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SYNTHESIS, ANTIPROLIFERATIVE EVALUATION AND DNA/RNA BINDING STUDY OF NOVEL AMIDINO-SUBSTITUTED PHENYLENE-BIS(BENZAZOLES)

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In continuation of our recent research in the synthesis and evaluation of antiproliferative activities of amidino-substituted 2-arylbenzazole derivatives [1,2], we present here a series of twelve novel amidino-substituted phenylene-bis(benzazoles), differing in heteroaromatic scaffolds as well as in type of amidine moiety.

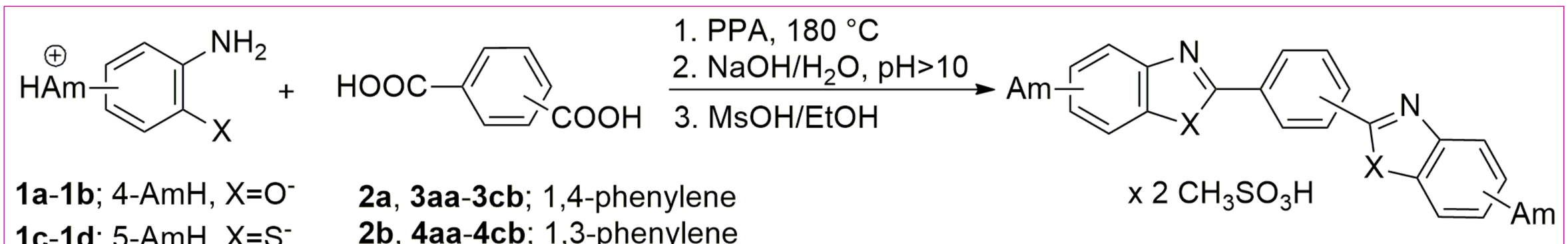


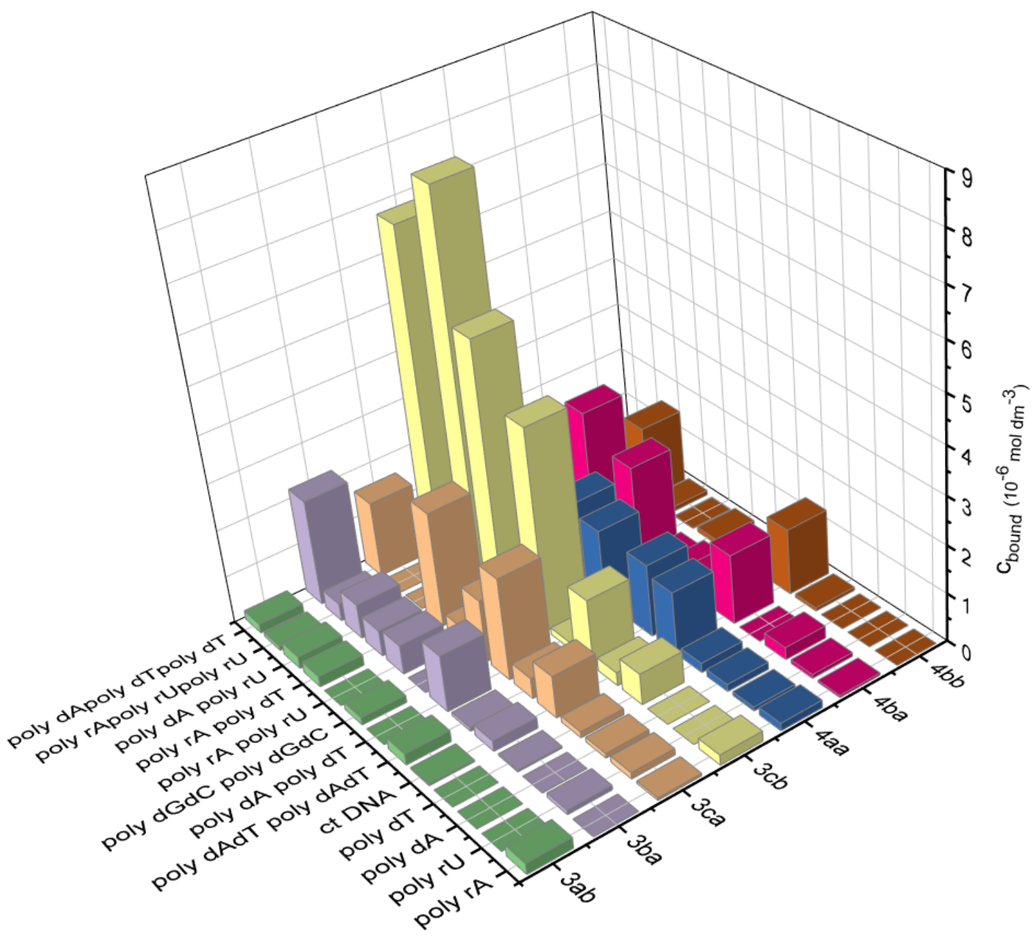
Figure 1. Synthesis of amidino-substituted aryl bisbenzazoles

Antiproliferative evaluations of compounds were performed in vitro on several human tumour cell lines (LN-229, Capan-1, HCT-116, NCI-H460, DND-41, HL-60, K-562, Z-138) and the results are presented in Table 1. It was observed that the antiproliferative activity strongly depends on heteroaromatic scaffolds, as well as on type of amidine moiety. The 2-imidazolinyl-substituted 1,3-phenylene-bisbezoxazole and bisbenzothiazole exhibited the highest activity and inhibited tumor cell proliferation (IC_{50}) in submicromolar concentration on almost all tested cell lines.

Table 1. Structure and *in vitro* antiproliferative activity of amidino-substituted compounds **3aa-4cb** on tumor cell lines

Compound	IC_{50}[a] (μM)							
	LN-229	**Capan-1**	**HCT-116**	**NCI-H460**	**DND-41**	**HL-60**	**K-562**	**Z-138**
3aa	65,3	59,2	>100	2,9	>100	>100	>100	74,9
3ab	**0,2**	**1,4**	**0,7**	**1,7**	**0,2**	7,2	2,5	**0,3**
3ba	>100	>100	>100	>100	>100	>100	>100	>100
3bb	15,8	10,8	44,5	25,8	7,8	36,1	32,6	24,6
3ca	>100	>100	>100	>100	>100	>100	>100	>100
3cb	12,8	10,5	49,2	19,6	44,0	43,4	50,9	55,1
4aa	33,8	59,1	81,5	60,1	71,9	>100	>100	51,1
4ab	**0,3**	**1,3**	**1,7**	2,6	**0,1**	**0,8**	**1,5**	**0,2**
4ba	>100	>100	>100	>100	>100	>100	>100	47,7
4bb	**0,5**	**0,4**	**0,3**	2,1	**0,5**	**0,3**	**0,6**	**0,2**
4ca	>100	>100	>100	>100	>100	>100	>100	>100
4cb	44,3	36,0	49,4	35,1	58,2	55,5	62,6	88,0

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



Several compounds have been further tested for their DNA/RNA binding ability using competition dialysis assay, UV/Vis (thermal denaturation), fluorescence and circular dichroism (CD) spectroscopy with the aim of investigating possible mechanisms of action (Figure 2).

Figure 2. Summary of competition dialysis results with seven selected compounds binding to 13 nucleic acid structures and sequences (c_{bound} = concentration of ligand bound to each nucleic acid in μM); sodium cacodylate buffer, I = 0.05 mol dm^{-3}, pH = 7, and +1 mM EDTA.

[1] Racané L, Ptiček L, Fajdetić G, Tralić-Kulenović V, Klobučar M, Kraljević Pavelić S, Perić M, Čipčić Paljetak H, Verbanac D, Starčević K (2020) Bioorganic Chemistry 95: 103537.
[2] Ptiček L, Hok L, Grbčić P, Topić F, Cetina M, Rissanen K, Kraljević Pavelić S, Vianello R, Racané L (2021) Organic & Biomolecular Chemistry 19: 2784-2793.

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