for the purpose of studying their acetyl- and butyrylcholinesterase inhibition and anti-inflammatory activity.<sup>[2]</sup> In our previous paper,<sup>[3]</sup> photoreactivity of 1,2,3-ditriazolostilbenes were investigated showing unreactivity toward the electrocyclization. In contrast, 1,2,3-triazolostilbenes gave electrocyclization photoproducts in high isolated yields providing especially interesting results on cholinesterase inhibition associated with the inhibition of TNF $\alpha$  cytokine production.



Additionally, the electronic structure of the obtained 1,2,3-triazolostilbenes and the thermodynamic stability of the 1,2,3-triazolostilbenes - cholinesterases complexes were investigated by computer modeling.

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## REVEALING DNA INTERACTIONS WITH HOECHST 33258 BY SURFACE-ENHANCED RAMAN SPECTROSCOPY

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Hoechst 33258 (H33258) is a small DNA binding molecule, known as a fluorescent dye. Driven by hydrogen bonding, it selectively binds to adenine-thymine (AT) rich sequences of DNA, though stacking interactions with guanine-cytosine (GC) sequences and electrostatic binding to the nucleic phosphate backbone have been also observed.<sup>[1]</sup> Besides, at high concentrations the H33258 molecules self-aggregate and can also form aggregates while interacting with DNA.<sup>[2]</sup> Considering the complexity of interactions between H33258 and DNA and aiming to a complete insight in the small molecule-DNA binding, various methods of structural analysis have been applied.

In this work interactions of H33258 with two synthetic DNA polynucleotides, poly dA – poly dT and poly dG – poly dC, and natural calf thymus (ct) DNA were studied using surface-enhanced Raman spectroscopy (SERS). Complexes were prepared in [H33258]/[DNA] molar ratios of 1/1, 1/5 and 1/10 in the silver colloidal suspension. Prior to analysis of binding modes with DNA polynucleotides, aggregation tendency of the dye in the silver colloid was studied in the concentration range  $1 \times 10^{-6}$ – $1 \times 10^{-4}$  mol/L. The SERS spectra distinctive of aggregated and monomeric H33258 species were obtained, additionally indicating the form of the molecules bound to DNA. The obtained SERS spectra of H33258 with homo-polymeric polynucleotides implied a deep insertion of the molecules into the AT minor groove, and a partial intercalation between the GC base pairs achieved by the access through the major groove. Spectral characteristics of the dye dominated in the spectra of the complexes with ct-DNA, most likely due to a random AT and GC sequences of the long natural DNA, affecting uniform binding of the dye and consequently the adsorption of the H33258/DNA complex onto the enhancing metallic surface.

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## ANTIPLASMODIAL ACTIVITY OF TRIAZOLE-TYPE HARMIQUINS

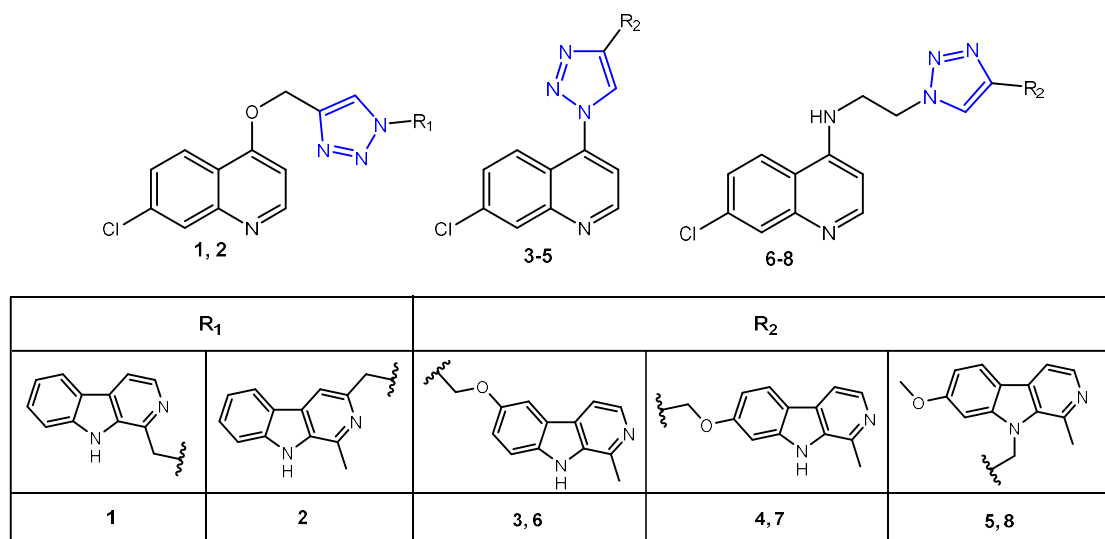
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Global malaria control is being disrupted by the emergence of drug resistance to most of the available antimalarials, necessitating the search for novel drugs.<sup>[1]</sup> A recent rational approach used in the antimalarial drug design involves linking two bioactive molecules into a single chemical entity, *i. e.* preparing hybrid compounds.<sup>[2]</sup> Herein, we represent harmiquins, hybrids constituted of two moieties with pronounced antimalarial properties,  $\beta$ -carboline alkaloid harmine and 7-chloroquinoline,<sup>[2,3]</sup> linked via 1*H*-1,2,3-triazole (**Figure**). Antimalarial activity of novel hybrids was evaluated *in vitro* against the erythrocytic stage of the *Plasmodium* life cycle, revealing compound **8** as the most active ( $IC_{50}$  value  $11.6 \pm 3.8$  nM). Furthermore, the diversity of harmiquins allowed us to draw several conclusions about the structure-activity relationship: 1) the activity decreased following the pattern of the  $\beta$ -carboline core substitution N-9 > O-7 > O-6 > C-3 > C-1, 2) hybrids containing aminoethylene linker (compounds **6-8**) exerted more pronounced antimalarial activity.



**Figure.** Structures of the triazole-type harmiquins.

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## CONFORMATIONAL ANALYSIS OF 1*N*,3*N*-SUBSTITUTED IMIDAZOLE 2-ALDOXIMES

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Full conformational analyses of *N,N*-disubstituted imidazole 2-aldoximes were performed by the grid search of potential energy surfaces (PES). PES were spanned by relevant torsional coordinates and the grid search was conducted using the *rigid scan*<sup>[1]</sup> as well as the *adaptive relaxed scan*.<sup>[2]</sup> Each scan was performed by the systematic variation in relevant torsional coordinates for a defined step size. These two scan algorithms differ in the type of quantum chemical calculation performed (single point calculation or molecular geometry optimization) where the geometry optimization is performed for those atoms that do not participate in the definition of a particular torsional coordinate. Additionally, in adaptive relaxed scan a fine control mechanism including a guided variable search of defined points on the *N*-dimensional surface was implemented. If the investigated system runs into the forbidden areas of PES due to the large step size, a guided variable search will reiterate and approach the forbidden areas with a smaller step thus insuring the smoothness in PES. PES were calculated at the semiempirical level of the theory using the PM7 method implemented in MOPAC2016.<sup>[3]</sup> All local minima in PES were determined from the generated surfaces and corresponding structures were further subjected to geometry optimization at the B3LYP-D3/6-311++G(d,p) level of the theory and clustered. The results of these conformational analyses will be compared, and the conformers relative content will be determined using the Maxwell-Boltzmann distribution at the room temperature.

**Acknowledgments.** This work was supported by Croatian Science Foundation: "Activity and *in silico* guided design of bioactive small molecules" (IP-2016-06-3775) and "Young researchers' career development - Training New Doctoral Students" ESF-DOK-01-2018.

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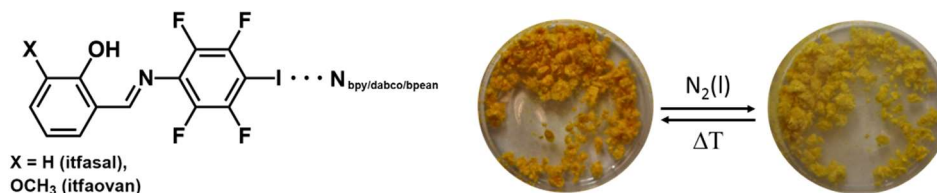
## THERMOCHROMIC IMINES AS HALOGEN BOND DONORS IN CRYSTAL ENGINEERING OF MULTI-COMPONENT CRYSTALS

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In the past few decades, halogen bonding has been shown as an efficient and predictable tool in crystal engineering.<sup>[1]</sup> It has been predominantly investigated in multi-component crystals consisting of organic perhalogenated compounds as halogen bond donors and various organic and metal-organic compounds as halogen bond acceptors.<sup>[2]</sup> While many multi-component systems contain imines as halogen bond acceptors,<sup>[3]</sup> there are scarce examples of those that contain them as halogen bond donors.<sup>[4]</sup> In this work, we have prepared two peripherally perhalogenated imines by reaction of 2,3,5,6-tetrafluoro-4-iodoaniline with salicylaldehyde (**itfasal**) or *ortho*-vanillin (**itfaovan**). Both imines were cocrystallized in 2:1 molar ratio with selected acceptors: 4,4'-bipyridine (**bpy**), 1,4-diazabicyclo[2.2.2]octane (**dabco**) and 1,2-bis(4-pyridyl)ethane (**bpean**). Cocrystals were prepared by liquid-assisted grinding and crystallization from ethanol, and characterized by X-ray diffraction methods. Structural characterization revealed that in all six cocrystals **itfasal** and **itfaovan** are bonded with acceptors *via* I...N halogen bonds. Both imines and their cocrystals show reversible thermochromic behavior when cooled in liquid nitrogen.



**Acknowledgments.** This research was supported by the Croatian Science Foundation under the project IP-2019-04-1868.

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## INCLUSION COMPLEXES OF MELOXICAM AND SELECTED CYCLODEXTRINS IN SOLUTION AND IN THE SOLID STATE

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Meloxicam (MEL) is a non-steroidal anti-inflammatory drug with low solubility and high permeability, used in the treatment of rheumatoid arthritis and osteoarthritis.<sup>[1]</sup>

Cyclodextrins (CD) are cyclic oligosaccharides containing six ( $\alpha$ -CD), seven ( $\beta$ -CD) or eight ( $\gamma$ -CD) glucose subunits, linked with ( $\alpha$ -1,4)-glycosidic bond. Their ability to improve the solubility of drugs by forming inclusion complexes is well known.<sup>[2]</sup>

The influence of  $\beta$ -CD and its hydroxypropyl derivative (HP $\beta$ CD) on MEL solubility in water and buffered solutions at different pH values has already been studied.<sup>[1,3,4]</sup>

Mechanochemical activation by grinding is a fast, efficient, and environmentally friendly method of preparing inclusion complexes in the solid state.<sup>[5]</sup> A previous study confirmed it as suitable for preparation of MEL/ $\beta$ -CD complex.<sup>[1]</sup>

The aim of this study was to investigate the influence of  $\beta$ -CD and its sulphobutylether derivative (SBE $\beta$ CD) on the solubility of MEL in water and biorelevant media (simulated gastric, pH 1; duodenal, pH 4.5 and intestinal media, pH 6.8) according to the method presented by Higuchi and Connors.<sup>[6]</sup> Phase solubility diagrams were constructed, and stability constants, complexation efficacies and solubility enhancement were determined. Inclusion complexes in the solid state were then prepared by grinding and characterized by IR spectroscopy.

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## THE EFFECT OF MESOGENIC CORE ON LIQUID-CRYSTALLINE BEHAVIOUR

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A liquid crystal (LC) is a state of matter that occurs between solid and liquid. The molecular shape influences the packing of molecules and also determines the longer-range attractive and repulsive forces responsible for the stability of liquid-crystalline phases. Changing the structures of the mesogenic units and the terminal groups attached to them, varying the length of the spacer and the links between it and the mesogenic units enables investigation of structure-property relations.<sup>[1]</sup> The chirality of molecules in LC has a remarkable influence on the macroscopic physical properties of these systems, including the appearance of new phases.

Our study has been focused on the synthesis of LC molecules with chiral aryl-3-hydroxy propanoate mesogenic core and its influence on the formation of mesophases (Figure 1). The utilisation of different aromatic groups changes the electron distribution within the mesogenic core. The incorporation of the naphthyl group broadens the molecule, while a biphenyl group extends its length and polarizability of the mesogenic core promoting interactions between identical mesogenic units.<sup>[2]</sup>

Synthetic pathway and a comparison of the mesomorphic properties of aryl-3-hydroxy propanoate compounds will be discussed.

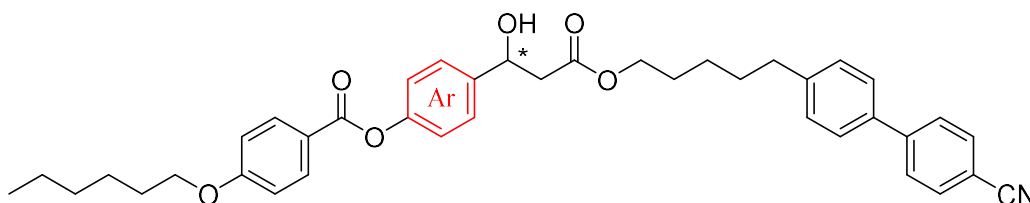


Figure 1. The general structure of target LC molecules.

**Acknowledgments.** The authors thank the Croatian Science Foundation [grant ref. IP-2019-04-7978] for financial support.

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## INFLUENCE OF THE SPACER LENGTH ON MESOGENIC PROPERTIES OF CHIRAL LIQUID CRYSTAL DIMERS

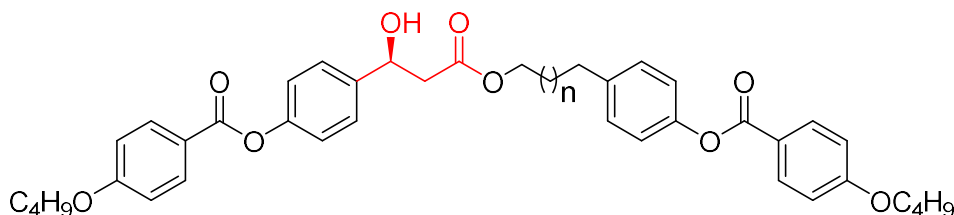
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Liquid crystal (LC) dimers consist of molecules containing two mesogenic units connected by a flexible spacer. This class of materials exhibits interesting phase behavior and the presence of a chiral center in such dimers can have various consequences as chirality may cause a formation of an intrinsic helical structure.<sup>[1]</sup> It is known that parity and the length of the spacer strongly affect the transitional behavior and molecular bending.<sup>[2]</sup> Also, recently was discovered the bent-shaped molecules can induce spontaneous chirality in systems composed of achiral molecules.<sup>[3]</sup> Knowing all of this, it is interesting to investigate the impact of molecular chirality and the influence of the spacer length on chiral LC phases of the bent-shaped dimers.

Our research is focused on the development of chiral liquid crystal dimers including phenyl-3-hydroxy propanoate ester moiety as a source of chirality. The difference in mesomorphic behavior by varying the length of the spacer of such chiral dimers will be discussed (Figure 1).



**Figure 1.** General structure of chiral bent-shaped dimers having different spacer length.

**Acknowledgments.** The authors thank the Croatian Science Foundation [grant ref. IP-2019-04-7978 and DOK-2020-01] for financial support.

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## SYNTHESIS AND BIOLOGICAL ACTIVITY OF NOVEL AMIDINO-SUBSTITUTED BENZIMIDAZOLES AND BENZOTHAZOLES

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Leentje Persoons, <sup>c</sup> Dirk Daelemans <sup>c</sup>

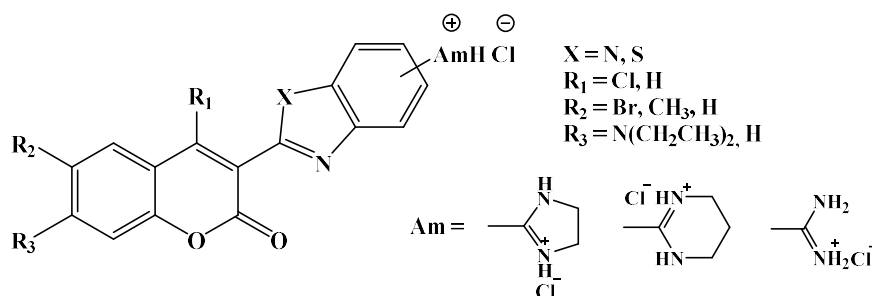
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Benzimidazole and benzothiazole are important scaffolds in pharmaceutical applications, associated with a wide variety of medicinal and biological activities. Amidine substituents at the termini of the molecule seem to contribute significantly to the molecule - possible biological target complex stability through H-bonding and electrostatic interactions.<sup>[1]</sup> This work presents the synthesis of novel amidino-substituted coumarine derived benzimidazoles and benzothiazoles as hydrochloride salts. Target compounds were prepared by conventional reactions of organic syntheses as well as by microwave assisted reactions. The synthesized compounds were explored for their antioxidative activity *in vitro* by using three biological assays, namely DPPH, FRAP and ABTS, as well as antiproliferative activity on several human cancer cells *in vitro*.<sup>[2]</sup>



**Figure 1.** The structures of newly prepared amidino-substituted benzimidazole and benzothiazole derivatives

**Acknowledgments.** This work was funded by the Croatian Science Foundation (HRZZ-4379, AntioxPot).

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## STABILITY OF AMIDINO SUBSTITUTED BENZOTHAZOLE DERIVATIVES WITH ANTITUMOR ACTIVITY

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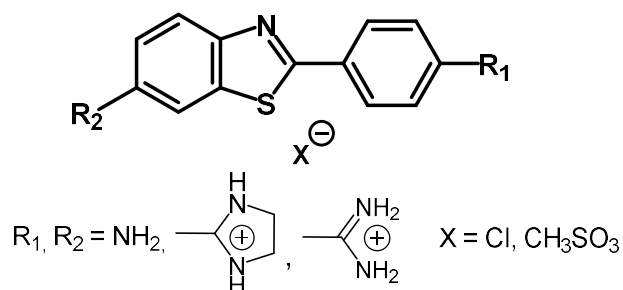
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Benzothiazoles have attracted attention in medicinal chemistry as potential biological agents with antitumor activity. Forced degradation tests<sup>[1]</sup> is necessary to conduct to determine and characterize newly formed by-products that may affect the safety and efficacy of the active ingredients. In order to investigate the intrinsic stability and identify degradation products, newly synthesized amidino-substituted benzothiazole derivatives were exposed to different conditions. Photolytic, hydrolytic, oxidative and thermal degradation of benzothiazole derivatives were performed. High resolution mass spectrometry (UHPLC-QTOF-MS/MS) was used for separation, identification and characterization of degradation products. Their structures as well as degradation pathways were given.



**Acknowledgments.** This study has been fully supported by the Croatian Science Foundation under the project IP-2018-01-4379.

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## NOVEL IMINOCOUMARIN DERIVED IMIDAZO[4,5-*B*]PYRIDINES AS POTENTIAL PH SENSORS

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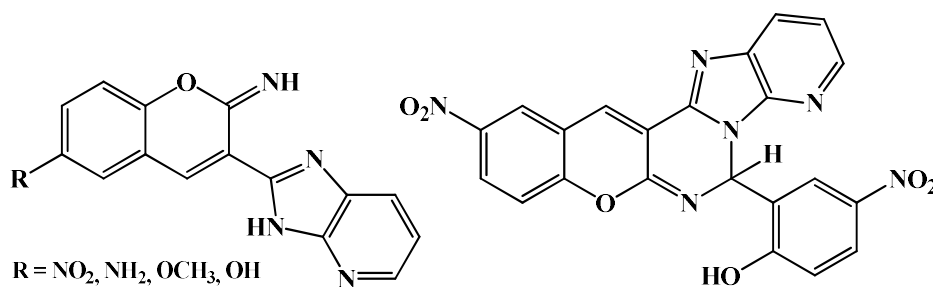
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Benzazoles and coumarins are among the most privileged heterocyclic subunits in the medicinal chemistry due to their wide range of bioactivity.<sup>[1]</sup> Iminocoumarine derivatives are known for their interesting spectroscopic properties as well as their application as fluorescent sensors. Monitoring pH range is crucial for studying many biological processes in live cell organelles. Conjugates of benzazoles and iminocoumarins are already being explored for pH sensing applications due to excellent spectroscopic response in correlation with pH value.<sup>[2]</sup>

This work presents the synthesis and spectroscopic characterization of novel iminocoumarine derived imidazo[4,5-*b*]pyridines. Main precursor, 2-cyanomethylimidazo[4,5-*b*]pyridine, was prepared in the cyclocondensation reaction with 2-cyanoacetamide, while targeted iminocoumarine derivatives were prepared in condensation with chosen 5-substituted salicyl benzaldehydes. Nitro-substituted iminocoumarin was further condensed with 5-nitro-salicylbenzaldehyd in order to explore additional conjugation on spectroscopic and pH sensing properties. The structures of newly prepared compounds were confirmed by means of <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy as well as MS spectrometry. pH spectroscopic titrations will be performed in order to determine possible application as pH sensors in solutions followed by determination of pK<sub>a</sub> values experimentally as well as by computational approaches.



**Figure 1.** Structures of potential pH sensors

**Acknowledgments.** This work was funded by the Croatian Science Foundation (HRZZ-8090, BenzpHSens)

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## STUDY OF THE GROWTH PROCESS OF NITROSOBENZENE ADLAYERS ON GOLD SURFACE

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Adsorption of organic molecules on solid surfaces followed by their arrangements into ordered self-assembled monolayers (SAMs) and/or multilayers offers a way for design of functional materials with potential applications in areas such as catalysis, sensing, medicine, molecular electronics, etc. Surface properties of SAMs can be finely tuned by incorporation of different terminal functionalities which can be used to link specific molecules or nanostructures. It is well-known that aromatic C-nitroso compounds can exist as monomers, and *Z*- and *E*-azodioxides. Our recent studies indicated that dimerization of aromatic C-nitroso derivatives to azodioxides is also possible at metal-solution interface resulting with formation of self-assembled bilayers (SABs).<sup>[1,2]</sup>

Here, we wish to gain new insights into the on-surface assembling dynamics of nitrosobenzenes by studying the influence of solution concentration and adsorption time on formation of monolayers and bilayers on an Au(111). For this purpose, two nitrosobenzene derivatives with alkyl chains of different lengths (propyl and hexyl) ending with thiocyanate headgroup for adsorption on gold were synthesized. The growth of monolayers and bilayers of nitrosobenzene derivatives on an Au(111) surface was studied at different solution concentrations and adsorption times by using ellipsometry, atomic force microscopy (AFM) and scanning tunneling microscopy (STM). The obtained results suggest formation of more ordered adlayers and increased tendency towards bilayers at higher solution concentration and longer adsorption times.

**Acknowledgments.** This work has been fully supported by Croatian Science Foundation under the project IP-2020-02-4467.

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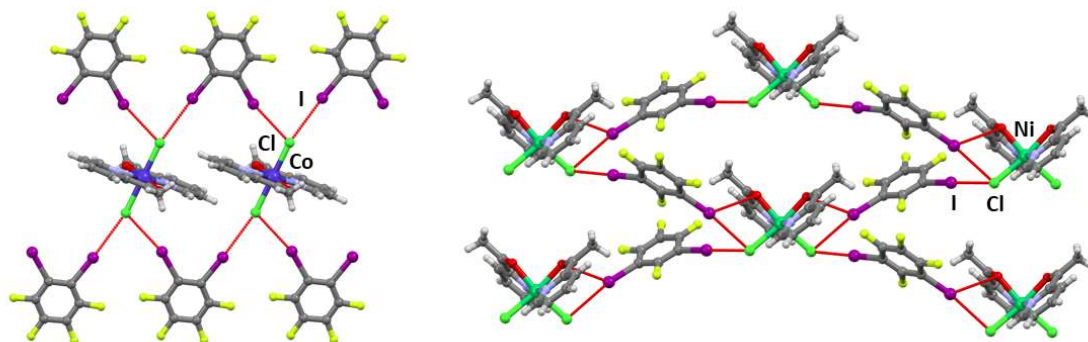
## COCRYSTALLIZATION OF COBALT(II) AND NICKEL(II) COMPLEXES WITH PERHALOGENATED HALOGEN BOND DONORS

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On the basis of our previous studies,<sup>[1,2]</sup> we report the synthesis of cocrystals derived from metal complexes  $MCl_2L_2$  ( $M = Co, Ni$ ;  $L = 2\text{-benzoylpyridine (bzpy)}$  and  $2\text{-acetylpyridine (acpy)}$ ) and six halogen bond donors: 1,4-diiidotetrafluorobenzene, 1,3-diiidotetrafluorobenzene, 1,2-diiidotetrafluorobenzene, 1,3,5-triiidotrifluorobenzene, iodopentafluorobenzene and octafluoro-1,4-diiidobutane. Cocrystals preparation was conducted by both mechanochemical and solution synthesis. Mechanochemical experiments yielded 25 new crystalline phases, while 5 cocrystals containing Ni(II) metal–organic units and 16 with Co(II) units were structurally characterized by single crystal X-ray diffraction. In all cocrystals the dominant supramolecular interaction is the  $I\cdots Cl$  halogen bond which connects halogen bond donors and metal–organic halogen bond acceptors into the discrete complexes, chains or 2D networks. Also, structure analysis revealed that cocrystals contain *cis*- as well as *trans*- $MCl_2L_2$  building blocks. For structures containing  $CoCl_2bzpy_2$  unit in 5 cocrystals *trans*-isomer is present, while in the other 5 cocrystals *cis*-isomer occurs. On the other hand, in cocrystals containing  $CoCl_2acpy_2$  unit *cis*-isomer dominates, occurring in 5 of 6 structures. Regarding cocrystals with  $NiCl_2L_2$  metal–organic units, which are all isostructural with Co(II) counterparts, 4 cocrystals with  $NiCl_2bzpy_2$  units include *trans*-isomer, whereas only one cocrystal obtained with  $NiCl_2acpy_2$  contains *cis*-isomer.



**Acknowledgments.** Croatian Science Foundation, project HaloBond IP-2019-04-1868

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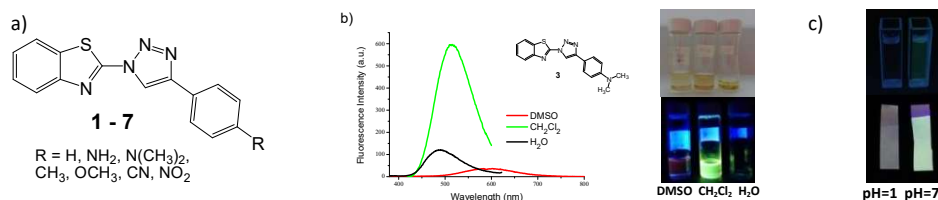
## SYNTHESIS AND OPTICAL SENSING PROPERTIES OF NOVEL 1,2,3-TRIAZOLYL-BENZOTHAZOLES

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Benzothiazole unit is an attractive building block in the design of novel fluorescent dyes because of its  $\pi$ -bridging and electron-withdrawing characteristics as well as high chemical and photophysical stability compared to other heteroaromatics. Introduction of different electron donating and/or electron-withdrawing substituents in the benzothiazole core can significantly affect the optical characteristics of the resulting molecule.<sup>[1]</sup> *Click*-derived 1,2,3-triazoles play important roles in sensing mechanisms as they can act as a covalent linkage between benzothiazole and a corresponding functional group or can directly participate in binding of the target analyte.<sup>[2]</sup> In this work we present the synthesis of novel benzothiazole-1,2,3-triazole conjugates using *click*-chemistry approach (Figure 1a). The compounds are examined as potential chemosensing molecules in solutions using UV-vis absorption and fluorescence spectroscopy (Figure 1b). To further investigate the potential use of these novel fluorophores in the design of sensing materials, paper test strips were prepared by drop casting the solution in  $\text{CH}_2\text{Cl}_2$  and are examined as pH probes (Figure 1c) as continuation of our ongoing research.<sup>[3]</sup>



**Figure 1.** a) Novel 4-aryl-substituted 1-benzothiazolyl-1,2,3-triazoles. b) Emission spectra and photographs of **3** in DMSO,  $\text{CH}_2\text{Cl}_2$  and  $\text{H}_2\text{O}$ . c) Effect of pH on optical properties of **3**.

**Acknowledgments.** This work was funded by the Croatian Science Foundation (project HRZZ-3386, iNFiNiTE-SENS).

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## NOVEL NAPHTHALIMIDE–BASED “ON-OFF” FLUORESCENT PROBES FOR DETECTING Hg<sup>2+</sup> AND Cu<sup>2+</sup> IONS

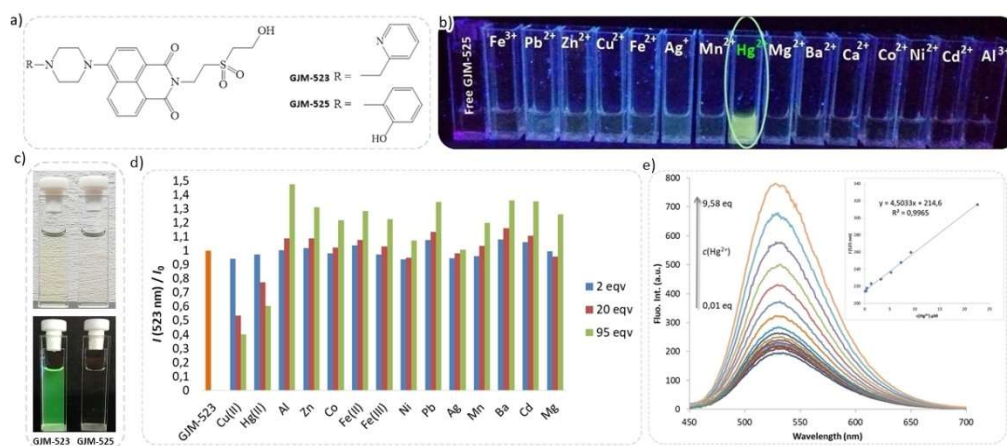
Kristina Pršir,<sup>a</sup> Mislav Matić,<sup>a</sup> Marlena Grbić,<sup>a</sup> Gerhard J. Mohr,<sup>b</sup> Svjetlana Krištafor,<sup>a</sup> Ivana Murković Steinberg<sup>a,\*</sup>

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Fluorescence-based optical sensors and chemosensors provide a simple, rapid, low-cost but highly sensitive method for measurement of metal ions at very low concentrations.<sup>[1]</sup> Photoinduced electron transfer (PET) sensors comprising 1,8-naphthalimides are particularly popular for molecular fluorescent “switch” designs.<sup>[2]</sup> We characterised two novel 1,8-naphthalimide-based fluorescent probes for Cu<sup>2+</sup> and Hg<sup>2+</sup>. Different functional groups attached at the C-4 position in **GJM-523** and **GJM-525** (Figure 1a) show a notable effect on the optical properties in the presence of metal ions. The fluorescence quenching of the highly emissive compound **GJM-523** (Figure 1c) is attributed to the formation of the 1:1 complex with either Cu<sup>2+</sup> or Hg<sup>2+</sup> (Figure 1d). The detection limits achieved with **GJM-523** are in the subnanomolar range. **GJM-525** forms a 1:2 complex with Hg<sup>2+</sup> ions, which hinders the PET process and induces the fluorescence into the ON state (Figure 1b). The results show remarkable selectivity towards Hg<sup>2+</sup> ions and a satisfactory limit of detection (Figure 1e).



**Figure 1.** a) Structures of **GJM-523** and **GJM-525**; b) **GJM-525** in the presence of metal ions; c) Images of free **GJM-523** and **GJM-525** in methanol ( $c = 10,0 \mu\text{M}$ ) in daylight (above) and under UV lamp (down); d) Change of fluorescence intensity at 523 nm for **GJM-523** in presence of metal ions; e) Fluorescence titration spectra of **GJM-525** with Hg<sup>2+</sup> and corresponding calibration curve (inset).

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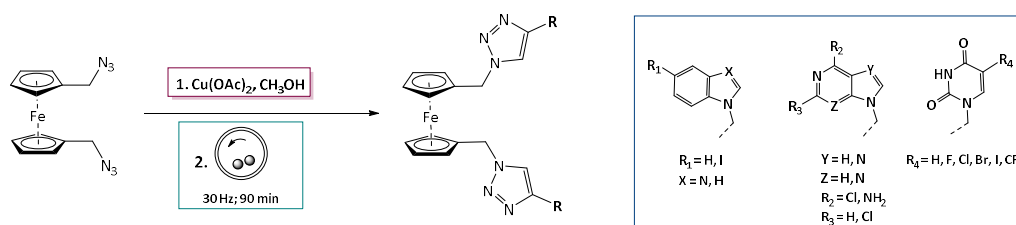
## SYNTHESIS OF NEW PURINE AND PYRIMIDINE 1,1'-DISUBSTITUTED FERROCENE CONJUGATES USING MECHANOCHEMISTRY

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Resistance to currently available antitumor drugs and their low specificity calls for an intensive search for new, more efficient and selective therapeutic agents. Ferrocene has attracted particular attention in cancer drug research due to its stability in aqueous media, steric, electronic and redox properties as well as low toxicity.<sup>[1]</sup> In our previous study,<sup>[2,3]</sup> we prepared a number of purine and pyrimidine mono-substituted ferrocene derivatives with good anticancer activity *in vitro*. Keeping in mind the biological potency of aforementioned mono-substituted ferrocenes, by employing both conventional Cu(I) catalysed 1,3-dipolar cycloaddition synthesis and liquid-assisted mechanochemical CuAAC synthesis, we have synthesised new conjugates of pyrimidine, purine and its bioisosteres and 1,1'-disubstituted ferrocenes linked through the 1,2,3-triazole ring (Scheme 1). The mechanochemical method was more effective in terms of reducing the reaction time and enhancing the product yield compared to the classical solution-based synthesis.



**Scheme 1.** Synthesis of novel purine and pyrimidine 1,1'-disubstituted ferrocenes.

**Acknowledgments.** This work was funded by *Croatian Science Foundation* (HRZZ-IP-2018-01-4682).

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## ION INFLUENCE ON PRETRANSITION OF MULTILAMELLAR PHOSPHATIDYLCHOLINE LIPOSOMES

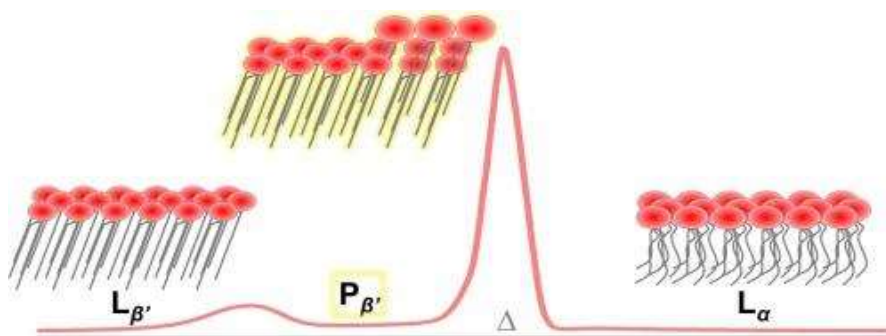
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Depending on temperature and composition, lipid bilayers can exist in different phases among which the most significant are those of gel ( $L_{\beta'}$ ) and fluid ( $L_{\alpha}$ ) phase, respectively. The transition between these phases ( $L_{\beta'} \rightarrow L_{\alpha}$ ) is assigned as the main phase transition and has a peak at melting temperature ( $T_m$ ).<sup>[1]</sup> One of the most puzzling phases in lipid bilayers constituted from 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) is ripple phase ( $P_{\beta'}$ ) which is characterized by periodically undulations of lipid bilayer, and usually appears few degrees below  $T_m$  ( $T_p$ ;  $T_p < T_m$ ) (Scheme 1).<sup>[2]</sup> A promising strategy in characterization of lipid phase transitions includes differential scanning calorimetry<sup>[1]</sup> and spectroscopic techniques, the results of which are supported with appropriate chemometric tool.<sup>[3]</sup> As small changes in aqueous environment can exert significant impact on the arrangement of lipid bilayers of DPPC, the effect of qualitatively different buffers of different pH values on ripple phase of DPPC was examined. All experimental results are supplemented with computational study.



**Scheme 1.** Phase transition of DPPC liposomes ( $L_{\beta'} \rightarrow P_{\beta'} \rightarrow L_{\alpha}$ ).<sup>[3]</sup>

**Acknowledgments.** We thank Croatian Science Foundation for the financial support within the project „Model of demyelination on a molecular scale at physiological and pathological conditions“ (HrZZ UIP-2020-02-7669).

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## ANTIMICROBIAL ACTIVITY OF QUATERNARY AMMONIUM COMPOUNDS DERIVED FROM PYRIDINIUM-4-ALDOXIME

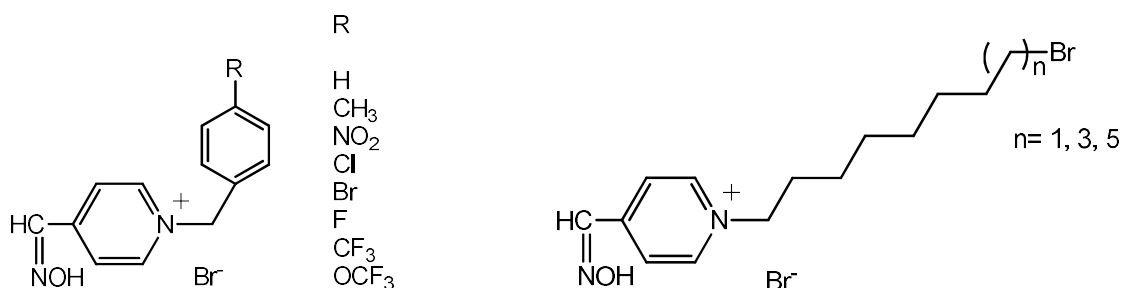
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Quaternary ammonium compounds (QACs) are known for their potent antimicrobial activity, however, new data show that environmental bacteria developed resistance pointing to the importance for new QACs discovery. Our previous studies have shown that quaternary salts of heterocyclic derivatives, 3-substituted quinuclidine and benzylimidazole, have good antimicrobial activity acting on the bacterial membrane and binding to DNA.<sup>[1,2]</sup>

Led by these findings, we used pyridinium-4-aldoxime as biologically active heterocyclic precursor known for its antidote application. For reactions of quaternization we used different aryl/alkyl bromides obtaining corresponding QACs in very good yields (Scheme 1). New compounds were tested against a panel of pathogenic Gram-positive and Gram-negative bacteria including standard benzyltrimethylammonium bromide (BAB). Preliminary data show that quaternization of pyridinium-4-aldoxime significantly affect its antimicrobial activity irrespective of the quaternization agent. Also, all QACs obtained with alkyl reagents show lower MIC values for both Gram negative and positive bacteria, however observed values (312 µg/mL) were 100-fold higher than for BAB (2 µg/mL). Regardless, refinement of these structures, using other reagent(s) for quaternization might lead to better biological activities of pyridinium-4-aldoxime.



**Scheme 1.** Structure of synthesized and tested QACs

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## EXTRACTION OF POLYBROMINATED DIPHENYL ETHERS FROM HUMAN MILK SAMPLES

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Polybrominated diphenyl ethers (PBDEs) are a class of persistent organic pollutants (POPs) widely used as flame retardants in a variety of everyday household products.<sup>[1]</sup> They easily migrate and can enter the human organism through contaminated food and inhalation/ingestion of house dust, which are the main routes of human exposure.<sup>[2]</sup> PBDEs are lipophilic, hence, they accumulate in human milk, the most commonly used biological matrix for monitoring POP concentrations in humans.<sup>[3]</sup>

Microwave-assisted extraction (MAE) has a number of advantages, such as lower solvent consumption and processing time, reduced analyte loss as well as higher sample throughput, but it is applied almost exclusively for solid samples. This is the first application of MAE to human milk samples - the influence of sample preparation and pretreatment were investigated, and extraction conditions (type and volume of solvent, temperature) were optimized. PBDEs were extracted from freeze-dried milk dissolved in ultrapure water with *n*-hexane:acetone (1:1, v/v) and formic acid and 2-propanol as denaturing agents were added at 80 °C for 20 min. Analytical recoveries ranged from 60 to 72 %, with good repeatability (RSD 4-9 %). Undoubtedly, MAE has the potential for future use in PBDE extraction from human milk and could, under appropriate conditions, be applied in the trace analysis of other POPs from liquid samples.

**Acknowledgments.** This work has been supported in part by Croatian Science Foundation under the (project HrZZ-UIP-2017-05-6713) and the Foundation of the Croatian Academy of Sciences and Arts (grant No. 10-102/384-152-2020).

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## 2,2'-BIPYRIDINE DERIVATIVES AS HALOGEN BOND ACCEPTORS IN MULTICOMPONENT CRYSTALS

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2,2'-bipyridine has been extensively studied as a metal chelating ligand due to its robust redox stability and ease of functionalization.<sup>[1]</sup> In terms of crystal engineering, 2,2'-bipyridine and its derivatives present interesting moieties because of their flexibility and ability to form different supramolecular architectures. The usage of 2,2'-bipyridine derivatives as halogen bond acceptors has been poorly studied and their properties were explored only in terms of arylated 2,2'-bipyridines utilizing 1,4-diiodotetrafluorobenzene as a donor molecule.<sup>[2]</sup> In this work, we explored how different substituents on 2,2'-bipyridine affect halogen bond formation, by using different donor molecules, including perfluorinated halobenzenes and *N*-haloimides. Four different 2,2'-bipyridine derivatives: 4,4'-dimethyl-2,2'-bipyridine (**1**), 4,4'-di-*tert*-butyl-2,2'-bipyridine (**2**), 6,6'-dimethyl-2,2'-bipyridine (**3**) and 2,2'-biquinoline (**4**) have been cocrystallized with seven different halogen bond donors. Cocrystallization experiments were performed both mechanochemically and from the solution. Using 2,2'-bipyridine derivatives as acceptor moieties, a series of 14 cocrystals was obtained, of which 10 were structurally characterized by single crystal X-ray diffraction. Dominant interactions in most obtained cocrystals are halogen bonds, while the geometry of 2,2'-bipyridine derivatives is dependent on the halogen bond donor used.

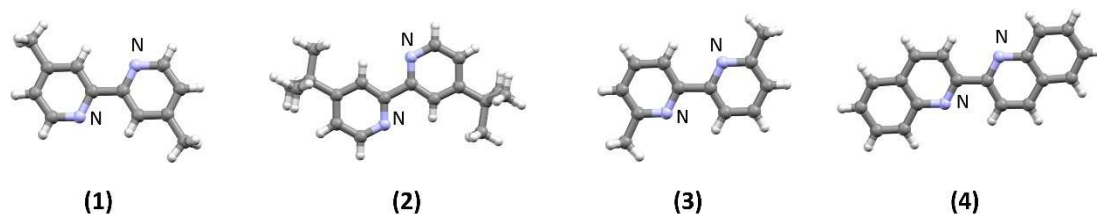


Figure 1. 2,2'-bipyridine derivatives used in this study.

**Acknowledgments.** Croatian Science Foundation (IP-2019-04-1868).

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## MOLECULAR DOCKING STUDY OF QUINUCLIDINE DERIVATIVES AGAINST CHOLINESTERASES USING MACHINE LEARNING

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Quinuclidine-based carbamates proved to be potent dual inhibitors of both acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) and can therefore be considered as potential central nervous system agents.<sup>[1]</sup> To gain better understanding of the drug-biomolecular interactions, extensive molecular docking simulations of quinuclidine derivatives and cholinesterases were performed using *ab initio* molecular dynamics (MD) coupled with extensive machine learning protocol. Binding modes of the following 3-substituted quinuclidine compounds were investigated: 3-(*N,N*-dimethylcarbamoyloxy)quinuclidine and 3-(*N,N*-diethylcarbamoyloxy)quinuclidine, as well as their quaternary *N*-methyl derivatives .

The dimensionality of the MD trajectories was first reduced by extracting only the necessary coordinates to describe the movement of the substrate within the enzyme's active site. Obtained trajectories were then further reduced in dimension by the 2<sup>nd</sup>-order tensor decomposition. In this reduced space, probability distributions (PD) of molecular geometries were calculated.<sup>[2]</sup> By finding all strict local maxima in PD functions, every possible binding mode of investigated compounds was determined. During the course of simulations strict local maxima *plateaus* in PD functions were calculated for each compound. The points at which the full configuration spaces were sampled were found by the machine learning protocol. For each molecule the minimal number of steps in MD simulations and principal components to obtain full configurational spaces was determined. For chosen Michaelis complexes QM/QM optimizations were performed and standard Gibbs energies of binding were calculated.

**Acknowledgments.** This research was funded by the Croatian Science Foundation, grants: "Young researchers' career development - Training New Doctoral Students" (ESF-DOK-2018-09-3416) and "Activity and in silico guided design of bioactive small molecules" (IP-2016-06-3775).

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## ANALYSIS OF SULFUR-CONTAINING VOLATILE COMPOUNDS FROM TWO WILD-GROWING BRASSICACEAE PLANTS BY HS-SPME/GC-MS

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The present study represents the continuation of our research on chemistry of volatile compounds from wild-growing Brassicaceae plants.<sup>[1–5]</sup> The organic compounds typically presented in plants of Brassicaceae family are glucosinolates. While glucosinolate are nonvolatile compounds, their decomposition products are volatile mostly sulfur-containing compounds. This study is focused on extraction of volatile compounds of two plants, *Capsella rubella* and *Cardaria draba*, using headspace solid phase microextraction (HS-SPME), and their analysis by gas chromatography-mass spectrometry (GC-MS). HS-SPME is a simple, fast, relatively inexpensive and solvent-free technique which is a widely used for the extraction of volatile compounds from fruits, vegetables and flowers while the GC-MS is the main analytical method for the analysis of volatile profiles of various origin.

*Capsella rubella* and *Cardaria draba* are wild-growing Brassicaceae plants widespread in mediterranean part of Croatia. They grow on open places exposed to sunlight such as fields, pastures, meadows, waste places, and along roadsides. The volatile sulfur-containing compounds have not been so commonly examined in these two plants,<sup>[1,2]</sup> especially not using above mentioned HS-SPME coupled with GC-MS.

Results presented in this study revealed that sulfur-containing compounds were qualitatively and quantitatively dominating constituents in headspaces of investigated plants. Thus, *C. rubella* headspaces were characterized by a high percentage of allyl isothiocyanate (79.3 and 67.2%) followed by allyl thiocyanate (11.0 and 8.8%). Dominating compound in headspaces of *Cardaria draba* was 4-(methylthio)butyl-isothiocyanate (91.4 and 94.2%). Considering the most abundant compounds in headspaces of investigated plants, it can be concluded that the main glucosinolate of *Capsella rubella* is sinigrin and of *Cardaria draba* is glucoerucin.

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## INTERACTIONS OF HUMAN DIPEPTIDYL PEPTIDASE III WITH COUMARINYL SCHIFF BASES

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Human dipeptidyl peptidase III (hDPP III) is a zinc-hydrolase that cleaves dipeptides sequentially from the N- terminal of different bioactive peptides. Although the physiological role of hDPP III is not yet fully elucidated, its involvement in pathophysiological processes such as mammalian pain modulation and blood pressure regulation emphasizes the need to find new hDPP III inhibitors.<sup>[1]</sup> Coumarins exhibit a variety of biological activities, and Schiff bases bearing coumarin moiety in conjunction with the imino group (-C=N-) form significant compounds in medicinal and pharmaceutical chemistry.<sup>[2]</sup> To find new potential inhibitors of hDPP III, in this research we selected 6 coumarinyl Schiff bases to investigate their interactions with hDPP III, combining experimental and computational approaches. hDPP III activity was determined using the spectrophotometric assay, while molecular docking was performed by AutoDock Vina software to obtain information regarding the possible interactions of the strongest inhibitor and hDPP III binding site. The experimental results showed that all analyzed compounds have an inhibitory effect against hDPP III activity at the physiological concentration i.e., 100  $\mu$ M. The strongest inhibition (87.9 %) has been obtained with compound **5**. Docking predicts that **5** interacts with amino acid residues of hDPP III mostly in the region of inter-domain cleft by forming hydrogen bonds with Ile386, His568 and Arg572,  $\pi$  – interactions with Phe109, Pro387 and Ala388, and numerous van der Waals interactions. Most of these residues are found to be constituents of the hDPP III substrate binding subsites S1, S1', S2, S2' and S3'. The results of this study provide an insight into the coumarinyl Schiff bases inhibitory activity and interactions toward hDPP III.

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## SYNTHESIS AND BIOLOGICAL ACTIVITY OF BIS-6-AMIDINO-BENZAZOLES LINKED THROUGH ALIPHATIC UNIT

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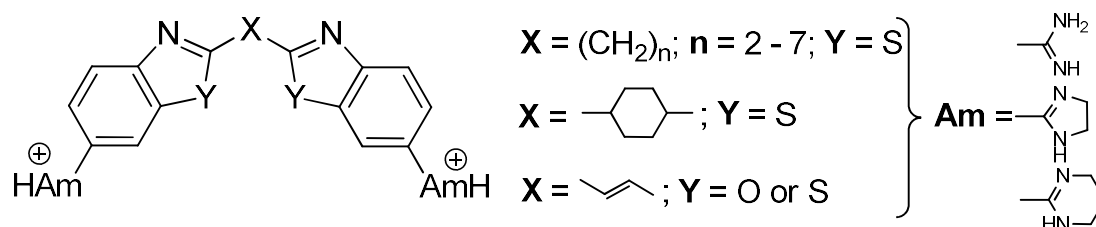
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Cationic amidine derivatives have been well established as potent antiparasitic and antitumor compounds. Our recent results of biological evaluation of amidino-substituted 2-arylbenzazole derivatives revealed strong and selective antiproliferative<sup>[1,2]</sup> as well as antitrypanosomal activities.<sup>[3]</sup> Newly designed and synthesized series of dicationic bis-6-amidinobenzazole derivatives linked with the aliphatic moiety were prepared by our previously developed method<sup>[2]</sup> and have been evaluated *in vitro* against four human tumor cell lines and protozoan parasite *Trypanosoma brucei*. Compounds with imidazolinyamidine showed activity on colorectal adenocarcinoma (SW620) with IC<sub>50</sub> = 0.2–9.7 μM, while unsubstituted amidines exhibited pronounced antitrypanosomal potency with IC<sub>50</sub> = 0.51–890 nM.



**Figure 1:** The structures of dicationic bis-6-amidinobenzothiazole and benzoxazole derivatives

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## ANION-TEMPLATED ASSEMBLY OF BIPHENYL-BIS-UREA RECEPTOR

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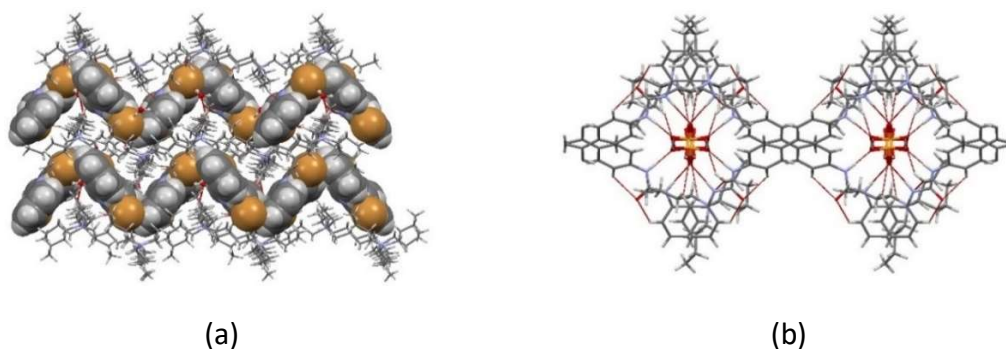
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Anionic species play an important role in many different aspects of modern society, in biology, medicine, and in the environment. Among hydrogen bonding receptors, urea derivatives play a prominent role, and therefore we designed bis-urea derivative featuring a biphenyl spacer, 1,1'-(4,4'-biphenylene)bis(3-phenylurea) (**1**). In this work we present anion binding properties of five receptor–anion complexes obtained using tetrabutylammonium salts, TBAX (X = AcO<sup>−</sup>, H<sub>2</sub>PO<sub>4</sub><sup>−</sup>, Br<sup>−</sup>, I<sup>−</sup> and NO<sub>3</sub><sup>−</sup>).<sup>[1]</sup> X-ray structures of receptor–anion complexes well demonstrate the nature of urea–anion interactions and reveal some interesting and unexpected solid-state architectures (Figure 1).



**Figure 1.** Part of the crystal structure of [1-((TBA)Br)<sub>2</sub>] (a) and [1-((TBA)H<sub>2</sub>PO<sub>4</sub>)<sub>2</sub>] (b), showing binding of anions on receptor.

**Acknowledgments.** This work has been supported by the Croatian Science Foundation under the project number IP-2016-06-5983.

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## CHEMICAL PROFILE AND ENZYME INHIBITION POTENTIAL OF WATER EXTRACTS FROM CENTAUREA PLANTS

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Inhibition of important enzymes is one of the fundamental therapies for treating diseases such as Alzheimer's dementia and Diabetes mellitus.<sup>[1]</sup> Genus *Centaurea* is one of the most important genera of the Asteraceae family, with a large number of species. In Croatia there are around 80 species of this genus, of which 27 are endemic.<sup>[2]</sup> In this study, the chemical profile and enzyme inhibition potential of the water extracts of five plants of the genus *Centaurea* was determined. The chemical profile of the extracts was determined by quantitative determination of the total phenol content and the total flavonoid content. Enzyme inhibition potential of the extracts were investigated in terms of the inhibition of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) by Ellman method<sup>[3]</sup> as well as  $\alpha$ -glucosidase enzymes by method described from Brueggeman and Hollingsworth.<sup>[4]</sup> The results showed that all *Centaurea* water extracts contain a relatively small content of phenolic and flavonoid compounds. *C. scabiosa* and *C. rhenana* extracts show low inhibition of AChE, *C. triumfetti* and *C. ragusina* show very low inhibition of AChE, whereas *C. alba* does not inhibit AChE. *C. alba*, *C. rhenana* and *C. scabiosa* extracts poorly inhibiting BuChE, while *C. triumfetti* and *C. ragusina* do not inhibit this enzyme. *C. scabiosa* extract show moderate inhibition on  $\alpha$ -glucosidase. *C. rhenana* extract show low inhibition on  $\alpha$ -glucosidase enzyme, while the other extracts do not inhibit this enzyme.

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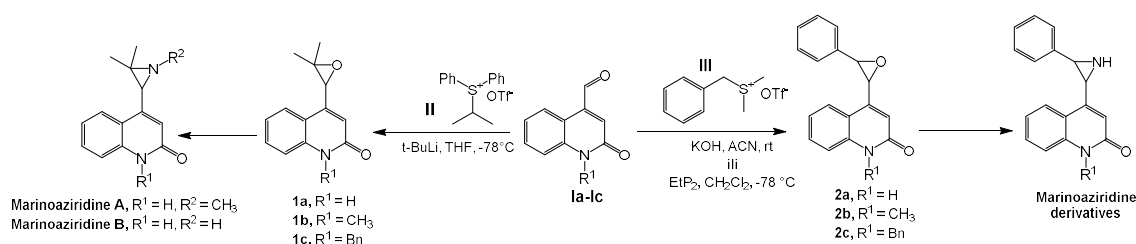
## SYNTHESIS AND ENANTIOSEPARATION OF (±)-MARINOAZIRIDINE PRECURSORS

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Aziridines are an important class of molecules present as the key structural component in a number of biologically active natural products.<sup>[1]</sup> Apart from their pharmacological purposes, aziridines are also valuable from a synthetic point of view as they can function as building blocks for the synthesis of numerous biologically active and natural compounds.<sup>[2]</sup> Our interest was primarily focused on the construction of epoxides **1a-1c** and **2a-2c** as important precursors in the total synthesis of marinoaziridines A, B and their derivatives (Figure 1). Marinoaziridines A and B are the first aziridine-based alkaloids isolated from Gram-negative bacteria from marine sediment.<sup>[3]</sup> In conducted research the (±)-marinoaziridine precursors **1a-1c** and **2a-2c** were prepared by the addition of the achiral sulfur ylide derived from sulfonium salt **I** or **II** to a carbon-oxygen double bond of the corresponding aldehydes **1a-1c** in good yield.



**Scheme 1.** Synthesis of (±)-marinoaziridine precursors **1a-1c** and **2a-2c**.

Enantioseparation of newly synthesized compounds was studied using HPLC on the "golden four" polysaccharide type chiral stationary phases. The obtained results showed that the *Chiralpak AD-3* chiral stationary phase with selector amylose *tris*-(3,5-dimethylphenyl-carbamate) proved to be the best choice in the enantioseparation of these compounds.

**Acknowledgments.** This work was supported by the program KK.01.1.1.01 of the Centre of Excellence for Marine Bioprospecting co-financed by the Croatian Government and European Regional Development Fund.

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## CONTROLLING THE PROPERTIES OF POLY(ALLYLAMINE HYDROCHLORIDE)/POLY(ACRYLIC ACID) ULTRATHIN MULTILAYER FILMS BY VARYING THE SUPPORTING ANION

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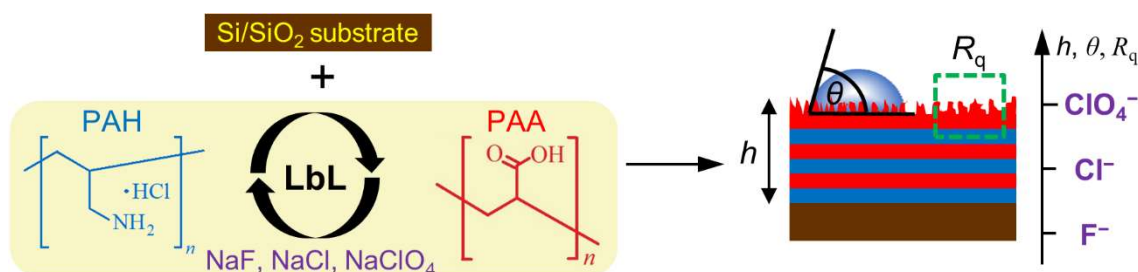
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Polyelectrolytes are macromolecules (*e.g.* polymers) with dissociating functional groups which can carry positive or negative charge in solution. By alternating adsorption of positively and negatively charged polyelectrolytes on a charged surface, polyelectrolyte multilayers are formed. These nanocomposites have interesting properties and are applied in various scientific fields, mainly in biomedicine and pharmacology.<sup>[1]</sup>

In this study, ultrathin films have been fabricated on silicon wafers from layer-by-layer assembled poly(allylamine hydrochloride), PAH and poly(acrylic acid), PAA. Ellipsometry, tensiometry, and atomic force microscopy were used to investigate the influence of the supporting sodium salt of polyelectrolyte solutions on the build-up and properties of PAH/PAA multilayer. It was found that the properties of prepared PAH/PAA multilayers follow the Hofmeister series. Thus, film thickness, hydrophobicity, and surface roughness increase in the order  $F^- < Cl^- < ClO_4^-$ . These results confirm that solely by choosing the electrolyte type, polyelectrolyte multilayers with various structures and properties can be obtained.



**Figure 1:** Changing the properties of PAH/PAA film by the nature of supporting anion.

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## SURFACE-ENHANCED RAMAN STUDY OF THE INTERACTIONS BETWEEN PYRENE DERIVATIVE OF POLYAMINE AND DOUBLE-STRANDED POLYNUCLEOTIDES

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Antitumor drugs, which bind as ligands to the double helix of deoxyribonucleic acid (DNA), are often structurally related to polyamines.<sup>[1]</sup> Since tumor cells use biogenic polyamines in much larger quantities than healthy cells, polyamines seem to be good candidates to synthesize new drugs or improve the activity of existing ones.<sup>[2]</sup>

In this work surface-enhanced Raman scattering (SERS) was used to study interactions between a new pyrene derivative of tripodal polyamine and double-stranded polynucleotides: poly dA – poly dT, poly dG – poly dC, poly rA – poly rU and calf thymus DNA. Citrate-reduced silver colloid was used as the metal substrate. Mixtures of polyamine with polynucleotides were prepared in [polyamine]/[polynucleotide] molar ratios of 1/1, 1/5 and 1/10, while concentration of polyamine was  $5 \times 10^{-6}$  mol/dm<sup>3</sup>. Polynucleotides bands were missing from the obtained SERS spectra of all prepared polyamine/DNA mixtures, while weak bands, originating from polyamine molecules, appeared in the SERS spectra of all complexes, even at large excess of polynucleotides. Pyrene rings probably intercalated between the base pairs of DNA analogues, while unbonded part of the molecules remained close to the metal surface. SERS spectra of polyamine/poly rA – poly rU mixtures showed negligible changes in intensity of polyamine bands, if compared to the SERS spectrum of free polyamine, probably due to lack of interactions between polyamine molecules and RNA.

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## SILVER AND GOLD COLLOIDS AS SUBSTRATES FOR SERS STUDY OF METHYLENE BLUE AND RHODAMINE B

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Surface-enhanced Raman scattering (SERS) spectroscopy provides a vibrational spectrum of a molecule located very close to a rough metal surface, where Raman scattering intensity increases up to a million times compared to classical Raman spectroscopy.<sup>[1]</sup> Organic dyes have been very often analyzed by SERS spectroscopy due to their aromatic structural motifs which strongly scatter radiation and fluorescence quenching of the molecules adsorbed onto the metal substrate, allowing structural studies of dyes at micromolar concentrations.<sup>[2]</sup>

In this work, colloidal suspensions of silver and gold nanoparticles, synthesized by citrate reduction of silver nitrate and tetrachloroauric(III) acid, respectively, were used as substrates for SERS study of organic dyes, methylene blue and rhodamine B, in concentration range  $1 \times 10^{-7}$ – $1 \times 10^{-4}$  mol/dm<sup>3</sup>.

When gold colloid was used as the metal substrate for SERS analysis of methylene blue, a decrease in dye concentration resulted in spectral differences. New bands appeared in the spectra and relative intensity of SERS bands, originated from phenothiazine ring vibrations, changed. Most probably, the dye molecules changed their position on the metal nanoparticles, in a way that sulfur atom from the aromatic system faced the gold surface, hence a stretching vibration of Au–S bond was observed. Using silver colloid as the SERS metal substrate, only small variations in intensity of methylene blue vibrational bands were observed, implying slight changes in position of the dye molecules on the silver surface.

In case of rhodamine B and regardless of using either gold or silver nanoparticles as the metallic substrates, concentration-dependent SERS spectra of dye showed very similar trend, including only band intensity changes with lowering dye concentration. It can be assumed that rhodamine B molecules were very similarly oriented on both metal surfaces.

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## SYNTHESIS AND CHARACTERIZATION OF OXAZOLINE AMINO ACID BIOCONJUGATES

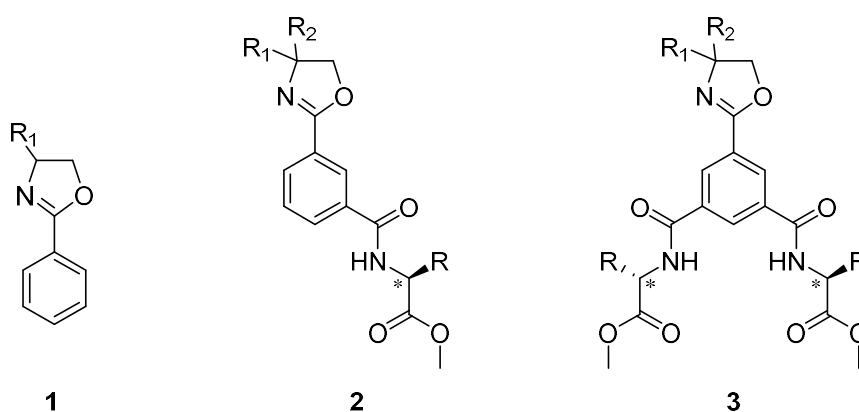
Marija Bakija,<sup>a</sup> Berislav Perić,<sup>a</sup> Srećko I. Kirin<sup>a,\*</sup>

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One of the main concerns of drug development is the transfer through the cell membrane, and even further, through the nuclear membrane via protein transduction domains, a class of diverse peptides that can target intracellular proteins.<sup>[1]</sup> In our previous work it was shown that attaching metal complexes to a protein transduction domain does facilitate the transport to the cell nucleus.<sup>[2]</sup>

In this communication, oxazoline amino acid bioconjugates **1-3** were prepared, containing none, one or two amino acid strands, Figure 1. The bioconjugates were characterized by NMR and IR spectroscopy and MS spectrometry. Initial synthetic studies with several inorganic or organometallic precursors will be reported. The metallated model compounds that show the best results will be chosen for further investigation with longer amino acid strands.



**Figure 1.** Oxazoline amino acid bioconjugates **1-3**; R, R<sub>1</sub> = H, Me or Ph, R<sub>2</sub> = H or Me.

**Acknowledgments.** This work was supported by CAT Pharma (KK.01.1.1.04.0013), a project co-financed by the Croatian Government and the European Union through the European Regional Development Fund – the Competitiveness and Cohesion Operational Programme.

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## SYNTHESIS, STRUCTURAL CHARACTERIZATION AND ANTITUMOR EVALUATION OF NOVEL 1,2,3-TRIAZOLE DERIVATIVES OF BENZOXAZOLE

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Tatjana Gazivoda Kraljević<sup>c</sup>

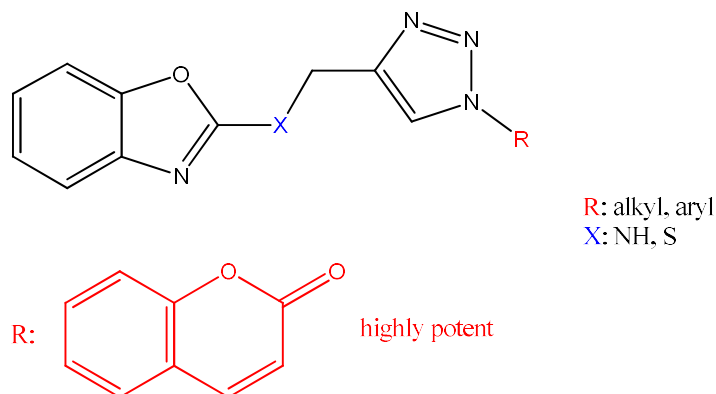
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Cancer is the result of unwanted transformations of normal cells into tumor cells that can spread uncontrollably. It is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020. The most common types of cancer in 2020. were: breast (2,26 million cases), lung (2,21 million cases), colon (1,93 million cases) and prostate cancer (1,41 million cases). Because of its frequency and high mortality rate, there is an increased demand to develop new, potent antitumor agents. Benzoxazoles represent an important class of heterocyclic compounds that exhibit a variety of pharmacological activities such as anticancer, antibacterial, antiviral, antifungal, anti-inflammatory and more.<sup>[1–3]</sup> In order to evaluate their antitumor activity, novel benzoxazole derivatives with 1,2,3-triazole ring as a linker were prepared by conventional and green synthetic methods. Benzoxazole derivative linked with coumarin ring through 1,2,3-triazole showed the most potent activity against acute lymphoblastic leukemia (DND-41, IC<sub>50</sub>= 1 μM).



**Acknowledgments.** This work was funded by the Pliva Hrvatska d.o.o. and Croatian Science Foundation (HRZZ-IP-2018-01-4682).

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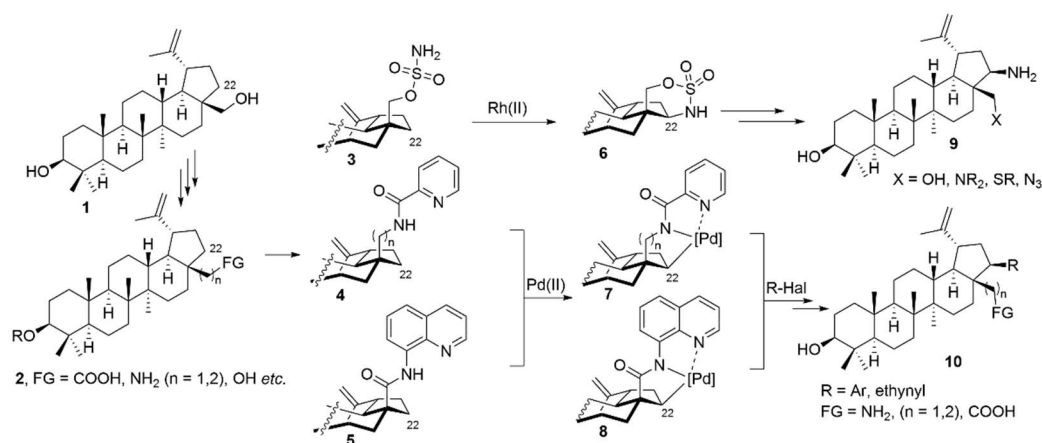
## C-H ACTIVATION OF LUPANE TYPE TRITERPENOIDS

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Betulin **1** is pentacyclic triterpenoid natural product that is observed as secondary metabolite in more than 200 different types of plants. Betulin and its derivatives exhibit several important pharmacological properties such as antitumor, anti-inflammatory, antiparasitic, and anti-viral activities.<sup>[1]</sup> The aim of this work is to obtain novel biologically active betulin derivatives by C–H functionalization at C(22). For this purpose, precursors bearing different directing groups were obtained.



8-Sulfamate ester **3** was used for *Du Bois*  $\gamma$ -C-H bond amination *via* formation of oxathiazinane **6**.<sup>[2]</sup> Intermediate **6** can be further converted into differently functionalized compounds **9** through the ring opening reactions.

8-Aminoquinoline amide **5** and picoline amides **4** were combined successfully with aryl halogenides and haloalkynes in the *Daugulis* C-H activation conditions.<sup>[3]</sup>

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## THERMODYNAMICS OF ASSOCIATION REACTION OF RUBIDIUM BROMIDE IN 2-METHYLPROPAN-2-OL + WATER MIXTURE WITH AN ALCOHOL MASS FRACTION OF 0.80

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Molar conductivities of rubidium bromide electrolyte in 2-methylpropan-2-ol + water mixture with an alcohol mass fraction of 0.80 were measured in the temperature range from 288.15 to 308.15 K at 5 K intervals. The obtained data were analyzed by using the Fuoss-Hsia conductivity equation,<sup>[1]</sup> but it was not possible to establish a reliable radius value of the formed ion-pairs ( $R$ ). The calculations were therefore repeated by using the same equation with  $R = q_{\text{Bjerrum}}$ .<sup>[2]</sup> The obtained association constants at different temperatures enable the determination of standard thermodynamic quantities ( $\Delta H^0$  and  $\Delta S^0$ ) for the discussed association reaction.

Our aim was to determine whether it was possible to apply the mentioned equation to this system. Then, from the comparison with analogous data for HBr<sup>[3]</sup> and NaBr<sup>[4]</sup> electrolytes in the mixtures of the same composition, we wanted to establish the influence of the cation exchange on the thermodynamics of the ion-pair formation. Finally, by comparing the thermodynamic quantities of RbBr electrolyte in butanol-2-ol + water mixtures,<sup>[5]</sup> we wanted to correlate a possible influence of the particular alcohol in the mixture on thermodynamic quantities of the association reaction.

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## STRUCTURAL AND ELECTROCHEMICAL STUDIES OF COBALT(II) AND NICKEL(II) COORDINATION POLYMERS WITH 6-HYDROXYNICOTINATE AND 4,4'-BIPYRIDINE

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Clive L. Oliver,<sup>b</sup> Boris-Marko Kukovec<sup>a,\*</sup>

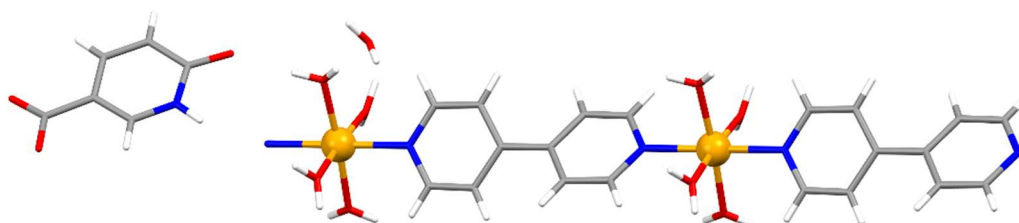
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A design of coordination polymers has become an important field of crystal engineering in the recent years due to their various functional properties and many possible applications e. g. in catalysis, gas storage and separation, magnetism, luminescence, molecular sensing etc. The control over the formation of coordination polymers with the desired frameworks and properties is especially affected by experimental conditions e. g. a choice of solvents, starting metal salts, additional ligands, temperature, hydrothermal conditions, pH value.<sup>[1–3]</sup>

The isostructural cobalt(II) and nickel(II) coordination polymers with 6-hydroxynicotinate (6-hydroxypyridine-3-carboxylate) and 4,4'-bipyridine (4,4'-bpy) were prepared under hydrothermal conditions. Their hydrogen-bonded frameworks consist of 1-D polymeric  $\{[M(4,4'-bpy)(H_2O)_4]^{2+}\}_n$  (M = Co, Ni) cations, 6-hydroxynicotinate anions and crystallization water molecules (Figure 1), resulting in a formation of various hydrogen-bond motifs. In spite of being isostructural, these coordination polymers showed different electrochemical behavior, which can be attributed to the nature of metal ions (cobalt(II) vs. nickel(II)).



**Figure 1.** The molecular structure of cobalt(II) coordination polymer.

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## MECHANICAL PROPERTIES OF COPPER(II) AND CADMIUM(II) HALIDES EQUIPPED WITH 3-NITROPYRIDINE LIGANDS

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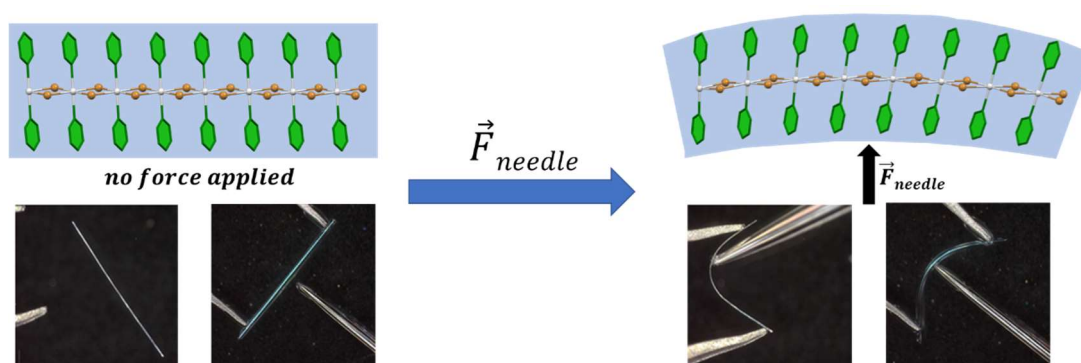
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For a long time crystals were considered to be brittle and rigid substances that readily break when external mechanical force is applied. Recent research has shown that crystals can also exhibit elastic and plastic deformations under mechanical force. Our research on 1D cadmium(II) halide coordination polymers equipped with halogen substituted pyrazine ligands has shown that the obtained crystals can deform elastically and revert to their original shape as mechanical force is applied and released.<sup>[1]</sup> It was also shown that intermolecular interactions could indeed play a crucial role in defining the mechanical properties of these compounds. Halogen bonds found in this class of compounds are classified as relatively weak and comparable to weak hydrogen bonds.<sup>[2]</sup> Therefore, if the organic ligands are replaced by similar small and rigid ones bearing weak hydrogen bond donors, crystals should also be able to produce similar mechanical output.

To test this hypothesis and further explore the effects of intermolecular interactions on mechanical properties of prepared crystals we opted to use 3-nitropyridine ligands as weak hydrogen bond donors and to further extend our research to copper(II) halides since they also form 1D coordination polymers. Coordination polymers of Cd(II) and Cu(II) halides (Cl, Br) with 3-nitropyridine ligands were prepared using the liquid diffusion method. All four possible coordination polymers were obtained, and their crystal structures were determined. Their mechanical properties were studied using a modified three point bending method and correlated with crystal structural features.



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## SURFACE REACTIONS IN AQUEOUS SOLUTIONS OF INSOLUBLE OXIDES (TiO<sub>2</sub>) AND POORLY SOLUBLE OXIDES (SiO<sub>2</sub>)

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Mineral/aqueous electrolyte interfaces play an important role in numerous environmental and technological processes. At the metal oxide surfaces the surface complexation and adsorption of ions and molecules take place.<sup>[1]</sup> However, in some cases dissolution, crystal growth, surface transformation and degradation may occur. Two oxides were selected for this purpose, titania (TiO<sub>2</sub>), the naturally occurring insoluble oxide, and silica (SiO<sub>2</sub>), most commonly found in nature as quartz. Surface charge of insoluble metal oxide TiO<sub>2</sub> depends on protonation and deprotonation reactions, while for SiO<sub>2</sub> the interfacial water molecules additionally affect the electrical charge.<sup>[2]</sup> The solubility of silicon dioxide in water strongly depends on its crystalline form, particle size and pH value. The surface properties of TiO<sub>2</sub> and SiO<sub>2</sub>, namely surface charge, surface potential, and electroneutrality points were examined by means of acid-base potentiometric titration, potentiometric mass titration and electrophoresis. The size distribution was measured by dynamic and static light scattering. Surface properties were determined under different compositions of electrolyte solutions (ionic strength and pH) in which the examined surfaces are insoluble but also under conditions in which dissolution occurs. Mineral dissolution can be either diffusion controlled or kinetically controlled by surface reactions. During the dissolution of the mineral surface, the formation of electrical interfacial layer and formation of the charged surface groups take place which influence diffusion and distribution of ions between the interfacial layer and bulk solution. The dissolution process was examined by electrophoretic and calorimetric measurements as well as time monitoring of particle size distribution by static light scattering. The aim of this research is to obtain detailed mechanism and coupling of surface reactions and dissolution at titania and silica aqueous electrolyte interfaces.

**Acknowledgments.** This research was supported by the Croatian Science Foundation (HRZZ) under the project IP-2020-02-9571.

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# SIMULTANEOUS REGRESSION ANALYSIS OF TITRATION DATA OBTAINED BY SEVERAL ANALYTICAL METHODS

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Host-guest binding is characterized by several thermodynamic reaction quantities, of which the stability constant is surely the most important one. This quantity is routinely determined from the titration data by regression analysis. When the number of equivalent binding sites is also a variable in the fitting procedure, in certain cases, a significant correlation between the stability constant and the number of binding sites can occur. This correlation can be averted by the simultaneous fit of the data obtained by multiple titrations that differ in the analytical concentration range of the reactants and, not necessarily, by the analytical method used. For the purpose of simultaneous multivariate fitting of spectrophotometric, fluorimetric, circular dichroism and calorimetric titration data a program named Globalfit was written in Wolfram Mathematica Language. The employed procedure for the stability constant determination from the multivariate spectrometric data was similar to the one described in the paper by Gampp et al.<sup>[1]</sup> Simplex optimization method was used for the optimization. Globalfit program was successfully tested on simulated and experimental titration data from Ref..<sup>[2]</sup>

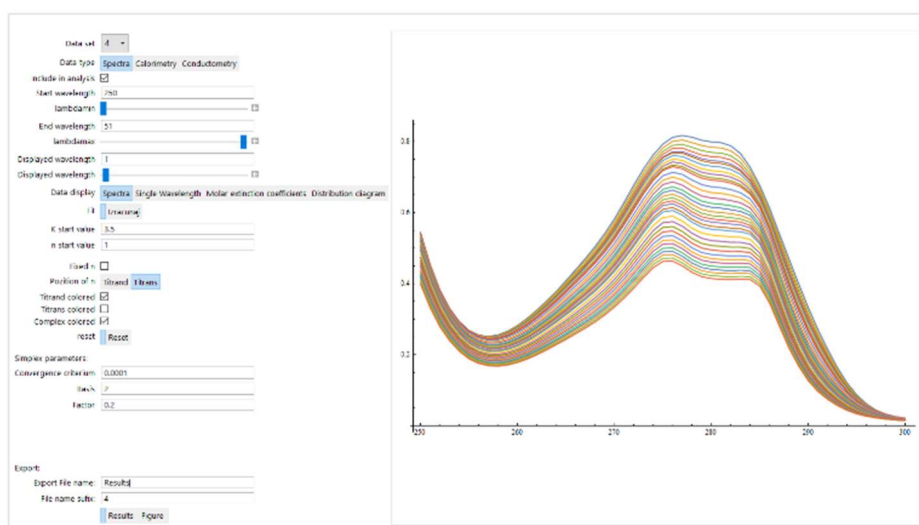


Figure 1: Graphical user interface of Globalfit software

**Acknowledgments.** This work was supported by the Croatian Science Foundation under project IP-2019-04-9560 (MacroSol).

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## ANION BINDING PROPERTIES OF TWO PENTAMERIC HOMOCYCLOPEPTIDES IN ACETONITRILE AND METHANOL

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A class of macrocyclic compounds that contains amide groups in their backbone and can be used as selective receptors of anionic species are cyclopeptides.<sup>[1,2]</sup> Rather good complexation properties of these compounds can be attributed to the remarkable hydrogen-bonding donor properties of the amide groups. In addition, the well-structured, yet sufficiently flexible structure of the cyclopeptides, as well as the presence of multiple functional groups oriented in the appropriate direction, with the additional possibility of modifying the peptide backbone and/or the side chains, contribute to the high efficiency and selectivity for anion binding of these receptors.

Here we present the studies of halides and oxoanions binding with two penta homocyclopeptide ligands, cyclopentaphenylalanine and cyclopentaleucine. In the case of cyclopentaphenylalanine binding studies were carried out in acetonitrile by spectrophotometric titrations making use of the phenyl rings as chromophores, while the affinity cyclopentaleucine towards several anions in methanol was tested by NMR and microcalorimetric titrations. Structural insight of free receptors and their anion complexes was obtained by molecular dynamics simulations.

**Acknowledgments.** This work was supported by the Croatian Science Foundation under project IP-2019-04-9560 (MacroSol).

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## THE REVERSIBLE ELECTRON TRANSFER WITHIN HYDROCHROMIC CHARGE-TRANSFER MATERIAL CONTAINING PYRIDINIUM OXIME AND HEXACYANOFERRATE(II) IONS

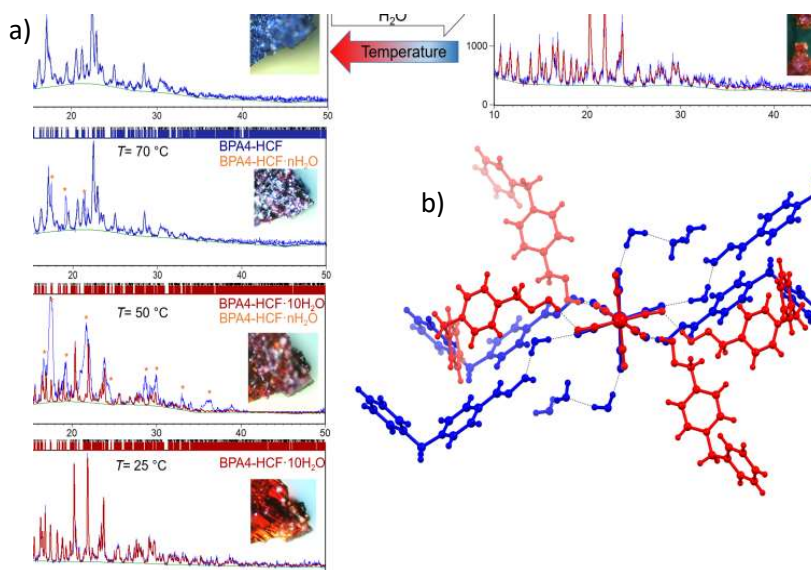
Igor Picek,<sup>a,\*</sup> Blaženka Foretić,<sup>a</sup> Dijana Žilić,<sup>b</sup> Ana Šantić,<sup>b</sup> Jasminka Popović<sup>b</sup>

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The complex of *N*-benzylpyridinium-4-oxime (BPA4<sup>+</sup>) and hexacyanoferrate(II) (HCF<sup>4-</sup>) has been recognized as the supramolecular charge-transfer material with distinct optical properties.<sup>[1]</sup> Herein, the novel insight into structural and electronic changes caused by dehydration of the reddish-brown (BPA4)<sub>4</sub>HCF·10H<sub>2</sub>O (**1**·10H<sub>2</sub>O) to blue (BPA4)<sub>4</sub>HCF (**1**) is presented. The crystal structure of **1** was solved by SCXRD and the temperature-induced dehydration was investigated by in-situ PXRD (Fig. 1). With increase in temperature, **1**·10H<sub>2</sub>O subsequently releases water molecules yielding fully dehydrated complex **1** which swiftly transforms back to **1**·10H<sub>2</sub>O with exposure to water (Fig. 1a), providing the evidence of a reversible hydrochromism. The crystal packing of **1**, where the hydroxyl group within oxime moiety forms a direct H-bond with cyano ligand, differs significantly from **1**·10H<sub>2</sub>O where the HCF<sup>4-</sup> core and BPA4<sup>+</sup> are bridged *via* H-bonded water molecules (Fig. 1b). The in-situ ESR study at different temperatures supplemented with DC conductivity and DRS spectral changes revealed that such reversible structural reorganization leads to the one electron transfer from HCF<sup>4-</sup> to BPA4<sup>+</sup> resulting in the formation of a stable radical BPA4<sup>•</sup> and a small quantity of BPA4<sup>•</sup>/HCF<sup>3-</sup> pair within complex **1**.



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## PREPARATION AND CONFORMATIONAL ANALYSIS OF 1,1'-BIADAMANTANE AND ITS DERIVATIVES

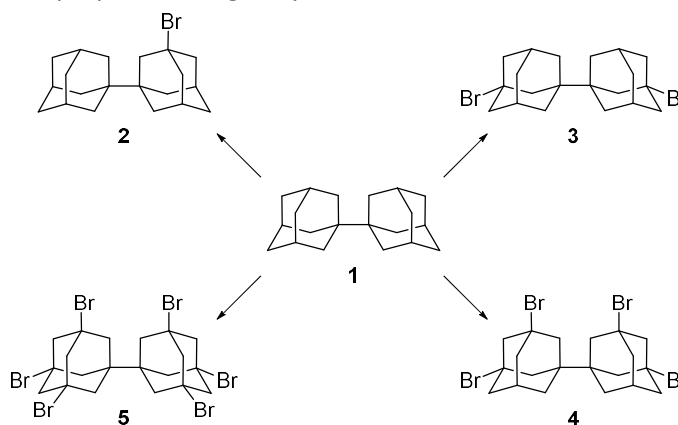
Zrinko Jurić,<sup>a</sup> Aleksandar Mandić,<sup>a</sup> Tatjana Šumanovac,<sup>b</sup>  
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Chemistry of adamantane derivatives has up to now been explored in depth,<sup>[1]</sup> but when two adamantane cages are connected through their bridgehead positions, a new cage scaffold, 1,1'-biadamantane (**1**), emerges. In the scope of this work **1** and its brominated derivatives **2–5** were obtained (Figure 1). We optimized the Wurtz reaction and the bromination reactions to achieve better yields and more effective preparation procedures when compared to the literature methods.<sup>[2,3]</sup> We found that the Wurtz reaction proceeds more effectively when using a high-pressure apparatus and when the concentration of the reactants is higher. The mono- and dibrominated derivatives **2** and **3** were prepared using only bromine, while the tetra- and hexabrominated derivatives **4** and **5** needed AlBr<sub>3</sub> catalyst as well. Target molecules were also explored by performing a DFT conformational analysis. Possible conformers are formed by a rotation around the central 1,1' C–C bond. We found that the methylene groups adjacent to the central C–C bond have a determining influence on the possibility of rotation. The brominated derivatives **2–5** will serve as a starting point in the preparation of new supramolecular host-guest systems.



**Figure 1.** Bromination of 1,1'-biadamantane (**1**).

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## DENSITY FUNCTIONAL STRUCTURE PREDICTION OF NEUTRAL PHYSIOLOGICAL COPPER(II) COMPOUNDS WITH L-CYSTEINE AND L-HISTIDINE

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To the best of our knowledge, there are no experimental data in the literature about the geometries of physiological electrically neutral (L-histidinato)(L-cysteinato)copper(II) [Cu(His)(Cys)] and bis(L-cysteinato)copper(II) [Cu(Cys)<sub>2</sub>]. These two amino acids can bind metals in a tridentate fashion and thus form many possible coordination patterns. To gain an insight into the stability of different coordination modes of these amino acids to copper(II), the density functional calculations were performed for the conformational analyses in the gas phase and in implicitly modeled aqueous solution using a polarizable continuum model.<sup>[1]</sup> The lower-energy conformations that the two compounds could form with the Cys ligand having either a protonated sulfur (as in the conventional zwitterion) or a protonated carboxylato oxygen (as in the unconventional zwitterion) were computationally examined. If deprotonated carboxylate groups in Cys are available, the bidentate glycine-like chelation of the metal atom seems to be highly preferred to a copper(II)–sulfur in-plane bonding in both cysteinato compounds. Whereas the conformers with N and thiol S as the copper(II) donor atoms are predicted to be the least stable, those with the Cu–N and Cu–S(thiolate) bonding (and protonated carboxylato group) are the most stable. The predicted metal-affinity values in aqueous solution suggest that when Cys has a protonated sulfur, the Cu<sup>2+</sup> affinity is greater for binding the Cys and His ligands than two Cys ligands; however, when the sulfur is deprotonated, the affinity of Cu<sup>2+</sup> to bind two Cys ligands in Cu(Cys)<sub>2</sub> is greater than to form the ternary Cu(His)(Cys) compound.

**Acknowledgments.** This work was supported by the Croatian Science Foundation under the project IP-2014-09-3500.

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## TRANSITION METAL COMPLEXES OF DIPICOLYLAMINE, IMINODIACETAMIDE AND BIS-TRIAZOLE DERIVATIVES

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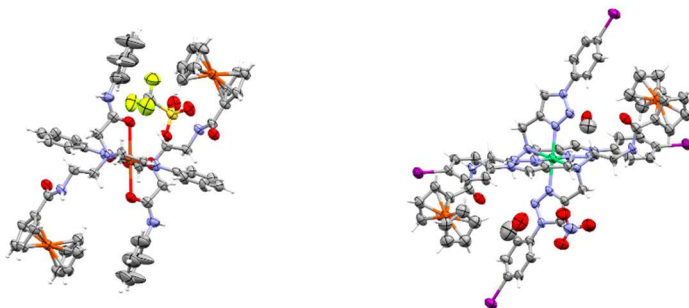
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Ferrocene compounds have attracted significant interest as biologically active derivatives. Introduction of the ferrocene moiety in drug-like molecules improves the physicochemical properties and stability of drug candidates, while the transition metals coordinated to biologically active ligands participate in metal-specific processes which enhance drug delivery and biological activity.<sup>[1]</sup> As part of our research of ferrocene derivatives and their transition metal complexes, we have prepared dipicolylamine, iminodiacetamide and bis-triazole derivatives connected to ferrocene through an ethylenediamine linker. The conjugates were used as ligands in the synthesis of Zn(II), Ni(II) and Cu(II) metal complexes. The stoichiometry and stereochemistry of the obtained complexes were examined by NMR and UV-Vis spectroscopy. We have obtained two crystal structures of metal complexes with bis-triazole ligands and one with an iminodiacetamide ligand (Figure 1). Investigation of antitumor activity is in progress.



**Figure 1.** Crystal structures of a Cu(II) complex of a bis-triazole ligand (left) and Ni(II) complex of an iminodiacetamide ligand (right)

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## DNA AND RNA BINDING STUDIES OF NOVEL AMIDINE- AND AMIDOXIME-SUBSTITUTED HETEROCYCLES

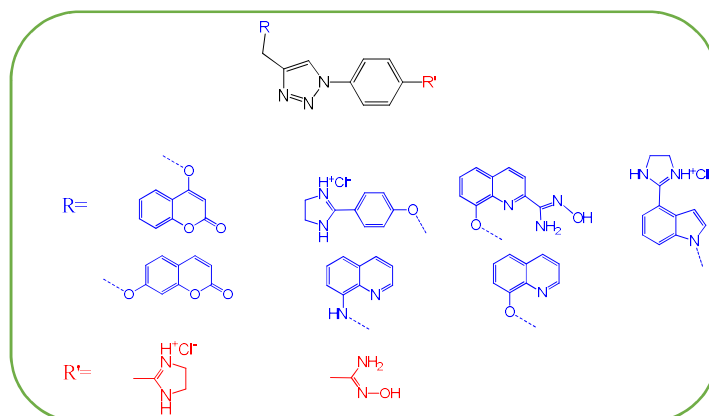
Suresh Shanmugam<sup>a,\*</sup>, Marijana Radić Stojković<sup>a</sup>, Silvija Maračić<sup>b</sup>, Silvana Raić-Malić<sup>b</sup>

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DNA is a major target for a large number of anticancer drugs due to their crucial functions in cells.<sup>1</sup> Based upon the antiproliferative activity, several compounds (**Figure 1**) from a series of novel amidine- and amidoxime-substituted heterocycles (Department of Organic Chemistry, Faculty of Chemical Engineering and Technology) were selected for the study with *calves thymus* DNA (ctDNA), alternating AT-DNA and AU-RNA.



**Figure 1.** Amidine- and amidoxime-substituted heterocycles.

Assessing the binding strength and mode of binding of small molecule-DNA interactions was performed using UV / Vis, fluorescence and circular dichroism (CD) spectroscopy. All studied compounds showed a greater stabilization effect of AT-DNA compared to ctDNA and AU-RNA. Only a derivative possessing two imidazole moieties at the end of the heteroaromatic structure stabilizes both DNA and RNA. The addition of some compounds to DNA solutions caused, either an appearance of positive induced CD spectra (ICD) or small negative ICD signals. Such changes in CD spectra suggest binding inside the DNA groove (positive ICD) or intercalative binding where the ligand is oriented "parallel" to the long axis of adjacent base pairs (negative ICD).<sup>2</sup>

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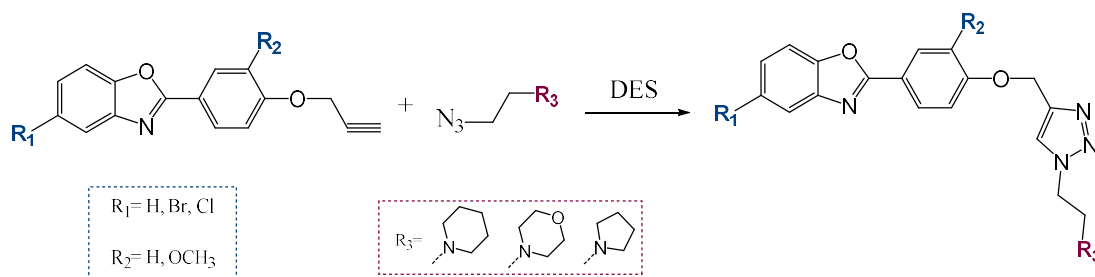
## SYNTHESIS OF NOVEL 1,2,3-TRIAZOLYL BENZOXAZOLE DERIVATIVES USING DEEP EUTECTIC SOLVENTS

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The incidence and mortality caused by cancer is growing rapidly worldwide and it is necessary to find drugs for prevention and treatment. The benzoxazole ring, as a privileged scaffold in medicinal chemistry, is widely incorporated in the structure of numerous biologically active compounds and is found in drugs such as flunoxaprofen and zoxazolamine<sup>[1]</sup>. Benzoxazole derivatives have a wide range of biological activities such as antitumor, anti-HIV, antimicrobial, anti-inflammatory, antifungal and antiviral. Furthermore, 1,2,3-triazole plays an important role as a pharmacophore and exhibits remarkable biological activity.<sup>[2]</sup> In this work, new benzoxazole derivatives substituted with 1,2,3-triazole ring were prepared by click reaction using deep eutectic solvents (DES) which are known as preferred alternative solvents for organic synthesis due to their non-toxic, stable, non-flammable and inexpensive nature.<sup>[3]</sup> The key precursors of Schiff bases for the synthesis of target benzoxazole derivatives were prepared by the condensation reaction of the corresponding 4-hydroxybenzaldehyde and 2-aminophenol in the presence of ZnO nanoparticles as catalyst. By cyclization reaction of Schiff bases with NaCN, the corresponding 2-arylbenzoxazoles were prepared, which were then converted to *O*-propargylated benzoxazole derivatives by microwave reaction with propargyl bromide. The target 1,2,3-triazolyl benzoxazole derivatives were synthesized by Cu(I) catalyzed click reaction of the corresponding azides and *O*-propargylated benzoxazoles in DES (ChCl/glycerol and D-sorbitol/urea/ NH<sub>4</sub>Cl), and their structures were confirmed by NMR spectroscopy.



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## SYNTHESIS AND ANTITUMOR EVALUATIONS OF NOVEL 2-ARYL SUBSTITUTED BENZIMIDAZOLE DERIVATIVES

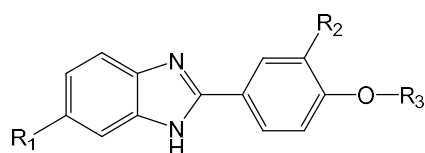
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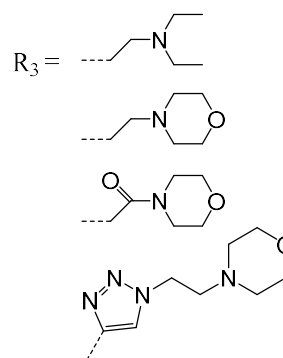
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Benzimidazole is an important pharmacophore and represents a privileged structure in medicinal chemistry.<sup>[1]</sup> Its derivatives show numerous pharmacological activities such as antituberculostatic, antimalarial, antimicrobial, antiviral, antitumor and anti-inflammatory.<sup>[2]</sup> The 1,2,3-triazole products are more than passive linkers, they readily associate with biological targets, through hydrogen-bonding and dipole interactions and attract a lot of attention as pharmacophores.<sup>[3]</sup> In this paper, we present ultrasonic and microwave cyclization reaction of *O*-alkylated benzaldehydes with variously substituted 1,2-diaminobenzene which gave 2-arylbenzimidazole derivatives. 1,2,3-triazolyl benzimidazole derivatives were prepared by Huisgen 1,3-dipolar cycloaddition reaction using copper(II) acetate as catalyst. Antitumoral evaluations of all tested compounds revealed that the 2-arylbenzimidazole derivative with *N,N*-diethyl substituent showed the most pronounced activity against antitumor cell lines: pancreatic adenocarcinoma (Capan-1, IC<sub>50</sub> = 2.2 μM), lung carcinoma (NCI-H460, IC<sub>50</sub> = 2.2 μM), acute lymphoblastic leukemia (DND-41, IC<sub>50</sub> = 2.6 μM), chronic myeloid leukemia (K-562, IC<sub>50</sub> = 2.0 μM) and non-Hodgkin lymphoma (Z-138, IC<sub>50</sub> = 2.0 μM).



R<sub>1</sub> = H, Cl, F

R<sub>2</sub> = H, F, OCH<sub>3</sub>



**Acknowledgments.** This work was funded by the Croatian Science Foundation (HRZZ-IP-2018-01-4682).

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## CHANGES IN RAT IMMUNOGLOBULIN G N-GLYCOSYLATION ARE ASSOCIATED WITH CHRONIC STRESS

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Immunoglobulin G (IgG) glycosylation corresponds well with immune system changes, so it can potentially be used as a biomarker for the consequences of chronic stress such as low-grade inflammation and enhanced immunosenescence in older animals. Here we present a high-throughput glycoproteomic workflow, including IgG enrichment, HILIC glycopeptide purification, and nano-LC-MS analysis of tryptic glycopeptides applied for the analysis of rat IgG. A cohort of 80 animals was exposed to seven stressors in a customized chronic stress protocol with blood and tissue sampling in three timepoints. Young female rats experienced an increase in agalactosylated glycoforms on IgG2a and IgG2c accompanied by a decrease in monogalactosylation. Among old females, increased galactosylation was observed in the IgG2b subclass, pointing to an anti-inflammatory activity of IgG. Additionally, IgG Fc N-glycosylation patterns in Sprague Dawley rats were analyzed, quantified, and reported for the first time. Our findings emphasize age-, sex- and subclass-dependent differences in IgG glycosylation related to chronic stress exposure, confirming the relevance of newly developed methods for further research in glycobiology of rodent immune response.<sup>[1]</sup>

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## OPTIMIZATION OF SYNTHETIC ROUTE TO FERROCENE ESTERS OF DESMURAMYL DIPEPTIDES

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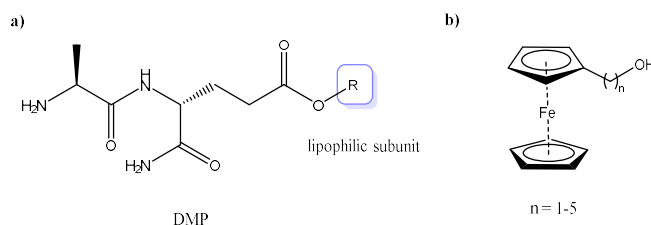
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Muramyl dipeptide (*N*-acetylmuramyl-L-alanyl-D-isoglutamine, MDP) is the smallest structural unit of peptidoglycans showing immunostimulating activity.<sup>[1]</sup> MDP analogues without the hydrophilic *N*-acetylmuramyl moiety are called desmuramyl peptides (DMP) and are extensively studied by our group as potential new adjuvants.<sup>[1]</sup> This work is a continuation of our ongoing SAR study of amphiphilic mannosyl DMP analogues and their synthesis. In order to prepare such compounds lipophilic DMP precursors are needed (Fig. 1a). Lipophilic subunits used so far have been adamantyl, adamantyl triazolyl, dodecyl and were introduced through an amide bond at the side chain or on  $\alpha$ -carbon atom of *D*-isoGln residue. In this work we are optimizing the synthesis of ferrocene esters of DMP. The lipophilic ferrocene part is introduced on the *D*-isoGln side chain *via* several ferrocene alcohols (Fig. 1b).<sup>[2]</sup> In order to obtain the ester bond modified Steglich procedure was envisioned. In the case of ferrocenemethanol this procedure was not successful due to low nucleophilicity of its hydroxyl group. Therefore, in this work, several other methods for the preparation of its ester were explored.



**Figure 1.** a) Lipophilic DMP precursors; b) ferrocene alcohols used as lipophilic subunits

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# THERMODYNAMICS OF COMPLEXATION OF ALKALI AND ALKALINE EARTH METAL CATIONS BY A PHENANTHRIDINE-BASED CALIX[4]ARENE GLYCOCONJUGATE

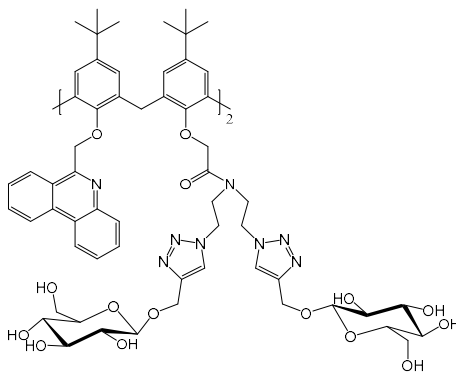
Matija Modrušan,<sup>a</sup> Renato Tomaš,<sup>b</sup> Lucija Glazer,<sup>a</sup> Nikola Cindro,<sup>a</sup>  
Katarina Leko,<sup>a</sup> Vladislav Tomišić<sup>a,\*</sup>

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Calixarene tertiary amide derivatives are well known to have very high affinities towards alkali and alkaline earth metal cations,<sup>[1–3]</sup> and can be glycosylated to produce potentially water-soluble compounds.<sup>[4]</sup> Those additionally bearing fluorescent moieties can be considered as very sensitive fluorimetric ion sensors due to the prominent sensitivity of fluorescence spectroscopy.<sup>[5]</sup> In the scope of this work the binding affinity of fluorescent, phenanthridine-based calix<sup>[4]</sup>arene glycoconjugate (Figure 1) towards alkali and alkaline earth metal cations was investigated by means of spectrophotometry, fluorimetry, microcalorimetry, and <sup>1</sup>H NMR spectroscopy. The thermodynamic parameters of the corresponding complexation reactions (*i.e.* stability constants of the complexes formed, standard reaction Gibbs energies, enthalpies, and entropies) were determined and discussed regarding the charge density and solvation of the cations as well as structural properties of the ligand.



**Figure 1.** Structure of phenanthridine-based calix[4]arene glycoconjugate.

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## MECHANISTIC INSIGHT INTO SOLID-STATE C–H BOND ACTIVATION IN AZOBENZENE BY PALLADIUM(II) CHLORIDE

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The recent advances of solid-state synthetic methods led to their application in the synthesis of palladacycles via C–H bond activation, a process known as cyclopalladation.<sup>[1,2]</sup> Since palladacycles are crucial intermediates in many organic reactions mediated by palladium catalysts, a thorough understanding of cyclopalladation pathways of different organic substrates is essential.<sup>[3]</sup> In contrast to the mechanism of palladation that is widely explored in solutions,<sup>[4]</sup> a mechanistic study of the solid-state C–H bond activation is still in its early stages.<sup>[2]</sup>

We have studied a mechanism of the ligand-directed C–H bond activation in azobenzene with palladium(II) chloride under mechanochemical conditions by *in situ* Raman monitoring and *ex situ* <sup>1</sup>H-NMR spectroscopy. *In situ* Raman monitoring revealed that solid-state dicyclopalladation azobenzene is a multi-step process including the formation of coordination and monocyclopalladated species as intermediates. Our results indicated that the mechanism of solid-state dicyclopalladation of azobenzene differs from that observed for the analog reaction in solution.<sup>[4]</sup>

**Acknowledgments.** This work has been supported by Croatian Science Foundation under project number IP-2019-04-9951 (MECHEMFUN).

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## MECHANISTIC STUDY OF MECHANOCHEMICAL REGIOSELECTIVE HALOGENATION OF AROMATIC C–H BOND WITH Pd<sup>II</sup> CATALYSTS

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Organohalides are very valuable synthetic precursors, and the transformation of carbon-halogen (C–X) bond is often one of the synthetic steps in the preparation of numerous organic and natural compounds, pharmaceutically active substances, and new materials.<sup>[1]</sup> Their preparation is traditionally limited to solvent-based synthetic procedures, and nowadays solid-state synthetic methods are increasingly being developed as their greener alternative, with mechanochemical reactions being the most prominent.<sup>[2]</sup>

Within this work, a mechanochemical procedure for regioselective halogenation of azobenzene C–H bond using Pd<sup>II</sup> catalyst has been developed and optimized. The mechanism of this process has been studied by *in situ* Raman spectroscopy accompanied by *ex situ* NMR and PXRD experiments. A strong effect of solid and liquid additives on the reactivity of the catalytically active Pd<sup>II</sup> species and intermediates has been established. Several possible palladacyclic intermediates have been synthesized and characterized, and their role in palladium-catalyzed *ortho*-halogenation of aromatic substrates has been discussed. Based on our results, a multistep reaction mechanism of this transformation has been proposed.

**Acknowledgments.** This work has been supported by Croatian Science Foundation under the project IP-2019-04-9951 (MECHEMFUN).

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## N-(4-HALOGENOBENZYL)-(3-HALOGENO)PYRIDINIUM CATIONS AS HALOGEN BOND DONORS

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Halogen bond is a valuable widely used tool for constructing supramolecular assemblies in the solid state.<sup>[1]</sup> Besides numerous studies on neutral halogen bond donors,<sup>[2]</sup> a few studies dealing with cationic halogen bond donors such as halogenopyridinium cations have been published.<sup>[3,4]</sup> In our previous work we have shown that halogen bonds in protonated iodopyridinium halogenides can even compete with hydrogen bond in binding halogenide anions.<sup>[5]</sup>

In this study, we have been interested in asymmetric ditopic monocationic halogen bond donor where one halogen bond donor atom is placed on positively charged pyridine ring while other one on “neutral” benzyl ring (the positive charge is mostly located on the pyridine nitrogen ring). We successfully prepared a series of six N-(4-halogenobenzyl)-(3-halogeno)pyridinium bromides. To study the halogen bonding potential of these cations with a wider range of (anionic) halogen bond acceptors the chloride and iodide salts were prepared by ion exchange. Single crystal X-ray diffraction experiments revealed that in these systems the halogen bonds with the halogen atoms on pyridinium rings with halogenide anions are generally relatively shorter (as compared to the corresponding van der Waals radii) than the halogen bonds with the halogen atoms on the “neutral” part of cations (benzyl ring).

**Acknowledgments.** This research was supported by the Croatian Science Foundation under the project IP-2019-04-1868.

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## SOLID-STATE SUZUKI-MIYaura CROSS-COUPPLING REACTIONS CATALYZED BY DIMERIC MONOPALLADATED AZOBENZENES

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Formation of C–C bond via metal-catalyzed cross-coupling reactions, such as Suzuki-Miyaura, Sonogashira, and Mizoroki-Heck reactions, remains of interest to organic chemists.<sup>[1]</sup> With chemistry shifting to designing new synthetic routes and protocols following a more sustainable and environmentally friendly approach, solid-state reactions have gained more traction.<sup>[2]</sup> The benefits of this approach are numerous, ranging from a broader reactants scope to the almost total omission of solvents in a chemical reaction.<sup>[3]</sup> Although solid-state methodologies provide access to a wide array of new products that are sometimes unattainable in solvent-based reactions, detailed insight into the reaction mechanisms and the role of metal catalysts in these transformations are still unexplored.<sup>[4]</sup>

Here we report the palladium(II)-catalyzed solid-state reactions of 4-halo-substituted azobenzene with phenylboronic acid as an arylating agent. Various phosphine-free dimeric monopalladated complexes of azobenzenes with different bridging ligands were synthesized, and their potential as catalysts in these reactions was studied. To gain insight into the mechanism of such processes, all reactions were monitored *in situ* by Raman spectroscopy. Results of Raman monitoring were compared with those obtained for the analogous reactions catalyzed commercially available Pd(II) catalysts.

**Acknowledgments.** This work has been supported by Croatian Science Foundation under the project IP-2019-04-9951 (MECHEMFUN).

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## APPLICATION OF MALDI-TOF-MSI METHOD ON 3D CELL MODELS

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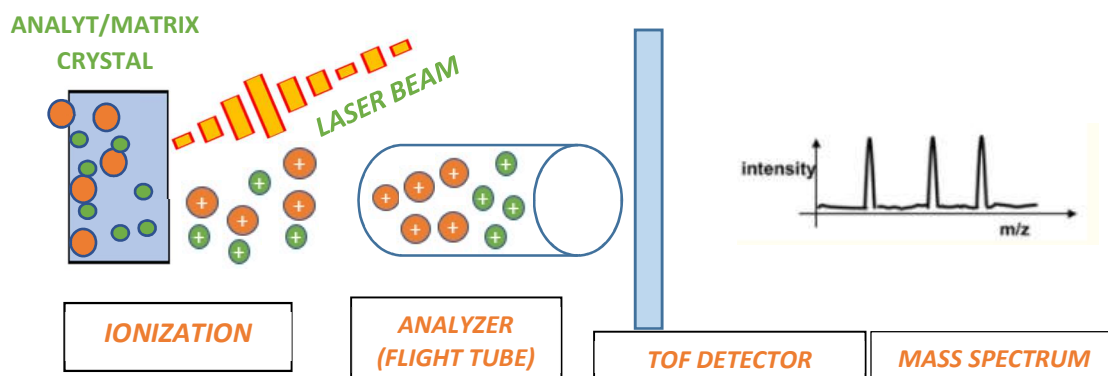
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Mass spectrometry with imaging (MSI) is an extremely powerful method that, in addition to being a research analytical technique, can also be used for targeted detection of significant molecular species. Unlike classical visualization methods, by using MSI technique, it is possible to identify hundreds of analytes simultaneously. The addition of TOF (Time of Flight) allows ion flight time to differentiate according to the value of ion mass/charge. Consequently - ions with lower  $m/z$  values travel faster. Characteristics such as the ability to scan a sample up to 20 times make this technique excellent for monitoring and reviewing the spatial distribution of different molecular species in many cell and tissue structures. Cells grown as 3D cultures are very attractive model for study in biological researches. The reason for this is the greater compatibility with *in vivo* conditions, since cells are cultured in the form of the spheroids whose microenvironment is similar to that in living tissues.<sup>[1-2]</sup> The above method with all its advantages will be used to detect the effect of organometallic compounds on 3D models of Caco-2 and Hep-G2 cell lines.



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[2] D.R. Ahlf Wheatcraft *et al.* *Jour.Vis.Exp.*, **2014**, *94*, 1-7.

## SITE-SPECIFIC GLYCOSYLATION MAPPING OF ENDOGENOUS FC GAMMA RECEPTOR IIIB DERIVED FROM NEUTROPHILS

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### Background:

Fc gamma receptors (FcγR) recognise the Fc region of immunoglobulins and together they constitute critical glycoprotein components of an antibody-dependent immune response. The crystal structure of FcγRIII and IgG complex revealed that this interaction is modulated by both protein and glycan moiety of the components. While glycosylation of IgG has been extensively studied, the glycosylation of FcγRIII receptor in either healthy or disease stage is largely uncharacterized. To address this issue, here we are presenting a comprehensive MS method which allows us to identify and relatively quantify FcγRIIIb glycosylation in a site-specific manner from individual donors. This constitutes a basis for further studies on the FcγRIIIb glycosylation involvement in autoimmune disease regulation.

### Method:

FcγRIIIb was immunoprecipitated from neutrophil cell lysate obtained by centrifugation from blood of healthy donors. It was further purified by SDS-PAGE and cleaved in-gel with chymotrypsin and endoproteinase GluC. Obtained glycopeptides, carrying a single glycosylation site each, were separated and analysed by liquid chromatography-mass spectrometry using an orbitrap Fusion Lumos MS (Thermo Fisher Scientific). Tandem mass spectrometry with higher-energy collision induced dissociation (HCD) was applied to obtain both glycan and peptide fragments from glycopeptides in single MS/MS spectrum. The analytes were annotated automatically by means of Byonic glycopeptide search, and remaining peaks were manually annotated using Xcalibur software. Relative quantification of all identified glycan composition was performed on the MS level using the in-house software LaCyTools.

### Results and Conclusion:

The study describes qualitatively and quantitatively five out of six glycosylation sites obtained from the neutrophils of healthy donors. It resulted in identification and quantification of 10 *N*-glycan compositions on N<sub>45</sub>, 11 on N<sub>74</sub>, 30 on N<sub>162</sub> and 6 compositions on N<sub>169</sub>. Furthermore, N<sub>64</sub> was not occupied and N<sub>74</sub> only partially. *N*-glycosylation microheterogeneity of FcγRIIIb showed a wide diversity of glycan structures. For instance, N<sub>45</sub> was exclusively occupied by low processed glycans, such as high mannose glycans. In contrast, N<sub>162</sub> was occupied by sialylated complex species. In the future, it would be of great interest to map glycosylation changes in correlation with antibody-mediated disorders.

**Acknowledgments.** This research was supported by the European Union (Glycosylation Signatures for Precision Medicine project, GlySign, Grant No. 722095), and the Netherlands Organization for Scientific Research (NWO) via Vernieuwingsimpuls Veni (Project No. 722.016.008) and Medium Investment (to P.A.V.; 91116004; partly financed by ZonMw) grants.

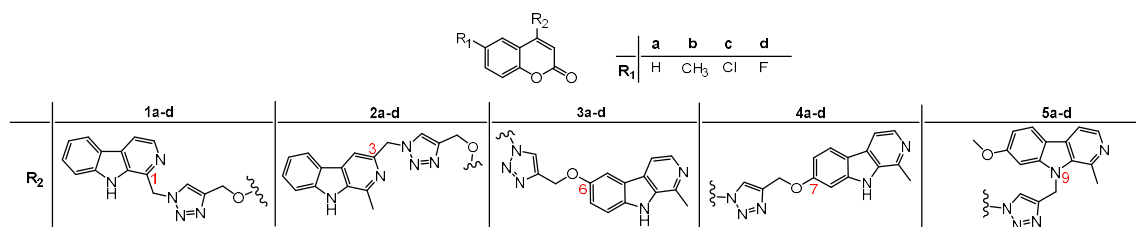
## ANTIPROLIFERATIVE ACTIVITY OF NOVEL HARMIRINS

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$\beta$ -Carbolines and coumarins are two classes of phytochemicals possessing a wide variety of biological activities, including anticancer properties.<sup>[1,2]</sup> As a continuation of our work on hybrid compounds, we have prepared a series of harmirins – novel hybrid molecules comprising harmine, a representative of  $\beta$ -carbolines, and coumarin moieties linked by a 1,2,3-triazole. Five series of harmirins, bearing coumarin substituents at positions 1, 3, 6, 7 and 9 of the  $\beta$ -carboline core were prepared (Figure).



Their antiproliferative activity was evaluated *in vitro* against human cell lines (HepG2, SW620, HCT116, MCF-7, HEK293T) and SAR analysis was performed for the most susceptible ones (HCT116 and MCF-7, IC<sub>50</sub>s in the one-digit micromolar range). The activity of harmirins towards MCF-7 decreased following the pattern **3** > **4** > **5** > **2** > **1**, while the activity of compounds **2-5** against HCT116 was in the same range. Series **1** was generally inactive against both MCF-7 and HCT116. Harmirins **3** and **5** with the smallest substituents (H or F) showed the highest cytotoxicity against all tested cell lines. On the other hand, harmirins **2b** and **4b**, bearing a methyl substituent on the coumarin ring, were the most active compounds with the most favourable selectivity indices. However, compound **4b** was selected for further investigation due to its high activity against both HCT116 and MCF-7 in low micromolar range.

**Acknowledgments.** This work was fully supported by the Croatian Science Foundation under the project number UIP-2017-05-5160.

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## APPLICATION OF TERNARY PHASE DIAGRAMS IN DEVELOPMENT OF SOLUTION CO-CRYSTALLIZATION PROCESS

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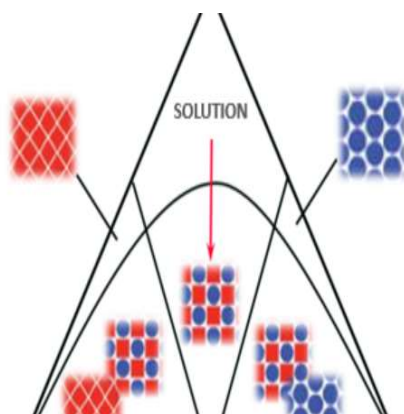
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Co-crystals are crystalline materials composed of two or more different molecules, typically active pharmaceutical ingredient (API) and co-crystal formers (“coformers”), in the same crystal lattice. The interaction between molecules present in co-crystal is non-ionic and non-covalent. From regulatory point of view co-crystal is considered analogous to a new polymorph of the API<sup>[1]</sup>. Co-crystals can also have advantageous physical properties, such as solubility, bioavailability and stability<sup>[2]</sup>. Due to all this exploitation potential in pharmaceutical industry, screening and preparation methods for co-crystals have been studied intensively. Solution crystallization is the most preferred process in terms of high volume production of co-crystals.<sup>[3]</sup> Crystallization process design for co-crystal of interest is a necessary step in pharmaceutical development.

During co-crystallization from solution expected obstacle is crystallizing a single component (API or conformer) or a mixture, instead of pure co-crystal. Ternary diagrams are used as a convenient tool in this step as they provide a specific concentration area in which the co-crystal is less soluble than the single component<sup>[4]</sup>.

In order to design a process for solution co-crystallization, multiple ternary diagrams were constructed. Each ternary diagram presents solubility relations between components for specific temperature. By comparison of ternary diagrams over temperature range we get an insight of potential changes of solubility relations. Ternary diagrams also provided information for solvent selection and API and conformer molar ratio necessary for co-crystallization from specific solvent.



**Acknowledgments.** This work was funded by Pliva Hrvatska d.o.o.

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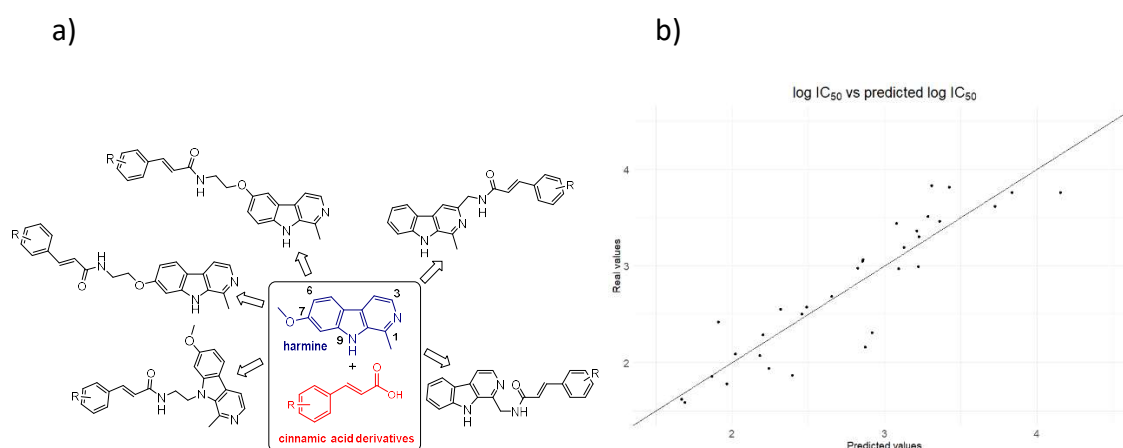
## A QSAR STUDY OF AMIDE-TYPE HARMICINES AS POTENTIAL ANTIMALARIALS

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Malaria is a devastating parasitic disease that causes considerable morbidity and mortality worldwide.<sup>[1]</sup> As a continuation of our research, a QSAR model of antimalarial activity of forty novel amide-type harmicines has been developed. A multiple linear regression model was constructed connecting the logarithm of the IC<sub>50</sub> for the selected compounds with their maximum projection area, number of atoms and the presence of the substituent in the *para* position of cinnamic acid derivatives. The RMSE, R<sup>2</sup>, and MAE values were 0.29, 0.89, and 0.25, respectively, showing a very good correlation between the predicted and the experimental IC<sub>50</sub> values.



**Figure 1.** a) Structures of novel amide-type harmicines and b) the developed QSAR model.

The obtained results will be useful for further development of novel and more effective amide-type harmicines.

**Acknowledgments.** This work was fully supported by the Croatian Science Foundation under the project number UIP-2017-05-5160 and by the Young researcher's career development project – training of doctoral students of the Croatian Science Foundation founded by the European Union from the European Social Fund.

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## OSL STUDY ON IRRADIATED AND NON-IRRADIATED DRIED TOMATOES AS INGREDIENT IN THE MEDITERRANEAN DIET

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Ingredients that play an important role in a healthy Mediterranean diet are olive oil, tomatoes and vegetables, in addition to being delicious, but more importantly prevent the ability of various chronic diseases due to different bioactive components. Tomatoes, a major ingredient in the Mediterranean diet, is linked to healthy protection as is the reduced risk of some cancers and other diseases due to a significant content of antioxidants, especially carotenoids (lycopene and beta-carotene), ascorbic acid and phenols, which play a role in inhibiting free radicals.<sup>[1]</sup> Considering its beneficial properties, further studies on tomatoes prepared by non-thermal methods are required. The main objective of this study was to compare the Optically Stimulated Luminescence (OSL) response of irradiated (10 kGy, as regulated by Ref. [2]), and non-irradiated tomato for two types of stimulation: IR (infrared,  $\lambda = 890$  nm) and BL (blue light,  $\lambda = 470$  nm). OSL is established tool for detection of irradiated food,<sup>[3]</sup> but further investigations of sensitivity and product-specific thresholds are necessary regarding difference in stimulation types and product content. Therefore, parameters such as salt content, preparation method (dried and lyophilized) and signal stability are also investigated and discussed. The results indicated that the proposed procedures based on differently prepared tomatoes, salt content and two types of simulation (IR and BL) showed that samples of dried tomatoes with higher salt content and blue light give a stronger signal than infrared stimulation.

**Acknowledgments.** This work has been fully supported by H2020 PRIMA Initiatives as part of the project No. 2032 Functionalized Tomato Products.

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## ADENYLOSUCCINATE SYNTHETASE FROM *HELICOBACTER PYLORI*: CHARACTERIZATION OF ACTIVE SITE USING X-RAY DIFFRACTION AND MOLECULAR DYNAMICS SIMULATIONS

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*Helicobacter pylori* is pathogenic bacterium which colonizes the gastric epithelia.<sup>[1]</sup> It is categorized as number one carcinogen inducer for gastric carcinoma.<sup>[2]</sup> Since *H. pylori* lacks the genes for *de novo* synthesis of purines, to maintain its viability, the pathogen uses purines from recycling pathway.<sup>[3]</sup> Adenylosuccinate synthetase (AdSS) is an essential enzyme in the purine synthesis and it operates in both purine *de novo* synthesis and purine recycling pathway. AdSS utilizes L-aspartate and IMP along with GTP and magnesium ions to form S-AMP which can be converted into AMP by adenylosuccinate lyase in the further step.<sup>[4]</sup> As one of the steps on the path to decipher and describe the catalytic mechanism of this enzyme, we obtained the crystals and solved the structure of AdSS complexed with substrates (IMP and GTP-Mg) and inhibitor hadacidin. Analysis of the active site showed the presence of stable intermediate 6'-phosphoryl-IMP. Molecular dynamics' simulations showed differences in conformation of the GTP binding loop depending on the presence of IMP in the active site.

**Acknowledgments.** To Croatian Science Foundation for the project: IP-2019-04-6764.  
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## ANTIPROLIFERATIVE PROPERTIES OF SYNTHETIC GRANULATAMIDE B AND ITS STRUCTURAL ANALOGUES

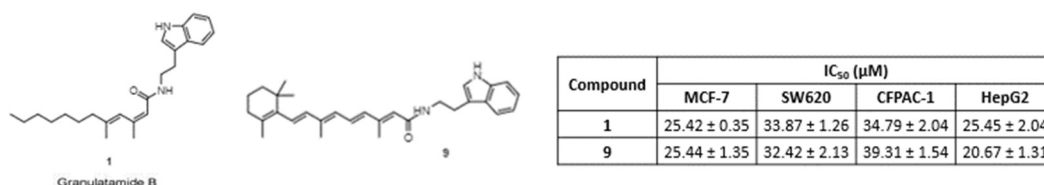
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Gorgonian corals of the genus *Eunicella* have been shown as a rich source of various secondary metabolites differing in structural characteristic with promising biological activities.<sup>[1]</sup> Among such is granulataamide B (**1**), a tryptamine-derived alkaloid, characterized by unsaturated *N*-fatty acyl moiety, which was found to exhibit high cytotoxicity against various cancer cell lines.<sup>[2]</sup> Therefore, within the Bioprospecting of the Adriatic Sea project, we have synthesized granulataamide B following the procedure of Fürstner's Fe-catalyzed synthesis<sup>[3]</sup> as well as structural analogues by the modification of the side chain (number of C-atoms and saturation degree). Currently, total of 13 compounds have been prepared and examined for anti-proliferative and cytotoxic activities applying MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide) assays. Granulataamide B (**1**) and **9** (analogue with retinoyl moiety) have exerted the most promising, non-selective anticancer activities against SW620, CFPAC-1, MCF-7 and HepG2 cancer cells with determined IC<sub>50</sub> values in the range 20-39 μM (Figure 1). Finally, the presented results highlight the importance of the indole skeleton as the pharmacophore group in medicinal chemistry and potential of fatty acids to modulate pharmacological properties of target molecules.



**Figure 1:** Structures of granulataamide B (**1**) and analogue **9** with exerted IC<sub>50</sub> values against four cancer cell lines.

**Acknowledgments.** We would like to thank Croatian Government and the European Union (European Regional Development Fund—the Competitiveness and Cohesion Operational Program - KK.01.1.1.01) for funding this research through project Bioprospecting of the Adriatic Sea (KK.01.1.1.01.0002) granted to The Scientific Centre of Excellence for Marine Bioprospecting - BioProCro. We also acknowledge the project “Research Infrastructure for Campus-based Laboratories at University of Rijeka”, co-financed by European Regional Development Fund (ERDF) and the University of Rijeka research grants UNIRI-prirod-18-102 and UNIRI-biomed-18-133. We would like to thank Croatian Science Foundation project ‘Career Development of Young Researchers-Training of New PhDs’ for funding PhD of D. Matulja and research project IP-2019-04-8846.

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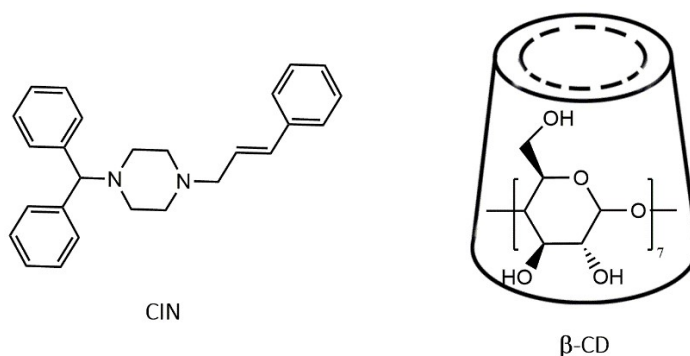
## HIGH-RESOLUTION MASS SPECTROMETRY CHARACTERIZATION OF CINNARIZINE – $\beta$ -CYCLODEXTRIN INCLUSION COMPLEXES

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Cinnarizine (CIN) is a piperazine derivative with antihistaminic and calcium channel blocking activity which is widely used for the treatment of vertigo and prevention of motion sickness. Due to its poor aqueous solubility, CIN is classified as a Class 2 drug substance according to The Biopharmaceutical Classification System.<sup>[1]</sup> It is known that cyclodextrins (CDs) can interact with poorly soluble drugs by forming inclusion and non-inclusion complexes and thus enhance drug aqueous solubility and bioavailability.<sup>[2]</sup>



**Figure 1.** Cinnarizine and  $\beta$ -cyclodextrin

The aim of our study was to characterize complexes of CIN with natural  $\beta$ -CD and its hydroxypropyl (HP $\beta$ CD) and randomly methylated (RM $\beta$ CD) derivatives by electrospray ionization mass spectrometry (MS) since this technique can offer direct determination of CD inclusion complexes formation and their stoichiometry.<sup>[3]</sup> High-resolution quadrupole time-of-flight (Q-TOF) mass spectrometer system was used for obtaining MS spectra. In order to determine binding strength of the complexes, MS/MS experiments were performed. Corresponding collision energy breakdown curves were constructed and fragmentation schemes were suggested as well.

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## COVID-19 INFECTION AND NEURODEGENERATION: A POTENTIAL LINK REVEALED BY COMPUTATIONAL SIMULATIONS

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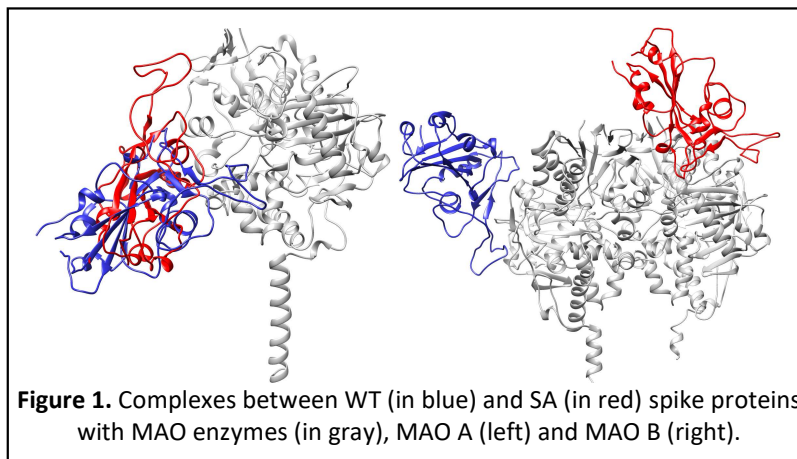
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Although COVID-19 has been primarily associated with pneumonia, recent data show that the SARS-CoV-2 virus can infect other vital organs, such as the heart, kidneys and the brain. The literature agrees that COVID-19 is likely to have long-term mental health effects on infected individuals, which signifies a need to understand the role of the virus in the pathophysiology of brain disorders that is currently unknown and widely debated.<sup>[1]</sup> Our docking and molecular dynamics simulations<sup>[2]</sup> show that affinities of spike proteins from the wild type (WT) and South African (SA) variant for MAO enzymes are comparable to those for their ACE2 receptors. This allows for the spike...MAO complex formation (**Figure 1**), which changes MAO affinities for its neurotransmitters, thus eventually impacting rates of their metabolic conversions and misbalancing their levels. Knowing this fine regulation is strongly linked with the etiology of various neurodegenerative disorders, these results highlight the possibility that the interference with the brain MAO activity is responsible for the increased neurodegeneration following the COVID-19 infection. Since the obtained insight suggests a more contagious SA variant would produce even larger disturbances, and with new and more problematic strains likely emerging in the near future, we firmly advise that the demonstrated prospect for the SARS-CoV-2 induced neurological complications should not be ignored, rather requires further clinical investigation in order to achieve early diagnosis and timely treatment.



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## MAGNETIC PROPERTIES OF MOF-525 AND PCN-223 DOPED WITH COPPER (II) IONS STUDIED BY EPR SPECTROSCOPY

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The magnetic properties of metal-organic frameworks MOF-525 and PCN-223 doped with copper (II) ions were examined by continuous wave (CW) and pulse electron paramagnetic resonance (EPR) spectroscopy. MOF-525 and PCN-223 have different topologies: MOF-525 cuboctahedron and PCN-223 hexagonal prism, as it is shown in Figure 1.<sup>[1]</sup> Fullerene was added to PCN-223 to investigate if it could be incorporated into its structure and what impact it has on spintronic properties. Computer simulations of the experimental EPR data were obtained using EasySpin software.<sup>[2]</sup> From the simulations of the experimental data we can see that the CW-EPR spectra of MOF-525 and PCN-223 exhibit different hyperfine tensors, that superhyperfine lines are more pronounced if copper ions are more diluted and that fullerene is incorporated into the structure of PCN-223. Pulsed EPR data regarding coherence signal properties are being analyzed.

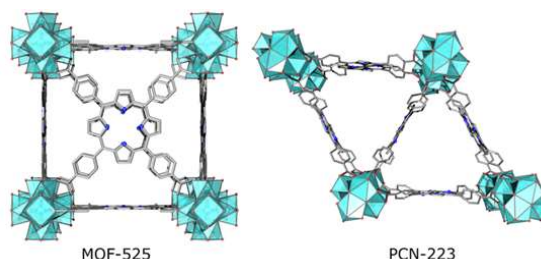


Figure 1. Structural building unit of MOF-525 and PCN-223. [1]

**Acknowledgments.** This research was supported in part by the Croatian Science Foundation through grant IP-2018-01-3168 and by the "Research Cooperability" Program of the Croatian Science Foundation funded by the European Union from the European Social Fund under the Operational Programme Efficient Human Resources 2014-2020, through grant PZS-2019-02-4129.

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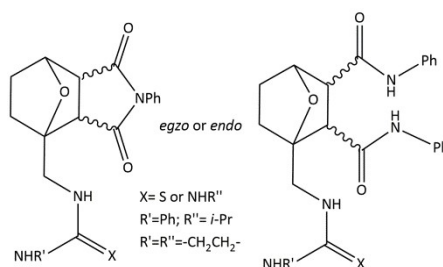
## COCATALYTIC ACTIVITY IN ALDOL REACTION OF A NOVEL THIOUREA- AND GUANIDINIUM-OXANORBORNANES

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Norbornane structures and their oxa-derivatives have rigid scaffold and are good mimics of secondary structures in polypeptides such as  $\beta$ -turn and  $\beta$ -hairpin. Norbornane motifs can serve as the inducers of well-defined hydrogen bonding patterns in peptides.<sup>[1]</sup> Hydrogen bond plays a crucial role in enzymes and small molecule organocatalysis. Thioureas and guanidines are two types of such organocatalysts.<sup>[2,3]</sup> Aldol reactions catalysed with L-proline are known to show poor diastereoselectivity in formation of *anti* and *syn* adducts and can be improved by adding guanidinium salts or thioureas as cocatalysts.<sup>[4,5]</sup>



Herein we report a synthetic route to a novel thiourea and guanidinium oxanorbornanes and their activity in L-proline catalyzed aldol reaction.

**Acknowledgments.** Croatian Science Foundation for finance support (IP-01-2018-3298) DOK-09-2018 (support for L.B. through the Young Researchers' Career Development Project)

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## FREE RADICAL SCAVENGING POTENCY OF 5-HYDROXYFERULIC ACID

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The main goal of this study was to examine possible scavenging mechanism underlying reaction of 5OHFA and  $\cdot\text{OH}$  radicals. To achieve this, two-state reactivity that involves spin inversion in the radical-radical coupling rate-determining step was considered. The DFT method with M06-2X functional and 6-311++G(d,p) basis set implemented in the Gaussian 09 program package<sup>[1]</sup> was used for geometry optimisations and frequency calculations. After finding transition state structure, intrinsic reaction coordinate calculation was carried out to find two related energy minima: reactant complex and product complex. Both structures were further optimized to obtain geometries with no imaginary frequency. All calculations were performed in gas-phase at 298.15 K.

Catecholic moiety of 5OHFA enables scavenging of two  $\cdot\text{OH}$  radicals. The first one is scavenged by 4-OH group of 5OHFA. From obtained kinetic data, it is obvious that this is a diffusion-controlled reaction. Reaction product phenoxyl radical of 5-hydroxyferulic acid (5OHFAPR) may scavenge another  $\cdot\text{OH}$  radical. The reaction between those two radicals occurs on the two potential energy surfaces and from obtained kinetic results, it can be seen that the second H-atom abstraction is also diffusion-controlled process. 5OHFAPR inactivates  $\cdot\text{OH}$  *via* PCET mechanism. Keto-enol tautomerization resulting in 5OHFA proceeds *via* hydrogen bond lattice of water molecules, leading to a high increase of reaction rate constant.

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## LOX INHIBITION AND IRON CHELATION BY FERULIC ACID – A THEORETICAL APPROACH

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The main goal of this study was to examine some of the underlying mechanisms of protection by ferulic acid (FA) from damage caused by free radicals, mainly mechanisms involving enzymes to suppress formation of free radicals and the sequestration of transition metal ions that catalyse free radical production. Hence, potential of FA to act as antioxidant *via* suppressing  $\cdot\text{OH}$  radical formation by sequestering the catalytic  $\text{Fe}^{2+}$  ion, and by inhibiting prooxidative lipoxygenase (LOX) enzyme, i.e., by suppressing formation of free radical precursors, was studied. The M06-2X functional and 6-311++G(d,p) basis set implemented in the Gaussian 09 program package<sup>[1]</sup> was used for geometry optimisations and frequency calculations. All calculations were performed in gas-phase at 298.15 K. The AutoDock 4.0 software package<sup>[2]</sup> was used to predict the binding mode between LOX and investigated compounds, FA and 5-hydroxyferulic acid (5-OHFA). The crystal structure of LOX was taken from Protein Data Bank. Discovery Studio 4.0<sup>[3]</sup> was used to prepare protein structures and for analysis of the obtained results. Polar hydrogen atoms were added using the hydrogen module in AutoDockTools (ADT) graphical interface. Grid maps were determined using the AutoGrid module with grid box of dimension 60×60×60 with point separated by 0.375 Å. The Lamarckian Genetic Algorithm (LGA) was implemented for rigid-flexible docking simulation.

Results of molecular docking calculations indicate favourable binding interactions of FA and 5OHFA with LOX active site. Exergonicity of chelation reactions of catalytic  $\text{Fe}^{2+}$  ion with FA and 5OHFA indicate potency of these chelators to prevent the formation of  $\cdot\text{OH}$  radicals *via* Fenton-like reactions. Based on obtained results, inhibition of LOX could be more relevant mechanisms of protection against oxidative stress than iron chelation.

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## NOVEL *PARA N*-ARYL SUBSTITUTED 3-HYDROXYPYRIDIN-4-ONES AND THEIR ADAMANTYL DERIVATIVES

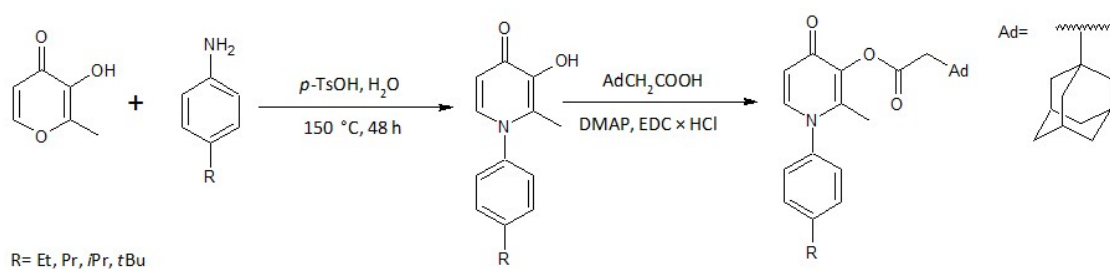
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3-Hydroxypyridin-4-ones are nowadays widely investigated for their broad spectrum of biological activities (antibacterial, antidiabetes, antiprotozoal, antineurodegenerative and anticancer).<sup>[1]</sup> In our previous work we investigated several *para N*-aryl substituted 3-hydroxy-2-methylpyridin-4-ones as well as their ester adamantyl derivatives for their *in vitro* antitumor properties on several cancer cell lines. All tested compounds showed antiproliferative activity ranging from moderate to strong on all inspected cell lines with lipophilic adamantane containing derivatives being active at low micromolar IC<sub>50</sub> concentrations.<sup>[2]</sup> Further structure-activity relationship study (SAR) of such and similar pyridinone derivatives as potential anticancer agents is now in progress. In this work, for the purpose of that study, novel *para N*-aryl substituted 3-hydroxy-2-methylpyridin-4-ones containing different substituents on the same position of the aryl part as well as their adamantyl derivatives were prepared (Fig. 1). All compounds were prepared with the aim of evaluating their *in vitro* antitumor properties on the panel of cancer cell lines. Antitumor properties of novel compounds started to elucidate the key elements, primarily the nature of the substituent on the aryl part on the adamantyl pyridinones, needed for their high antiproliferative activity.



**Figure 1.** General procedure for preparation of new *para N*-aryl substituted 3-hydroxypyridin-4-ones and their adamantyl derivatives

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## ISPITIVANJA INHIBICIJE DIPEPTIDIL PEPTIDAZE III METALNIM DIKATIONIMA [ DIPEPTIDYL PEPTIDASE III INHIBITION TESTS BY METAL DICATIONS ]

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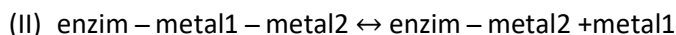
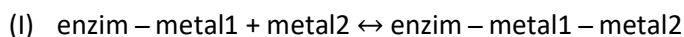
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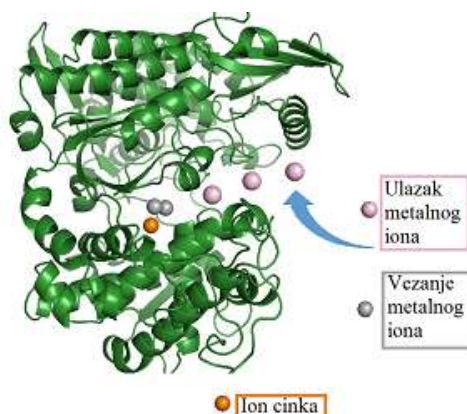
Od ranije je poznato da peptidaznu aktivnost ljudske dipeptidil peptidaze III (hDPP III) inhibira suvišak iona cinka.<sup>[1]</sup> Cilj moga doktorskoga rada je utvrditi utjecaje različitih koncentracija metalnih dikationa: Zn<sup>2+</sup>, Mn<sup>2+</sup>, Co<sup>2+</sup> i Cu<sup>2+</sup> na aktivnost hDPP III te identificirati inhibitorno vezno mjesto metala. Postojanje inhibitornog veznog mjesta pretpostavljeno je na temelju smanjenja aktivnosti hDPP III pri višim koncentracijama cinka te sličnosti aktivnog mjesta hDPP III s onima kod karboksipeptidaze A i termolizina u čijim je kristalografskim strukturama opaženo vezanje drugog iona metala u neposrednoj blizini katalitički aktivnog iona.<sup>[1]</sup>

Inhibiciju hDPP III metalnim dikationima (Zn<sup>2+</sup>, Mn<sup>2+</sup>, Co<sup>2+</sup> i Cu<sup>2+</sup>) ispituje se koristeći se raznim eksperimentalnim i računalnim metodama. 'Stop flow' metodom pratimo smanjenje enzimatske aktivnosti hDPP III uzrokovano suviškom metalnih dikationa, a korištenjem molekulske dinamike u kombinaciji s računom slobodnih energija vezanja te kvantno mehaničkim - molekulske mehaničkim računima identificirali smo inhibitorno mjesto vezanja cinka i njegov utjecaj na strukturu i dinamiku hDPP III. Također smo, praćenjem puta izmjene iona cinka zaključili da se, kao u slučaju antraks letalnog faktora,<sup>[2]</sup> radi o tzv. asocijativnom načinu izmjene opisanog relacijama:



Rezultati ovog istraživanja omogućili su nam da predložimo mehanizam pomoću kojeg inhibitorni cinkov ion smanjuje aktivnost enzima.

**Grafički prikaz:**



**Acknowledgments.** This work has been fully supported by Croatian Science Foundation under the project IP-2018-01-2936

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## COMPUTATIONAL STUDY OF REACTIVITY OF GUANIDINE SUBSTITUTED *SYM*-TETRAZINES IN CYCLOADDITION REACTIONS

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The cycloaddition properties of novel 2-pyridyl-*sym*-tetrazines (1,2,4,5-tetrazines)<sup>[1]</sup> bearing a guanidine functional group were studied computationally in inverse electron demand Diels-Alder [4+2] cycloaddition reactions<sup>[2]</sup> with norbornenes and fullerene C<sub>60</sub>. Density functional theory calculations (DFT) with B3LYP and M06-2X functionals indicate that guanidine *sym*-tetrazines are reactive towards strained polycyclic alkenes such as norbornene, whereas reactions with fullerene have estimated higher activation energies. Evaluation of series of tetrazines indicated that the guanidine substituents lowers their cycloaddition reactivity, which is an opposite effect than observed for the normal electron-demand Diels-Alder cycloadditions.<sup>[3]</sup>

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## CYTOTOXICITY OF HARMIQUINES, HYBRIDS BASED ON HARMINE AND CHLOROQUINE SCAFFOLDS

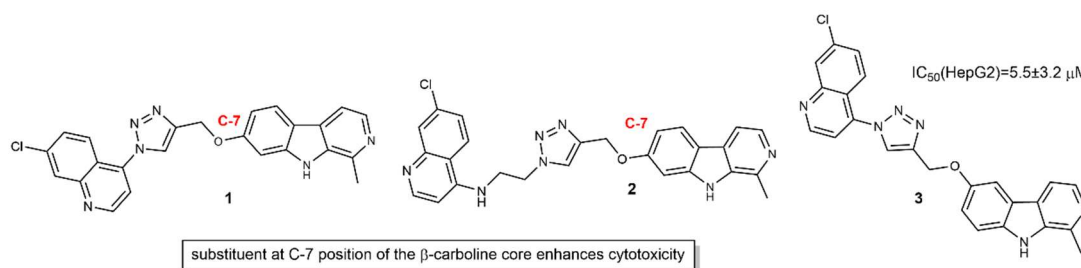
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Cancer, a disease characterized by uncontrolled growth of abnormal cells, is the second leading cause of death globally, accounting for an estimated 9.6 million deaths in 2018.<sup>[1]</sup> The emergence of cancer drug resistance remains a significant global public health and economic burden, emphasizing the need for new and effective anticancer agents. Herein, we represent harmiquines, hybrid compounds based on harmine and chloroquine, two moieties with confirmed anticancer properties.<sup>[2,3]</sup> The cytotoxic potential of novel hybrids was examined *in vitro* against a panel of human cell lines (Hek293T, MCF-7, HepG2, SW620, HCT116). The cell growth rate was evaluated using the MTT assay with respect to untreated cells. Cytotoxicity, expressed as an IC<sub>50</sub> value, was determined from concentration–response curve using nonlinear regression analysis. The compounds differentially affected the growth of tumor cell lines, whereby MCF-7 and HCT-116 cell lines appeared generally sensitive towards most of the tested compounds. Hybrids **1** and **2** (C-7-tethered derivatives) proved to be the most cytotoxic, affecting all tumor cell lines (IC<sub>50</sub> values in the range of 1–8 μM) (**Figure 1**). Harmiquine **3** exerted the most selective activity towards HepG2, in comparison to Hek293T (IC<sub>50</sub> = 5.5 ± 3.2 μM, selectivity index > 9).



**Figure 1.** Structures and cytotoxicity of the selected harmiquines.

**Acknowledgments.** This work was fully supported by the Croatian Science Foundation under the project number UIP-2017-05-5160.

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## THE KINETICS OF BOVINE SERUM ALBUMIN ADSORPTION ONTO CaP/TiO<sub>2</sub> NANOCOMPOSITES

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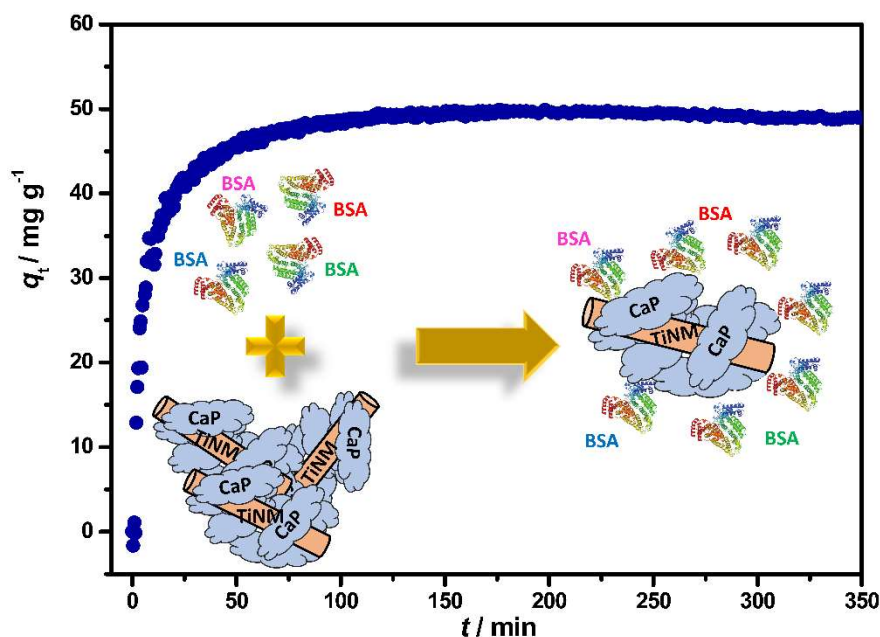
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The constantly growing need for improved bone regeneration materials motivates the research and development of novel biomaterials.<sup>[1]</sup> Thus, nanocomposites based on calcium phosphates (CaPs) and TiO<sub>2</sub> nanomaterials (TiNMs) attract special attention as they combine good bioactivity of CaPs and good mechanical properties of TiNMs.<sup>[2,3]</sup> Among key factors determining the fate of bioimplants *in vivo* are their interactions with blood serum proteins which adsorb at the surface of the implants immediately upon implantation. Depending on how proteins are adsorbed, the implant can either be successfully integrated or rejected/encapsulated.<sup>[4]</sup> The most abundant soluble protein that interacts with implants is albumin.

The aim of this work was to systematically investigate the adsorption kinetics of bovine serum albumin (BSA) on TiNMs and their composites with CaPs. TiNM materials of different morphology and composition (nanoparticles (TiNP), nanotubes (TiNT), nanowires (TiNW), and nanoplates (TiNPI)) were synthesized by the hydrothermal method. Nanocomposites of CaPs and TiNMs (CaP/TiNMs), and calcium deficient hydroxyapatite (CaDHA) were synthesized by precipitation at conditions close to physiological.<sup>[5,6]</sup> The TiNMs and CaP/TiNMs were characterized before and after adsorption by Fourier-transform infrared spectroscopy (FTIR), powder X-Ray diffraction (PXRD), scanning electron microscopy (SEM) and atomic force microscopy (AFM). The kinetics of BSA adsorption onto TiNMs and CaP/TiNMs was determined by UV-VIS measurements at 37 °C for 24 h. The non-linear forms of pseudo-first (PFO), pseudo-second reaction order models, as well as Weber and Morris intraparticle diffusion model, were used to fit the obtained data and to evaluate the performance of the adsorbent and investigate the adsorption mass transfer mechanism.<sup>[7]</sup>

The kinetic data were best fitted by the PSO model for all materials. Also, for CaDHA, CaP/TiNT, and CaP/TiNW kinetics of adsorption is controlled by the intraparticle diffusion process. The adsorption capacity was higher for nanocomposites compared to nanomaterials, while the rate of adsorption was lower.

The obtained results represent a comparable set of data that can be used in the design of novel biomaterials for predicting their behaviour *in vivo*.



**Acknowledgments.** This project is financially supported by Croatian Science Foundation, Grant HRZZ- IP-2018-01-1493.

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## A GAMMA IRRADIATION METHOD FOR THE SYNTHESIS OF IRON OXIDE/GOLD NANOSTRUCTURES

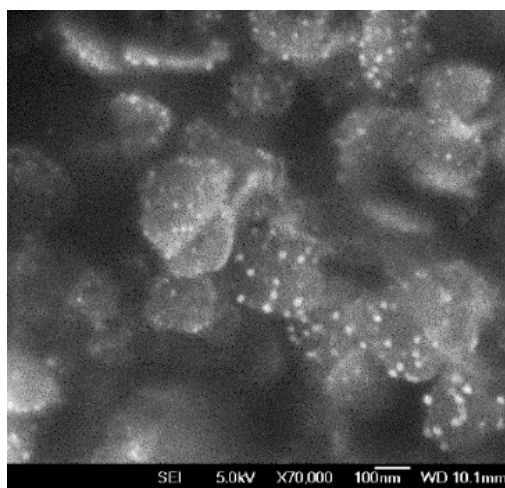
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Magnetic iron oxide nanoparticles (MNPs) due to their unique magnetic and electrical properties have applications as sensors, contrast agents, in drug delivery, hyperthermia cancer treatments, etc. For these uses, the surface of the particles should be modified with a suitable surface coating that can easily bind the appropriate biomolecules for the selected application. Gold has become one of the favored coatings because it is non-toxic, biocompatible, chemically inert, enables additional functionalization and can protect MNPs from oxidation without significantly reducing magnetic properties. In this work, we have used  $\gamma$ -irradiation as an attractive and ecologically friendly technique for the synthesis of magnetic composite nanoparticles at room temperature. The phase composition, stoichiometry, and morphology of MNPs were controlled by adjusting the  $\gamma$ -irradiation dose. Irradiation with doses 10–36 kGy resulted in the formation of very small 4 nm spherical magnetite NPs, whereas at a higher dose (50 kGy or more) the major phase was magnetic  $\delta$ -FeOOH (feroxyhyte) in the form of nanodiscs. The Au nanoparticles formed were spherical; the quantity and size of Au nanoparticles depended on the amount of initially added HAuCl<sub>4</sub> aqueous solution. In this way, it was possible to obtain magnetic spherical magnetite/Au and thin nanodisc  $\delta$ -FeOOH/Au nanostructures (Figure 1) from the same starting suspension by varying just one experimental factor: the absorbed dose.



**Figure 1.** SEM micrograph of thin  $\delta$ -FeOOH nanodiscs decorated with Au nanoparticles

**Acknowledgments.** This work has been supported by the Croatian Science Foundation under the project UIP-2017-05-7337 (POLRADNANOP).

## A METHOD FOR FAST ANALYSIS OF PAHS AND NITRO-PAHS IN AMBIENT PARTICULATE MATTER

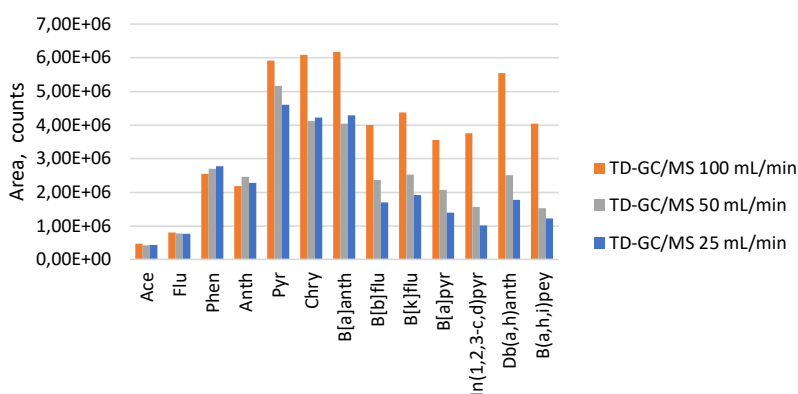
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Polycyclic aromatic hydrocarbons (PAHs) and their derivate compounds are common air pollutants which are very harmful to human health due to their cancerogenic and mutagenic properties. With increasing traffic in urban areas, the concentration of these compounds rapidly increases every year. Previous researches have shown that PAHs and their derivates can be found in the gas phase or in ambient particulate matter (PM).<sup>[1]</sup> In this work, the focus is on the optimization of a relatively new method for analyzing PAHs and nitro-PAHs in PM using thermal desorption gas chromatography coupled with mass spectrometry (TD-GC-MS). The main goal is to circumvent extraction procedures that are time-consumable and the use of organic solvents that are not environmentally friendly. Therefore, the possibility of systematic errors is minimized and for this technique, the smallest amount of sample is needed.

For optimizing the TD-GC-MS (TD3.5+; CIS4, Gerstel; GC, 7890B; MS, 5977B, Agilent) method, 13 PAHs and 4 nitro-PAHs dissolved in acetone were spiked on one-eighth of a 47 mm quartz filter. Every time, the filter was placed in an empty glass TD tube (being cleaned and conditioned prior to analysis). We found out that glass wool liner is the best for the above analytes. Various instrumental parameters, such as carrier gas flow, temperature ramp, and well-optimized time events, were tested for the best performance. As could be seen in Figure 1, by increasing the desorption flow, desorption from the filter generally improves, which is not the case for the first two analytes. The reason may be their greater volatility and too high trap temperature (5 °C) in CIS4. After the optimization, certificated material ERM-CZ100 was used for validation and real PM samples from Ljubljana were analyzed.



**Figure 1.** Influence of carries gas flow on the desorption of PAHs from quartz filters

**Acknowledgments.** The authors acknowledge the financial support from the Slovenian Research Agency (research core funding No. P1-0034 and project J1-1707).

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## NOVEL SUPRAMOLECULAR NANOCOMPOSITE HYDROGELS FOR BIOMEDICAL APPLICATIONS

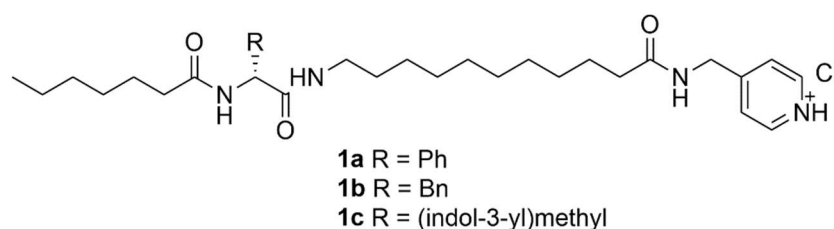
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Supramolecular hydrogels are emerging as versatile soft materials with many potential applications arising from their structure and ability to self-assemble along with their stimuli-responsive. Some of these applications include sensors, actuators and various biomedical applications.<sup>[1]</sup> However, since supramolecular hydrogels are dynamic materials, their mechanical stability can be low which can in turn affect their practical use.<sup>[2]</sup> It was recently reported that addition of polyvinyl alcohol (PVA) could enhance the properties of supramolecular hydrogels.<sup>[3]</sup> Here, we present the synthesis and characterization of new nanocomposite hydrogels system, consisting of low molecular weight gelators (LMWG) based on 11-amino-*N*-(pyridin-4-ylmethyl) undecanamide with incorporated amino-acids (Figure 1.) and PVA. In order to determine the effects of the addition of PVA to hydrogels, the addition of PVA in the range of 1 – 5% wt in the hydrogel was studied. This was done in order to attain more stable hydrogels for biomedical applications. The self-assembly of nanocomposite hydrogels was characterized by FT-IR and NMR spectroscopy, morphology of the gel network was determined by transmission electron microscopy (TEM). The release of doxorubicin (DOX) from composite of **1a** and PVA was analyzed by UV/Vis spectroscopy and kinetic measurements. From the results it is possible to conclude that addition of PVA to hydrogels enhanced the thermal stability and it has also influenced the morphology of the gel network system. Preliminary measurements of the release kinetics of DOX suggest that the release is possible to control by the addition of PVA in a hydrogel network system. Somewhat faster DOX release was achieved from cross-linked PVA hydrogels.



**Figure 1.** General structure of LMWGs

**Acknowledgments.** This work was supported by the Croatian Science Foundation project IP-2018-01-6910.

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## RAPID AND SIMPLE MICROFLUIDIC METHODS FOR DETECTION OF BIOACTIVE COMPOUNDS IN COMPLEX SAMPLES

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In modern nutrition research amino acids and peptides have a broad potential therapeutic applications, and are used as supplements or as functional food ingredients.  $\beta$ -alanine, L-histidine and carnosine are common used in the form of dietary supplements. Carnosine is dipeptide produced by condensation of  $\beta$ -alanine and L-histidine.<sup>[1]</sup> Standard methods for analysis of amino acid and peptides have a number of disadvantages. They are expensive, complex and time consuming. Microchip electrophoresis (ME) evolved from capillary electrophoresis with purpose of reducing the time and cost of analyzes, the amount of reagents, samples and waste.<sup>[2]</sup> ME with capacitively-coupled contactless conductivity detection allows fast and environmentally friendly analysis of ions and ionisable molecules in complex samples. During the study various parameters was investigated to provide high resolution and to optimize the separation. A key point was to optimize the separation buffer in order to avoid overlapping of the amino acids with the other constituents in the analyzed sample. The detection limits were below 1 mg/mL. The proposed microfluidic methods are environmentally friendly and offer great promises for routine multi-analyte pharmaceuticals and food analyses.

**Acknowledgments.** This work was supported by the European Structural and Investment Funds grant for the Croatian National Scientific Center of Excellence for Personalized Health Care, Josip Juraj Strossmayer University of Osijek (grant #KK.01.1.1.01.0010).

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## DESIGN AND SYNTHESIS OF NEW SUPRAMOLECULAR NANO-STRUCTURED MATERIALS BASED ON PEPTIDE HYDROGELATOR Ac-L-Phe-L-Phe-L-Ala-NH<sub>2</sub> AND EMBEDDED LIPOSOMES

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The aim of the present study was preparation and characterization of supramolecular systems based on peptide hydrogelator Ac-L-Phe-L-Phe-L-Ala-NH<sub>2</sub> and liposomes. In recent years design and synthesis of self-assembled nanomaterials with diversified structures and functionalities via fine tuning of supramolecular building blocks increased rapidly.<sup>[1]</sup> Liposomes have been researched for their ability to reduce side effects and improve drug delivery.<sup>[2]</sup> Lipid carrier and hydrogel combinations offer oral and transdermal drug delivery of great potential to enhance systemic effects of both hydrophilic and lipophilic drugs. Self-assembling peptides have been widely recognized as nanomaterials with high potential for an extensive range of biomedical applications from drug delivery to tissue engineering, owing to their hydrophilic character and biocompatibility.<sup>[3–5]</sup> The gelling properties of the hydrogelator Ac-L-Phe-L-Phe-L-Ala-NH<sub>2</sub> with addition of liposomes and proteins were studied. Liposome formulations of bovine serum albumin (BSA) incorporated in the hydrogel were characterized by electron microscopy. Transmission electron microscopy (TEM) confirmed incorporation of liposomes into the hydrogel. In gel samples with built-in BSA, the gel network preserved integrity, but it was noticed that the gel fibers were thinner and longer. It was also shown that liposomes do not impair the gel network of hydrogelator at lipid concentrations lower than the gelator concentration. We confirmed that use of higher amounts of protein albumin BSA resulted in slower gel formation or inability to transition into gel.

**Acknowledgments.** We acknowledge the financial support of the Croatian Science Foundation Project: IP-2018-01-6910; “Synthesis of Supramolecular Self-assembled Nanostructures for Construction of Advanced Functional Materials”.

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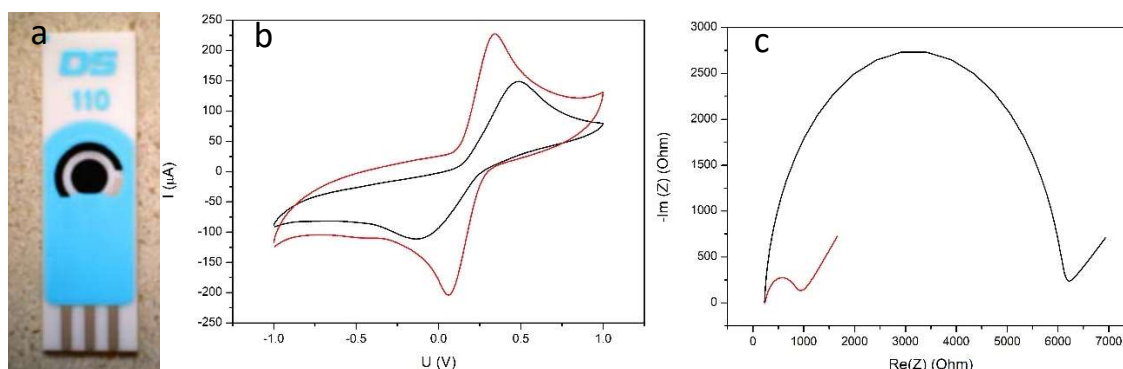
## ANODIC PRETREATMENT OF CARBON GRAPHENE PASTE MODIFIED SCREEN PRINTED ELECTRODE FOR ENHANCING THE ELECTROCHEMICAL SENSING CHARACTERISTICS

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Graphene is emerging as a material with extraordinary physical and chemical properties. Due to its electrochemical properties, it offers vast potential applicability as an effective electrode material.<sup>[1]</sup> With anodic pretreatment, it is possible to enhance the electrochemical sensing properties of graphene-modified electrodes. In the present study, electrochemical sensing properties of graphene-modified screen printed electrodes are investigated before and after anodic pretreatment of the electrode. The prepared electrode is electrochemically characterized by cyclic voltammetry and electrochemical impedance spectroscopy. The electrode surface is investigated by scanning electron microscopy, energy dispersive X-ray spectroscopy, and Raman spectroscopy. The heterogeneous electron transfer rate and capacitance is calculated from obtained cyclic voltammograms and electrochemical impedance spectroscopy respectively. Both values are compared before and after anodic pretreatment.



**Figure 1.** a) Image of used screen printed electrode, b) cyclic voltammograms, and c) Nyquist plots obtained with screen printed electrode before anodic pretreatment (—) and after anodic pretreatment (—).

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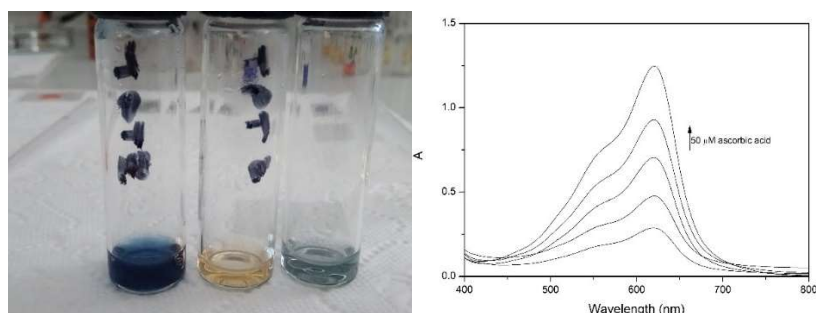
# PREPARATION AND CHARACTERIZATION OF CHITOSAN HYDROGEL-BASED OPTICAL SENSOR FOR TOTAL ANTIOXIDANT CAPACITY DETERMINATION

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Total antioxidant capacity (TAC) measures the total antioxidants present in the sample, including their synergic and redox interaction between different molecules present in the sample.<sup>[1]</sup> From the introduction of TAC as a concept until today, many different analytical methods have been developed and applied in different systems for its evaluation. However, the complexity of TAC as a concept and analyte results in inconsistent results, and because of that, there is no universal and straightforward method for TAC evaluation.<sup>[2]</sup> Here we report the preparation of hydrogel-based sensor for TAC evaluation based on change of optical properties in interaction with antioxidants. Hydrogel sensor is prepared by crosslinking of chitosan with 2,2'-bipyridine-4,4'-dicarboxylic acid. Addition of Fe(II) salts and 2,4,6-Tri(2-pyridyl)-1,3,5-triazine (TPTZ) as additional ligand results a blue-colored hydrogel-(2,2'-bipyridine-Fe(II)-TPTZ) complex that loses color if oxidized. The color restores reversibly in the reaction with antioxidants. The hydrogel-based sensor is characterized by UV-VIS spectroscopy regarding its optical and sensory properties.



**Figure 1.** Left: Suspension of hydrogel-(2,2'-bipyridine-Fe(II)-TPTZ) complex (first vial), oxidized suspension (second vial) and partially reduced with ascorbic acid (third vial); Right: UV-VIS spectra of hydrogel after sequential addition of ascorbic acid

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## ADAMANTANE-CONTAINING DESMURAMYL PEPTIDES: SYNTHESIS AND STRUCTURAL INSIGHT INTO NOD2 BINDING

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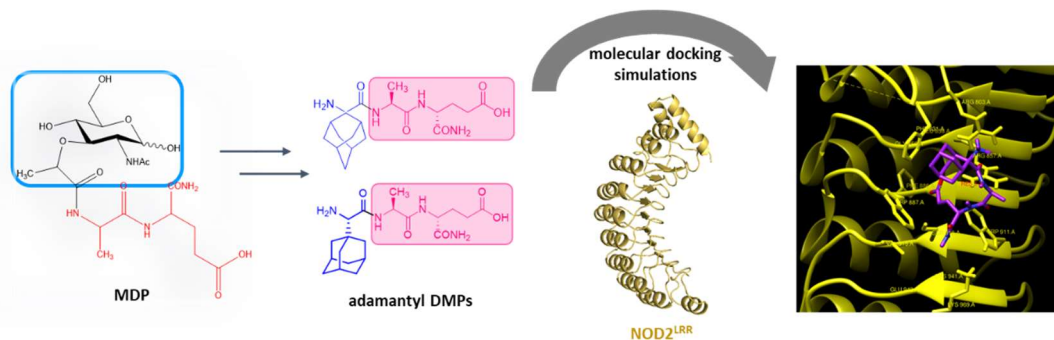
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Muramyl dipeptide (MDP, *N*-acetylmuramyl-L-alanyl-D-*isoglutamine*) is a conserved fragment of a bacterial cell walls and the smallest peptidoglycan fragment competent to trigger the immune response. MDP binds to NOD2 (nucleotide binding and oligomerization domain-containing protein 2) with affinity in the nanomolar range.<sup>[1]</sup> Activation of NOD2 by MDP stimulates downstream signaling pathways and promote immune responses.<sup>[2]</sup> Minor MDP structure modifications affect molecular recognition by NOD2, and thereby influence the modulation of the immune response.<sup>[3]</sup>

Here we present the synthesis of MDP analogs, desmuramyl peptides (DMPs) with incorporated lipophilic adamantyl groups at the N-terminus of the dipeptide pharmacophore. The adamantyl group was introduced in two ways, via 2-aminoadamantan-2-carboxylic acid and via (*R*)-adamantylglycine. Molecular docking simulations of NOD2 receptor and prepared adamantyl DMPs were also performed in order to investigate interactions established between DMPs and receptor protein.



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## INNER FILTER EFFECT CORRECTIONS FOR PROTEIN FLUORESCENCE MEASUREMENTS IN MICROPLATES USING VARIABLE Z-FOCUS POSITION

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Inner filter effect (IFE) can often be an important attributing factor to the non-linear response of the relative fluorescence intensity signal with respect to the analyte concentration. This effect is due to the partial reabsorption of the excitation and/or emission radiation. The apparent fluorescence intensity and spectral distribution are functions of the sample's optical density as well as the geometrical parameters of the sample illumination.<sup>1-3</sup> A commonly used and simple IFE correction method proposed by Lakowicz<sup>1</sup> relies on the absorbance measurements of the excitation and emission wavelengths. Most modern microplate readers have the ability to measure fluorescence intensities at different positions along the z-axis (perpendicular to the sample well). This feature was used to perform the IFE corrections for the solutions of the human serum transferrin protein, as well as for the solutions of a well-known non-protein fluorophore quinine sulfate. The proposed IFE correction method does not require separate absorbance measurements. Advantage of the variable z-focus method is that it can also be performed in the more affordable non-transparent microtiter plates.

**Acknowledgments.** This work was supported by funding from the Croatian Science Foundation grant UIP-2017-05-9537 - Glycosylation as a factor in the iron transport mechanism of human serum transferrin (GlyMech).

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## PHENOLIC PROFILE AS A TOOL FOR THE AUTHENTICITY ASSESMENT OF CULTIVATED BERRY SEEDS

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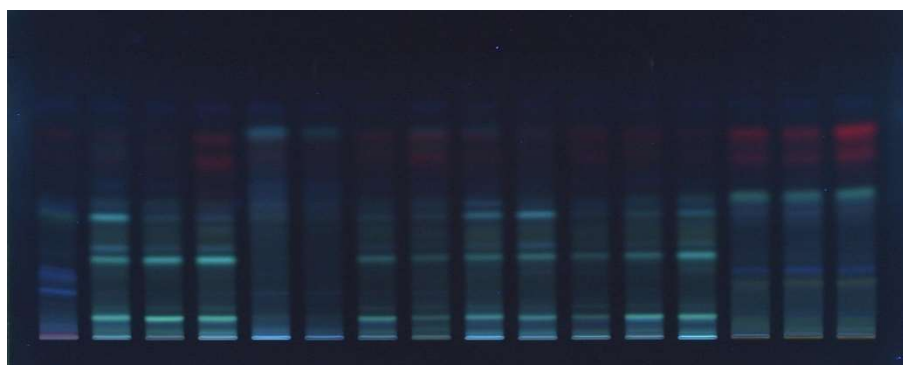
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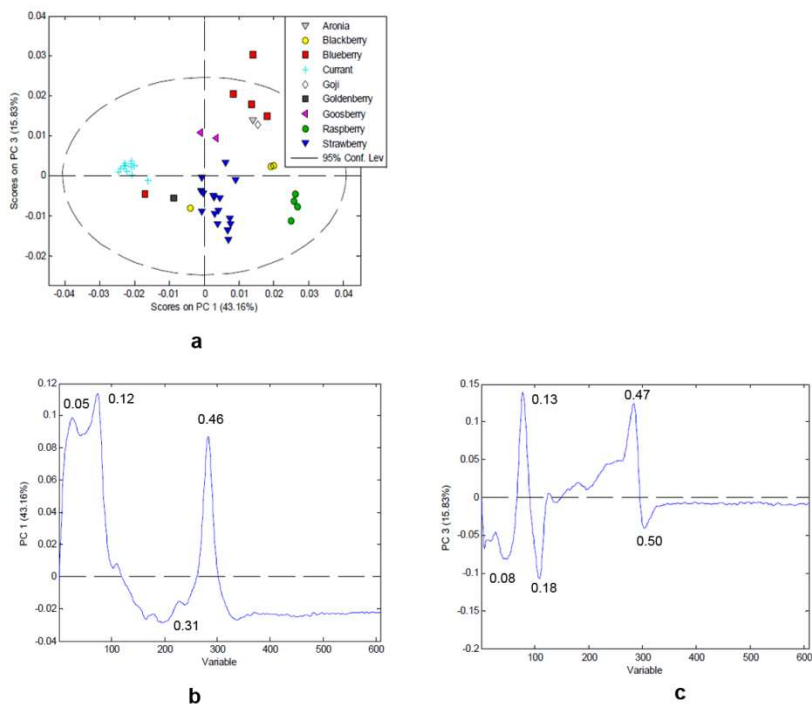
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Berry fruits are rich in bioactive compounds such as phenolic acids, flavonoids, anthocyanins, stilbenes, and tannins, as well as nutritive components such as sugars, carotenoids, essential oils, vitamins, and minerals.<sup>[1]</sup> In addition to their nutritional value, the authenticity of fruit and fruit products has recently become a topical issue due to the importance of food quality assurances.<sup>[2]</sup> Along with berry fruits, their seeds are a source of valuable compounds and their recovery and possible utilization has become a promising and economically attractive field. Therefore, more information about seeds composition and the variability of nutrients among cultivars are required.



**Figure 1.** HPTLC chromatograms of phenolics in berry seeds.

Phenolic profile of fruit seeds could be used as potential chemical marker of its botanical and geographical origin. The aim of this work is characterization of seeds of 45 different genuine Serbian fruit cultivars (raspberry, gooseberry, blackberry, strawberry, blueberry, currant, aronia) by evaluation of their phenolics. For that purpose, high-performance thin-layer chromatography (HPTLC) and ultra-high performance liquid chromatography (UHPLC) coupled with linear ion trap-orbitrap (LTQ Orbitrap) mass spectrometry (MS) technique were used. A set of HPTLC chromatographic signals, as unique multivariate fingerprint, was used for sample characterization. Phenolic profiles indicate the uniformity within each fruit species, but also revealed differences in chemical composition depending on the origin (Figure 1). Intercultivar discrimination and differentiation of investigated berries was confirmed after chemometric analysis of data obtained by image evaluation of HPTLC chromatograms (Figure 2).



**Figure 2.** Principal component analysis (PCA) performed on data obtained from polyphenolic profile of seeds from berry fruit cultivars, a) score plot, b,c) loading plots.

The UHPLC–LTQ OrbiTrap MS revealed that ellagic acid, methyl 3,5-dicaffeoylquinic acid, quercetin, methyl gallate, aromadodrin *O*-hexoside isomer, taxifolin, methoxybenzoic acid isomer, dimethoxycinnamic acid and kaempferol were present in all samples, but also that each berry species contained specific phenolics characteristic for each cultivar.

**Acknowledgments.** This work was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia, Contract numbers: 451-03-9/2021-14/200168 and 451-03-9/2021-14/200116, as well as the European Commission, under the Horizon2020 FoodEnTwin project, GA No. 810752.

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## FAST DETECTION OF APRICOT JUICE FRAUDS BY PUMPKIN JUICE BASED ON PLANAR CHROMATOGRAPHY, IMAGE ANALYSIS AND CHEMOMETRICS

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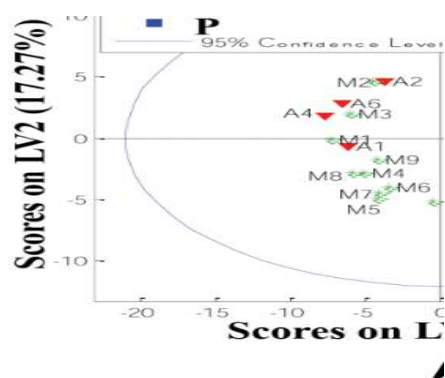
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The European Commission requires that fruit products distributed on the market meet standards of high quality and authenticity.<sup>[1]</sup> As fruits are the most expensive ingredients in juices, nectars, and jams, potentially the most lucrative method of adulteration is their partial substitution with cheaper alternative fruits such as pumpkin, vegetables or sugars.<sup>[2]</sup> Current analytical methods cover identification of adulteration in admixtures at levels below 10%. They are also time consuming, expensive, with low sample throughput. Hence, an eco-friendly, simple, and low-cost analytical method for the quality assessment of apricot juices was developed. A carotenoid fingerprint was developed by high-performance thin-layer chromatography multi-imaging (HPTLC-FLD/Vis) and applied for the analysis of 7 apricot juices, 5 pumpkin juices and 11 apricot juices mixed with pumpkin juice in a range 2.5–53% to simulate falsified apricot juices.

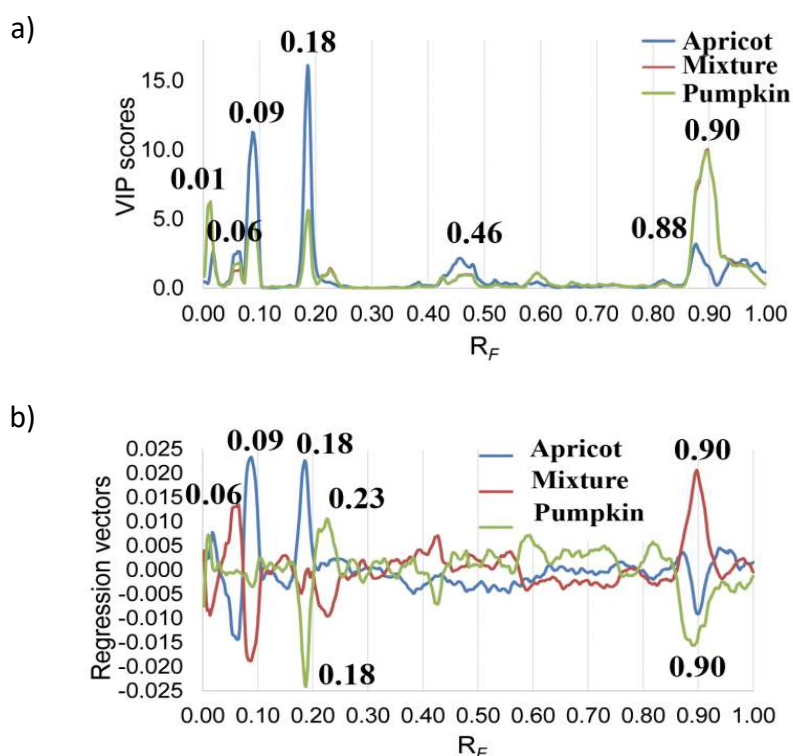
Partial least square – discriminant analysis (PLS-DA) performed on HPTLC signals obtained after derivatization by Neu reagent, followed by plate illumination under the UV light (366 nm) and further filtering of images through the blue channel resulted in the most complex classification model with the highest predictive power ( $R^2_{\text{CAL}} = 0.877$ ,  $R^2_{\text{CV}} = 0.715$ ,  $R^2_{\text{PRED}} = 0.646$ ; misclassification rate 9 – 13%).

Scores on the first two PLS-DA components demonstrate good separation between pure apricots, pure pumpkins, and mixtures (Figure 1).

PLS-DA VIP scores that are > 1 (above the average) were obtained at the  $R_f$  values of 0.01, 0.06, 0.09, 0.18, 0.46, 0.88, and 0.90 (Figure 2a), implying that these chromatographic signals play important role in discrimination. Additionally, PLS-DA regression vectors revealed that compounds corresponding to  $R_f$  values of 0.09, and 0.18, have the highest positive coefficients in the case of apricots, thus most likely being present in these samples in higher amounts, and consequentially being responsible for discrimination against the mixtures and pure pumpkins (Figure 2b). Also, the highest positive regression coefficients in the case of pure pumpkins were obtained at  $R_f$  values of 0.06, and 0.23, and in the case of mixtures at  $R_f$  0.06 and 0.90 (Figure 2b), additionally identifying possible chemical markers responsible for successful discrimination among mixtures and pure juices.



**Figure 1.** PLS-DA score plot; HPTLC data are obtained after Neu reagent derivatization, illumination under 366 nm, and filtering of images through the blue channel; A – apricot, P – pumpkin; M – mixtures.



**Figure 2.** PLS-DA analysis of HPTLC data obtained after Neu reagent derivatization, illumination under 366 nm, and filtering of images through blue channel; a) VIP scores and b) regression vectors.

**Acknowledgments.** This work was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia, Contract number: 451-03-9/2021- 14/200168; German Academic Exchange Service (DAAD), GA No. 6210045; as well as the European Commission, under the Horizon2020, FoodEnTwin project, GA No. 810752.

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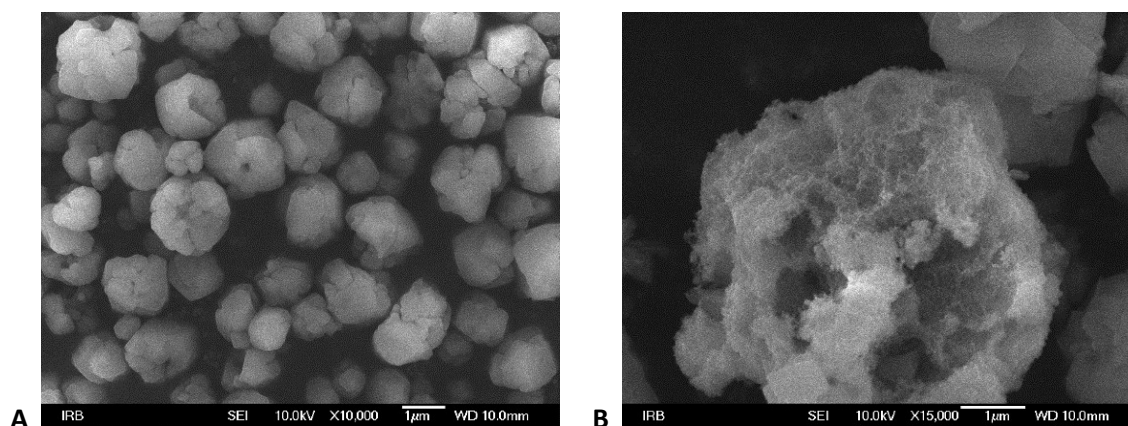
## EFFECT OF METAL CATIONS ON ZEOLITE ACIDITY

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Zeolites of faujasite type (FAU) are one of most widely used ones in fuel industry. The tridimensional 12-member ring cages make them suitable as catalysts for fluid catalytic cracking (FCC) and support for platinum or palladium in a hydrocracking process. There are two subtypes of synthetic FAU type zeolites depending on their Si/Al ratio: the X type when the ratio is between 2 and 3 and Y type if ratio is 3 or higher. The high amount of aluminum in X type zeolite results in number of Brønsted's acid sites much higher than in the Y type. While high number of active sites can speed up catalytic process significantly it can also lead to unwanted byproducts and formation of coke. These problems can be avoided with post synthetic modifications by wet impregnation with metal salts to tune in acidity of active sites. The synthesis gel of composition  $4\text{Na}_2\text{O}:\text{Al}_2\text{O}_3:10\text{SiO}_2:158\text{H}_2\text{O}$  was used for the preparation of FAU type zeolite. The reaction was conducted in teflon lined autoclaves for 48 h at  $100^\circ\text{C}$ .<sup>[1]</sup> One part of synthesized zeolite was modified during synthesis using cetrimonium bromide (CTAB) while the other part was post synthetically treated with aqueous solution of sodium hydroxide. This was done in order to create mesopores (Figure 1.) which can facilitate diffusion through crystal during catalysis.<sup>[2]</sup> The prepared parent materials were then wet impregnated using metal salts of magnesium(II), cobalt(II), nickel(II) or zinc(II).



**Figure 1.** SEM images of FAU type zeolite treated with CTAB (A) and the one etched with  $\text{NaOH}_{(\text{aq})}$

**Acknowledgments.** This work was supported by Croatian Science Foundation, project IP-2016-06-2214.

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## EFFECT OF C-5 SUBSTITUENT ON THE REGIOSELECTIVITY OF N-FERROCENOYLATION OF URACIL

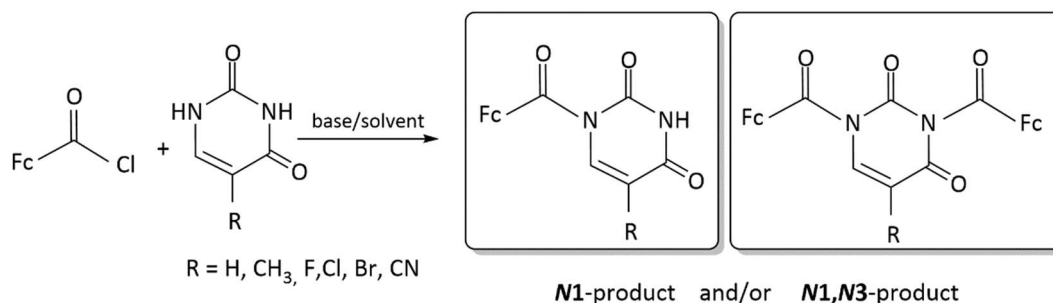
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Nucleosides and their analogs have a significant role in drug discovery and development due to their remarkable chemotherapeutic activities. In this regard, the extensive endeavors have been performed so far to synthesize the various structurally diverse nucleosides. The presence of multiple nucleophilic sites in nucleobases with comparable reactivity, traditionally affords a complex mixture of products through in reactions with low regioselectivity.<sup>[1]</sup> Also it has been found that the position of N-acylation depends on the reaction temperature, base catalyst, and acylation agent employed.<sup>[2]</sup> Our research group have developed a one-step synthetic route to prepare ferrocenoyl derivatives of nucleobases, the Fc–C=O fragment has been linked to “standard” pyrimidine bases. In aforementioned reactions the bases have been ferrocenoylated selectively at N1-position of the pyrimidine ring.<sup>[3]</sup> Consequently, here we will focus on examining the effect of the substituent at position C-5 uracil and various deprotonating agents (NaH, Et<sub>3</sub>N) and solvents (DMF, CH<sub>3</sub>CN) on the regioselectivity of N-ferrocenoylation of the nucleobase (Fig 1). The position of substitution in products and their proportion will be confirmed by NMR-spectroscopy.



**Figure 1.** N-ferrocenoylation of C-5 uracil derivatives

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## DEVELOPMENT OF A NOVEL DISPERSIVE LIQUID-LIQUID MICROEXTRACTION METHOD FOR THE SIMULTANEOUS ANALYSIS OF SIX ANTICANCER DRUGS IN HUMAN PLASMA

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Palbociclib, ribociclib and abemaciclib are novel anticancer agents used in combination with anastrozole, letrozole or fulvestrant in breast cancer treatment. They significantly improve therapeutic outcomes, but still exhibit an array of side-effects and a potential for inter-individual variabilities, so therapeutic drug monitoring (TDM) could prove beneficial.<sup>[1]</sup> A suitable bioanalytical method therefore needs to be developed, encompassing both the sample preparation procedure and the analytical system parameters. Optimal sample preparation ensures maximal analyte extraction recoveries, while minimizing matrix effect and prolonging the instrument lifetime.<sup>[2]</sup> Dispersive liquid-liquid microextraction is a technique in which a mixture of an organic extractant and disperser solvents is quickly injected into an aqueous solution, forming an emulsion that facilitates fast and efficient extraction. In biological sample preparation, protein precipitation (PPT) usually precedes the extraction. Since acetonitrile is commonly used as both a PPT agent and a disperser solvent, the supernatant after PPT can immediately be mixed with an extractant solvent and injected into an aqueous solution.<sup>[3]</sup> In this work, various conditions affecting analytes' extraction recoveries were investigated: type and volume of the extractant and disperser solvent, aqueous phase pH, addition of salt, and ultrasonication. In optimal conditions, for 50  $\mu\text{L}$  of plasma sample, 200  $\mu\text{L}$  of acetonitrile is added for PPT. 200  $\mu\text{L}$  of the supernatant is withdrawn, mixed with 400  $\mu\text{L}$  of chloroform and injected into 100  $\mu\text{L}$  of 5 % w/V aqueous sodium citrate solution. The organic layer is evaporated to dryness, reconstituted in 40  $\mu\text{L}$  65 % V/V methanol and analysed by liquid chromatography. The proposed method is fast, simple, with low sample and solvent consumption, and offers very high extraction yields (87.2 to 97.8 %) with significantly less matrix interferences compared to PPT alone.

**Acknowledgments.** This work has been fully supported by the Croatian Science Foundation under the project number UIP-2019-04-8461.

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## SURFACTANT SENSOR BASED ON 1,3-DIHEXADECYL-1H-BENZO[D]IMIDAZOL-3-IUM FOR ANIONIC SURFACTANTS IN INDUSTRIAL WASTEWATERS

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Anionic surfactants, or anionic surface active agents, are a group of surfactants usually used for washing and cleaning in household and industry. The population growth and rapid industrialization resulted in increased demands for anionic surfactant. Consequently, this resulted in water pollution with negative environmental and health impact. For this reason, there is a need to develop rapid and reliable analytical tools - surfactants sensors, for anionic surfactant monitoring. We developed a surfactant sensor, based on the 1,3-dihexadecyl-1H-benzo[d]imidazol-3-ium-tetraphenylborate ionophore incorporated in the PVC liquid membrane, for anionic surfactants in wastewaters. The sensor was characterized and used for measurement of anionic surfactants in ten real samples of industrial wastewaters. The results were compared with the referent analytical method and showed good agreement.

## THERMODYNAMIC PROPERTIES OF SURFACTANT BENZYLDODECYLDIMETHYLAMMONIUM BROMIDE IN BINARY MIXTURE OF PROPANE-1,2-DIOL AND WATER

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Micellar systems are colloids with various applications in different branches of industry such as cosmetic, petrochemical, pharmaceutical or food industry. Micelles can be used as nanocarriers of poorly water-soluble substances. This property is often used for drug delivery in medical treatments. Micelle formation is a complex process where multiple interactions take place, but most important are hydrophobic interactions.<sup>[1]</sup>

Propane-1,2-diol (PG) is a substance commonly used as a food additive while benzyl-dodecyldimethylammonium (benzododecinium) bromide is quaternary ammonium salt used as preservative and antiseptic in pharmaceutical products. The latter is highly soluble in water and acts like cationic surfactant in aqueous solutions. The nature of the additive (PG) influences the micellar structure and properties of benzododecinium bromide. When increasing the mass fraction of propane-1,2-diol in binary mixtures, the critical micelle concentration (CMC) values increase because the polarity of water is greater than that of the PG, the polarity of the system decreases with increasing PG mass fraction, and the repulsive electrical force of the ionic group is strengthened. Consequently, micelle formation becomes more difficult, which results in increasing CMC values. Increasing the temperature will increase the CMC for every mass fraction PG-water mixture.<sup>[2]</sup>

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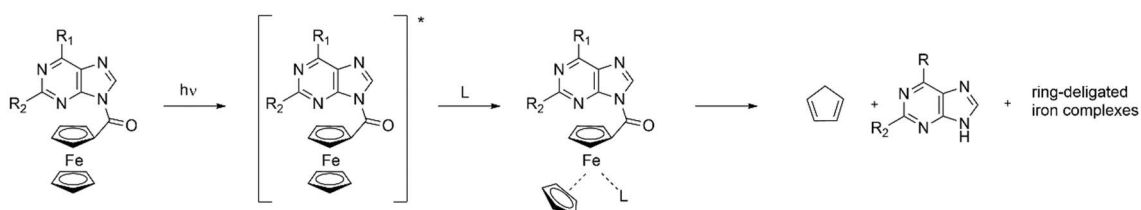
## LIGHT INDUCED DECOMPOSITION OF FERROCENOYL-NUCLEOBASES

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When dissolved in organic solvents, e.g. DMSO, and exposed to light, ferrocenoyl-substituted nucleobases start to decompose and the release of free nucleobase occurs, whereas the ferrocene moiety degrades. The photochemical reaction of N9-ferrocenoyl-(6-benzyloxy)purine and N1-ferrocenoyl-5-fluorouracyl in DMSO was studied by NMR spectroscopy in different reaction conditions. DMSO-assisted displacement of cyclopentadiene ring from ferrocene moiety occurs and ring-delegated iron complexes form. The reaction rate and order depend on reaction conditions (dissolved gasses, water from solvent) and molar absorption (extinction) coefficients of ferrocene conjugates. Pseudo-first order kinetics occurs when the red lamp ( $\lambda = 645$  nm) is used to trigger the reaction, whereas the pseudo-zero order kinetics is observed when the blue lamp ( $\lambda = 405$  nm) is used. When the nucleobase moiety is replaced by the N,N-diphenyl-carboxamide, the light-sensitivity is also observed. In the contrary when the ferrocene moiety is replaced by a benzene ring, as in N7-4-fluorobenzoyl-purine, the compound is not light-sensitive.



**Figure 1.** Light induced heterolytic metal-ring bond cleavage (the release of cyclopentadiene) and the cleavage of the N-CO bond (the release of free nucleobase). L = solvent (DMSO, DMF, acetone, or acetonitrile), wavelengths used: 645, 405, and 394 nm.

## ANION BINDING AFFINITIES OF LINEAR PENTA-HOMOPEPTIDES IN SOLUTION

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In the recent past cyclic peptides have attracted an increasing interest due to their unique chemical and biological properties. These compounds generally exhibit improved metabolic stability and bioavailability as well as enhanced binding affinity and selectivity toward substrates compared to their more flexible linear analogs.<sup>[1–3]</sup> In the synthesis of cyclic peptides, regardless of the macrocyclization strategy, the main factor that affects the success of a ring closure reaction is the conformational preorganization, that is the ability of a linear precursor to bring its reactive termini in the close spatial proximity. We have recently reported that not only cations but also chloride anion is able to act as directing agent for promoting the cyclization of linear peptides.<sup>[1]</sup> In the scope of this work, we have tested the binding affinities of two linear peptides (Figure 1) towards several anions in solution by means of microcalorimetric and <sup>1</sup>H NMR titrations as well as classical molecular dynamics simulations. The results of these investigations could point to the new anion templating agents for the intramolecular head-tail linear peptide cyclization.

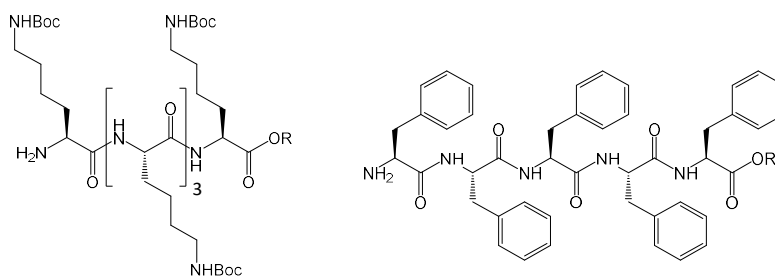


Figure 1. Structures of linear peptides.

**Acknowledgments.** This work was supported by the Croatian Science Foundation under project IP-2019-04-9560 (MacroSol).

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## CONSTRUCTION OF 1D ZIG-ZAG CHAIN COORDINATION POLYMERS UTILISING (ISO)NICOTINOYL HYDRAZONATO LIGANDS AND DIOXOMOLYBDENUM CORE

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Coordination polymers are structures formed by the continuous connection of mononuclear units, and can be one-, two- and three-dimensional, depending on the branching and denticity of the ligand(s) as well as coordination geometry of the metal cation.<sup>[1]</sup> There are multiple applications of coordination polymers, most common being adsorption<sup>[2]</sup> and catalysis<sup>[3]</sup> due to channels and cavities in their structures. Catalytical properties are further promoted by labile coordination sites and structural flexibility in terms of transformations to catalytic active species.<sup>[2]</sup> One-dimensional zig-zag chain coordination polymers were synthesized using bridging tetradentate ligands and dioxobis(pentane-2,4-dionato)molybdenum(VI). The used ligands, hydroxysalicylaldehyde (iso)nicotinoylhydrazones functionalized with hydroxy and metoxy groups on positions 3 or 4, apart from the nature of possible intermolecular interactions, also differ in electron-donating abilities. Additional tuning of the supramolecular structure was achieved by varying the medium in which the syntheses were performed, which enabled the formation of porous and non-porous structures. When choosing solvents, special attention was paid to their coordination ability. The aforementioned must have been necessarily less favorable from that of the bridging nitrogen atom to avoid the formation of mononuclear complex compounds. Characterization of coordination polymers was performed by X-ray diffraction method in mono and polycrystalline samples, NMR and FTIR-ATR spectroscopies, and thermogravimetric analysis.

**Acknowledgments.** This work has been fully supported by Croatian Science Foundation under the project IP-2016-06-4221. “Young researchers' career development project – training of doctoral students” of the Croatian Science Foundation funded by the European Union from the European Social Fund.

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## NATURAL DEEP EUTECTIC SOLVENT AS EXTRACTION MEDIA FOR THE MAIN PHENOLIC COMPOUNDS FROM *RUBI IDAEI* LEAVES

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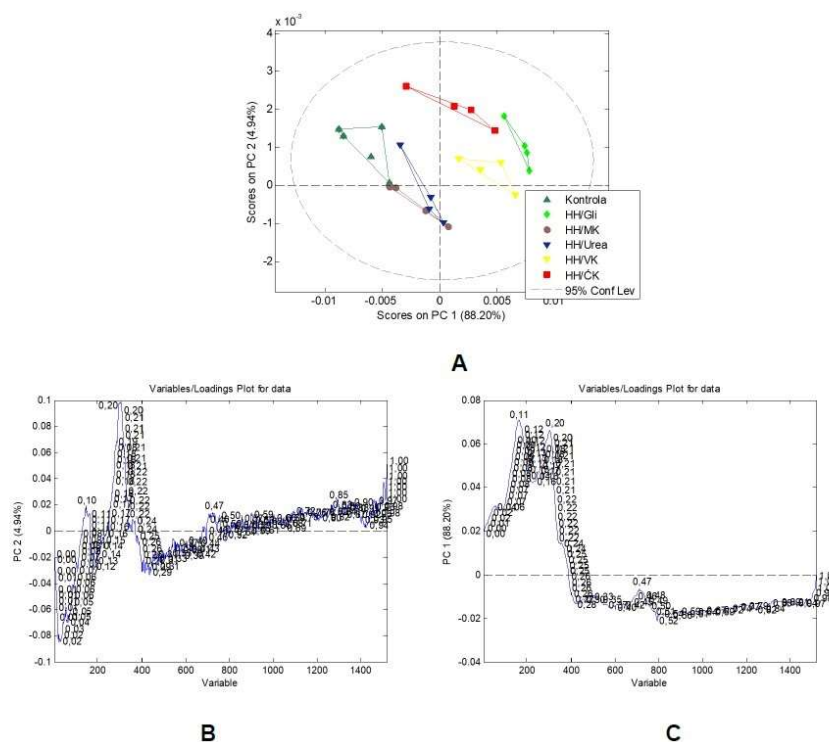
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Upper-respiratory-tract infections (URTI) are contagious diseases caused by a variety of bacteria and viruses. Based on European Union reports for Serbia, usage of antibiotics in pediatrics is extremely high compared to other European countries. Thus, there is growing demand for herbal-based products for the prevention of URTI as an alternative for antibiotics. Due to therapeutic properties such as antimicrobial, cytotoxic, antioxidative, and anti-inflammatory *Rubi idaei* leaves were used in Serbian folk medicine against URTI. Additionally, commercially available herbal products most often comprise ethanolic extracts. However, high-alcohol content makes such products unsuitable for patients' intolerant to alcohol, especially children or other sensitive group of patients.

Due to mentioned drawbacks, proposed study was focus on the development of novel natural, edible, and safe alternative using NADES (Natural Deep Eutectic Solvent), as a new-generation solvents that resemble the plants' intracellular environment. Due to the unique, tuneable solvation properties, NADES are getting more attention as solvents in natural product research.

This study aimed to present the green approach by using ultrasound assisted extraction and twenty various NADES systems as well as ethanol, methanol, and water as control solvents. The obtained extracts were evaluated in terms of their chemical composition by high-performance thin-layer chromatography (HPTLC), as well as in individual compounds by high-performance liquid chromatography (HPLC) coupled with mass spectrometry.

Chromatographic profiles revealed differences in chemical composition depending on the applied extraction system. Ten phenolic compounds such as chlorogenic acid, caffeic acid, rutin, isoquercetin, astragalin, isorhamnetin 3-*O*-glucoside, apigetrin, quercetin, kaempferol were quantified in *Rubi idaei* leaves. Astragalin, isoquercetin, and rutin were major constituents, while other compounds were found in minor amount. Kaempferol was found in high amount in almost all extracts, except in systems cholin chloride : glycerol with higher amount of water and cholin chloride : urea. Chemometric evaluation was applied to compare the extraction profile of NADES systems and their quantitative composition. Extraction systems discrimination revealed by principal component analysis confirming specific chemical profiles depending on the solvents used (Figure 1).



**Figure 1.** Principal component analysis based on data obtained from red channel HPTLC profile: a) score plot, b, c) loading plot.

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## INFLUENCE OF *N*-GLYCOSYLATION ON HORSERADISH PEROXIDASE STABILIZATION

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Horseradish peroxidase (HRP) is an enzyme that catalyzes H<sub>2</sub>O<sub>2</sub> dependent oxidation of a wide variety of substrates. HRP contains four structurally essential disulfide bonds and two calcium ions, and moreover, requires presence of a heme cofactor to be functional. Martell and coworkers introduced an active form of split horseradish peroxidase (sHRP), showcasing its potential application in elucidation of communication mechanisms between a varieties of cell types in protein–protein interactions.<sup>[1]</sup> HRP and sHRP contain nine and eight *N*-linked glycosylation sites, respectively, which are of particular importance, as it is established that glycosylation plays an essential role in HRP and sHRP activity.

To obtain a detailed understanding of the influence of *N*-glycosylation on HRP and sHRP, we performed a series of molecular dynamics (MD) simulations with and without *N*-glycosylation on HRP and sHRP. Thereby we also considered three previously elucidated glycoforms of both proteins.<sup>[2]</sup> In this respect, we find that the conformations of both HRP and sHRP are stabilized when *N*-glycosylation is introduced, with no significant difference between different glycoforms. Nevertheless, we find that the most stable glycoform matches with the highest degree of *N*-glycosylation. The obtained results suggest that glycans protect specific parts of the protein surface of both investigated forms of protein. This finding implies that glycosylation represents an important feature for horseradish peroxide protein stability and its function, being in agreement with previous studies regarding glycosylation effects.<sup>[3]</sup>

**Acknowledgments.** MARILIA - European Union's Horizon 2020 research and innovation program under grant agreement No 952110.

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## SYNTHESIS OF NEW AMPHIPHILIC TRIAZOLE DERIVATIVES OF MANNOSYLATED DESMURAMYL DIPEPTIDE

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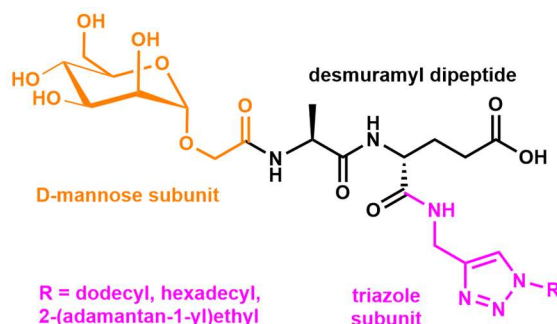
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Adjuvants or immunostimulators are substances that are added to vaccines to improve the specific human immune response to a specific antigen. Derivatives of muramyl dipeptide (MDP, *N*-acetylmuramyl-L-alanyl-D-*isoglutamine*) as well as desmuramyl dipeptide derivatives (L-Ala-D-*isoGln*), MDP analogs without the sugar *N*-acetylmuramyl unit are the well-known adjuvants.<sup>[1]</sup> Introduction of lipophilic substituent in MDP or L-Ala-D-*isoGln* pharmacophore can increase its adjuvant activity<sup>[2]</sup> and binding of mannose to the structure enables mannosylated compounds to interact with lectins specific for mannose. Some of amphiphilic derivatives of DMP have been prepared in our laboratory and their adjuvant activity was tested *in vivo* (e.g. adamantyl triazole derivative with or without mannose subunit).

A further goal of our research is the preparation of various mannosylated desmuramyl dipeptides with different aliphatic subunits linked to  $\alpha$  position of D-*isoGln* through an amide bond via triazole ring (Fig. 1). The protected dipeptide Boc-L-Ala-D-Glu-(OBn) was prepared first as a peptide precursor and then modified successfully in the amidation reaction with various pre-prepared aliphatic (hexadecyl, dodecyl and 2-(adamantan-1-yl)ethyl) 1,4-disubstituted triazole subunits. The amidation method was also optimized and successfully applied for the introduction of the aliphatic triazole subunits into the structure of the dipeptide. Previously prepared benzyl protected mannose subunit was synthesized from methyl- $\alpha$ -D-mannopyranoside and linked via glycolyl linker to the terminal amino group of alanine. Target amphiphilic derivatives were prepared by removal of protecting group in the last step and they will be tested for their adjuvant activity.



**Figure 1.** Aliphatic triazole derivatives of desmuramyl dipeptide with mannose subunit

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## ROLE OF DIPEPTIDYL PEPTIDASE III IN PAIN REGULATION THROUGH CLEAVAGE OF NEUROPEPTIDES

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Dipeptidyl peptidase III (DPP III) is a zinc-dependent exopeptidase that hydrolyses dipeptides from the N-terminus of endogenous peptides, such as angiotensin II, enkephalins and endomorphins.<sup>[1]</sup> It is widely expressed in human tissues, but its colocalization with opioid peptides in the central nervous system suggest a role for this enzyme in the mammalian endogenous pain regulation system.<sup>[2]</sup> To identify new peptide substrates of DPP III, we used HPLC-MS to quantify enzymatic activity of human DPP III towards a selected list of untested neuropeptides, as well as known DPP III substrates. Peptide binding affinity was analysed using isothermal titration calorimetry (ITC), and we measured an entropic contribution characteristic for DPP III for all peptides cleaved by the enzyme. We show here that hemorphin-4, valorphin, Leu-valorphin-Arg and  $\beta$ -casomorphin are cleaved by the enzyme, while vasopressin, hemopressin and  $\beta$ -neoendorphin are not substrates of human DPP III. Hemorphin-4 and valorphin are opioid peptides with antinociceptive properties, derived from proteolytic cleavage of hemoglobin.<sup>[3]</sup> The value for  $K_D$  of valorphin is similar to that of angiotensin II, and  $K_D$  of hemorphin-4 is similar to that of endomorphin-2. In addition, we attempt to directly measure the kinetic parameters for peptide cleavage using HPLC-MS. Our results should help to clarify the role of DPP III in pain regulation.

**Acknowledgments.** This work has been supported by Croatian Science Foundation under the project IP-2018-01-2936.

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## EFFECTS OF AGRICULTURAL PRODUCTION SYSTEMS ON PROTEIN PROFILES OF FOUR DIFFERENT VARIETIES OF POTATO TUBERS

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A number of studies have compared the level of nutritionally relevant compounds in crops from organic, integral and conventional agricultural systems, but there are very limited data on the influence of cultivation systems and their key components on the protein composition of plants. We solved this lack by quantifying the effects of different cultivation systems on the protein profiles of 48 potato tubers of four varieties that were grown in three systems of production (organic, integral, and conventional). Extractable protein composition of the defatted samples was detected by the sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) performed in the presence of  $\beta$ -mercaptoethanol. The proteomic profiling study was used to address genetic differences among potato varieties, between tuber peel and bulk, and to characterize tuber responses to different agronomic regimes. The results indicate that the accumulation of proteins is more active in tubers grown in organic production, which is consistent with the fact that organic crops generally grew under increased stress due to an insufficient supply of nutrients.<sup>[1]</sup> Also, these results showed that the main source of differences in protein profiles between types of production may be the fertilization regime because organic fertilization leads to an increased stress response in potato tubers.<sup>[2]</sup> Finally, the protein profiles indicated differences between the peel and the bulk of the tubers, as well as between the four varieties of potatoes, with the yellow varieties being richer than the red ones.

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## DIAMANTANE ALCOHOLS AND HYDROPHOBIC CAVITIES: THE PERFECT PAIR ALSO IN NON-AQUEOUS SOLUTION?

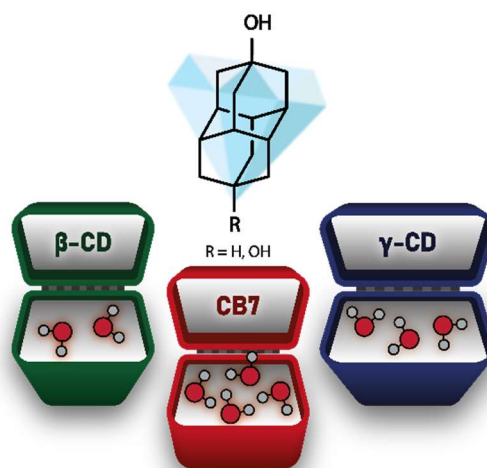
Iva Markuš,<sup>a</sup> Andrea Usenik,<sup>a,\*</sup> Katarina Pičuljan,<sup>a</sup> Marija Alešković,<sup>b</sup>  
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Diamantane derivatives are excellent guests for cucurbiturils in aqueous solutions, forming complexes with stability constants reaching above petamolar values.<sup>[1]</sup> On the other hand, their complexation with cyclodextrins has been scarcely explored. We therefore studied temperature and solvent effects on the complexation of diamantane alcohols with cucurbit[7]uril,  $\beta$ - and  $\gamma$ -cyclodextrin by means of isothermal titration calorimetry and NMR spectroscopy. The stability constant among all investigated complexes was by far the highest in the case of the diol derivate with cucurbit[7]uril in water. A pronounced temperature dependence of  $\Delta_r H^\circ$  and  $\Delta_r S^\circ$ , resulting in an almost complete enthalpy-entropy compensation, was observed for most studied host-guest systems. The corresponding complexation thermodynamics were in line with the classical rationale of the solvophobic effect at lower temperatures, and the non-classical explanation at higher ones.<sup>[2,3]</sup> The results of <sup>1</sup>H NMR titrations and ROESY experiments were in line with the thermodynamic studies and have revealed an interesting difference in complex formation kinetics between cucurbit[7]uril and  $\beta$ -cyclodextrin.



**Acknowledgments.** This research was fully supported by the Croatian Science Foundation (projects MacroSol, IP-2019-04-9560 and DiamMat, UIP-2017-05-9653)

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## CALIX[4]ARENES BEARING UREA MOIETIES - INVESTIGATION OF SUPRAMOLECULAR BEHAVIOUR

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Calixarenes are a useful family of compounds that can bind cationic, anionic, and neutral species, when properly functionalised at upper and/or lower rim.<sup>1</sup> Although (thio)urea-derivatives of calixarenes are known for three decades,<sup>2</sup> their applicability for selective binding<sup>3</sup> or transport<sup>4</sup> of biologically important species is still widely unexplored.

Receptors **M1** and **M2** (Figure 1), which belong to this compound class, have been recently investigated as anion binders. Thermodynamics of their complexation with various anions ( $\text{Cl}^-$ ,  $\text{HSO}_4^-$ ,  $\text{H}_2\text{PO}_4^-$ , benzoate, and hydrogen pyrophosphate) was studied in acetonitrile. Complexes of 1:1 stoichiometry were observed with all examined anions except  $\text{H}_2\text{PO}_4^-$  and hydrogen pyrophosphate which also formed 2:1 complexes (anion:receptor). Due to the larger number of urea groups in **M2**, the anion binding equilibrium constants for this receptor were proven to be significantly higher than those for hybrid amide-urea analogue **M1**.

In this work the supramolecular behaviour of these two calix[4]arenes was characterized in more detail. Firstly, the cation binding abilities of **M1** and **M2** were examined focusing on alkali and alkaline earth metal cations using several experimental methods (NMR, ITC, UV/Vis). Further on, the ability of **M1** and **M2** to act as ion-pair receptors was investigated. Structural features of the complexes were elucidated by means of NMR spectroscopy and the cooperative effect of binding two oppositely charged species was evaluated and discussed from the thermodynamic point of view.

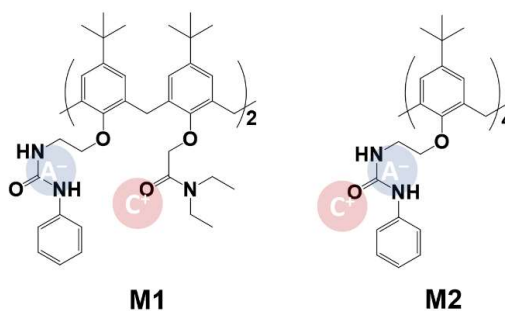


Figure 1. Structures of the investigated calixarenes.

**Acknowledgments.** This work has been fully supported by Croatian Science Foundation under the project IP-2019-04-9560 (MacroSol).

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## ELECTROCOAGULATION AND ELECTROCHEMICAL ADVANCED OXIDATION PROCESSES IN OILY WASTEWATER TREATMENT

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With the growth of industrial production, the amount of oily wastewater generated is increasing worldwide.<sup>[1]</sup> In these effluents, oil and grease along with other constituents such as heavy metals, cyanides, etc. are classified as hazardous wastes and must be disposed of before discharge to the environment or their reuse.<sup>[2]</sup> In recent years, there has been increased research on new wastewater treatment technologies that would not only increase the treatment efficiency, but also the economic efficiency, environmental sustainability and social acceptability. A recent approach to wastewater treatment is the application of electrochemical processes such as electrocoagulation (EC) and electrochemical advanced oxidation processes (EAOP), among which the electro-Fenton process (EF) stands out, which is a combination of Fenton's reagent chemistry and electrochemistry. The EF process oxidizes organic materials using electrochemically generated reactive oxygen species such as chlorine, hypochlorite, hydrogen peroxide and ozone.<sup>[3]</sup> In this work, stainless steel, iron and aluminum electrodes were used. In order to investigate the efficiency of the EF process, experiments were carried out using wastewater from oil and grease separators to which diesel was added to increase the concentration of mineral oil. The tests showed that the EF process can achieve the removal efficiency of mineral oil up to 98% and of COD up to 82%. Additional tests were performed with increased loads in raw wastewater by addition of used engine oil and emulsion from metallurgical industry. The results obtained showed a removal efficiency of mineral oil up to 99,9% and of COD up to 67%.

**Acknowledgments.** This work has been fully supported by Croatian Science Foundation under the project "IP2019-04-1169 - Use of treated oily wastewater and sewage sludge in brick industry production of innovative brick products in the scope of circular economy".

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## SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF NOVEL AMIDINO SUBSTITUTED BENZOTHAZOLES AND BENZIMIDAZOLES

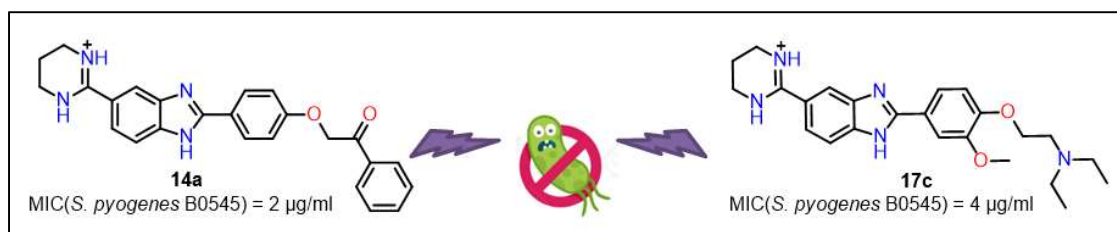
Valentina Rep,<sup>a,\*</sup> Rebeka Štulić,<sup>a</sup> Hana Čipčić Paljetak,<sup>b</sup> Mario Matijašić,<sup>b</sup> Mihaela Perić,<sup>b</sup> Silvana Raić-Malić<sup>a</sup>

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Benzothiazole and benzimidazole scaffolds have become unavoidable structural motifs in the rational drug design because of their versatile pharmacological features. Additionally, it was found that amidines are structural parts of numerous biologically active compounds showing particularly antibacterial and anticancer activity.<sup>[1–3]</sup> Design of novel amidino derivatives was focused on diversification of three regions of target molecules: changing type of amidino substituent on left-hand side and type substituents on right-hand side of a molecule, as well as changing central heterocycle from benzimidazole to benzothiazole to modulate biological properties. Herein we present the synthesis and *in vitro* antibacterial activity of novel benzazole amidines. Novel amidino substituted benzazole derivatives were synthesized through formation of benzimidazole moiety by oxidative coupling of *o*-phenylenediamines with aldehydes or by condensation of 2-aminothiophenoles with corresponding aldehydes to obtain benzothiazole ring. Novel compounds were evaluated for their activity against Gram-positive and Gram-negative bacteria. Pyrimidino-substituted benzimidazoles **14a** and **17c** showed good antibacterial activity against Gram-positive strain *S. pyogenes*.



**Acknowledgments.** Financial support from the Croatian Science Foundation under the project HRZZ-IP-2018-01-4682 is gratefully acknowledged.

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# INTERACTIONS OF METHYL VIOLOGENS OF BIS-(4'-ETHYNYLPYRIDYL)ARENES WITH DNA/RNA AND THEIR BIOLOGICAL ACTIVITY

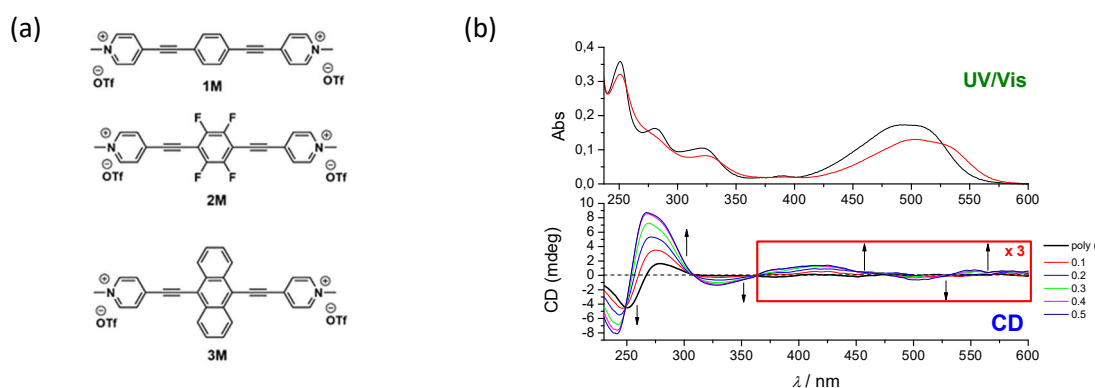
Ivo Piantanida,<sup>a</sup> Goutam Kumar Kole,<sup>b</sup> Todd B. Marder,<sup>b</sup> Marta Koščak<sup>a,\*</sup>

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The 4,4'-bipyridyl salts (viologens), extensively investigated in the past<sup>[1,3]</sup> recently again attracted more attention.<sup>[2]</sup> Based on previous results of Marder et al on bis-(4'-ethynylpyridyl)arenes,<sup>[3]</sup> here we studied their bis-cationic analogues (Scheme 1). **1M** and **2M** showed only non-selective emission quenching upon binding to various ds-DNA/RNA, at variance to anthracene analogue, **3M**, yielding an opposite fluorescence response for GC-DNA (quenching) in comparison to AT-DNA (strong increase). In the CD experiments **3M** at ICD bands at  $\lambda > 300$  nm (Scheme 1) strongly supported intercalation, whereas **2M** ICD band (330–450 nm) agreed with DNA/RNA groove binding. MTT assays and confocal microscopy showed that **3M** efficiently enters the living cells, accumulating in lysosomes.



**Scheme 1.** General structure of **1M**, **2M** and **3M** (a); CD titrations of poly(dG–dC) at various ratios  $r[\text{dye}]/[\text{polynucleotide}]$  with **3M** (b).

**Acknowledgments.** We thank Croatian Science Foundation for the financial support within the project „BioMultiChromoProbes“ (HrZZ IP-2018-01-5475).

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## CYCLIC CARBAMATE FORMATION THROUGH TRANSITION METAL-CATALYZED CO<sub>2</sub> CAPTURE

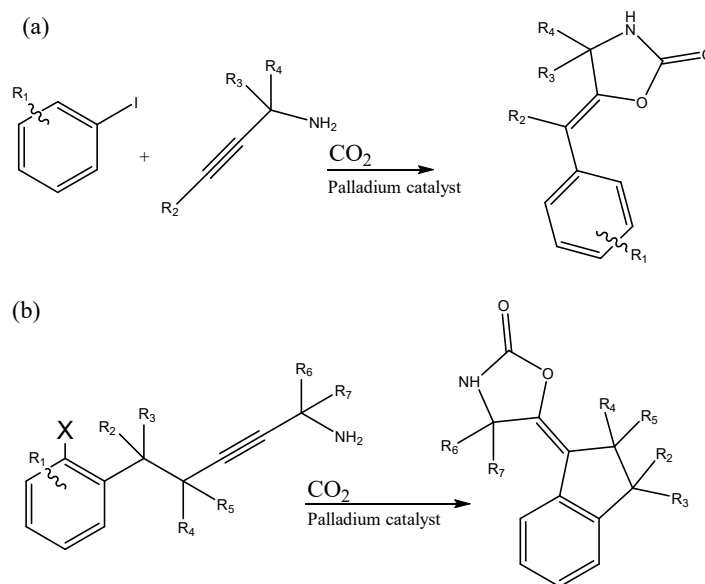
Filip Vranješević,<sup>a</sup> Maria Kolypadi Markovic,<sup>a</sup> Valerije Vrčec,<sup>b</sup> Dean Marković<sup>a,\*</sup>

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The optimization of reaction substrates and conditions using *in silico* methods represents the future of organic synthesis. We have evaluated potential substrates for a novel Pd-catalyzed CO<sub>2</sub> capture reaction (Figure 1b) using QM analysis of reaction thermodynamics (with B3LYP/B2PLYP functionals) and selected several amines that appeared promising.



**Figure 1.** (a) The type of reaction reported by Nevado [1] that forms carbamates with a tetrasubstituted alkene from CO<sub>2</sub> using a Pd catalyst; (b) Our (intramolecular) version of this cascade reaction.

These substrates have been synthesized and are currently being tested for CO<sub>2</sub> capture under a range of experimental conditions and catalysts. A similar reaction has been reported by Nevado's group in 2016.<sup>[1]</sup> However, if successful, our intramolecular cascade reaction will enable us to produce a complex cyclic carbamate motif in one step using a simple reaction under mild conditions and a very cheap, environmentally friendly reactant (CO<sub>2</sub>). In addition, the mechanism of this reaction will be studied to further optimize the reaction conditions *in silico*. Finally, as cyclic carbamate moieties are often present in many small molecule therapeutics (e.g. Efavirenz and Linezolid), the products of this reaction will be tested for anti-cancer and antibacterial activity.

**Acknowledgments.** This project is funded by the Croatian Foundation for Science (HRZZ-IP-2019-04-8846).

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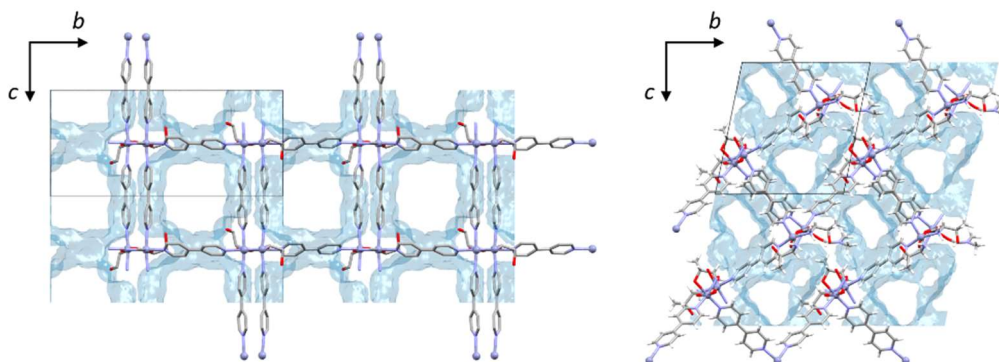
## SYNTHESIS AND CRYSTAL STRUCTURE ANALYSIS OF 3D ZINC METAL-ORGANIC FRAMEWORKS INVOLVING AMINO ACIDATES

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Metal-organic frameworks (MOFs) are materials of great interest in the scientific community due to their vast variety of potential applications.<sup>[1]</sup> These materials are investigated mostly as potential gas/solvent storage materials, and for enantioselective catalysis or separation of enantiomers.<sup>[1,2]</sup> Studies involving zinc MOFs composed of standard amino acids and 4,4'-bipyridine are quite scarce. Only 11 crystal structures of such MOFs are published in Cambridge Structural Database (CSD), and only one is a 3D MOF.<sup>[3,4]</sup> We report synthesis and crystal structures of two novel 3D zinc MOFs with 4,4'-bipyridine (bipy), amino acidates L-serinate (Ser) and L-threoninate (Thr) and DMF/water molecules:  $\{[\text{Zn}_2(\mu\text{-Ser})_2(\mu\text{-bipy})_3](\text{NO}_3)_2 \cdot (\text{DMF}/\text{H}_2\text{O})\}_n$  (**1**) and  $\{[\text{Zn}_4(\mu\text{-Thr})_4(\text{H}_2\text{O})(\mu\text{-bipy})_4(\text{DMF})](\text{NO}_3)_4 \cdot (\text{DMF}/\text{H}_2\text{O})\}_n$  (**2**) (Figure 1). **1** has a large volume ratio of solvent molecules ( $\approx 44\%$ ), forming 2D channels, while **2** has a 25% volume ratio of solvent molecules which form 1D channels.



**Figure 1.** Backbones of 3D chiral cationic MOFs with solvent and nitrate contact surface in channels (**1** left and **2** right).

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## HIGH-THROUGHPUT ENRICHMENT OF COMPLEMENT C3 PROTEIN FROM HUMAN PLASMA USING LECTIN AFFINITY MATRIX

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The third component of the complement system - glycoprotein C3, plays a central role in the activation of the complement system, both in classical and alternative complement activation pathway.<sup>[1]</sup> Being the most abundant complement protein with plasma concentrations of approximately 1.2 mg/ml, its position in immune surveillance is pivotal.<sup>[2]</sup> However, its glycosylation, as one of the most significant post-translation modifications, is not well investigated, but from the literature it is known that C3 has only high mannose N-glycans.<sup>[1,3]</sup> Given the growing recognition of complement's involvement in various disease processes, it is important to have high-throughput methods for the detailed analysis of this key complement protein. The aim of this research was to obtain a C3 enrichment protocol from human plasma for downstream C3 glycopeptide analysis on LC-MS. Knowing the C3 N-glycosylation profile consists of only high mannose structures, glycoprotein enrichment was achieved using lectin affinity matrix. Different volumes of plasma samples and enrichment conditions were tested to get a more specific and effective enrichment. Obtained protocol for C3 enrichment and glycopeptide analysis was applied on 14 healthy male individuals measured in three time points in order to determine the C3 N-glycome stability. This method showed for the first time that the C3 N-glycome is stable in healthy individuals.

**Acknowledgments.** This research was funded by the project CEKOM - Center for Competence in Molecular Diagnostics. The studies involving human participants were reviewed and approved by the Ethical Committee of the University of Zagreb, Faculty of Pharmacy and Biochemistry.

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## DEVELOPMENT AND VALIDATION OF HPTLC METHOD FOR DETERMINATION OF SUGAR PROFILES OF HONEY AND ITS SYRUP ADULTERANTS

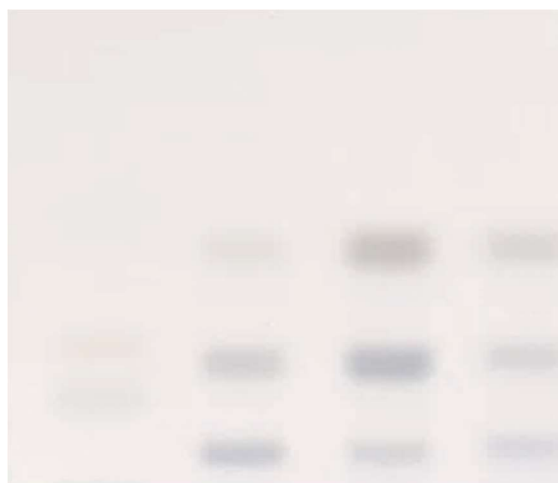
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Honey is a natural sweet product of honeybees widely consumed by people as both a food and a medicine. It is mainly composed of carbohydrates, primarily fructose and glucose, followed by sucrose and other oligosaccharides present in lower quantity. Due to its nutritional and health benefits and relatively high price, honey is frequently subjected to adulteration either by addition of sugar syrups or cheaper and lower quality honey, or by mislabeling of declaration. Numerous analytical methods, such as chromatographic, spectroscopic, isotopic, and electrochemical, have been developed to detect honey adulterants.<sup>[1]</sup> Application of thin-layer chromatography (TLC) in the detection of syrup adulterants is limited due to the hydrolysis of polysaccharides and a presence of false positive components such as smaller oligosaccharides (from 3 to 6 monosaccharide units). However, with the development of high-performance layers and sophisticated instrumentation, high-performance TLC (HPTLC) should become a method of choice in determination of honey authenticity.



**Figure 1.** HPTLC chromatograms, 1-3 carbohydrates standards, 4-6 sugar syrups, 7,8 honey.

The aim of this study was to develop and validate an HPTLC-imaging method for reliable determination of syrups added in honey. The proposed method was validated on the basis of the linearity, precision, detection and quantitative limit and results compared with those obtained by high-performance anion exchange chromatography coupled with pulsed amperometric detection (HPAEC-PAD). The detection method was sensitive enough to allow the determination of lower concentrations of carbohydrates, while also being robust enough to handle higher concentrations of the major components, glucose and fructose. The presence of

sugar syrups in honey led to significant changes in the amount of carbohydrates that normally are only present in minor quantities or the appearance of new compounds which could be used as markers for tracking honey authenticity.<sup>[2]</sup> Main advantages of developed HPTLC method are efficiency with small amounts of sample (0.5-2.0  $\mu$ L), parallel analysis of samples (up to 8 on 10×10 cm plates), low consumption of solvents (5-10 mL) and time efficiency (15-25 min). These preliminary results (Figure 1) show potential for obtaining simple, economic, efficient and environmental friendly method for verifying honey authenticity regarding description.

**Acknowledgments.** This work was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia, Contract numbers: 451-03-9/2021-14/200168 and 451-03-9/2021-14/200026, as well as the European Commission, under the Horizon2020 FoodEnTwin project, GA No. 810752.

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## ISOLATION AND CHEMICAL ANALYSIS OF IMMORTELLE ESSENTIAL OIL

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Coastal immortelle (*Helichrysum italicum* (Roth) G. Don) is a perennial semi-shrub plant from the Asteraceae family that grows up to 60 cm in height. It inhabits coastal areas throughout the Mediterranean region.<sup>[1]</sup> Quality oil is considered to be clear oil of golden yellow color with a characteristic intense odor, content of  $\alpha$ -pinene less than 25% and neryl acetate greater than 5%.<sup>[2]</sup> For the commercial needs, immortelle essential oil is produced using water-steam distillation method.<sup>[3]</sup> In this paper, we analyze the possibility of applying other distillation methods for production purposes and their influence on the chemical composition of immortelle essential oil. Using the scanning electron microscopy (SEM), it has been established that the containers of essential oil in immortelle are located on the surface of the aboveground parts of the plant. Therefore, the plant material does not need to be further ground and processed before the distillation process. From plant material collected in the area of Kaštela, Plano, Marina and Kornati, the essential oil was isolated by water-steam distillation ( $w = 0.15\%$ ), hydrodistillation in Clevenger apparatus ( $w = 0.30\%$ ) and microwave assisted distillation ( $w = 0.12\%$ ). The analysis of essential oil samples was performed by GC-MS technique. All isolated oils were of exceptional quality with the contents of  $\alpha$ -pinene 0.10–12.10% and neryl acetate 6.72–16.76%. By applying a certain distillation method, the individual compounds ratio can be influenced and thus produce immortelle essential oil of a certain composition according to market requirements.

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## CYCLOBUTANETETRAAMINO ACID DERIVED HOMOCHIRAL METAL-ORGANIC FRAMEWORKS

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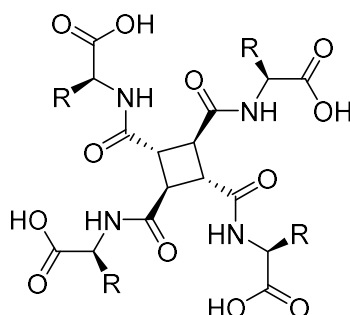
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Homochiral metal-organic frameworks (MOF) have been gaining increasing attention as novel chiral stationary phase materials for chromatographic separations in the past decade due to their high porosity and chemical stability.<sup>[1–3]</sup> In an effort to find new homochiral MOFs we synthesized a series of tetratopic, D<sub>2</sub> symmetric linkers by coupling trans,trans,trans-cyclobutanetetracarboxylic acid and various amino acid benzyl esters followed by hydrogenolysis of the ester protecting groups. These linkers, easily prepared on multigram scale, were used in the synthesis of zirconium based MOFs whose performance as chiral stationary phase materials is being evaluated in resolutions of various racemic mixtures of small molecules.



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## FABRICATION OF ALL-SOLID-STATE AMMONIUM SELECTIVE ELECTRODE ON A PAPER SUBSTRATE

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Potentiometric ion-selective electrodes (ISEs) based on specific selective ionophores are nowadays important analytical tools for the detection of various ions. Among these sensors, ammonium ISEs have proven to be the most useful indicator electrodes for environmental monitoring.<sup>[1,2]</sup> In this work, we present a novel planar solid-state ammonium selective electrode, which is made of low-cost and commercially available materials and suitable for mass production. For this purpose, an inkjet printed silver wire was used as an internal contact, while a mixture of graphite particles embedded in a polyvinyl butyral (PVB) matrix served as an ion-to-electron transducer, top-coated with a conventional ammonium ionophore I selective membrane. The resistance of the graphite-PVB layer, a key parameter of planar sensor viability, was evaluated by applying electrochemical impedance spectroscopy (EIS). Several transduction mixtures with different mass fractions of graphite to PVB were tested; the lowest electron transfer resistance (15 k $\Omega$ ) was achieved with a formulation consisting of 65 wt % graphite. Analytical performance of the array under steady-state conditions (potentiometric analysis) revealed linearity over a concentration range of  $10^{-5}$  to  $10^{-1}$  M, while flow injection analysis (FIA) showed linear response range from  $10^{-4}$  to  $10^{-1}$  M. A near-Nernstian slope of 58.34 mV/decade and 60.91 mV/decade is achieved using both techniques, respectively. The proposed electrode is miniaturized, can be easily integrated into portable devices of various sizes and shapes, and has potential application in monitoring  $\text{NH}_4^+$  content in water samples over a wide range of pH values.

**Acknowledgments.** This work was fully supported by the University of Zagreb, Grant No. 121053.

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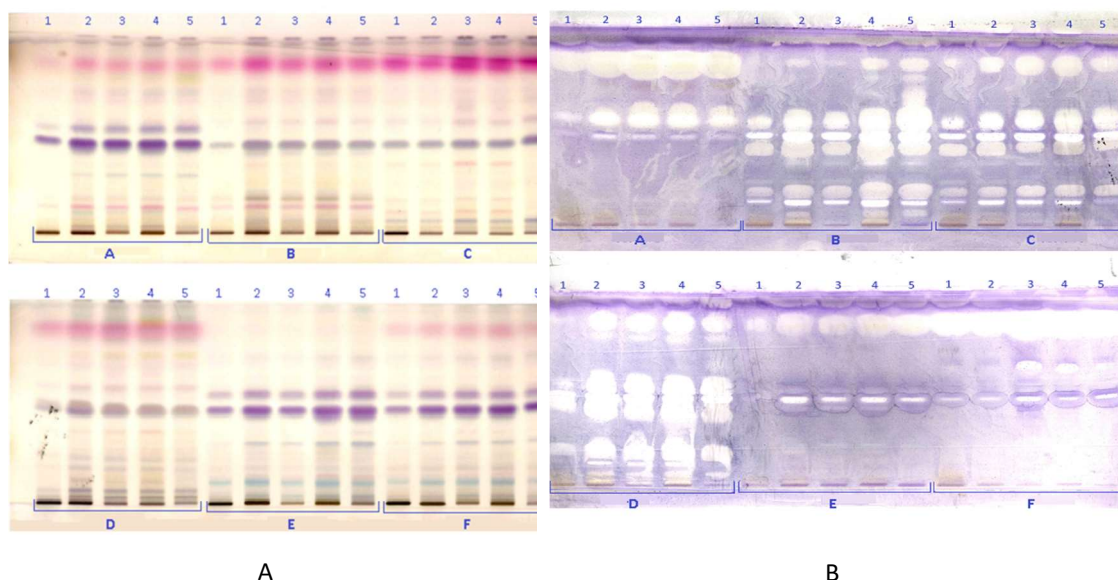
# STATISTICAL ANALYSIS BASED GREEN PLANAR CHROMATOGRAPHIC METHODOLOGY FOR QUALITY CONTROL OF FOOD SUPPLEMENTS: CASE STUDY ON *ORIGANUM VULGARE*

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The guarantee of food safety and quality along the food chain has become an important issue which challenges the worldwide and attracts the extensive attention. In order to ensure food safety and quality, efficient analytical methodologies must be applied in the detection of food authenticity, origin, product quality control, food microbiology, genetically modified ingredients, pesticide residues, allergens and toxins.<sup>[1]</sup> The aim of this study was to develop a green, simple, and high throughput procedure for the quality assessment of food supplements using a high-performance thin-layer chromatography (HPTLC)/bioautography with multivariate statistics. Bioautography assays were developed for the identification of constituents with radical scavenging (DPPH assay), antimicrobial (*Bacillus subtilis*, *Escherichia coli*, *Micrococcus luteus*), and enzymes (alpha-amylase) activities of different oregano samples (Figure 1). Further, the combination of chemical screening/bioprofiling and chemometrics was used for identification of target, most potent compounds and additionally, search of the most potent oregano samples.



**Figure 1.** HPTLC chromatograms for six samples of oregano obtained with different solvents (1 - methanol, 2 - ethanol, 3 - ethyl acetate, 4 - acetone, 5 - dichlormethane);  
A – chemical profile, B – *B. subtilis*.

Due to several advantages such as minimum requirements for sample preparation and minimal amount of investigated sample, possibility of selection of eco-friendly and harmless organic solvents, *in situ* identification of target compounds, multi detection of investigated compounds, and low solvent consumption (200-500  $\mu$ L per sample) planar chromatography/bioautography is recognized as green technique. Methodology suggested in this study confirmed its possible application in quality control of food supplements.

**Acknowledgments.** This work was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia, Contract numbers: 451-03-9/2021-14/200168, as well as the European Commission, under the Horizon2020 FoodEnTwin project, GA No. 810752.

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## APPLICATION OF BETULIN-DERIVED NITRILE OXIDES IN THE CONSTRUCTION OF CYTOSTATIC LUPANE-TYPE TRITERPENOID-ISOXAZOLE CONJUGATES

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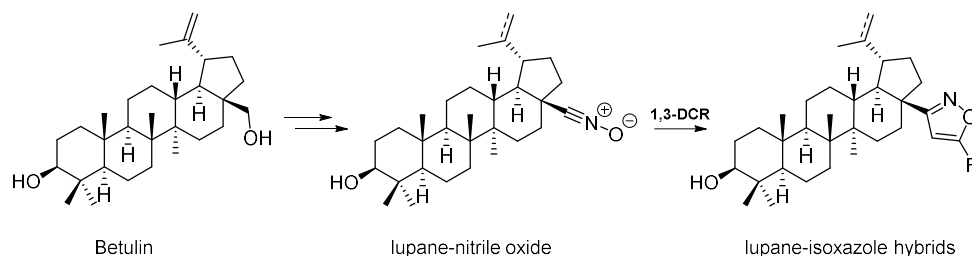
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Betulin is a naturally occurring pentacyclic triterpenoid that is found in the bark of birch tree, with content up to 35% of bark dry weight. Research reveals, that betulin and its semisynthetic derivatives possess wide spectrum of biological activity.<sup>[1]</sup>

Here we present a method for the preparation of novel lupane-type triterpenoid-isoxazole conjugates using successful combination of electro-organic synthesis and conventional approaches.<sup>[2]</sup> The exceptionally stable and isolable nitrile oxides allowed creation of isoxazole library by 1,3-dipolar cycloaddition reactions with various alkynes. Some of the title conjugates exhibit cytostatic properties against breast cancer cell line MCF7, glioblastoma multiform cell line U-87 MG and lung carcinoma cell line A549 with growth inhibition (GI<sub>50</sub>) concentrations up to 11 μM, while being harmless to immortalized human fibroblasts hTERT (GI<sub>50</sub> > 100 μM).



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## REACTIVITY AND THERMAL BEHAVIOUR OF 7-METHYL-2*H*,3*H*,7*H*-IMIDAZO[2,1-*b*]THIAZOL-4-IUM CHLORIDE

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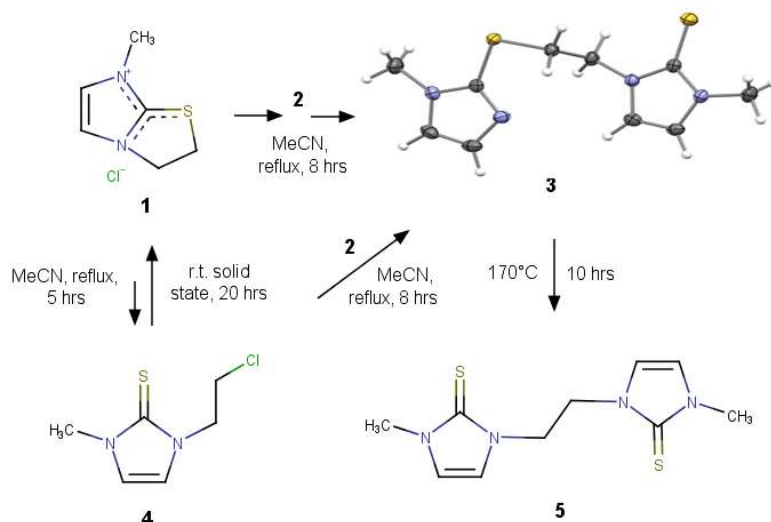
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Recently, in the course stability study of thyrostatic drug methimazole (1-methyl-1,3-dihydro-1*H*-imidazole-2-thione, **2**) in DCE we reported synthesis and characterisation of 7-methyl-2*H*,3*H*,7*H*-imidazo[2,1-*b*]thiazol-4-ium chloride (**1**) as a novel and stable thiiranium ion isomer.<sup>[1]</sup>



To gain more insight into its reactivity we performed reaction of **1** with **2** in boiling MeCN which unexpectedly led to the formation of 2,3-dihydro-3-methyl-1-[(1-methyl-1*H*-imidazole-2-yl) thioethyl]-1*H*-imidazole-2-thione (**3**) in low yield. Furthermore, we found that **1** underwent thermal ring opening isomerisation to 1-chloroethyl-2,3-dihydro-3-methyl-1*H*-imidazole-2-

thione (**4**) in low yield (25 %) due to its equilibrium to **1**. In addition, isolated, solid **4**, after 20 hours at room temperature, spontaneously and quantitatively isomerized back to **1**. Finally, in reaction of **4** with **2** in boiling MeCN, dimeric product **3** is obtained in 92 % yield. It, by heating at 170°C during 10 hours, also underwent to thermal isomerization to its regio-isomer 1,2-bis(2,3-dihydro-3-methyl-1*H*-imidazole-2-thione-1yl)ethane (**5**) in 88% yield. Isomerization was studied using spectroscopic and computational methods as well.

All products were characterized using spectroscopic and thermal methods, while structure of **3** [C<sub>10</sub>H<sub>14</sub>N<sub>4</sub>S<sub>2</sub>], (*M*<sub>r</sub>=254.37) was additionally determined by single crystal X-ray analysis. It crystallizes in centrosymmetric space group *P*2<sub>1</sub>/*c* and its molecules consist of two methyl imidazole rings separated with a thioether –CH<sub>2</sub>–CH<sub>2</sub>–S– spacer. The crystal data are as follows: *a* = 12.1442(5), *b* = 6.9640(3), *c* = 14.1111(6) Å, *V* = 1191.48(9) Å<sup>3</sup>, *Z* = 4, *R* = 0.0321, *R*<sub>w</sub> = 0.0803, *S* = 1.076, 8232 reflexes with *I* > 2σ(*I*).

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## BIOACCESSIBILITY OF PHYTIC ACIDS AND TOTAL PHENOLIC CONTENT IN GRAIN OF PLANT *AMARANTHUS CRUENTUS* UPON SIMULATED GASTROINTESTINAL DIGESTION

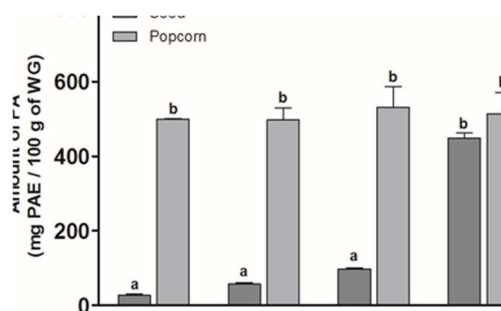
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The plants of the genus *Amaranthus* were represented in the everyday diet of the ancient civilizations of the Incas, Mayas, and Aztecs, they served as analogues of wheat and rice. The plant species *Amaranthus cruentus* is a good candidate for use in functional food production since amaranth seeds are characterized by a high content of beneficial nutrients compared to other types of grain. However, the high content of phytic acids, which are chelating agents, and the way in which food is prepared, stored, and processed can have significant impact on its quality. Thus, the aim of this study is to determine the bioaccessibility of phytic acids (PA), phenolics (PC) and ABTS and DPPH radical scavenging activity in “digesta” from the *A. cruentus* seeds (S) and popcorns (P) upon simulated gastrointestinal digestion, and mechanical (grind (G) and non-grind (NG)) and thermal (boiled (B) and non-boiled (NB)) pretreatment of amaranth grain.

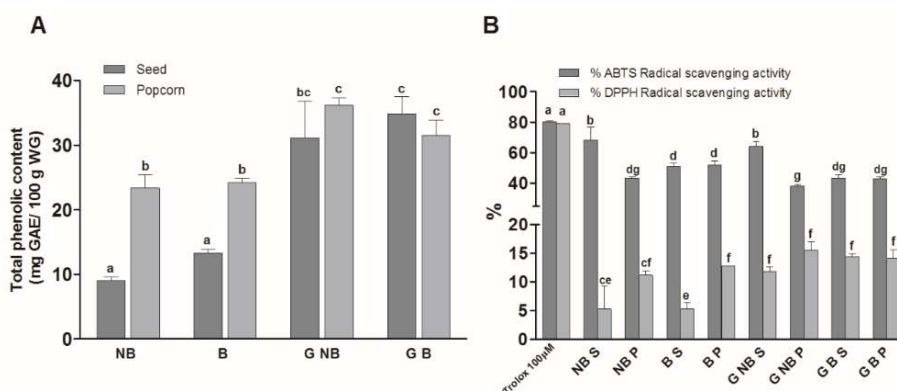
The PA content in „digesta“ samples was determined by the method of Gao, Shang<sup>[1]</sup> using Wade reagent and extrapolation from a standard curve of series of standard phytic acid solutions. PA content was expressed as mg phytic acid equivalents (PAE) per 100 g of weighted grain (WG), seed and popcorn. Folin-Ciocalteu reagent was used for the assessment of total phenolics content (TPC) according to Singleton and Rossi<sup>[2]</sup> with some modifications and TPC was expressed as mg gallic acid equivalents (GAE) per 100 g of WG, seed or popcorn. The DPPH radical-scavenging activity of the „digesta“ samples was determined, with slight modification, using the method of Blois.<sup>[3]</sup> The ABTS radical-scavenging activity of samples was determined according to the modified method of Re, Pellegrini.<sup>[4]</sup>

In seed, PA content (Figure 1.) after simulated *in vitro* gastrointestinal digestion increases with the pretreatment and it is the highest in mechanically and thermally pretreated seed,  $449.24 \pm 12.73$  mg PAE per 100 g of WG. Contrary to seed, in popcorn pretreatment doesn't have an influence on the PA content released upon digestion. Total phenolics content of digested seed showed the following order NB S ( $8.99 \pm 0.69$ ) < B S ( $13.30 \pm 0.63$ ) < G NB S ( $31.16 \pm 5.62$ ) < G B S ( $34.81 \pm 2.67$ ) mg GAE /100 g of WG. The total PC content (Figure 2.A) was higher in popcorn compared to seed, probably due to the difference in dry weight amount between seeds and popcorn (NB P  $23.39 \pm 2.05$ ; B P  $24.19 \pm 0.71$ ; G NB P  $36.19 \pm 1.14$  and B G P  $31.48 \pm 2.39$  mg of GAE per 100 g of WG). However, it should be highlighted that phenolics content is influenced by environmental factors, species, genotype and geographical origin of an amaranth plants.<sup>[5]</sup>



**Figure 1.** The phytic acids content in amaranth seed and popcorn. The graph shows means  $\pm$  SD ( $n=3$ ), different letters indicate statistical significance ( $P < 0.05$ ). NB – non-boiled, B – boiled, G – grinded.

The digested amaranth seed and popcorns exhibited higher ABTS than DPPH radical scavenging activity (Figure 2.B). Moreover, the phytic acid content released upon digestion is in high positive correlation with DPPH radical scavenging activity and noticeably negative correlation with ABTS radical scavenging activity with Pearson's correlation coefficients of 0.85 and  $-0.35$ , respectively. Phytic acids are a natural plant antioxidants,<sup>[6]</sup> suggesting that phytic acids are the main contributors to DPPH radical scavenging activity in digested amaranth seed and popcorn.



**Figure 2. (A)** Total phenolics content and **(B)** ABTS and DPPH radical scavenging activity. The graph shows means  $\pm$  SD ( $n=3$ ), different letters indicate statistical significance ( $P < 0.05$ ). S – seed, P – popcorn, NB – non-boiled, B – boiled, G – grinded.

The obtained results indicates that pretreatment of amaranth seed and popcorn has a great impact on the composition of an active species that are released during digestion, and in addition, the higher release of the PA contributes to the DPPH radical scavenging activity.

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## EXPERIMENTAL AND COMPUTATIONAL APPROACH TO CATALYZED DOMINO REACTIONS BETWEEN PROPARGYL ALCOHOLS AND CO<sub>2</sub>

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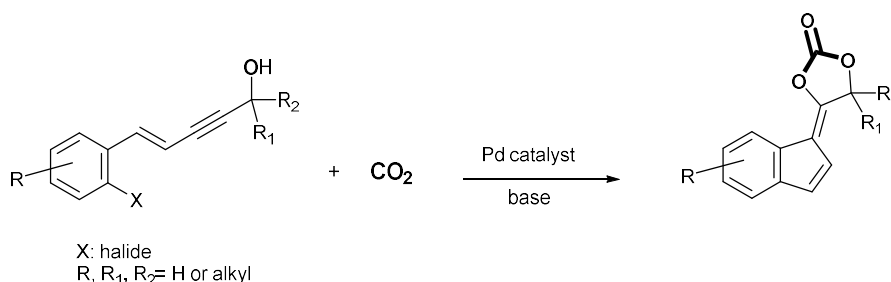
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Although carbon dioxide is a nontoxic and inert gas, it represents an environmental hazard because it is mainly responsible for the greenhouse effect. On the other hand, due to its abundance and renewability, CO<sub>2</sub> is considered as an attractive C1 building block in modern organic synthesis for producing highly valued and biologically active chemicals, such as carbonates and carbamates.<sup>[1–4]</sup> To overcome the thermodynamical stability of CO<sub>2</sub>, we have envisaged energetically favored Pd-catalyzed intermolecular domino reactions on suitable propargylic alcohols bearing an aryl halide moiety to produce  $\alpha$ -alkylidene cyclic carbonates.



Notably, calculations based on density functional theory (DFT) method predict that these reactions are exergonic owned to product stabilization through the formation of additional C-C bonds. Our combined studies -experimental and computational- enable the rational design of new CO<sub>2</sub> trapping substrates.

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## SPECTROSCOPY AND STATISTICS - A POWERFUL COMBINATION FOR DRUG COMPATIBILITY EVALUATION

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Fourier-transform infrared spectroscopy (FTIR) and X-ray powder diffraction (XRPD) are widely used techniques in the drug compatibility studies. As obtaining results in both techniques are based on the same principle sometimes the interpretation of obtained spectra can be difficult. Comparing obtained spectra of pure substances with the spectra of their blends can lead to ambiguous conclusions due to the overlapping of peaks in the obtained spectra. In this work we introduced a multivariate statistical approach, the principal component analysis (PCA) followed by cluster analysis (CA). Two 5-aminosalicylates (5-ASAs), olsalazine (OSZ) and balsalazide (BSZ) as well as their blends with folic acid (FA), prepared in different ratio (10:1, 5:1, 2:1, 1:1, 1:2, 1:5, 1:10), were measured using FTIR and XRPD and compared to evaluate any changes in the spectra which could indicate the chemical reaction of the components of blends. PCA followed by CA was performed on spectral region from 550 – 1800  $\text{cm}^{-1}$  (using Pearson correlation, Euclidean distance measure and Ward's agglomerative clustering). A 9 x 625 matrix was created. The number of rows represents the used 5-ASA and FA as well as their blends, whilst spectral data was placed in columns. In the case of BSZ and FA as well as OSZ and FA all blends were positioned in the plot in the increasing PC1 values as the ratio of 5-aminosalicylates reduces and FA share in blends increases, with the 1:1 being placed between measured blends. Placement of pure compounds and their blends in the PCA plot, as well as the formation of clusters in CA dendrogram, are in favour of BSZ/FA and OSZ/FA compatibility. Any deviation from the obtained order in which blends are positioned would indicate incompatibility between compounds, as well as the formation of clusters with random blends. Pearson's correlation was calculated between obtained diffractogram of blend and theoretical diffractogram (calculated as the average of two spectra of pure compounds). Obtained correlation coefficients ( $r$ ) for BSZ/FA and OSZ/FA blends are 0.99 and 0.98, respectively. High correlation value between observed and theoretical spectra indicates lack of component interaction. These results indicate that FA can be in the same formulation containing BSZ or OSZ.

**Acknowledgments.** This work has been supported by the Croatian Science Foundation under the grant numbers HRZZ-UIP-2017-05-3949 and HRZZ-DOK-2018-01-9047.

## POLARONIC CONDUCTIVITY IN VANADIUM PHOSPHATE GLASSES AND THE EFFECT OF MOLYBDENUM OXIDE ADDITION

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Electronic conduction has been detected in various melt-quenched oxide glasses which contain transition-metal oxides (TMO) such as  $V_2O_5$ ,  $MoO_3$ ,  $WO_3$ , and  $Fe_2O_3$ . These materials are of great scientific interest due to their potential application in many fields such as photonics, electronic circuit elements, gas sensors, etc. The electronic conductivity in these glasses occurs via small polaron hopping between transition metal ions in different oxidation states and strongly depends on the amount of transition metal oxide and a fraction of transition metal ions in different valence states. Among various TMOs which can be incorporated into oxide glasses, vanadium (V) oxide is especially attractive since it participates in the glass network formation and hence can be added in large amounts. Also, it is interesting to investigate how the addition of a second TMO influences the polaronic conductivity in these glasses due to the possible transfer of electrons via different TM ions as well as modification of the structural network which may or may not favor the transport of polarons. In this study, a series of binary  $xV_2O_5-(100-x)P_2O_5$  glasses with a wide range of composition from  $x = 37$  to  $x = 89$  mol%, and ternary  $(60-x)MoO_3-xV_2O_5-40P_2O_5$  glasses with  $x = 10-49$  mol%, and binary  $60MoO_3-40P_2O_5$ , were prepared by the melt quenching method. The structure and electrical properties of obtained glass samples were investigated by Raman and impedance spectroscopies. The fraction of  $V^{4+}$  ions,  $V^{4+}/V_{tot}$  (binary system), and the sum fraction of  $V^{4+}$  and  $Mo^{5+}$  ions,  $(V^{4+}+Mo^{5+})/(V+Mo)_{tot}$  (ternary system) were determined from the temperature dependence of magnetization, measured with SQUID magnetometer, and analyzed using the Curie constant attributed to the isolated paramagnetic centers  $V^{4+}$  and  $Mo^{5+}$ . With the increase of  $V_2O_5$  content bands attributed to the stretching vibrations of V–O, V–O–P, and V–O–V bonds increase in intensity indicating the formation of mixed vanadium-phosphate glass network and clustering of vanadium units at high  $V_2O_5$  content. The DC conductivity of glasses in the binary system increases nearly linearly with the increase of  $V_2O_5$  due to an increase in the concentration of vanadium ions reaching the highest conductivity of  $1.03 \times 10^{-4} (\Omega \text{ cm})^{-1}$  at 30 °C for glass with 89 mol%  $V_2O_5$ . On the other hand, the systematic replacement of  $MoO_3$  with  $V_2O_5$  in ternary glass series causes a strong increase in conductivity up to 20 mol% of  $V_2O_5$  followed by a slight increase for higher  $V_2O_5$  contents, Figure 1. The comparison of glasses from binary and ternary series with approximately the same amount of  $V_2O_5$  showed higher conductivity values for glasses with  $MoO_3$  which indicates that molybdenum actively participates in the polaron conductivity via the transport of electrons between molybdenum and vanadium ions.



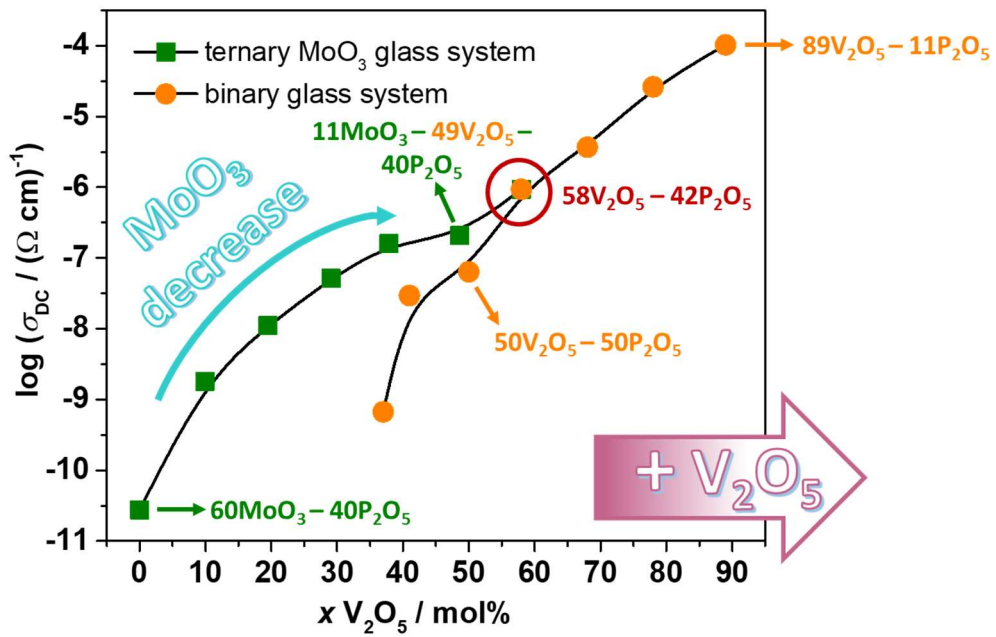


Figure 1. Polaronic conductivity as a function of V<sub>2</sub>O<sub>5</sub> content for the binary and ternary glass series.

## MAGNESIUM DECREASES THE ELECTRICAL DOUBLE LAYER (EDL) FORCES BETWEEN CARBONATE PARTICLES

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Carbonates are the most widespread minerals and dominate sediments and sedimentary rocks in the Earth's crust.<sup>[1,2]</sup> Understanding of carbonate nucleation, growth, stability, and dynamics remain a challenge due to many possible and often concurrent transformation pathways.<sup>[3]</sup>

Experimental insight into the significance of the electrical double layer forces in complex solutions during the carbonate nucleation process is limited - especially in complex solutions with several interfering, coprecipitating, and adsorbing ions.<sup>[4]</sup>

In our work, we show how the electrical double layer formed at the interface between carbonate and electrolyte in the presence of  $Mg^{2+}$  changes in time by using time-resolved electrophoresis and potentiometric measurements.<sup>[5]</sup>

The presence of  $Mg^{2+}$  ions not only stabilizes metastable carbonate phases – like vaterite – but also reduces the magnitude of the repulsive EDL - forces. The first effect has been previously observed and it is usually attributed to the large dehydration energy barrier for  $Mg^{2+}$  ions,<sup>[6]</sup> the second one has not been studied yet.

Our results suggest that the role of the additives on carbonate nucleation pathways is more complex than previously anticipated.  $Mg^{2+}$  can affect not only the carbonate nucleation pathways, but also sediment stability via the additional screening of the long-range electrostatic forces.

**Acknowledgments.** Collaboration: Chunhui Li, Wojciech Piasecki, Karolina Lament, Tajana Begović.  
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## SYNTHESIS, CONFORMATIONAL ANALYSIS AND PRELIMINARY BIOLOGICAL EVALUATION OF CONJUGATES OF FERROCENE AND HYDROPHOBIC AMINO ACIDS

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Conjugates of different ferrocene scaffolds and amino acids are recognized as peptidomimetics because they are able to adopt different elements of peptide secondary structure (turns, coils, sheets) based on intramolecular hydrogen bonding.<sup>[1–3]</sup> Peptide sequences rich in hydrophobic amino acids have desirable properties (high solubility, stability and bioavailability) that allow them to enhance the biological activity of the corresponding peptidomimetics.<sup>[4]</sup>

To investigate the influence of the chirality of the hydrophobic amino acid and protecting groups (Ac or Boc) on the conformational properties and biological activity, we prepared ferrocene dipeptides Ac (Boc)–L(D)–AA–NH–Fn–COOMe (**I**) [Fn=ferrocenylene, AA= valine, leucine or phenylalanine, (Figure 1)] by the standard HOBt/EDC method. Dipeptides **I** are subjected to detailed spectroscopic analysis (IR, NMR and CD) in order to determine their conformational properties. Their preliminary biological evaluation is carried out by measuring the antimicrobial and antioxidant activity (DPPH and FRAP methods).

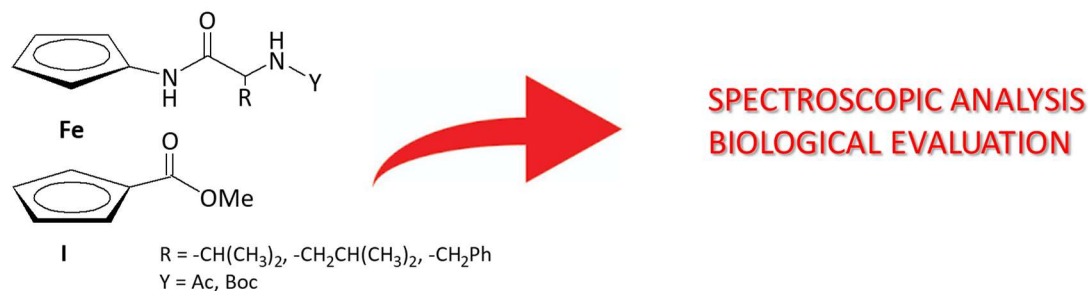


Figure 1. Ferrocene dipeptide **I**

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## PRESERVATION OF PYRIDONE HOMOSYNTHON IN HALOGEN-BONDED COCRYSTALS

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It is well known that species containing 2-pyridone (**pdon**) fragment easily undergo tautomerization process which includes two tautomeric forms – lactame and lactime.<sup>[1]</sup> In solid state, both tautomers can aggregate in robust hydrogen-bonded dimers (**pdon**)<sub>2</sub> by pyridone homosynthon involving two N–H···O or O–H···N hydrogen bonds.<sup>[2]</sup> Constancy of such dimers is noticed in systems with carboxylic diacids (CA),<sup>[3]</sup> in which (**pdon**)<sub>2</sub> fragments are linked with CA molecules into alternating O–H···O hydrogen-bonded chains through keto oxygen atom. However, coexistence of **pdon** dimers with halogen bond donors in crystals has not been noticed to date. To investigate hierarchy of supramolecular interactions in systems including **pdon** and halogen bond donors, we synthesized a series of cocrystals of 2-pyridone and six perhalogenated hydrocarbons (1 monotopic and 5 ditopic donors). In all prepared compounds, 2-pyridone is present in lactame form and expectedly connected in centrosymmetric dimers through two N–H···O hydrogen bonds. Halogen bond donor molecules participate in I···O halogen bonding with (**pdon**)<sub>2</sub> fragments, while cocrystal stoichiometry is conditioned by donor topicity: 1:1 cocrystal is formed with monotopic donor, while 2:1 with ditopic donors. In former case molecules are connected in discrete complexes, while in the latter, supramolecular chains have formed.

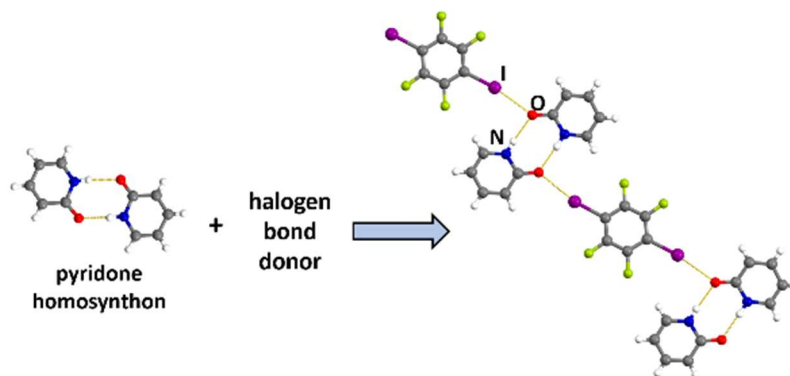


Figure 1. Halogen and hydrogen bonding in (**pdon**)(14tfib).

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## INFLUENCE OF VARIOUS METAL CATIONS ON THE FORMATION AND PROPERTIES OF $\alpha$ -Fe<sub>2</sub>O<sub>3</sub> (HEMATITE) NANORODS

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Nanosized  $\alpha$ -Fe<sub>2</sub>O<sub>3</sub> (hematite) is a widely investigated material due to high stability, low toxicity, abundance and low cost.<sup>[1]</sup> As a semiconductor ( $E_g = 2.2$  eV)<sup>[1]</sup> with a strong absorption of UV and visible light with  $\lambda < 600$  nm,  $\alpha$ -Fe<sub>2</sub>O<sub>3</sub> has found various ways to be used in traditional and advanced technologies. It can be used as a UV protective pigment, photoelectrode for hydrogen production by water splitting using solar energy or as a photocatalyst for decomposition of harmful and toxic compounds. Some specific properties of  $\alpha$ -Fe<sub>2</sub>O<sub>3</sub>, like magnetic, electrical and optical properties, as well as photoelectrochemical or photocatalytic activity, can be significantly improved by doping with various metal cations and/or morphology modification.<sup>[2–5]</sup>

One step hydrothermal synthesis of uniform hematite nanorods using Fe(III) chloride aqueous solution and 1,2-propanediamine (1,2-diaminopropane) has been reported by Li et al.<sup>[6]</sup> In the present work, the influence of the replacement of a fraction of Fe<sup>3+</sup> ions in this synthesis with other metal cations (Al<sup>3+</sup>, Cr<sup>3+</sup>, Mn<sup>2+</sup>, Co<sup>2+</sup>, Cu<sup>2+</sup>, Zn<sup>2+</sup>, Sn<sup>4+</sup>) on the properties of prepared hematite samples was investigated. Structural properties of prepared samples were studied using powder X-ray diffraction (PXRD) and Mössbauer spectroscopy, particle size and shape were determined using field emission scanning microscopy (FE-SEM), while optical properties were investigated using diffuse reflectance UV-Vis-NIR spectroscopy.

**Acknowledgments.** This research was supported by the Croatian Science Foundation (Project No. IP-2016-06-8254)

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## CO-CRYSTALS OF Cd(II) COORDINATION POLYMERS WITH SIMPLE ORGANIC COMPOUNDS

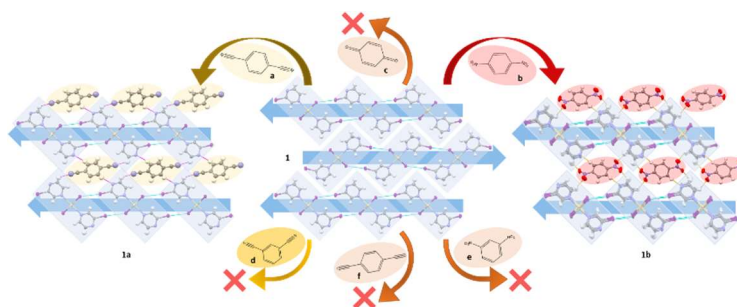
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To this day, syntheses and characterizations of organic co-crystals have spanned through numerous synthetic routes and instrumental methods, while co-crystals involving coordination compounds have been substantially less studied.<sup>[1]</sup> Having in hands specific mechanical properties of metal-organic compounds, *e.g.* mechanically induced crystal flexibility,<sup>[2]</sup> co-crystallization emerged as a promising study approach to resolve a maze of structural features that may impact and dictate a particular mechanical output.

Therefore, we opted for a family of Cd(II) coordination polymers, namely  $[\text{CdI}_2(\text{l-pz})_2]_n$  (**1**),  $[\text{CdI}_2(\text{Br-pz})_2]_n$  (**2**) and  $[\text{CdBr}_2(\text{Br-pz})_2]_n$  (**3**) and a number of simple organic co-formers, 1,4-dicyanobenzene (**a**), 1,4-dinitrobenzen (**b**), 1,4-benzoquinone (**c**), 1,3-dicyanobenzene (**d**), 1,3-dinitrobenzen (**e**) and 1,4-bis(iodoethynyl)benzen (**f**) for the preparation of structurally modified their supramolecular solid-state networks. Co-crystal synthesis was performed *via* solvent-assisted grinding, while characterization of the resulting products confirmed a formation of several targeted co-crystalline products. Crystal structure determination (SCXRD) combined with the calculated molecular electrostatic potential surfaces values (MEPs) enabled rationalization of the co-crystallization outcomes against the relative strength of potential hydrogen-/halogen-bond donors and acceptors in the studied systems.



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## NITROGEN-CONTAINING COVALENT ORGANIC POLYMERS: SYNTHESIS, CHARACTERIZATION AND COMPUTATIONAL STUDY

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Selective binding of gas molecules is very important in the design of new nanoporous materials with increased potential for CO<sub>2</sub> capture and air separation. Covalent organic frameworks (COFs) and polymers (COPs) complement other porous materials, such as zeolites, MOFs (metal-organic frameworks), etc., and have shown excellent potential for the gas storage and separation, catalysis, and usage in optoelectronics. Choosing precursor molecules of precisely defined geometry, functionality and selectivity can result with spontaneous association of molecules into 2D or 3D amorphous COPs or crystalline COFs.<sup>[1]</sup>

A series of new azo-bridged COPs was successfully synthesized by condensation reactions of 1,3,5-tris(4-nitrophenyl)benzene and various aromatic diamino compounds used as linkers. Their structural and thermal features were characterized by using different experimental techniques. A computational strategy to investigate the potential of precursor molecules toward selective binding of N<sub>2</sub> and CO<sub>2</sub> in these systems were developed. A detailed conformational search was performed with molecular mechanics, and the resulting complexes were reoptimized by the DFT method in vacuum, and finally, binding energies of N<sub>2</sub> and CO<sub>2</sub> were calculated for each of the obtained complexes. The various aromatic building blocks were divided in two groups: (i) central units composed of three phenyl rings attached to nitrogen, benzene, pyridine and triazine, (ii) linkers including biphenyl and those in which two phenyl rings were separated by oxygen, sulphur, carbonyl, one and two methylene groups. In addition, the effect of different types of bonds (azo, azoxy, azodioxy) on N<sub>2</sub> and CO<sub>2</sub> binding was investigated. A greater selectivity toward CO<sub>2</sub> binding in comparison to N<sub>2</sub> was confirmed in our calculations for all of the investigated complexes.

**Acknowledgments.** This work has been fully supported by Croatian Science Foundation under the project IP-2020-02-4467.

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## SYNTHESIS AND BIOCATALYSIS OF PROPARGYLIC EPOXIDES

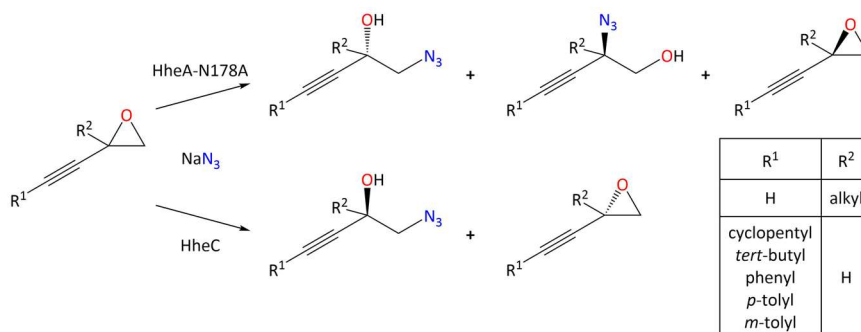
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Halohydrin dehalogenases (HHDHs) are important biocatalysts that facilitate the reversible conversion between halohydrins and epoxides. Their ability to catalyze enantioselective epoxide ring-opening reactions with different nucleophiles (azide, cyanide, cyanate, thiocyanate etc.) can be used in synthesis of optically active epoxides,  $\beta$ -substituted alcohols and heterocyclic compounds. Further transformation (hydrolysis, reduction, intermolecular click reactions) gives rise to valuable building blocks (e. g. amino alcohols, aziridines, triazoles, oxazolidinones) in synthesis of pharmaceutical and natural compounds.<sup>[1]</sup>

Propargylic epoxides and alcohols, owing to the presence of a triple bond, undergo various intermolecular and intramolecular reactions.<sup>[2,3]</sup> Unfortunately, there are few described methods for enantioselective synthesis of these compounds, and those available require expensive or custom-made catalysts. However, halohydrin dehalogenases can be used to obtain enantiomerically pure starting compounds from racemic propargylic epoxides for triple bond and/or nucleophile transformations. Therefore, the synthesis of mono- and disubstituted propargylic epoxides and subsequent enantioselective ring opening by halohydrin dehalogenases (HheC and HheA-N178A) was described (Figure 1).



**Figure 1.** Kinetic resolution of synthesized propargylic epoxides with sodium azide catalysed by halohydrin dehalogenases HHeC and HheA-N178A

Internal propargylic epoxides were synthesized from the corresponding terminal acetylenes by introduction and epoxidation of a double bond (cyclopentyl, *tert*-butyl and phenyl). Also, *p*- and *m*-tolyl derivatives were synthesized in a similar reaction sequence, starting from the corresponding iodotoluene and trimethylsilylacetylene. 2,2-Disubstituted epoxides were prepared from corresponding methyl ketones.

Biocatalytic kinetic resolution reactions in the presence of sodium azide were catalyzed by two HHDHs with opposite stereopreference (HHeC and HheA-N178A). With both enzymes reactions yielded enantiomerically pure secondary azido alcohols (*ee* > 99%, *E* > 200). While HheC yielded almost exclusively (*R*)- $\beta$ -azido alcohol (up to 99:1), HheA-N178A gave mostly (*S*)- $\beta$ -azido alcohol ( $\beta$  :  $\alpha$  ratio between 90:10 and 54:46),

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## EXPLORATION OF VARIOUS ELECTROPHILE-INDUCED TRANSFORMATIONS OF PROPARGYL SILANES

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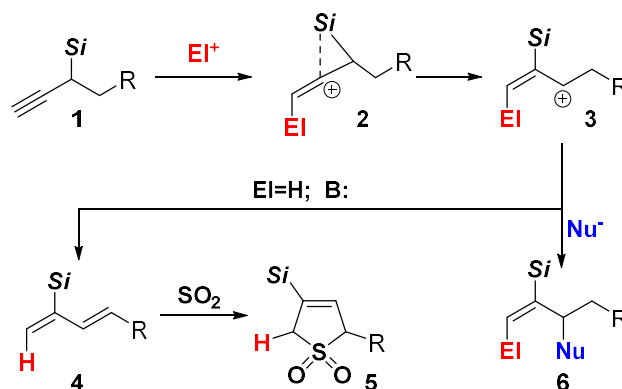
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Stabilizing properties of silicon in reactions, that proceeds via  $\beta$ -silyl carbenium ion, is commonly known as  $\beta$ -silicon effect. Mechanistic insights show two possible pathways of stabilization – vertical (e.g. hyperconjugation) or non-vertical (e.g. silonium ion).<sup>[1]</sup> Formation of closed silonium ion with combination of other stabilizing effects explains why many reactions involving  $\beta$ -silyl carbenium ion tend to undergo 1,2-silyl shift.

Previously we have reported the use of propargylsilanes **1** in the synthesis of silyl dienes and indenenes by the catalytic amounts of strong Brønsted acids (TfOH, Tf<sub>2</sub>NH, Tf<sub>3</sub>CH) that involves 1,2-silyl shift.<sup>[2]</sup>

Herein, we report the use of liquid sulfur dioxide for this transformation as a highly polar and Lewis acidic reaction media, which offers possibility to use weaker acids (e.g. BzOH, TsOH). Moreover, in a tandem cheletropic addition process silyl sulfolenes **5** are obtained from the *in situ* formed dienes **4**.<sup>[3]</sup>

To expand this concept further, other electrophiles have been used to activate propargyl silane moiety to obtain intermediate **3**. The latter can react with various nucleophiles to obtain compounds **6**.



**Scheme 1.** Electrophile induced transformations of propargyl silanes

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## ION METATHESIS AND DOUBLE SALT FORMATION IN THE SOLID STATE

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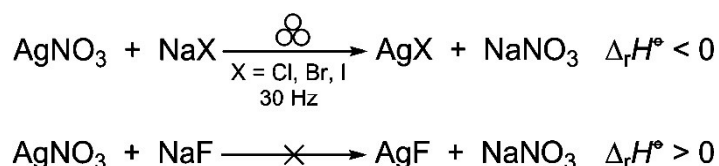
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Mechanochemical milling was successfully applied to prototypical metathesis reaction between  $\text{AgNO}_3$  and  $\text{NaX}$  ( $X = \text{Cl}, \text{Br}, \text{I}$ ).<sup>[1]</sup> This approach also successfully demonstrated the synthetic path to  $\text{Ag}_2\text{XNO}_3$  double salts. Real-time and in situ reaction monitoring using synchrotron powder X-ray diffraction (PXRD) and Raman spectroscopy revealed that only in the case with  $\text{NaBr}$  metathesis reaction underwent without the formation of intermediate phases. With  $\text{NaCl}$ , the  $\text{Ag}_2\text{ClNO}_3$  appeared as the intermediate, while with  $\text{NaI}$ , a short-living intermediate phase was observed in PXRD (on average living for 30 seconds) and could not be fully characterized. As expected from standard reaction Gibbs energies of reactants and products, milling with  $\text{NaF}$  gave the mixture of starting materials. In comparison to performing this reaction in solution, where it is driven by the extremely low solubility of silver products and their immediate precipitation, in the solid state, reactions proceed through the formation of reactive intermediates and provide an elegant way of preparing corresponding double salts.



**Figure 1.** Ion metathesis reactions between  $\text{AgNO}_3$  and  $\text{NaX}$  ( $X = \text{Cl}, \text{Br}, \text{I}$ ).

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## SEPARATION OF THE NATIVE AND DESIALYLATED HUMAN ALPHA-1-ACID GLYCOPROTEIN SIALOFORMS USING LOW-PRESSURE PH GRADIENT ION-EXCHANGE CHROMATOGRAPHY

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Alpha-1-acid glycoprotein (AGP) is an important plasma protein involved in the binding and transport of many basic and neutral drugs.<sup>[1]</sup> According to the free drug hypothesis, only the unbound drug is available to act at physiological sites of action, thus the importance of plasma protein binding primarily resides in its impact on pharmacokinetic properties such as clearance and volume of distribution.<sup>[2]</sup> The purpose of this study is to separate the native (sialylated) AGP from the desialylated AGP using low-pressure pH gradient ion-exchange chromatography which will further be used in drug-binding studies of different AGP sialoforms. Desialylated AGP is prepared by incubation of native AGP in the Immobilized SialEXO Microspin columns (Genovic AB, Sweden) with end-over-end mixing at room temperature. Sialoform separation is performed using specialized pH gradient chromatography buffers (pIsep, CryoBioPhysica Inc., USA). The mixture of both native and desialylated AGP in buffer A (pH = 6) is injected onto HiTrap Q HP 1 mL anion exchange chromatography column (GE Healthcare Bio-Science AB, Sweden). Elution is done by single-step linear gradient (0-100 % pIsep B, pH = 2) using ÄKTA Start FPLC system (GE Healthcare, USA). Protein quantity in the eluate is monitored by absorbance measurement at 280 nm. Afterward, the pH of each fraction is measured. The obtained pH values are used for the pI value approximation of the native and desialylated AGP. The observed pI values of sialoforms differ significantly and hence can be fully separated. This method provides quick, simple, and cost-effective AGP sialic acid content testing, and can be easily modified for other glycoproteins.

**Acknowledgments.** This work was supported by funding from the Croatian Science Foundation grant IP-2016-06-3672 – Glycosylation of alpha-1-acid glycoprotein – route to personalized medicine (GlycoDrugs).

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## THE EFFECT OF OXALATE ON THE THERMODYNAMIC PARAMETERS FOR THE BINDING OF IRON TO HUMAN SERUM TRANSFERRIN

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Human transferrin is a serum glycoprotein that has ability to bind, transport and release ferric ions with two binding sites for metal ions, the C-site and N-site. Each bound metal ion is hexacoordinated: four ligands to the metal are provided by the transferrin amino acid residues, while the remaining two are provided by an external anion, termed the synergistic anion. This synergistic anion is carbonate *in vivo*, however, other anions (such as oxalate, pyruvate, glycine, etc.) with similar structure can substitute for carbonate *in vitro*.<sup>[1]</sup> In this study we determined the thermodynamic parameters for the binding of ferric ion to human serum transferrin in the presence of different synergistic anions (carbonate and oxalate) using isothermal titration calorimetry (ITC).

Resulting ITC curves displayed two inflection points typical for a model of two binding sites. Data analysis of the curves was based on the model of two sets of independent sites and best-fit parameters were calculated using Marquardt algorithm. Different slope in the two binding regions on the titration curve can be attributed to different binding affinities of ferric ion to human serum transferrin in the presence of different synergistic anions, suggesting lower affinities in the presence of oxalate. Also, the observed differences in the heat released in the first part of titration suggest different binding enthalpy for the C-site of transferrin. Similar effect on the two binding sites having different metal binding properties in the presence of different synergistic anions is known.<sup>[2]</sup>

**Acknowledgments.** This work was supported by funding from the Croatian Science Foundation grant UIP-2017-05-9537 - *Glycosylation as a factor in the iron transport mechanism of human serum transferrin (GlyMech)*.



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## SYNTHESIS AND CHARACTERIZATION OF NOVEL HYBRID CARBAMATES

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Oximes and carbamates have a wide spectrum of bioactivities. Some oximes are considered as powerful reactivators of phosphorylated cholinesterase (antidotes for organophosphorus poisoning),<sup>[1]</sup> while some carbamates are used for inhibition of cholinesterases (protection of enzyme from phosphorylation).<sup>[2]</sup> Therefore, novel hybrid oxime carbamates have been designed to serve as carbamoylating agents (protection of enzyme) as well as oxime reactivators upon reaction. A series of *N*-benzylimidazole-2-aldoxime carbamates have been prepared. *N*-alkylation of commercially available imidazole was carried out with benzyl bromide in THF with sodium hydride as a base. *N*-benzylimidazole was converted to 2-carbaldehyde derivative by the reaction with *n*-butyllithium and DMF.<sup>[3]</sup> *N*-benzylimidazole-2-aldoximes were synthesized using hydroxylamine hydrochloride in solution and without solvent in mechanochemical reactions.<sup>[4]</sup> In order to synthesize desired oxime carbamates appropriate carbamoyl chlorides and isocyanates were used. Structures of compounds were deduced from FTIR, ATR, one- and two-dimensional NMR spectra. Stability of compounds in aqueous solutions and in organic solvents was determined.

**Acknowledgments.** The study was prepared within the projects of the *Croatian Science Foundation*: "Young researchers' career development - Training New Doctoral Students" ESF-DOK-01-2018 and "Activity and *in silico* guided design of bioactive small molecules" (IP-2016-06-3775).

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## SYNTHESIS AND EXPLORATION OF 1,3-DIPOLAR CYCLOADDITION REACTIONS OF GUANIDINE AZIDES

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Novel guanidine azides protected by the *tert*-butyloxycarbonyl (Boc) groups were prepared and subjected to cycloaddition reactions in order to establish their reactivity and synthetic suitability as guanidine cycloaddition 'delivery' reagents.<sup>[1,2]</sup> Thermal reactions without catalysts and copper catalyzed 1,3-dipolar cycloadditions (CuAAC)<sup>[3]</sup> were applied in conjunction with various dipolarophiles and alkynes. Sharpless 'click' reaction has been shown as synthetically very suitable and applied reactions conditions are compatible with Boc-guanidine functional group, providing corresponding 1,4-disubstituted [1,2,3]-triazole linked products.

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## COMPUTATIONAL STUDIES OF THE MYCOBACTERIUM TUBERCULOSIS TRANSCRIPTIONAL REPRESSOR MNTR

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Manganese homeostasis in *Mycobacterium tuberculosis*, the causative agent of tuberculosis, is regulated by the transcriptional repressor MntR from the IdeR family of transcriptional regulators. Tuberculosis is an important health concern in the world today, which is exacerbated by the advent of multi-drug resistant strains.<sup>[1]</sup>

MntR is allosterically activated for DNA-binding by manganese. It harbors two manganese binding sites, of which one is a binuclear site accommodating two manganese ions. MntR is composed of three domains - the N-terminal DNA-binding domain, the central dimerization domain and the C-terminal FeoA domain and it binds to DNA as a dimer.<sup>[1]</sup> The FeoA domain is present in many members of the IdeR family. However, its function has only recently been partially explained for the protein MtsR.<sup>[2]</sup>

To start our investigation of *M. tuberculosis* MntR, we parametrized the interaction of protein and manganese ions using a bonded model approach. First, we optimized the binding site geometry using DFT calculations at the B3LYP/SDD:6-31G(d,p) level of theory. We then developed force field parameters using the approach by Li.<sup>[3]</sup> Finally, we used molecular dynamics simulation to study the dynamic behavior of MntR both in its apo and manganese-bound forms.

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## THE *ENDO* AND *EXO* TRANSITION STATES FOR THE DIELS-ALDER REACTION BETWEEN VINYL CARBODIIMIDES WITH *N*-ALKYL IMINE

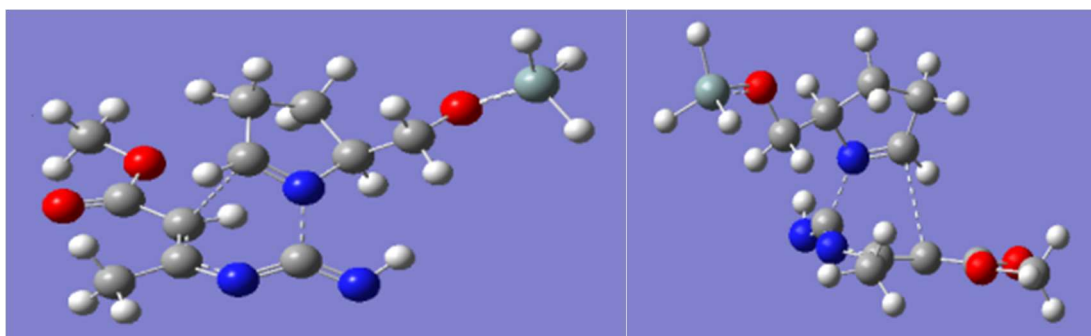
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Guanidines are commonly occurring functionality in nature and aminoacid arginine plays an important role in biosynthesis of proteins.<sup>[1]</sup> The physico-chemical properties of guanidines, especially their high basicity are particularly interesting.<sup>[2]</sup> Various synthetic methods were employed in synthesis of guanidines, and cycloaddition reactions involving guanidines and cycloaddition reactions employed in the synthesis of cyclic guanidines are not well explored.<sup>[3]</sup>

Here we present the results of computational study of Diels-Alder cycloadditions of vinyl carbodiimides with *N*-alkyl imines which were used in synthesis of bicyclic guanidines, but the mechanism was not fully investigated.<sup>[4]</sup> DFT calculations using the B3LYP (Becke 3-parameter, Lee-Yang-Parr) hybrid functional and 6-31G(d) basis set indicate that the asynchronous concerted [4+2] cycloaddition process proceeds through the *endo*- or *exo*- transition states.



Scheme 1. *Exo*- and *endo*- transition states

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## COCRYSTALLIZATION OF DASATINIB WITH PERFLUORINATED IODO- AND BROMOBENZENES

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In this work, an active pharmaceutical ingredient, dasatinib (**dsa**), has been studied in cocrystallization experiments with selected perfluorinated halogen bond donors of different topology and geometry: iodopentafluorobenzene (**ipfb**), bromopentafluorobenzene (**brpfb**), 1,2-diodotetrafluorobenzene (**12tfib**), 1,4-diodotetrafluorobenzene (**14tfib**) and 1,4-dibromotetrafluorobenzene (**14tfbb**). Dasatinib is used to treat certain cases of leukemia and has a thiazole nucleus which plays vital roles in many drug structures.<sup>[1]</sup> From a crystal engineering standpoint, **dsa** is interesting due to the presence of various hydrogen bond donor species and potential halogen and hydrogen bond acceptor species. Mechanochemical synthesis and conventional solution-based crystallization experiments resulted in five new cocrystals. The obtained products were characterized by powder X-ray diffraction, thermogravimetric analysis and differential scanning calorimetry. The crystal and molecular structures of two cocrystals, (**dsa**)<sub>2</sub>(**14tfbb**) and (**dsa**)<sub>2</sub>(**14tfib**), were determined by single crystal X-ray diffraction. Structural analysis of both cocrystals reveals that the dominant supramolecular interactions are N–H⋯N and N–H⋯O hydrogen bonds between **dsa** molecules. Surprisingly, in both cocrystals halogen bond donors, **14tfib** and **14tfbb**, are connected to neighboring **dsa** molecules only by C–H⋯F contacts.

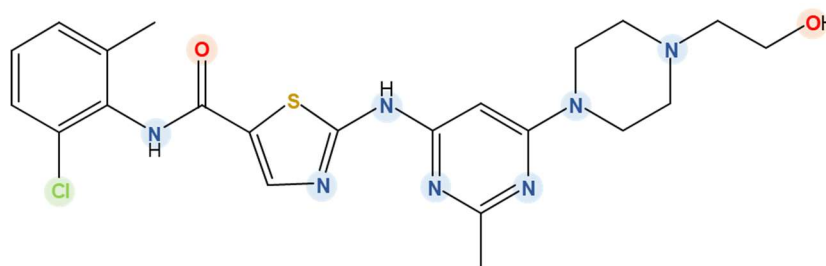


Figure 1. Structure of dasatinib

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# THERMODYNAMIC AND STRUCTURAL STUDIES OF COMPLEXATION REACTIONS OF PHENANTHRIDINE-BASED CALIX[4]ARENE DERIVATIVE WITH ALKALINE EARTH METAL CATIONS

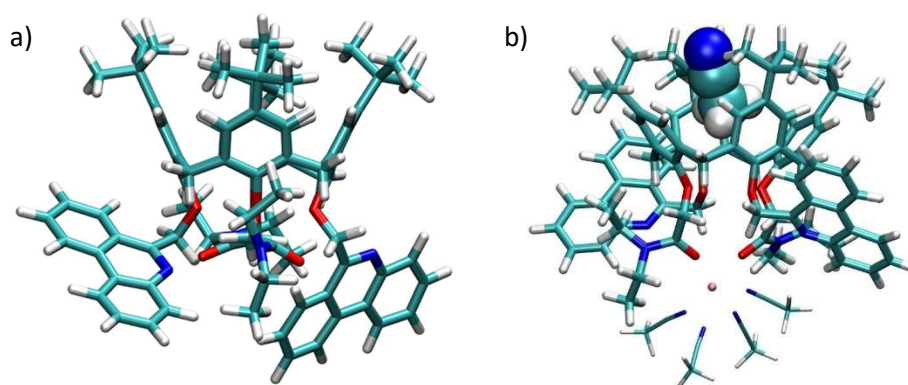
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Calixarenes are a class of supramolecular hosts that can be easily functionalized to give receptors for various chemical species.<sup>[1]</sup> Due to the prominent sensitivity of fluorescence spectroscopy and high affinity of these macrocyclic ligands towards cations, it is possible to prepare highly sensitive ion sensors by introducing fluorescent substituents into the calixarene moiety.<sup>[2–6]</sup> In the scope of this work, the binding affinities of calix<sup>[4]</sup>arene derivative **L** (Figure 1) towards alkaline earth metal cations in several organic solvents were investigated by means of isothermal titration calorimetry, UV and fluorescence spectroscopies, as well as molecular dynamics simulations. The obtained results provided a detailed insight into the complexation thermodynamics and structures of the ligand and complexes formed.



**Figure 1.** Structures of a) **L** and b)  $\text{MgL}(\text{MeCN})_2^+$  in acetonitrile obtained by MD simulations.

**Acknowledgments.** This research was fully supported by the Croatian Science Foundation (project MacroSol, IP-2019-04-9560).

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## COMPLEXATION OF TRANSITION METAL CATIONS BY A LOWER-RIM PHENANTHRIDINE CALIX[4]ARENE DERIVATIVES

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Calixarenes are macrocyclic compounds comprised of phenolic units *ortho*-linked by methylene bridges.<sup>[1]</sup> Depending on their size and substituents at upper or lower rim, these ligands have been found to be very efficient receptors for various ionic and/or neutral species. Calixarenes bearing suitable binding sites as well as fluorescent moieties (*e. g.* naphthalene, anthracene, pyrene, phenanthridine) have been recognized as highly sensitive ion sensors, which can be attributed to the prominent sensitivity of fluorescence spectroscopy.<sup>[2-6]</sup> In this work the binding affinities of fluorescent calix<sup>[4]</sup>arene derivatives **L1** and **L2** (Figure 1) towards transition metal cations in acetonitrile were investigated by means of UV, fluorescence, and NMR spectroscopies, as well as isothermal titration calorimetry. The obtained results were discussed regarding the hosts and guests structural properties.

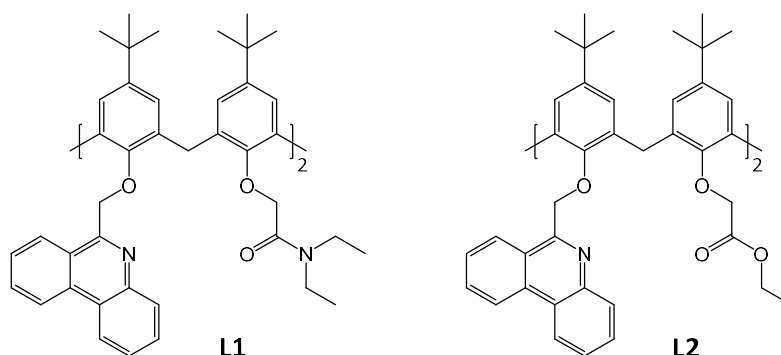


Figure 1. Structures of phenanthridine-based calix[4]arene derivatives.

**Acknowledgments.** This research was fully supported by the Croatian Science Foundation (project MacroSol, IP-2019-04-9560).

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## STRUCTURAL STUDIES ON THE HOST-GUEST COMPLEXES OF CARBOXYLATED PILLAR[5]ARENE WITH AMIDINE AND GUANIDINE DRUGS

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Supramolecular chemistry concentrates on the complex structures and studies of intermolecular interactions such as hydrogen bonds,  $\pi$ - $\pi$  and electrostatic interactions that are responsible for aggregation of molecules into larger systems. The supramolecular chemistry assumptions are based on the phenomena of molecular recognition and self-organization. A host molecule with a cavity or pockets on its surface recognizes and binds the guest molecule. As a result of such self-organization a host-guest complex is formed. The most commonly used hosts in such supramolecular systems are macrocyclic compounds.

Carboxylated pillar<sup>[5]</sup>arene (CPA5), first reported by Ogoshi in 2010,<sup>[1]</sup> is highly symmetrical pillar-shaped compound, composed of hydroquinone units linked by methylene bridges at the para-positions and substituted by ten carboxylic acid groups. Its rigid hydrophobic, electron-rich cavity makes it great candidate as host molecule for various electron-deficient guests or other neutral molecules. Under basic conditions it acts as receptor for cations in water.

Here we want to present X-ray structures of the carboxylic acid substituted pillar<sup>[5]</sup>arene host-guest complexes with amidine and guanidine drugs. Chosen guest molecules are biologically and pharmaceutically important compounds used as antidiabetics (phenformin), antiseptics (alexidine), *pneumocystis carinii* pneumonia drug (pentamidine) and reversible competitive inhibitor of trypsin (benzamidine). Under physiological conditions they are protonated to form stable cations. The formation of supramolecular complexes between CPA5 and amidine and guanidine drugs may prevent side effects and potentially enable the obtaining of new transport and drug release systems under different conditions.

**Acknowledgments.** This work was supported by funding from Polish National Science Centre (PRELUDIUM 14, No. 2017/27/N/ST5/01931).

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## PROPERTIES OF SPONTANEOUSLY AND ELECTROCHEMICALLY FORMED Ti/TiO<sub>2</sub> LAYERS IN SODIUM CHLORIDE SOLUTION

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Titanium, like most metals and metal alloys, when exposed to oxidizing conditions such as water, air or other oxygen-containing fluids, undergoes the spontaneous formation of a thin passive oxide film that determines the corrosion behavior of the underlying metal.<sup>[1–3]</sup> Consequently, understanding of passive film electronic properties in application specific environments is a vital step in assessing materials lifetimes.

In this study, TiO<sub>2</sub> oxide layer on titanium was formed spontaneously (S) and potentiostatically in phosphate buffer solution (EC). It was shown by means of ellipsometry and atomic force microscopy, that the Ti/TiO<sub>2</sub> surface is very flat with an average roughness of only 2.3 nm (S) and 3.4 nm (EC) and oxide layer thickness of 4.1 nm (S) and 16.1 nm (EC). The electrochemical properties and corrosion protective effectiveness were examined by means of cyclic voltammetry (CV), electrochemical impedance spectroscopy (EIS) and single crystal electrode (SCrE). The CV indicates the behavior of the valve metals with the anodic formation of the barrier oxide film. The semiconducting properties were studied by Mott-Schottky analysis. A preponderance of anion vacancies, which act as electron donors, over cation vacancies within the passive film formed electrochemically, was established providing n-type semiconducting behavior of the film. The obtained EIS data were modelled utilizing electrical equivalent circuit. The corrosion protection effectiveness value of 94.7 % indicates that the corrosion properties were greatly enhanced upon modification by TiO<sub>2</sub> oxide layer. The EIS results also indicate that the oxide film on the Ti surface consists of two layers, an inner barrier layer associated with higher impedance values and responsible for corrosion protection, and an outer porous layer characterized by lower impedance values and lower compactness.

**Acknowledgments.** This research was supported by the Croatian Science Foundation (HRZZ) under the project IP-2020-02-9571.

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# ISOLATION AND DERIVATIZATION OF SAPONIN FROM *QUILLAJA SAPONARIA* TREE BARK FOR THE SYNTHESIS OF A CONJUGATE WITH DESMURAMYL DIPEPTIDE

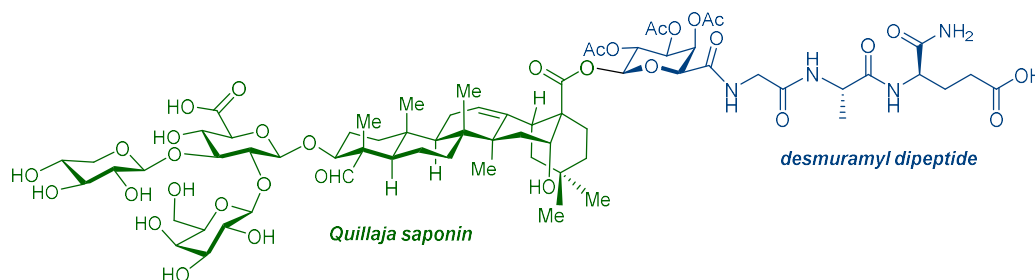
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Natural compounds are of particular interest in the development of new vaccine adjuvants. Saponins isolated from the bark of the *Quillaja saponaria* (QS) Molina tree have proven to be one of the strongest immunoadjuvants known to date. The lead compound from this series, QS-21, has been approved for human use after over 100 clinical trials, and can now be found in the Shingrix<sup>®</sup> vaccine (GSK). However, QS-21 has several major drawbacks: chemical instability, limited source, and demanding purification process. Therefore, the development of simplified adjuvants based on this structure is a very promising area of research.<sup>[1,2]</sup> Muramyl dipeptide (MDP) is the smallest peptidoglycan fragment capable of inducing an immune response to the present antigen. Although MDP is toxic and pyrogenic, its lipophilic derivatives overcome those side-effects and are in clinical use, e.g. mifamurtide and murabutide.<sup>[3]</sup>

In this work, the design and synthesis of a *Quillaja* saponin-MDP conjugate will be described. Both compounds separately, *Quillaja* saponin and MDP, show high immunoadjuvant activities. The active pharmacophore subunit of the QS-21 is coupled with the desmuramyl dipeptide following the principle of molecular hybridization. Based on that, it is expected that their combination in a new, single chemical entity, can lead to significant enhancement of immunoadjuvant activity due to the synergistic effect.



**Acknowledgments.** Zaklada HAZU, Potpore istraživanjima Sveučilišta u Zagrebu

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## HPLC METHOD FOR QUANTIFICATION OF NAPHTHOQUINONES IN PLANT EXTRACTS

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Plants produce a variety of secondary metabolites with a potential for treatment of human diseases. One such group of metabolites are naphthoquinones (NQs) which recently sparked an interest for use as novel therapeutics [1]. The aim of this study was to optimize a method for quantification of naphthoquinones (NQs), in particular 2-hydroxy-1,4-naphthoquinone (2-HNQ) and 2-methoxy-1,4-naphthoquinone (2-MNQ) and to determine the level of NQs in species *Impatiens glandulifera* Royle and *Impatiens balfuorii* Hook.f., present in Croatia.

The leaves and the flowers of *I. glandulifera* and *I. balfuorii* were collected in the continental part of Croatia (Čučerje) in the summer of 2016. After air-drying, the plant material was grounded and for each plant sample two types of extractions were used: ultrasound extraction and decoction. Quantification of NQs was performed on HPLC Agilent 1100 (Santa Clara, CA, USA), which consisted of a gradient pump, an autosampler and a diode-array detector controlled by the ChemStation for LC 3D software. For the mobile phase, methanol and 2% acetic acid were used (gradient elution: 0-10 min, 75:25; 10-20 min, 68:32; 20-35 min 55:45, 35-42 min, 75:25) with a flow rate set to 1 mL/min. The injection volume was 20 µL and separation was achieved using a RP-C18 analytical column (150 mm x 4.6 mm, particle size 5 µm; Merck, Darmstadt, Germany). Chromatograms were recorded at 280 nm. Retention time of 2-HNQ was 16.45 min and of 2-MNQ was 21.68 min. The method was validated using 2-HNQ and 2-MNQ standards prepared in the concentration range from 2 to 100 µg/mL. Both calibration curves were linear; the correlation coefficient ( $R^2$ ) for 2-HNQ was 0.9841 and for 2-MNQ it was 0.9826, while the calibration curve intercepts were -0.0028 and -0.003, respectively. For both, 2-HNQ and 2-MNQ, the calculated limit of detection (LOD) was 0.1 µg/mL and the limit of quantification (LOQ) was 0.5 µg/mL while the relative standard deviation (RSD) for the intra-day precision was below 5% and for the inter-day precision it was below 10%. Validation parameters indicate that the method is linear and precise and therefore can be used for the quantification of 2-HNQ and 2-MNQ in the prepared *I. glandulifera* and *I. balfuorii* plant extracts.

In both the leaves and the flowers extracts of *I. glandulifera* and *I. balfuorii* only 2-MNQ was detected, while the concentration of 2-HNQ was under the LOD of the method (Table 1). From the two tested extraction procedures, decoction enabled a detection of a higher 2-MNQ concentration than ultrasound extraction. Both the *I. glandulifera* and the *I. balfuorii* species had a higher 2-MNQ concentration in flowers than in leaves. In general, *I. balfuorii* had a lower 2-MNQ concentration compared to *I. glandulifera*. In conclusion, the developed method enabled detection of NQs in plant extracts. Additionally, the decoction extraction procedure, compared

to the ultrasound extraction, enabled detection of higher levels of NQs. Due to higher 2-MNQ levels, *I. glandulifera* can be considered as a better source of NQs than *I. balfuorii*.

**Table 1.** Concentration of naphthoquinones 2-hydroxy-1,4-naphthoquinone (2-HNQ) and 2-methoxy-1,4-naphthoquinone (2-MNQ) in *I. glandulifera* and *I. balfuorii* extracts.

SPECIES	SAMPLE	EXTRACTION PROCEDURE	2-HNQ (µg/mL)	2-MNQ (µg/mL)
<i>I. glandulifera</i>	leaves	USOUND	ND	17.5 ± 0.7
	leaves	Decoc	ND	20.6 ± 1.4
<i>I. glandulifera</i>	flowers	USOUND	ND	36.6 ± 1.3
	flowers	Decoc	ND	60.6 ± 1.9
<i>I. balfuorii</i>	leaves	USOUND	ND	ND
	leaves	Decoc	ND	ND
<i>I. balfuorii</i>	flowers	USOUND	ND	0.7 ± 0.05
	flowers	Decoc	ND	2.2 ± 0.3

ND – not detected

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## BIOPROSPECTING OF THE ADRIATIC SEA TUNICATE, *Phallusia mammillata*

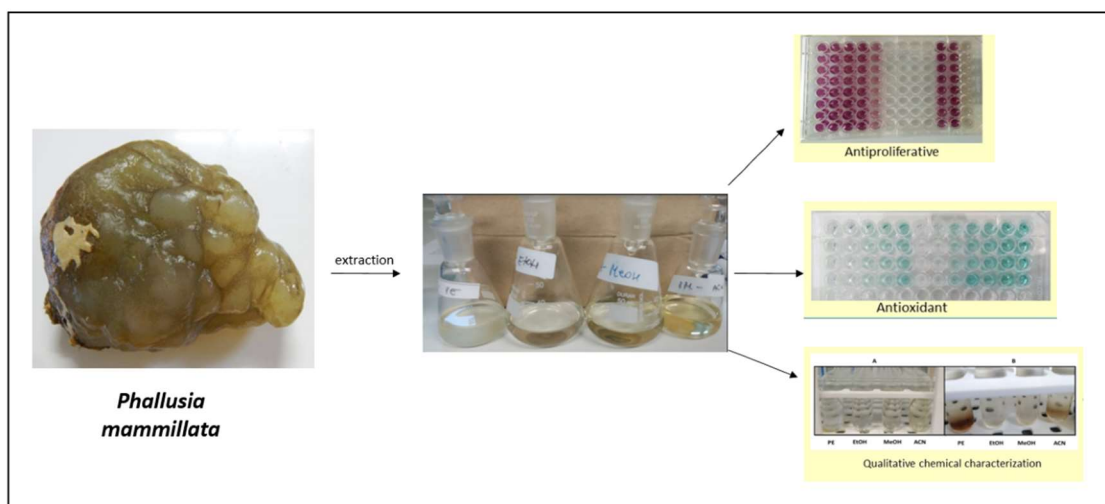
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Due to sedentary lifestyle and harsh environmental conditions, marine invertebrates, such as sponges and ascidians have been known as a rich source of diverse and structurally complex bioactive secondary metabolites of promising biotechnological potential.<sup>[1]</sup> Ascidians of the genus *Phallusia* have recently been discovered as natural resources for potential pharmaceutical exploitation. However, the majority of the studies on *Phallusia mammillata* (Cuvier, 1815) investigated its basic development processes, while information about biological activities of extracts or pure metabolites are very scarce.<sup>[2,3]</sup> In light of these information, we have decided to evaluate *in vitro* biological potential of crude organic extracts of *P. mammillata* regarding the scavenging activity against ABTS and DPPH radicals associated with antiproliferative and cytotoxic effects towards cancer and normal cell lines. Alcoholic and acetonitrile extracts displayed the highest ABTS scavenging activity while no sample showed remarkable inhibition against DPPH radical. Furthermore, antiproliferative and cytotoxic activity was demonstrated only by petroleum ether extract. The latter was found to consist of phenolic compounds, terpenoids, sterols, glycosides and alkaloids as detected by qualitative chemical screening. Further investigations will focus on the isolation and structural elucidation of the major active metabolites responsible for the observed biological activities.



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## ELASTICALLY DEFORMABLE CRYSTALS OF Cd(II) COORDINATION POLYMERS

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Crystalline solids are in general considered as brittle materials which easily crack and break upon application of even smallest amount of the mechanical stress. But, during the past few years, a newly described property of crystalline solids, mechanically induced flexibility, has been reported, and since then attracting considerable attention of the scientific community.<sup>[1]</sup> Deformation of crystals can be categorized as plastic or elastic; while upon applied mechanical stimuli, elastic materials undergo reversible bending, the plastic materials exhibit a permanent change in their shape (irreversible deformation). So far, mechanical flexibility has been reported for a significant number of organic molecular crystals, but mechanical properties of metal-organic crystalline solids have been much less explored and understood.

As a part of our previous research on several series of 1-D coordination polymers of cadmium(II) halides, we have shown that the intermolecular interactions together with structural interlocking are crucial for imparting elastic flexibility to crystalline 1-D coordination polymers,<sup>[2]</sup> but also that small differences in the strength and geometry of intermolecular interactions can substantially change the nature and extent of mechanical response.<sup>[3]</sup> In order to improve our understanding on structure-function correlation in mechanically flexible crystalline coordination polymers, we have prepared needle-like crystals of Cd(II) halide polymers with 2(1*H*)-pyrazinone and 4(3*H*)-pyrimidinone. The elastic deformation was thoroughly investigated and correlated with structural features.

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## ELECTROCHEMICAL INSIGHTS INTO SPATIAL COMPLEXITY OF HEMATITE - DICARBOXYLATE INTERACTIONS AT THE INTERFACE

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Adsorption of soil organic matter (SOM) at minerals surface is very important phenomena in the environment resulting in organic matter (OM) protection against degradation.<sup>[1]</sup> Hematite is known to play important role in carbon accrual in the on Earth, however its role may be reversed in some conditions.<sup>[2]</sup> To shed light on the interactions of organic matter with iron oxides, we investigated the properties of the hematite/electrolyte electrical double layer in the presence of dicarboxylate ions.

Here by combining of three electrochemical descriptors (surface charge density ( $\sigma_0$ ), surface potential ( $\psi_0$ ) and electokinetic potential ( $\zeta$ ) we gain new insight into pH-dependent malonates interactions with hematite surface in the solution. Malonates adsorb to hematite surface in a wide pH range between 3 and point of the zero charge ( $\text{pH}_{\text{pzc}} = 8.7$ ). However, the mode of coordination depends on a pH value. We distinguished two different malonates complexation types: inner-spherical complexes at pH below 4 and outer-spherical above pH 5. The surface charge and potential are sensitive to malonate concentration in acidic conditions. As the pH increases, we only observe the zeta potential sensitive to malonate ions as a response to their accumulation in the shear plane. The transition from the inner to the outer sphere geometries is smooth, suggesting that both types of complexes geometries exist simultaneously with a ratio depending on the pH.

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Collaboration: Wojciech Piasecki, Karolina Lament

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## COMPARISON OF THE COMPOSITION OF FREE VOLATILE COMPOUNDS OF THE SPECIES *Veronica chamaedrys* L. ISOLATED BY HYDRODISTILLATION AND MICROWAVE EXTRACTION

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Studied *Veronica chamaedrys* L. (germander speedwell, family Plantaginaceae) belongs to the European-Mediterranean hemicryptophytes.<sup>[1]</sup> The plant material was collected from Delnice (Croatia) in July 2021 and was air dried. Free volatile compounds (FVCs) were isolated using two techniques: hydrodistillation (Hy) in Clevenger apparatus and microwave extraction (Me) in Etos X. The lipophilic (essential oils) and water (hydrosols) fractions were collected separately in both apparatuses. The aim of this study was to investigate the similarities and differences in the composition of the free volatile compounds isolated by these two techniques. The composition of the isolated compounds was analysed by gas chromatography coupled with mass spectrometry.<sup>[2]</sup> The composition of the lipophilic fraction obtained by both isolation techniques was dominated by the oxygenated sesquiterpenes caryophyllene oxide (Hy 18.63%; Me 24.36%), followed by viridiflorol (Hy 7.89%; Me 8.19%). Also, caryophyllene oxide (Hy 20.65%; ME 20.26%) and viridiflorol (Hy 9.35%; Me 12.36%) are the most abundant compounds in the hydrosol fractions. In our previous study FVCs of the genus *Veronica*, caryophyllene oxide was the main constituent of the Croatian endemic species *V. saturejoides* Vis. ssp. *saturejoides*.<sup>[3]</sup> Most of the identified compounds in the oil fraction obtained by both techniques are similar, and the most significant differences in percentage identification are for the compound *E*-caryophyllene (Hy 12.93%; Me 1.57%) and phytol (Hy 5.26%; Me 11.96%). In the hydrosol fractions, there were significant differences in the percentage identification of  $\alpha$ -muurolol (Hy 12.15%; Me 5.53%) and bornyl acetate (Hy 3.27%; Me 10.67%). Overall, the difference in the composition of the FVCs of the lipophilic and hydrosol phases is that of a monoterpene hydrocarbons compound group. This group was identified in the hydrosol fractions using both isolation techniques. The differences in the composition of these FVCs are primarily due to different conditions in the isolation techniques as well as the solubility of the compounds. The different isolation techniques identified different compounds and thus obtained a more complete composition of the special metabolites. The plant produces special metabolites in response to stressful environmental conditions<sup>[4]</sup> and people use this product in natural treatments. New methods of extraction of FVCs are being introduced as greener solutions that consume less energy in the extraction processes are needed for the future usage of these compounds. The evaluation of the differences between the compositions of FVCs coming from different extraction techniques are valuable for the estimation of the quality of the product at the end of the extraction process. It is possible that greener solution will not be better for the composition of extracted FVCs for some plants. The FVCs identified in the species *V. chamaedrys* are a contribution to the knowledge of metabolites important for adaptation to environmental conditions in the genus *Veronica* and for potential biological activity testing.

**Acknowledgments.** This research was funded by Croatian Scientific Foundation under project “Croatian Veronica Species: Phytotaxonomy and Biological Activity”, CROVeS-PhyBA, IP-2020-02-8425.

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## 5<sup>TH</sup> GRADE CHEMISTRY? KEMIJA U PETOM RAZREDU?

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U ovom radu usporedili smo ishode poučavanja nastavnih tema prema novom kurikulumu nastavnog predmeta Kemija u 7. razredu<sup>[3]</sup> i Priroda u 5. razredu osnovne škole<sup>[2]</sup> i to prema prijedlogu Okvirnih godišnjih izvedbenih kurikuluma Ministarstva znanosti i obrazovanja 2020.<sup>[1]</sup>

Naime, donošenjem novih kurikuluma u Republici Hrvatskoj neki se ishodi ova dva predmeta na određeni način preklapaju, pa je važno učiteljima nastavnog predmeta Kemije ukazati na predznanja s kojima učenici dolaze u 7. razred. Također su analizirani tiskani udžbenici triju izdavača: Profil Klett, Alfa i Školska knjiga, kako bi se ukazalo na konkretan sadržaj kojima je predloženo razraditi ishode za koje smo pronašli najviše „preklapanja“, a to su: Tvari, Energija te Voda i zrak.

Zaključno, donosimo kratki pregled važnijeg sadržaja po navedenim temama iz nastavnog predmeta Priroda u 5. razredu koji može poslužiti za sistematičnu organizaciju rada (kao plan poučavanja) za učitelje nastavnog predmeta Priroda, a učiteljima nastavnog predmeta Kemija će omogućiti detaljniji uvid u nastavne teme koje su uvode nastavni predmet Priroda u 5. razredu. Također, ovakav pregled sadržaja može poslužiti kao pomoć pri izradi inicijalnog ispita za 7. razred u nastavnom predmetu Kemija.

Budući da se novi kurikulum nastavnoga predmeta Priroda za 5. razred provodi u svim školama RH od školske godine 2019./2020., u ovoj školskoj godini, prva generacija učenika po novom kurikulumu pohađa sada sedmi razred.

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## PHOTOCATALYTIC DEGRADATION OF ESSENTIAL OILS – A SCHOOL PROJECT

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As part of teaching organic chemistry with a group of advanced students, we decided to make completely vegan soaps by using essential oils (lavender, rose, and lemongrass) and olive oil by the standard hot process. It is known that with some essential oils when applied to the skin, and exposed to the Sun, unwanted side effects can occur. We investigated further this phenomenon but with the use of a spectrophotometer instead of skin testing. During the investigation, the students have been shown all stages of the research work (literature search, asking the right question, planning the experiment, and finally being able to explain everything we noticed). The students learned about the importance of testing procedures in food and cosmetics industry. They also found that research procedures take much more time than shown in popular media (i.e. TV). We chose UV/VIS spectrophotometry as a method to detect the changes that occur to the essential oils in our soaps after they are exposed to UV irradiation. Instead of exposing the samples to the natural sunlight, which is unstable and hard to measure, the wide-spectrum electric UV lamp was chosen, and the exposure was timed by a stopwatch. For practical reasons, we used ethanol solutions of pure oils. The photodecomposition of essential oils was visible in a UV/VIS spectrum within minutes of exposure to high-energy UV radiation. A linear time dependence could also be observed. The products of decomposition can be reactive or toxic, which can be harmful to the skin or cause severe allergic reactions.

**Acknowledgments.** The authors and students wish to thank the Laboratory of Physical Chemistry, Department of Chemistry, Faculty of Science, University of Zagreb for the support and use of instruments.

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## VALENCE – BASIC CHEMICAL CONCEPT VALENCIJA – TEMELJNI KEMIJSKI POJAM

Nikolina Penić,<sup>a,b</sup> Draginja Mrvoš-Sermek<sup>b</sup>

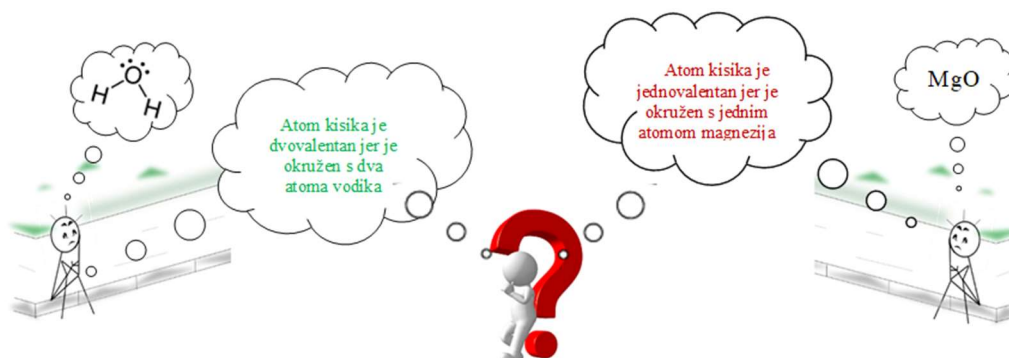
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“Od svih koncepata u modernoj kemiji, koncept valencija je jedan od najtemeljnijih” je navod profesora Colina Russella s kojim bi se i danas mnogi kemičari ili povjesničari znanosti složili. Povijest tog pojma je izuzetno složena jer usprkos raznim studijima s različitim pogledima na valenciju, teško se može kronološki govoriti o razvoju koncepta valencije kao cjeline. Razvoj ideje o sposobnosti vezanja atoma kemijskih elementa s točno određenim brojem atoma nekog drugog ili istog elementa kroz povijest se protezao kroz razne teorije (dualističku, radikalnu, supstitucijsku), a predstavljao je glavni problem znanosti 19. i 20. stoljeća kao jedan od najvećih prijedora u povijesti kemije.<sup>[1]</sup>

Vodeći se time načinjen je pregled pojma valencija u udžbenicima za osnovnu školu izdanih u proteklih 80 godina u našem jezičnom području s ciljem proučavanja njihovog utjecaja na razvoj učeničkih poteškoća vezanih za ovaj pojam. Na temelju tih i drugih literaturnih podataka osmišljeno je i provedeno preliminarno istraživanje očekivanih poteškoća vezanih za pojam valencija u studentskoj populaciji različitih godina studija. U sklopu ovog kratkog priopćenja dan je: (a) uvid u neujednačenost definicije pojma valencija atoma kemijskog elementa prisutne i u današnjim udžbenicima; (b) pregled rezultata provedenog istraživanja, (c) uvid u konstruirani ispitni materijal i (d) prijedlog definicije pojma valencija atoma nekog kemijskog elementa u početnom poučavanju koji bi bio primjenjiv na ionske i kovalentne spojeve, a na višoj razini poučavanja i dalje znanstveno konzistentan.<sup>[2]</sup>



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## EFFECTS OF ESTRADIOL ON BIOLOGICAL AGE MEASURED BY THE GLYCAN AGE INDEX

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Glycan age is a recently developed biomarker based on glycans attached to immunoglobulin G (IgG).<sup>[1]</sup> In large population cohorts, glycan age associates well with lifestyle and disease-risk biomarkers, while some studies suggested that glycan changes precede the development of several age-associated diseases.<sup>[2]</sup>

We evaluated the effects of estrogen on the glycan age by analyzing glycan profiles of serum IgG antibodies using the ultra-performance hydrophilic interaction liquid chromatography.<sup>[3]</sup> Gonadal hormones were suppressed in 36 healthy young women by gonadotropin-releasing hormone agonist therapy for 6 months. Estradiol was supplemented in 15 of them, while 21 women received a placebo resulting in very low estrogen levels during an intervention. IgG was isolated from plasma samples before the intervention, after 6 months of intervention and after subsequent 4-month recovery.

Deprivation of gonadal hormones resulted in a median increase of glycan age for 9.1 years (IQR 6.8 – 11.5 years,  $p = 3.73 \times 10^{-8}$ ), which was completely prevented by transdermal estradiol therapy. After the recovery period, glycan age returned to baseline values in both groups. These results suggest that IgG glycans and consequently the glycan age are under a strong influence of gonadal hormones and that estradiol therapy can prevent the increase of glycan age in the perimenopausal period.

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## SMART LABORATORY FUME HOOD – STUDENT PROJECT

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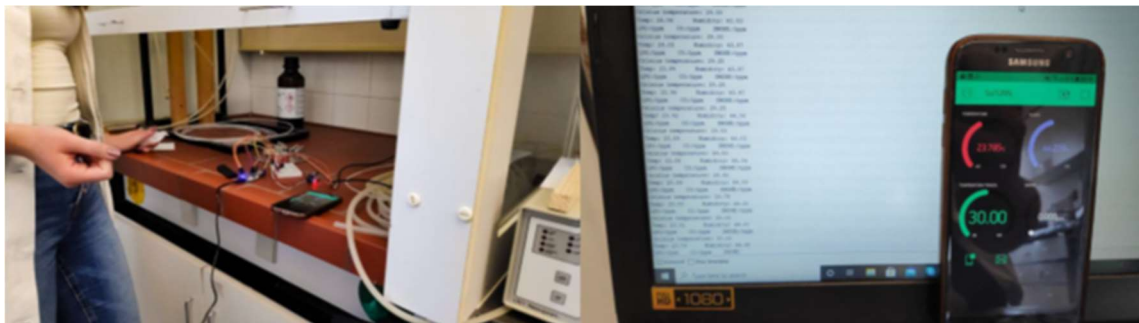
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This abstract contains all important information about a student project *Smart Laboratory Fume Hood*.

*Smart Laboratory Fume Hood* is an innovation that offers greater automatization, the use of various sensors and voice control of the fume hood. This ensures safer working chamber and product quality, as well as better time management. The system *SMART Rhea.lity* would contain temperature, humidity, gas, flow and washing liquid level sensors, a sash wipers and an UV lamp for disinfection and two high resolution cameras for process monitoring. Parameter values of any ongoing process would be adjustable via touchscreen and computers. All components of the *SMART Rhea.lity* system would be operable via voice commands, computer and mobile application, with a help of virtual assistant *Rhea*.

The first prototype was made using Arduino technology, since it is known as affordable for beginners in programming. The prototype (Figure 1.) contains 3 sensors: waterproof temperature sensor, humidity and temperature sensor and a gas sensor.



**Figure 1.** Testing the first prototype (left) and the display while listing measured parameters on a computer and *Blynk* mobile application (right)

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## BIOENGINEERING APPROACH FOR BIOREMEDIATION OF PHARMACEUTICAL WASTEWATER

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The increasing use of pharmaceuticals in modern society is accompanied by their disposal into the environment. The presence of new contaminants derived from pharmaceuticals in water bodies, even at low concentrations, may pose a long-term risk to human health and aquatic ecosystems.<sup>[1]</sup> A bioremediation technique aims to treat xenobiotics through microbial transformation so that the water becomes less toxic and more stable than its original polluted state.<sup>[2]</sup> Microbial degradation involves the use of microorganisms and their associated unique enzyme systems to break down, degrade, detoxify or transform environmental pollutants.<sup>[3]</sup>

In this work, bioremediation of real pharmaceutical wastewater was carried out, involving the processes of biosorption and biodegradation of organic pollutants using activated sludge. The biosorption experiment was carried out to study the binding of pollutants from the wastewater to the cellular structure of the activated sludge. Langmuir's model showed good agreement with the experimental data, with the value of  $F$ -test =  $0.97 \pm 0.01$ . Based on the values of the estimated model parameters and the evaluation of the acceptability of the model, it can be concluded that the model Endo-Haldane can well describe the biodegradation of pharmaceutical wastewater with activated sludge ( $F$ -test =  $0.96 \pm 0.02$ ).

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## APPLICATION OF THE RELATIVE GAIN ARRAY IN THE CONTROL SYSTEM DESIGN OF THERMALLY COUPLED DISTILLATION SEQUENCES

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The separation of mixtures by distillation requires an enormous amount of energy, which can be somewhat mitigated by using various process intensification techniques. One of the approaches to intensify the distillation sequences of two or more distillation columns is so-called thermal coupling, that is, the use of heat flow from one reboiler for all separations in the sequence. If thermally coupled columns are realised within a single shell as a dividing wall column, savings can be made not only in energy expenses but also in the required installation space and capital costs.<sup>[1]</sup> A dividing wall column is a fully thermally coupled distillation column in which mixtures of three or more components can be separated into high purity products. Although it has numerous advantages, the practical application is progressing slowly due to its complex internal configuration, which makes the hydraulic design, as well as the design of the control system much more complex.<sup>[2]</sup> In this paper, for a given separation task, static and dynamic models of a dividing wall column for four products were developed, using process simulators *CHEMCAD* and *Aspen HYSYS*, with the aim of studying dynamic properties of the system. The control scheme was developed based on the sensitivity analysis (SA)<sup>[3]</sup> and singular value decomposition (SVD),<sup>[4]</sup> and the application of a relative gain array (RGA)<sup>[5]</sup> methods. The developed control structure was tested in a closed loop by introducing disturbances and monitoring the product purity response.

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## PHOTODEGRADATION OF NEONICOTINOIDS ON A TiO<sub>2</sub>-BASED PHOTOCATALYSTS - EFFICIENCY OF REACTIVE OXYGEN SPECIES

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In our previous work, different methods were used to modify the photocatalytic properties of TiO<sub>2</sub>-based photocatalysts and improve their performance for the degradation of imidacloprid as a representative of neonicotinoids.<sup>[1]</sup> This work aims to investigate the efficiency of reactive oxygen species (ROS) generated by TiO<sub>2</sub>-based photocatalysts. The identification and quantification of ROS is very important for understanding the photodegradation mechanism, improving the degradation efficiency as well as for practical application.

Photocatalytic degradation of imidacloprid (10 ppm) was carried out using aqueous suspensions of different TiO<sub>2</sub>-based photocatalysts (0.08 g) in an 80 mL batch reactor equipped with a UVP Pen Ray lamp (UVA,  $\lambda=365$  nm). The generation of hydroxyl radicals (OH<sup>•</sup>), singlet oxygen (<sup>1</sup>O<sub>2</sub>) and superoxide radicals (O<sub>2</sub><sup>•-</sup>) formed by the UVA irradiation were determined using appropriate quenchers such as isopropanol, sodium azide and p-benzoquinone. To test the possibility that degradation occurs via direct oxidation of the adsorbed reactant molecules with holes (h<sup>+</sup>) in the valence band, additional experiments were performed using EDTA-Na<sub>2</sub> as a hole scavenger. The effect of H<sub>2</sub>O<sub>2</sub> addition in different concentrations on imidacloprid degradation was also investigated. Finally, to detect the presence of the short-living ROS in the aqueous medium, the electron paramagnetic resonance (EPR) spin-trap technique was employed using 5,5-dimethyl-1-pyrroline-N-oxide (DMPO) as a scavenger reagent. The spectra were recorded under the UVA irradiation at different reaction times. Based on the results obtained, conclusions were drawn about the major ROS responsible for the efficient degradation of imidacloprid.

**Acknowledgments.** The research was funded by Croatian Science Foundation under the project IN-PhotoCat (IP-2018-01-8669)

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## EMERGING MONOLITHIC CATALYSTS FOR THE CATALYTIC OXIDATION OF AROMATIC VOLATILE ORGANIC COMPOUNDS

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The preparation of monolithic catalysts with high activity and stability is crucial for the catalytic oxidation of aromatic volatile organic compounds (AVOCs). Monoliths are mainly used as inert carriers for various catalytically active components, which are subsequently deposited on the monolithic structure.

This work aimed to examine the adhesion between 3D-printed ceramic ( $\text{SiO}_2$ ) catalyst carriers (plates) and the catalytically active layer (manganese based mixed oxides). Two methods, impregnation and sol-gel method, were chosen for the deposition of the catalyst layer on inert ceramic carriers (Figure 1). The mechanical stability, i.e. the adhesion of the catalytic layer to 3D-printed ceramic plates was tested by exposing the coated plates to the ultrasonic vibrations, i.e. by determining the difference in mass of individual plates before and after the exposure.

Due to the low mass loss of the catalyst (<2 %) for all prepared carriers, both methods of applying the catalytically active layer showed to be suitable for their production from the point of view of mechanical stability. However, there is a possibility of partial blocking of the catalytically active sites due to the structure of the sol, which could negatively affect the catalytic properties of the prepared monolithic catalysts in the same temperature range compared to the impregnation method. To test this hypothesis in the continuation of the research, special emphasis will be placed on these tests in the monolithic reactor.

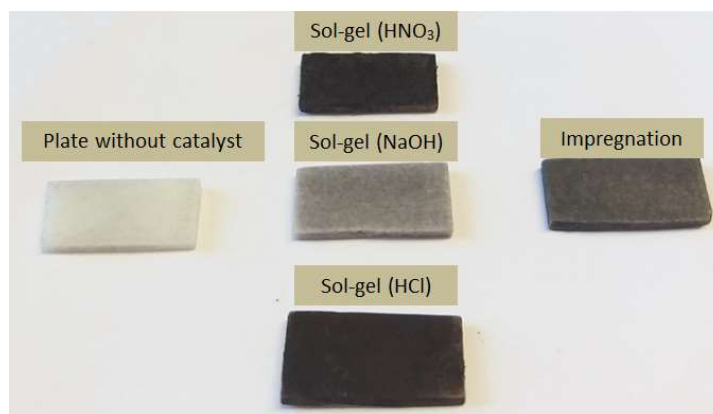


Figure 1. Comparison of the prepared catalyst carriers

**Acknowledgments.** This work has been supported by Croatian Science Foundation under the project IN-PhotoCat (IP-2018-01-8669).

## DESIGN OF LINEAR AND CYCLIC PEPTIDES FOR ESTER HYDROLYSIS

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Enzymes are large protein structures that are necessary for most of the catalytic processes in living systems. The complexity of amino acid interactions and the large combinatorial space of proteins suggest that the earliest enzymes could have emerged from self-assembled peptides.<sup>[1]</sup> There are 20 proteinogenic amino acids that in different combinations and chain lengths constitute active peptide sequences. Short peptides consisting of up to 10 amino acids can be exploited as catalysts for ester hydrolysis. Peptides can be easily synthesized in the laboratory and can act as simplified versions of enzymes. The main objective of this study is the design of linear and cyclic catalytic peptides and the comparison of their ability to catalyze ester hydrolysis examined by the model reaction of pNPA hydrolysis. For this purpose, we have chosen two peptides, IHIHINI and IHINIHI inspired by Rufo et al. These sequences should be able to self-assemble into catalytic amyloids that could act as Zn<sup>2+</sup>- dependent esterases.<sup>[1]</sup> We want to investigate the effect of changing the position of asparagine (N) on the self-assembly and catalytic properties of the proposed peptides. The cyclic peptides will be designed through the addition of cysteine residues to allow the cyclization through disulfide bridge formation. After synthesizing the peptides, using the Fmoc solid phase peptide synthesis (SPPS) method, they were analyzed by MALDI, liquid chromatography coupled to mass spectrometry and purified. To verify the propensity of the designed peptides to form  $\beta$ -sheet like structures FTIR-ATR was used. By using cyclization to form intra-connected peptide structures, we expect that the increased rigidity introduced by cyclization will improve the catalytic efficiency of short peptides.

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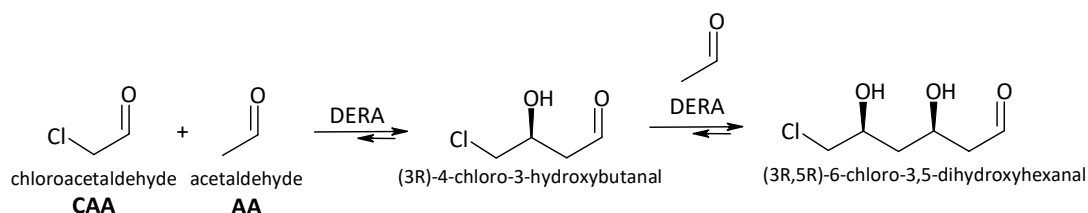
## ACTIVATION AGENT OPTIMIZATION IN ALDOLASE IMMOBILIZATION ON MESOPOROUS SILICA

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In the field of pharmaceutical synthesis one of the most researched and utilized reaction is the synthesis of statins, drugs used for lowering cholesterol levels in blood. Important statin side-chain precursor with two optically active centers can be produced by double aldol addition catalyzed by 2-deoxyribose-5-phosphate aldolase (DERA, EC 4.1.2.4) (Figure 1).<sup>[1]</sup>



**Figure 1.** Aldol addition reaction for synthesis of a lactol intermediate.

While this reaction offers a lot of benefits associated with enzyme-catalyzed reactions, its main drawback is the enzyme inactivation due to the presence of high concentrations of both substrate and reaction intermediates. One of the methods to successfully combat this issue is enzyme immobilization which often leads to increased operational stability.<sup>[2]</sup>

The aim of this work was to immobilize aldolase on mesoporous silica by covalent bonding with benzoquinone. Mesoporous silica was synthesized using the sol-gel method and functionalized with 3-aminopropyltriethoxysilane. Four different concentrations of benzoquinone were used for surface activation. In addition, the influence of temperature on the immobilization process was examined. In order to determine the optimal activation agent concentration and temperature, the success of immobilization was followed by measuring retained activity, stability and efficiency of the immobilized biocatalyst.

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## CHOLINE CHLORIDE: PROPYLENE GLYCOL (1:4) DEEP EUTECTIC SOLVENT FOR EXTRACTIVE GASOLINE PURIFICATION

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The advantage of deep eutectic solvents (DESs) is in the arbitrary selection of their components and their composition (in terms of component's molar ratio), which directly affects the appropriate properties of solvents for certain application. The choice of choline chloride as HBA component<sup>[1,2]</sup> and propylene glycol<sup>[3]</sup> as HBD component results in a DES that achieves good gasoline denitrification.<sup>[4]</sup> In this paper, choline chloride : propylene glycol (ChCl:PG) in a molar ratio of 1:4 was tested for denitrification and desulfurization of model and real FCC gasoline. A batch extraction process was performed at a temperature of 25 °C and atmospheric pressure, a stirring speed of 1000 rpm, an extraction time of 30 minutes and a DES:gasoline volume ratio of 1:1. The DES physical properties essential for extraction were determined. In a one-stage extraction experiment, the efficiency of denitrification and desulfurization reached ~86 % and ~21 %, respectively. By increasing the number of extraction stages, a decrease in DES extraction capacity was observed which was successfully resolved by DES recovering between stages. In a real gasoline sample, 36.8 % denitrification efficiency and only 10.5 % desulfurization efficiency was achieved. Hence, ChCl:PG 1:4 can be proposed as a suitable extraction agent for gasoline denitrification.

**Acknowledgments.** The authors acknowledge the contribution of the laboratories of INA Sisak oil refinery and Comprehensive Water Technology.

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## BIOCATALYTIC SCOPE OF HALOHYDRIN DEHALOGENASE FROM *Mycobacterium* sp. GP1 (HheB2) AND MUTANT HheB2-T120A

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Halohydrin dehalogenases (HHDHs) belong to a distinct group of enzymes catalyzing the removal of a halide ion and a proton from a vicinal halohydrin with formation of an epoxide.<sup>[1]</sup> Moreover, these enzymes can catalyze the epoxide ring-opening reactions with a range of anionic nucleophiles affording  $\beta$ -substituted alcohols as products.<sup>[2]</sup> Based on sequence similarities, they are divided into 7 phylogenetic groups: A, B, C, D, E, F and G. Activity, enantioselectivity and enantioselectivity are dependent on the type of enzyme and the substrate structure.<sup>[3]</sup> Among all, the enzyme HheC from *Agrobacterium radiobacter* (group C) is the most studied because of its high enantioselectivity and wide nucleophile scope.<sup>[3]</sup> However, the major shortcoming of HheC is its narrow substrate tolerance, due to the relatively small active site. To expand the catalytic relevance of HHDHs we focus our attention to an enzyme from different organism.

There are two similar enzymes in group B, one found in *Corynebacterium* sp. N1074 (HheB) and the other in *Mycobacterium* sp. GP1 (HheB2). They share high sequence identity (95%) with only 4 amino acid substitutions HheB/HheB2: F36/I36, T120/A120, C124/Y124, H125/Q125.<sup>[4]</sup> HheB exhibits higher enantioselectivity than does HheB2. Because of that HheB2 has been previously characterised as non-enantioselective enzyme, and neglected as biocatalyst.<sup>[5,6]</sup> In this work HheB2 was investigated in the ring-opening reaction on a set of 21 structurally different aliphatic and aromatic epoxides using sodium azide as nucleophile (Figure 1). In order to gain more insight into the difference in enantioselectivity of HheB2 and HheB, mutant HheB2-T120A was also investigated in the ring opening reactions.



**Figure 1.** Nucleophilic ring-opening of epoxides catalysed by HheB2 from *Mycobacterium* sp. GP1 and mutant HheB2-T120A

The screening confirmed low to moderate enantioselectivity of HheB2 towards monosubstituted epoxides, however high activity and enantioselectivity in conversion of 2,2-disubstituted ( $E$ -values up to  $>200$ ). Similar to HheC, the large enhancement of enantioselectivity is obtained when a second substituent (methyl or ethyl) is present at the chiral centre. T120A mutation has been shown to be a key mutation for increasing enantioselectivity in aliphatic epoxides, which is not the case for aromatic epoxides. The results further extend the repertoire of enantioselective HHDHs and their application in the kinetic resolution of epoxides.

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## VALIDATION OF KINETIC MODEL OF HALOHYDRIN DEHALOGENASE-CATALYSED SYNTHESIS OF (*R*)-EPICHLOROHYDRIN

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Epichlorohydrin (ECH) is a valuable product that is commonly used as an intermediate in the preparation of synthetic rubbers, as a starting material in the production of insecticides, pharmaceuticals, etc.<sup>[1]</sup> This prominent product can be obtained through biocatalysis. Halohydrin dehalogenases (HHDHs) are adaptable and important biocatalysts that are mostly used for the industrial synthesis of enantiopure ECH.<sup>[2]</sup> The reasons why the biocatalytic approach takes precedence over the traditional one are high enantioselectivity, low production cost, extensive enzyme sources and environmentally friendly conditions of this synthesis.<sup>[3]</sup>

The operational stability of an enzyme generally relates to the retention of activity when an enzyme is in use. On an industrial level, the long-term operational stability of biocatalysts is of crucial importance for deciding whether a process can be viable as opposed to the traditional approach.<sup>[4]</sup> Operational stability is necessary to determine at which process conditions enzyme can work properly.

In this work the kinetic model of HheB2-T120A-catalysed synthesis of (*R*)-ECH from 1,3-dichloro-2-propanol was developed. Model validation was performed in batch reactor experiments. It was found that a substrate (1,3-dichloro-2-propanol) deactivates the enzyme and the rate of deactivation is dependent upon its concentration.

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## REMOVAL OF ACETAMIPRID OVER TiO<sub>2</sub>/PERLITE PHOTOCATALYST

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The large-scale use of pesticides in agriculture and veterinary medicine has led to their widespread occurrence in the natural aquatic environment. Since they are difficult to remove from the aquatic medium by conventional treatment techniques, advanced oxidation processes focusing on heterogeneous photocatalysis are preferred.<sup>[1]</sup> In this work, the photocatalytic degradation of the neonicotinoid insecticide acetamiprid was studied in a batch reactor using TiO<sub>2</sub>-based "floating" photocatalysts under UVA - LED irradiation. All experiments were performed with the same stirring rate, catalyst mass and solution pH. The effect of irradiation intensity via the change of source voltage (31, 31.5 and 32 V), initial acetamiprid concentration (5, 10 and 15 ppm) and catalyst type on the degradation efficiency was investigated. Before conducting the experiments, an experimental design was prepared using the software package Design-Expert.<sup>[2]</sup> The degree of acetamiprid photodegradation was determined by measuring the change in its concentration during the reaction using high performance liquid chromatography. The obtained experimental data were also tested with a kinetic model for the pseudo-first order reaction. The experimental results showed that the irradiation intensity has the greatest influence on the reaction rate and efficiency of the photocatalytic degradation of acetamiprid. The reaction rate and conversion increase with increasing irradiance, as does the reaction rate constant.

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## DIBUTYL PHTHALATE DEGRADATION BY ADVANCED OXIDATION PROCESSES

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Dibutyl phthalate (DBP) is an additive widely used in cosmetics and plastics. Since DBP does not form chemical bonds with the polymer matrix, there is a high potential for it to leach out of the products during their usage or disposal. DBP is listed as Substance of Very High Concern due to its endocrine disrupting behavior and reproductive toxicity, which increases the awareness for its removal from the environment.<sup>[1]</sup>

In this study, the photochemical degradation of DBP in UV-C/H<sub>2</sub>O<sub>2</sub> and UV-C/Na<sub>2</sub>S<sub>2</sub>O<sub>8</sub> processes was conducted. The influence of pH-value and oxidant concentration was observed, and the optimal conditions were determined. The results showed pseudo-first order degradation constants for both processes, while UV-C/Na<sub>2</sub>S<sub>2</sub>O<sub>8</sub> process showed several times higher degradation rate of DBP.

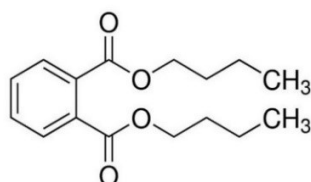


Figure 1. Structure of dibutyl phthalate

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## CHANNEL SURFACE MODIFICATION OF 3D PRINTED DROPLET GENERATORS

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The use of emulsions is increasing in the food, cosmetics and pharmaceutical industries. The size of the droplets has a strong influence on the final product.

The aim of this study was to investigate the influence of channel size, shape and connection type, as well as the influence of different types of surface modifiers on the liquid flow in the channel and the droplet size obtained. Test samples of different materials were made to determine the optimum material in terms of surface free energy. The droplet generators were fabricated using a stereolithographic 3D printer. Fourier transform infrared spectroscopy (FTIR) was used to analyze the surface coating. In addition, contact angle measurements were performed on untreated and surface-treated samples. A system of two immiscible liquids, water and oil, was used to form the emulsion in the droplet generators. From the results obtained in the experiment, the optimum combination of material and surface agents was selected. In the final part of the study, two surface modifiers were tested to see the influence of connection and surface modifiers on the stability of the formed emulsion.

The influence of the surface modifiers was confirmed, as the hydrophilic/hydrophobic properties strongly influenced the shape and number of droplets generated in the channel (Figure 1). Moreover, the droplet formation could be easily controlled by changing the flow ratio of the two liquids in the droplet generator. The emulsions formed were unstable and an emulsifier must be used for stabilization.



**Figure 1.** Droplet size is controlled by surface modification and changing the flow ratio of the two liquids in the droplet generator

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## ARTIFICIALLY OBTAINED SULPHATE-CARBONATE PATINA ON BRONZE SUBSTRATES - PREPARATION AND CHARACTERIZATION

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In the atmospheric corrosion condition bronze artefacts are gradually covering with patina. The color and composition of patina depend on concentration of aggressive compounds in the environment. In the presence of increased concentration of SO<sub>2</sub> in the environment, sulphate patina occurs in form of brochantite (Cu<sub>4</sub>(SO<sub>4</sub>)(OH)<sub>6</sub>). Accordingly, in the presence of increased concentration CO<sub>2</sub> in the environment, carbonate patina occurs in form of malachite (Cu<sub>2</sub>CO<sub>3</sub>(OH)<sub>2</sub>). Because the formation of patina is lengthy process artificial patination is using instead, according to recipes from literature. It is a common practice to artificially patinate the objects of art in order to form sulphide patina, which can be additionally treated to form an upper layer of sulphate or carbonate patina. Patina has an aesthetic purpose but it should also provide corrosion protection to bronze substrate.

In this work sulphate-carbonate patina is artificially formed on various bronzes (CuSn12, CuSn6, RG7). Pre-step is formation of sulphide patina using the potassium sulphide solution. Furthermore, sulphate-carbonate patina is formed both chemically and electrochemically. The samples are exposed to continuous immersion in simulated rainwater or accelerated aging performed in corrosion chamber. Electrochemical properties are examined by using electrochemical impedance spectroscopy (EIS). Composition and morphology of patina are examined by FTIR spectroscopy, SEM/EDX and optical microscopy. The influence of the substrate on the stability of patina is observed.

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## APPLICABILITY OF THE PASTE ELECTROLYTE CELL FOR *IN SITU* ELECTROCHEMICAL TESTING THE SURFACE PROTECTION OF BRONZE

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Various electrochemical techniques can be used to obtain information about the condition of bronze artefacts as well as other metallic cultural artefacts exposed to the atmospheric corrosion condition *in situ*. In particular, electrochemical impedance spectroscopy (EIS) has proven to be a suitable method to generate valid data. A major challenge in performing EIS measurements *in situ* is the placement of a liquid electrolyte cell on an irregular, uneven and thin surface of the artefact. One approach to solve this problem is based on the use of a paste electrolyte cell instead of a liquid electrolyte cell. In this study, the applicability of the paste electrolyte cell for EIS testing of non-patinated copper and bronze as well as patinated bronze without and with the protective coating is investigated. Comparative measurements were made with three-electrode and two-electrode electrochemical cells and in three different types of electrolytes, an aqueous solution of sodium chloride, tap water, and electrolyte paste in the solid state. The aim of this work was to compare the measurements in the two types of electrochemical cells previously mentioned, to evaluate the repeatability and reproducibility of the measurements and to determine the influence of the different electrolytes. The EIS spectra were measured and the numerical values of impedance at 0.1 Hz were used as an indicator of the degree of surface protection by patina or coating. By comparing the impedance for different electrolytes, it was found that the aqueous solution of sodium chloride did not provide a reasonable indication of the degree of surface protection. By comparing the corrosion potential of samples in different electrolytes, an aqueous solution of sodium chloride and tap water was found to be a more aggressive electrolyte than electrolyte paste in the solid state. The surface of non-patinated bronze was changed after measurement in an aqueous solution of sodium chloride and tap water, while the plate remained unchanged after measurement with electrolyte paste. Electrolyte paste in the solid state proved to be a promising candidate for *in situ* measurements by determining the impedance in the following order: copper > bronze > patinated bronze > patinated bronze with a protective coating. It was also investigated whether the paste electrolyte cell detects any insulating layer as well as surface damage.

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## OPTIMIZATION OF POLYMERIC MILLIREACTORS PRODUCED BY ADDITIVE MANUFACTURING

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In this research work, a new approach of producing simple tubular polymeric millireactors and polymeric millireactors with static mixers using additive manufacturing technologies is used to study process intensification. Millireactors with different channel dimensions were fabricated, and static mixers were added to the successfully fabricated millireactors. The fabrication principle - adding material layer by layer - allows the formation of complex geometric structures within the millireactor channel. Static mixers create large interphase regions between reactants, so the applicability of the millireactors to multiphase immiscible systems was tested. Transesterification of sunflower oil to FAME was chosen as a model reaction. The rapid conversion of FAME, causally due to the efficient mass and energy transfer in millireactors, was monitored by infrared spectroscopy (FTIR).

The obtained results represent a contribution to the use of millireactors and millireactors with static mixers, as well as reactors with oscillating fluid flow, as replacements for already known microreactors, where the production volume is smaller and the pressure drop is larger than in millireactors.

The results indicate that longer retention times in millireactors lead to higher conversions, also higher temperatures and narrower channels lead to higher conversions. Tube baffled reactor provide even greater process intensification compared to millireactors without baffles due to the different mixing mechanism.

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## DESIGN AND PRODUCTION OF A MILLIREACTOR SYSTEM WITH A pH-SENSITIVE COATING

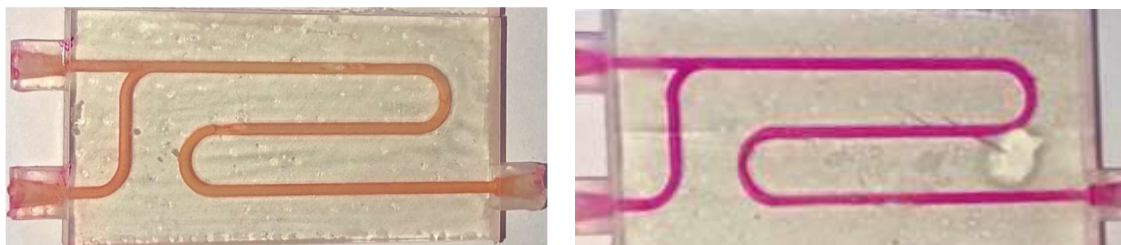
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The aim of this work was to design a millireactor system and to coat the surface of the channel with a pH-responsive sensor film. The sol-gel method was used to prepare the sensor film. The main objective was to obtain a functional pH sensor film that shows a clear response in real time within the channels of the millireactor.

For the sol-gel method, tetraethoxysilane (TEOS) and phenyltrimethoxysilane (FTMS) were used as precursors with ethanol as solvent, the reaction was acid catalyzed using hydrochloric acid and methyl red was used as pH indicator. The obtained sensor films were first tested on plates and then applied in millireactor channels. Both the test plates and the millireactors were fabricated using stereolithography (SLA) 3D-printing technology. Tests on the plates showed that excessive thickness of the film leads to cracking, which causes leaching of the indicator and detachment of the film from the surface. Therefore, different methods were used to obtain thinner films. The results show a change in the color of the sensor films with the change in the pH of the solution inside the channels of the millireactor (Fig. 1). The time interval of the change was 5 minutes.



**Figure 1.** Sensor films in the channels of the millireactors 24 h after the base cycle (left) and the acid cycle (right).

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# INFLUENCE OF ANTISOLVENT ADDITION ON CRYSTALLIZATION KINETICS AND GRANULOMETRIC PROPERTIES OF FOSANPRENAVIR CALCIUM

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The focus of the pharmaceutical industry is the research and development of an active pharmaceutical ingredient (API) that can be successfully applied for preparing various drug dosage forms.

API are complex organic compounds that tend to agglomerate, oiling out, or form hydrates and/or solvates during crystallization. Therefore, crystallization of the API is the first and critical step that needs to be taken to successfully prepare a drug formulation. By developing a controlled crystallization process, obtaining the desired size distribution, yield, form, and purity of crystals is possible. Crystallization can be carried out by various methods that affect supersaturation which is the main factor in the formation of crystals with defined crystal's properties. Addition of an antisolvent is potentially the best method to achieve controlled and unimodal crystal size distribution (CSD).

The research investigates the antisolvent crystallization of fosamprenavir calcium used as an active ingredient for the treatment of HIV. In preliminary study, the width of the metastable zone same as the dependence of fosamprenavir calcium solubility on the added water content for the selected solvent mixture (80 wt% methanol and 20 wt% ethanol) was defined. At constant antisolvent addition rate, the influence of the initial concentration of the solution and a mass fraction of antisolvent on granulometric properties of obtained crystals were examined. Furthermore, a MatLab based program (CrySiV v.1.1)<sup>[2]</sup> was used for population balance modeling and subsequent simulation of experiments at 30 °C. Solubility parameters were estimated for a pre-defined solubility model and a simple kinetic model consisting of primary nucleation and crystal growth is proposed. Kinetic parameters were estimated by minimization of the objective function using high resolution finite volume algorithm. The objective function takes into account the differences between simulated and measured values of concentration profile during crystallization and final product CSD in equal proportions.

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## THE EFFECT OF HOT MELT EXTRUSION ON THE THERMAL PROPERTIES OF POST-CONSUMER PET BOTTLES

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Poly(ethylene terephthalate) (PET) is one of the most important thermoplastic used for a broad range of applications, from drinking bottles to textile fibers. The first recycling effort of post-consumer PET bottles in the world was in 1977.<sup>[1]</sup> Since the price of virgin PET remains high, new and cheaper technologies for recycling PET are beneficial to the PET recycling industry. Hence, the physical recycling of PET by melt reprocessing is very important; it is relatively simple, requires low investments, utilizes established equipment, is flexible in terms of feedstock volume, and has little adverse environmental impact.<sup>[1]</sup> Among other operations, recycling of PET includes the re-extrusion for the production of new PET products.<sup>[1]</sup> However, re-extrusion process at high temperatures could cause changes in PET structure and properties.<sup>[2]</sup> In this work post-consumer PET bottles were gathered, separated from other materials, washed, dried, cut out to smaller pieces and extruded at 235 °C. PET samples (PET - bottle and rPET - re-extruded) were characterized by FTIR spectroscopy to investigate the effect of re-extrusion on the structure of PET. Likewise, differential scanning calorimetry (DSC) was utilized in order to determine characteristic thermal transitions; glass transition, crystallization and melting. Finally, thermogravimetric analysis (TG) was used in order to evaluate the effect of extrusion on the thermal stability of samples. Position and intensity of PET characteristic groups (peaks) remained almost unchanged upon extrusion. DSC results indicated the influence of re-extrusion on melting and crystallization temperatures of PET. TG analysis revealed that thermal stability of the investigated PET samples wasn't affected by the re-extrusion process.

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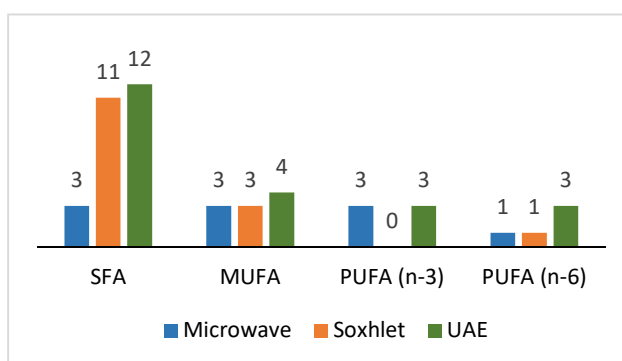
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## FATTY ACID DETERMINATION IN HENS FEED MIXTURE

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It has long been known that fatty acids (FA) are essential for maintaining the health of the human body. The amount and composition of fatty acids in our body depends, among other things, on the composition of the food we consume, so it is necessary to monitor the food quality. Chicken meat and eggs are often consumed and are important sources of fatty acids. The composition of the feeding mixture for chickens affects the FA profile found in chicken meat and eggs, therefore it is necessary to control the composition of the feeding mixture. Three methods of FA extraction (Soxhlet, microwave and ultrasound-assisted extraction) were applied to 6 feed mixtures and compared. After Soxhlet and ultrasound-assisted extraction, the solvent was removed and samples were prepared according to a standard Fatty acid methyl ester (FAME) boron trifluoride method, while after microwave extraction, the samples were ready for the analysis by gas chromatography (GC). The significance of these comparisons lies in the, shortening of the sample preparation time and the greater number of peaks detected. Microwave extraction resulted in the lowest number of peaks detected, Soxhlet extraction showed a slightly higher number of peaks while ultrasound-assisted extraction gave the best results with the highest number of total FA detected (Figure 1).



**Figure 1.** Total number of FA detected in each group (SFA – saturated fatty acids, MUFA – mono unsaturated fatty acids, PUFA – poly unsaturated fatty acid) after Soxhlet, microwave and ultrasound-assisted extraction and followed by GC analysis

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## LYOPHILIZATION CONDITIONS FOR THE STABILIZATION OF HALOHYDRIN DEHALOGENASES

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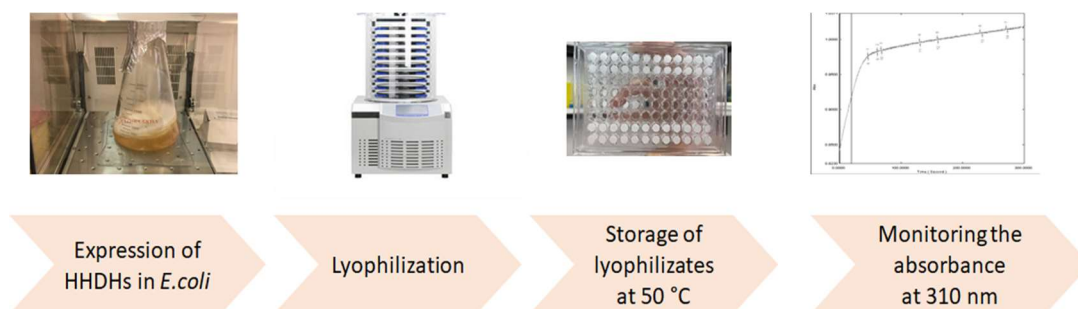
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Halohydrin dehalogenases (HHDHs) catalyse enantioselective formation and conversion of epoxides. Their exceptional selectivity, regioselectivity, and ability to employ different nucleophiles make the enzymes attractive for biocatalysis.<sup>[1]</sup> The enzyme from *Agrobacterium radiobacter* AD1 (HheC) is usually expressed in *E. coli*, isolated in TEMG buffer (50 mM Tris-SO<sub>4</sub>, 10 mM EDTA, 10 % glycerol, and 1 mM mercaptoethanol), and usually is stored as a cell-free extract at -70 °C for at least three months without significant loss of activity.<sup>[2]</sup>

Both storage (before use) and operational stability (during use) are highly relevant for biotechnological applications.<sup>[3]</sup> Lyophilization is an attractive approach for the long-term storage of enzymes at ambient temperature. It also facilitates the use of enzymes in non-aqueous media.<sup>[4]</sup>

In this work, the storage stability of HheC isolated in TEMG and TEM buffer is evaluated at room temperature. With a focus on establishing the optimal lyophilized formulation, different additives were tested for enzyme stabilization during lyophilization. Optimal conditions for the lyophilization of several HHDHs have been investigated. Lyophilized HheC was incubated at 50 °C to intensify the differences induced by additives. Enzyme activity is determined by following the absorbance at 310 nm (Figure 1).



**Figure 1.** Determination of storage stability of lyophilized HHDHs.

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## THEORETICAL EVALUATION OF ENZYME ACTIVE SITES AND CATALYTIC PEPTIDES INVOLVED IN ESTER HYDROLYSIS

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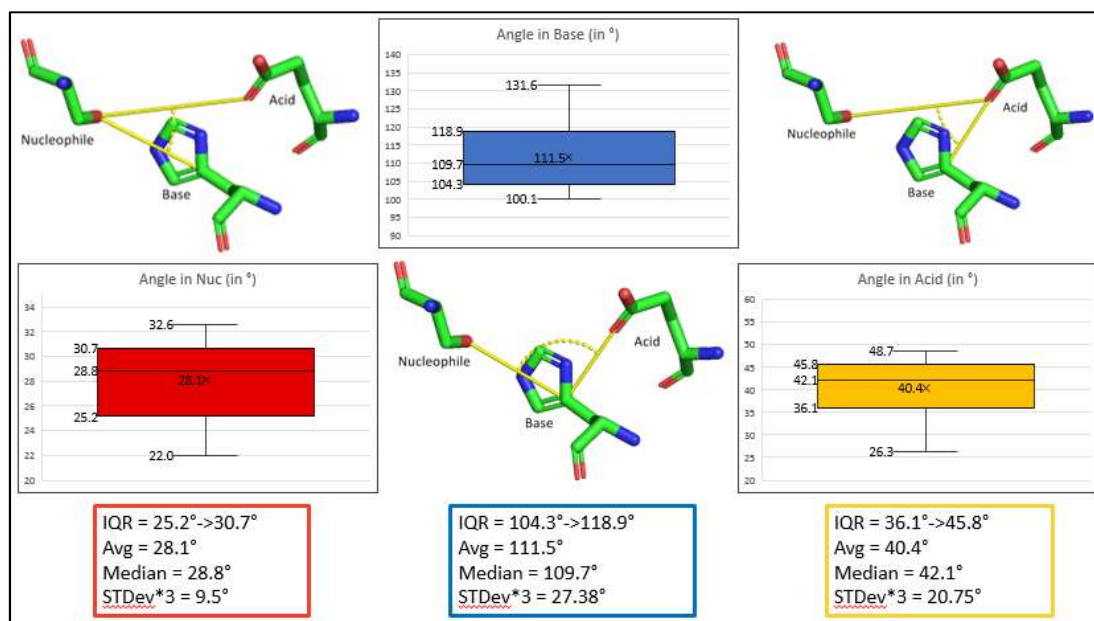
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Rational design of proteins and peptides has made significant improvements in medicine efficacy and more sustainable chemical synthesis pathways.<sup>[1–3]</sup> It requires knowledge of protein function down to the amino acid level.<sup>[4–6]</sup> In this project, the focus was put on active sites of enzymes and the drivers of catalytic function in natural enzymes. The analysis of natural enzyme active sites was compared to synthetic peptides with identical catalytic function to improve peptide design and enzyme understanding.

A data set was built to analyze enzymes from the EC 3.1. (Hydrolases acting on ester bonds) class looking at both amino acid content and geometry of active site residues. We searched for patterns in existing data by statistically analysing 96 esterases. In this process, 23 enzymes with known catalytic triads were selected for further evaluation. Based on the primary structure of the selected enzymes, the composition profiles were created for: (1) the full sequence, (2) the “long active site” including the residues between the first and the last active amino acid and (3) the “short active site” containing only active residues (catalytic triad and oxyanion hole).

To analyze the dataset we used two approaches. The first approach was based on composition and chemical property analysis. The second approach consisted in using crystal structure PDB files obtained via X-ray, only considering a below 3.0 Å resolution and in measuring the residue geometries in PyMol. Molecular dynamics (MD) simulations were used to observe how the active sites of natural esterases behave in solution. In addition, MD was performed on synthetic *de novo* peptides with confirmed esterase activity. These simulations were done in GROMACS and analyzed via VMD.

The results showed that the distances within which natural enzymes function are less than 1 Å in variation and that the angles conform within a 10% variation in the interquartile range compared to the average angle (Figure 1). Moreover, the qualitative amino acid analysis showed an increase of non-polar and a decrease in basic, hydroxylic and polar residues near the catalytically active residues. This suggests a strict functional geometry for the optimal enzymatic activity as well as a specific local amino acid content tolerated in active sites. These findings will allow the development of algorithms for prediction and optimization of enzyme functions and of new theoretical models of modular peptide design.



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**Figure 1.** Angles observed in catalytic triad members - All y-axis are in degrees. The stick representations show from which atom the measurements were performed.

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## RAZVOJ SIMULACIJE PROCESA IZMJENE TOPLINE U CIJEVNOM REAKTORU

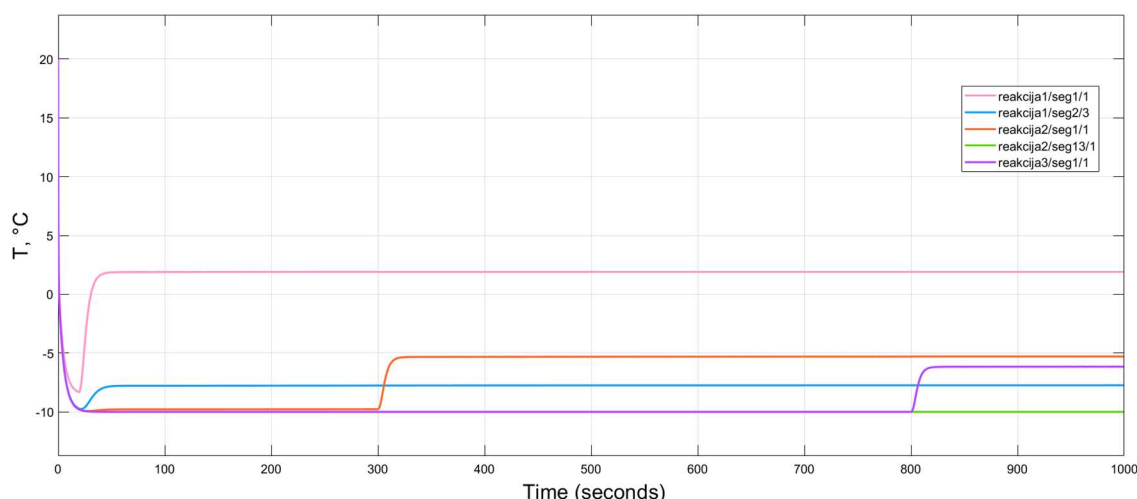
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U ovom radu modeliran je sustav za provedbu kemijskih reakcija i izmjenu topline u cijevnom reaktoru. U procesu izmjene topline glavna vođena varijabla je temperatura. Temperatura je ključna varijabla za stabilan rad i djelotvornost samog procesa izmjene topline te ostalih vezanih toplinskih i/ili separacijskih procesa. Također je bitna za potrošnju energije i pomoćnih medija te u konačnici za kvalitetu proizvedenih intermedijara i proizvoda.

Razvijen je teorijski model procesa izmjene topline za različite režime rada izmjenjivača topline na temelju fundamentalnih jednadžbi, a parametri modela (koeficijenti prijenosa topline) određeni su iz empirijskih formula.<sup>[1]</sup> Uz to ispitan rad samog modela te su, simulacijom u *Simulinku*, određene vrijednosti temperatura u reaktoru (Slika 1.), prilikom čega je simuliran i utjecaj predhlađenja reaktanata.



**Slika 1.** Simulacija promjene temperature s vremenom u cijevnom reaktoru

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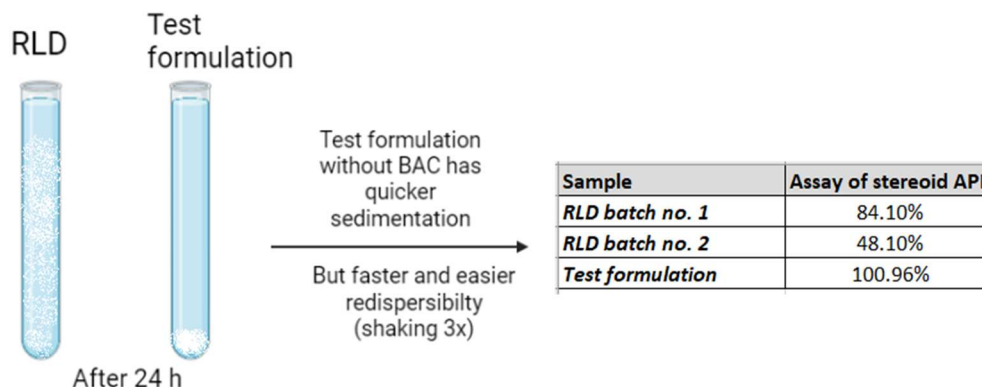
## PREFORMULATION APPROACH FOR THE DEVELOPMENT OF PRESERVATIVE FREE STEROID-BASED FORMULATION

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Clinical experience with benzalkonium chloride (BAC), preservative commonly used in eye formulations, proved its toxicity on ocular surface and connectivity to dry eye disease (DED), especially associated with chronic use.<sup>[1]</sup> BAC also acts as a cationic surfactant and impacts suspension stability.<sup>[2]</sup> Aim of this study was to develop stable preservative-free suspension, containing steroid based active pharmaceutical ingredient (API) with similar safety and efficacy as Referent listed drug (RLD) that contains BAC. The 1-ethenyl-2-pyrrolidone homopolymer (Kollidon®), in three grades (25, 30 and 90) and 4-(1,1,3,3-Tetramethylbutyl) phenol polymer with formaldehyde and oxirane (Tyloxapol) were selected as suspending agent and surfactant. Quantitative composition, as well as Kollidon grade, were set up by the analytical deformation study of RLD, purchased from USA market. Different prototypes of test formulation, together with RLD, were subjected to preliminary stability study at conditions 25 °C/60 %RH and 50 °C/75 %RH for 28 days. Physio-chemical parameters tested during the study were zeta potential, viscosity, particle size distribution (PSD), rheology, assay of API through redispersibility (imitation of patient use) and related substances. Results were compared between prototypes.



**Figure 1.** Redispersibility test of RLD and Test formulation

Prototype containing Kollidon®, grade 30 had viscosity, PSD and rheology characterization comparable to RLD and aligned with the results of deformation study. Difference is observed in zeta potential, attributed to BAC removal. With redispersibility test (Figure 1.) it is confirmed that preservative-free formulation ensures stable and uniform dosing of steroid based API thus confirming selection of lead formulation for further laboratory examination and manufacturing process scale-up studies.

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## DEVELOPMENT OF THE CALIBRATION MODEL FOR REAL-TIME MEASUREMENT OF GLYCINE CONCENTRATION IN GLYCINE-WATER SYSTEM USING ANN

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The subject of this research is the development of a calibration model based on in-situ ATR-FTIR measurements using artificial neural network (ANN) for monitoring concentration of glycine in glycine-water system in a batch crystallizer. Supersaturation, as a driving force of batch cooling crystallization processes, has a strong effect on product properties, i.e. crystal morphology, purity and crystal size distribution.<sup>[1]</sup> Therefore, the application of process analytical techniques plays a vital role for real-time monitoring and controlling of crystallization processes in order to obtain high-quality products.

Attenuated total reflectance - Fourier transform infrared spectroscopy (ATR-FTIR) is used for in-line measurement of solute concentration. IR spectrum is characteristic of the vibrational structure of the substance in immediate contact with the ATR immersion probe.<sup>[2]</sup> To obtain useful information from the spectral data, a calibration model is needed.

A calibration model for glycine concentration was developed based on experimental data. Experiments were conducted with different process conditions, including changes of solute concentration and the operating temperature.

The developed ANN model has a multilayer perceptron structure. ANN was trained using FTIR spectral data with the corresponding temperature values collected in the laboratory crystallizer. Validation of the model was performed on an independent dataset not used during the neural network training. The application of the developed model for monitoring the concentration in real-time combined with solubility curve and metastable zone width provides information about supersaturation in real-time. That allows the application of a process control method for maintaining the desired degree of supersaturation and thus, obtaining uniform product properties.

**Acknowledgments.** This research is funded by European Structural and Investment Funds, grant number KK.01.1.1.07.0017 (*CrystAPC – Crystallization Advanced Process Control*).

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## CYTOTOXIC ACTIVITY OF THE COMMON JUNIPER ESSENTIAL OIL

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The common juniper (*Juniperus communis* L.) is a tall shrub or low tree that can grow up to 15 meters in height. This species grows in lowland to premountain areas, and has a natural distribution range across Asia, North America, Europe and North Africa. The fruit are small, round berries of dark blue color, 6-9 millimeters in diameter, which are harvested during autumn.<sup>[1]</sup> This paper investigates the cytotoxic activity of the common juniper essential oil extracted from its berries. The sampling of plant material was performed at the following locations in the territory of Bosnia and Herzegovina: Konjuh, Majevisa, Srebrenica and Romanija. After drying, the extraction of essential oils from collected plant material was carried out in a 3-hour long process of hydrodistillation in a Clevenger apparatus. The content of essential oil in the berries was between 1.77 and 1.90%. The chemical composition of the essential oil was determined by an instrumental technique that combines gas chromatography and mass spectrometry (GC-MS). A total of 33 compounds were identified that make up 99.31-99.54% of the oil. The three most common compounds were determined as:  $\alpha$ -Pinene (30.64–40.66%), Sabinene (21.82–26.02%) and  $\beta$ -Myrcene (6.14–11.74%). The cytotoxic effects of the common juniper essential oil was investigated on breast cancer cell lines (MDA-MB-231) and lung cancer (A549). Cell treatment was performed with essential oil that was dissolved in nutrient medium, with DMSO (<1%) used to improve oil solubility. Cell viability was determined relative to control cells by MTT reagent and by absorbance measurement at a wavelength of 570 nm. The estimated IC<sub>50</sub> value in tests with breast cancer cells was 118.17–498  $\mu$ g/mL after 24 h and 94.67–445  $\mu$ g/mL after 48 h. In tests performed on lung cancer cells, the IC<sub>50</sub> was 137.33–404  $\mu$ g/mL after 24 h and 92–419  $\mu$ g/mL after 48 h.

**Acknowledgments.** This work was supported by Croatian company Euro-V.A.L. d.o.o.

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## CYTOTOXIC ACTIVITY OF LAUREL ESSENTIAL OIL

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Laurel (*Laurus nobilis* L.) is a Mediterranean plant from the Lauraceae family that grows in the form of an evergreen shrub or medium-tall tree (10–15 m). Laurel is rich in biologically active compounds that are mostly found in the leaves. Aromatic laurel leaves are simple, elliptical and oblong, with wavy edges and pointed tips, on the upper side they are dark green and shiny, on the lower side they are green, without shine, bare.<sup>[1]</sup> This paper investigates the cytotoxic activity of essential oil isolated from leaves of cultivated laurel. Sampling of laurel was performed on a plantation of aromatic plants near Unešić, which is located at about 340 meters above sea level, in an area where the Mediterranean and mild continental climate meet. Laurel plantations are two years old and the cultivation was carried out in an environmentally friendly way. Essential oil was isolated from the dried plant material by hydrodistillation in a Clevenger apparatus for 3 hours. The yield of essential oil was 1.42%. The analysis of the essential oil was performed by GC-MS instrumental technique. The cytotoxic activity of essential oil isolated from laurel leaves was investigated on breast cancer cell lines (MDA-MB-231) and lung cancer (A549). Cell treatment was performed with essential oil dissolved in nutrient medium with DMSO (<1%) used to improve oil solubility. Cell viability was determined relative to control cells by MTT reagent and by absorbance measurement at a wavelength of 570 nm. The estimated IC<sub>50</sub> value in tests with breast cancer cells was 336.83 ± 24.17 µg / mL after 24 hours and 276.83 ± 25.03 µg / mL after 48 hours. In tests performed on lung cancer cells, the IC<sub>50</sub> value was 354 ± 15.10 µg / mL after 24 hours and 361 ± 22.50 µg / mL after 48 hours.

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## ALGAE-DERIVED PLASMA MEMBRANE CARRIERS

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The development of a new generation of drug delivery systems closely resembling the living cell membrane is of interest for fundamental and applied research. The potential of the isolated plasma membrane of marine algae has not been sufficiently explored. Hypoosmotic shock in wall-less and soft algae<sup>[1]</sup> leads to cell bursting, release of intracellular contents, spontaneous membrane rearrangement, fusion, and formation of plasma membrane vesicles in micrometer-size range. The reconstructed plasma membrane is highly permeable to anionic fluorescent dyes<sup>[2]</sup> due to the heterogeneous distribution of nanopores revealed by atomic force microscopy. The aim of this study is to develop a protocol for plasma membrane reinforcement and to investigate the encapsulation of labeled dyes. Actin<sup>[3]</sup> monomers (concentration from 1 to 15  $\mu\text{M}$ ) were added during algal osmotic shock. After the formation of plasma membrane vesicles, 40 mM of crosslinker  $\text{Mg}^{2+}$  was added to form the actin network. Two molecular dyes, calcein and fluorescein-labeled concanavalin A, ConA-FITC, were used to examine the permeability of the plasma membrane. Confocal laser scanning microscopy revealed that unmodified plasma membrane vesicles were spontaneously permeable to calcein and semipermeable to ConA-FITC. Actin-modified plasma membrane vesicles, on the other hand, were permeable to calcein, and impermeable to ConA-FITC. The differences in the transport of molecular dyes across the plasma membrane could be related to the size of the dyes, the specific surface interactions of ConA with glycoproteins, and the number and size of the pores.

**Acknowledgments.** This work is supported by the Croatian Science Foundation Project “From algal cell surface properties to stress markers for aquatic ecosystems” (IP-2018-01-5840).

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## MONITORING AND CONTROL OF CRITICAL PARAMETERS IN FERMENTATION PROCESSES BY HPLC AND RAMAN SPECTROSCOPY

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The production of biopharmaceuticals includes a wide range of techniques for control of fermentation parameters during the production. Bioprocess control must overcome the challenges that arise from variability and complexity of biotech processes. Common techniques for bioprocess control include HPLC for determination of parameters such as glycerol and acetate in the fermentation media, but the major disadvantage of HPLC as control technique is that results are determined after the batch is produced, without the possibility to control and modify the feed during the process. Also, HPLC require pretreatment, manipulation of samples and is time consuming.

Raman spectroscopy emerged as a new technique for process control. By using an immersion probe to record Raman spectra directly in the fermentation media, it provides *in situ* measurements and enables real-time process control.

Kaiser Raman Rxn™ analyzer and BioProbe from Endress+Hauser were used to obtain Raman spectra directly in the media during several fermentations, parallel to the off-line HPLC analysis. Model for on-line determination of glycerol and acetate in the media from Raman spectra was created based on HPLC results as reference data.

Additional fermentation batch was used for validation of Raman spectra model. Amount of glycerol and acetate in the media was independently determined by both off-line HPLC method and in-line Raman spectra model. It proved that results obtained by the Raman spectra are accurate and precise, with the additional benefit of real-time process monitoring which allows fine-tuning of process parameters in order to increase the yield of final product.

# THREE ELECTRODE ELECTROCHEMICAL INVESTIGATION OF DIFFERENT SALT/SOLVENT ELECTROLYTE COMBINATIONS IN A SYMMETRICAL CARBON/CARBON DOUBLE LAYER SUPERCAPACITOR

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To grasp a clear image of the processes inside a supercapacitor, their effect on cell performance and the contribution of both the positive and negative side, it is of great importance to perform simultaneous measurements on both sides using a three electrode setup.

Therefore, such measurements were performed on a double-layer carbon/carbon supercapacitor assembled in a three-electrode sandwich cell design. Sixteen different combinations of salts and solvents were used to prepare the electrolytes – four salts (tetraethylammonium tetrafluoroborate, tetrabutylammonium tetrafluoroborate, tetraethylammonium hexafluorophosphate and tetrabutylammonium hexafluorophosphate) and four solvents (acetonitrile, dimethyl sulfoxide, dimethylformamide and propylene carbonate). Constant current charging/discharging, cyclic voltammetry and electrochemical impedance spectroscopy techniques were employed for testing.

As shown in our previous work<sup>[1]</sup> the impedance measurements are affected by asymmetries in the cell design and show predictable artefacts in single electrode measurements. Whole cell measurements show to be qualitatively and quantitatively comparable to the sum of the single electrode results which confirms the validity of the measurements.

The results of DC measurements did not show sensitivity to cell design asymmetries and provide valuable insight to the applicability of certain solvent-salt combinations for their use as supercapacitor electrolytes.

Simultaneous measurements of both the anode and cathode side allowed us to observe the differences in the performance of individual electrolyte combinations and their applicability in supercapacitors.

**Acknowledgments.** The support of Croatian Science Foundation under the project ESUP-CAP (IP-11-2013-8825) is greatly acknowledged.

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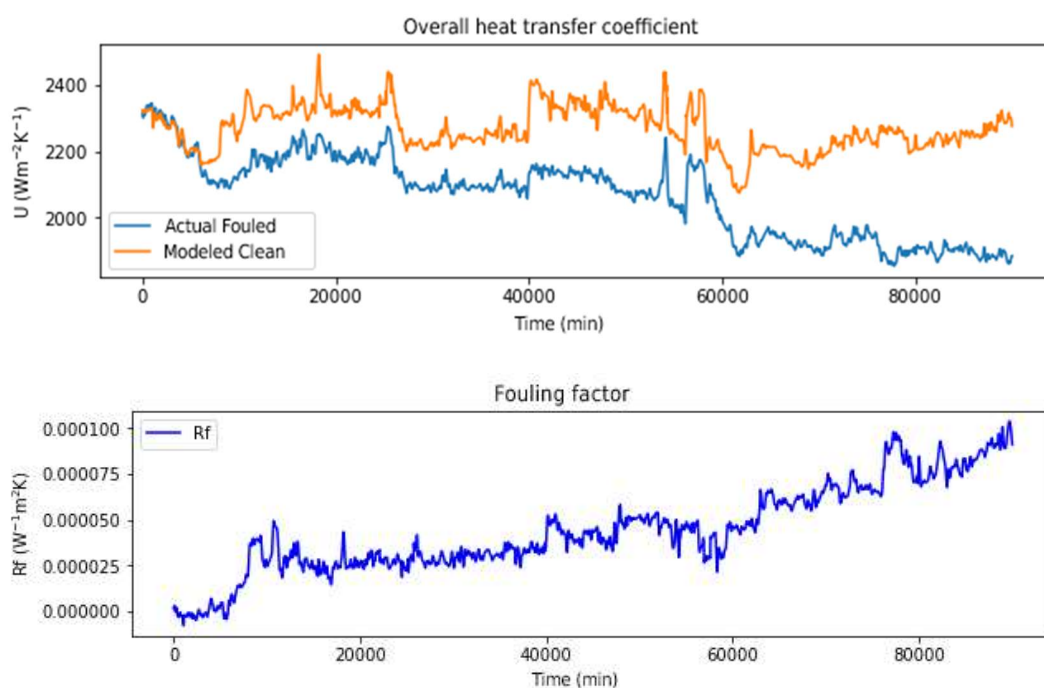
## FOULING DETECTION IN INDUSTRIAL HEAT EXCHANGER USING RECURRENT LSTM NEURAL NETWORK MODEL

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There is a need of continuous detection of fouling formation due to its side effects to the process. Fouling formation in heat exchangers is one of major problems in oil refinery which significantly impacts mechanical and thermal characteristics of heat exchangers. Corrosion and increased pressure drop, as well as lower heat transfer are one of main fouling side effects which lead to production losses and additional energy costs.<sup>[1]</sup> Also, real plant processes operate in dynamic conditions with frequent process regime changes making fundamental models difficult to develop, therefore require more complex methods.<sup>[2]</sup> Machine learning models which do not give physical insight into the process mechanisms but describe input-output variable relations can be developed and used.<sup>[3]</sup> In this work, model for fouling detection based on Long-Short Term Memory recurrent neural network is presented. LSTM recurrent neural network is capable learning order dependence in sequential data like time dependent data continuously acquired from industrial heat exchanger. Number of steps into data history and its impact on model results was examined. Various optimizers and activation functions of LSTM network were examined during model training and testing to give optimal results. Model is developed in *Python* programming language using *Keras* library on continuously acquired data from industrial heat exchanger. Model results show its possibility to determine fouling in examined oil refinery heat exchanger.



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## OPTIMIZING THE EXTRACTION OF POLYPHENOLS FROM PLANTAIN LEAVES

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Polyphenolic compounds found in plants can be easily extracted and used as valuable antioxidant in cosmetic and pharmaceuticals products. Their big positive impacts on human health are the reason for the recently significant increase in research revealing new positive effects. As it mentioned before solid-liquid extraction is one of the most efficient method for polyphenolics separation and deep eutectic solvents (DESs) which have received much attention in modern green chemistry is the best candidate to use as solvents.

Generally, DES can be prepared by mixing different natural products and in this study, it is composed of cosmetics-compatible components (mixture of glycerol and other natural compounds) and applied as solvents for polyphenol extraction from dried plantain leaves at ambient operating conditions.

Since the most of the prepared DESs have very high viscosity which influence the ability of mixing and therefore polyphenols extraction, it is required to add certain amount of water in DESs. The addition of 10 wt % of water in investigated DESs, mostly improves polyphenol extraction while 70 wt% of water decreases concentration of polyphenols in DES after extraction.

Among the seven prepared DESs the one with the best extraction efficiency was chosen for the further investigations. It is prepared from lactic acid, fructose and glycerol, in a molar ratio of 2: 1: 2 (La Fru Gly 2: 1: 2).

Different extraction methods were applied for the polyphenols separation with La Fru Gly 2: 1: 2. The highest concentration of polyphenols was obtained by extraction with a magnetic stirrer, while the shortest time to reach equilibrium is achieved by ultrasonic assisted extraction using an ultrasonic probe.

The toxicity of DES was tested on a clove of garlic in a La Fru Gly diluted with water (10, 30 and 70 wt%) in duration of 60 days. In addition, the diffusion coefficient and the mass transfer coefficient of the substance from plantain leaves were determined using the selected solvent.

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## DEGRADATION OF POLYETHYLENE AND POLYPROPYLENE MICROPLASTICS BY ADVANCED OXIDATION PROCESSES

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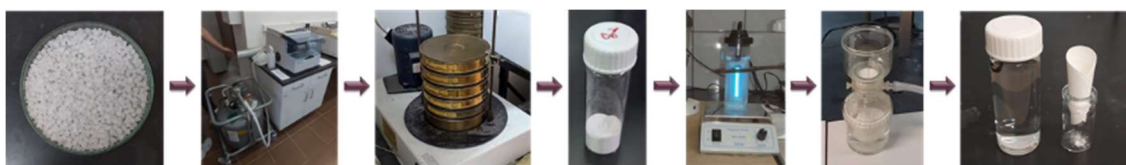
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Plastic, due to its many advantages, is an inevitable material in everyday lives. Production and utilization are growing daily, and consequently, these types of materials are accumulating in the environment. Plastic particles smaller than 5 mm, called microplastics (MP), pose a major threat to aquatic organisms. MP can cause different harmful effects on various organisms.<sup>[1]</sup> Since classical removal methods are not effective enough, the use of advanced oxidation processes (AOPs) to degrade MP has recently been considered.<sup>[2]</sup> In this paper, two AOPs were conducted: UV-C/H<sub>2</sub>O<sub>2</sub> and UV-C/S<sub>2</sub>O<sub>8</sub><sup>2-</sup>. Tested MP were polyethylene (PE) and polypropylene (PP), with particle sizes between 25 and 100 μm. The influence of pH value, MP mass, oxidant concentration, and process duration was investigated. The results indicated that UV-C/S<sub>2</sub>O<sub>8</sub><sup>2-</sup> had a greater impact on both used MP.



**Figure 1.** Schematic overview of the experiment.

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## GASIFICATION OF SEWAGE SLUDGE AS A SUSTAINABLE CIRCULAR ECONOMY PERSPECTIVE

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Sewage sludge (SS) is a by-product of wastewater treatment that needs to be further processed. There are numerous processes for treating SS, and nowadays much attention is paid to the gasification process. Gasification of SS produces synthesis gas or syngas, and the sewage sludge ash (SSA) remains as a non-hazardous waste that needs to be disposed of properly. In this paper, the gasification of SS is studied in a semi-industrial pilot plant consisting of a rotary reactor. The gasification process was preceded by drying the SS in an integrated tubular rotating structure with built-in worm conveyors, to increase the dry matter (DM) content in the SS (>90 wt%). The released hydrogen-rich syngas from the gasification process of SS has calorific value of approximately 8830 kJ/Nm<sup>3</sup> (equal to 2.45 kWh / Nm<sup>3</sup>) due to the high content of combustible gases H<sub>2</sub> (41.5 vol%) and CH<sub>4</sub> (3.2 vol%). The paper also investigates the incorporation of SSA generated in the process of gasification as a partial substitute for clay. In the production of clay bricks, 5 wt% of clay was replaced by SSA. The obtained results show that the use of SSA in the construction industry is feasible and justified. By incorporating SSA at 5 wt%, the new brick product achieves 7.5 % higher compressive strength compared to the control brick.

**Keywords.** sewage sludge, gasification, syngas, SSA, brick production, circular economy

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## PHOTOLYSIS OF *N*-NITROSODIPROPYLAMINE, MEBENDAZOLE AND CLOTHIANIDIN IN DRINKING WATER

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Industrialization, urbanization, intensive population growth and accelerated lifestyle consequently lead to an increase in the consumption of pharmaceuticals, pesticides and other xenobiotics. Xenobiotic substances and their degradation products after application end up in surface waters, but also in groundwater, soil, and even in drinking water. However, their interactions in the ecosystem are not fully known, nor are the transformations, persistence or degradability of pharmaceuticals and metabolites and should be investigated.<sup>[1,2]</sup>

Therefore, the photolytic process of elimination of pesticides (clothianidin), antiparasitics (mebendazole) and *N*-nitrosodipropylamine (NDPA) in the aquatic environment was studied in this paper with the aim of examining the fate and impact on the environment and ecosystem. The effect of one component solutions, binary solutions and ternary solution of clothianidin, mebendazole and NDPA on *Vibrio fischeri* as a rapid indicator of toxicity was examined (ISO 11348-3: 2007). Photolytic degradation by artificial sunlight over 5 hours showed that all three components were photosensitive. Clothianidin achieved 98.54 % ± 0.31 % removal after 5 hours, 100 % removal of NDPA was achieved after only 20 min, while removal of mebendazole was 49.69 % ± 7.42 %. Photodegradation of mebendazole resulted in the formation of a new transformation or degradation compound. Toxicity was studied with *Vibrio fischeri* before and after photolysis. It was shown that the inhibition of the ternary solution is greater than the inhibition of single and binary solutions and that there is a significant increase in the same after 5 hours of photolysis. The formation of a new compound during photolytic degradation indicated the need for further experiments to identify the newly formed compound.

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## REMOVAL OF *N*-NITROSODIPROPYLAMINE, MEBENDAZOLE AND CLOTHIANIDIN FROM DRINKING WATER BY REVERSE OSMOSIS

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Excessive use of fertilizers and pesticides, as well as uncontrolled discharges of industrial effluents and domestic wastewater, has resulted in elevated concentrations of pollutants in source water. In addition, wastewater chemicals and chemicals added during drinking water treatment can produce numerous disinfection byproducts such as *N*-nitrosamines, which have been classified as "probable human carcinogens." In addition, pesticides and pharmaceuticals containing secondary or tertiary amines or carbamate moieties are also known precursors of *N*-nitrosamines.<sup>[1,2]</sup>

In this study, clothianidin (CLO), mebendazole (MEB) and *N*-nitrosodipropylamine (NDPA) were selected as representatives of pesticides, pharmaceuticals and *N*-nitrosamines, respectively. The removal of NDPA, MEB and CLO was investigated using four commercial nanofiltration membranes (NF, NF-DL, NF270, NF90) and one reverse osmosis membrane (XLE). All experiments were performed in a laboratory setup consisting of six stainless steel membrane units connected in series. Furthermore, the operating pressure in all experiments was 10 bar. The rejection of selected compounds was compared in single component, binary and ternary solutions. The concentration of the selected compounds in the permeate was determined by HPLC-DAD. The highest rejections were obtained with XLE and NF90 membranes, which showed rejection rates of >90 % and >89 %, respectively for all the compounds studied. The rejection values of NDPA and CLO increased in binary and ternary solutions compared to the single component solution i.e. the rejection increased up to 7 % and 20 % for NDPA and CLO, respectively. These significant variations in the rejection of NDPA and CLO suggest the existence of a synergistic effect of membrane rejection mainly due to size exclusion and adsorption of MEB on the membrane surface.

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## ENHANCEMENT OF SOLAR DRIVEN DEGRADATION OF CIPROFLOXACIN BY PHOTODEPOSITED FE ONTO ISO-TYPE HOMOJUNCTION BiVO<sub>4</sub> SURFACE

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The presence of antibiotics in the environment may threaten both humans and wildlife because of their resistance and chronic toxicity. Ciprofloxacin (CIP) is one of the antibiotics included in the European Commission's Watch list which should be concerned for removal from groundwaters. Among the various strategies, the solar driven photocatalytic process using semiconducting materials seems to be one of the effective methods to remove antibiotics from aqueous solutions. In this research, a series of transition metal Fe-modified BiVO<sub>4</sub> materials were synthesized employing photo-deposition technique using different amounts of iron. The as-prepared materials were characterized via FTIR, XRD, SEM, UV-vis DRS and electrochemistry measurements. Photoelectrochemical properties of materials showed that photo-deposited iron (nano)particles are markedly beneficial for reducing e<sup>-</sup>/h<sup>+</sup> recombination in synthesized iso-type homojunction BiVO<sub>4</sub>. The photocatalytic activity of as-prepared materials was examined by monitoring the degradation of ciprofloxacin (CIP) as a model organic pollutant under solar irradiation within different pH range (4 to 8) employing Fe-BiVO<sub>4</sub> with different Fe content photo-deposited (1 to 15%) and compared to that of pristine iso-type homojunction BiVO<sub>4</sub>.

## DETERMINATION OF CARBOHYDRATES IN ATMOSPHERIC PARTICULATE MATTER BY HIGH-PERFORMANCE ANION-EXCHANGE CHROMATOGRAPHY WITH PULSED AMPEROMETRIC DETECTION

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The presence of carbohydrates in atmospheric particulate matter can be caused by various natural or anthropogenic sources. There are three main groups of carbohydrates that can be found in air aerosols: saccharides, saccharide polyols and anhydrosaccharides. Primary saccharides like glucose, fructose, manose, xylose and galactose are released from diverse micro-organisms, plants, and animals, while saccharide polyols, also denoted as sugar alcohols like erythritol, sorbitol, arabitol and manitol are produced by fungi, lichens and bacteria. On the other hand, anhydrosaccharides (levoglucosan, manosan and galactosan) are formed during biomass burning where cellulose and hemicellulose thermal decomposition occur. Until recently, the most common method for carbohydrate analysis was gas chromatography-mass spectroscopy; however, due to a demanding sample preparation the simpler and less time-consuming method of high-performance anion-exchange chromatography with pulsed amperometric detection (HPAEC-PAD) is preferred. In the HPAEC-PAD method, the carbohydrates are ionized in the presence of a strong base eluent, separated via anion-exchange mechanism and then oxidized at the gold electrode during the pulsed amperometric detection step.

Because of the high  $pK_a$  values of carbohydrates, the separation of some saccharide alcohols and anhydrosaccharides can be challenging, so in order to obtain an acceptable separation resolution and retention time, the eluent concentration, column temperature and sample preparation procedure must be optimized. The aim of this paper was to develop analytical methods for analysis of twelve carbohydrates: erythritol, xylitol, sorbitol, arabitol, mannitol, manose, glucose, galactose, fructose, levoglucosan, manosan and galaktosan by HPAEC-PAD. The developed methods were validated through the estimation of the selectivity, linearity, limits of detection and quantification, repeatability, reproducibility, stability and matrix effects. Results confirmed the suitability of developed methods for routine analysis of carbohydrates in atmospheric aerosol samples.

## SPATIAL DISTRIBUTION OF POLYCYCLIC AROMATIC HYDROCARBONS IN THE AIR OF ZAGREB DURING WINTER

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Polycyclic aromatic hydrocarbons (PAHs) bound to airborne particulate matter are a group of organic compounds of significant interest with regard to human health. They generally occur as complex mixtures and products of incomplete combustion processes originating from natural and anthropogenic sources. One important source of PAHs are vehicle exhaust gases and domestic heating, which explains their usually high concentrations in winter. Benzo(a)pyrene (BaP) is the most widely studied PAH and is often used as an indicator of carcinogenic hazard in polluted environments. In this study, PM<sub>10</sub> samples (particulate matter with a diameter < 10 μm) were collected simultaneously at eight measuring sites in Zagreb, with different environmental conditions. 24-hour samples were collected on quartz filters from about 55 m<sup>3</sup> of air over 30 days in winter. The measuring sites were located in the west (site A and B), east (site C), north (site D), south (site E), south-east (site F and H) and center (site G) of Zagreb. The analysis of the PAHs was performed using an Agilent Infinity 1260 high-performance liquid chromatography (HPLC) with a fluorescence detector and programmed changes in excitation and emission wavelengths. There were no statistical differences for PM<sub>10</sub> mass concentrations between the measuring sites. For most of the PAHs, a statistically significant difference was not found between the sites, except for fluoranthene and pyrene at sites D and H, and for fluoranthene at sites E and H and sites E and F. Also, a statistically significant difference was found for mass concentrations of dibenzo(a,h)anthracene between site G and E. The highest average mass concentrations of BaP were measured at site H (3,725 ng m<sup>-3</sup>), while the lowest average mass concentrations were recorded for site C (1,897 ng m<sup>-3</sup>). The results show elevated PAH concentrations at all locations during winter, without significant differences in their levels between sites.

**Acknowledgments.** The measurements were carried out within regular national and local (City of Zagreb) air quality monitoring networks (sites D, E, G and H), and within the programme “Ecological map of the City of Zagreb” (sites A, B and C), funded by the City Office for Economy, Energetics and Environment protection and Environmental Protection and Energy Efficiency Fund

## ALGAL MOTILITY AS AN INDICATOR OF ENVIRONMENTAL STRESS

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The increasing instability of climate dynamics, caused by pervasive anthropogenic pressures, demands profound ecosystem management through environmental protection and sustainable development. The most widely used environmental indicator for monitoring climate change is temperature, while heavy metals such as cadmium reflect anthropogenic activities. Nowadays, there is a high need to use a parameter for direct and high-throughput analysis of the behavior of intact cells in aquatic samples. This study aims to investigate the potential of cell motility as a direct indicator of environmental stress using two flagellated green algae that differ in cell barrier and flagellar system morphology. The open-source image processing software was used to quantitatively characterize changes in motility behavior in terms of swimming speed and search radius based on video data acquisition. The results showed that the change in growth temperature from favorable conditions caused a decrease in swimming speed and search radius of the two green algae studied. Moreover, the presence of heavy metal cadmium in the growth medium caused a decrease in the swimming speed and search radius of species possessing a soft cell envelope in contrast to species with a rigid cell envelope. Thus, the response of algae to stressors in batch culture appears to be species-specific, with cell morphology contributing to stress tolerance. Algal cells with soft glycocalyx membranes appear to be more sensitive to temperature and heavy metals than cells encased in a stiffer calcite theca. Concurrent studies revealed concomitant changes in algal cell surface properties and physiological activity when exposed to the corresponding stressors, which contributes to the understanding of motility behavior at the single-cell level.<sup>[1,2]</sup> Based on the presented results, the changes in algal motility may be used to indicate disturbances in the aquatic system and serve for monitoring needs.

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## TROPOSPHERIC PHOTOSMOG POLLUTION IN DUBROVNIK FROM 2015 TO 2017

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Elevated ozone levels are one of the major causes of the known health and pollution problems in the world.<sup>[1]</sup> Tropospheric ozone is a constituent of photosmog which is formed from the precursors especially in the periods of high insolation. Photosmog causes respiratory problems for the whole biota, both in flora or fauna including humans. On the other side, Dubrovnik is the worldwide known seaside touristic destination with lots of sunny days. Because of that, it is potentially prone to photosmog formation since high levels of traffic, especially by airplanes and cruiser ships, can elevate levels of NO<sub>x</sub> and particulate matter which are known precursors for ozone formation. Although our research does not show that any major long-term negative influence is observable yet, at least for the initial period between 2015 and 2017, some highly elevated maxima values of all previously mentioned air components are the reason for concern and further observation. Our research confirms other tropospheric ozone assessment, including the modelling results, applicable on this part of Europe.<sup>[2]</sup> Since tourism and with tourism connected increase of traffic is, by far, the major contributor to local air pollution in the area, and since the same is true for the majority of southeastern Adriatic coast, these findings may be helpful in assessing situation there.

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## BIOREMEDIATION OF WATER POLLUTED WITH PS AND PVC MICROPLASTICS BY BACTERIA *Bacillus cereus* AND *Pseudomonas alcaligenes*

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Microplastics are considered as particles lower than 5 mm and are ubiquitous in the environment.<sup>[1]</sup> Due to the fact that microplastics are present in the environment, different effects on aquatic organisms may occur. Accordingly, ecotoxicological studies are performed with various testing organisms such as algae, *Daphnia magna*, *Danio rerio*, fishes etc.<sup>[1]</sup> However, a lot of processes, physical, chemical and biological, have been investigated in the purpose to remove the microplastics from the environment.<sup>[2]</sup> Bioremediation is environmentally acceptable and economical treatment that can be used in the mentioned purposes. In this study, biodegradation of polystyrene (PS) and polyvinyl chloride (PVC) by bacteria *Bacillus cereus* and *Pseudomonas alcaligenes* were investigated. Experiments were performed according to Taguchi design. The influence of seven factors - pH-value, temperature, size of microplastic particles, concentration of microplastics, agitation speed, optical density of bacterial suspension, and addition of glucose, were examined. According to the CFU values, higher biodegradation rate was noticed for *B. cereus* in comparison with *P. alcaligenes*.

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## PREDICTIVE QUANTITATIVE STRUCTURE–PROPERTY RELATIONSHIP (QSPR) AND RESPONSE SURFACE MODELING FOR ADSORPTION PROCESSES OF CONTAMINANTS OF EMERGING CONCERN IN WATER ONTO TiO<sub>2</sub>

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Presence of contaminants of emerging concern (CECs) in the aquatic environment has raised strong concerns due to their potential bioaccumulative and toxic characteristics. Photocatalytic treatment may ensure their complete removal or at least partial degradation forming less toxic and more biodegradable structures. In order to achieve significant degradation of CECs, adsorption on the photocatalyst surface is one of crucial steps. However, adsorption interactions and structure dependence are still scarce in the literature.

This study present combined modeling performance, employing response surface methodology (RSM) and quantitative structure–property relationship (QSPR) approaches to simulate adsorption processes of CECs. Adsorption experiments of 30 selected CECs were performed on TiO<sub>2</sub> in suspension system, employing pH values ranging from 4 to 10, TiO<sub>2</sub> mass concentrations from 0.4 g/L to 1.2 g/L and constant (room) temperature (i.e. 25 °C). The removal extents of selected CECs during adsorption experiments were monitored by HPLC. Adsorption constants (K) were calculated for each CEC at experimental points set by 3<sup>2</sup> full factorial design (FFD). Quadratic polynomial equations (QPE) were derived for CEC using parameter K as a system response. In addition, the coefficients in QPE were used as responses in QSPR modeling to establish dependence of the structural features of studied CECs and adsorption phenomena onto TiO<sub>2</sub> surface occurred.

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## IMPACT OF LIGHT POLLUTION

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Any change in the level of natural light at night caused by the introduction of artificial light sources constitutes light pollution. Our window to the universe is increasingly threatened by light pollution, from street lighting, through various advertising lighting fixtures, to light coming from sources like smartphones and other gadgets without which life today is unthinkable. Preserving our nighttime environment is a global issue which requires extreme attention worldwide. The ecological consequences of artificial night lighting, they become profound and they must not be neglected.

Today, as we strive to regain a quality of life; let us realize that with modernization and economic progress, we have set light pollution as a prominent environmental problem.<sup>[1]</sup> We forget that our grandparents appreciated the richness of plant and animal life around them during the day and night. Today, we turn night into day. The problems caused by excessive light scattering are ecologically very important because they cause the extinction of entire populations of nocturnal birds, turtles, impedes the ecological balance of wildlife also causes harmful changes in plant species, as well as and leads to an increase disorders in human health.<sup>[2]</sup>

This paper provides an overview of the impact of light pollution, where we are today and what we can do for future.

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## TRENDS OF POLYCYCLIC AROMATIC HYDROCARBONS IN PM<sub>10</sub> PARTICLE FRACTION IN ZAGREB FROM 2016 TO 2020

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Polycyclic aromatic hydrocarbons (PAHs) are organic compounds primarily associated with fine particles that originate mainly from incomplete combustion of organic materials. PAHs are highly investigated because of their mutagenic and carcinogenic potential. One of the most widely investigated PAHs is benzo(a)pyrene (BaP) which has been classified as carcinogenic to humans (Group 1) by International agency for research on cancer. The Regulation on levels of pollutants in the air (Official Gazette 117/2012) sets a target value of 1 ng/m<sup>3</sup> for annual average BaP concentration in PM<sub>10</sub> particle fraction. The aim of this study was to determine mass concentrations of ten PAHs of environmental interest in order to assess the contribution of BaP in total PAHs and to examine their five-year period trends. Twenty-four-hour samples of PM<sub>10</sub> particle fraction were collected in the northern, residential part of Zagreb from approximately 55 m<sup>3</sup> of ambient air on quartz filters from 2016 to 2020. The following PAHs were analyzed by liquid chromatography (HPLC) with a fluorescence detector and programmed changes in excitation and emission wavelengths: fluoranthene (Flu), pyrene (Pyr), benzo(a)anthracene (BaA), chrysene (Kri), benzo(b)fluoranthene (BbF), benzo(k)fluoranthene (BkF), benzo(a)pyrene (BaP), dibenzo(a,h)anthracene (DahA), benzo(ghi)perylene (BghiP), and indeno(1,2,3-cd)pyrene (IP). The average sum of ten measured PAHs ranged between 6.570 ng/m<sup>3</sup> (in 2019) and 14.832 ng/m<sup>3</sup> (in 2016) showing significantly decreasing trend. The same decreasing trend was observed for all measured PAHs, except for DahA. However, the values of all ten studied PAHs in 2020 were higher compared to 2019. The average annual BaP values ranged between 0.950 ng/m<sup>3</sup> (in 2019) and 1.347 ng/m<sup>3</sup> (in 2016). The average BaP contribution in the sum of PAHs showed an increasing trend from 9.9 % in 2016 to 14.4 % in 2020, contrary to BaP mass concentrations. The same increasing trend was also observed for BaA, BbF, BkF and IP contributions in the total sum of PAHs. Only Flu contribution (from 9.8 % to 4.8 %) and Pir contribution (from 10.7 % to 4.8 %) displayed significantly decreasing trend during the investigated five-year period.

## PHOTOCATALYTIC BEHAVIOR OF ANTICANCER DRUGS: KINETIC STUDY AND TOXICITY ASSESEMENT

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Drinking water supplies and water quality are increasingly affected by the presence of various classes of, until recently undetectable, micropollutants, including pharmaceuticals as one of the most important emerging environmental contaminants. One subcategory of pharmaceuticals that can enter and cause problems in various water resources through many pathways (hospital effluents, sewage systems) are anticancer drugs. Due to their physicochemical properties leading to mobility and persistence in the aquatic environment, many of these substances with their metabolites can cause side effects on various organisms. It should also be noted that such components are often transformed or degraded by various biotic and abiotic processes, which may lead to the formation of more polar and toxic products compared to the parent drug. The elimination of small molecules by standard wastewater treatment is not efficient, so photocatalysis is often used to remove pharmaceuticals from water by generating reactive species. The aim of this research was to investigate the photocatalytic activity of imatinib and crizotinib, two anticancer drugs used in patients with leukemia and lung cancer, respectively. TiO<sub>2</sub> immobilized on a glass fibers mesh was used as the photocatalyst. To obtain optimal process parameters for the removal of pharmaceuticals from the synthetic waters, the mutual influence of the micropollutant initial concentration under environmentally relevant pH values was investigated using the software Design-Expert. Toxicity evaluation was also investigated.



**Figure 1.** Graphical description of experiment

**Acknowledgments.** Authors would like to thanks to Igor Jajčinović and Ivan Brnardić for the preparation of TiO<sub>2</sub> catalyst.

## DYNAMICS OF ORGANIC MATTER IN ROGOZNICA LAKE AS AN INDICATION OF GLOBAL CHANGE

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Global i.e. climate change cause the change in the characteristics and concentration of organic matter (OM) in marine system, which can lead to eutrophication. Those changes can be detected by measuring dissolved (DOC) and particulated (POC) organic carbon, as well as their surface-active fractions (SAS).<sup>[1]</sup> In seawater, OM is a complex mixture of dissolved and particulate organic compounds (proteins, carbohydrates, lipids, humic and fluic acid), with different surface-active properties.<sup>[1]</sup> The boundary between dissolved and particulated fraction of OM is 0.7  $\mu\text{m}$ , and these fractions are separated by filtration. DOC passes through filter, and represents relatively simple molecules from decomposing materials, supporting growth of microorganisms and plays an important role in the global carbon cycle through the microbial loop.<sup>[2]</sup> POC is collected on the filter, and retains evidence of its original cellular structure such as phytoplankton, zooplankton, larvae or detritus. POC is important for vertical transport of OM through the water column, being a link between surface primary production, the deep ocean, and sediments.<sup>[3]</sup> The OM (SAS) in the sea is mainly autochthonously produced by biological activity (primary production, releases of secondary metabolites under feeding pressure), while part of OM can also be allochthonously introduced (terrestrial and atmospheric origin).

The Rogoznica Lake (RL) is a good study-site for monitoring of OM related to global change RL is an isolated and unique marine environment on the eastern shore of the Adriatic Sea (43°32'N, 15°58'E), with strong eutrophic and euxinic (free sulfide in the water column) characteristics.<sup>[4]</sup> Due to its relative isolation (weak connection with the sea through the porous carst), small volume and stable stratification, RL allows the study of OM variability on a small spatial and time scales. The chemistry and biology of this system has been studied since 1990,<sup>[4]</sup> what is now very relevant as long-term research in context of climate change. Since the early 1990s, the volume of the anoxic layer has increased by 4-5 times. Consequently, we noticed a trend of DOC accumulation in the bottom-anoxic layer, while its concentration is decreasing through the oxic-surface layer (0-5 m depth). In the same time SAS is increasing in the oxic surface layer and decreasing in the anoxic bottom layer, indicating certain changes in the quality of the DOC, i.e. OM in general. Furthermore, there is a evidence for POC accumulation through the water column, and an increase in the proportion of POC in the fraction of total organic carbon (TOC). On a long-term scale (1992-2021) this study will show a noticeable change in the quantity and quality of the OM in RL water column as an indication of the pronounced eutrophication probably affected by global change.

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## COMBINED THERMAL - AND UV - DEGRADATION OF POLYETHYLENE TEREPHTHALATE - CHARACTERIZATION OF AGED MATERIAL

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Increasing pollution from microplastics (MPs), i.e. polymer particles smaller than 5 mm, is one of the most recent environmental concerns worldwide. A study has shown that approximately 0.4 particles of microplastics per 1 L can be detected in the environment.<sup>[1]</sup> Among detected MPs polyethylene terephthalate (PET) is very common. Degradation due to weathering and aging of commercial PET is inevitable despite anti-UV and anti-hydrolysis additives. Degradation of PET leads to change in micro- and macro-scale properties.<sup>[2]</sup> The aim of this work was to establish the nature and extent of changes which occurred in samples of shredded PET bottles (PET/B/C) and commercial films (PET/F/C) during cyclical exposure to thermal and hydrolytic degradation, namely: (i) at 70 °C for 18 hours without moisture addition, (ii) -18 °C for 2 h without moisture addition and (iii) at 70 °C with moisture. The cycles were repeated for 14, 28 and 42 days. Furthermore, the effects of UV aging on shredded bottles (PET/B/UV) and films (PET/F/UV) during periods of 14, 28 and 42 days were investigated. The UV degradation experiments were carried out in a Suntest CPS (Heraeus, Germany) solar simulator. The samples were characterized by the following methods: Fourier-transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), contact angle and differential scanning calorimetry (DSC). The experimental results indicate that there is little to no change in the structure of the thermally aged samples in comparison to the UV-aged samples in which structural changes are more obvious.

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## INHIBITION OF *Bacillus subtilis* GROWTH BY FLUORINATED PYRAZOLE DERIVATIVES

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There are many useful biological properties of pyrazole and its derivatives and they are used in the pharmacy and agrochemical industry, in plant protection products in the form of insecticides and fungicides. Fluorinated 4,5-dihydro-1H-pyrazole derivatives represent a series of potential new drugs whose antibacterial properties are already being documented. These compounds as also potential new pesticides, and this study aim to determine their impact on the beneficial bacterial soil population. The obtained results determined that a series of tested pyrazole derivatives had no antibacterial inhibitory effect on the tested gram-positive bacterium *Bacillus subtilis*. This research result is very promising since *B. subtilis* is a representative of the beneficial bacterial soil population with an important role in soil phosphorus solubilization, siderophore production, plant hormone biosynthesis, and belongs to the group of plant growth - promoting rhizobacteria. Further research is needed which should clarify the impact of these pyrazoles on the growth of other beneficial representatives of soil microorganisms.

## APPLICATION OF RED MUD IN GEOPOLYMER TECHNOLOGY

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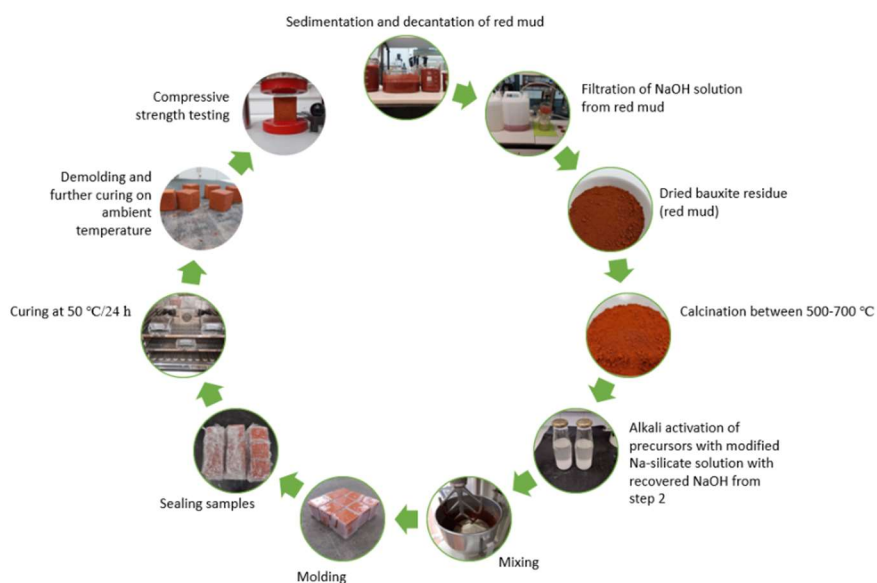
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Cement respectively concrete is the most commonly used building material. Accordingly, the global demand for cement, from year to year, is growing. After fossil fuels and the conversion of green areas (e.g. logging), cement production is considered to be the third largest source of anthropogenic carbon dioxide emissions.<sup>[1]</sup> Today and in the future a major challenge is to align human activities on earth with the key pillars of environmental management, sustainability and preservation of life forms. With the aim of reducing the impact of Portland cement on the environment respectively the impact of CO<sub>2</sub> on the environment and the desire to recover large amounts of waste inorganic (aluminosilicate) material - today, science and industry are increasingly turning to alternative aluminosilicate binders such as geopolymers. Red mud or bauxite residue is a by-product of bauxite ore processing in the Bayer process for alumina production (Al<sub>2</sub>O<sub>3</sub>) and as such is considered technological waste. Due to its dangerous corrosive nature, *pH* = 10.5 – 12.5, red mud is a very serious and alarming environmental problem.<sup>[2]</sup> It is estimated that approximately 150 million tonnes of red mud is produced annually worldwide; of which 5 – 6 million tonnes are generated in Europe, and most of this waste is disposed of in open landfills.<sup>[3]</sup> In this paper, the possibility of application of red mud in geopolymer technology is investigated. Compressive strength of geopolymer material was used as the main parameter of successful geopolymerization and successful application of red mud. Also the influence of the calcination temperature (105, 500, 600 and 700 °C) of bauxite residue and water to binder ration on the compressive strength of geopolymers was investigated.

**Keywords.** red mud, bauxite residue, geopolymer, compressive strength



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## COMPARISON OF TOXICITY TESTS FOR MICROPLASTIC USING FRESHWATER MICROALGAE *Chlorella* sp. AND *Scenedesmus* sp.

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Pollution of aquatic ecosystems by plastics with a particle size <5 mm, or microplastics, is becoming a global problem. This presents a threat to aquatic organisms but also to other organisms due to the possibility of transmission through trophic levels. The toxic effects of these particles have been partially proven, but a large part is still unexplored. Microalgae, as primary producers, are at the bottom of the trophic chain in the aquatic ecosystem. They are often used as tested organisms in various ecotoxicological studies. In this study, the toxicity of microplastics: polyethylene (PE), polypropylene (PP), polystyrene (PS), poly (vinyl chloride) (PVC) and poly (ethylene terephthalate) (PET), has been observed on freshwater microalgae *Chlorella* sp. and *Scenedesmus* sp. The influence of three particles sizes - 100-300, 300-500 and 500-700 µm at three different concentrations of microplastics, 50, 500 and 1000 mg/L during 72 hours was investigated. According to the results, the toxic effect of microplastics on microalgae depends on the type, concentration and particle size of the tested microplastics. The highest toxicity was observed for PE with inhibition of 12,99 % for *Scenedesmus* sp., and 8,62 % for *Chlorella* sp., followed by PS, PVC, PP and PET.

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## STRUCTURAL CHARACTERISATION OF MODIFIED BIOADSORBENTS

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Development of low-cost bioadsorbents produced from various waste biomass became the focus of many research studies due to their eco-friendly, sustainable and high efficiency removal of heavy metals, nutrients, pesticides, dyes and similar pollutants removal from water and wastewaters by adsorption.

Waste biomass obtained from agriculture or the food industry is especially interesting since those materials are usually cheap, available in large quantities during the whole year and harmless. In most cases, the adsorption capacity of those biomaterials can be increased by chemical modification.

In this study three various lignocellulosic waste biomass produced by food industry: pumpkin peel, cocoa bean shell and sunflower shell were chemically modified in order to increase adsorption capacities of named biosorbents by quaternization reaction using N,N-dimethylformamide and epichlorohydrin (ETM method). Obtained bioadsorbents and their base materials were structurally characterized in order to determine the content of following elements: C, O, N, Cl, Nb, Rh, Zr, Cu and Rb by energy-dispersive X-ray spectroscopy (EDS). The surface structures and morphology were examined using Field Emission Scanning Electron Microscope (FE SEM) while a high-resolution tool Transmission Electron Microscope (TEM) was used to analyze atomic arrangement.

**Keywords.** bioadsorbent, structural characterization, EDS, FE SEM, TEM



## A NEW APPROACH FOR STUDYING ADSORPTION PROCESSES ON SOLID ELECTRODES IN SEAWATER CONDITIONS

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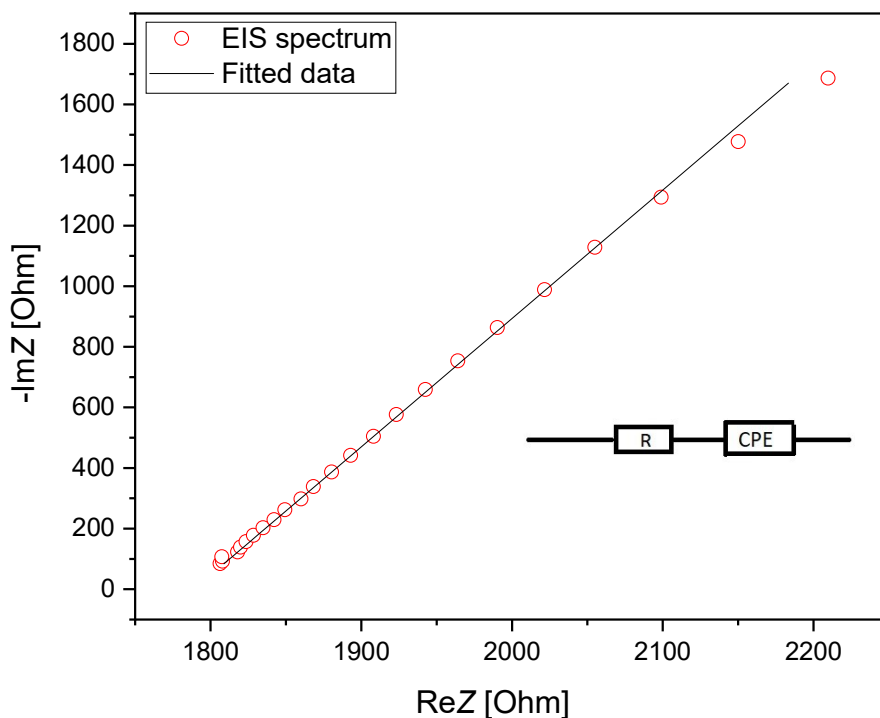
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Electrochemical detection is one of the most commonly used and still challenging approaches for studying various environmental processes.<sup>[1]</sup> Hitherto, mercury (Hg) electrodes have been usually employed for investigating critical environmental processes, both naturally and anthropogenically perturbed, that influence the ecosystem and human health.<sup>[1]</sup> Although Hg is one of the most suitable electrode materials for such environmental studies, partially because of the homogeneity and reproducibility of its surface and partially because of its wide cathodic potential window, the current trends in “green” chemistry preclude the use of toxic substances.<sup>[1]</sup> Accordingly, the recent EU regulation confined the use, storage, and export of metallic Hg, which have led to the search for new environmentally friendly electrode materials with similarly favorable electroanalytical characteristics as those of Hg.

One of the desirable properties of the Hg electrode is the ability to study adsorption processes on its hydrophobic surface.<sup>[1,2]</sup> The adsorption process can be represented with simple equivalent electrical circuits when using electrochemical impedance spectroscopy (EIS)/ AC voltammetry. In most literature dealing with the adsorption processes on Hg electrodes, AC voltammetry is used as a primary tool. Thus, the main goal of this study is to find environmentally friendly electrode material as an alternative to Hg, where the adsorption process can be followed similarly. However, solid electrodes are characterized by a non-homogenous surface, limiting the use of AC voltammetry for adsorption studies. Therefore, a new approach needs to be introduced based on, e.g., EIS in combination with a suitable “green” electrode material for such adsorption studies.<sup>[3]</sup>

In this work, we first applied the EIS to examine the potential of zero charge (pzc) for different electrode materials, such as gold (Au), platinum (Pt), glassy carbon (GC), and bismuth (Bi) in seawater relevant conditions. After finding the pzc(s) for different electrode materials, the adsorption was studied using a model non-ionic surface-active substance such as Triton-X-100. The preliminary results show that Bi, as an environmentally friendly electrode material, is the most promising one (Figure 1), and definitely deserves further attention.



**Figure 1.** Complex-plane impedance plot of the bismuth electrode obtained in 0.55 M NaCl solution at  $E = -0.7\text{V}$  vs. Ag/AgCl. This potential is in the vicinity of the pzc.

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## LABORATORY PYROLYSIS OF BIOMASS: GAS PRODUCT ANALYSIS

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Pyrolysis is a thermal process in which materials can be degraded to useful products. Biomass is biodegradable material which has origin as waste from food and agricultural production, forestry and related industries. In pyrolysis processes biomass has high ratio of useful products to raw material. There are three main biomass pyrolytic products: synthetic gas, biooil and biochar.

In this paper, five types of biomasses were characterized in term of calorific value, CHNS and heavy metal elemental analysis: coffee, hop, mulched grass, oak sawdust and pine sawdust. Process of pyrolysis was performed for oak sawdust: 10 mg of sample was pyrolyzed for 30 seconds on 550 °C. Main pyrolysis/degradation gas products were analyzed by gas chromatography coupled with mass spectrometry, GCMS. On these process conditions, 31 % of all analyzed gases were phenols, especially 2-methoxy phenol and 4-ethyl-2methoxy phenol; 13 % were furans and volatile organic acids, 12 % ketones while less than 10% were aldehydes, nitrides and other hydrocarbons.

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## OPTIMIZATION OF BIOMASS PYROLIZATION ON LABORATORY PYROLYSIS SYSTEM

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Pyrolysis is a thermal process in inert atmosphere. In these conditions three main byproducts occur: oil, gas and char. In biomass pyrolyzation all three products occur in different proportions depending on process conditions. High biochar yield will be achieved if a low temperature and low heating rate is performed. To maximize the yield of liquid products resulting from biomass pyrolysis, a low temperature, high heating rate and short duration of process would be required. If the purpose was to maximize the yield of fuel gas, a high temperature, low heating rate, long duration of process would be preferred. One of the main disadvantages of pyrolyzation is production of dioxins and furans which are very toxic. Their formation also depends on the process conditions.

In this paper, goal is to optimize laboratory scale pyrolysis process conditions to achieve maximal biochar yield and minimal production of dioxins and furans. For this purposes oak sawdust is used as biomass material. Oak sawdust was previously characterized by ICP-MS, CHNS analyzer and calorimeter. The pyrolysis processes were performed on three temperatures: 350, 550 and 750 °C. Gas products were analyzed by GCMS system. The highest yield of biochar is on lowest temperature, as well as highest concentration of dioxins and furans. The highest temperature has almost not existing yield of biochar as well as dioxins and furans. Optimal temperature is on 550 °C.

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## LONG-TERM (30 YEARS) STUDY OF DISSOLVED ORGANIC MATTER IN THE NORTHERN ADRIATIC SEA; AN INDICATION OF GLOBAL CHANGES AND THE BIOS VARIATIONS

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Long-term data sets from freshwater, estuarine and marine ecosystems provide a unique information on complex dynamics within the ecosystems themselves, especially when they respond to anthropogenic pressure and climate change. Today, they become even more important since they play a key role in comprehensive discussions and conclusions concerning the climatic and anthropogenic pressure. The importance of long-term research in the aquatic environment is crucial for many reasons, such as: the interpretation of main processes within ecosystems, detecting the occurrence of complex conditions which might be indiscernible in short-time scale, documenting physical, chemical and biological phenomena and discovering the complexity of interactions as well as dynamics and the population ecology. Therefore, long-term research is an ideal basis for the evaluation and creation of legislation focused on environmental quality and pollution control, and monitoring and prediction of climate change.

In this paper an unique time series of dissolved organic carbon (DOC) and its surface active fraction (SAS) that were collected between 1989 and 2020 with monthly or bimonthly temporal resolution along the transect Po River delta - Rovinj in the northern Adriatic (NA) will be presented.

The organic matter (OM) shows very pronounced changes in its amount and properties.<sup>[1,2]</sup> During the investigated years the periods of high and low carbon content change may be noticed with evident changes in reactivity regarding to SAS type content. The changes indicate altering episodes of eutrophication and oligotrophication, embedded to an overall oligotrophication trend in the considered period. Observed changes on a long-term scale are dominantly due to (a) annual fluctuations of freshwater input, mainly driven by the Po River, (b) water circulation and alteration of water masses in the Adriatic Sea, being as a consequence of the Adriatic-Ionian Bimodal Oscillating System (BiOS),<sup>[1–3]</sup> and (c) unusual phenomena such as mucilaginous algal blooms, red tides, gelatinous zooplankton blooms,<sup>[4,5]</sup> which contribute to eutrophication characterized by anomalous accumulation of organic carbon in the sea.

The BiOS is responsible for advection of either highly saline ultraoligotrophic Levantine Intermediate Water from the Eastern Mediterranean or nutrient-richer less saline Western Mediterranean waters that reflects on OM amounts (DOC, SAS) and properties at different phase lags of -1 to -4 years.

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## SYNTHESIS OF FATTY ACID OCTYL ESTERS COMBINED WITH GLYCEROL EXTRACTION AND REUSE OF ACID CATALYST

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The transesterification of triglycerides is an equilibrium reaction catalyzed by base, acid or enzymatic catalysts. When fatty acid octyl esters are synthesized, the reaction mixture has one phase, unlike the synthesis of fatty acid methyl esters where methanol is not miscible with triglycerides and/or fatty acid octyl esters. The monophasic characteristic of this reaction mixture creates difficulties with the separation of glycerol and residual octanol. Transesterification with base catalysts is susceptible to the presence of free fatty acids and water in feedstocks such as waste cooking oil and waste animal fat. In this study, octanol and waste animal fat or waste cooking oil comprised one phase, while the acid catalyst (20 wt% H<sub>2</sub>SO<sub>4</sub>) is dissolved in water and represents the second phase. This way, octanol ( $\log K_{ow} = 3.00$ ) is mixed with the triglycerides, while the formed glycerol ( $\log K_{ow} = -1.76$ ) is extracted in the water phase, shifting the equilibrium towards the formation of fatty acid octyl esters. As the catalyst (H<sub>2</sub>SO<sub>4</sub>) is predominantly present in the water phase ( $\log K_{ow} = -2.20$ ), when the water phase is removed, so is most of the catalyst and glycerol. Even at full conversion, the formed glycerol represents a small percentage of the reaction mixture (4.6 wt%). Therefore, the water phase with the catalyst could be reused and the fatty acid octyl esters can be washed with water and octanol can be evaporated. This study examined the reaction kinetics (9:1 alcohol triglyceride molar ratio, 80 °C, different ratio of triglyceride/oil to water), and reusability of the water phase (with the catalyst) by adding glycerol.

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## CONTENT OF IONIC COMPOUNDS IN THE AMBIENT FINE PARTICULATE MATTER FRACTION

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Because of its negative impact on human health, the climate and environment, the fine particulate matter fraction (PM<sub>2.5</sub>) presents a prominent environmental issue and is in the center of scientific concern. The most common natural sources of PM<sub>2.5</sub> are sea spray and dust, while vehicular exhausts, shipping emissions, industrial emissions, agricultural activities and biomass burning are common anthropogenic sources. PM<sub>2.5</sub> may also be formed as secondary aerosols from gaseous precursors through heterogeneous or homogeneous chemical reactions. Therefore, the complex chemical composition of PM<sub>2.5</sub> is an outcome of the nature of the source. The aim of this study was to determine the mass concentrations of PM<sub>2.5</sub> and water-soluble anions (Cl<sup>-</sup>, NO<sub>3</sub><sup>-</sup>, SO<sub>4</sub><sup>2-</sup>) and cations (Na<sup>+</sup>, NH<sub>4</sub><sup>+</sup>, K<sup>+</sup>, Mg<sup>2+</sup>, Ca<sup>2+</sup>) in PM<sub>2.5</sub> and to investigate the possible seasonality in their levels, relations and contribution to the total PM<sub>2.5</sub> mass. During the summer and winter of 2019, at an urban measuring station located at the northern part of the Adriatic coast in the city of Rijeka, daily samples of PM<sub>2.5</sub> particle fraction were collected on PTFE filters using the Sven Leckel SEQ 47/50 low volume sampler. The mass concentration of PM<sub>2.5</sub> was determined by gravimetric method. The content of water-soluble inorganic anions and cations were determined using a capillary ion chromatograph. Determined daily PM<sub>2.5</sub> mass concentrations ranged from 1.4 µg m<sup>-3</sup> to 47 µg m<sup>-3</sup>. No significant difference in average PM<sub>2.5</sub> mass concentrations was obtained between summer and winter. The determined daily mass concentrations of ions in PM<sub>2.5</sub> particle fraction content ranged from 0 µg m<sup>-3</sup> to 11.9 µg m<sup>-3</sup>. Results show significantly higher average mass concentrations of Cl<sup>-</sup>, NO<sub>3</sub><sup>-</sup>, Na<sup>+</sup>, K<sup>+</sup>, Mg<sup>2+</sup>, Ca<sup>2+</sup> ion in PM<sub>2.5</sub> in winter in comparison with the determined average values for summer, while the higher average mass concentration for SO<sub>4</sub><sup>2-</sup> and NH<sub>4</sub><sup>+</sup> ion in PM<sub>2.5</sub> were obtained in summer. Contributions of each ion to the total PM<sub>2.5</sub> mass ranged from 0.01 % to 29.2 %. The highest contribution to the total PM<sub>2.5</sub> mass was obtained for SO<sub>4</sub><sup>2-</sup> and NH<sub>4</sub><sup>+</sup> in both seasons. The average contribution of total anion mass and total cation mass to the total PM<sub>2.5</sub> mass was 29% and 13.4% in summer and 17.4% and 9.3% in winter, respectively. The obtained seasonal variations in mass concentrations of ionic species in PM<sub>2.5</sub> and its contribution to the total PM<sub>2.5</sub> mass indicated its different air pollution sources or formation pathways present in air in each season.

## DIFFERENT PERFORMANCES OF A BULK COLLECTOR FOR THE DETERMINATION OF PAHS AND PCBs IN TOTAL DEPOSITED MATTER

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Total deposited matter includes dry and wet atmospheric deposition. For collecting deposition samples, different types of collectors can be used. The aim of this paper was to determine the influence of bulk collector performance on polycyclic aromatic hydrocarbon (PAHs) and polychlorinated biphenyl (PCBs) sampling efficiency. Two different bulk collectors were tested: an open cylindrical glass bottle with a diameter of 100 mm (BULK) and a glass bottle connected to a funnel with a diameter of 150 mm (BL). Sampling of biweekly bulk deposition samples was simultaneously performed during the BiREADI field campaign from 7 February to 10 July 2019 at the Martinska rural station located within the coastal zone of the Šibenik archipelago in the central part of the eastern Adriatic coast. The chemical analysis of 12 PAHs (fluoranthene, pyrene, benz(a)anthracene, chrysene, benzo(b)fluoranthene, benzo(k)fluoranthene, benzo(j)-fluoranthene, benzo(a)pyrene, benzo(e)pyrene, indeno(1,2,3-cd)pyrene, dibenz(a,h)anthracene and benzo(g,h,i)perylene) was performed using a gas chromatograph coupled to a tandem mass spectrometer operating in electron ionization mode (GC-EI/MS/MS). Six indicator PCB congeners (PCB-28, PCB-52, PCB-101, PCB-138, PCB-153 and PCB-180) were analyzed by gas chromatograph equipped with two micro electron-capture detectors (GC- $\mu$ ECD) and two gas chromatographic columns.

During the measurement period, the deposition fluxes ( $\text{ng m}^{-2} \text{d}^{-1}$ ) of  $\sum_{12}\text{PAHs}$  varied between 12 and 459 for BULK and from 14 to 943 for BL, respectively. Furthermore, the deposition rates ( $\text{ng m}^{-2} \text{d}^{-1}$ ) of  $\sum_6\text{PCBs}$  ranged between 9 and 44 for the BULK and from 5 to 13 for BL, respectively. The *t*-test showed a statistically significant difference ( $p < 0.05$ ) in the deposition levels of PYR, PCB-28, PCB-52, PCB-138 and  $\sum_6\text{PCBs}$  for the different bulk collector performances. For the other PAHs and PCBs, there was no statistically significant difference ( $p > 0.05$ ) in the deposition levels between the collectors. Fluoranthene, pyrene and chrysene were the major compounds detected, regardless of the performances of the bulk collectors. The largest contribution to the total mass of  $\sum_6\text{PCBs}$  came from PCB-101 in BL and PCB-153 in BULK. From these results, it can be concluded that the performance of the bulk collectors can significantly influence the reported levels of PAHs and PCBs in atmospheric deposition samples.

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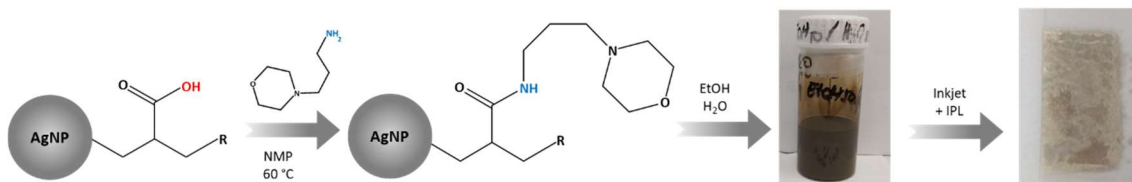
## AMPHIPHILIC SILVER NANOPARTICLES FOR INKJET PRINTED ELECTRONICS ON FLEXIBLE PLASTIC SUBSTRATES

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Inkjet printing of metal nanoparticle-based conductive inks has recently been utilized abundantly as an attractive technology to replace traditional electronics manufacturing processes. Due to their remarkable electrical conductivity, silver nanoparticles (AgNPs) are the material of choice for printed flexible electronics, but formulating inks which are stable in different solvents, meet printer requirements, and adhere well to plastic substrates remains a challenge.<sup>[1]</sup> In this work, amphiphilic AgNPs which can easily be dispersed in alcohols were synthesized. In the first step, poly(acrylic acid) stabilized AgNPs (PAA-AgNPs) were obtained by using hydrazine for silver nitrate reduction. Amphiphilic AgNPs were then prepared by modifying PAA-AgNPs with 3-morpholinopropylamine (MPA) via an amidation reaction. The stability of the AgNP suspensions in several solvents was investigated by UV-vis and zeta-potential measurements. Dynamic light scattering measurements revealed that the amphiphilic AgNPs had an average size of less than 10 nm, which did not pose a risk of clogging printer nozzles. A conductive ink formulation consisting of a 5 wt % AgNP dispersion in a 50 vol % water/ethanol mixture was selected for inkjet printing. Viscosity, surface tension and density of the ink were optimized to match the printer requirements. Multiple layers were printed on PET sheets and electrical properties of the printed films were evaluated with a four-point probe. Photonic annealing (IPL) was used to improve the film conductivities, achieving sheet resistances below 1  $\Omega$ /sq.



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## DEVELOPMENT AND CHARACTERIZATION OF ANTIBACTERIAL COATING WITH NANOPARTICLES ACTIVE AGAINST *MRSA AND MSSA*

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Covid-19 is not the only threat to the global human health. It is estimated that by the year 2050, from the infections caused by antibiotic-resistant bacteria, more people could die than from AIDS, tuberculosis and viral hepatitis together. Only in Europe 25 000 deaths per year and costs over € 1.5 billion are the consequences of the resistant microorganisms activity. Therefore, in this work new antimicrobial materials containing nanoparticles active against *Methicillin-resistant Staphylococcus aureus (MRSA)* and *Methicillin-sensitive Staphylococcus aureus (MSSA)*, microorganism strains resistant to antibiotics, are developed. Antimicrobial water-repellent coatings are intended for materials foreseen as: bedding hospital items, disposable antimicrobial lining and bandages for chronic wounds. In the development of the antimicrobial formulation, we apply the *Response surface methodology (RSM)* and mathematical modeling for predicting the optimal antimicrobial activity of nanoparticles and their mixtures. The thus-calculated antimicrobial mixtures are applied on the surface of biodegradable polymers (textiles or 3D printed surfaces) by sol-gel process. Polymers are characterized by different spectroscopic, microscopic and chromatographic methods and investigated for their newly obtained functional properties (water repellency, antimicrobial efficiency and others). Our results show that by applying RSM methodology and mathematical modeling, and by changing the process parameters excellent water repellency is achieved,<sup>[1]</sup> as well as a very good antibacterial efficiency against *MRSA* and *MSSA* microorganisms.<sup>[2]</sup> In our future activities we plan to optimize the antimicrobial properties further in order to enhance the efficiency and reduce the time required for total antimicrobial effects in time interval shorter than few hours.

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## PERMANGANOMETRIC DETERMINATION OF OXYGEN NONSTOICHIOMETRY IN MANGANITES

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Lanthanum strontium manganite,  $\text{La}_{1-x}\text{Sr}_x\text{MnO}_3$ , belongs to an extensive group of rare-earth manganites with the general formula  $\text{Re}_{1-x}\text{A}_x\text{MnO}_3$ , where Re is the rare-earth ion (La) and A is a divalent ion (Sr). The rare-earth manganites are nowadays the subject of extensive research because of their promising electrical and magnetic properties.<sup>[1]</sup> These properties are strongly affected by oxygen nonstoichiometry and  $\text{Mn}^{3+}/\text{Mn}^{4+}$  ratio, so the aim of this study was to examine the application of permanganate back titration on the determination of oxygen content in manganites.<sup>[2,3]</sup> In our study,  $\text{SrMnO}_3$  was successfully prepared by citrate-nitrate autocombustion (CNA) and by the coprecipitation method. These methods were then applied to the synthesis of  $\text{La}_{1-x}\text{Sr}_x\text{MnO}_3$  ( $x = 0, 0.1, 0.2$  and  $0.3$ ). The optimal phase formation conditions were determined by thermogravimetry and differential scanning calorimetry. Crystallization of precursors and calcined powders was studied by X-ray diffraction. Powders in which pure manganite phase was obtained, were analyzed by permanganate titration with Mohr's salt to determine oxygen nonstoichiometry. Oxygen stoichiometry was achieved in  $\text{SrMnO}_3$  powders obtained by the CNA method and calcined at  $1000\text{ }^\circ\text{C}$  as well as in powders obtained by the coprecipitation method and calcined at  $1200\text{ }^\circ\text{C}$ . The  $\text{La}_{1-x}\text{Sr}_x\text{MnO}_3$  phase was oxygen stoichiometric for  $x = 0.3$  and  $0.18$  while the decreasing of  $x$  resulted in cation deficiency, i.e. oxygen excess. Oxygen deficit was achieved for  $x = 0.09$  upon calcination at  $1200\text{ }^\circ\text{C}$ . The obtained results were confirmed by thermogravimetry.

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## TRIPLE PEROVSKITE-BASED TRIBOELECTRIC NANOGENERATOR: A FACILE METHOD OF ENERGY HARVESTING AND SELF-POWERED INFORMATION GENERATOR

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A modified aqueous sol-gel reaction is used to synthesize a triple perovskite with a composition  $\text{Sr}_3\text{Co}_2\text{WO}_9$  (SCWO). The structural analysis conducted at room temperature reveals the presence of the cubic phase with space group  $Fm\bar{3}m$ . The microstructure of the as-synthesized SCWO particles shows a different size of particles depicting a polycrystalline nature. Triboelectrification is a trending and unique concept in energy scavenging methodologies with flexibility in choosing from a variety of materials. This paves the way to evolve eco-friendly triboelectric energy harvesters as a replacement for the limitation of batteries. The outstanding dielectric properties and low loss make triple perovskite a promising candidate for TENG. A triboelectric nanogenerator (TP-TENG) was designed, which operates in vertical contact separation mode generating an electrical response of voltage and current of 300 V and 2.2  $\mu\text{A}$ , respectively, for 10 wt% polydimethylsiloxane-  $\text{Sr}_3\text{Co}_2\text{WO}_9$  (PDMS-SCWO) composite film. The power density of the rough surface TP-TENG was 30.5  $\mu\text{W}/\text{cm}^2$ , which is much higher than the power density of 5.5  $\mu\text{W}/\text{cm}^2$  of plain surface TP-TENG. The positive and negative triboelectric layers of the TP-TENG were made up of aluminum and PDMS-SCWO composite film, respectively. Furthermore, the excellent flexibility and durability of TP-TENG make it suitable for sensing various gaits and information signaling (Morse code) in real-time applications, as well as for charging commercial capacitors.<sup>[1]</sup>

**Acknowledgments.** This work has been fully supported by the Croatian Science Foundation under the project number IP-2016-06-3115, entitled "Solution chemistry routes towards complex multiferroic materials".

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## IMPACT OF ALIOVALENT/ISOVALENT IONS (Gd, Zr, Pr, AND Tb) ON THE CATALYTIC STABILITY OF MESOPOROUS CERIA IN THE HCl OXIDATION REACTION

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CeO<sub>2</sub> is a promising material in the catalytic recovery of Cl<sub>2</sub> from HCl by oxidation with O<sub>2</sub> due to its beneficial redox properties (Ce<sup>3+</sup>/Ce<sup>4+</sup>) and accompanied oxygen storage capacity (OSC). Two options to tailor the OSC are the usage of dopants and nanostructuring. Here, we report the synthesis of mesoporous doped Ce<sub>0.9</sub>M<sub>0.1</sub>O<sub>2</sub> (M = Zr, Gd, Pr, and Tb) powders with identical mesopore size, shape, and specific surface area (≈90 m<sup>2</sup> g<sup>-1</sup>) to investigate the impact of aliovalent (Gd), isovalent (Zr), and aliovalent/isovalent (Pr and Tb) dopants on the OSC as well as on the catalytic activity/stability. The cubic arrangement of spherical 12 nm mesopores surrounded by a crystalline framework is obtained by using a diblock copolymer as structure directing agent in the sol-gel-based preparation approach, indicated by small angle X-ray scattering (SAXS) and scanning electron microscopy (SEM). Pr-doped CeO<sub>2</sub> revealed the highest oxygen storage capacity but the lowest catalytic activity/stability in the HCl oxidation together with the Tb- and Gd-doped samples. By contrast, the Zr-doped mesoporous CeO<sub>2</sub> powders showed the highest catalytic performance and stability in the CO and HCl oxidation of all samples but a lower OSC. These findings suggest that the OSC should therefore be treated with caution when relating to the catalytic performance in oxidation reactions. The differences in the stability are in agreement with recent studies of the HCl oxidation on model cerium oxide films with defined stoichiometry: the low stability of the aliovalent doped CeO<sub>2</sub> materials in the HCl oxidation reaction can be attributed to a large number of oxygen vacancies.<sup>[1]</sup>

**Acknowledgments.** This work has been fully supported by the Croatian Science Foundation under the project number PZS-2019-02 2467, entitled “The study of the role of rare earth metal promoters and ordering on the redox properties of CeO<sub>2</sub> - ZrO<sub>2</sub> system”.

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## MAGNETRON SPUTTERING DEPOSITION OF 3D NETWORKS OF NANOPORES IN ALUMINA

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Peter Nadazdy,<sup>c</sup> Sigrid Bernstorff,<sup>d</sup> Maja Mičetić<sup>a</sup>

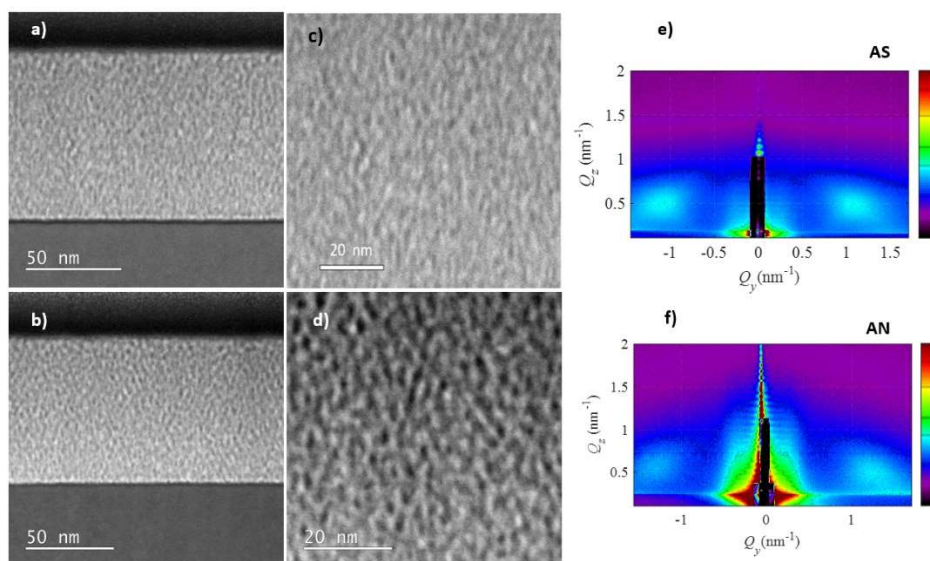
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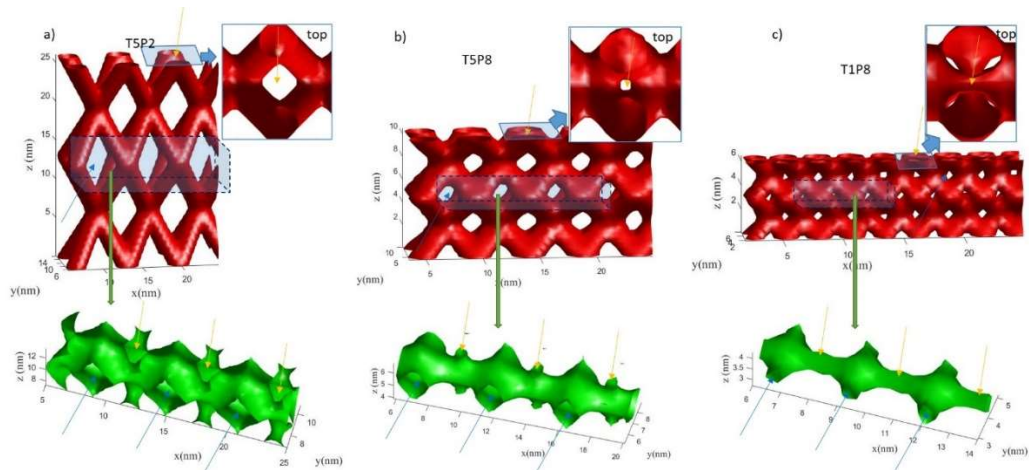
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In this work we demonstrate the production of continuous 3D networks of nanopores in alumina matrix produced by annealing of 3D networks of Ge nanowires in alumina fabricated by magnetron sputtering deposition. These nanoporous structures differ by the nanopores length, radius, and geometry of their network. The arrangement and shape of the nanopores in alumina are nearly the same as were the arrangement and shape of Ge nanowire networks, that were present in the alumina prior to the annealing. The production process is discussed and the limiting factors in the production of such nanoporous alumina films are found. We show that the unit cell parameters of the network combined with the percentage of Ge in the thin film prior to annealing, are the main limiting factors. It was found that the nanoporous structure is easily formed when the Ge atomic percentage in the film is lower than 40%, however, for the larger percentages of Ge, the alumina matrix in a unit cell is not connected to the neighboring cells in the vertical direction so the structure collapses during the annealing process. Additionally, we have shown the possibility to tune the index of refraction for alumina in a large range by varying the porosity, i.e. the parameters of the Ge nanowire network. This method allows for continuous modulation of porosity depending on the specific desired application. We believe these films could be used successfully for various sensing applications or as anti-reflective coatings for silicon-based solar cells.



**Figure 1.** HAADF TEM and GISAXS images before and after annealing. (a)-(c) TEM images before annealing; (b)-(d) TEM images after annealing; (e) GISAXS before annealing; (f) GISAXS after annealing.



**Figure 2.** Model of the structure of the nanoporous networks (the pores are shown by red colour) and the shape of the alumina matrix surrounded by the pores (shown by green colour).  
 (a) Film T5P2; (b) T5P8; and (c) T1P8.

## PREPARATION AND CHARACTERIZATION OF SILICA-*Nigella sativa* L. HYBRID MATERIALS

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Silica-*Nigella sativa* L. hybrid materials were prepared and characterized as a potential new material for plasters and wound dressings. *Nigella sativa* L. commonly known as black cummin are used extensively for flavouring and medicinal purposes.<sup>[1]</sup> The oil and the seed constituents have shown anti-inflammatory effects on several inflammation-based models including experimental encephalomyelitis, colitis and arthritis through suppression of the inflammatory mediators prostaglandins and leukotriens.<sup>[2]</sup> All mentioned activities are necessary for antibacterial coatings and are very important for e.g. chronic wounds. In textile technology sol-gel process offers great opportunities by creating new surface properties, especially in this case where nanosol contains plant essential oil. Target of this paper was to prepare a coating with black cummin essential oil by sol-gel process with 3-glycidoxypropyltrimethoxysilane (GLYMO) and without GLYMO. Coatings were applied by dip-coating on the cotton and polyamide. It was concluded that the retention of textile character as an important requirement of new textile materials was successfully met. Absorbency of Textiles, pH of the Water Extract and measuring of the angle of recovery was carried out. The coatings were characterized by infrared spectroscopy (FTIR-ATR) and agar diffusion plate test (antibacterial activity) by determining bacterial reduction of *Escherichia coli* and *Staphylococcus aureus*. Based on obtained results it can be concluded that good antibacterial effect show all treatments on fabrics.

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## MAGNETRON SPUTTERING DEPOSITION OF CORE/SHELL Ge/Al QUANTUM DOT LATTICES IN AMORPHOUS Al<sub>2</sub>O<sub>3</sub> MATRIX

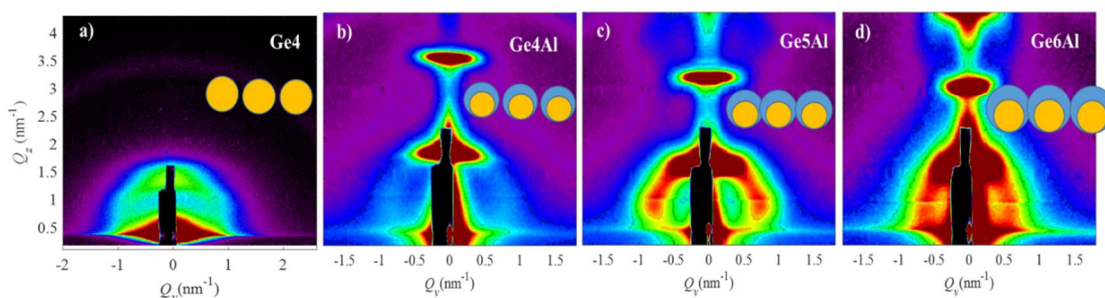
Ivana Periša,<sup>a,\*</sup> Marija Tkalčević,<sup>a</sup> Lovro Basioli,<sup>a</sup> Mile Ivanda,<sup>a</sup> Sigrid Bernstorff,<sup>b</sup> Maja Mičetić<sup>a</sup>

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In this study, we demonstrate the production of thin films made of 3D-ordered Ge/Al core/shell quantum dots embedded in an alumina matrix. The films were produced by a magnetron sputter deposition of the Ge/Al/Al<sub>2</sub>O<sub>3</sub> multilayer. The Ge core size was tuned by varying the Ge-layer deposition time while the other parameters were kept constant. The influence of the Ge core size on the structural, optical, and electrical properties was investigated. The results confirm the formation of Ge/Al core/shell quantum dots, differing by the sizes of the core and shell, that are arranged in a 3D-ordered network. The optical properties of the materials, their photo-generation ability, and quantum efficiency show a strong dependence on the Ge core size. Also, the materials bandgap is strongly tuneable by the size of the Ge core. The investigated materials are very promising for application in solar cells, photodetectors, and sensors.



**Figure 1.** GISAXS maps of all studied samples. The insets show schematic images of different QDs structures that appear in the investigated films. The Ge core is indicated by yellow colour, and the Al shell by blue colour.

**Acknowledgments.** This research was funded by the Croatian Science Foundation (No. IP-2018-01-3633) and the Centre of Excellence for Advanced Materials and Sensing Devices (Grant KK.01.1.1.01.0001).

## SYNTHESIS AND PROPERTIES OF ELECTROSPUN FIBRES IN THE SYSTEM $\text{Er}_2\text{O}_3\text{-Fe}_2\text{O}_3$

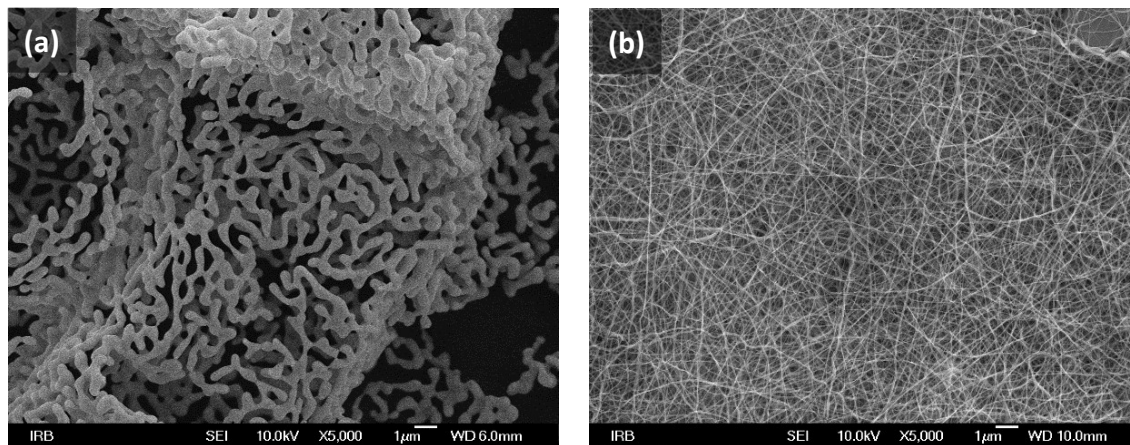
Marko Robić,<sup>a,\*</sup> Mira Ristić,<sup>a</sup> Stjepko Krehula,<sup>a</sup> Svetozar Musić<sup>a,b</sup>

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The chemistry and physics of RE doped hematite (RE=rare earths), RE orthoferrites and RE-iron garnets were the subject of numerous investigations. These investigations were scientifically motivated due to their specific magnetic, magneto-optical, luminescence and photocatalytic properties. Also, these materials found applications in advanced technologies. In the synthesis of these materials the ceramic and coprecipitation methods are dominantly used. In the present work we report a new synthesis method for their production based on the electrospinning. Electrospun fibres of the system  $x\text{Er}(\text{NO}_3)_3\text{-(1-x)Fe}(\text{NO}_3)_3$  in polyvinylpyrrolidone/ethanol solution were prepared, then heated at high temperatures. The samples were characterized with XRD, Mössbauer, FT-IR and FE SEM. In the presence of smaller amounts of Er (<10 mol %), besides Er-doped hematite phase, magnetic phase was obtained due to the presence of maghemite ( $\gamma\text{-Fe}_2\text{O}_3$ ) phase. For the ratio Er:Fe=1:1 the erbium orthoferrite ( $\text{ErFeO}_3$ ) was formed and for the ratio Er:Fe=3:5 the erbium iron garnet ( $\text{Er}_3\text{Fe}_5\text{O}_{12}$ ) was formed. FE SEM confirmed that all these components preserved (or at least partially preserved) 1D (fibres) microstructure.



**Figure 1.** FE SEM images of nanofibres made up of hematite/maghemite composite (a) and  $\text{Er}_3\text{Fe}_5\text{O}_{12}$  (b).

**Acknowledgments.** This research has been supported by the Croatian Science Foundation (project number IP-2016-06-8254).



## AGING OF PHOTOCATALYSTS TiO<sub>2</sub>, TiO<sub>2</sub> / MULTIWALL CARBON NANOTUBES AND TiO<sub>2</sub> / GRAPHENE OXIDE IN AIR

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Environmental pollution, and especially water, is causing a growing problem in the world. The use of the chemical and pharmaceutical industry products is the main reason for water pollution by micropollutants, which is being talked about more and more.<sup>[1]</sup> Micropollutants in water arouse the interest of scientists in how to solve this problem. Advanced oxidation processes such as photocatalysis can be used to purify this type of pollutants.<sup>[2]</sup> The presence of a photocatalyst is required for the photocatalysis process, and common one used are TiO<sub>2</sub>, CdS and ZnO.

In this paper photocatalyst were prepared by immobilization of TiO<sub>2</sub> on glass fibers mesh, and with the aim to improve the photocatalytic activity of TiO<sub>2</sub> in the visible part of solar radiation<sup>[3]</sup> by using TiO<sub>2</sub> in combination with multiwall carbon nanotubes and separately with graphene oxide. The influence of aging in air of prepared photocatalysts was investigated through photocatalytic activity before and after aging for 6 months. Also, photocatalysts were examined using scanning electron microscopy and energy-dispersive spectroscopy. After the analysis, it was determined that there was no weakening of photocatalytic activity.

**Acknowledgments.** This work has been supported by following projects “Waste & Sun for photocatalytic degradation of micropollutants in water” (OS-Mi), supported by European Regional Development Fund, KK.01.1.1.04.0006. and “PV-WALL” PZS-2019-02-1555 in the Research Cooperability Program of the Croatian Science Foundation funded by the European Union from the European Social Fund under the Operational Programme E\_cient Human Resources 2014–2020.

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## IMPROVEMENT OF ACOUSTIC AND FIRE RESISTANT PROPERTIES OF WOOD-WOOL CEMENT COMPOSITE PANEL

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Wood-wool cement composite panel (WWCP) is a building material produced using thin spruce shavings bonded with Portland cement inorganic binder. It finds numerous applications because of its good mechanical, thermo-insulation and acoustic properties. By varying the mass fraction of cement and wood wool along with the form pressure, it is possible to achieve different porosity of WWCP. Distribution of pore sizes and pore connectivity is crucial for achieving good sound absorption of panels. Increasing porosity increases sound absorption coefficient and decreases apparent density, stiffness, and bending strength of the WWCP. In this work, the influence of wood-wool to cement ratio on the acoustic, elastic and bending strength of WWCP has been investigated. The sound absorption coefficient of prepared samples was measured by impedance tube (Kundt tube) method according to ISO 10534-2. The dynamic Young modulus of WWCP was determined by resonant frequency method and the bending strength was determined by three-point bending test. Fire resistance of wood in WWCP is naturally enhanced by a thin layer cover of cement paste. A further increase of fire resistance is obtained by chemical treatment of wood-wool. By applying one or several liquid chemicals, the precipitation of incombustible inorganic material in pores and on the surface of wood-wool occurs, impeding the rate of oxygen diffusion and combustion rate of WWCP. Morphology of the thin film precipitate and its chemical composition has been investigated by optical microscopy, scanning electron microscopy (SEM), infrared spectroscopy (FTIR) and X-ray diffraction analysis (XRD). The rate of combustion of mineralized wood-wool has been determined by simultaneous DTA-TGA thermal analysis, while the influence of the chemicals on the hydration and strength increase of Portland cement has been determined by semi-isoperibolic calorimetry measurements. It was found that chemical treatment of wood-wool significantly increases fire resistance and does not interfere with the normal cement setting and hardening. Simultaneous achievement of good acoustic absorption and mechanical properties needs further optimization of pore structure by modification of wood-wool dimensions (length and thickness).

**Acknowledgments.** This work has been supported by European Regional Development Fund under the project KK.01.2.1.0299

## SOLVOTHERMAL SYNTHESIS, CHARACTERIZATION AND PHOTOCATALYTIC PROPERTIES OF TiO<sub>2</sub>/Fe<sub>2</sub>O<sub>3</sub> NANOCOMPOSITES

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The occurrence of trace amounts of antibiotics in various bodies of water was directly linked to the development of antibiotic resistant pathogens. Recently, Amoxicillin (AMX) was added on the second EU “watch list” based on the proposed European Decision 2018/840/EU. Its presence in wastewater effluents is related to the limited removal by common municipal wastewater treatment plants based on primary and secondary treatment processes. Therefore, new remediation techniques must be applied to remove such recalcitrant substances. One of the promising solutions is the application of advanced oxidation technologies, e.g. sustainable solar-assisted TiO<sub>2</sub>-based photocatalysis.

In this study, TiO<sub>2</sub>/Fe<sub>2</sub>O<sub>3</sub> nanocomposites were synthesized directly via solvothermal reaction of titanium (IV) butoxide and different amounts iron (III) nitrate in the mixed solvents of acetic acid and ethanol. The as-prepared TiO<sub>2</sub>/Fe<sub>2</sub>O<sub>3</sub> nanocomposites were inspected for their structure, morphology, composition, surface, electrochemical and optical properties by: XRD, XPS, SEM/EDXS, TEM, BET, EIS, PL and DRS analysis. Photocatalytic activity under solar irradiation was assessed by treating targeted pharmaceutical pollutant AMX in the presence and absence of additional oxidant, persulfate (S<sub>2</sub>O<sub>8</sub><sup>2-</sup>). The influence of pH, % Fe<sub>2</sub>O<sub>3</sub> composition and persulfate concentration on AMX degradation rate was established by the means of statistical planning and response surface modeling, while Reactive Oxygen Species (ROS) scavenging was also employed for further understanding of AMX degradation mechanism.



## INKJET PRINTABLE CONDUCTIVE INKS BASED ON MELAMINE INTERCALATED GRAPHENE NANOSHEETS

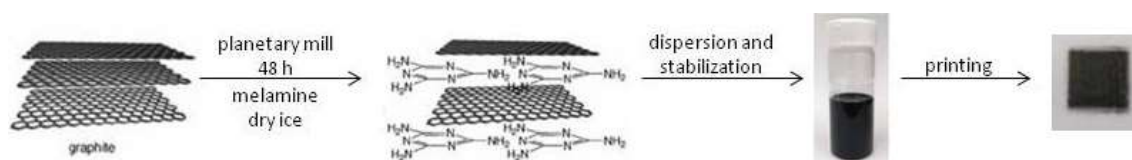
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The miniaturization and persistent presence of smart devices has led to their mass production, with digital inkjet printing technology standing out as a simple, fast, and economical manufacturing method. Such an approach requires the formulation of an electrically conductive ink based on dissolving and stabilizing the functional material in a suitable solvent or solvent mixture. Due to its outstanding electrical conductivity and mechanical durability, intensive research has been focused on the manufacturing techniques of graphene. Presented here is a study on the preparation and optimization of graphene inks suitable for inkjet printing on a PET substrate. We have adopted a facile mechanochemical route for single and two layered graphene nanosheet fabrication, by melamine induced exfoliation in a planetary ball mill. Stability of the melamine intercalated graphene nanosheets (M-GNs) was evaluated in several solvents. Finally the M-GNs were dispersed in a mixture of water and ethanol with the aid of commercial polymeric dispersants Solspense 20000 and 12000S at a concentration of 3 mg/mL. Surface tension, viscosity and density of this ink were optimized to match the inkjet printer requirements. Dynamic light scattering measurements revealed an adequate average particle size of 200 nm. Multiple layers of the ink were printed and electrical properties of the samples were evaluated. The printed features were exposed to intense pulsed light (IPL), thereby lowering their sheet resistance by an order of magnitude.



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## SYNTHESIS OF STRETCHABLE AND SELF-HEALABLE CONDUCTIVE POLYMER BASED ON POLY(3,4-ETHYLENEDIOXYTHIOPHENE)

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Wearable electronics has attracted considerable attention for use in electronic skin and health monitoring systems for comfortable and safe living. They are tunable at the molecular level, easy to process, mechanically flexible, and can form nanoscale structures through supramolecular, self-assembling bottom-up patterning. Hydrogen bonds are particularly well suited for skin-inspired electronics due to their spontaneous formation and healing ability. These non-covalent crosslinks can undergo an energy dissipation mechanism upon strain by breaking the bonds. After the stress is removed, the bonds can be reformed to restore the original mechanical property and heal themselves.

The aim of this study was to synthesise an intrinsically stretchable and healable conductive polymer (CP) by atom transfer radical polymerization (ATRP). For this purpose, poly(3,4-ethylenedioxythiophene) (PEDOT) was synthesised as a backbone, while poly(acrylate-urethane) (PAU) was used to graft onto the CPs backbones to form graft polymers PEDOT-g-PAU. Hydrogen bonds between the PAU side chains provide stretchability and self-healing, while the PEDOT backbone retains its high charge capabilities. Characterization of the obtained intermediates and products (PEDOT-g-PAU) was carried out using different techniques. Nuclear magnetic resonance (NMR) and Fourier transform infrared spectroscopy (FTIR) confirmed the success of the synthesis of all intermediates as well as the PEDOT-g-PAU product itself. PEDOT-g-PAU has shown the ability to stretch by more than 500%, which is shown in Figure 1, and therefore could potentially be used in wearable electronics.



**Figure 1.** Fully stretched synthesized PEDOT-g-PAU

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## POLYMER NANOCOATINGS CROSSLINKED BY $\gamma$ -RAYS

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Crosslinking of a well-ordered layer of self-assembled molecules (SAMs) on the surface of copper additionally enhances SAMs protective properties by improving their functional properties as well as reducing penetration of external molecules into the coatings.<sup>[1]</sup> Thus, the obtained polymer nanocoating (PNC) has significantly higher stability and better protective properties while retaining SAMs numerous advantages. In this work elaidic acid (EA), a non-toxic unsaturated fatty acid (FA) was used as the self-assembling molecule, while crosslinking was initiated by ionizing irradiation. By using irradiation toxic agents that are used for classical crosslinking can be avoided, while on the other hand the process is homogeneous, fast and simple to perform. Since FAs are environment friendly molecules and crosslinking is performed without toxic agents the process can be considered as a Green Technology.<sup>[2]</sup>

The aim of this work was to reduce the irradiation dose needed for successful crosslinking of a SAM of EA on copper by changing the irradiation media from air to water. Namely, previous research has shown that EA SAMs can be successfully crosslinked in air with 110 kGy. Reducing the applied irradiation dose would reduce the treatment price. This work has shown that when irradiated in water doses can be reduced to 40 kGy, but the polymer coatings obtained by crosslinking in air have somewhat better properties. The obtained coatings properties were investigated by contact angle measurements and FTIR Spectroscopy, while their behavior in atmospheric conditions was studied by electrochemical methods (Tafel extrapolation method and electrochemical impedance spectroscopy).

**Acknowledgments.** We thank the Croatian Science Foundation (HRZZ IP-2020-02-4344) for supporting the research.

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## APPLICATION OF RADIATION TECHNOLOGY FOR PRESERVATION OF CULTURAL HERITAGE MADE OF LEATHER

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A big part of our cultural heritage (CH) is made from natural materials which are very sensitive to surrounding conditions and thus get easily infected. Disinfection through ionizing radiation has been proven to be very effective, because it is based on electromagnetic radiation from radioactive <sup>60</sup>Co, which causes chemical damage of DNA molecules of all biological pollutants, while on the other hand in most cases leaving the materials constituting the object intact. Contrary to all other methods gamma rays are highly penetrating acting on all pests present in the whole volume of a treated object in their whole life cycles; from spores to grown pests. Among all the advantages of radiation technology it needs to be outlined that it is harmless for humans and damage of the material is minimal, when using optimal conditions.

In the process of irradiating a CH object the most important parameter to pay special attention to is the irradiation dose. The used dose depends on the type and degree of contamination, the desired reduction of pests and their radio sensitivity, as well as type of material and its condition. It is necessary to apply the smallest possible dose for deactivation of biological contaminants, which should also be smaller than the dose that would induce any changes in the material or change its appearance.

In this work, we investigated the influence of radiation on natural leather which is used for restoring leather book covers using gama rays. With this research, we wanted to investigate the effect ionizing radiation has on natural leather, treated and non-treated. The main objective was to determine can radiation technology be used for preservation of cultural heritage made of leather and in which conditions.

Applying radiation to objects made of leather, such as clothing, book covers or furniture is still rare due to insufficient research into the effects of radiation on leather. This work investigates the effect of ionizing radiation on natural leather, unimpregnated and impregnated, in order to determine whether radiation technology can be used for protection and preservation of CH made from leather. Goatskin was used for the investigations with two types of common impregnation agents: Leather preservative and Talas SC600 preservative. The samples were tested by colorimetry and pH measurements, as well as FTIR. In the dose range used on cultural heritage at both investigated dose rates no observable changes were noticed, according to colorimetry, pH or FTIR.

## INVESTIGATION OF THE CONDITIONS FOR THE SYNTHESIS OF POLY(3,4-ETHYLENEDIOXYTHIOPHENE) ATRP MACROINITIATOR

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In the fast growing wearable electronics industry, conductive polymers play a significant role as their properties and structure can easily be customised to the specific application. One of the most commonly used conductive polymers is poly(3,4-ethylenedioxythiophene) (PEDOT), whose main advantages are good thermal and chemical stability, conjugated backbone, and easy functionalization. The main disadvantage of PEDOT for use as wearable electronics is the lack of stretchable and self-healing properties. To achieve the desired properties, a new thiophene derivative, 2-(thiophen-3-yl) ethyl 2-bromo-2-methylpropanoate (ThBr) is synthesized as monomer precursor for the synthesis of poly(EDOT-co-ThBr) ATRP macroinitiator (Figure 1.). After the synthesis of macroinitiator, new polymers are introduced by atom transfer radical polymerization to obtain different properties. Before this final synthetic step, the conditions for the synthesis of ATRP macroinitiator should be investigated.

In this study, 9 new copolymers with different monomer ratios were synthesized to investigate the reactivity of each monomer. The ratios used in the different syntheses were: EDOT:ThBr = 1:0.2, 1:0.4, 1:0.6, 1:0.8, 1:1, 0.8:1, 0.6:1, 0.4:1 and 0.2:1. In addition, with aim to discover the influence of the reaction time on the final properties of the polymer, the 1:1 ratio macroinitiator synthesis was carried out in different durations: 8 h, 16 h, 24 h and 48 h. The obtained products were characterized using different techniques. Nuclear magnetic resonance (NMR) and Fourier transform infrared spectroscopy (FTIR) confirmed the desired structures and the difference in monomer ratios obtained in different syntheses.

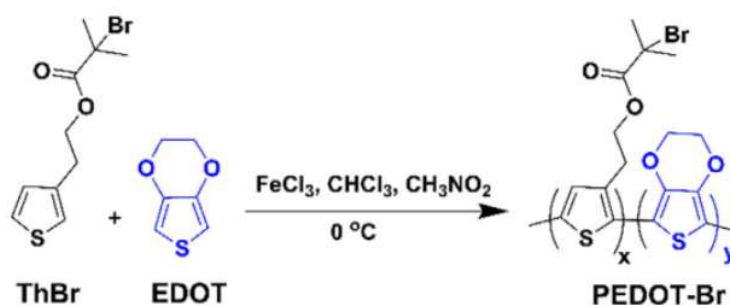


Figure 1. Reaction scheme of macroinitiator synthesis

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## THE INFLUENCE OF UV AGEING ON THE PROPERTIES OF LOW DENSITY POLYETHYLENE/HEMATITE COMPOSITES

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Polymer composites with hematite ( $\alpha\text{-Fe}_2\text{O}_3$ ) may exhibit many improved properties in comparison to the pure polymer, especially if the fine dispersion of non-aggregated particles is achieved.<sup>[1]</sup> This study determines the efficiency of hematite's particles of different size in the protection of low density polyethylene (LDPE) from UV radiation-induced degradation. The work also evaluates the effect of hematite mass fraction (0.25, 0.5 and 1 %) on the properties of polyethylene matrix. Two types of hematite particles with well-defined cubic shape and uniform size were used: HC1 (average size of about 2  $\mu\text{m}$ ) and HC2 (average size of about 1  $\mu\text{m}$ ). Prepared polyethylene/hematite composites were characterized by thermogravimetric analysis (TGA), FTIR spectroscopy and diffuse reflectance UV-Vis-NIR spectroscopy. The water vapour permeability of the composite samples is also determined.

In comparison with a pure polyethylene, the results show that such composites have improved all mentioned properties (thermal, UV/VIS absorption and vapor permeability) especially the composites with hematite HC2 due to its fine particles (lower size than hematite HC1) and large surface. Hematite can be used as UV blocking agent for polyethylene. Obtained results reveal that such composites may be a promising material for wide range of applications.

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## SOLID STATE DISPERSIONS OF PLATINUM IN THE SnO<sub>2</sub> NANOMATERIALS

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Cassiterite (SnO<sub>2</sub>) nanoparticles were synthesized by activating Sn(II) acetate in a planetary mill followed by heat treatment at 600 °C. FTIR results showed that milling of the acetate precursors in a planetary mill did not result in the degradation of acetate groups (FTIR bands at ~ 1517 and ~ 1391 cm<sup>-1</sup>). The volume averaged domain size of the cassiterite was estimated to be ~29 nm. The results of Williamson-Hall analysis of the cassiterite sample indicated the presence of anisotropy, with a slightly larger crystallite size in the direction parallel to the broadening axis *hk2* (estimated at ~ 34 nm). Platinum (Pt) in the samples was detected directly by EDXS analysis and indirectly by TPR results (Temperature Programmed Reduction in hydrogen, H<sub>2</sub>). SnO<sub>2</sub> was reduced with H<sub>2</sub>, according to the simplified equation  $\text{SnO}_2 + 2 \text{H}_2 \rightarrow \text{Sn} + 2 \text{H}_2\text{O}$ . The H<sub>2</sub>-TPR curve of the pristine SnO<sub>2</sub> sample showed that the reduction of SnO<sub>2</sub> started at about 180 °C and ended with an "incomplete" maximum at 643 °C. The incomplete reduction of SnO<sub>2</sub> to Sn can be attributed to the formation of the Sn metal shell around the SnO<sub>2</sub> particles. The melting point of tin is very low at 232 °C, so molten tin on the surface of SnO<sub>2</sub> particles can protect Sn<sup>4+</sup> from reduction. The addition of Pt promotes the reduction of SnO<sub>2</sub>, and the reduction started at a lower temperature (~100 °C) and ended with a well-defined maximum at 652 or 733 °C. UV-Vis spectroscopy also responded to a platinum addition of only 1 mol%. In the pristine SnO<sub>2</sub> sample the gap energy is estimated to be 3.4 eV, while in the Pt-decorated sample the gap energy shifts to the visible region of the spectrum and has a value of 3.0 eV.

**Acknowledgments.** This work was financially supported by Croatian Science Foundation under the project UIP-2019-04-1195 "Platinum decorated iron tin oxide solid solutions for hydrogen gas sensing" (HydGasSens).



## MECHANOCHEMICAL SYNTHESIS AND CHARACTERISATION OF Pt-Fe<sub>2</sub>O<sub>3</sub> NANOMATERIALS

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Nanocrystalline samples of hematite ( $\alpha$ -Fe<sub>2</sub>O<sub>3</sub>) were synthesized by activating Fe(II) acetate in a planetary mill followed by heat treatment at 600 °C. The results of XRD line broadening analysis showed that the hematite had a volume average crystal domain size of 26 nm, whereas the upper limit of microstrain was estimated to  $\sim 1 \times 10^4$ . Hematite samples were decorated with platinum in three ways, (i) in one step by mixing powdered Fe (II) acetate precursor with Pt (Acac)<sub>2</sub> and activation in a planetary mill followed by annealing at 600 °C, (ii) in two steps, where first hematite were synthesized at 600 °C and then the pristine powder samples were mixed with Pt (Acac)<sub>2</sub> powder precursor, homogenized for 2 h in a planetary mill and annealed to 400 °C, (iii) the samples were synthesized in two steps, with the difference that a certain amount of Pt (Acac)<sub>2</sub> was dissolved in toluene and then homogenized with Fe (II) acetate precursors in a planetary mill and annealed to 400 °C. The Atomic Resolution Scanning Transmission Electron Microscopy (AR STEM) showed that the platinum was well-dispersed on the  $\alpha$ -Fe<sub>2</sub>O<sub>3</sub> support in the form of very small platinum nanoparticles (Pt NPs). The mean size distributions of the Pt NPs in the hematite samples were 2.2, 1.2 and 0.8 nm depending on the synthesis conditions. Moreover, Pt was indirectly detected in the samples by the TPR (Temperature Programmed Reduction in hydrogen) technique. In the pristine Fe<sub>2</sub>O<sub>3</sub> sample, the reduction started at 300 °C and showed two peaks at 421 and 629 °C. Decoration with platinum in one step significantly increased the reduction of Fe<sub>2</sub>O<sub>3</sub>, two reduction peaks at 421 and 629 °C integrated a broad peak at 360 °C, and a new small and very broad reduction peak at 146 °C could be attributed to Pt<sup>2+</sup> reduction in Pt. When Pt is decorated in two steps, two reduction peaks were again present, with the maximum shifted to lower temperatures (281 and 270 °C) due to Fe<sub>2</sub>O<sub>3</sub> → Fe<sub>3</sub>O<sub>4</sub> reduction, while Fe<sub>3</sub>O<sub>4</sub> → FeO → Fe reduction was shifted to higher reduction temperatures (678 and 635 °C).

**Acknowledgments.** This work was financially supported by Croatian Science Foundation under project UIP-2019-04-1195 "Platinum decorated iron tin oxide solid solutions for hydrogen gas sensing" (HydGasSens).



## PREPARATION AND CHARACTERIZATION OF CELECOXIB AND CHEESE WHEY GRANULES

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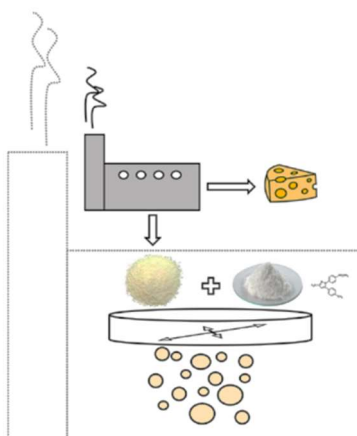
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The main by-product of the dairy industry in cheese making is whey. Because it is a waste product, it can be used as a cheap source of lactose and protein in the pharmaceutical industry. In recent years, whey protein is a dietary strategy widely used in the field of oncology and for the prevention of cardiovascular disease.<sup>[1,2]</sup> In this study, crystalline celecoxib was used as a model drug, which was characterized as a cohesive powder with bioavailability problems.<sup>[3]</sup> Wet granulation of cheese whey and celecoxib was performed to overcome the aforementioned problems with the powder.

The experiments were carried out on a laboratory mixer-granulator Diosna P1-6 with the addition of 96% ethanol and different contents of polyvinylpyrrolidone (PVP) as binder (0.2 – 2%). Morphology, particle size distribution, compressibility and flow properties were determined on the dried material. In the analysis, the proportion of small particles (*finer*) played a major role in the estimation of flowability. It was also found that the addition of cheese whey had a great influence on the physical properties of celecoxib powder in relation to the handling of this type of material.

### Graphical abstract



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## NMR STUDY OF INTERACTION OF L-DOPA AND DOPAMINE WITH GOLD NANOPARTICLES

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The growing interest in applying gold nanoparticles (AuNPs) as a drug-delivery system in the treatment of Parkinson's disease (PD) contributes to the examination of their interactions with dopamine, whose deficit causes PD, and L-DOPA, a drug employed in the therapy of PD.<sup>[1]</sup> In AuNPs synthesis, catechols (dopamine and L-dopa) may serve both as reducing and surface capping agents.<sup>[2]</sup> Thus, it is crucial to understand in which form these capping layer surfactants exist on nanoparticle's surfaces since they may produce oxidation products such as quinones, which can consequently change their pharmacological and therapeutic effects and cause exacerbation of PD.<sup>[3]</sup> In this study, nanoparticles were synthesized by reduction of tetrachloroauric acid with catechols. In order to determine which oxidation product was bound to the nanoparticles surface, the molar ratio between tetrachloroauric acid and catechols was modulated. The interaction between catechols and AuNPs surface was monitored by NMR spectroscopy. <sup>1</sup>H NMR spectra were recorded immediately after mixing the reagents, and subsequently every 30 minutes until AuNPs formation finished. When catechols were in excess compared to tetrachloroauric acid, no change in proton signals was observed for 120 min. Conversely, when there was much more tetrachloroauric acid than catechols, original signals disappeared and different oxidation products were observed. In the case of dopamine, new signals correspond to dopamine-*o*-quinone, in contrast to L-DOPA where oxidation went one more step further via cyclization to dopachrome.

**Acknowledgments.** This study was financially supported by the HRZZ-PZS-2019-02-4323 grant.

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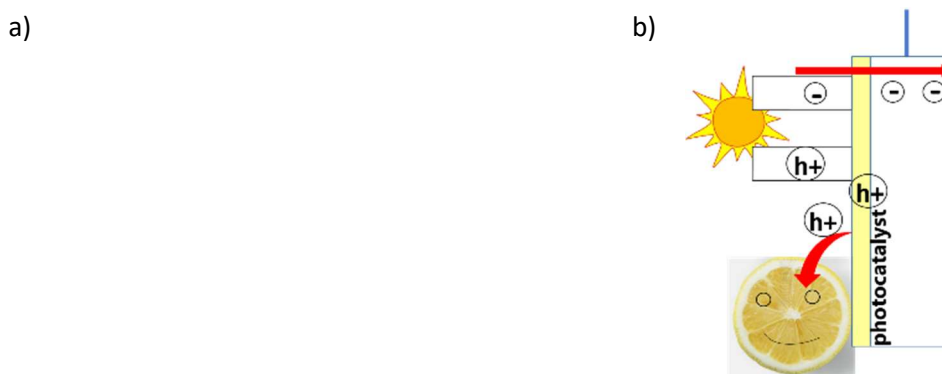
## ASCORBIC ACID INFLUENCE ON THE PHOTOELECTROCHEMICAL RESPONSE OF TiO<sub>2</sub> AND SnS<sub>2</sub>

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TiO<sub>2</sub> is already a well-studied photocatalytic material because of its excellent properties such as chemical stability, low price, non-toxicity. However, the fact that its band gap (3,2 eV) allows it to absorb only the UV light limits its use. On the other hand, SnS<sub>2</sub> (band gap ~2,2 eV) absorption range is well within the visible light spectrum which is more suitable for solar harvesting. Both of these materials are semiconductors which yield rapidly recombining electron-hole pairs upon photoexcitation. This recombination can be prevented by the addition of hole scavengers, which increase the survival probability of the electrons. Over the years there have been various efforts to improve such reaction efficiency using different organic hole scavengers. This work was focused on the influence of ascorbic acid (AA) as a scavenger for photogenerated holes and its influence on the photoelectrochemical response of TiO<sub>2</sub> and SnS<sub>2</sub>. Since the formal potential of the AA redox couple is 0.5 V (vs SCE) it means it can be easily oxidized by the photogenerated holes. The aim of this investigation was to compare the electrochemical responses of different photocatalytic materials (TiO<sub>2</sub> and SnS<sub>2</sub> electrodes) in the presence and absence of ascorbic acid. Using the techniques of linear sweep voltammetry (LSV) and electrochemical impedance spectroscopy (EIS) it was found that the addition of ascorbic acid increases the photocurrents and lowers the resistances. Open circuit potential (OCP) monitoring in chopped light irradiation suggested an increase in photocatalytic activity in the presence of AA. The obtained results indicate that ascorbic acid can be used as an efficient hole scavenger.



**Figure 1.** Open circuit potential (OCP) (a) and illustration of AA hole scavenger mechanism (b)

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## COMBUSTION SYNTHESIS OF COPPER-DOPED CERIUM ALUMINATE

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Intensive use of internal combustion vehicles has caused significant air pollution, which is a major environmental problem of modern society. As a potential solution, various exhaust gas purification systems have been developed, such as three-way catalytic (TWC) converters for automobile exhaust systems. Important parts of this catalytic systems are alumina ( $\text{Al}_2\text{O}_3$ ) support with a large surface area and ceria ( $\text{CeO}_2$ ) serving as oxygen storage promotor. Combustion synthesis is a simple, inexpensive method which enables the preparation of highly porous materials with good control over their composition, homogeneity and particle size. Our previous research focused on the preparation of ceria-alumina mixed oxides with addition of other catalytically active substances such as Cu and Mn. The addition of copper proved extremely beneficial resulting in a higher reaction temperature and less unreacted residue, with the main reaction product being cerium aluminate ( $\text{CeAlO}_3$ ), a perovskite-type material which is used in TWC converters and solid oxide fuel cells.<sup>[1]</sup> In this work,  $\text{CeAlO}_3$  doped with different amounts of Cu (0, 0.5, 1 and 2 mol. %) was prepared by combustion synthesis using metal nitrates as oxidants and glycine as fuel. The prepared samples were analyzed using X-ray diffraction analysis (XRD), scanning electron microscopy (SEM), differential thermal and thermogravimetric analysis (DTA-TGA) and Fourier transformed infrared spectroscopy (FTIR). The XRD analysis showed that the samples with 0 and 0.5 mol. % of Cu consist only of ceria, which means that the combustion temperature was not sufficient for  $\text{Al}_2\text{O}_3$  crystallization or  $\text{CeAlO}_3$  formation. On the other hand, 1 and 2 mol. % Cu doped samples consist of  $\text{CeAlO}_3$  phase. The higher is the amount of Cu, the higher is the reaction temperature, as well as crystallinity and porosity of the obtained  $\text{CeAlO}_3$ , while there is consequently less remaining organics and nitrates in the samples. The DTA-TGA analysis showed that  $\text{CeAlO}_3$  decomposes to  $\text{CeO}_2$  and  $\text{Al}_2\text{O}_3$  above 800 °C.

**Acknowledgments.** This work has been fully supported by Croatian Science Foundation under the project IP-01-2018-2963.

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## THE COMPARISON OF ADVANCED SYNTHESIS METHODS FOR CERIA NANOPARTICLES DOPED WITH MANGANESE

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Ceria ( $\text{CeO}_2$ ) is a material with many uses related to environmental protection and industry. Many of its applications depend on fluorite structure and easy shift between  $\text{Ce}^{3+}$  and  $\text{Ce}^{4+}$  oxidation states. During this interchange oxygen vacancies occur but thanks to its stable nature, the shift does not affect the cubic lattice. Some of the applications involving ceria are in catalysis, in solid oxide fuel cells and as a polishing material. Reducing dimensions to nanoscale is a good way to ensure greater specific surface area and catalytic activity. This makes the shift between  $\text{Ce}^{4+}$  and  $\text{Ce}^{3+}$  easier improving oxygen storage and mobility within the lattice. Another way of advancing ceria is doping. Ceria is mostly doped with transition metals. Most transition metals can enter the lattice thus enhancing catalytic activity and improving other properties while some don't even enter the lattice. Manganese has many oxidation states and as such can improve oxygen storage and mobility and even thermal stability. There are many methods of synthesis for nanoparticles while advanced methods include hydrothermal, sol-gel and mechanochemical synthesis. Each of these methods has its advantages as well as problems such as harmful organic solvents, lack of temperature control or very small sample gain. In this work, our aim was to compare above mentioned methods of synthesis to prepare ceria as well as manganese doped ceria. The prepared samples were characterized by X-ray diffraction (XRD), infrared spectroscopy with Fourier transformation (FTIR) and  $\text{N}_2$  adsorption-desorption isotherms. Catalytic activity was tested on thermally treated samples at 500 °C for 2 hours. X-ray diffraction patterns were used to calculate ceria crystallite size via Scherrer equation. Each method of synthesis results with nanocrystalline ceria particles but in two of the used methods a minor phase appears beside  $\text{CeO}_2$ . Smallest crystallite size was gained by the sol-gel synthesis. All samples show improved thermal stability with manganese incorporation.

**Acknowledgments.** This work has been fully supported by Croatian Science Foundation under the project IP-01-2018-2963.

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## THERMAL STABILITY OF GAMMA RADIATION INDUCED RADICALS IN ION-SUBSTITUTED HYDROXYAPATITES

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Hydroxyapatite (HA,  $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ ) is the thermodynamically most stable calcium phosphate phase and also among the most frequently used hard tissue regeneration materials.<sup>[1]</sup> However, bone mineral itself is non-stoichiometric, ion-substituted, poorly crystalline HA.<sup>[2]</sup> Inspired by nature, doping of HA with ions which have different biological roles, like Mg, Si, Zn, Sr, is applied as a method of improving its bioactivity. Frequent method of sterilization of such materials is  $\gamma$ -irradiation, which can result in formation of radicals and structural changes in the material itself. Therefore, for the safe application of ion-substituted HA, it is important to determine not only the stability of the formed radicals, but also get an insight in the induced structural changes.

In this work, HA and 3 different ion-substituted HAs doped with 2% Mg; 2% Mg + 0.4% Si and 2% Mg + 1.25% Si were irradiated to 25 kGy with  $^{60}\text{Co}$   $\gamma$ -rays and studied. Their relative radical concentration, determined by electron paramagnetic resonance (EPR) spectroscopy, was monitored as a function of time at different temperatures in the presence of air. The temperature and time dependence of each sample is presented and discussed, as well as the changes in the X-ray diffraction patterns.

**Acknowledgments.** This study was supported by Croatian Science Foundation, Grant HRZZ- IP-2018-01-1493, Croatian-Serbian bilateral project “Ion substituted hydroxyapatites for bone tissue engineering” and COGITO project “Systematic investigation of adsorption of proteins on calcium phosphate based bioceramics for bone tissue engineering”.

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## NOVEL HONEYCOMB SILICON STRUCTURE AS POTENTIAL ANODE MATERIAL FOR LI-ION CELLS

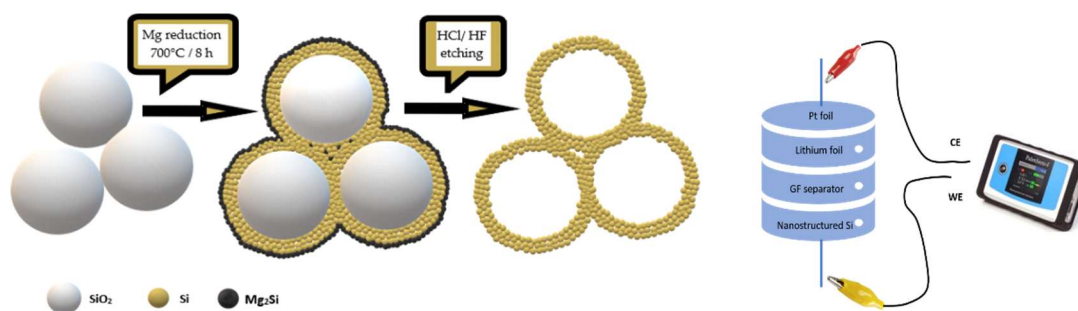
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Silicon stands out as next generation anode material due to its superior theoretical specific capacity of 4200 mAh / g which is a result of intercalation 4.4 Li into Si at high temperature to form  $\text{Li}_{15}\text{Si}_4$ .<sup>[1]</sup> The porous structure can provide a large space to accommodate volume expansion and provide a large surface area for lithium-ion transport from electrolyte to silicon. Porous silicon with high surface can improve accessibility of the electrolyte to silicon and increase lithium diffusion length which increase capacity<sup>[2]</sup>. Magnesiothermic reduction (MRR) of silica ( $\text{SiO}_2$ ) is a facile method for the synthesis of porous silicon spheres at lower temperatures than conventional silica reduction methods<sup>[2]</sup>. In this work, honeycomb Si nanostructure was prepared by MRR method and treated with silver ions ( $\text{Ag}^+$ ) which are reduced to form Ag nanoparticles. The Ag nanoparticles were placed within the pores thus being directly connected to both the silicon structure as well as the current collector, which results in improved electrochemical performance of the honeycomb structure<sup>[3]</sup>. The aim of this work is to investigate the mechanism and kinetics of  $\text{Li}^+$  ions intercalation in the porous structure of newly prepared materials as potential anodes for Li-ion batteries.



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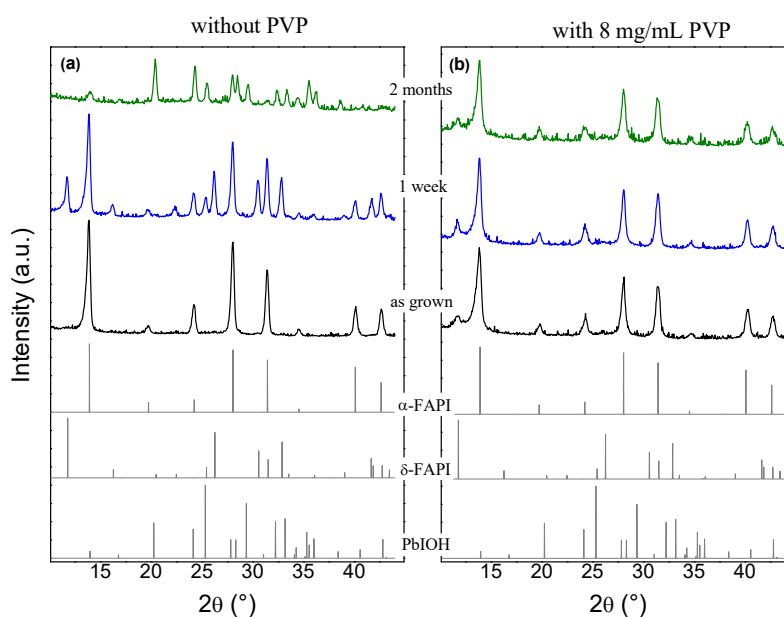
## IMPROVED OPTICAL AND ELECTRICAL PROPERTIES OF FORMAMIDINIUM LEAD IODIDE PEROVSKITE FILMS ON ZnO NANORODS WITH POLYVINYLPIRROLIDONE ADITIVE

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Kojima et al.<sup>[1]</sup> published their findings of an easy-to-synthesize organometal lead perovskite material for use in photovoltaic devices. One of the ongoing issues of the material is the instability of the perovskite thin film in ambient environment.<sup>[2]</sup> In this work we investigate the role of polyvinylpyrrolidone on the stability of FAPbI<sub>3</sub> perovskite thin film on glass and ZnO nanorods in the ambient environment as well as its impact on optical and electrical properties.



**Figure 1.** Time dependence XRD patterns of FAPbI<sub>3</sub> thin films

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## NANOSTRUCTURED SnO<sub>2</sub> THIN-FILMS FOR SOLAR CELLS

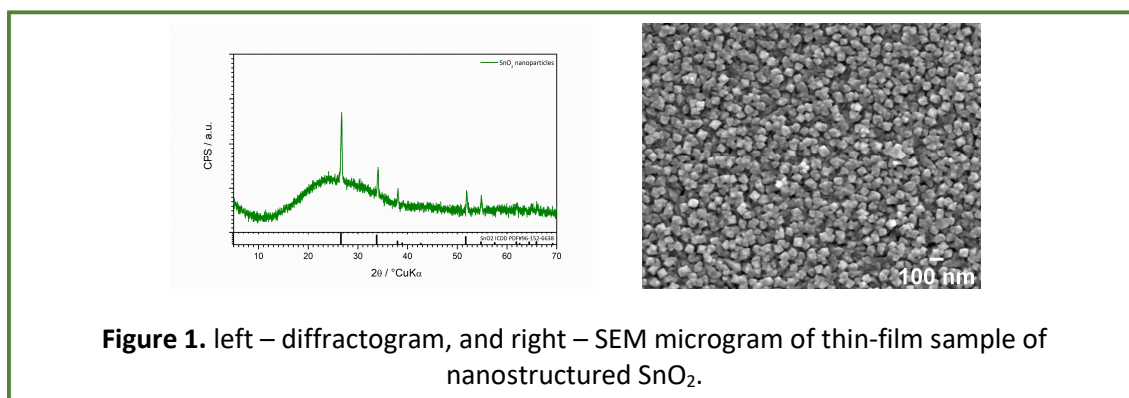
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For sensing, catalytic and various optoelectronic materials, where nanocomposites based on semiconducting oxides find application, the major challenge is to elucidate a configuration that will improve functional performances.<sup>[1]</sup> Tin(IV) oxide is earth-abundant, important and widely used semiconductor (with a bandgap of 3.6 eV), a part of the transparent conductive oxide (TCO) family. It is investigated for application in photovoltaic devices due to the deep conduction band level and high electron mobility which can lead to more efficient electron extraction and transport of charge carriers. Synthetic wise, various routes to derive SnO<sub>2</sub> nanocrystals and nanostructures have been examined, including flame pyrolysis, thermal evaporation, hydrothermal synthesis, and various sol-gel methods.<sup>[2]</sup> In this work, we report on the synthesis and characterisation methods of SnO<sub>2</sub> nanoparticles and nanostructured thin-films in order to control size and morphology on behalf of varying the reaction conditions. We try to shed more light on the processes behind the forming of the domains, depending on the reaction settings. Prepared samples are thoroughly (micro)structurally and electrically characterised using XRD, AFM, SEM, impedance spectroscopy (IS) and deep level transient spectroscopy (DLTS) analysis. All of these point out the level of chemical and structural homogeneity (Fig. 1), and the influence of temperature and other reaction conditions on the growth and properties of nanostructures. We strive to achieve more precise control of the SnO<sub>2</sub> surface properties, including film quality, defects, and surface states, to facilitate the charge transfer and mitigate the recombination.



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## PREPARATION AND CHARACTERIZATION OF POLY(ETHYLENE OXIDE)/CLOISITE 20A NANOCOMPOSITES

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Environmental and safety regulations require modifications of recently used chemical power sources. In last four decades, scientists made considerable effort in trying to substitute common liquid electrolytes with solid electrolytes.<sup>[1]</sup> Among these, polymer systems based on poly(ethylene oxide) (PEO) have attracted considerable attention, especially in the field of batteries such as lithium-ion batteries.<sup>[2]</sup> Although PEO is known to dissolve a large number of lithium salts, his high degree of crystallinity is thought to be the main reason for low ionic conductivity of PEO based solid polymer electrolytes. In order to improve the ionic conductivity of solid polymer electrolyte (SPE) various strategies have been developed, among which is the modification of the polymer matrix by incorporation of nanofillers. In this work nanocomposites of poly(ethylene oxide) with viscometric average molecular weight of 1 000 000 (PEO10) and 5 000 000 (PEO50) and organically modified montmorillonite Cloisite 20A as nanofiller were prepared by melt intercalation. Nanocomposites PEO10/20A and PEO50/20A with different weight ratios of polymer matrix to clay were analysed by differential scanning calorimetry (DSC) and dynamic thermogravimetry (TG) in order to investigate the crystallinity and thermal properties. Differential scanning calorimetry shows that the glass temperatures of PEO10 and PEO50 are not significantly altered by the addition of Cloisite 20A. Values of characteristic melting temperatures of nanocomposites show that the extrapolated onset temperatures remained practically unchanged while the peak temperatures and extrapolated end temperatures are lowered compared to pure PEO. The influence of nanofiller on the degree of crystallinity of polymer matrix becomes more pronounced with the addition of Cloisite 20A over 40 wt. %. The thermogravimetric analysis revealed that the degradation of nanocomposites occurs through one degradation step for PEO10/20A nanocomposites with up to 70 wt. % and for PEO50/20A nanocomposites with up to 90 wt. % of Cloisite 20A. Addition of Cloisite 20A decreases the thermal stability of both PEO10 and PEO50. The onset degradation temperatures and the temperatures at the maximum degradation rate show lower values compared to pure PEO regardless of matrix molecular weight.

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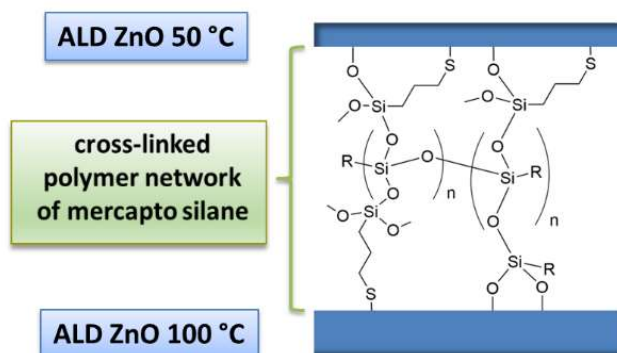
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## PREPARATION OF ZnO/ORGANOSILANE/ZnO HYBRID THIN FILMS VIA ATOMIC LAYER DEPOSITION (ALD) AND SOLUTION SURFACE MODIFICATION

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Stable organic-inorganic hybrid thin films with the “sandwich” structure, ZnO/organosilane/ZnO, were prepared using ALD grown ZnO layers and surface modification with the bifunctional (3-mercaptopropyl)trimethoxysilane (MPTMS) in solution.<sup>[1]</sup> Formation of monolayer or multilayers of MPTMS molecules are driven by the strong S-Zn bonds. Silane self-condensation reaction led to the growth of a cross-linked polymer. A top layer of ALD ZnO was deposited on the free thiol –SH and silanol Si-OH groups exposed on this soft polymer substrate. Thermal removal of the organic part induced morphological changes due to the template effect of the sacrificial polymer. The resulting ZnO thin films showed improved UVA photocatalytic activities against the degradation of methyl orange, compared to the initial ALD ZnO layer and to control samples. The resulting materials were characterized by XPS spectroscopy, SEM and AFM microscopies, and SIMS mass spectrometry.



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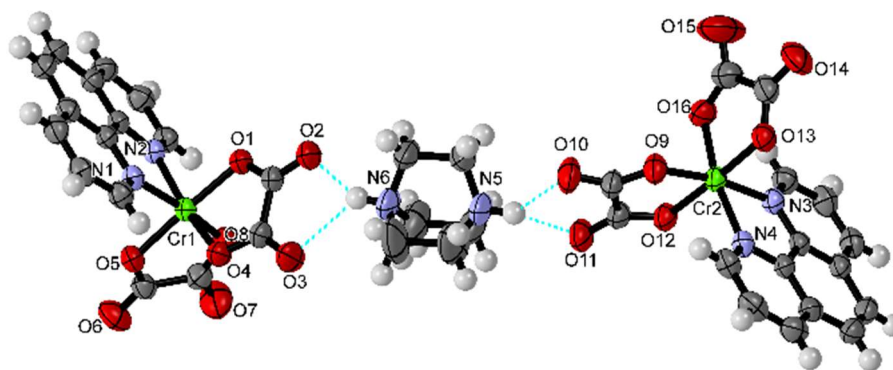
## STRUCTURAL AND DIELECTRIC STUDIES OF BIS(OXALATO)CHROMIUM(III) COMPLEXES WITH AZABICYCLIC CATIONS

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In ferroelectric materials spontaneous electric polarization ( $P_s$ ) can be reversibly switched under an external applied electric field. While homochirality provides an important bridging effect between structure and properties, the discovery of new ferroelectrics is often random rather than strategically designed.<sup>[1]</sup> Here we report on the synthesis and characterization methods of two metal-organic complexes containing bicyclic amine cations, DABCO<sup>2+</sup> (1,4-diazabicyclo[2.2.2]octane) and COOH-OH-ABCO<sup>+</sup> (3-hydroxy-1-azabicyclo[2.2.2]octane-3-carboxylic acid), and bis(oxalato)chromium(III) anions, [Cr(bpy)(C<sub>2</sub>O<sub>4</sub>)<sub>2</sub>]<sup>-</sup> (bpy = 2,2'-bipyridine) and [Cr(phen)(C<sub>2</sub>O<sub>4</sub>)<sub>2</sub>]<sup>-</sup> (phen = 1,10-phenanthroline). Complex salts were prepared using mechanochemical synthesis, whereupon we obtained single crystals by slow evaporation of their aqueous solutions. Crystal structures were determined from single-crystal X-ray diffraction analysis. Complexes were also characterized by IR spectroscopy, thermal analysis and impedance spectroscopy. Moreover, COOH-OH-ABCO<sup>+</sup> was characterized using <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy. The ferroelectric properties of prepared complex salts have been further tested by the P–V measurements. Crystals of (DABCO)[Cr(phen)(C<sub>2</sub>O<sub>4</sub>)<sub>2</sub>]<sub>2</sub>·9H<sub>2</sub>O exhibit pleochroism when observed under polarized light, changing color from pink to orange.



**Figure 1.** Asymmetric unit of (DABCO)[Cr(phen)(C<sub>2</sub>O<sub>4</sub>)<sub>2</sub>]<sub>2</sub>·9H<sub>2</sub>O. Crystallization water molecules have been omitted for clarity.

**Acknowledgments.** Financial support from the Croatian Science Foundation (UIP-2019-04-7433) is gratefully acknowledged.

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## USAGE DURABILITY OF KNITWEAR MADE OF MAN-MADE ARTIFICIAL FIBERS FROM CELLULOSE

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Cellulose is a raw material with a wide variety of uses in the chemical industry for producing man-made textile fibers. Conventional regenerated cellulosic fibers are generally produced by the indirect viscose process (viscose fibers), while high-tenacity modal fibers are produced using a modification of the basic procedure. Viscose production is based on deriving cellulose with carbon bisulphide. Lyocell fibers are produced by a more environmentally friendly procedure from a solution of non-derivative cellulose in a solvent spinning process, where cellulose is dissolved directly in the organic solvent N-methylmorpholine-N-oxide, without the formation of derivatives.<sup>[1]</sup> Different production processes cause differences in the structure of the fibers despite the same chemical composition.

Knitwear that are worn in direct contact with the skin, are often made of viscose, modal or lyocell fibers, that provide silky touch, high hydrophilicity and exceptional comfort. They were usually knitted with spun yarns produced by conventional ring spinning system. More recently unconventional rotor and air-jet spun yarns have been appeared, resulting with yarns of different structure and properties.<sup>[2]</sup> Therefore, in this paper circular weft double jersey knitted fabrics for lingerie made of single ring, rotor and air-jet spun yarns, all made of bright staple viscose, modal and lyocell fibers of the same linear density were evaluated. Raw and finished knitwear usage durability were compared by determination of moisture regain, breaking strength and breaking elongation, dimensional change after laundering, air permeability, propensity to surface piling and abrasion resistance, all according to the standardized test methods.

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## COMFORT OF SOCKS MADE OF INNOVATIVE CELLULOSE MATERIALS

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The socks are knitted next-to-skin-type garments worn on the feet and often covering the ankle and some part of the calf. They have to fulfill high demands of functionality, comfort, durability and design. As the comfort of socks depends on their construction and materials used, it is very important to select fibers and yarns for their production. The number of European standards related to testing of knitwear and socks are low.<sup>[1]</sup> With increasing demand for garment comfort, there are many studies related to the comfort properties of fabrics. However, there are significantly less studies examining the thermal comfort of socks, which are using thermal foot model.<sup>[2]</sup>

The socks are usually made from cotton yarns for softness and comfort and blended with polyamide or Lycra for improved fit, durability and shrink resistance. Therefore, and with the fact that the applicability of modal fibers and microfibers (man-made artificial fibers from cellulose which provide silky touch and exceptional contact comfort) in knitting of socks is insufficiently researched, as well as yarns made from them by unconventional rotor and air-jet process, in this paper properties of two groups of socks, made of innovative materials – single ring, rotor and air-jet spun yarns of the same linear density (all made of bright staple modal fibers of linear density of 1.3 dtex and modal microfibers of 1.0 dtex respectively) in full plating by textured polyamide 6.6 yarns of different linear density were evaluated. Evaluation of sock comfort was carried out by investigation of water vapor absorption and air permeability of socks knitted fabrics and socks thermal comfort before and after five repeated washing and drying cycles by measuring of thermal resistance on the thermal foot.

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## PREPARATION OF POLY(ETHYLENE OXIDE) FILM WITH VARIATION OF DRYING TEMPERATURE

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Different applications of polymers demand different processing procedures, among which is the film preparation for solid polymer electrolyte (SPE) by solution casting technique. Solution casting technique is widely used technique to prepare flexible films of SPE with different thickness. The main obstacle is to prepare films without solvent residue, that is primarily connected to the drying procedure. Poly(ethylene oxide) (PEO) as water-soluble and biodegradable polymer is one of the polymers that is used as the host polymer for a salt and other additives to prepare SPE.<sup>[1]</sup> Since the ionic conductivity in PEO with lithium salts was discovered, the significant effort was devoted to preparation of a good quality film with higher conductivity value. This can be improved by lowering the amount of crystalline phase because the ionic transport is correlated with amorphous phase that is preferred for the faster ion transfer.<sup>[1]</sup> The procedure of the film preparation can influence the crystallinity of the film. PEO films with different PEO molecular weights (100 000 and 300 000 g mol<sup>-1</sup>) were prepared by casting the films from the aqueous solutions of different PEO concentrations (1 and 1.5 wt%). The optimal conditions for dissolving the polymer in water was found. Successfully prepared solutions were casted and dried at 40, 50 and 60 °C, to find the optimal drying conditions. Films with higher molecular weight has better quality. Differential scanning calorimetry (DSC) was applied to investigate the influence of different molecular weights, film thicknesses and drying temperatures on the thermal properties and crystallinity of PEO. The formation of different PEO crystals was observed, and in general it can be concluded that thermal characteristics of the films doesn't differ significantly. The thermal stability of the films was investigated using non-isothermal thermogravimetry (TG). PEO films decompose in one decomposition stage and there is no large difference in the thermal stability by variation of the molecular weight, film thickness or drying temperature, with one exception. Due to the successful removal of the solvent from the dried films at 40 °C, it is not necessary to use a higher temperature but only to investigate the minimum drying time to optimize the preparation procedure.

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## TOWARDS NANOBIOSENSOR FOR CORONAVIRUS (COVID-19) DETECTION: CONJUGATION OF MONOCLONAL ANTI-SARS-COV-2 ANTIBODIES TO GOLD NANOPARTICLES

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Gold nanoparticles (AuNPs) are extensively used as biophysical tools in the area of biomedicine and bionanotechnology due to their exceptional properties.<sup>[1]</sup> They are characterized by surface plasmon resonance, which may significantly enhance diagnostic applications. Antibody-coated nanoparticles have recently attracted considerable attention for the detection of SARS-CoV-2 virus which causes COVID-19 disease.<sup>[2,3]</sup>

In the present study, we investigate the effect of three different conjugation strategies of AuNPs for more efficient binding of monoclonal anti-SARS-CoV-2 antibodies: a) direct conjugation of antibodies by electrostatic interactions or physical adsorption on nanosurface, b) conjugation mediated by glycopeptide using peptidoglycan monomer GlcNAc-MurNAc-L-Ala-D-isoGln-mesoDAP(NH<sub>2</sub>)-D-Ala-D-Ala (PGM) and c) covalent conjugation using EDC chemistry. The AuNPs-antibodies conjugates were characterized by UV-Vis, DLS and TEM techniques. Preliminary results showed that covalent conjugation using EDC/NHS chemistry enabled the most stable nano-enabled conjugate with high potential for use in SARS-CoV-2 virus detection.

**Acknowledgments.** We acknowledge the financial support of Croatian Science Foundation (HrZZ, Project No: IP-2018-01-6910)

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## SYNTHESIS OF 1,2-DIKETONES FROM ALDEHYDE USING NOVEL CERIA-ZIRCONIA HIGH-ENTROPY OXIDES AS ACTUAL CATALYSTS

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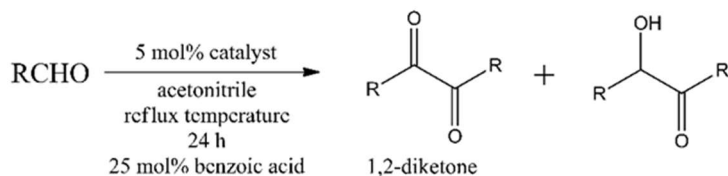
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Four high-entropy oxide (HEO) heterogeneous catalysts were developed and synthesized via an ecologically acceptable synthetic route.<sup>[1]</sup> They were structurally characterized and, as synthesized, they were subjected to catalytic testing as actual catalysts for promotion of aldehydes to desired products - 1,2-diketones. Synthesis of 1,2-diketones attracted much scientific attention over the years due to the various applications across many scientific fields.<sup>[2,3]</sup> Recently, notable progress has been achieved with precious metal catalysts,<sup>[4]</sup> but no heterogeneous catalysts were reported yet with the ability to provide such versatile catalytic behavior as homogeneous ones. Oxidative Pinacol-type coupling reactions were performed, using synthesized HEOs as catalysts. Results indicate high selectivity and catalytic activity towards the transformation of aldehydes to 1,2-diketones, highly comparable with Pd-based homogeneous catalysts.<sup>[4]</sup>



**Scheme 1.** Pinacol-type oxidative coupling reaction of the aldehydes.

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## ANALYSES ON CHEMICAL AND MECHANICAL STRIPPING OF COATINGS ON METAL PLATE MOCK-UPS

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The Conservation of Art in Public Spaces (CAPuS) project, which was funded through the Erasmus+ Knowledge Alliances Programme,<sup>[1]</sup> included research into the products and methods that can be used for specific conservation treatments on contemporary public artworks, predominantly murals and sculptures. The Croatian research group, which was comprised of the METRIS Research Centre, Sisak Municipal Museum and the University of Split – Arts Academy, focused on a large collection of outdoor metal sculptures in Sisak. The sculptures were produced by the artists who participated in the Sisak Steelworks Fine Artists' Colony (1971 – 1990).<sup>[2,3]</sup> Due to decades of outdoor exposure, most of the painted pieces require paint stripping and repainting. Through the CAPuS project, a methodology was devised for identifying the best method for the removal of aged coatings from a steel substrate. METRIS and Sisak Municipal Museum as partners cooperated on jointly carried out experimental work: selected test analyses for the removal of artificially aged paint coatings.<sup>[4]</sup> Since conservation-restoration interventions must not inflict damage to the object, various available methods (chemical and mechanical) and products used for the removal of aged coatings needed to be examined in order to find the most suitable one(s).<sup>[5,6]</sup>

Thirty mock-up test plates were produced: steel plates coated with commercially available alkyd-based coating system consisting of primer and topcoat, artificially aged in neutral salt spray chamber for 1440 h in C5 corrosivity conditions before being either chemically or mechanically stripped of the paint coatings. The methods used were chemical stripping with 6 commercially available products (four paint-stripping products and two solvents) and mechanical removal of coatings with different abrasive blasting methods, thermo-mechanical method and composite brushes.

This poster reports on the visual examination, microscopy (LM, SEM) and chemical analytical methods (EDS, FTIR) that were performed in order to determine the most effective method of stripping of coatings and/or to determine the residues left on the mock-ups after the treatments.

Although none of the tested methods completely removed the coatings from the steel substrate, the best results were obtained by dry ice blasting with addition of glass beads, and also blasting with aluminium oxide. The obtained results serve as guidelines for the future restoration works on the painted sculptures from the Sisak Steelworks Sculpture Park.

**Acknowledgments.** This work has been funded by European Commission, project Conservation of Art in Public Spaces (acronym CAPuS) funded by Erasmus+ Knowledge Alliances Programme, Project N° 588082-EPP-A-2017-1-IT-EPPKA2-KA. Exposition of the samples in salt spray chamber according to HRN EN ISO 9227 was performed by ReCorrTech Ltd., 10000 Zagreb, Croatia. Dry ice blasting of a group of samples was performed by Hladni Val Ltd., 35400 Nova Gradiška, Croatia.

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## GAS SENSORS ON FLEXIBLE POLYIMIDE, RIGID ALUMINA AND SILICON SUBSTRATE FOR THE NITROGEN DIOXIDE (NO<sub>2</sub>) AND AMMONIA (NH<sub>3</sub>) GAS DETECTION

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Gas related accidents such as toxic gas leakage in Industries, carbon monoxide leakage of boilers, or toxic gas suffocation during manhole cleaning continue to claim lives and cause injuries, gas sensors are life. Developing a sensor that can quickly detect toxic gases or biochemical is still an important issue in public health, environmental monitoring, and military sectors<sup>1</sup>. However, conventional gas sensing devices are not widely used due to their high cost of being made with complex machines and electronic devices<sup>2</sup>. In addition, commercial gas sensors have limitations in that they are difficult to use, and have poor portability and reaction speed<sup>3</sup>. Wearable electronics is expected to be one of the most active research areas in the next decade. Today, flexible and stretchable sensing devices are in great demand due to their promising applications in wearable electronics, especially for healthcare industries. People like to use nanomaterials for sensing because their large surface-to-volume ratio makes them highly sensitive<sup>3</sup>. Nanomaterials like Carbon nanotubes (CNT), and Graphene has major role in fabricating flexible gas sensors for the detection of various hazardous gases, including nitrogen dioxide (NO<sub>2</sub>), ammonia (NH<sub>3</sub>), hydrogen (H<sub>2</sub>), carbon dioxide (CO<sub>2</sub>), sulfur dioxide (SO<sub>2</sub>), and humidity in wearable technology<sup>4,5,6</sup>.

In this contribution, three different Sensor configuration has been used for the detection of Nitrogen dioxide (NO<sub>2</sub>) and Ammonia (NH<sub>3</sub>) Gas. Firstly, we use simple and cost effective spray coating method to coat the wearable flexible Graphene/PANI on polyimide substrate working at room temperature. The Sensor show responses towards and Ammonia (NH<sub>3</sub>) Gas. The Second Configuration, Zinc Oxide nanowires (NWs) were grown by Chemical vapor deposition (CVD) on Silicon substrate. This sensor is based on Printed circuit board (PCB) system. On the backside of the PCB a heater is placed to apply in-situ annealing while measuring Ammonia (NH<sub>3</sub>) Gas.

In the third Sensor configuration, Specifically, commercial alumina substrates were used to deposit these nanomaterials. Which has the platinum screen-printed interdigitated electrodes (IDE) to coat thin film of Zinc Oxide thin film by Aerosol Assisted Chemical Vapor Deposition (AA-CVD) method. In-addition on top slide coating method was used to deposited Single wall carbon nanotube (SWCNT). This nanomaterial has been expose NO<sub>2</sub> and NH<sub>3</sub> gases which has 10 min pulses of 10,20,30,40,50 ppm working at RT and 200°C. The concentrations tested were obtained by diluting the gases on synthetic air.

**Acknowledgments.** I would like to acknowledge CONTEXT Cost Action (CA17107) for support.

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## ENVIRONMENTAL ASPECT OF PHOTOCATYLSIS FOR THE DEGRADATION OF OXYTETRACYCLINE IN WATER: N-S-TiO<sub>2</sub> vs TiO<sub>2</sub>

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Antibiotics are among the most commonly used pharmaceutical in human and veterinary medicine and have increasingly become a problem for the environment. Oxytetracycline (OTC) is a broad-spectrum antibiotic belonging to the tetracycline class and due to its antibiotic nature, stable naphthalene ring structure and hydrophilic properties, its removal by conventional wastewater treatments is difficult.<sup>[1]</sup>

On the other hand, titanium dioxide is one of the most studied semiconductors in photocatalytic processes for water treatment due to its unique properties such as chemical inertness, photostability and biocompatibility.<sup>[2]</sup> One of the major drawbacks of TiO<sub>2</sub> as a photocatalyst is the wide band gap (3.2 eV) of the material, which limits the light absorption only to the ultraviolet region (wavelength <390 nm), thus limiting the practical applications for solar light harvesting.<sup>[3]</sup> Doping TiO<sub>2</sub> with metal, non-metal, or co-doping increases its photocatalytic activity under a broader solar spectrum. In this sense, nitrogen and sulphur have been found to be effective doping elements to enhance the photocatalytic activity under visible light illumination.<sup>[4]</sup>

In this work Sulphur- and Nitrogen-dope TiO<sub>2</sub> (S-N-TiO<sub>2</sub>) photocatalyst and benchmark TiO<sub>2</sub> P25 have been employed for the degradation of OTC under solar and visible irradiation at three pH, corresponding with OTC pKa values (3.2, 7.5 and 8.9). OTC concentration, mineralization, degradation by-products, and associated changes in biodegradability and toxicity (*A. fishery*, *D. Magna* and *P. Subcapitata*) were monitored during the treatment.

Composites were deposited on round glass plates, according to the procedure described in bibliography.<sup>[5]</sup> Spin coating of the photocatalytic film was performed at 1500 rpm, using the KW-4A spin coater, Chemat Technology, USA.

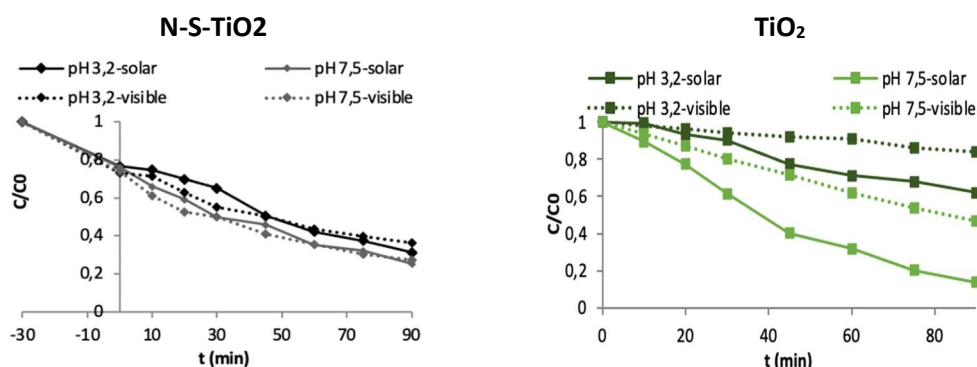
Photocatalytic activity of the composites for the removal of OTC was evaluated employing a water-jacket cooled batch reactor and a solar simulator (Oriel/Newport, USA) equipped with a 450 W xenon arc lamp (Osram, Germany) as irradiation source; a glass filter was used (when visible light is needed) to cut off radiation with  $\lambda < 300$  nm.

Aqueous OTC solution was prepared at the initial concentration (0.1 nM) and pH was adjusted to the desired value: 3.2, 7.5 or 8.9. The glass plates with catalysts thin films were placed in the reactor, the reaction solution was then added and irradiated for 90 minutes. Adequate mixing of the solution was ensured with an orbital shaker DOS-20 (90 rpm, Neo-lab, Germany). Samples were periodically taken during the experiments, filtered using Chromafil XTRA RC (25 mm, 0.45  $\mu$ m; Macherey Nagel, Germany) and submitted to analysis (HPLC, TOC, DQO, DBO<sub>5</sub> and toxicity).

A set of blanks experiment (hydrolysis, photolysis and adsorption) were first performed at the three selected pH. A high photolysis was observed at pH 8.9 for both source of light (visible and solar), reaching the complete elimination of OTC after 8 hours of illumination so this pH was

discarded for further experiments. Regarding adsorption experiments equilibrium was reached after 30 min for N-S-TiO<sub>2</sub>, while for TiO<sub>2</sub> no adsorption was observed, taking that into account 30 min of dark period was applied for further experiments with N-S-TiO<sub>2</sub>, while for TiO<sub>2</sub> dark period was not needed.

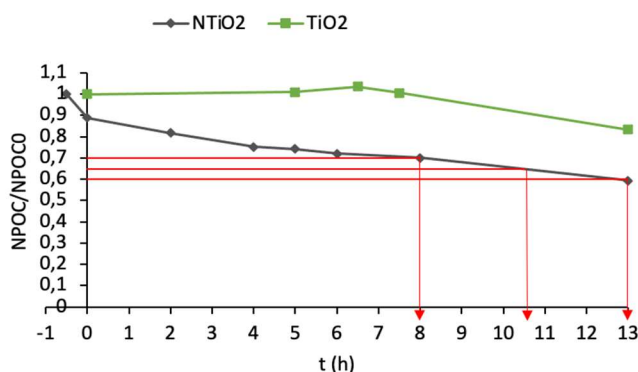
Figure 1 represents OTC removal obtained using N-S-TiO<sub>2</sub> (left) and TiO<sub>2</sub> (right) for the two selected pH and source of light. As can be observed there in N-S-TiO<sub>2</sub> case no big differences in degradation were obtained, being slightly high the degradation at pH 7.5. Regarding TiO<sub>2</sub>, as was expected, the degradation is higher at pH 7.5 under solar irradiation. Comparing both catalysts, the doping of TiO<sub>2</sub> with sulphur and nitrogen improve the catalyst activity for OTC degradation only under visible irradiation, while under solar TiO<sub>2</sub> is more effective.



**Figure 1.** Activity of immobilized composites N-S-TiO<sub>2</sub> and TiO<sub>2</sub> under visible and solar irradiation for OTC removal at pH 3.2 and 7.5

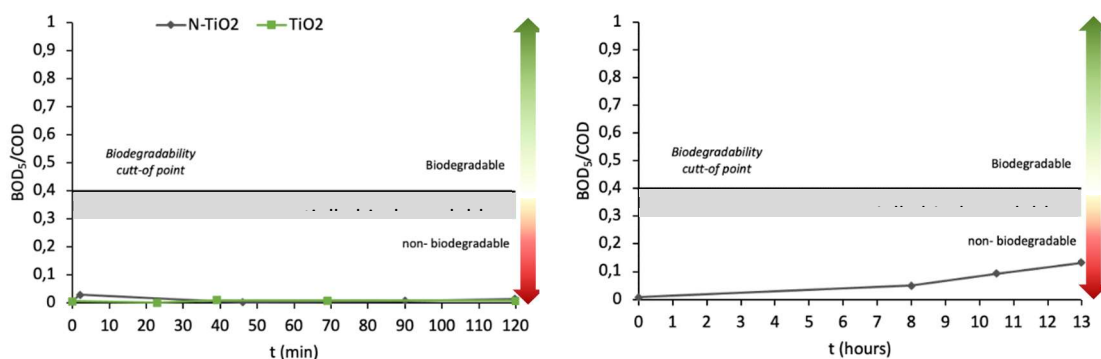
Considering those results pH 7.5 and solar irradiation were selected to study the mineralization kinetics, biodegradability and toxicity evolution during the treatment. For that purpose, reference treatment time (RTT) were selected for both catalyst corresponding with the 25, 50, 75 and 100% removal of OTC

Since in previous experiment no mineralization was observed after 90 minute of irradiation the treatment time was increased up to 13 hours. As can be seeing in Figure 2 despite with TiO<sub>2</sub> a higher OTC removal is achieved almost no mineralization is observed after 13 hours of illumination while with N-S-TiO<sub>2</sub> around 40% of mineralization was observed. RTT were also selected (only for N-S-TiO<sub>2</sub> in that case) corresponding with 30, 35 and 40% (red narrow in Figure 2) of mineralization for biodegradability and toxicity assays.



**Figure 2.** Activity of immobilized composites N-S-TiO<sub>2</sub> and TiO<sub>2</sub> under solar irradiation for mineralization kinetics at 7.5

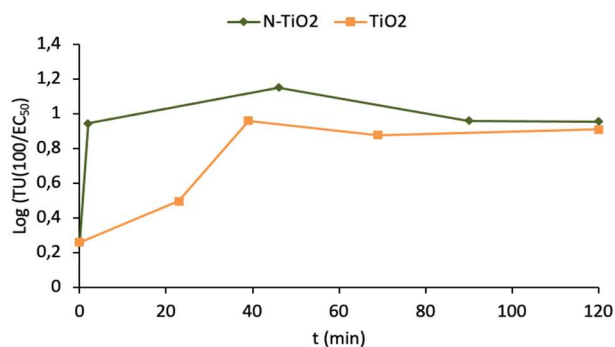
Figure 3 represent biodegradability evolution during the treatment for OTC RTT (left) and for mineralization RTT (right). Regarding OTC RTT no biodegradability improvement was reached for any catalyst. In the case of mineralization RTT only an increase of around 20% was reached.



**Figure 3.** biodegradability evolution during the treatment for OTC RTT (left) and for mineralization RTT (right)

Finally, toxicity bioassays were also performed with *Vibrio Fischeri* experiment (for OTC RTT), *Daphnia Magna* and *Selenastrum Capricornutum* (for mineralization RTT).

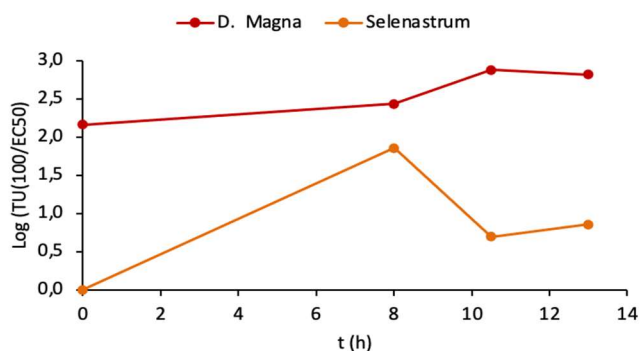
In *Vibrio Fischeri* assays an increase of the toxicity was observed for both photocatalyst, (Figure 4), indicating that the formed by-products were more toxic. In the case of N-S-TiO<sub>2</sub>, in the first 2 minutes of reaction a high increase of toxicity was observed then reached the maximum (log (TU) = 1,15) and after that decreased slowly. In the case of TiO<sub>2</sub> toxicity is more constant during the experiment, reaching the same values of log (TU) as the N-S-TiO<sub>2</sub> (log (TU) = 0,956).



**Figure 4.** Toxicity evolution (V. Fisheri) during the degradation of OTC with N-S-TiO<sub>2</sub> and TiO<sub>2</sub> catalysts at pH 7.5 under solar irradiation

*D. Magna* assays were performed and measured after 24 hours and 48 hours of contact. For *S. Capricornutum*, contact times used were 24 hours, 48 hours and 72 hours, according protocols. As it can be seen in Figure 5, toxicity increases for *D. Magna* as mineralization increases, which indicates that the possible by-products formed in the reaction are more toxic than the parent pollutant. It starts at log(TU) = 2,16; and it ends at 13 hours with log(TU) = 2,82. Similar results were obtained for *S. Capricornutum*, the toxicity has a tendency to increase throughout the experiment. The initial sample starts with a log(TU) near 0, then there is a considerable increase in toxicity and finally it decreases again until log(TU) = 0,85.





**Figure 5.** Toxicity evolution (D. Magna and S. Capricornutum) during the degradation of OTC with N-S-TiO<sub>2</sub> catalysts at pH 7.5 under solar irradiation for selected mineralization RTT

The obtained results show that despite the degradation of the OTC is reached, the effluent is still being non-biodegradable and toxic probably due to the formation of degradation by-products that are toxic and non-biodegradable.

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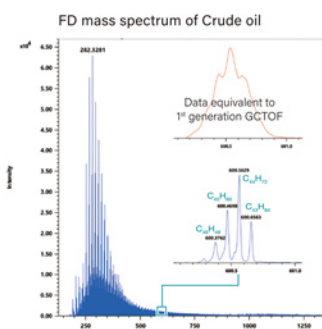
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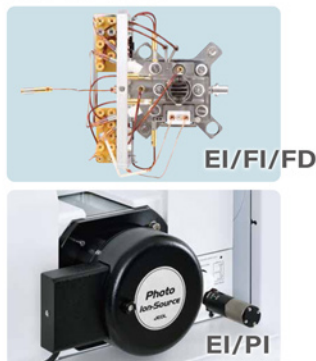
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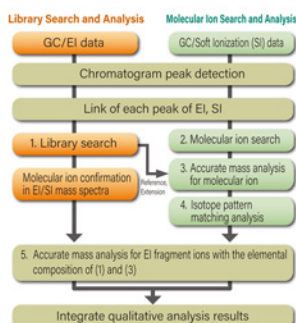
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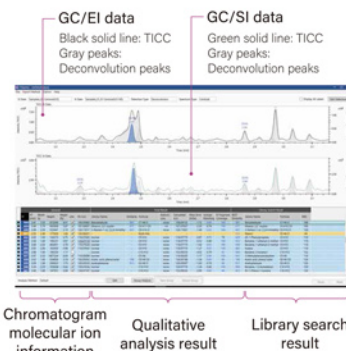
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## VERTIKALNA POVEZANOST KURIKULUMSKIH SADRŽAJA KEMIJE I PRIRODE OD ISHODA NA RAZINI AKTIVNOSTI PREKO POKUSA DO VREDNOVANJA

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Učenički pokus je važna osnova za aktivno učenje sadržaja prirodoslovlja, posebno kemije, pri čemu učenik razvija svoje praktične, perceptivne i misaone kompetencije.<sup>[1]</sup> Autonomija učitelja pri razradi odgojno-obrazovnih aktivnosti<sup>[4]</sup> omogućuje mu da pojedine ishode ostvari u okviru različitih tematskih cjelina, neke usporedno i integrirano, a neke kroz vertikalnu povezanost. Isti pokus može biti polazište za ostvarivanje više različitih odgojno-obrazovnih ishoda<sup>[2]</sup> na različitim razinama poučavanja za što je u osnovnoj školi poželjna i potrebna suradnja učitelja prirode i učitelja kemije.

Sudionici će tijekom radionice (radom u skupinama) analizirati primjere pet pokusa za 5. razred. Za predložene će pokuse iz Kurikuluma nastavnog predmeta Priroda za 5. razred pronaći odgovarajući jezgrovni ishod te pripadni ishod iz njegove razrade. U Kurikulumu nastavnog predmeta Kemija za 7. razred pronaći će poveznice s odgojno-obrazovnim ishodima nastavnoga predmeta Kemija za 7. razred te po potrebi osmisliti nadogradnju predloženih pokusa sukladno kontekstu poučavanja. U svrhu vrednovanja sudionici će temeljem odabranih odgojno-obrazovnih ishoda i pokusa, dati prijedloge pitanja za provjeru njihove ostvarenosti. Odredit će kognitivnu razinu predloženih pitanja (prema Crooks-u, 1988.) te dati prijedlog brojčanog ocjenjivanja za učenike koji se školuju po redovnom programu, posebno za nastavni predmet Prirodu i posebno za nastavni predmet Kemiju.

Opisane pokuse i pripadne primjere zadataka temeljenih na problemski orijentiranom poučavanju<sup>[5]</sup> moguće je koristiti i u metodi poučavanja obrnute učionice,<sup>[3]</sup> posebno u sklopu nastave na daljinu uz potrebu većeg angažmana učitelja u smislu vođenja kroz aktivnosti.<sup>[6]</sup>

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## RADIONICA AROMATERAPIJE U OŠ MARIA MARTINOLIĆA

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### Radionica aromaterapije

Svaki jadranski otok jest vrt omeđen morem. U vrtu, kao i u netaknutom prirodnom krajoliku, sklad bilinskih oblika i boja raznježuje naša osjetila. Ako pak biljke još mirišu – miomirišu, zar nismo u predvorju raja?!

Radionice aromaterapije namijenjene su našem najvećem bogatstvu, a to su naša djeca.

Radionicom aromaterapije želimo pobuditi sva djetetova osjetila kao i približiti ih prirodi na djeci svojstven i zanimljiv način.

Prenošenjem znanja na najmlađe, sigurni smo da nasljeđuju neprocjenjivo.

Na taj način možemo biti sigurni da formula sreće i zdravlja neće utonuti u zaborav

MIOMIRISNO + LJEKOVITO = ZDRAVO

**Cilj radionice:** izrada prirodnih preparata uz pomoć autohtonih biljaka otoka Lošinja (prirodni melem za usne, "komarcotjer" i prirodni sprej za dezinfekciju učionica).

**Obrazloženje cilja:** korištenjem prirodnih materijala, sudionici radionice će shvatiti važnost očuvanja okoliša kao i prednosti primjene prirodnih preparata

**Očekivani ishodi/postignuća:** sudionici će se upoznati s postupcima izrade prirodnih preparata te razlikovati eterična ulja nekih zavičajnih biljaka Lošinja (lavanda, maslina, smilje...)

Prepoznati važnost primjene postupaka sigurnih za ljude i okoliš vrednovati primjenu prirodnih preparata za zdravlje.

Radionicom aromaterapije možemo biti sigurni da formula sreće i zdravlja neće utonuti u zaborav.

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## POKUSI I ISHODI U NASTAVI KEMIJE

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Učenici su znatiželjni prije početka nastave u sedmom razredu zbog uvođenja novih nastavnih predmeta. Kemija je jedan od tih, *novih* predmeta. Često pobuđuje interes kod učenika zbog očekivanja da će se tijekom nastave kemije izvoditi zanimljivi pokusi. Učitelji i nastavnici kemije prepoznaju potrebe svojih učenika, tako da na prvim satima motiviraju učenike izvedbom različitih pokusa. Pokus je osnovni izvor znanja pri metodičkom oblikovanju nastave kemije.<sup>[1]</sup> Stoga učitelji i nastavnici kemije nastoje izvoditi redovito pokuse u uvjetima nastave uživo, ali i online uporabom različitih digitalnih alata i metoda rada. Na temelju planiranih ishoda poučavanja za nastavni predmet Kemija u osnovnoj i srednjoj školi,<sup>[2]</sup> učitelji i nastavnici kemije odabiru pokuse za izvođenje te ih usklađuju s predznanjima i vještinama svojih učenika, imajući u vidu ekstenzitet i intenzitet obrade sadržaja. Tijekom izvedbe radionice, sudionici će izvesti nekoliko različitih pokusa (sa lako dostupnim potrebnim tvarima i opremom), te će svoja opažanja i objašnjenja uočenih promjena raspraviti u skupinama s ciljem ostvarenja didaktičkih načela zornosti i sistematičnosti pri izvođenju nastave kemije.<sup>[3]</sup> Sudionici će raspravljati na temelju opažanja o dobivenim rezultatima kemijskih i fizikalnih promjena. Tijekom rada sa sudionicima bit će naglašena potreba poticanja suradničkog odnosa pri radu u skupini, te zadovoljstva zbog doprinosa svakog člana skupine pri postizanju zajedničkog rezultata. U završnom dijelu radionice, rasprava će se voditi o izboru pokusa, a vezano za zadane ishode poučavanja u osnovnoj i srednjoj školi. Očekuje se da će izvođenje radionice pridonijeti poboljšanju ostvarivanja ciljeva nastave kemije zbog prijedloga sudionika o odgovarajućim rješenjima pri planiranju i realizaciji nastave kemije u osnovnoj i srednjoj školi.

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## ANALIZA INICIJALNE PROVJERE ZNANJA IZ KEMIJE U SREDNJOJ ŠKOLI

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Procjena usvojenosti kemijskih koncepata učenika na početku nove školske godine je poželjna nastavna praksa. Rezultati inicijalne provjere učeničkih postignuća, nastavniku mogu poslužiti kao smjernice pri planiranju daljnjeg poučavanja. U situaciji prošlogodišnje online nastave te prelaska na izvođenje nastave uživo početkom ove nastavne godine, provedba inicijalne provjere znanja je i preporuka institucija iz sustava.<sup>[1]</sup> Iz navedenih razloga će se tijekom radionice prikazati strukutra jedne inicijalne provjere znanja iz kemije u gimnaziji. U radionici će biti analizirana struktura zadataka prema razini ishoda poučavanja,<sup>[2]</sup> procjeni *težine* i *kognitivne razine*.<sup>[3]</sup> Sudionici radionice će analizirati inicijalnu pisanu provjeru prema tipovima zadataka (zadaci višestrukog odgovora, produljenog odgovora, otvorenog i zatvorenog tipa) te prema ukupnom broju zadataka koje učenici trebaju riješiti u određenom vremenskom roku.<sup>[4]</sup> U središnjem dijelu radionice će sudionici biti upoznati s primjenom ovakve analize inicijalne provjere na satu kemije u 4. razredu gimnazije. Također će vidjeti i neke od najčešćih učeničkih pogrešaka i miskoncepcija. Posebitost analize svakog pojedinog zadatka te riješenosti zadataka će zacijelo biti zanimljiva nastavnicima kemije u srednjim školama i zbog pripreme učenika za polaganje ispita državne mature iz Kemije. Ispitni katalog iz kemije je dopunjen i službeno objavljen u rujnu 2021.<sup>[3]</sup> Na temelju dosadašnjih provedenih inicijalnih provjera, sudionici će imati prilike iznijeti svoja iskustva te procijeniti u završnom dijelu radionice o mogućnosti primjene ovakvog modela analize inicijalne provjere znanja iz kemije.

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## ENTREPRENEURIAL SKILLS – WORKSHOP

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Engaging in entrepreneurship requires understanding of business in the field of activity as well as developing and practicing different skills. There are different approaches by which a particular area can be mastered and applied in practice. Another specificity of entrepreneurship is decision-making and undertaking activities based on a limited set of data without the possibility of additional slowdowns in decision-making.

During this workshop, an exercise in acquiring new skills will be conducted in such a way that the team of participants will determine how to complete the task and will determine for themselves the goal they want to achieve. After the exercise, the team will conduct an analysis and suggest a new way to try to achieve better results.

The process of task execution, analysis, modification of the procedure by which the task is performed will be carried out through several iterations.

In the second part of the workshop, an analysis of the achievements of all teams involved in the exercise will be made. The obtained results will give an insight into the relative progress of each team separately. Results for all teams will also be considered. The data obtained will be used to discuss how to make certain business decisions.

## SPIRIDION BRUSINA MEDAL LECTURE: SOLVENT-FREE NOTES ON NATURAL SCIENCES

### ***PREDAVANJE POVODOM MEDALJE SPIRIDION BRUSINA: NARAVOSLOVNE CRTICE BEZ OTAPALA***

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#### EN

The Midnight Lecture is organised to accompany the Spiridion Brusina Medal, awarded by the Croatian Natural Sciences Society,<sup>[1]</sup> and its aim is to highlight in layman's terms several brief notes on chemical transformations conducted in absence of solvents. Particular attention will be given to the history, geological significance and early synthetic applications of solvent-free chemistry, such as the preparation of the lead white pigment. The synthesis of the latter pigment, which was of outstanding importance in the context of renaissance and baroque art, is also an excellent example of solvent-free industrial manufacturing, as the material was at one point produced in amounts of tens of thousands of tons annually.<sup>[2]</sup> Specific attention will also be dedicated to highlighting the potential importance of solventless chemistry in avoiding large-scale industrial accidents based on solvent spills, illustrated by recent environmental catastrophes that took place in Bayer process aluminium production plants in Hungary, Brazil, and elsewhere. The ecological significance of this theme also provides a suitable opportunity to highlight the work and efforts of Prof. Brusina,<sup>[3]</sup> which were aimed not only towards the development of the natural sciences in Croatia, but also towards learning about and sustainable use of Croatia's natural resources and heritage.

#### HR

Ovo ponoćno predavanje održava se povodom dodjele nagrade Spiridion Brusina Hrvatskog Prirodoslovnog Društva,<sup>[1]</sup> te će na način koji je pristupačan općenitom slušateljstvu prikazati nekoliko crtica iz područja kemijskih transformacija bez otapala. Posebna će pažnja biti posvećena povijesnom pregledu, geološkom značaju i ranim sintetskim primjerima bezotopinske kemije, poput pripreme pigmenta olovog bjelila. Priprava ovog bijelog pigmenta, izvanredno popularnog u slikarstvu renesanse i baroka, također je i izvanredan primjer industrijske bezotopinske reakcije koja se obavljala u količinama od desetaka tisuća tona godišnje.<sup>[2]</sup> Pažnja će također biti posvećena potencijalnoj ulozi bezotopinske kemije u izbjegavanju velikih industrijskih nesreća koje se temelje na izljevu raznoraznih otopina, a koje vrlo dobro ilustriraju nedavne katastrofe vezane uz Bayerov postupak za proizvodnju aluminijske u Mađarskoj, Brazilu i šire. Ekološki značaj ove teme također pruža izvanrednu priliku za spomenuti rad i napore Prof. Brusine<sup>[3]</sup> usmjerene ne samo razvoju prirodnih znanosti u Hrvatskoj, nego i upoznavanju te održivoj uporabi hrvatske prirodne baštine.

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# INA

*Više od pola stoljeća iskustva u naftnom  
i plinskom poslovanju širom svijeta.*



## INDEX

Agić, Dejan .....	111, 113, 157	Bertoša, Branimir .....	43, 194, 232, 272
Akrap, Karla .....	286	Bešlić, Ivan .....	333, 356
Akšić, Milica M. Fotirić .....	218	Bešlo, Drago .....	111, 157
Alebić-Juretić, Ana .....	87	Beus, Maja .....	190
Alešković, Marija .....	236	Bijelić, Jelena .....	126, 361
Alič, Jasna .....	57	Bilić, Josipa .....	396
Alonso-Lerma, Borja .....	39	Biliškov, Nikola .....	267
Amat, Ana M. ....	400	Biljan, Ivana .....	58, 146, 264
Ambrožić, Gabriela .....	255, 389	Bilušić, Tea .....	97
Amić, Ana .....	200, 201	Bizdēna, Ērika .....	18, 112, 119
Amidžić Klarić, Daniela .....	28, 35	Bjelopetrović, Alen .....	184, 185, 187
Andrić, Filip .....	220, 230, 235, 249	Blažević, Ivica .....	97
Andričić, Branka .....	393	Blažić, Roko .....	372, 375
Andrijić, Željka Ujević .....	324	Boček, Ida .....	145
Androš Dubraja, Lidija .....	81, 390	Boček, Željka .....	86
Antonić Jelić, Tatjana .....	384	Bodroža-Solarov, Marija .....	253
Antonijević, Marko .....	201	Bogdanov, Nikita E. ....	124
Anzulović, Lucija .....	336	Bogle, David .....	3
Ardila-Fierro, Karen J. ....	40	Bohač, Mario .....	69, 386
Ashurbekova, Karina .....	39	Bohinc, Klemen .....	89, 162
Ashurbekova, Kristina .....	39	Bojić, Mirza .....	108, 117, 280
Ašperger, Danijela .....	71, 101, 329, 330	Bolanča, Tomislav .....	22, 304, 327, 328, 336, 347, 352
Babić, Bruna .....	71, 101, 329, 330	Boldyreva, Elena V. ....	124
Babić, Darko .....	185	Bolf, Nenad .....	316, 318
Babić, Marko .....	314	Bolješić, Leo .....	347
Babić, Sandra .....	71	Borko, Valentina .....	269
Babić, Tea .....	276	Borović, Teona Teodora .....	129
Bacchiocchi, Corrado .....	159	Borovina, Mladen .....	170
Badurina, Valentina .....	170	Bosak, Anita .....	61
Badurina-Petričević, Amadea .....	336	Bosiljkov, Tomislav .....	103
Bafti, Arijeta .....	387	Bošković, Perica .....	226
Bajan, Ivan .....	393	Bosnar, Martina .....	135
Bajić, Danica .....	246	Bošnjaković, Anja .....	78
Bajić, Miroslav .....	109	Božić, Ana Lončarić .....	337, 351
Bakarić, Danijela .....	151	Božičević, Lucija .....	380
Bakija, Marija .....	165	Božičević, Marin .....	372, 375
Balog, Marta .....	181	Božinović, Ksenija .....	85
Bandić, Ivana .....	311	Brahmbhatt, Harshad .....	113
Banjanac, Mihailo .....	130	Brajenić, Petra .....	338
Baran, Nikola .....	377, 378	Brajković, Mislav .....	272
Barandiaran, Leire .....	39	Brajša, Karmen .....	130
Bardak, Ana .....	181	Bralić, Marija .....	102
Barešić, Luka .....	199	Brdek, Dora .....	347
Barić, Danijela .....	135	Bregović, Nikola .....	237
Barišić, Antun .....	43, 232	Brekalo, Ivana .....	247
Barišić, Dajana .....	184, 185, 187	Briš, Anamarija .....	205
Barišić, Dario .....	80	Brizić, Ilija .....	394
Barišić, Lidija .....	260	Brkić, Hrvoje .....	203
Basarić, Nikola .....	59	Brkić, Lana .....	372
Basioli, Lovro .....	366	Brkljača, Zlatko .....	151
Bastić, Marijana .....	405	Brkljačić, Lidija .....	234
Bazulis, Māris .....	251	Brlaković, Filip .....	369
Bebek, Iva .....	322	Brnardić, Ivan .....	368
Bebić, Nikol .....	229	Bronić, Josip .....	222
Beč, Anja .....	143	Brozović, Anamaria .....	177
Bedeković, Nikola .....	20, 186, 261	Brusač, Edvin .....	28, 35, 256
Begović, Tajana .....	128, 171, 259, 278, 285	Bubalo, Anđelina .....	328
Bektić, Sanida .....	319, 320	Bubaš, Matej .....	363
Belančić, Anita .....	288	Bubić, Ante .....	194
Beļauņieks, Rūdolfs .....	266	Bubnjar, Karlo .....	114, 115
Belovari, Mateja .....	110	Bucić-Kojić, Ana .....	76, 78
Benković, Goran .....	117	Budetić, Mateja .....	114, 115
Bernstorff, Sigrid .....	363, 366	Bukarica, Ivana .....	298
Bertagna Silva, Danilo .....	71	Bulatović, Vesna Očelić .....	22

Bule, Kristina	22, 304, 327, 336, 347	Domazet Jurašin, Darija	151
Buljac, Maša	94, 96, 102	Domijan, Ana-Marija	280
Buljan, Anđela	161	Dong, Huiyu	348
Buljubašić, Martin	289	Dorić, Hrvoje	318
Burazer, Sanja	80	Došlić, Nađa	59
Burić, Nataša	83	Dragoš, Matea	193
Burnić, Filip	129	Dramićanin, Aleksandra	235
Bušić, Valentina	99	Draženović, Josip	59
Bušljeta, Mia	233	Dražević, Emil	29
Butkiewicz, Helena	277	Dražić, Goran	89, 363, 377, 378
Butković, Kristina	130	Drčić, Danijela	127
Buttiglieri, Gianluigi	71	Drenjančević, Mato	132
Buzuk, Marijo	94, 96	Drinković, Nikša	66
Čačković, Mirjana	356	Drmić, Katarina Marija	382
Cametti, Massimo	159	Drušković, Morana	238
Capan, Ivana	387	Drventić, Ivana	210, 246
Car, Filip	296	Dubaić, Karla	317
Car, Željka	182, 202, 233	Dufreche, Jean-Francois	89
Carić, Dejana	295	Dujić, Lovro	46
Čerepinko, Filip	292	Dujmović, Tea	246
Cetina, Mario	159	Duka, Ivan	280
Čevid, Ivana	302	Dukarić, Ana-Marija	76
Chamaray, Shaan	384	Dumić, Miljenko	252
Chatterjee, Nabanita	169	Dunatov, Marko	81, 390
Ciglenečki, Irena	88, 341, 353	Dunić, Natalija	353
Ciglenečki-Jušić, Irena	349	Dunkić, Valerija	286
Čikeš Čulić, Vedrana	97, 319, 320	Duplančić, Marina	295, 383
Čikoš, Ana	252, 375	Đurasović, Izabela	164
Cinčić, Dominik	131, 139, 147, 154, 261, 274	Dutour Sikirić, Maja	207, 384
Cindrić, Maja	130	Dutour-Sikirić, Mathieu	341
Cindro, Nikola	173, 183, 228, 237, 247	Dvorščak, Marija	153
Cingesar, Ivan Karlo	53, 305, 309	Dydio, Pawel	21
Čipčić Paljetak, Hana	239	Džolić, Zoran	110, 159
Čipor, Ivona	211	Erceg, Ina	207, 384
Čižmar, Tihana	69, 257	Erceg, Matko	388
Colobert, Françoise	23	Ercegović, Matej	369
Čolović, Božana	384	Ernst, Wolfgang E.	57
Cop, Pascal	362	Ertap, Hüseyin	92
Ćosić, Jasenka	116	Esch, Patrick	362
Ćosović, Božena	353	Falck, David	189
Crnčec, Dražen	49	Faraguna, Fabio	67, 75, 355
Crnčević, Doris	152	Faraho, Ivan	135
Crnolatac, Ivo	44	Fazinić, Stjepko	92
Cuculić, Vlado	74	Feringa, Ben L.	8
Čugalj, Antonela	382	Fernandes, Pedro Alexandrino	272
Ćurić, Manda	184, 185, 187	Fiket, Lucija	372, 375
Ćurlin, Marija	66	Filipčev, Bojana	253
Cvetković, Sara	351, 352	Filipović, Nikolina	188
Cvetković-Kišlin, Mirjana	52	Findrik Blažević, Zvezdana	77, 300, 302, 313
Cvetnić, Marija	237	Foretić, Blaženka	174
Cvetnić, Matija	22, 304, 327, 336, 337, 340, 347, 351, 352	Fotović, Luka	20, 186, 261
Cvjetović, Vladimir	324	Foucaud, Mallaurie	64
Daelemans, Dirk	143, 166, 180	Franov, Silvia-Maria	128
Đaković, Marijana	31, 79, 170, 263, 284	Friganović, Tomislav	217, 269
Dandić, Andrea	202	Friščić, Maja	118
Danylyuk, Oksana	277	Friščić, Tomislav	267, 410
Dautović, Jelena	353	Frka, Sanja	357
Davor, Gracin	386	Frkanec, Leo	211, 213, 394
Debeljak, Željko	66, 188	Frkanec, Ruža	213, 321, 394
Dejanović, Igor	294	Gabričević, Mario	100, 268
Dekkers, Gillian	189	Gajović, Andreja	69, 257, 386
dela Rosa, Francis M.	370	Gajović, Srećko	12
Đilović, Ivica	252	Galić, Emerik	66
Dimitrić Marković, Jasmina M.	201	Galić, Nives	140, 144, 196
Divjak, Toni	228	Galović, Olivera	312
Djaković, Senka	223	García-Ballesteros, Sara	400
Djerdj, Igor	361, 362, 395	García-España, Enrique	163
Dokli, Irena	141, 142, 265	Gašić, Uroš M.	218

Gašo-Sokač, Dajana.....	99	Jajčinović, Igor.....	340, 368
Gaspar, Robert.....	181	Jakanovski, Mihajlo.....	230
Gavin, Kathleen M. ....	291	Jakić, Marija.....	212
Gavran, Matea.....	318	Jakić, Miće.....	311, 393
Gazdek, Nika.....	213	Jakopec, Silvio.....	177
Gazivoda Kraljević, Tatjana.....	144, 180	Jakovljević Kovač, Martina.....	84
Gebavi, Hrvoje.....	398	Jakovljević, Ivana.....	73, 333, 339
Genta-Jouve, Grégory.....	24	Jakupec, Nikola.....	276
Glasovac, Zoran.....	199, 273	Jakuš, Ivana.....	173
Glavaš-Obrovac, Ljubica.....	109	Jambriško, Donata.....	387
Glazer, Lucija.....	183	Janković, Patrizia.....	297
Glumac, Mateo.....	246	Jankovičs, Kristiāns.....	167
Gluščić, Valentina.....	356	Jansons, Edijs.....	120
Godec, Ranka.....	73	Janssen, George M. C.....	189
Goliškina, Svetlana Marija.....	112	Janton, Nikolina.....	379
Gomzi, Vjeran.....	295	Jazbišek, Ivana.....	336
Gornik, Olga.....	243	Jažo, Zvonimir.....	246, 319, 320
Gorup, Dunja.....	66	Jelić Matošević, Zoe.....	43, 232, 272
Gotić, Marijan.....	209, 377, 378	Jeličić, Mario-Livio.....	28, 35, 256
Gotovuša, Mia.....	75, 355	Jelovica Badovinac, Ivana.....	389
Graaf, Erik L. de.....	189	Jeminejs, Andris.....	112, 119
Grbčić, Petra.....	158, 195, 282	Jerković, Igor.....	118
Grbić, Marlena.....	149	Jović, Marko.....	249
Grčević, Manuela.....	312	Jozanović, Marija.....	212, 225
Grčić, Ivana.....	69	Jozinović, Katarina.....	53, 292, 305
Gredičak, Matija.....	25	Jukić, Ante.....	5
Grego, Timor.....	384	Jukić, Jasmina.....	128
Grgurić, Toni.....	159	Jukić, Marijana.....	109
Gudan Pavlović, Iva.....	358	Jukić, Vladimir.....	132
Gudelj, Martina.....	226	Juraić, Krunoslav.....	69, 386
Gulbe, Krista.....	120	Jurasović, Jasna.....	125
Gúnday-Túreli, Nazende.....	66	Jurić, Julija.....	291
Gusić, Klaudija.....	319	Jurić, Marijana.....	80, 82, 133
Habazin, Siniša.....	181	Jurić, Sandra.....	122
Habuda-Stanić, Mirna.....	348	Jurić, Zrinko.....	175
Hajra, Sugato.....	361	Jurić-Babaj, Maja.....	50
Halasz, Ivan.....	86, 185, 267, 371	Juričić, Ana.....	292
Hasenay, Dragutin.....	171	Jurkin, Tanja.....	209, 377, 378
Hashikawa, Yoshifumi.....	205	Kahlina, Josipa.....	248
Heffer, Marija.....	181	Kalac, Martina.....	406
Heiles, Sven.....	362	Kalafatović, Daniela.....	297, 314
Held, Jana.....	137, 206	Kalčec, Nikolina.....	66, 380, 394
Hernández, José G.....	40	Kalenda, Petr.....	64
Hinc, Paulina.....	106	Kanižai Šarić, Gabriella.....	116, 344
Hočevar, Samo.....	349	Kanižaj, Lidija.....	80, 82, 133
Hočevar, Samo B.....	34	Kapitanović, Angela.....	306
Hok, Lucija.....	197, 275	Kapustić, Tea.....	303
Horvat, Anamarija.....	372	Karabulut, Mevlüt.....	92
Horvat, Gordana.....	172, 173, 203, 228	Karačić, Zrinka.....	157, 203, 234
Horvat, Lucija.....	213, 321, 394	Karadeniz, Bahar.....	198
Hranjec, Marijana.....	130, 143, 144, 145	Kardum, Kristina.....	160
Hrenar, Tomica.....	138, 155, 270	Karnaš, Maja.....	113, 116, 132, 157, 344
Hrnjak-Murgić, Zlata.....	343	Kassal, Petar.....	86, 309, 358, 371
Hruševac, Dario.....	280	Kasum, Damir.....	334
Hudika, Petra.....	163	Katalinić Paić, Iva.....	53
Huseinović, Samira.....	319	Katančić, Zvonimir.....	372, 375
Husetović, Vlatka.....	405	Katava, Robert.....	127
Husinec, Ana.....	170	Katić, Jozefina.....	278
Isailović, Jelena.....	34	Katušić, Viktorija.....	305
Ivanda, Mile.....	366, 385, 398	Kędra, Karolina.....	259, 285
Ivanišević, Irena.....	248, 358, 371	Kelly, John M.....	158
Ivanković, Petra.....	53	Kendel, Adriana.....	136, 163, 164
Ivić, Ena.....	246, 320	Keran, Laura.....	53
Ivković, Ivana Katarina.....	383	Kerep, Robert.....	100, 268
Ivković, Sofija.....	317	Keser, Toma.....	243
Ivošević DeNardis, Nadica.....	321, 334	Khalid, Omeir.....	362
Jaćimović, Tatjana.....	288	Kiener, Daniel.....	27
Jagić, Karla.....	153	Kifer, Domagoj.....	291

Kim, Hoe Joon .....	361	Kučić Grgić, Dajana .....	22, 304, 327, 336, 338, 347
Kinart, Zdzislaw .....	129	Kujundžić, Toni .....	132
Kinēns, Artis .....	120	Kukovec, Boris-Marko .....	96, 168, 169
Kirin, Srećko I. ....	165, 177	Kukovecz, Ákos .....	395
Kiss, László .....	114, 115	Kulcsár, Marina Juribašić .....	187
Klačić, Tin .....	134, 162, 278	Kultan, Igor .....	316
Klarić, Daniela Amidžić .....	256	Kumpinš, Viktors .....	251, 266
Klarić, David .....	196	Kurajica, Stanislav .....	382, 383
Klaser, Teodoro .....	64	Kurtanjek, Želimir .....	56
Klasiček, Elena .....	125	Kurtović, Tihana .....	394
Kletečki, Nataša .....	52, 288	Kušić, Hrvoje .....	68, 331, 337, 351, 352, 370, 381, 400
Klinčić, Darija .....	153	Kussayeva, Akmaral .....	273
Kljaković-Gašpić, Zorana .....	125	Kuštro, Marija .....	347
Ključe, Laura .....	311	Kuzman, Ivana .....	223
Knez, Mato .....	11, 37, 39, 389	Kveder, Marina .....	198
Knežević, Zdravka .....	317	Kwokal, Željko .....	74
Kodrin, Ivan .....	58, 264	Lackner, Florian .....	57
Kohrt, Wendy M. ....	291	Landeka, Ivana .....	274
Kojić, Vedran .....	69, 386	Lapić, Jasmina .....	223
Kojić-Prodić, Biserka .....	30	Lasgorceix, Marie .....	384
Kole, Goutam Kumar .....	85, 240	Lauc, Gordana .....	181, 243, 291
Kolman, Robert Junior .....	265	Lavrenčić Štangar, Urška .....	331, 370
Kolymjadi Markovic, Maria .....	42, 241, 389	Łazarczyk, Marzena .....	259, 285
Komar, Mario .....	84, 113, 116, 157	Legović, Tarzan .....	334
Komatović, Katarina .....	61	Leko, Katarina .....	183, 275, 276
Kondža, Martin .....	108	Lepur, Adriana .....	322
Konjević, Lucija .....	75	Lerliche, Anne .....	384
Koprivnjak, Marina .....	146	Lesac, Andreja .....	141, 142
Korade, Karla .....	171	Leščić Ašler, Ivana .....	194
Koraj, Natan .....	224	Leškovskis, Kristaps .....	123
Kordić, Lorena .....	191	Linden, Martin .....	251
Koren, Rajna .....	54	Lisac, Katarina .....	147
Korica, Milenko .....	126, 216	Ljolić Bilić, Vanja .....	359
Kosalec, Ivan .....	359	Ljubić, Anabela .....	292
Kosanović, Martina Medvidović .....	214	Ilobet, Eduard .....	398
Kosar, Vanja .....	303	Logožar, Ivan .....	279
Košćak, Marta .....	85, 240	Lončarić Božić, Ana .....	68, 331, 343, 352, 370
Košćak, Tajana .....	225	Lončarić, Ivor .....	267
Kosiorek, Sandra .....	277	Lončarić, Melita .....	84, 111
Kostić, Aleksandar .....	235	Lovrić, Mila .....	224
Košutić, Krešimir .....	329, 330	Lovrić, Suzana .....	51
Kovač, Anja .....	317	Lozančić, Ana .....	133
Kovač-Andrić, Elvira .....	126, 335	Lugiņina, Jevgeņija .....	120, 167, 251
Kovačević, Davor .....	17, 89, 128, 134, 162	Lukač, Goran .....	294
Kovačević, Monika .....	182, 260	Lukić, Marija .....	308, 345
Kovačić, Marin .....	68, 331, 337, 343, 370	Lukin, Stipe .....	184, 267
Kralik, Zlata .....	312	Macan, Jelena .....	360, 369
Kralj, Magdalena .....	86, 371	Madunić-Čačić, Dubravka .....	225
Kralj, Suzana .....	292	Maile, Ruben .....	362
Kraljević Pavelić, Sandra .....	158, 195	Majdak, Mislav .....	359
Kraljević, Tatjana Gazivoda .....	166, 179	Majerić Elenkov, Maja .....	77, 265, 300, 302, 313
Kraljić Roković, Marijana .....	68, 331, 370, 381	Majhen, Dragomira .....	85, 110
Krčelić, Blanka .....	338	Majić, Ivana .....	111, 113, 344
Krehula, Ljerka Kratofil .....	376	Malčić, Mirta .....	51
Krehula, Stjepko .....	262, 367, 376	Maldini, Mislav .....	46
Kremer, Dario .....	286	Maleš, Petra .....	151
Krešić, Irena .....	388	Maleš, Željko .....	108, 117, 118, 280
Krištafor, Svjetlana .....	148, 149	Maljković, Danica .....	238, 328
Kristek Janković, Antonija .....	348	Maltar-Strmečki, Nadica .....	193, 384
Kristek, Kristina .....	48	Mandarić, Mirna .....	229
Krivačić, Sara .....	86, 358, 371	Mandić, Aleksandar .....	175
Krnić, Silvija .....	48	Mandić, Dario .....	66
Kroflič, Ana .....	210	Mandić, Vilko .....	27, 36, 387
Kroškina, Vladislava .....	167	Mandić, Zoran .....	323
Krstić Ristivojević, Maja .....	253	Maračić, Silvija .....	178
Krstić, Đurđa D. ....	218, 244	Maraković, Nikola .....	61
Krstulović, Luka .....	109	Marcelić, Eugen .....	316
Kučas, Filip .....	154	Marcelja, Marijana .....	294

Marder, Todd B.....	85, 240	Milanović, Žiko.....	201
Margetić, Davor.....	199, 205, 271, 273	Milardović, Stjepan.....	248, 358
Marguš, Marija.....	341	Milašinović, Valentina.....	30, 124
Marić, Ivan.....	209, 377, 378	Milčić, Nevena.....	77, 302, 313
Marić, Tihana.....	118, 280	Milenković, Dejan.....	200, 201
Marić, Tomislav.....	146	Miletić, Aleksandar.....	395
Marijan, Sara.....	147	Miletić, Vedran.....	54
Marijanović, Zvonimir.....	156	Milinčić, Danijel.....	235
Marin, Petra.....	313	Milinković, Andrea.....	357
Marinović, Marina.....	192	Miljanić, Snežana.....	136, 163, 164
Markeš, Marina.....	322	Miljković-Opšena, Dušanka.....	218, 220, 230, 235, 244, 249
Markić, Marinko.....	22, 304, 327, 336	Miloloža, Martina.....	22, 304, 327, 336, 338, 347
Marković, Berislav.....	188, 395	Mišetić, Mislav.....	67
Marković, Dean.....	42, 195, 225, 241, 255, 282, 389	Mishnev, Anatoly.....	123, 251
Markovic, Maria Kolympani.....	255	Mišković Špoljarić, Katarina.....	188
Marković, Marijan-Pere.....	309	Mišura, Ozana.....	263
Marković, Zoran.....	201	Mitar, Anamarija.....	326
Markuš, Iva.....	236	Mitić, Božena.....	280
Marojević, Ana.....	344	Mlakić, Milena.....	135
Maršavelski, Aleksandra.....	216	Mlinarević, Dražen.....	181
Martinaga, Lela.....	359	Modin, Evgeny.....	37, 39
Martinez, Sanja.....	307	Modrušan, Matija.....	183, 228, 276
Martinić, Olgica.....	407, 408	Moguš-Milanković, Andrea.....	64, 92
Martinko, Alen.....	270	Mohammed, Yassene.....	189
Martinović, Manuel.....	54	Moharić, Josip.....	211
Marušić, Katarina.....	373, 374	Mohr, Gerhard J.....	149
Mastilák Cagardová, Denisa.....	201	Molčanov, Krešimir.....	30, 80, 82, 121, 124, 133
Matasović, Brunislav.....	212, 335	Molnar, Maja.....	84, 99, 111, 113, 116, 157, 344
Matečić Mušanić, Sanja.....	191	Momirović, Nebojša.....	235
Mateša, Sarah.....	88	Morlock, Gertrud.....	220
Matić, Antonia.....	203	Mornar, Ana.....	28, 35, 256
Matić, Mislav.....	149	Morović, Silvia.....	329, 330
Matić, Sara.....	45	Mošner, Petr.....	64
Matijaković, Nives.....	374	Mrvčić, Jasna.....	260
Matijašec, Dora.....	327	Mrvoš-Sermek, Draginja.....	290
Matijašić, Gordana.....	379, 383	Murata, Yasujiro.....	205
Matijašić, Mario.....	239	Muriqi, Arbresha.....	39
Matković-Čalogović, Dubravka.....	242	Murković Steinberg, Ivana.....	148, 149
Matošević, Ana.....	61	Musić, Svetozar.....	262, 367
Matovina, Mihaela.....	45	Mutavdžić Pavlović, Dragana.....	144, 340
Matulja, Dario.....	195, 282	Mužina, Katarina.....	382
Matusinović, Zvonimir.....	351, 352	Nadazdy, Peter.....	363
Mauša, Goran.....	314	Nagy, Zoltan K.....	4
Mavri, Janez.....	60, 197	Namjesnik, Danijel.....	171, 278, 285
Medak, Glorija.....	222	Nazlić, Marija.....	286
Medić, Mihovil.....	75	Nemec, Vinko.....	131, 154
Mehić, Emina.....	265, 300	Nestić, Davor.....	110
Meier, Chris.....	2	Neves, Rui P. P.....	272
Mendaš, Gordana.....	357	Nigović, Biljana.....	28, 35, 224, 256
Meščić Macan, Andrijana.....	150	Nigrovic, Peter A.....	291
Mesek, Luka.....	338	Nikolić, Juraj.....	134
Messner, Roman.....	57	Nikolić, Milan.....	13, 407
Meštrović, Ernest.....	293, 409	Nikolić, Patrik.....	54
Metrangolo, Pierangelo.....	7	Ninčević Grassino, Antonela.....	103, 104
Micek, Vedran.....	66	Nolan, Michael.....	39
Mičetić, Maja.....	363, 366	Novokmet, Mislav.....	181, 243
Michiel, Marco di.....	267	Novosel, Nives.....	334
Mifka, Boris.....	87	Novosjolova, Irina.....	18, 105, 112, 119, 123
Mihaljević, Branka.....	373, 374	Ocelić Bulatović, Vesna.....	336, 338, 347
Mihaljević, Ivan.....	392	Odak, Ilijana.....	135
Mihanović, Hrvoje.....	353	Odorčić, Ivica.....	54
Mihelec, Danijela.....	233	Odžak, Renata.....	152
Mijić, Helena.....	373	Oh, Dong Ik.....	361
Mikac, Lara.....	385	Oliver, Clive L.....	169
Mikelić, Ana.....	155	Opačak, Andrea.....	351, 352
Mikić, Slavica.....	312	Opačak-Bernardi, Teuta.....	109
Milaković, Kristijan.....	322	Opšena, Dejan.....	61
Milanović, Igor.....	267	Orct, Tatjana.....	125



Oršolić, Davor .....	16	Poje, Goran .....	137, 190, 206
Ostojić, Lucija .....	54	Politeo, Olivera .....	160, 319
Ostrički, Robert .....	166	Poljanić, Leon .....	32
Otmačić Ćurković, Helena .....	306	Popov, Nina .....	222, 262, 376
Over, Herbert .....	362	Popović, Jasminka .....	80, 174
Ožegović, Antonija .....	141, 142	Popović, Marin .....	331
Pajić, Damir .....	80, 82, 257	Popović, Nina .....	317
Pajić, Mario .....	184, 187	Posavac, Luka .....	53
Panić, Barbara .....	58, 146, 264	Posavec, Lidija .....	154
Pantalon Juraj, Natalija .....	177	Povijač, Kristina .....	292
Panžić, Ivana .....	27, 36, 387	Požar, Josip .....	10, 32, 236
Papac, Josipa .....	400	Prah, Alja .....	60
Papović, Snežana .....	129	Prenc, Sara .....	179
Parčina, Antonija .....	319, 320	Presečki, Ana Vrsalović .....	298
Parlov-Vuković, Jelena .....	75	Prevarić, Viktorija .....	22, 304, 327, 336, 347
Patrčević, Paula .....	336	Primožič, Ines .....	138, 155, 270
Paurević, Marija .....	216, 312	Priščan, Gabrijela .....	101
Pavelić, Sandra Kraljević .....	282	Prlić Kardum, Jasna .....	310, 326
Pavić, Kristina .....	190	Prlić, Domagoj .....	53
Pavić, Luka .....	82, 92, 257, 387, 390	Prpić, Mateja .....	171
Pavić, Monika .....	50	Pršić, Sara .....	338, 368
Pavlešić, Tomislav .....	255	Pršir, Kristina .....	148, 149
Pavlović, Gordana .....	127	Prugovečki, Biserka .....	242
Pehar, Ines .....	53	Ptiček, Lucija .....	158
Pehnac Pavlović, Gordana .....	63	Pucić, Irina .....	74, 373
Pehnac, Gordana .....	332, 333, 339, 356, 357	Pucko, Ivan .....	67, 355
Pejić, Jelena .....	176	Pukleš, Iva .....	212, 225
Peko, Neven .....	396	Puriņš, Mikus .....	266
Pem, Barbara .....	380	Puškaric, Andreas .....	81, 222, 390
Penić, Nikolina .....	290	Pustak, Anđela .....	209, 377, 378
Perčić, Marko .....	389	Racané, Livio .....	44, 130, 144, 158
Perez-Jimenez, Raul .....	39	Racar, Marko .....	67, 75, 355
Perić, Berislav .....	165, 177	Radan, Mila .....	320
Perić, Mihaela .....	239	Radanović, Tatjana .....	335
Perica, Jana .....	260	Radić Stojković, Marijana .....	44, 130, 178
Perin, Nataša .....	130	Radić, Gabrijela .....	381
Perinović Zojić, Sanja .....	311, 388, 393	Radić, Josip .....	102
Periša, Ivana .....	366	Radičić, Rafaela .....	389
Perković, Ivana .....	137	Radin, Edi .....	377, 378
Peroković, Vesna Petrović .....	182	Radonić, Ani .....	156
Perović, Klara .....	68, 381	Radonić, Doroteja .....	32
Peršić, Ana .....	376	Radošević, Karmen .....	213
Persoon, Leentje .....	166	Radovanović, Vedrana .....	130
Persoons, Leentje .....	143, 180	Radovanović-Perić, Floren .....	36
Pešić, Mirjana .....	235	Raić, Matea .....	377, 378, 385
Peter Jelenčić, Helena .....	408	Raić-Malić, Silvana .....	62, 150, 158, 177, 178, 179, 180, 239
Peter, Robert .....	389	Rajić, Zrinka .....	137, 190, 192, 206
Peterlin Mašić, Lucija .....	19	Rakas, Anja .....	179, 180
Petravić, Mladen .....	37, 39	Ramek, Michael .....	176
Petrić, Robert .....	215	Rastija, Vesna .....	111, 113, 116, 132, 157, 344
Petrić, Vedran .....	323	Rath, Thomas .....	36
Petrinec, Lana .....	33, 227	Razum, Marta .....	257
Petroselli, Manuel .....	159	Renka, Sanja .....	64, 80
Petrović Peroković, Vesna .....	32, 202, 233	Rep, Valentina .....	62, 239
Petrušić, Sanja .....	115	Rezić, Iva .....	91, 359, 365
Petters, Ivan .....	173	Ribić, Rosana .....	182, 216, 233
Pezer, Marija .....	291	Rimac, Hrvoje .....	192, 197, 280
Piantanida, Ivo .....	85, 163, 240	Rimac, Nikola .....	324
Picek, Igor .....	174	Ristić, Davor .....	398
Pičuljan, Katarina .....	236	Ristić, Mira .....	262, 367
Piljić, Mateja .....	365	Ristivojević, Petar .....	218, 220, 230, 249
Pisačić, Mateja .....	31, 170, 284	Ritere, Agnija .....	119
Piškor, Martina .....	150	Robić, Marko .....	367
Pišonić, Helena .....	374	Roca, Sunčica .....	260
Planinić, Mirela .....	76, 78	Rogošić, Marko .....	299
Plenča, Karla .....	351, 352	Roje, Marin .....	161
Pocrnić, Marijana .....	140, 144	Rončević, Ivana Škugor .....	169
Podreka, Tina .....	303	Rosić, Anđelka M. .....	244

Rother, Dörte.....	15	Smiglak, Marcin.....	106
Rožić, Tomislav.....	59	Smith, Ana-Sunčana.....	6
Ru, Arnoud H. de.....	189	Smoljanić, Goran.....	71
Ruić Funčić, Renata.....	46	Šmuc, Tomislav.....	16
Rukavina, Marko.....	345	Šoić, Dinko.....	243
Runjavec, Monika Šabić.....	293	Šoić, Ivana.....	307
Runje, Mislav.....	144	Sokol, Ivana.....	180
Ruščić, Mirko.....	160, 286	Sokol, Vesna.....	168, 169
Sabolović, Jasmina.....	176	Šola, Marina.....	102
Sačar, Denis.....	372, 375	Soldin, Željka.....	284
Sačar, Leon.....	150	Šoljić, Ines.....	307
Sacher, Josip.....	310	Somogyi Škoc, Maja.....	359, 365
Safundžić Kučuk, Maša.....	317	Sopčić, Suzana.....	73, 332
Sahu, Manisha.....	361	Sović, Karlo.....	138
Sakač, Nikola.....	212, 225	Špada, Vedrana.....	368, 396
Šakić, Davor.....	107, 217	Špadina, Mario.....	89
Salamon, Krešimir.....	386	Spahić, Zlatan.....	138, 270
Samardžić, Mirela.....	114, 115	Spalj, Sara.....	103, 104
Sancho Parramon, Jordi.....	363	Speranza, Giovanna.....	173, 228
Šango, Marina.....	104	Šporec, Anita.....	322
Šantić, Ana.....	64, 80, 92, 133, 174, 257	Šprung, Matilda.....	152
Šarić, Iva.....	37, 39, 389	Šrajer Gajdošik, Martina.....	312
Sashuk, Volodymyr.....	277	Srzentić, Sunčica.....	226
Ščavničar, Andrijana.....	224	Stamač, Veronika.....	391
Schwander, Florian.....	132	Stanić, Petra.....	121
Šeba, Tino.....	100, 268	Starčević, Kristina.....	143
Šebešćen, Dora.....	125	Stare, Jernej.....	60
Sebris, Armands.....	105	Štefan, Leo.....	252, 317
Sečenji, Aleksandar.....	214, 215	Štefanić, Goran.....	377, 378
Šegan, Sandra B.....	244	Štefanić, Zoran.....	194
Šegota, Suzana.....	207	Stepanić, Višnja.....	16
Sekovanić, Ankica.....	125	Stilinović, Vladimir.....	20, 186, 261
Šekutor, Marina.....	57, 83, 175, 236	Štimac Tumara, Barbara.....	41
Šeler Namjesnik, Martina.....	289	Stipanelov Vrandečić, Nataša.....	388
Selimović, Samela.....	319	Stolar, Tomislav.....	267
Selmani, Atiđa.....	89	Štrbac, Petar.....	271
Šelo, Gordana.....	76	Štulić, Rebeka.....	239
Semenčić, Mojca Čakić.....	260	Šubarić, Domagoj.....	111, 113, 157
Sénard, Thomas.....	189	Sučeska, Muhamed.....	41
Šenjuga, Pavla.....	82	Sudar, Martina.....	77
Sepčić, Sabino.....	297	Šumanovac, Tatjana.....	175
Serdar, Marijana.....	345	Sun, Yu.....	362
Sermek, Nikolina.....	225	Supina, Antonio.....	86
Sertić, Miranda.....	224	Šupljika, Filip.....	44, 45, 234
Sever Štrukil, Zdravka.....	73, 333, 339	Šurlina, Karlo.....	282
Shanmugam, Suresh.....	130, 178	Sušanj, Ivan.....	317
Sharifi, Tayebah.....	331, 370	Sušić, Iva.....	104
Shkunnikova, Sofia.....	107	Šutalo, Petar.....	58, 264
Siboulet, Bertrand.....	89	Svedružić, Željko.....	314
Šiljeg, Mario.....	238	Svedružić, Željko M.....	54
Šilović Hujić, Martina.....	73	Syed, Kamran.....	398
Silovski, Tajana.....	224	Széchenyi, Aleksandar.....	114, 115
Šimanović, Aleksandra.....	141, 142	Szpecht, Andrea.....	106
Šimatović, Valentina.....	310	Szűcs, Kálmán Ferenc.....	181
Šimić, Anja.....	319	Talajić, Gregor.....	247
Šimić, Iva.....	357	Talić, Stanislava.....	135
Simonović, Niki.....	341, 353	Tandarić, Tana.....	60
Sinković, Paola.....	161	Tatar, Dalibor.....	126, 362, 395
Šipušić, Juraj.....	369	Tavra, Dubravka.....	347
Širić, Klara.....	260	Taylor, Martin C.....	158
Širola, Manuel.....	396	Terzić, Marija.....	126
Škalamera, Đani.....	26, 175, 279	Tirić Unetić, Marija.....	75
Skenderi, Zenun.....	392	Tišma, Marina.....	76, 78
Skendrović, Dino.....	298	Tkalčević, Marija.....	363, 366
Škorić, Irena.....	135	Tolić, Kristina.....	144, 340, 368
Škugor Rončević, Ivana.....	94, 96	Toma, Mateja.....	33, 223, 227
Škulj, Sanja.....	43, 232	Tomaš, Renato.....	129, 183
Smarsly, Bernd M.....	362	Tomašić Paić, Ana.....	234



Tomašić, Vesna .....	295, 296, 303	Vrdoljak, Višnja .....	229
Tomić, Antonija .....	203, 337	Vrsaljko, Domagoj .....	53, 296, 305, 308, 309
Tomić, Sanja .....	44, 45, 157, 203, 234	Vučemilo, Marko .....	246
Tomišić, Vladislav .....	173, 183, 228, 237, 275, 276	Vučković, Frano .....	181
Tomljenović, Antoneta .....	391, 392	Vujasinović, Magdalena .....	375
Tomljenović, Emanuel .....	292	Vujević, Lucija .....	198
Tonković, Stefani .....	343	Vuk, Dragana .....	36
Topić, Edi .....	229, 247	Vukorepa, Gracia .....	53
Topić, Nea Baus .....	139	Vuković Domanovac, Marija .....	293
Tosti, Tomislav B. ....	244	Vušak, Darko .....	242
Tot, Aleksandar .....	129	Waldvogel, Siegfried R. ....	251
Traskovskis, Kaspars .....	105	Weitner, Tin .....	100, 217, 269
Trifković, Jelena .....	218, 220, 230, 244, 249	Wittine, Ozren .....	316
Tumir, Lidija Marija .....	44	Wójcik, Iwona .....	189
Túreli, Emre .....	66	Wuhrer, Manfred .....	189
Turković, Lu .....	224	Wurmshuber, Michael .....	27
Turks, Māris .....	18, 105, 119, 120, 123, 167, 251, 266	Yurkevich, Oksana .....	37
Ukić, Šime .....	22, 304, 327, 336, 347	Zagajski Kučan, Kristina .....	299
Uran, Erik .....	276	Žagar, Patricia .....	372
Usenik, Andrea .....	32, 236, 275, 276	Zakharov, Boris A. ....	124
Užarević, Krunoslav .....	198, 247	Zanella, Davor .....	125
Vadlja, Denis .....	313	Zarzycki, Piotr .....	259, 285
Vanstreels, Els .....	166, 180	Zavidić, Virna .....	136
Vari, Sandor G. ....	181	Zekić, Marina .....	156
Veelen, Peter A. van .....	189	Zeko-Pivač, Anđela .....	78
Veličković, Tanja Ćirković .....	253	Zelić, Ivana Elizabeta .....	295, 303
Vianello, Robert .....	60, 145, 197, 252, 275	Zemunik, Petra .....	353
Vidardsson, Gestur .....	189	Zielinski, Dawid .....	106
Vidotto, Monica .....	193, 384	Žilić, Dijana .....	174, 198, 295
Vidović, Kristijan .....	34, 349	Žilić, Ljilja .....	156, 246
Vidović, Nikolina .....	173, 228	Živičnjak, Juro .....	391, 392
Vilibić, Ivica .....	353	Živković Radovanović, Vukosava .....	249
Vinković Vrček, Ivana .....	66, 380, 394	Živković, Pavo .....	126, 214, 215
Vinković, Kristinka .....	101	Žižek, Krunoslav .....	14
Visentin, David .....	54	Žlabravec, Veronika .....	292
Vladislavić, Nives .....	94, 96, 169	Zlatac, Ivo .....	130
Vojvodić, Vjeročka .....	353	Žonja, Lucija .....	143
Vouk, Dražen .....	238, 328	Zonjić, Iva .....	44
Vrandečić, Karolina .....	116	Zorinc, Maja Levak .....	321
Vraneš, Milan .....	129	Zovko Končić, Marijana .....	326
Vranješević, Filip .....	42, 241, 255	Zozoli, Karla .....	284
Vrban, Ivan .....	316	Zubčić, Gabrijel .....	107
Vrbnjak, Katarina .....	54	Žutinić, Petar .....	334
Vrca, Ivana .....	97	Žuvić, Iva .....	75
Vrček, Valerije .....	33, 42, 223, 227, 241, 255, 380	Žužić, Andreja .....	360



# EYCN

European Young Chemists' Network

Europska mreža mladih kemičara (EuChemS)

[www.eycn.eu](http://www.eycn.eu)



## Povezivanje mladih kemičara diljem Europe

Svaki EuChemS član mlađi od 35 godina je dio EYCN-a.

Mreža povezuje mlade kemičare unutar EuChemS okvira sa ciljem pronalaženja zajedničkih interesa i novih inicijativa. Također promovira suradnju između kemičara u industriji, akademiji, profesionalnim udruženjima te europskim upravljačkim tijelima. Mladi kemičari tako zajedno pridonose razvoju europskih inicijativa koje se odnose na znanstvene programe u kemiji i molekularnim znanostima te u drugim znanstvenim i tehnološkim poljima poput primjerice nanoznanosti, biološke znanosti, znanosti o okolišu, elektronici, itd.

## EYCN ciljevi

Nastojimo...

- Otvoriti put komunikacije između ljudi aktivnih u različitim poljima kemije;
- Stvoriti zajednicu koja podupire mlade kemičare diljem Europe;
- Stvoriti organizirani i ujedinjeni glas koji vodi računa o potrebama mladih kemičara u znanosti, obrazovanju i europskoj politici;
- Poticati rasprave i suradnje između europskih kemičara;
- Pružiti platforme za lakše osmišljavanje novih ideja koje bi pridonijele budućim ulogama molekularnih znanosti u Europi.

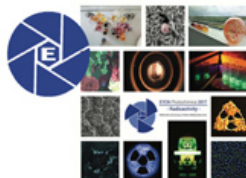


Države koje trenutno imaju delegate u EYCN-u putem nacionalnih kemijskih društva.

## Aktivnosti



**Chemistry across Europe** je izvor informacija o kemijskom obrazovanju i mogućnostima zaposlenja u akademskom sektoru i kemijskim tvrtkama za svaku od država članica EYCN-a.



**EYCN Photochimica** je natjecanje u fotografijama na kojem mogu sudjelovati kemičari mlađi od 35 godina te podijeliti svoju fascinaciju kemijom.



**EYCN Interviews project** nastoji stupiti u kontakt s renomiranim znanstvenicima koji mogu približiti kemiju javnosti predstavljajući svoje priče.

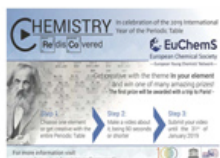


Prepoznavamo važnost sposobnosti mladih u STEM područjima; **EYCA - European Young Chemists Award** predstavlja rad najtalentiranijih kemičara koji su na početku svoje karijere.

**Young Chemists Crossing Borders**  
a transatlantic exchange program



Naš temelj je povezanost s Europom i unutar Europe; naš program **Young Chemists Crossing Borders** povezuje kemičare na drugim kontinentima.



**Chemistry Rediscovered** je video natjecanje za mlade ljude zainteresirane za kemiju (12-35 godina); potiče se slanje njihovih video uradaka na temu "In Your Element".



**EYCN Webinars Series** nastoji podupirati i mentorirati sve europske mlade kemičare u njima relevantnim temama (npr. ERC StG i MSCA stipendije).



**EuChemS Sekcija mladih kemičara HKD-a** je ogranak Hrvatskog kemijskog društva koji predstavlja Hrvatsku u EYCN-u te informira mlade hrvatske kemičare o aktivnostima EYCN-a.



### GLAVNI DOGAĐAJI

EYCN dva puta godišnje organizira skupove **Early Career Conference (ECC)** i **European Young Chemists' Symposium (EYCheM)**, a jednom godišnje **EYCN Delegate Assembly**, sastanak svih nacionalnih predstavnika u svrhu diskusija i planiranja projekata.

### Platforma za organizacijske vještine

Imamo na raspolaganju materijale o dizajnu postera, pisanju radova, pravilima EU projekata, pisanju životopisa, itd. Dostupno na upit!

Novi članovi **EuChemS Sekcije mladih kemičara HKD-a** dobrodošli!





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