SYNTHESIS AND *IN VITRO* ANTITUMOR ACTIVITY OF NOVEL 6-AMIDINO-SUBSTITUTED 2-ALKYL-BISBENZOTHIAZOLES

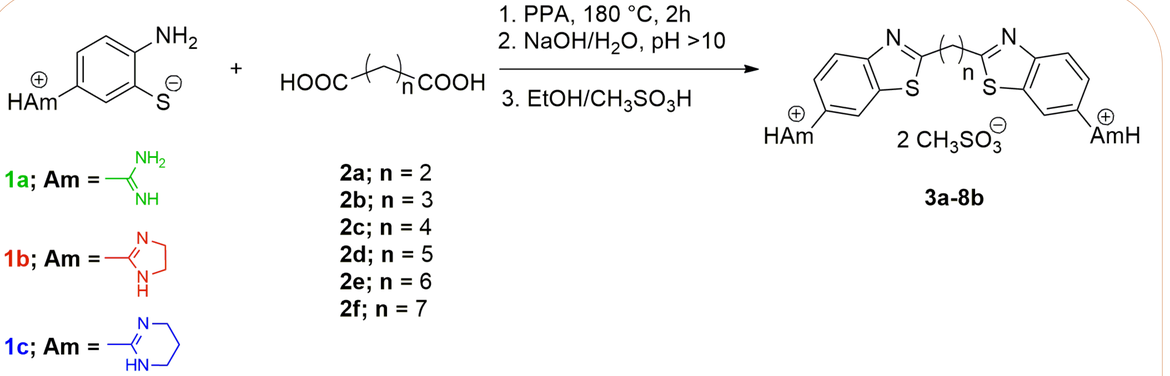
Livio Racané and **Lucija Ptiček**, Department of Applied Chemistry, Faculty of Textile Technology, University of Zagreb, Zagreb, Croatia
Petra Grbčić and **Sandra Kraljević Pavelić**, Department of Biotechnology, Centre for high-throughput technologies, University of Rijeka, Rijeka, Croatia

INTRODUCTION

In the field of drug discovery and development, biologically important heterocyclic molecules known as "privileged structures" play an important role as promising future drug candidates because of their versatile binding properties for different biotargets. Moreover, benzothiazoles and their derivatives have shown a wide range of biological activities such as anticancer, antimicrobial, antiviral and antioxidant. The benzothiazole nuclei is already a structural part of some drugs used in clinical applications, such as for example *zopolrestat* for the treatment of diabetes*, riluzole* for the treatment of amyotrophic lateral sclerosis, or *frentizole* used as an antiviral or immunosuppressive agent [1]. In continuation of our previous research in the synthesis and evaluation of antiproliferative activities of amidino-substituted 2-aryl(heteroaryl)bisbenzothiazole derivatives [2-5], we present here the design, synthesis and antiproliferative activity of a series of dicationic 6-amidino-2-alkylbisbenzothiazole derivatives.

RESULTS AND DISCUSSION

The synthesis and structure of dicationic 6-amidino-2-alkylbisbenzothiazole derivatives is outlined in Scheme 1. Previously, we developed robust methods for the preparation of a number of 6-amidino-2-aryl/heteroaryl-benzothiazole derivatives by condensing 5-amidino-substituted 2-aminothiophenoles (**1a-1c**) with carboxylic acids in polyphosphoric acid (PPA) [2, 3] and following this methodology we prepared novel 6-amidino-substituted 2-alkyl-bisbenzothiazoles (**3a-3c**, **4a**, **4b**, **5a-5c**, **6a**, **6b**, **7a-7c**, **8a** and **8b**) in moderate to good yields. The structures of compounds were determined by using ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis. Antiproliferative activity was studied on four human tumor cell lines *in vitro*: CFPAC-1 (ductal pancreatic adenocarcinoma), SW620 (metastatic, colorectal adenocarcinoma), HepG2 (hepatocellular carcinoma) and HeLa (cervical carcinoma), as well as on normal fibroblasts HFF-1 (human skin fibroblasts). As a positive control, 5-fluorouracil was used. The results obtained are summarized in Table 1.



Scheme 1. Synthesis of dicationic 6-amidino-2-alkylbisbenzothiazole derivatives **3a** – **8b**

Table 1. Antiproliferative activity of compounds **3a** – **8b** on four human tumor cell lines

Compound	n	IC_{50}*(mM)				
		SW620	HepG2	CFPAC-1	HeLa	HFF
3a	2	>100	34.75±3.13	81.30±19.06	50.10±16.75	0.58±0.09
3b	2	4.13±1.20	3.75±0.55	4.90±0.05	2.39±0.03	0.29±0.13
3c	2	>100	>100	>100	>100	6.04±1.32
4a	3	>100	93.78±21.50	>100	>100	4.47±1.92
4b	3	9.68±1.27	22.25±0.96	21.48±2.08	8.29±1.07	2.34±0.37
5a	4	48.71±10.86	23.92±7.00	37.56±6.04	15.57±6.77	0.02±0.01
5b	4	3.41±1.05	3.03±0.26	3.90±0.12	1.99±0.21	0.11±0.04
5c	4	98.17±7.49	13.83±1.46	78.99±6.16	5.77±1.18	3.56±2.05
6a	5	31.14±4.78	22.24±12.43	28.57±5.14	9.67±1.65	0.05±0.01
6b	5	2.50±1.04	3.38±0.59	3.98±0.33	2.40±0.88	0.03±0.01
7a	6	4.68±1.93	3.94±1.05	12.98±4.33	2.57±0.12	<0.01
7b	6	1.14±0.93	1.81±0.51	0.94±0.06	1.04±0.14	<0.01
7c	6	79.35±4.51	37.53 ± 4.43	76.03 ± 6.38	3.84±1.16	2.82±0.58
8a	7	4.86±1.82	3.20±1.79	6.19±1.33	1.71±0.54	<0.01
8b	7	0.59±0.90	2.78±0.01	2.22±0.84	2.42±0.47	0.10±0.01
5-Fluorouracil		0.80±0.07	55.20±3.22	0.14±0.10	8.81±1.05	0.94±0.13

*IC_{50} values are the concentrations that cause 50% inhibition of cancer cell growth.

CONCLUSIONS

The tested compounds exhibited moderate to strong antiproliferative activity towards tumor cell lines. Low micromolar potency (IC_{50} < 5 μM) of dicationic 6-imidazolinyl derivatives **3b**, **5b**, **6b**, **7b** and **8b** was observed on almost all tested cell lines, which is in agreement with our previous data on the antiproliferative activity of 6-amidino- and 6-imidazolinyl-2-arylbenzothiazole derivatives [4, 5]. Based on these results, compounds **5b** and **8b** were chosen as the leading compounds for further rationalized design of the benzothiazole skeleton.

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