SYNTHESIS, ANTI-PROLIFERATIVE ACTIVITY AND 3D-QSAR ANALYSIS OF NOVEL SERIES OF AMIDINO-SUBSTITUTED ARYL-BISBENZAZOLES

L. Racané[1], L. Ptiček[1], P. Grbčić[2], S. Kraljević Pavelić[2], B. Bertoša[3]

[1]Department of Applied Chemistry, Faculty of Textile Technology, University of Zagreb, Prilaz baruna Filipovića 28a, 10000 Zagreb, Croatia; [2]Department of Biotechnology, Centre for high-throughput technologies, University of Rijeka, Radmile Matejčić 2, 51000 Rijeka, Croatia; [3]Division of Physical Chemistry, Department of Chemistry, Faculty of Science, University of Zagreb, Horvatovac 102A, 10000 Zagreb, Croatia

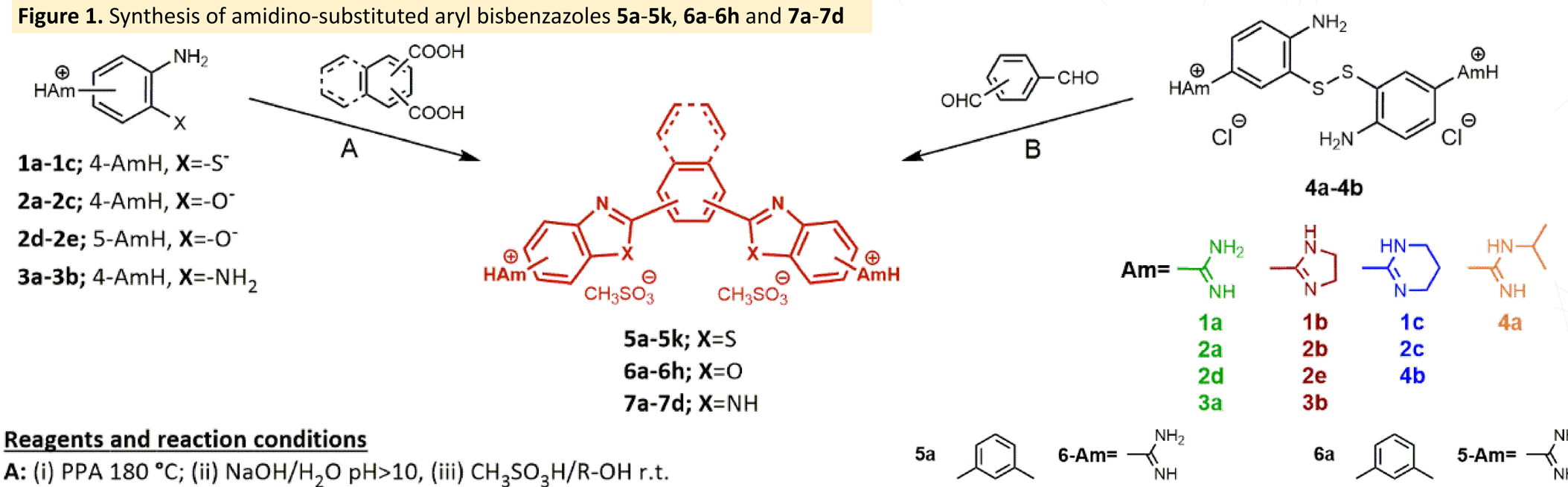
INTRODUCTION

Amidino-substituted benzazole compounds show a wide spectrum of biological activity and are investigated by several research groups during last 40 years. Our recent results revealed strong anti-proliferative effects on some tumor cell lines for isomeric imidazolinyl-substituted phenylene-bisbenzothiazole[1] and imidazolinyl-substituted phenyl- and naphtyl-benzothiazoles.[2] These findings have led us to further investigate this class of compounds by introducing different types of amidinic substituents and heteroaromatic substructure: benzothiazole, benzimidazole and benzoxazole.

RESULTS AND DISCUSSION

Presented compounds **5a**-**5k**, **6a**-**6h** and **7a**-**7d** were synthesized by condensation reaction of amidino-substituted 2-aminothiophenols, 2-aminophenols, bis(2-aminophenyl) disulphides or *o*-phenylenediamines with isomeric benzene and naphthalene dialdehydes or dicarboxylic acids (Fig. 1). Anti-proliferative activity screening was performed *in vitro* on four tumor cell lines (SW620, HepG2, CFPAC-1 and HeLa) as well as on normal human fibroblasts (HFF). Results are presented in Table 1. In order to identify molecular properties that are correlated with anti-proliferative activity, 3D-QSAR models for tested tumour cell lines were derived based on obtained anti-proliferative activities. Compounds were built *in silico* and the descriptors of their structural properties were generated using Volsurf program (Fig. 2). Principal component analysis (PCA) was performed on the dataset of 23 compounds. The first two principal components (PC1 and PC2) explain 89 % of variance of the descriptor matrix. From the PCA scores plot clustering of the compounds can be seen (Fig. 3).

Figure 1. Synthesis of amidino-substituted aryl bisbenzazoles **5a**-**5k**, **6a**-**6h** and **7a**-**7d**



Reagents and reaction conditions

A: (i) PPA 180 °C; (ii) NaOH/H_2O pH>10, (iii) CH_3SO_3H/R-OH r.t.

B: glycerol 160 °C

Table 1. *In vitro* anti-proliferative activity of amidino-substituted derivatives **5a**-**5k**, **6a**-**6h** and **7a**-**7d** on tumor cell lines and human fibroblasts

Compound	IC_{50} [a] (μM)				
	SW620	HepG2	CFPAC-1	HeLa	HFF
5a	8.20	>100	>100	4.38	0.07
5b	0.08	0.16	0.09	0.07	0.04
5c	0.40	5.95	6.41	0.74	0.06
5d	7.13	5.01	9.09	1.31	0.09
5e	0.09	3.16	5.90	0.65	0.23
5f	0.26	0.30	2.10	0.41	0.31
5g	0.08	0.94	42.5	0.71	0.05
5h	0.09	1.53	5.92	1.34	0.03
5i	0.22	0.39	1.08	0.68	0.07
5j	9.43	2.54	8.13	2.79	0.16
5k	>100	>100	>100	>100	<0.01
6a	9.86	8.23	20.4	5.23	0.15
6b	0.30	0.30	0.42	0.48	0.05
6c	0.20	0.24	0.30	0.09	0.07
6d	>100	>100	>100	>100	<0.01
6e	6.84	0.97	4.55	1.36	0.03
6f	0.06	0.08	0.32	0.16	0.03
6g	0.10	0.22	0.36	0.14	0.04
6h	>100	30.0	>100	45.2	0.24
7a	>100	10.5	>100	0.34	0.06
7b	>100	>100	>100	46.0	0.09
7c	>100	>100	>100	0.60	0.05
7d	>100	34.6	20.4	0.08	29.4

[a]Compound concentration required to inhibit tumor cell proliferation by 50%; standard deviation was omitted for clarity

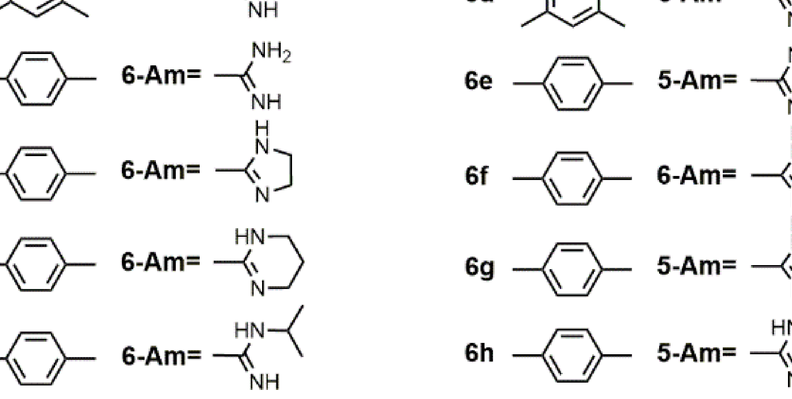


Figure 2. PCA loadings plot

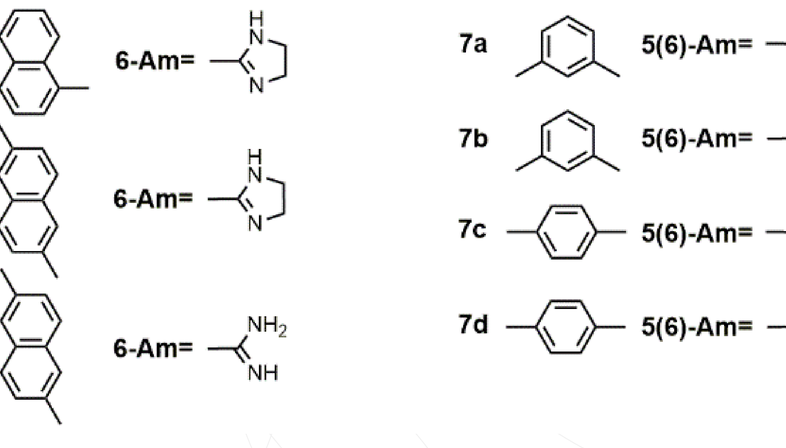


Figure 3. PCA scores plot

CONCLUSION

All tested compounds showed strong to moderate anti-proliferative activity depending on the type of amidinic substituent as well as heteroatom in benzazole moiety. From the PCA loadings plot it is visible that the largest variation between the compounds was observed for the descriptors related to the polarizability (W1-W3, D1), H-bond capacities (WO1, WN1, WN2), volume (V), surface (S), molecular mass (MW) and sum of hydrophobic areas (HSA). More detailed QSAR analysis is in progress.

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