SYNTHESIS AND CYTOSTATIC ACTIVITY OF NOVEL 1,2,3-TRIAZOLYL-TAGGED COUMARIN AND IMINOCOUMARIN DERIVATIVES

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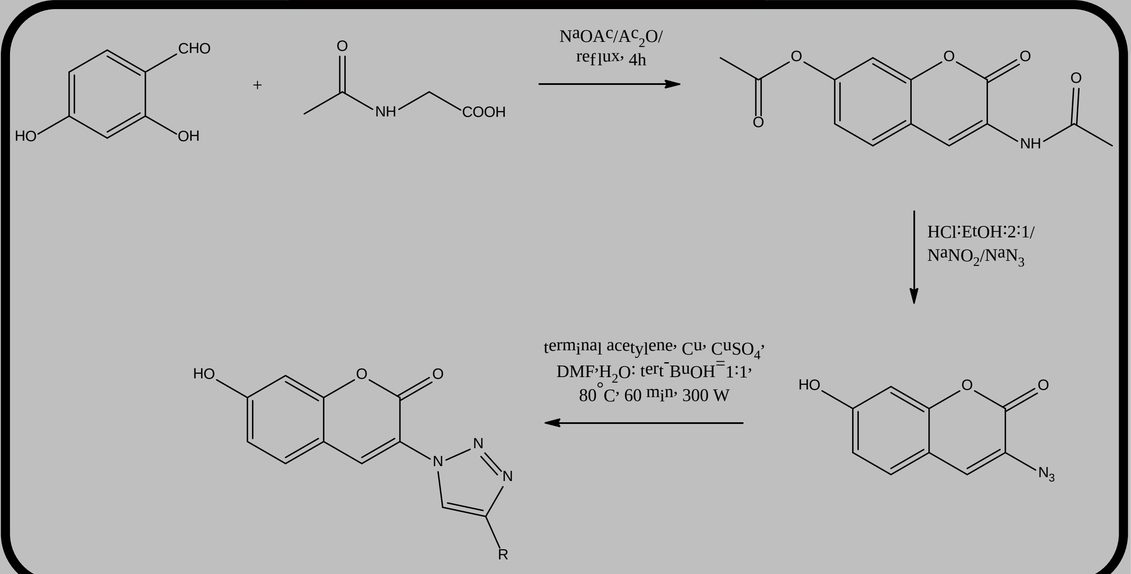
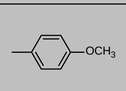
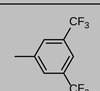
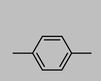
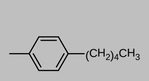
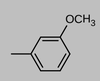
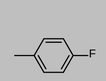
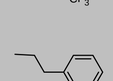
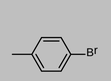
BACKGROUND

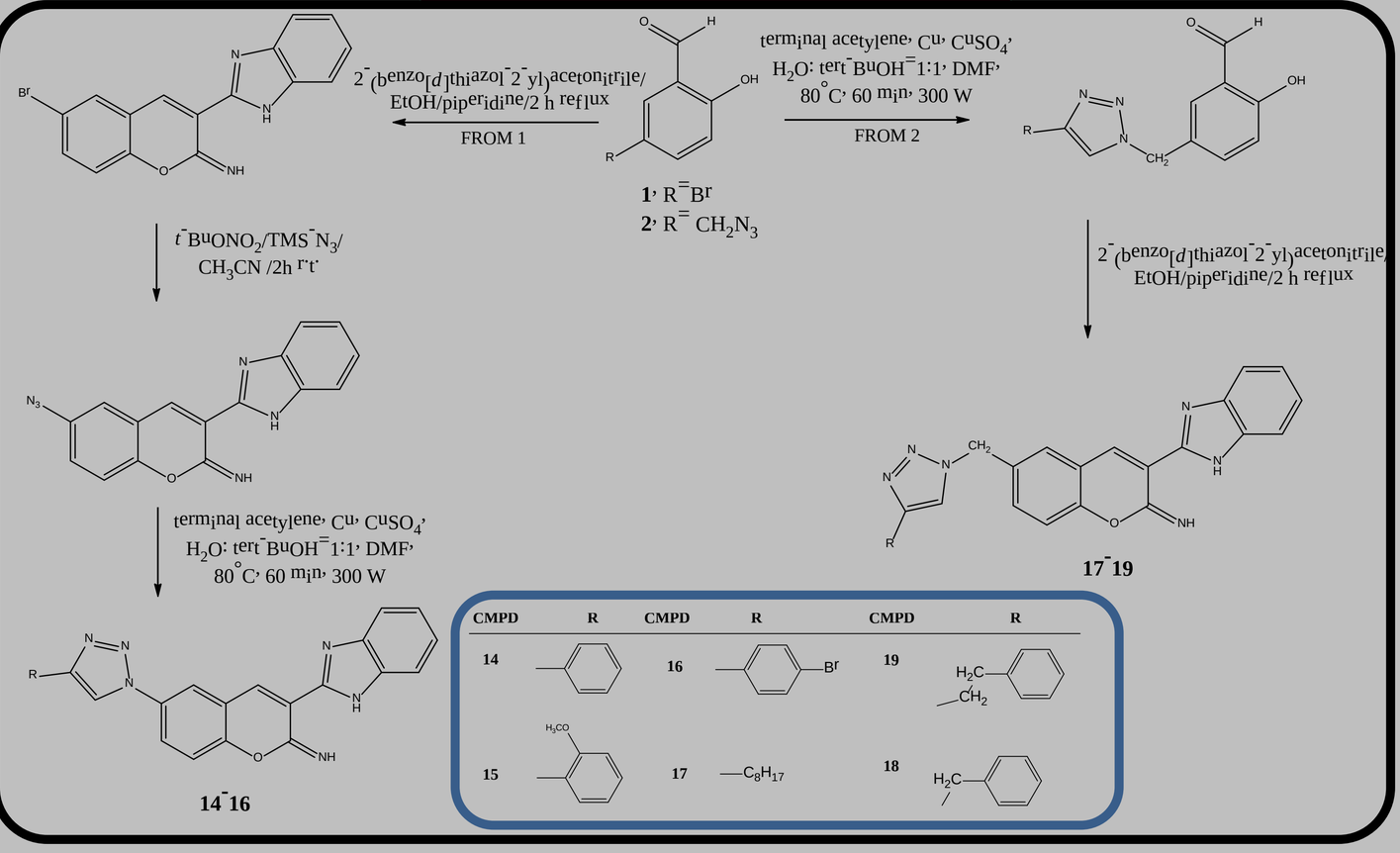
Coumarin derivatives are important motifs, which can be widely found in many natural products, and many of them displaying diverse biological activities. . Of particular interest in breast cancer chemotherapy, some coumarins and their active metabolite 7-hydroxycoumarin analogs have shown sulfatase and aromatase inhibitory activities [1]. Benzofused derivatives of coumarin bridged with 1,2,3-triazole emerged as the class of compounds exhibiting the highest antiproliferative activity.[2] Because of stability *in vivo* and wide range of biological activities (eg. against various viruses, malignant cells, microorganisms and their inhibitory enzyme activities) 1,2,3-triazole derivatives have attracted considerable attention in recent years [3].

SYNTHESIZED COUMARINS



CMPD	R	CMPD	R	CMPD	R	CMPD	R	CMPD	R	CMPD	R	CMPD	R
1		4		5		7		9		11		13	
2		3		6		8		10		12			

SYNTHESIZED IMINOCOUMARINS



CMPD	R	CMPD	R	CMPD	R
14		16		19	
15		17		18	

SCHEME 1. Synthesis of novel 1,2,3-triazolyl-tagged coumarin derivatives

SCHEME 2. Synthesis of novel 1,2,3-triazolyl-tagged iminocoumarin derivatives

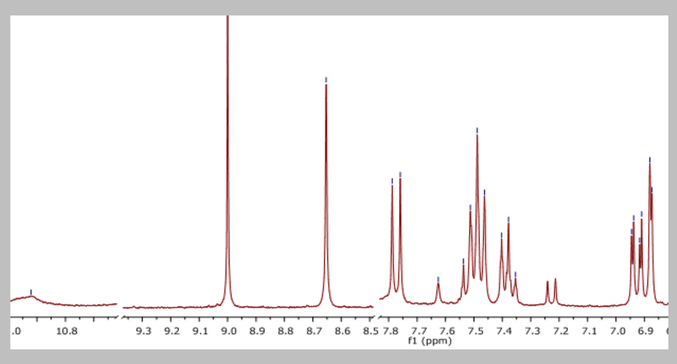


FIGURE 1: ^{1}HNMR spectrum of compound 1

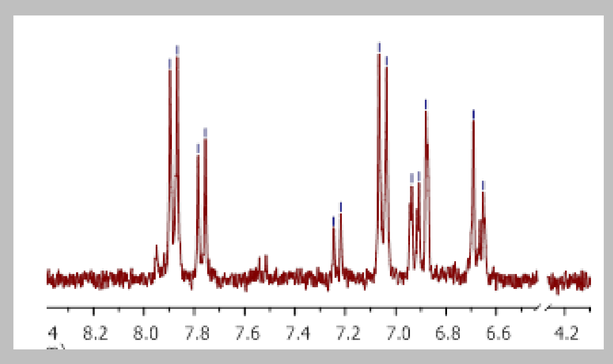


FIGURE 2: ^{1}H NMR spectrum of compound 4

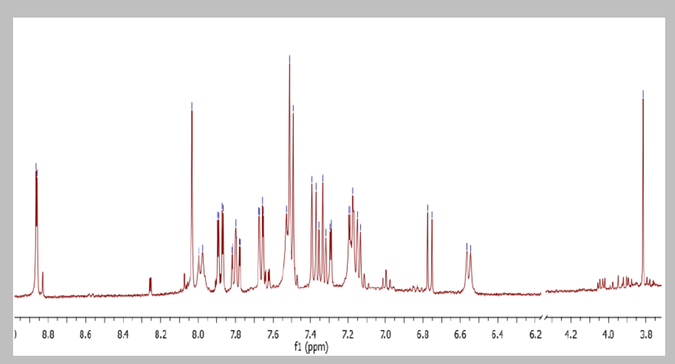


FIGURE 3: ^{1}HNMR spectrum of compound 15

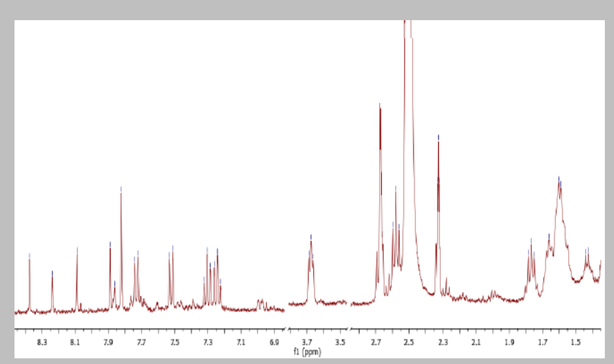


FIGURE 4: ^{1}H NMR spectrum of compound 17

BIOLOGICAL EVALUATION

CMPD	IC_{50} (μM)*		
	CEM	HeLa	HMEC-1
3	> 100	> 100	> 100
4	> 100	> 100	> 100
5	71 ± 41	26	58
6	> 100	> 100	> 100
7	> 100	94	97
8	72	26	64
9	> 100	26	> 100
10	≥ 100	85	80
11	59	9.9	67
12	> 100	> 100	> 100
13	> 100	> 100	81
14	30	40	80
15	> 100	> 100	> 100

CONCLUSION

Novel 1,2,3-triazole derivatives of coumarin and iminocoumarine have been synthesized by click reaction of 3-azido-7-hydroxycoumarin or 6-azidoiminocoumarines with corresponding terminal acetylenes in the presence of copper as a catalyst. Antiproliferative activity of novel coumarin compounds was carried out against human lymphoblastic leukemia cells (CEM/C1), human cervix carcinoma cells (HeLa) and human dermal microvascular endothelial cells (HMEC-1). Of the all evaluated compounds against malignant human cell lines, 1,2,3-triazole-coumarin derivative with 3, 5-ditrifluoromethylphenyl substituent exhibited the most pronounced activity against HeLa cell lines.

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[2] T. Gazivoda Kraljević, A. Harej, M. Sedić, S. Kraljević Pavelić, V. Stepanić, D. Drenjančević, J. Talapko, S. Raić-Malić, *Eur. J. Med. Chem*. 124 (2016) 794.

[3] S. Raić-Malić, A. Meščić, *Curr. Med. Chem*. 22 (2015) 1462

ACKNOWLEDGMENT:

Financial support from the Croatian Science Foundation under the project IP-2018-01-4682