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Short communication

Synthesis and QSAR studies of novel 1-substituted-2-aminobenzimidazoles derivatives

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Abstract

A series of novel 1-substituted-2-aminobenzimidazole derivatives were synthesized. The structures of the synthesized compounds were confirmed by ^{1}H-NMR spectra and by elemental analysis. Acute toxicities of these compounds were detected on mice via toxicity ($\log LD_{50}$). QSAR analysis of these chemicals was studied on the relationship between acute toxicity and the octanol/water partition coefficient (Log*P*). The products were identified by the results of elemental analysis and ^{1}H-NMR spectra. The toxicity ($\log LD_{50}$) of 2-aminobenzimidazole 1-substituents were correlated well with the partition coefficient Log*P*, $r = 0.9243$. The bioactivity (toxicity) of 2-aminobenzimidazoles can be predicted by the molecular structural parameter such as Log*P*.
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Keywords: 2-aminobenzimidazole derivatives; Synthesis; Acute toxicity; QSAR

1. Introduction

Heterocyclic compounds containing nitrogen occurred widely in roast food and drugs and possess different pharmacological properties due to the oxidation of nitrogen in molecule [1]. The studies recently carried out in many laboratories dealt mainly with the synthesis of 2-aminobenzimidazole derivatives exhibiting antilipidemic or platelet antiaggregatory activity [2], antimicrobial [3], antiinflammatory and analgesic properties [4], anti-HIV and antitumor activity [5], antiallergic [6], immunosuppressive, and antiviral activity [7]. Many of these compounds display affinity at the benzodiazepine receptor [8]; some of them are selective inhibitors of nitric oxide [9] and the neuronal calcium channel blockers [10]. The 1-substituted-2-aminobenzimidazoles were not only a sort of vermifuge, but also an intermediate for synthesis of many drugs. Their biological activities were susceptible to the substituted groups attaching to the nitrogen atom on the ring [11]. The goal of the present investigations was to synthesize a series of novel 1-substituted-2-aminobenzimidazole derivatives and elucidate their preliminary relationships between structures and acute toxicities as well as QSAR analysis. At present, there are four primary QSAR methods in common use: octanol/water partition coefficient (Log*P*); linear solvation energy relationship (LSER); molecular connectivity index, and molecular group contribution. Our choice was to estimate the acute toxicity by QSAR analysis using measured Log*P* values derived via the protocol described by Ruilan et al. [12], because it is simple and feasible.

2. Chemistry

Eight compounds were synthesized as below: The potassium salt of 2-aminobenzimidazole was first prepared by reaction with powdered potassium hydroxide in acetone at room temperature, and then submitted to the reaction with a slight excess of the alkyl halides to give the desired monoalkylated products (Scheme 1).

3. Results and discussion

3.1. Chemistry

The most common method for the synthesis of 1-substituted-2-aminobenzimidazoles derivatives was the *N*-alkylation

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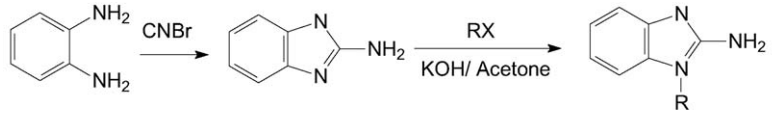

R= -H -CH_3 -C_2H_5 -$CH_2CH_2CH_3$ -$CH_2CH{=}CH_2$ - $CH_2CH_2CH_2CH_3$ - $CH_2C_6H_5$ -$CH_2C_6H_4F$

X = Br, I

Scheme 1. The new synthesized compounds were characterized by elemental analyses and ^{1}H-NMR spectra.

in the presence of alkaline reagents using benzimidazole as starting material and then amination at 2-position with sodamide (prepared in liquid ammonia [13]). This method, however, was scarcely used at present because of its difficult operation. Herein we reported a new facile method for the *N*-alkylation at 1-position of 2-aminobenzimidazole. The potassium salt was well formed when the powdered potassium hydroxide used, which was favorable to the alkylation. The use of excess of alkyl halides and longer reaction time leaded to the alkylation on the amino group and to an increase in side products. Melting points and spectral data of the compounds were collected in Table 1.

3.2. Assessment of acute toxicities

The LD_{50} values for acute toxicities of the selected 1-substituted-2-aminobenzimidazole derivatives in mice after administration were summarized in Table 2. Neurotoxicities were the principal acute toxic effects observed in mice after receiving the 1-substituted-2-aminobenzimidazole derivatives via intraperitoneal (i.p.) route. All the tested compounds resulted in acute toxic manifestation including tremor, jerky breath, twitch, jumping. Death occurred mostly within 30 min. For survived animals, it could return to normal gradually. Autopsy of the animals that died in the course of experiment and the

Table 1
Some characteristics and spectral data of the compounds

Compound	R	m.p. (°C) [lit.][a]	Analyses[b]			^{1}H-NMR DMSO δ
			C	H	N	
1	H	182~184	63.32	5.17	31.51	9.72(s,1H,NH) 6.37(s,2H,NH_2) 6.86~7.11(m,4H,ArH)
			63.14	5.30	31.56	
2	CH_3	201~203	65.08	6.07	28.85	3.48 (s,3H,CH_3) 6.36(s,2H,NH_2) 6.87~7.12(m,4H,ArH)
		(202~203) [14]	65.29	6.16	28.55	
3	CH_3CH_2	158~159	66.97	6.71	26.32	1.18~1.21(t,3H,CH_3) 3.98~4.03(m,2H,CH_2) 6.37(s,2H,NH_2)
		(158) [15]	67.06	6.88	26.07	6.85~7.13(m,4H,ArH)
4	$CH_3CH_2CH_2$	130	68.73	7.56	23.70	0.96~1.01(t,3H,CH_3) 1.79~1.87(m,2H,CH_2) 3.89~3.92(t,2H,CH_2)
		(132~133) [16]	68.54	7.48	23.98	6.37(s,2H,NH_2) 6.88~7.14(m,4H,ArH)
5	$CH_3(CH_2)_2CH_2$	127~128	69.67	7.86	22.47	0.93~0.97(t,3H,CH_3) 1.35~1.45(m,2H,CH_2) 1.73~1.80(m,2H,CH_2)
		(127~128) [16]	69.81	7.99	22.20	2.89~3.93(t,2H,CH_2) 6.38(s,2H,NH_2) 6.85~7.10(m,4H,ArH)
6	CH_2=CH–CH_2	129~130	68.95	6.54	24.51	4.58~4.59(d,2H,–CH_2–) 5.14~5.31(m,2H,=CH_2) 5.93~6.00(m,H,
			69.34	6.40	24.26	CH) 6.39(s,2H,NH_2) 6.89~7.15(m,4H,ArH)
7	$C_6H_5CH_2$	195~196	75.02	6.02	18.96	5.16(s,2H,CH_2) 6.39(s,2H,NH_2) 6.88~7.12(m,9H,ArH)
		(194~195) [17]	75.31	5.87	18.83	
8	$FC_6H_4CH_2$	192	69.68	4.93	17.65	5.17(s,2H,CH_2) 6.39(s,2H,NH_2) 6.74~7.18(m,8H,ArH)
			69.70	5.01	17.42	

[a] Upper values: found; lower ones: data from reference.
[b] Upper values: found; lower ones: calculated.

Table 2
Acute toxicity and overall Log*P* value in the QSAR studies

Compound	R	Log*P*	LD_{50} (mg·kg^{-1})	$logLD_{50}$	
				Observed	Calculated[a]
1	H	1.047	681	2.833	3.049
2	CH_3	1.396	147	2.167	2.141
3	CH_3CH_2	1.836	75	1.875	1.557
4	$CH_3CH_2CH_2$	2.270	36.9	1.567	1.592
5	$CH_3(CH_2)_2CH$	2.704	88	1.944	2.236
6	CH_2=CH–CH_2	2.727	92.6	1.967	2.287
7	$C_6H_5CH_2$	2.951	1080	3.033	2.729
8	$FC_6H_4CH_2$	2.969	681	2.833	2.776

[a] Values calculated according to Eq. (1).

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