NOVEL 2-SUBSTITUTED BENZOTHIAZOLES: SYNTHESIS AND ANTIPROLIFERATIVE EVALUATION

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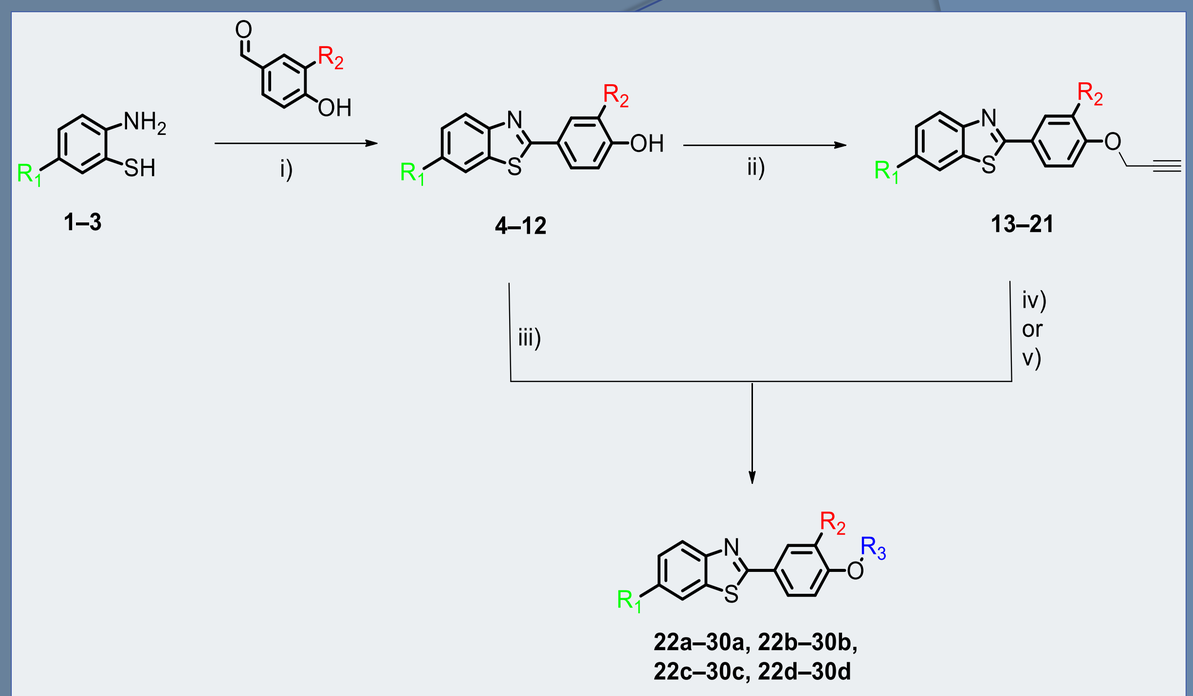
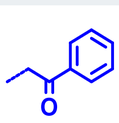
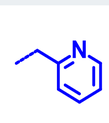
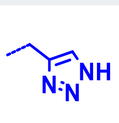
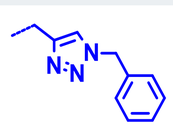
Introduction

The benzothiazoles are constituents of bioactive heterocyclic compounds that exhibit wide spectrum of biological and pharmacological activities. Functionalization of the benzothiazole scaffold at the C-2 and C-6 positions was found to be a key determinant for their enhanced biological activity, mainly as cytostatic and antimicrobial agents. Some benzothiazole-based anticancer agents were found to target tyrosine kinase, topoisomerase, microtubule, cytochrome P450, heat shock protein 90 (Hsp90), epidermal growth factor receptor (EGFR) and apoptosis by reactive oxygen species (ROS) activation. Anticancer effects of 2-arylbenzothiazoles involved metabolic activation by cytochrome P450 to electrophilic reactive species, which generated DNA adducts in sensitive tumor cells. Therefore, 2-arylbenzothiazoles have emerged as an important pharmacophore in the development of antitumor agents. [1-4]



R_1	R_2				
Cl	H	22a	22b	22c	22d
F		23a	23b	23c	23d
H		24a	24b	24c	24d
Cl	F	25a	25b	25c	25d
F		26a	26b	26c	26d
H		27a	27b	27c	27d
Cl	OMe	28a	28b	28c	28d
F		29a	29b	29c	29d
H		30a	30b	30c	30d

Scheme 1. Synthesis of 6-substituted 2-arylbenzothiazole derivatives. Reagents and conditions: (i) $Na_2S_2O_5$, DMF, 100 °C, 2 h; (ii) propargyl bromide, K_2CO_3, ACN, rt, 24 h; (iii) corresponding alkyl halogenide, K_2CO_3, ACN, rt, 24 h; (iv) CuI, trimethylsilyl azide, DMF : MeOH = 1:1, 100 °C, 24h; (v) benzyl chloride, NaN_3, Et_3N, *t*-BuOH: H_2O = 1:1, rt, 12 h, $Cu(OAc)_2$.

Table 1. *In vitro* growth inhibitory effects of synthesized compounds (**22a-30a, 22b-30b, 22d-25d,** and **27d-29d**) on selected tumor cell lines

	IC_{50} / μM					IC_{50} / μM			
Compd	**MDCK1**	**HeLa**	**CaCo-2**	**HuT78**	**Compd**	**MDCK1**	**HeLa**	**CaCo-2**	**HuT78**
22a	>100	>100	>100	>100	**26b**	/	/	/	/
23a	87.3 ± 6.9	>100	>100	>100	**27b**	94.2 ± 18.4	>100	28.7 ± 6.7	>100
24a	>100	>100	>100	>100	**28b**	/	/	/	/
25a	>100	>100	>100	>100	**29b**	1.1 ± 0.0	>100	>100	>100
26a	25.8 ± 9.4	>100	89.3 ± 15.8	69.8 ± 15.5	**30b**	85.9 ± 15.7	>100	89.2 ± 16.8	64.7 ± 11.3
27a	>100	>100	>100	>100	**22d**	11.4 ± 4.5	>100	>100	>100
28a	79.3 ± 14.4	>100	>100	>100	**23d**	8.2 ± 1.8	>100	>100	>100
29a	6.8 ± 6.2	>100	>100	>100	**24d**	36.7 ± 8.0	>100	>100	>100
30a	78.0 ± 27.8	>100	>100	>100	**25d**	8.8 ± 1.3	>100	>100	>100
22b	/	/	/	/	**27d**	64.8 ± 8.5	>100	>100	>100
23b	10.1 ± 0.2	>100	>100	>100	**28d**	41.1 ± 7.2	82.8 ± 22.3	>100	49.6 ± 8.0
24b	65.7 ± 11.8	>100	>100	>100	**29d**	22.8 ± 4.9	>100	77.6 ± 43.3	>100
25b	/	/	/	/					

Chemistry

Taking into consideration biological relevance of benzothiazole scaffold, novel 6-substituted 2-arylbenzothiazole derivatives (**22a-30a, 22b-30b, 22c-30c** and **22d-30d**) were synthesized with varied aromatic unit at phenyl ring with the aim to assess their influence on antiproliferative activity. Key benzothiazole intermediates (**4–12**) were obtained by condensation of 2-aminothiophenoles with corresponding benzaldehydes using $Na_2S_2O_5$ and then converted to propargylated derivatives (**13–21**). Targeted 2-(4-alkoxyphenyl)benzothiazole derivatives (**22a-30a, 22b-30b**) were obtained by an *O*-alkylation reaction. Finally 1,4-disubstituted 1,2,3-triazole benzothiazole analogues (**22c-30c, 22d-30d**) were synthesized by copper catalysed reaction of the corresponding terminal alkynes and azides (Scheme 1).

Biological evaluation

2-Arylbenzothiazole derivatives **22a-30a, 22b-30b** and **22d-30d** were evaluated for their antiproliferative activity against cervix adenocarcinoma (HeLa), colon adenocarcinoma (CaCo2), T-cell lymphoma (HuT78) as well as normal Madin-Darby canine kidney fibroblast cells (MDCK1). Compound **27b**, with fluorine and pyridine substituents on aryl ring, showed marked antiproliferative activity against colon adenocarcinoma cells (IC_{50} = 28.7 μM), while compound **28d** showed moderate activity against T-cell lymphoma cells (IC_{50} = 49.6 μM). However, with exception of compound **27b**, tested compounds that exhibited antiproliferative activity were also cytotoxic in the non-tumor MDCK1 cell line.

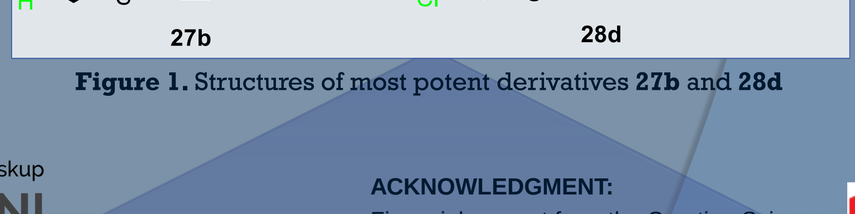


Figure 1. Structures of most potent derivatives **27b** and **28d**

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