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Synthesis and antiviral activity against Coxsackie virus B3 of some novel benzimidazole derivatives

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Abstract—Some benzimidazole derivatives were synthesized and evaluated for their antiviral properties. Compounds **20** and **21** showed potent selective activity against Coxsackie virus B_3 in VERO cells. Some structure–activity relationships were discussed.

Benzimidazoles are regarded as a promising class of biologically active agents. For example, some others served as PARP inhibitors[1] and some benzimidazole derivatives showed potent antiviral activity.[2,3] A series of 2-pyridyl-1*H*-benzimidazole-4-(*N*-R_2-carboxamide) derivatives (compounds **9**–**26**, general structure shown in Fig. 1) were synthesized in this work, and it was found that they had excellent inhibitory activity against Coxsackie virus B_3 (CVB3), a non-enveloped single positive-strand RNA virus belonging to the picornaviridea family, which is the major cause of virus-induced human myocarditis.[4] The IC_{50} value of ribavirin (RVB), a well-known nucleoside analogue virustatic drug,[5] was provided as comparable data. In these synthesized compounds, compounds **20** and **21** had excellent IC_{50} values (1.43 and 0.54 μg/mL, respectively), far more active than RVB with IC_{50} value of more than 400 μg/mL.

Biological activity data demonstrated that 2-pyridyl derivatives were much better than 3- and 4-pyridyl derivatives, and the introduction of phenyl group in R_2 moiety could enhance the biological activity and selectivity. The synthesis of 2-pyridyl-1*H*-benzimidazole-4-(*N*-R_2-carboxamide) derivatives and the results of evaluation of their antiviral activity were reported herein.

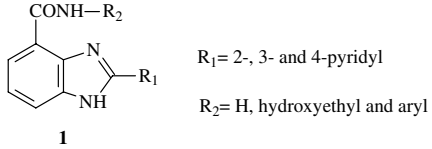

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Figure 1. The general structure of synthesized compounds.

Synthetical route of the primary compound **5**, 2,3-diaminobenzoic acid is shown in Scheme 1. The syntheses of 3-nitrophthalamic acid **3** and 3-nitroanthranilic acid **4** starting from 3-nitrophthalic anhydride **2** were reported by Chapman and Stephen,[6] and the compound **5** was obtained in good yield (95%) by the reduction of compound **4** with hydrazine hydrate in the presence of Ranney Ni.

Following William's method,[7] the cyclization of 2,3-diaminobenzoic acid **5** with 2-pyridylaldehyde, 3-pyridylaldehyde and 4-pyridylaldehyde, respectively, in the presence of copper acetate gave the corresponding 2-pyridyl-1*H*-benzimidazole-4-carboxylic acids (**6**–**8**) in about 50% yield. However, a large quantity of reagent methanol had to be used to dissolve 2,3-diaminobenzoic acid **5** because of its poor solubility in non-alkaline medium, since an acidic medium was necessary for the existence of copper acetate. In addition, the post-treatment was very complicated. Therefore, potassium ferricyanide was chosen as an oxidant to act in an alkaline medium, and with that a yield similar to the William's method was obtained. The synthetic route is shown in Scheme 2.

As outlined in Scheme 3, at first 2-pyridyl-1*H*-benzimidazole-4-carboxylic acids (**6**–**8**) were transformed to the

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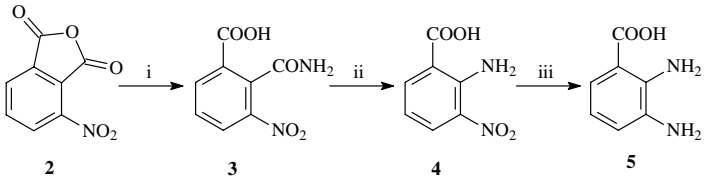
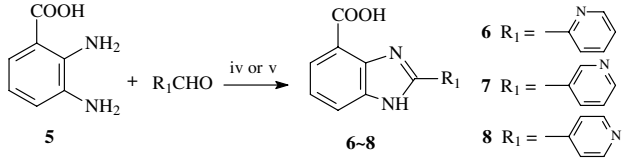
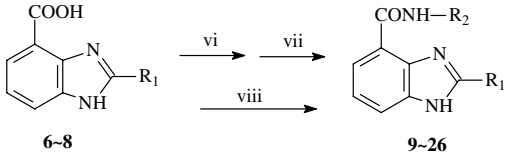


Scheme 1. Reagents and conditions: (i) NH_3 (aq), 70 °C; (ii) KOH, Br_2, H_2O, 80 °C; (iii) NaOH, CH_3OH, Ranney Ni, $N_2H_4{\cdot}H_2O$, reflux.



Scheme 2. Reagents and conditions: (iv) CH_3OH, $Cu(Ac)_2$, reflux, then Na_2S; (v) CH_3OH, $K_3Fe(CN)_6$, reflux.



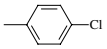
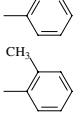
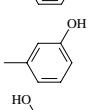
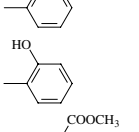
Scheme 3. Reagents and conditions: (vi) $SOCl_2$, reflux; (vii) NH_3 (aq) or R_2NH_2, rt; (viii) DCC, DMAP, R_2NH_2, rt.

corresponding carboxylic chlorides by the treatment of thionyl chloride. Then 2-pyridyl-1*H*-benzimidazole-4-(*N*-R_2-carboxamide)s (**9**–**26**) were obtained by the reaction of the corresponding carboxylic chlorides with aqueous ammonia or amines, respectively. The condensation of carboxylic acids and amides could also be carried out in one step in the presence of DCC (dicyclohexylcarbodiimide) and DMAP (*para*-dimethylaminopyridin). However, the yields were low because of the occurrence of by-products.

2-Pyridyl-1*H*-benzimidazole-4-carboxamide derivatives were evaluated for their antiviral activity against Coxsackie virus B_3 in VERO cells. Antiviral activities of 4-pyridyl derivatives were tested at first (as shown in Table 1), and those of 2- and 3-pyridyl derivatives were characterized later (as shown in Table 2). In order to make biological data in Tables 1 and 2 comparable, compound **14** and ribavirin (RVB) were also listed in the table. It is found that most of the synthesized compounds had excellent antiviral activity, far more active than RVB with IC_{50} value of more than 400 μg/mL. The IC_{50} value of compounds (**13**, **14**, **17**, **20**, **21**, **24** and **25**) were even less than 5 μg/mL. Moreover, compounds **20** and **21** had particularly excellent IC_{50} values (1.43 and 0.54 μg/mL, respectively), together with eminent selective indexes (38.8 and 28.3, respectively).

These results led to some considerations. 2-Pyridyl derivatives (**19**–**21**) had greater antiviral activity and selectivity than 3-pyridyl derivatives (**23**–**25**). Although compound **22** was slightly less active and selective than

Table 1. Activity of benzimidazole derivatives against Coxsackie virus B_3 in VERO cells

Compd	R_1	R_2	TC_{50}[a] (μg/mL)	IC_{50}[b] (μg/mL)	SI[c]
9			15.64	3.85	4.06
10			20.45	8.72	2.35
11		–CH_2CH_2OH	140.6	NA[d]	—
12			12.3	NA	—
13			8.24	4.12	2.0
14			27.8	2.42	11.48
15			55.5	18.52	2.99
16			5.9	NA	—
17			18.5	4.05	4.56
18			NT[e]	NT	—
RVB	—	—	>1000	447.8	>2.23

[a] Cytotoxic concentration required to inhibit VERO cell growth by 50%.
[b] Concentration required to inhibit Coxsackie virus B_3 growth by 50%.
[c] Selective Index values equal to TC_{50}/IC_{50}.
[d] Not active in the largest concentration which were not toxic to VERO cells.
[e] Not tested.

compound **26**, generally the introduction of 2-pyridyl group was better than that of 3-pyridyl group. Moreover, 2-pyridyl derivatives were more efficient than 4-pyridyl derivatives from the biological data provided in the two tables. With regard to R_2 moiety, the presence of phenyl group enhanced inhibitory activity greatly, because compounds **20** and **21** in 2-pyridyl derivatives and compounds **24** and **25** in 3-pyridyl derivatives were obviously more active and selective than compounds **19** and **22** (R_2 = H and hydroxyethyl, respectively) and compounds **23** and **26**. On the one hand, the introduction of hydroxyethyl group reduced inhibitory activity, and on the other hand, its existence enhanced TC_{50} value; so hydroxyethyl analogues resulted in a modest selective index.

Table 2. Activity of benzimidazole derivatives against Coxsackie virus B_3 in VERO cells

Compd	R_1	R_2	TC_{50}[a] (μg/mL)	IC_{50}[b] (μg/mL)	SI[c]
14			10.74	2.23	4.81
19		H	53.4	7.29	7.32
20			55.6	1.43	38.8
21			15.33	0.54	28.3
22		$-CH_2CH_2OH$	160.2	37.0	4.32
23		H	18.5	6.2	2.98
24			10.74	1.17	9.17
25			37.0	3.23	11.4
26		$-CH_2CH_2OH$	192.4	25.59	7.51
RVB	—	—	>1000	411.7	>2.42

[a] Cytotoxic concentration required to inhibit VERO cell growth by 50%.

[b] Concentration required to inhibit Coxsackie virus B_3 growth by 50%.

[c] Selective Index values equal to TC_{50}/IC_{50}.

In conclusion, it is evident that 2-pyridyl-1*H*-benzimidazole-4-carboxamide derivatives[8] have an excellent antiviral activity. Moreover, 2-pyridyl derivatives are much better than 3- and 4-pyridyl derivatives, and the introduction of phenyl group in R_2 moiety improves biological activity and selectivity. In addition, although hydroxyethyl group in R_2 moiety brings on a modest selective index, it is not essential to enhance the antiviral activity.

Acknowledgements

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8. Selected ^1H NMR data. Compound **19**: ^1H NMR (400 MHz, DMSO) δ: 7.34–7.38 (t, 1H), 7.55–7.59 (m, 1H), 7.71–7.73 (m, 1H), 7.81–7.82 (d, 1H), 7.87–7.89 (m, 1H), 8.00–8.05 (m, 1H), 8.43–8.45 (m, 1H), 8.75–8.78 (m, 1H), 9.27–9.28 (d, 1H), 13.59 (s, 1H). Compound **20**: ^1H NMR (400 MHz, $CDCl_3$) δ: 7.14–7.18 (t, 1H), 7.41–7.47 (m, 4H), 7.64–7.66 (d, 1H), 7.92–8.00 (m, 3H), 8.27–8.29 (d, 1H), 8.45–8.47 (d, 1H), 8.67–8.69 (m, 1H), 11.07 (s, 1H), 12.11 (s, 1H). Compound **21**: ^1H NMR (400 MHz, DMSO) δ: 7.14–7.19 (m, 1H), 7.24–7.28 (m, 1H), 7.40–7.48 (m, 2H), 7.60–7.63 (m, 1H), 7.80–7.83 (d, 1H), 8.02–8.04 (d, 1H), 8.12–8.16 (t, 1H), 8.45–8.47 (d, 1H), 8.64–8.68 (t, 1H), 8.80–8.81 (d, 1H), 12.52 (s, 1H), 13.84 (s, 1H). Compound **22**: ^1H NMR (400 MHz, DMSO) δ: 3.52–3.57 (q, 2H), 3.63–3.67 (q, 2H), 4.98–5.00 (t, 1H), 7.34–7.38 (t, 1H), 7.56–7.59 (m, 1H), 7.69–7.72 (d, 1H), 7.87–7.90 (d, 1H), 8.02–8.06 (m, 1H), 8.45–8.47 (d, 1H), 8.76–8.77 (m, 1H), 10.14–10.16 (t, 1H), 13.62 (s, 1H).