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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*.

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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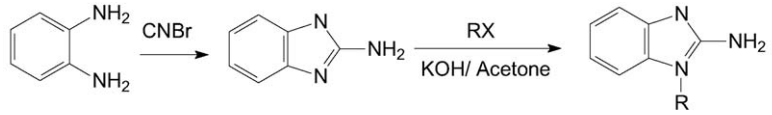

R= -H -CH_3 -C_2H_5 -$CH_2CH_2CH_3$ -$CH_2CH{=}CH_2$ - $CH_2CH_2CH_2CH_3$ - $CH_2C_6H_5$ -$CH_2C_6H_4F$

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).

necropsy finding in surviving animals at the end of experimental period (7 days) revealed no apparent changes in any organs. These compounds perhaps had acute toxicity towards central nervous system (CNS). Table 2 summarized the results of the acute toxicity and QSAR study.

Analysis of the experimental data on the acute toxicity (LD_{50}) after i.p. application shows that compound **4** is more toxic than any other compounds. Compounds **1**, **8** and **7** show low toxicity. Others are mid toxic. Substituent at position N1 of 2-aminobenzimidazole plays a crucial role in determining their effect on acute toxicity. From this table, we can find that the ranking of toxicity was: **4** > **3** > **5** > **6** > **2** > **1**,**8** > **7**.

3.3. QSAR studies

QSAR studies were carried out by the existence of correlation between $\log LD_{50}$ and log*P* as below:

$$\log LD_{50} = 7.380 - 5.719\log P + 1.404(\log P)^2 \quad (1)$$

$N = 8$, $r = 0.9243$, $s = 0.2458$, $F = 14.67$, $R^2 = 0.8543$.

In the above equation, R^2 is the square of correlation coefficient; *S* is standard error; *F* is mean square radio; *N* is the number of compounds; *r* is correlation coefficient. According to the equation, plots of $\log LD_{50}$ against Log*P* are shown in Fig. 1.

The Eq. (1) enable us to conclude that the acute toxicity of the 2-aminobenzimidazole was related to partition coefficient Log*P*, $r = 0.9243$. If Log*P* < 2.037, $\log LD_{50}$ is inversely proportional to log*P* and if Log*P* > 2.037, it ($\log LD_{50}$) is directly proportional to Log*P*. As value of $\log LD_{50}$ is least at Log*P* = 2.037 point. If we dropped two values of *N* (compounds **7** and **8**), we can get another Eq. (2):

$$\log LD_{50} = 0.929(\log P)^2 - 4.0279\log P + 6.026 \quad (2)$$

$r = 0.9856$, $N = 6$.

When we decrease values of *N* (compounds), the corresponding values of *r* approaches 1.

Compounds **8** and **7** have different chemical structures, compound **7** containing benzyl substituent and compound **8** containing –F at position 4 of the benzyl ring substituent.

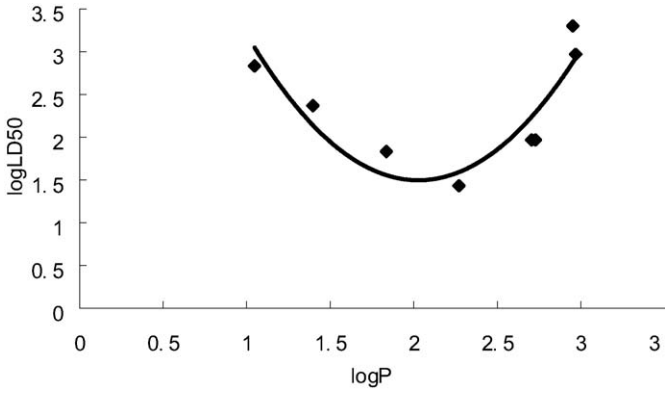

Fig. 1. Plot of $\log LD_{50}$ versus log*P* values.

Electron-withdrawing group (e.g.–F) and large group (e.g. benzyl) in the molecule seem to be related to the low toxicity.

According to the equation, we can predict the toxicity of 2-aminobenzimidazole derivatives and more compounds with different substituents at other positions can be designed on the basis of QSAR studies.

4. Experimental

4.1. Chemistry

Melting points of the compounds were determined using microscopy melting point apparatus and were reported uncorrected. The ^{1}H-NMR spectra were recorded in DMSO-d_6 by the Avance 400 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Elemental analyses were performed by 240C Analyzer and results for C,H,N were within ± 0.4% of calculated values. All the chemicals and solvents used in this study were of analytical grade.

4.2. Pharmacology

4.2.1. Acute toxicities

Acute toxicity experiments were carried out using ICR mice of both sexes weighing 18–30 g. The food and water were provided according to institutional guidelines. All animals were provided by Zhejiang Laboratory animal center of Chinese Academy of science. Prior to each experiment, mice were fastened overnight and allowed free access to water. Various doses of the 1-substituted-2-aminobenzimidazole derivatives dissolved in 0.5% carboxymethyl cellulose sodium (CMC–Na) salt solution were given via intraperitoneal (i.p.) to different groups of healthy ICR mice, and each group contained 10 mice (five males and five females). After the administration of the compounds, mice were observed continuously for any gross behavioral changes and deaths, and intermittently for 1 week. All animals were sacrificed at seventh day after drug administration and checked macroscopically for possible damage to the heart, liver, spleen, lung, kidneys and stomach. Mice of immediate death following drug administration were also examined for any possible organ damage. LD_{50} values were calculated graphically. To ensure that the solvent had no acute toxicities on ICR mice, a control test was performed with test medium supplemented with CMC–Na at the same dilutions as used in the experiment.

4.2.2. QSAR studies

Quantitative structure-activity relationship (QSAR) could provide correlations between toxicological properties and physico-chemical descriptors of a chemical. We could estimate the toxicities of chemicals with the QSAR models based on their easily measured or calculated characteristics. And the application of QSAR models could provide scientific basis for the risk assessments of chemicals.

Octanol/water partition coefficient (Log*P*) was one of the most important physico-chemical descriptors in the toxicology

study. Log*P* described the partition of a chemical between in organic solvent and in water. The lipophilic aptitude of a chemical increased with increasing Log*P*. The relationship between Log*P* and the active toxicity ($\log LD_{50}$) of an organic chemical was very satisfactory. The QSAR equation was built by means of the stepwise linear regression method of the statistical software JME Molecular Editor [18].

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