SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL 2-(HETERO)ARYL-6-(2-IMIDAZOLINYL)BENZOTHIAZOLES AS ANTICANCER AGENTS

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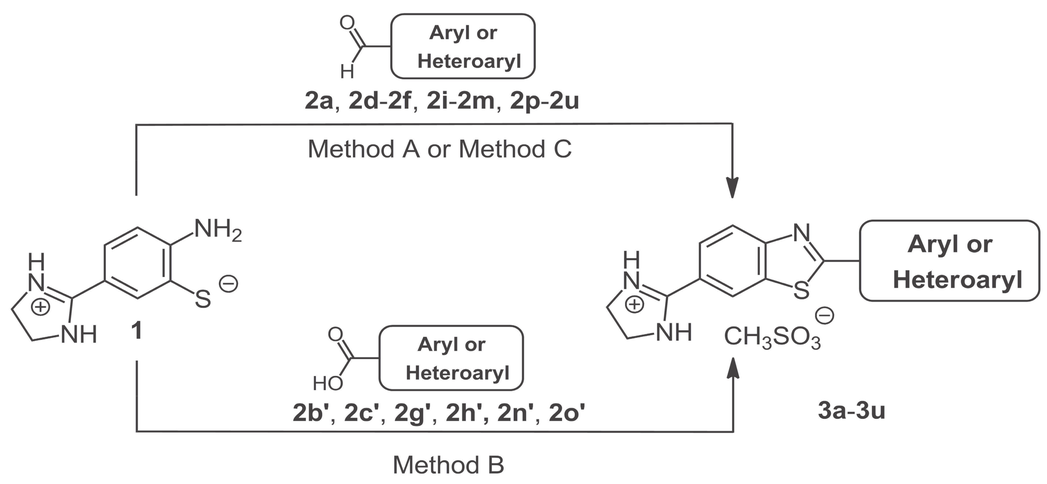
Scheme 1

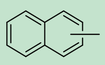
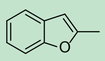
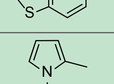
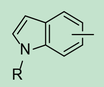
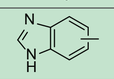
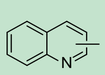


Method A (i) HOAc, reflux 2-4 h, then NaOH p*H* 10-12; (ii) EtOH or 2-PrOH, 1.1 eq MSA, rt

Method B (i) PPA, 110-180 °C, 3 h; (ii) 2.5 M NaOH; (iii) EtOH, 1.1 eq MSA, rt

Method C (i) glycerol, 50 °C, 24-72 h, then NaOH p*H* 10-12; (ii) EtOH or 2-PrOH, 1.1 eq MSA,

Table 1

2-aryl/2-heteroaryl-substituted benzothiazole		Method / Yield			IC_{50}[a] (μM) Cell lines				
		A/%	B/%	C/%	CFPAC-1	SW620	HepG2	HeLa	WI38/BJ/ HFF-1
	**3a** = phenyl	56			4.7	4.4	5.6	29.1	5.4[3]
	**3b** = naphthalene-1-yl		48		2.1	2.9	1.2	3.2	1.4[3]
	3c = naphthalene-2-yl		54		0.6	0.9	1.2	0.3	0.9[3]
	**3d** = furan-2-yl	0	0	45	45.5	15.6	58.9	48.1	29.1[1]
	**3e** = benzofuran-2-yl	51	0	53	2.0	0.1	1.0	0.7	0.4[2]
	**3f** = thiazole-2-yl			56	46.7	26.5	66.8	54.6	35.2[1]
	**3g** = benzothiazole-2-yl		53		2.3	3.8	2.0	2.8	N.A.
	3h = benzothiazole-6-yl		72		3.9	3.5	3.0	1.8	3.2[1]
	3i = *N*-methylpyrrole-2-yl	0		56	21.8	22.4	22.5	20.1	34.5[1]
	**3j** = indole-3-yl	37		56	1.2	0.5	2.4	1.9	3.0[1]
	3k = indole-5-yl	37		0	2.3	0.3	2.4	2.4	1.7[1]
	3l= *N*-methylindole-3-yl	31		55	3 .3	2.9	2.4	1.1	2.1[1]
	**3m** = *N*-methylimidazole-2-yl	33		60	35.8	24.9	48.2	47.7	28.6[1]
	**3n** = benzimidazole-2-yl		56		2.4	3.5	3.6	2.8	N.A.
	3o = benzimidazole-5(6)-yl		62		9.0	5.5	9.3	5.2	6.0[1]
	**3p** = pyridin-2-yl			63	28.5	7.8	44.4	31.1	22.6[1]
	3q = pyridin-3-yl	67		64	46.3	20.3	75.1	35.8	19.0[1]
	3r = pyridin-4-yl	55			30.3	25.9	58.9	38.1	34.5[1]
	**3s** = quinoline-2-yl	74			0.5	0.2	1.5	1.7	0.3[1]
	3t = quinoline-3-yl	72			1.5	0.7	3.7	2.2	0.7[1]
	3u = quinoline-4-yl	62			5.8	3.2	7.8	7.1	1.9[1]

[a]Compound concentration required to inhibit tumor cell proliferation by 50%
[1]Compounds **3d, 3f, 3h**-**3m, 3o**-**3u** were tested on WI38 cell line. [2]Compound **3e** was tested on BJ cell line. [3]Compounds **3a**-**3c** were tested on HFF-1 cell line

INTRODUCTION

Benzothiazole as an important pharmacophore, has recently emerged as a privileged scaffold in drug discovery [1] due to a variety of pharmacological properties, and its derivatives offer a high degree of structural diversity that has proven useful for the search of new therapeutic agents [2].Through last decade, our scientific focus has been placed on this particular series of heterocyclic compounds, with an emphasis on their synthesis, study of anticancer activities and DNA binding properties [3-6]. Recently, we efficiently synthesized a series of 2-thienyl- and 2-benzothienyl-substituted 6-(2-imidazolinyl) benzothiazole derivatives, investigated their antitumor effects and explored the possible involvement of key enzymes regulating sphingolipid metabolism [7]. We have found in this group of sulphur-containing heterocycles the 2-benzothienyl derivative to have remarkable and selective cytostatic activity. One of the major mechanisms accounting for observed cytostatic effects was induction of apoptosis, probably due to specific inhibition of acid ceramidase activity. Based on these results a novel series of title compounds are synthesized and evaluated for their potential as anticancer agents.

RESULTS AND DISCUSSION

A general approach for the synthesis of monocationic 2-aryl/2-heteroaryl-substituted 6-(2-imidazolinyl)benzothiazoles, is outlined in Scheme 1. An efficient synthesis used for the preparation was achieved by three complementary simple two steps synthetic protocol based on the condensation reaction of aryl/heteroaryl carbaldehydes in acetic acid (Method A) or in glycerol (Method C) or aryl/heteroaryl carboxylic acid in PPA (Method B) with 2-amino-5-(2-imidazolinium) benzenethiolate. We developed an eco-friendly synthetic protocol using glycerol as green solvent particularly appropriate for the condensation of thermally and acid sensitive heteroaryl carbaldehydes such as furane, benzofurane, pyrrole and indole (Table 1). Screening of antiproliferative activity of was performed 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 human cell lines Wi38 (human lung fibroblasts), BJ and HFF-1 (human skin fibroblasts). Obtained results are presented in Table 1.

All tested compounds showed strong to moderate non-specific antiproliferative activity on tested tumor cell lines and fibroblasts in dependence of aryl/heteroaryl moiety coupled at position 2- to 6-(2-imidazolinyl)benzothiazole moiety. However, it is clear that benzofused heterocycles show a more pronounced antiproliferative activity in comparison with unfused one.

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