SYNTHESIS AND ANTI-PROLIFERATIVE ACTIVITY OF NOVEL AMIDINO-SUBSTITUTED ARYL-BISBENZOTHIAZOLES

Sinteza i antiproliferativna aktivnost novih amidino-supstituiranih arilnih bisbenzotiazola

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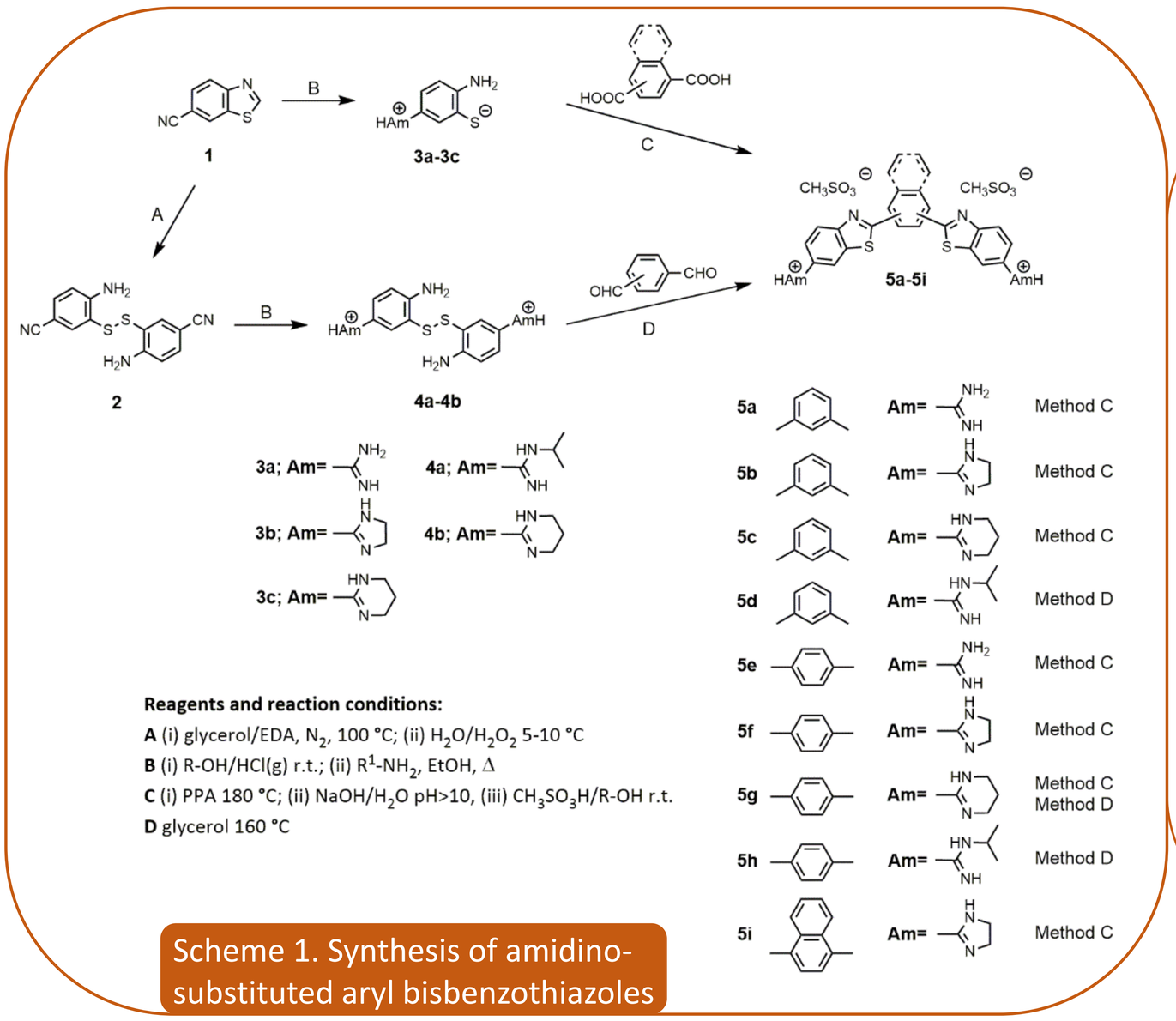
INTRODUCTION

2-Arylbenzothiazole derivatives are of considerable interest due to their diverse pharmaceutical properties and have emerged as a privileged scaffold in drug discovery bearing remarkable activity profiles in non-invasive diagnosis of Alzheimer's disease and antitumour effects [1]. Strong anti-proliferative effects on some tumour cell lines were previously shown for 2-arylbenzothiazole derivatives [1], isomeric imidazolinyl-substituted phenylene-bisbenzothiazole [2] and imidazolinyl-substituted phenyl- and naphtyl-benzothiazoles [3]. These findings have led us to further investigate this class of compounds by introducing different types of amidinic substituents into the structure with the aim of improving activity and selectivity on different human tumour cell lines.

RESULTS AND DISCUSSION

We found new synthetic method for preparation of isomeric amidino-substituted derivatives of bisbenzothiazolyl-phenylenes and naphtalenes (scheme 1). Screening of anti-proliferative activity was performed on four human tumour cell lines *in vitro*: CFPAC-1 (ductal pancreatic adenocarcinoma), SW620 (metastatic, colorectal adenocarcinoma), HepG2 (hepatocellular carcinoma) and HeLa (cervical carcinoma). Obtained results are presented in Table 1. *In vitro* anti-proliferative screening of novel diamidino-bisbenzothiazolyl derivatives **5a**-**5i** revealed strong activity on tested cell lines, depending on the type of amidinic substituent as well as positions of benzothiazolyl moieties.



Scheme 1. Synthesis of amidino-substituted aryl bisbenzothiazoles

Table 1. I*n vitro* anti-proliferative activity of amidino-substituted derivatives **5a-5i** on four different tumour cell lines

Compound	IC_{50}[a] / mM			
	Tested cell lines			
	SW620	HepG2	CFPAC-1	HeLa
5a	8.20±1.12	>100	>100	4.38±0.69
5b	0.08±0.02	0.16±0.09	0.09±0.01	0.07±0.09
5c	0.40±0.12	5.95±0.64	6.41±1.36	0.74±0.51
5d	7.13±1.65	5.01±0.96	9.09±1.47	1.31±0.96
5e	0.09±0.01	3.16±0.68	5.90±0.09	0.65±1.41
5f	0.26±0.06	0.3±0.09	2.10±0.84	0.41±0.90
5g	0.08±0.74	0.94±0.35	42.46±8.86	0.71±0.09
5h	0.09±0.85	1.53±0.29	5.92±1.88	1.34±0.76
5i	0.22±0.11	0.39±0.24	1.08±0.15	0.68±0.43

[a]Compound concentration required to inhibit tumor cell proliferation by 50%

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26. CROATIAN MEETING OF CHEMISTS AND CHEMICAL ENGINEERS

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