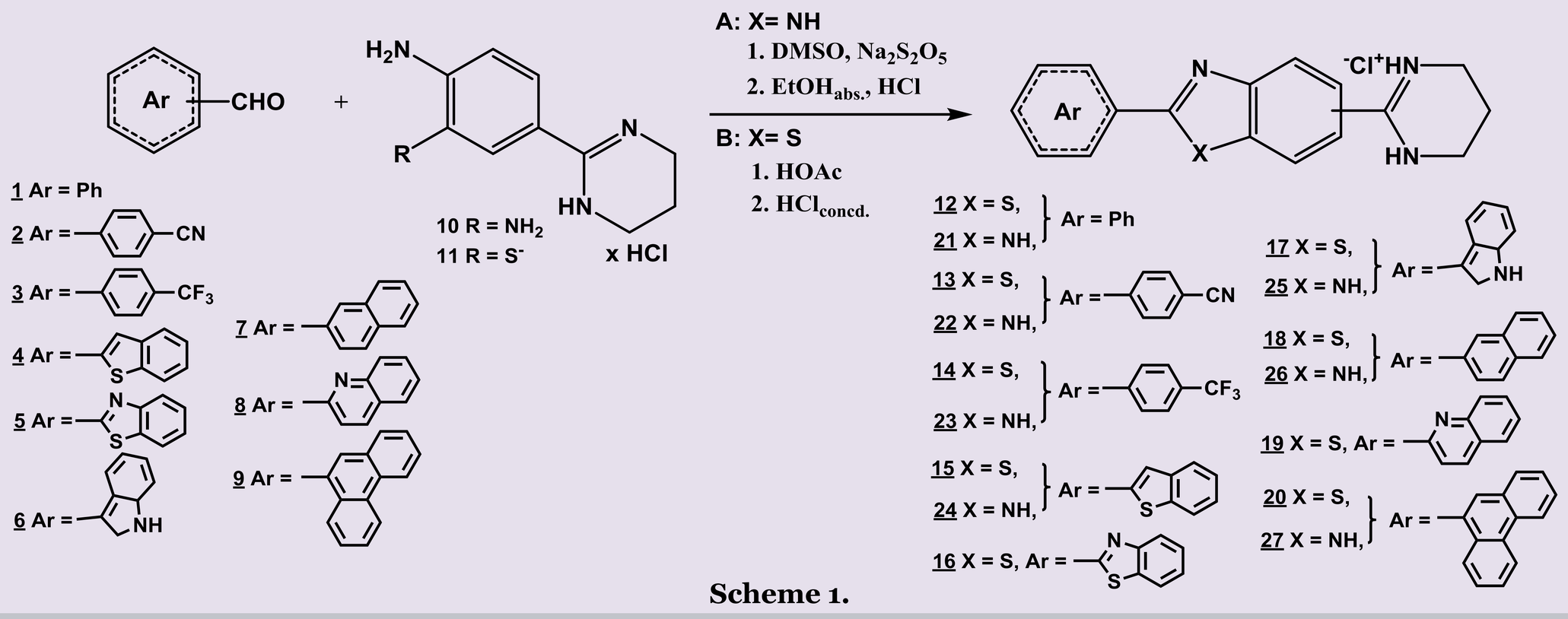
Antiproliferative activity of amidino substituted benzimidazoles and benzothiazoles explored by 2D and 3D cell culture system

Maja Cindrić,[1] Livio Racané,[2] Nataša Perin,[1] Ida Boček,[1] Anja Beč,[1] Ivo Zlatar,[3] Karmen Brajša[3] and Marijana Hranjec[1]

[1]Department of Organic Chemistry, Faculty of Chemical Engineering and Technology, University of Zagreb, Marulićev trg 20, 10000 Zagreb, Croatia; [2]Department of Applied Chemistry, Faculty of Textile Technology, UZ, Prilaz Baruna Filipovića 28a, 10000 Zagreb, Croatia; [3]Pharmacology *in vitro*, Fidelta Ltd., Prilaz Baruna Filipovića 29, 10000 Zagreb, Croatia
mcindric@fkit.hr

It is well known that amidines are structural parts of numerous compounds of biological interest including important medical and biochemical agents. Amidine substituents placed at the termini of the molecule have great importance in the molecule - biological target interactions allowing the formation of the stable complex with biologically molecules. In our previous studies we have proved that by engrafting amidine extremities as positively charged substituents at the end of the heteroaromatic substructures we could significantly improve the biological activity and orient the function of the molecule toward the binding to an electronegatively charged biological molecule such as DNA [1].



Scheme 1.

Table 1. Antitumor activity of compounds 12-27 in 2D and 3D cell cultures.

Cpd	Viability assay IC_{50} (μM)±SD; N=2					
	A549		HCC827		NCI-H358	
	2D	3D	2D	3D	2D	3D
12	>50	>100	>50	>100	>50	>100
13	>50	60±1.44	>50	>100	>50	>100
14	34±8.65	16±0.65	7±0.45	12±0.16	23±0.79	34±0.70
15	36±6.37	23±6.24	7±0.12	22±9.45	16±0.98	34±0.16
16	41±0.54	15±1.35	19±2.21	17±0.93	26±0.30	31±0.05
17	>50	>100	>50	>100	>50	>100
18	38±3.68	14±0.38	6±0.05	12±0.26	10±1.00	31±0.33
19	>50	16±1.3	14±2.09	>100	20±2.53	40±4.89
20	>50	>100	>50	>100	>50	>100
21	15±1.70	13±1.46	6±0.5	9±3.05	13±0.28	17±1.94
22	>50	>100	>50	>100	>50	>100
23	>50	>100	>50	>100	>50	>100
24	>50	>100	>50	>100	>50	>100
25	>50	>100	>50	>100	>50	>100
26	>50	>100	>50	>100	>50	>100
27	>50	>100	>50	>100	>50	>100
Doxorubicin	2±0.23	5±0.26	0.39±0.05	0.78±0.08	0.11±0.01	0.25±0.03
Staurosporine	1±0.07	0.16	0.15±0.01	0.02±0.00	0.15±0.02	0.12±0.0
Vandetanib	>50	>100	0.81±0.05	2±0.11	3±0.85	0.30±0.02

Antitumor activity in 2D and 3D cancer cell culture assays on three human lung cancer cell lines (A549, HCC827, NCI-H358) was tested. Doxorubicin, staurosporine and vandetanib were used as control compounds [2]. The most pronounced activity was displayed ba compounds 14, 15, 18 and 21 which were chosen for additional biological experiments.

[1] M. Cindrić, S. Jambon, A. Harej, S. Depauw, M.-H. David-Cordonnier, S. Kraljević Pavelić, G. Karminski-Zamola and M. Hranjec, *European Journal of Medicinal Chemistry* **136** (2017) 468-479.
[2] I. Zlatar, D. Jelić, V. Kelava, M. Cindrić, I. Jarak, S. Koštrun, G. Karminski-Zamola, V. Gabelica Marković, M. Hranjec and K. Brajša, *Croatica Chemica Acta* **90** (2017) 413-424.

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