Synthesis, antitumor and antioxidative activity of nitro and amino substituted benzimidazole and benzothiazole 2-carboxamides

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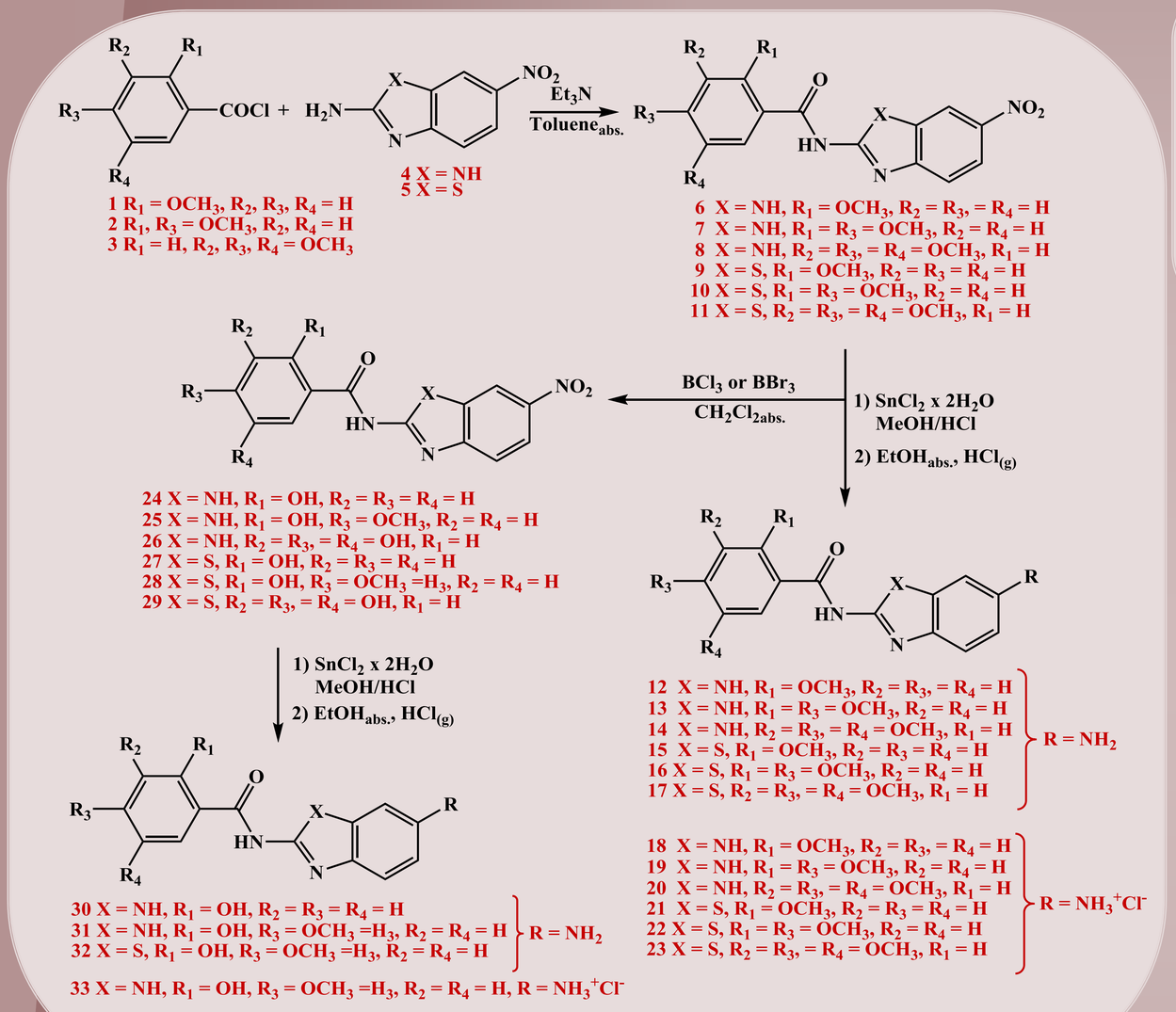
Oxidative stress, as a result of excessive production and accumulation of free radicals, is one of the leading causes of many degenerative diseases. Heterocyclic compounds containing benzimidazole and benzothiazole have been found very interesting to medicinal and organic chemists and are extensively studied due to their well known and wide biological activities. In this report we present synthesis, antitumor and antioxidative activity of novel nitro and amino substituted benzimidazole and benzothiazole. The compounds were synthesized according to the Scheme 1.



Scheme 1. Synthesis of compouns

Antiproliferative activity *in vitro* was tested agains three human cancer cells, HTC116, MCF-7 and H-460. The most active compound, namely trimethoxy nitro-benzimidazole derivative showed selective activity against HTC116 cells.

Table 2. Antiproliferative activity *in vitro*

Cpd	GI_{50}[a] (μM) *Cell lines*		
	HCT116	MCF-7	H-460
6	6±1	4±0,3	6±5
7	3±0.2	2±0,9	4±2
8	0,6±0,03	1±0,2	2±0,2
9	44±25	9±1	46±3
10	9±7	5±2	20±3
13	17±8	20±4	24±8
15	6±4	3±2	3±0,9
16	6±1	5±0,3	43±29
17	28±4	5±3	≥100
19	≥100	34±24	>100
21	10±8	3±0,7	4±0,1
22	8±2	3±0,2	50±8
25	31±4	28±6	18±0,01
26	4±0,1	3±1	3±0,5
27	6±1	2±0,6	3±0,2
28	7±0,4	10±8	8±1
29	7±1	4±0,7	2±1
30	46±0,2	30±0,8	>100
33	50±13	80±4	≥100

Antioxidative activity of prepared compounds was evaluated by DPPH and FRAP method. Obtained results revealed the high antioxidative potential of compounds bearing amino protonated groups. Furthermore, results obtained from FRAP method pointed out that trimethoxy substituted nitro-benzothiazole derivative showed the most pronounced activity. Also, the number of methoxy and/or hydroxy groups together with the type of heteroatom strongly influenced the antioxidative activity.

Table 1. Antioxidative activity *in vitro* of most active compounds

R1	R2	R3	R4	X	R	DPPH (μM)	FRAP $mmol_{Fe^{2+}}/mmol_c$
OH	H	OCH_3	H	NH	NO_2	1990±25,4	150,40±3,4
H	OH	OH	OH	NH	NO_2	8,1±1,9	244,90±4,8
H	OH	OH	OH	S	NO_2	2,0±0,15	6139,22±22,7
OH	H	OCH_3	H	NH	NH_2	9,24±0,6	258,40±6,4
H	OCH_3	OCH_3	OCH_3	NH	NH_2	10,7±0,23	1102,54±14,1
H	OCH_3	OCH_3	OCH_3	NH	$NH_3^+Cl^-$	8,06±0,03	267,44±1,4
H	OCH_3	OCH_3	OCH_3	S	NH_2	40,4±0,4	235,37±2,8
H	OCH_3	OCH_3	OCH_3	S	$NH_3^+Cl^-$	1,46±0,5	241,31±1,6

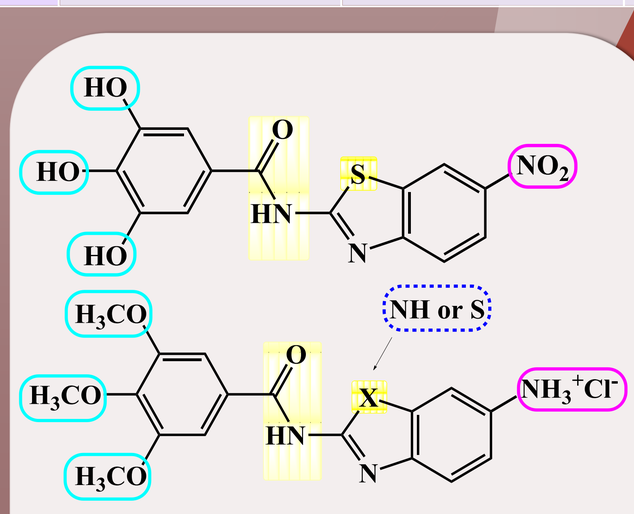


Figure 1. The most promising antioxidants

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