Synthesis and biological activity of novel *N*-substituted benzimidazole acrylonitriles

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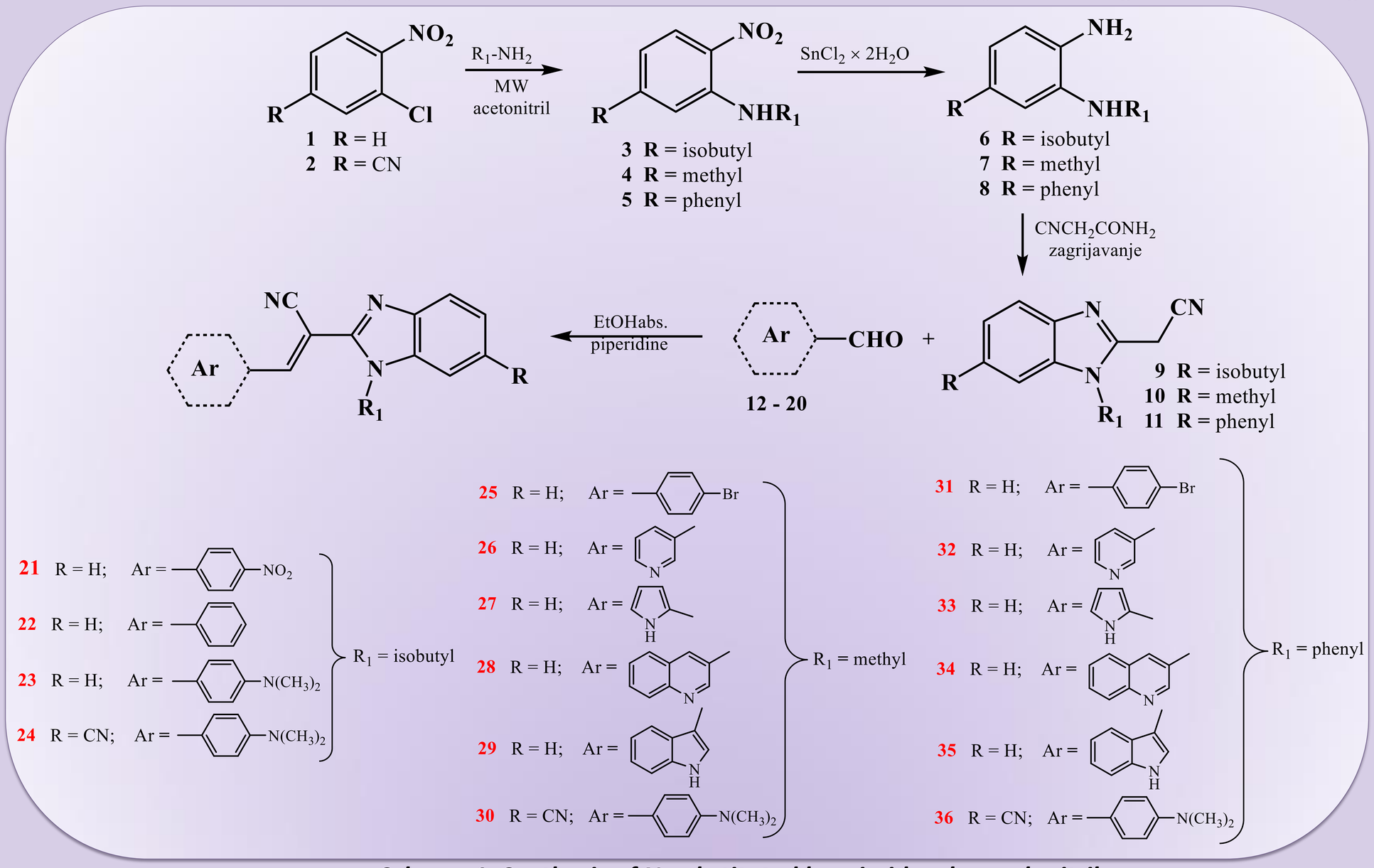
Small heteroaromatic molecules, like nitrogen-containing heterocycles play an important role in medicinal chemistry due to variety of their possible chemical, pharmacological and industrial applications. Benzimidazole structural motifs, as an important bioactive heterocyclic building block in medicinal chemistry, are widely incorporated in the structure of numerous natural or synthetic medical and biochemical molecules possessing versatile biological features.[1, 2]



Scheme 1. Synthesis of N-substituted benzimidazole acrylonitriles

The targeted benzimidazole acrylonitriles were prepared from corresponding *N*-substituted-1,2-phenylene-diamines and aromatic aldehydes in the reaction of condensation in abs. EtOH and piperidine.*N*-substituted 1,2-phenylene-diamines obtained from the MW assisted uncatalyzed amination followed by reduction with $SnCl_2 \times_2 H_2O$. All prepared derivatives were tested on 9 cancer cell lines and non-cancerous cell line using staurosporin and docetaxel as standards. Results presented in Table 1 revealed the moderate to strong antiproliferative activity. The most active compounds are proven to be 23 and 24 with activity in nanomolar range of inhibitory concentrations.

Table 1. Antiproliferative activity of tested compounds

Cpd	IC_{50} / μM									
	Cell line									
	hTERT RPE-1	Capan-1	Hap-1	HCT-116	NCI-H460	DND-41	HL-60	K-562	MM.1S	Z-138
21	53.8	30.3	43.6	50.4	14.8	54.6	33.4	>100	72.9	45.4
22	44.9	20.6	38.9	42.4	26.1	60.0	29.1	53.4	66.7	40.1
23	**4.3**	**0.3**	**0.3**	**0.6**	**0.4**	**0.2**	**0.3**	**2.1**	**1.5**	**0.4**
24	**1.7**	**0.2**	**0.2**	**0.4**	**0.6**	**0.3**	**0.2**	**1.4**	**1.3**	**0.4**
25	47.3	20.5	32.7	52.2	32.1	41.3	24.3	57.6	95.7	30.7
26	60.1	57.1	72.8	85.1	59.3	>100	58.6	>100	>100	>100
27	>100	84.4	73.5	>100	67.9	73.7	>100	>100	>100	>100
28	39.4	66.9	66.4	>100	22.4	49.9	33.0	>100	>100	45.0
29	27.3	13.3	10.1	29.0	12.1	14.9	13.5	37.0	71.0	9.9
30	80.9	55.9	85.0	68.5	>100	>100	68.1	>100	>100	96.5
31	22.8	12.9	10.9	16.0	12.0	12.3	8.6	39.3	35.7	11.0
32	54.4	44.0	47.6	50.6	45.6	60.5	31.3	>100	59.5	30.2
33	32.4	14.2	10.0	49.4	27.4	41.2	42.0	>100	>100	67.5
34	12.2	10.0	10.6	12.4	13.6	14.1	15.3	>100	62.4	12.6
35	12.9	5.1	8.7	7.1	5.3	10.1	6.7	13.6	24.8	12.1
36	27.8	3.1	14.9	26.8	45.7	55.8	10.9	>100	>100	17.4
Docetaxel	0.0553	0.0088	0.0096	0.0017	0.0024	0.0125	0.0072	0.0152	0.0118	0.0142
Stauroporine	0.0055	0.0123	0.0588	0.0281	0.0597	0.0160	0.0076	0.0768	0.0442	0.0067

Table 2.

Cpd	IC_{50} / μM		
	PBMC		
	donor 1	donor 2	donor 3
23	98,8	>100	>100
24	76,0	>100	>100
Stauroporine	0.001	0.0002	0.003

Additionally, the most active compounds 23 and 24 were tested on normal cells (PBMCs) and the obtained results revealed that compound 24 did not affect these cells while 23 was toxic to normal cells. Mechanism of action studies demonstrated that two most active compounds inhibited the polymerisation of tubuline.

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