SYNTHESIS AND BIOLOGICAL ACTIVITY OF AMIDINO SUBSTITUTED BENZIMIDAZOLES AND BENZOTHIAZOLES

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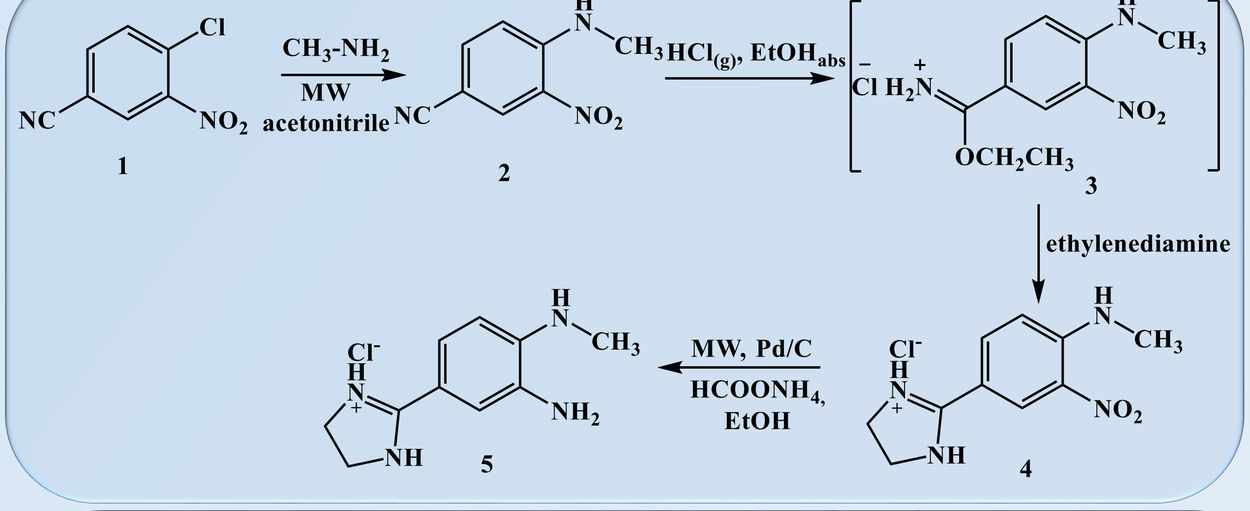
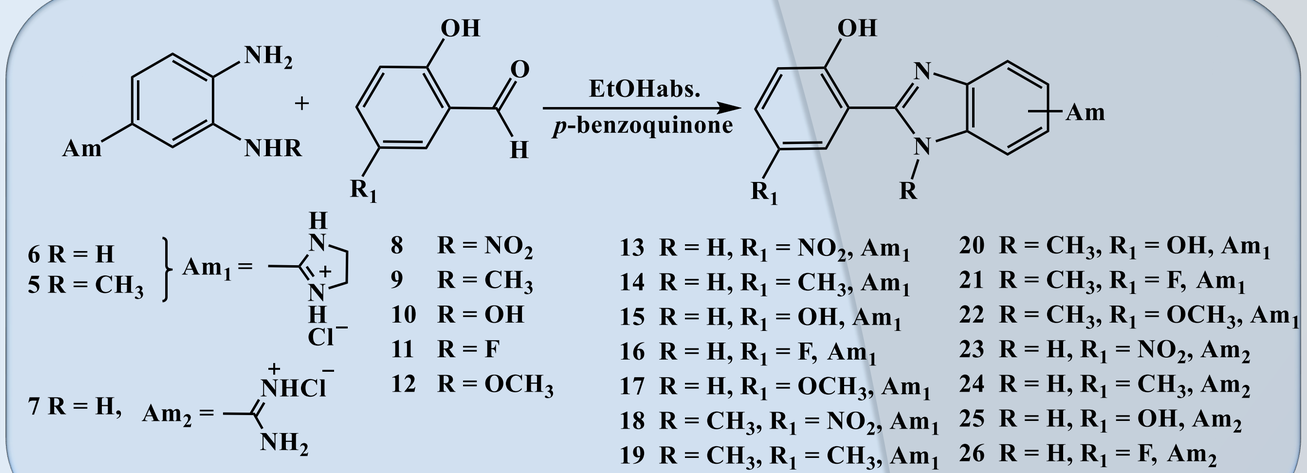
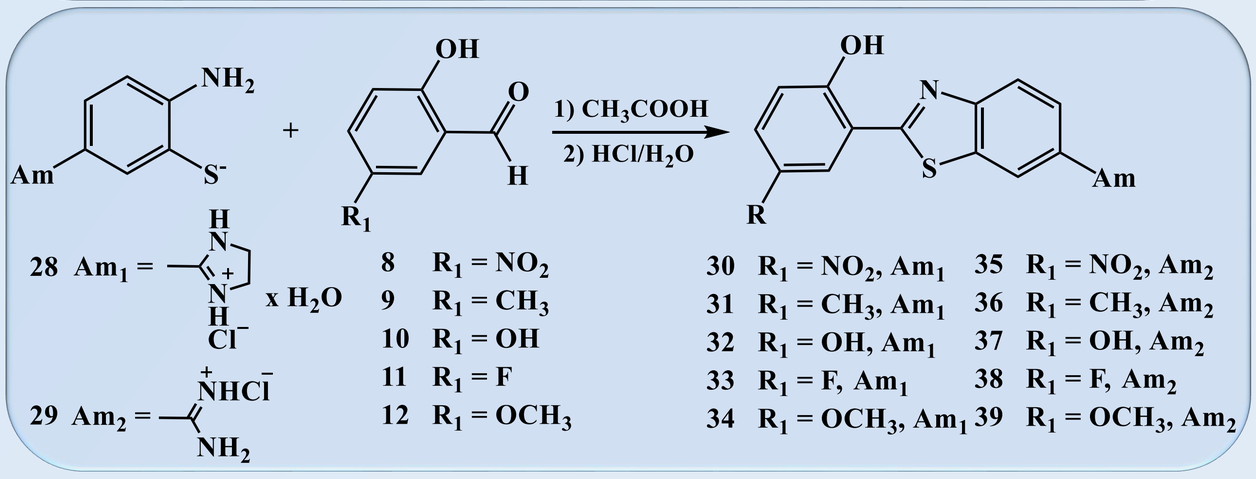
Due to the great biological importance of benzimidazole and benzothiazole derived derivatives, nowadays there is still an increasing interest in medicinal and pharmaceutical chemistry for using this unavoidable structural motifs in the rational design of novel drugs [1]. By introduction of amidino functional groups at the termini of the molecule, the biological activity could be significantly improved because of interaction with an electronegatively charged biological molecule such as DNA [2,3].







Target compounds **13-27** were synthesized by condensation of the prepared precursors **5-7** with the corresponding aldehydes **8-12** using *p*-benzoquinone as an oxidant. Within the cyclocondensation in refluxing acetic acid between aldehydes **8-12** and amidino-substituted benzenethiolates **28, 29**, followed by quenching with hydrochloric acid, benzothiazoles **30-39** as hydrochloride salts were obtained in moderate yields. Precursor **5** was prepared from corresponding cyano substituted precursor in Pinner reaction.

Table 2. Antiproliferative activity *in vitro*

Cpd	IC_{50}/mM							
	Cell line							
	Capan-1	HCT-116	LN-229	NCI-H460	DND-41	HL-60	K-562	Z-138
13	>100	>100	>100	>100	>100	85,1	>100	>100
14	6,2	32,0	2,2	48,4	2,4	8,7	13,0	6,6
15	63,8	58,8	44,0	>100	62,3	49,3	47,5	25,4
16	5,6	37,1	10,4	39,8	4,3	35,8	37,4	43,8
17	49,2	56,5	22,6	44,7	10,3	45,5	48,2	14,1
18	64,4	>100	>100	>100	77,9	50,0	>100	58,0
19	48,5	>100	51,3	>100	55,6	48,7	48,6	68,1
20	57,4	82,8	50,7	>100	39,8	36,2	51,9	29,7
21	51,2	>100	51,5	>100	60,4	33,1	49,7	14,5
22	66,7	>100	>100	>100	77,9	55,6	>100	59,0
23	64,4	>100	>100	>100	77,9	50,0	>100	58,0
24	48,5	>100	51,3	>100	55,6	48,7	48,6	68,1
25	57,4	82,8	50,7	>100	39,8	36,2	51,9	29,7
26	51,2	>100	51,5	>100	60,4	33,1	49,7	14,5
27	66,7	>100	>100	>100	77,9	55,6	>100	59,0
30	>100	>100	>100	>100	>100	85,1	>100	>100
31	6,2	32,0	2,2	48,4	2,4	8,7	13,0	6,6
32	63,8	58,8	44,0	>100	62,3	49,3	47,5	25,4
33	5,6	37,1	10,4	39,8	4,3	35,8	37,4	43,8
34	49,2	56,5	22,6	44,7	10,3	45,5	48,2	14,1
35	62,9	51,9	51,5	36,7	60,2	62,7	>100	73,9
36	2,1	33,7	3,7	10,2	5,4	2,5	8,1	5,6
37	49,3	77,2	39,8	60,9	73,2	62,4	56,4	55,8
38	1,9	4,8	2,5	1,8	5,5	2,0	8,9	1,4
39	2,5	6,9	3,9	7,2	3,8	4,0	6,4	4,0
Etoposide	0.03	3,4	3,7	6,1	1,0	0,8	4,0	0.7
Nocodazole	0.02	0.04	0.4	0.5	0,7	0,04	0,04	0.04

The *in vitro* antibacterial activity of all compounds was evaluated against four bacterial strains sensitive to antibiotics. The assessed antibacterial activity revealed that compounds did not show significant activity toward Gram-positive bacteria *S. aureus* and *S. pneumoniae* and Gram-negative bacteria *E. coli*. Benzothiazole derivatives were more active than benzimidazole analogues.

Table 1. Antibacterial activity *in vitro*

Compounds	*S. aureus ATCC* 29213	*E. coli ATCC* 25922	*E. coli efflux del*	*S. pneumoniae* ATCC 49619
13	32	>64	16	>64
14	32	>64	16	32
15	64	>64	64	>64
16	64	>64	32	64
17	64	>64	32	>64
18	>64	>64	>64	>64
19	>64	>64	>64	>64
20	32	>64	64	>64
21	>64	>64	>64	>64
22	>64	>64	>64	>64
23	64	64	>64	>64
24	16	64	16	>64
25	64	>64	64	>64
26	32	64	32	>64
27	64	>64	16	>64
30	16	32	16	>64
31	>64	>64	>64	>64
32	32	>64	64	>64
33	>64	>64	64	>64
34	32	>64	>64	>64
35	8	16	8	>64
36	32	64	32	>64
37	16	>64	64	>64
38	32	>64	16	64
39	64	>64	32	>64
Ampicillin	0,5	2	2	<0.125
Ceftazidime	8	<0.125	0,25	0,5
Ciprofloxacin	0,125	<0.125	<0.125	0,5
Meropenem	<0.125	<0.125	<0.125	<0.125

All prepared compounds were tested for their antiproliferative activity *in vitro* on eight human cancer cells. The most significant activity was displayed by benzothiazole derivative **38** substituted with fluorine and unsubstituted amidine group. Benzothiazole derivatives with unsubstituted amidine group were more active than benzimidazole analogues. The introduction of a methyl group on the N atom of the benzimidazole core did not improve the activity.

[1] S. R. Brishty *et al.*, *Front. Pharmacol.* 12 (2021) 762807.
[2] A. Irfan *et al.*, *J. Enz. Inhib. Med. Chem.* 35 (2021) 265.
[3] M. Hranjec *et al.*, *J. Med. Chem.* 50 (2007) 5696.

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