Antitumor activity of novel amino substituted pentacyclic benzimidazole derivatives tested in 2D and 3D cell culture system

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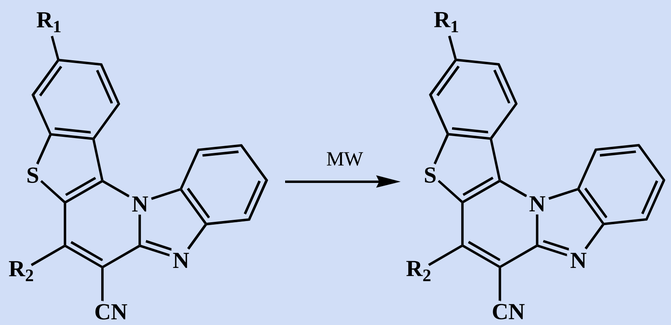
Over the past few years substituted benzimidazoles, as a one of the most important groups of nitrogen heterocycles, are important and fundamental building skeletons of various essential synthetic and natural pharmacological compounds. Due to the structural similarity with naturally occurring compounds such as purine, benzimidazole derivatives can easily interact with biomolecules of the living systems. Recently, we have reported on the synthesis and biological activity of several groups of tetracyclic benzimidazo[1,2-*a*]quinolines [1,2]. Detailed biological studies confirmed the promissing anticancer potential of this class of compounds.

As a part of our continuing research in the field of medicinal chemistry, novel amino substituted pentacyclic benzimidazole derivatives were synthesized by uncatalyzed microwave assisted amination from halogeno substituted precursors.

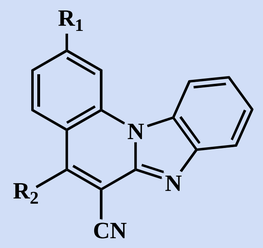


1 R_1=F; R_2=H
2 R_1=H; R_2=Cl
3 R_1=F; R_2=Cl

Scheme. 1.

4 R_1= —N⟨ ⟩ ; R_2 = H
5 R_1= —N⟨ ⟩NH ; R_2 = H
6 R_1= —$NHCH_2CH(CH_3)_2$; R_2 = H
7 R_1= —$NH(CH_2)_3N(CH_3)_2$; R_2 = H
8 R_1= H; R_2 = —N⟨ ⟩
9 R_1= H; R_2 = —N⟨ ⟩NH
10 R_1= H; R_2 = —$NHCH_2CH(CH_3)_2$
11 R_1= H; R_2 = —$NH(CH_2)_3N(CH_3)_2$
12 R_1= R_2 = —N⟨ ⟩
13 R_1= R_2 = —N⟨ ⟩NH
14 R_1= R_2 = —$NHCH_2CH(CH_3)_2$

15 R_1= F; R_2=H
16 R_1= —N⟨ ⟩ ; R_2 = H
17 R_1= —N⟨ ⟩NH ; R_2 = H
18 R_1= —$NHCH_2CH(CH_3)_2$; R_2 = H
19 R_1= —$NH(CH_2)_3N(CH_3)_2$; R_2 = H



20 R_1= H; R_2 = Cl
21 R_1= H; R_2 =═O
22 R_1= H; R_2 = —N⟨ ⟩
23 R_1= H; R_2 = —N⟨ ⟩NH
24 R_1= H; R_2 = —$NHCH_2CH(CH_3)_2$
25 R_1= H; R_2 = —$NH(CH_2)_3N(CH_3)_2$

26 R_1= F; R_2 = Cl
27 R_1= F; R_2 =═O
28 R_1= R_2 = —N⟨ ⟩
29 R_1= R_2 = —N⟨ ⟩NH
30 R_1= R_2 = —$NHCH_2CH(CH_3)_2$

Figure 1.

Table 1. IC_{50} of compounds **1-30** on 2D and 3D assay

Comp.	IC_{50} (μM)					
	2D			3D		
	MDA-MB-231	SK-BR-3	T47-D	MDA-MB-231	SK-BR-3	T47-D
1	>30	>30	1	>30	>30	>30
4	>30	>30	>30	>30	>30	>30
5	4±0.09	2±0.41	5±0.00	19±10.36	24±3.63	26±5
6	3±0.26	5±1.04	2±0.00	>30	>30	12±2
7	2±0.04	4±0.21	5±0.00	5±1.27	27±1.39	>30
2	>30	>30	1	>30	>30	>30
3	>30	>30	>30	>30	>30	>30
8	6±0.11	>30	5±0.11	>30	>30	>30
9	5±0.12	4±0.14	5±0.48	5±0.22	>30	>30
10	9±0.70	>30	5±0.00	>30	>30	>30
11	3±0.08	1±0.06	4±0.00	4±1.14	10±0.16	23±7
12	>30	>30	>30	>30	>30	>30
13	4±0.43	8±0.27	12±2.00	17±9.81	>30	>30
14	>30	>30	4±0.00	>30	>30	8±2
15	30±0.00	>30	>30	>30	>30	>30
16	7±0.21	3±0.15	>30	>30	>30	>30
17	3±0.15	2±0.37	15±6.00	5±0.90	>30	>30
18	5±0.60	1±0.12	3±0.00	>30	>30	19±7
19	3±0.08	4±0.21	12±1.00	11±0.10	>30	>30
20	>30	>30	1±0.00	>30	>30	>30
21	>30	>30	>30	>30	>30	>30
22	>30	>30	>30	3±0.67	>30	>30
23	8±0.97	9±0.13	>30	7±0.25	>30	>30
24	>30	4±0.12	>30	>30	>30	>30
25	6±0.32	4±0.07	29±0.00	7±2.46	>30	>30
26	11	5	2	>30	>30	>30
27	>30	>30	>30	>30	>30	>30
28	>30	>30	>30	>30	>30	>30
29	2±0.18	7±1.54	5±0.00	9±2.43	>30	>30
30	>30	5±0.12	12±1.00	>30	>30	19±7

Antitumor activity *in vitro* of novel pentacyclic and earlier prepared tetracyclic benzimidazole derivatives was tested on tree breast cell lines (MDA-MB-231, SK-BR-3 and T-47D) in 2D and 3D cell culture system [3].

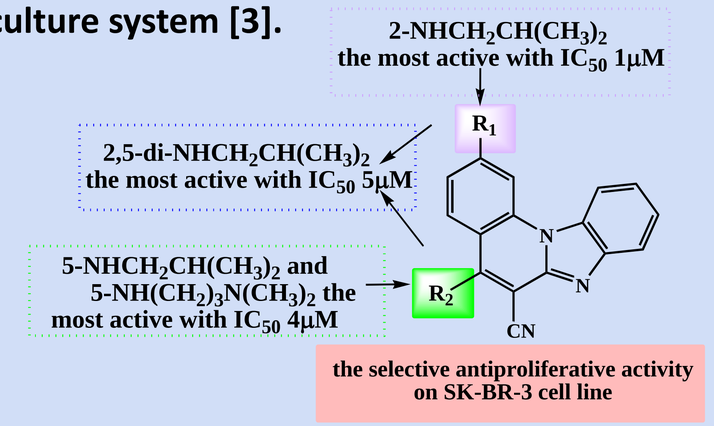


Figure 2. SAR of amino substituted benzimidazo[1,2-*a*]quinolines **15-30** in 2D assays

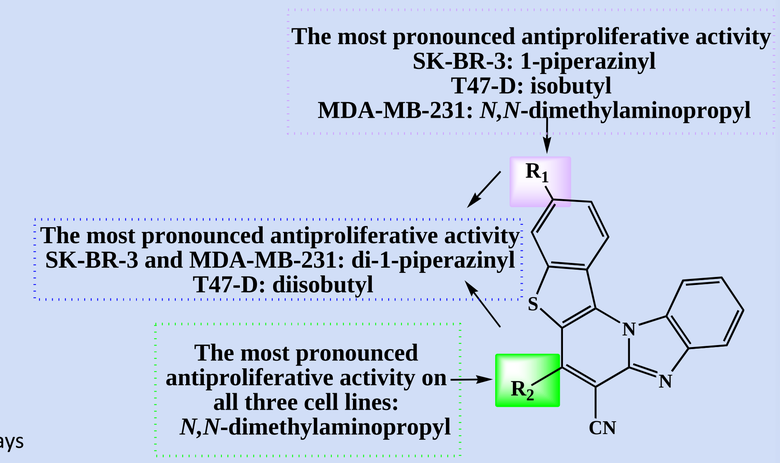


Figure 3. SAR of amino substituted benzo[*b*]thieno[2,3-*b*]pyrido [1,2-*a*]benzimidazoles **1-14** in 2D assays

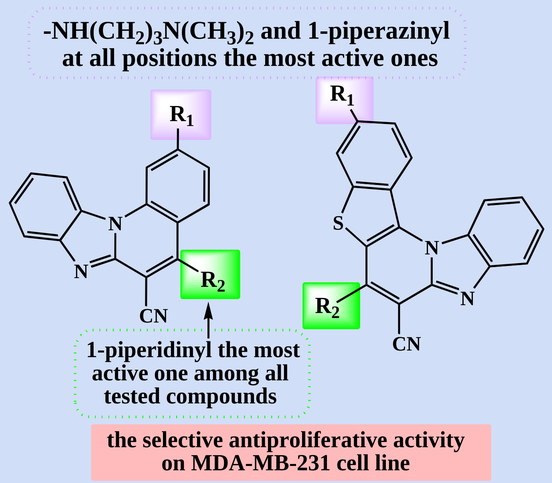


Figure 4. SAR of amino substituted benzimidazo[1,2-*a*]quinolines **15-30**and benzo[*b*]thieno [2,3-*b*]pyrido[1,2-*a*]benzimidazoles **1-14** in 3D assays

References

1. Hranjec, M.; Kralj, M.; Piantanida, I.; Sedić, M.; Šuman, L.; Pavelić, K.; Karminski-Zamola, G.; Part 3, J. Med. Chem. 2007;50:5696-5711.
2. Perin, N.; Martin-Kleiner, I.; Nhili, R.; Laine, W.; David-Cordonnier, M. H.; Vugrek, O.; Karminski-Zamola, G.; Kralj, M.; Hranjec, M. *Med. Chem. Commun.* 4 (2013) 1537–1550.
3. Brajša, K.; Vujasinović, I.; Jelić, D.; Trzun, M.; Zlatar, I.; Karminski-Zamola, G.; Hranjec, M.; *J. Enzyme. Inhib. Med. Chem.* (2015) doi: 10.3109/14756366.2015.1101093.