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Synthesis and antiviral assays of some 2-substituted benzimidazole-*N*-carbamates

L. Garuti [a,*], M. Roberti [a], G. Gentilomi [b]

[a] *Dipartimento di Scienze Farmaceutiche, Università di Bologna, I-40126 Bologna, Italy*
[b] *Dipartimento di Medicina Clinica Specialistica e Sperimentale, Sezione di Microbiologia, Università di Bologna, via Massarenti 9, I-40126 Bologna, Italy*

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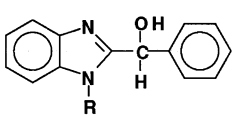
Abstract

Some 2-substituted benzimidazole-*N*-carbamates were synthesized and tested in vitro for antiviral activity. Two derivatives were active at noncytotoxic concentrations. The results confirmed the importance of the substituents at the 2-position of benzimidazole; an isopropylcarboxamide group led to the best activity. © 2000 Elsevier Science S.A. All rights reserved.

Keywords: Benzimidazoles; Carbamates; Synthesis; Antiviral activity

1. Introduction

The versatility of benzimidazole and its potentiality to yield derivatives with a wide range of biological activity have made it a useful structure for further molecular exploration. The substituents at the 1- and 2-positions of this heterocycle have been intensively studied and led to derivatives with good antiviral activity. It is well known that several 1,2-disubstituted benzimidazoles **1** [1], **2** [2], **3** [3], **4** [4], **5** [5], **6** [6] were potent inhibitors of RNA viruses and this effect prompted intensive efforts to prepare and evaluate other derivatives. Recently, studies on quinoline and quinoxaline bearing the carbamoyl moiety on the nitrogen in position 1 afforded compounds with antiviral activity [7,8]. A number of benzimidazole-2- or -5-carbamates demonstrated significant antifilarial [9] and antineoplastic activities, in addition to a broad spectrum of anthelmintic action [10]. Instead, there is little information concerning benzimidazole-*N*-carbamates. Therefore we decided to study a series of *N*-carboxylated benzimidazoles to evaluate if the presence of this moiety is useful for antiviral activity. Moreover, we expanded our research on the substitution at the 2-position. The choice of chains linked at the C-2 was made in view of their presence in other classes of antiviral compounds.



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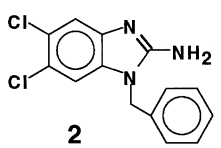

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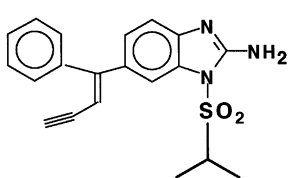

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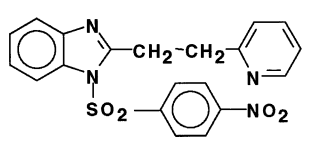

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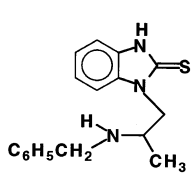

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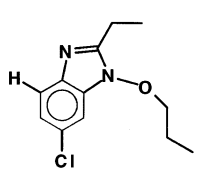

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* Corresponding author. Tel.: +39-51-2099715; fax: +39-51-2099734.

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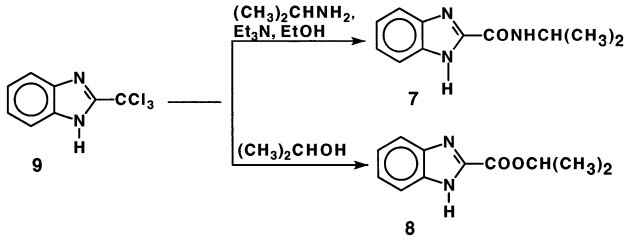
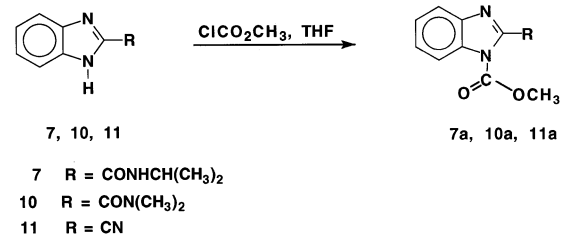
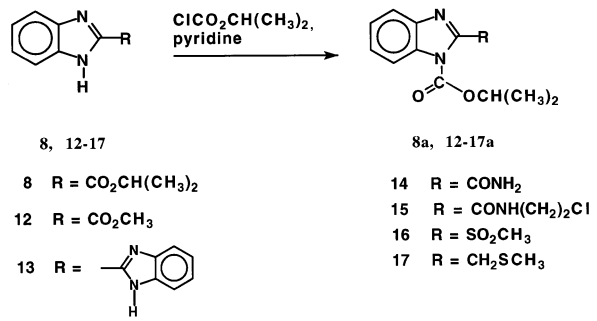


Scheme 1.



Scheme 2.



Scheme 3.

An amide group appeared in L-737,126 [11]; an ester function was crucial for activity in some aryl pyrrolyl sulfone derivatives [12]. The sulfonyl group led to important derivatives [12,13], moreover the thioether moiety was useful in certain 2-(alkylthio)-5,6-dichloro benzimidazoles [14,15]. In this study we describe the synthesis and antiviral activity of some 1,2-disubstituted benzimidazoles.

2. Chemistry

1H-Benzimidazole-2-*N*-isopropylcarboxamide (**7**) and isopropyl 2-benzimidazolecarboxylate (**8**) were prepared treating 2-trichloromethylbenzimidazole (**9**) [16], respectively, with a mixture of isopropylamine and triethylamine and with isopropanol in the presence of 10% sodium carbonate (Scheme 1).

Treatment of derivatives **7**, **10** [17], **11** [17], with methyl chloroformate, heated under reflux, gave the corresponding **7a**, **10**–**11a** (Scheme 2).

The reaction of **8**, **12** [17], **13** [16], **14** [17], **15** [17], **16** [18], **17** [19] with isopropyl chloroformate in pyridine afforded compounds **8a**, **12**–**17a** (Scheme 3).

3. Pharmacology

In the present study we describe the inhibitory effects of some benzimidazole derivatives on viral replication in vitro.

All compounds were investigated with respect to inhibition of Herpes Simplex Virus type 2 (HSV 2) and Coxsackievirus B2 replication in VERO cells.

In order to verify the antiviral effect of all compounds against HSV 2 and Coxsackievirus B2, several experiments on cytotoxicity in infected and uninfected cell cultures, tested in parallel with inhibition of virus-induced cytopatic effect, were carried out.

Table 1
Cytotoxicity of benzimidazole derivatives on VERO cells

Concentration (μM)	% Viability of cells [a]									
	7a	**8a**	**10a**	**11a**	**12a**	**13a**	**14a**	**15a**	**16a**	**17a**
200	65.3	<40	<40	<40	55.6	40.8	<40	<40	<40	72.8
100	88.2	76.6	86.1	80.2	81.9	84.2	78.5	80.6	78.5	92.4
50	88.6	80.9	87.0	82.7	85.7	84.5	80.2	81.3	80.2	94.4
25	86.2	81.4	87.8	86.6	87.2	89.6	81.3	83.3	81.3	96.8
12.5	90.0	83.5	90.3	88.1	91.2	92.7	84.0	85.7	83.0	99.2
6.25	90.0	85.0	94.8	90.9	91.9	96.2	86.5	87.2	87.2	99.7
3.12	93.8	89.0	96.3	93.2	93.3	97.8	89.3	90.4	90.0	100.1
1.56	95.6	90.8	100.6	94.7	100.5	99.2	90.7	92.5	92.2	102.3
0.78	103.0	98.9	105.4	101.3	101.2	99.8	97.8	98.2	96.7	105.5

[a] Values are the average of three independent experiments (MTT test).

Table 2
In vitro inhibition of Coxsackievirus B2 replication

% inhibition [a]			
Concentration (μM)	Controls [b]	**7a** [c]	**17a** [d]
0	0	0	0
0.78	0	9.3 ± 3.1	ND
1.56	0	11.2 ± 3.2	ND
3.12	0	17.4 ± 3.5	ND
6.25	0	22.5 ± 2.3	5.4 ± 1.3
12.5	0	24.8 ± 0.3	9.8 ± 3.4
25	0	29.9 ± 0.9	15.3 ± 3.5
50	0	41.1 ± 0.6	28.7 ± 0.7
100	0	52.4 ± 2.5	48.1 ± 2.5
200	0	62.3 ± 0.2	51.8 ± 1.2

[a] Values are the average of three independent experiments.
[b] Uninfected cells.
[c] EC_{50} for **7a** is 95 mM.
[d] EC_{50} for **17a** is 193 mM. ND = not determined.

Table 3
Comparative cytotoxicity and potency of benzimidazole derivatives **7a** and **17a** in Coxsackievirus B2 infected VERO cells.

Compound	CC_{50} [a]	EC_{50} [b]	S.I. [c]
7a	153	95	1.6
17a	138	195	0.7

[a] Cytotoxic concentration (μM) of compound required to reduce the viability of mock-infected VERO cells by 50%.
[b] Effective concentration (μM) of compound required to achieve 50% protection of VERO cells against cytopathic effect of Coxsackievirus B2.
[c] Selectivity index: ratio CC_{50}/EC_{50}.

The results presented in Table 1 show the cytotoxicity of compounds for VERO cell cultures obtained by the MTT method and trypan blue (TB) exclusion method.

4. Results and discussion

None of the compounds included in this study had a significant effect on HSV 2 replication, but the derivatives **7a** and **17a** showed modest antiviral activity on Coxsackievirus B2.

To confirm their inhibition on Coxsackievirus B2 replication, virus yield assays were performed. The compounds suppressed the viral growth in VERO cells in a non-cytotoxic concentration (Table 2). Compound **7a** is the most active with an EC_{50} of 95 μM, reducing the virus titre (from 10^6 to 10^3) and being non-cytotoxic at the same concentration (Table 3). This result is important because the activity is well separated from cytotoxicity. Compound **17a** shows moderate antiviral activity, with a EC_{50} of 195 μM, therefore the methylthiomethyl group is also promising. These results indicate that the presence of the carbamoyl moiety at the nitrogen in position 1 of the benzimidazole is not useful for antiviral activity and confirm the importance of substituents at the 2-position. The presence of the isopropyl carboxamide is crucial; when the amide is unsubstituted or bears other alkyl groups, the derivatives are inactive (**14a**,**10a**,**15a**). Otherwise the carboxamide is important: in fact, when it is replaced by a carboxylate function, the inactive derivative **8a** is obtained. The methyl-thiomethyl group is also useful, confirming the importance of this substituent. In conclusion, only two compounds are poorly active but show antiviral activity well separated from cytotoxicity.

5. Experimental

5.1. Chemistry

Reaction courses and product mixtures were routinely monitored by thin-layer chromatography (TLC) on silica gel (precoated F_{254} Merck plates) and visualized with iodine or aqueous potassium permanganate. Infrared spectra (IR) were measured on a Perkin–Elmer 683 instrument. ^{1}H NMR spectra were determined in DMSO-d_6 solutions with a Varian VXR 300 spectrometer, peaks positions are given in ppm downfield from tetramethylsilane as internal standard. Melting points were determined on a Büchi–Tottoli instrument and are uncorrected. Chromatography was performed with Merck 60–200 mesh silica gel. All products reported showed IR and ^{1}H NMR spectra in agreement with the assigned structures. Organic solutions were dried over anhydrous magnesium sulfate. Elemental analyses were performed by the microanalytical laboratory of Dipartimento di Chimica, University of Ferrara, and agreed within ± 0.4% of the theoretical values.

5.1.1. 1H-Benzimidazole 2-N-isopropylcarboxamide (7)

2-Trichloromethylbenzimidazole **9** (0.200 g, 0.85 mmol) was slowly added to a mixture of isopropylamine (0.06 g, 1 mmol) and triethylamine (0.1 g, 1 mmol) in ethanol (20 ml). The solution was kept at room temperature for 1 day, diluted with water and basified with sodium carbonate to give the amide **7** (85%) as a white solid, m.p. 203°C. ^{1}H NMR (DMSO-d_6): δ 1.20 (s, 3H), 1.23 (s, 3H), 4.2 (m, 1H), 7.2 (m, 2H), 7.6 (m, 2H), 8.3 (sb 2H).

5.1.2. Isopropyl 2-benzimidazolecarboxylate (8)

A suspension of 2-trichloromethylbenzimidazole (**9**) (0.200 g, 0.85 mmol) in 2-propanol (10 ml) was heated with a 10% sodium carbonate solution for 10 h. Dilu-

tion of the reaction mixture with water yielded the isopropyl ester (**8**) (70%) as a white solid, m.p. 215°C. ^{1}H NMR (DMSO-d_6): δ 1.37 (s, 3H), 1.40 (s, 3H), 5.3 (m, 1H), 7.5 (m, 2H), 7.8 (m, 2H), 9.3 (sb, 1H).

5.1.3. General procedure for methylcarbamates (**7a**, **10–11a**)

Methyl chloroformate (0.09 ml, 1.2 mmol) was added dropwise to a cold solution of the appropriate benzimidazole **7**, **10**, **11** (1 mmol) in dry THF (15 ml). The mixture was stirred for 2 h at room temperature, then refluxed for 1 h. The solvent was removed and the residue was purified by column chromatography on silica gel eluting with 7:3 ethyl acetate–petroleum ether. **7a**: (80%); m.p. 130°C; ^{1}H NMR (DMSO-d_6): δ 2.30 (s, 3H), 3.07 (s, 3H), 4.07 (s, 3H), 7.5 (m, 2H), 7.8 (m, 1H), 8.00 (m, 1H). **10a**: (60%); oil; ^{1}H NMR (DMSO-d_6): 1.15 (s, 3H), 1.18 (s, 3H), 3.8 (m, 1H), 4.01 (m, 3H), 7.5 (m, 2H), 7.8 (m, 1H), 8.00 (m, 1H), 8.8 (sb, 1H). **11a**: 70%; m.p. 126°C; ^{1}H NMR (DMSO-d_6): δ 4.19 (s, 3H), 7.6 (m, 2H), 7.9 (m, 1H), 8.00 (m, 1H).

5.1.4. General procedure for isopropylcarbamates (**8a**, **12–17a**)

Isopropyl chloroformate (1.3 ml, 1 mmol) was slowly added to a stirred solution of the appropriate benzimidazole **8**, **12–17** (1 mmol) in pyridine at 0°C. The mixture was stirred for 8 h at room temperature, then poured into ice water and extracted with ethyl acetate (3×30 ml). The organic phase dried on Na_2SO_4 was concentrated in vacuo and purified on column chromatography on silica gel eluting with 7:3 petroleum ether–ethyl acetate. **8a**: 75%; m.p. 48°C; ^{1}H NMR (DMSO-d_6): δ 1.36 (s, 3H), 1.41 (s, 3H), 3.96 (s, 3H), 5.2 (m, 1H), 7.5 (m, 2H), 7.8 (m, 2H). **12a**: 60%; m.p. 35°C; ^{1}H NMR (DMSO-d_6): δ 1.37 (s, 3H), 1.40 (s, 3H), 1.44 (s, 3H), 1.47 (s, 3H), 5.2 (m, 2H), 7.5 (m, 2H), 7.8 (m, 2H), 8.00 (m, 2H). **13a**: 70%; m.p. 110°C; ^{1}H NMR (DMSO-d_6): δ 0.97 (s, 6H), 1.00 (s, 6H), 5 (m, 2H), 7.6 (m, 4H), 7.9 (m, 1H), 8.1 (m, 1H). **14a**: 68%; m.p. 163°; ^{1}H NMR (DMSO-d_6): δ 1.39 (s, 3H), 1.33 (s, 3H), 5.2 (m, 1H), 7.3 (m, 2H), 7.8 (m, 1H), 7.9 (m, 1H), 8.1 (sb, 1H), 8.3 (sb, 1H). **15a**: 50%; oil; ^{1}H NMR (DMSO-d_6): δ 1.42 (s, 3H), 1.43 (s, 3H), 3.6 (m, 2H), 3.8 (m, 2H), 5.2 (m, 1H), 7.8 (m, 2H), 8.00 (m, 2H), 9.3 (sb, 1H). **16a**: 80%; m.p. 53°C; ^{1}H NMR (DMSO-d_6): δ 1.49 (s, 3H), 1.46 (s, 3H), 2.62 (s, 3H), 5.2 (m, 1H), 7.9 (m, 2H), 7.6 (m, 1H), 7.8 (m, 1H). **17a**: 86%; oil; ^{1}H NMR (DMSO-d_6): δ 1.44 (s, 3H), 1.46 (s, 3H), 2.07 (s, 3H), 4.12 (s, 2H), 5.2 (m, 1H), 7.4 (m, 2H), 7.7 (m, 1H), 7.9 (m, 1H).

5.2. Biology

5.2.1. Cells and viruses

VERO cells (African green monkey kidney cell line) were used. Cells were propagated in MEM (Minimal Essential Medium) with 10% FCS (fetal calf serum), 1% L-glutamine, 100 U/ml of penicillin and 100 U/ml of streptomycin. All experiments were performed using two laboratory strains; one of HSV 2 and one of Coxsackievirus B2.

5.2.2. Peroxidase staining for determination of virus titers

VERO monolayers in 96-well plates (Nunc Denmark) were overlaid with 100 ml of each virus dilution (dilutions from 10^{-1} to 10^{-8}). After adsorption for 1 h at 37°C and 5% CO_2, the medium was removed and replaced with 100 ml of fresh complete MEM. After 24 h of incubation, peroxidase staining was performed [20].

After fixation of cells with methanol for 15 min at −20°C, the monolayers were incubated for 15 min with PBS supplemented with 1% bovin serum albumin (PBS/BSA) at 37°C.

Pools of reference sera against HSV 2 or Coxsackievirus B2 (dilution of 1:20 in PBS/BSA) were added. After 45 min incubation at 37°C the monolayers were washed three times with PBS and peroxidase-conjugated antibodies anti-human immunoglobulinG (Dako Denmark) were added.

After 45 min incubation at 37°C the monolayers were washed three times with PBS and substrate (HRP color development reagent, Bio-Rad Laboratories S.r.l.) was added.

Plaques were counted under a light microscope. The viral titres for HSV 2 were 2×10^3 PFU/ml and 1.8×10^6 PFU/ml for Coxsackievirus B2.

5.2.3. Antiviral assays

Evaluation of anti-HSV 2 and anti-Coxsackievirus B2 activity was based on the 3-(4,5-dimethylthiazol-2yl)-2,5-diphenyltetrazolium bromide (MTT) (Boehringer Mannheim) assay as previously described [21]. Briefly, a serial twofold dilution of compounds starting at 200 μM (100 ml aliquots in DMSO diluted in MEM) was prepared in a 96-well tissue culture tray (Nunc Denmark) with three wells used for each concentration.

To each well, 5×10^4 cells (in 50 ml of DMSO/MEM) were added. When the monolayers had become confluent, usually after 24 h, the medium was aspirated and viruses, at the M.O.I. of 10^{-3} PFU/cell (in 50 ml of DMSO/MEM), were added.

After 1 h adsorption at 37°C the inoculum was removed and the culture medium, or, in the case of the controls DMSO/MEM, was then added to the compounds dissolved in DMSO. Each compound was assayed in triplicate.

To determine the median effective concentration (EC_{50}) of the compounds, 10 ml of MTT (Boehringer Mannheim) was added to each well.

The mixture was incubated at 37°C for 4 h, and reduced MTT (formazan) was extracted from the cells by

the addition of 100 ml of solubilization mixture (Boehringer Mannheim).

After an overnight incubation at 37°C the absorbance of the formazan was measured by using a microplate reader (Labsystems Multiscan MS–DASIT S.p.A.) at two different wavelengths (550–690 nm).

The EC_{50} of each compound was defined as the concentration that achieved 50% protection of virus-infected cells from virus-induced destruction [21].

5.2.4. Cytotoxicity assays

Confluent monolayers of VERO cells grown in 96-well tissue culture plates were incubated with MEM supplemented with 2% of FCS, 1% L-glutamine in the presence of different concentrations of compounds dissolved in DMSO in triplicate.

Cell cultures were incubated at 37°C, 5% CO_2 for 96 h. The viability of the cells was assessed by the MTT method and trypan blue (TB) exclusion method [21]. The cytotoxicity of compounds against VERO cells was evaluated in terms of the 50% cytotoxic concentration (CC_{50}), i.e. the compound concentration required to reduce cell number by 50% with respect to the number of cells in the untreated control cell cultures [22].

Acknowledgements

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