Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 6, No. 11, pp. 1195-1198, 1996

0960-894X/96 $15.00 + 0.00

PII: S0960-894X(96)00200-4

NOVEL BENZIMIDAZOLE-4-CARBOXYLIC ACID DERIVATIVES AS POTENT AND SELECTIVE 5-HT$_3$ RECEPTOR LIGANDS

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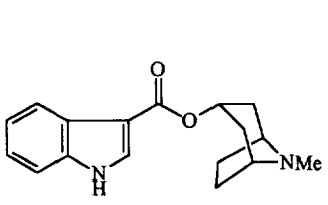
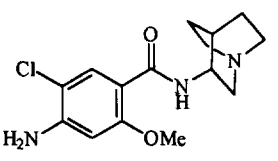
Abstract: A series of benzimidazole-4-carboxylic acid derivatives was synthesized and evaluated for affinity at 5-HT$_3$ and 5-HT$_4$ serotoninergic receptors. Compounds **1b**, **c** and **j** exhibited high affinity for the 5-HT$_3$ receptors (K_i=6.1, 3.7 and 4.9 nM, respectively) and no significant affinity for 5-HT$_4$ (K_i>1000 nM) and 5-HT$_{1A}$ (K_i>10 000 nM) sites. Preliminary studies showed that **1c** displayed activity in the two-compartment behavioural model.

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter involved in a wide range of pharmacological effects in several peripheral as well as central nervous tissues[1]. Of the multiple serotoninergic receptor subtypes[2] identified to date, the 5-HT$_3$ and 5-HT$_4$ receptors are of special interest due to their implication in various (patho)physiological processes.[3] 5-HT$_3$ receptor antagonists —ondansetron, granisetron— are used clinically for the treatment of chemotherapy-induced emesis in cancer patients.[4] Further therapeutic indications,[5] such as control of anxiety, squizophrenia, drug withdrawal and cognitive disorders, are being currently investigated.

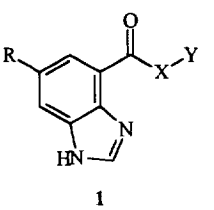
As most of the known 5-HT$_3$ receptor antagonists (e.g. tropisetron, zacopride) also exhibit activity in the 5-HT$_4$ subtype, there is considerable interest in the medicinal chemistry of both receptors and significant effort has been made towards the discovery of potent and selective ligands. Thus, on the basis of the generally accepted three-dimensional model of the 5-HT$_3$ receptor pharmacophore,[6] we have designed a series of novel benzimidazole-4-carboxylic acid derivatives **1**, which belong to a new structural class of 5-HT$_3$ receptor ligands. In the present communication, we report the synthesis of **1** and their affinities for 5-HT$_3$ and 5-HT$_4$ receptors, obtained by radioligand binding assays.



Tropisetron
(ICS 205-930)



Zacopride



1

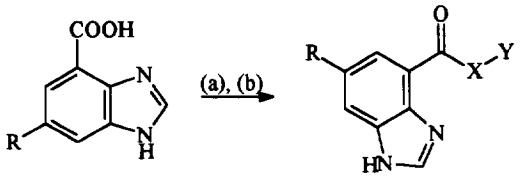
R = H, Cl
X = O, NH
Y = 1-methyl-4-piperidinyl, 3-granatanyl, 3-quinuclidinyl

Chemistry

Benzimidazole-4-carboxylic acid[7] (**2**) and 6-chlorobenzimidazole-4-carboxylic acid (**3**) were suitably activated with 1,1'-carbonyl diimidazole (CDI), and the corresponding imidazolides were coupled with the appropriate amines and alcohols in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in N,N-dimethylformamide (DMF) solution to give the desired amides and esters **1a-k**[8] (Scheme 1).

Acid **3** was obtained as described in Scheme 2. Condensation of 2-amino-5-chloro-3-methylaniline[9] **4** with formic acid gave 6-chloro-4-methylbenzimidazole **5** in quantitative yield. Oxidation of **5** with potassium permanganate in hot aqueous NaOH afforded 6-chlorobenzimidazole-4-carboxylic acid **3** in 40% yield.

Scheme 1

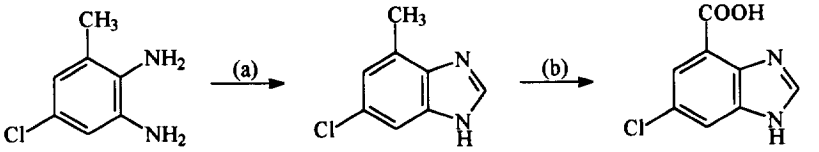


2: R=H
3: R=Cl

1a-k

Reagents and conditions: (a) CDI, DMF, 40°C, 1h;
(b) Y-NH_2 or Y-OH, DBU, DMF, 50°C, 20h.

Scheme 2



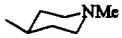
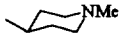
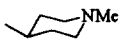
4 **5** **3**

Reagents and conditions: (a) HCOOH, H_2O, 100°C, 6h; (b) $KMnO_4$, NaOH 1N, 100°C, 5h.

Results and Discussion

Target compounds **1a-k** were assessed by their *in vitro* affinity for serotoninergic 5-HT_3 and 5-HT_4 receptors by radioligand assays, using [^{3}H]LY 278584 in the rat cerebral cortex[10] and [^{3}H]GR 113808 in the rat striatum,[11] respectively. The data expressed as K_i (nM) are shown in Table 1.

Table 1. Binding Data.[a]

Compd	R	X	Y	K_i ± SEM (nM)	
				5-HT_3 [^{3}H]LY 278584	5-HT_4 [^{3}H]GR 113808
1a	H	NH		145 ± 10	719 ± 58
1b	H	NH		6.1 ± 0.8	>1000
1c	H	NH		3.7 ± 0.1	>1000
1d	Cl	NH		29.5 ± 4.4	54.0 ± 2.8
1e	Cl	NH		154 ± 24	167 ± 32
1f	Cl	NH		0.29 ± 0.08	168 ± 6
1g	H	O		>1000	>10 000
1h	H	O		129 ± 1	>10 000
1i	H	O		185 ± 3	>10 000
1j	Cl	O		4.9 ± 0.8	>1000
1k	Cl	O		9.3 ± 1.0	440 ± 87
	tropisetron[11,12]			1.28 ± 0.27	63
	zacopride[11,12]			0.42 ± 0.10	158

[a] K_i values are means ± standard errors of two to four assays, performed in triplicate. Inhibition curves were analyzed by a computer-assisted-curve-fitting program (Prism GraphPad) and K_i values were determined from the Cheng-Prusoff equation.

Most of the synthesized compounds exhibit moderate-to-high affinity for the 5-HT_3 receptor binding site and low-to-no significant affinity for the 5-HT_4 site. An examination of the 5-HT_3 binding data shows that, in general, the amides are more potent than their corresponding esters; only derivative **1j** displayed *ca.* 30-fold higher affinity than its directly related amide **1e**. Concerning the Y moiety, piperidine derivatives are either inactive (**1g**) or not selective (**1d**). On the other hand, with respect to the introduction of a chloro atom at the 6-position of the benzimidazole ring, a general trend was not observed in the affinity of the carboxamides. However, the 6-chloro

substitution induces a remarkable increase in the potency of the carboxylates [K_i(**1h**)=129 nM *vs* K_i(**1j**)=4.9 nM; K_i(**1i**)=185 nM *vs* K_i(**1k**)=9.3 nM].

Of special interest are analogues **1b**, **c** and **j**, as they exhibit an excellent 5-HT_3/5-HT_4 selectivity [K_i(5-HT_3)=6.1, 3.7 and 4.9 nM, respectively; K_i(5-HT_4)>1000 nM]. Consequently, these agents are more selective over the 5-HT_4 receptor than the classic 5-HT_3 ligands tropisetron and zacopride, used as reference compounds (Table 1). Moreover, they had no affinity for the serotoninergic 5-HT_{1A}[13] binding site (K_i > 10 000 nM). On the basis of its selectivity for the 5-HT_3 receptor, **1c** was selected for pharmacological studies. In preliminary behavioural models, it has displayed activity in the two-compartment (light-dark) test, suggesting that this agent is a 5-HT_3 antagonist.

Further pharmacological properties of **1c**, synthesis and biological evaluation of new analogues of **1** as well as the series of related derivatives are currently in progress in our laboratory. The results will be reported in due course.

Acknowledgment

We are grateful to L. Orensanz of Hospital Ramón y Cajal for his assistance in binding assays. We also thank U.N.E.D. for a predoctoral grant to B. Benhamú. This work was supported by the DGICYT (PB94-0289) and the Universidad Complutense (PR218/94-5657).

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8. Final compounds **1a-k** were purified by flash chromatography on silica, using mixtures of $CHCl_3$/MeOH as the eluent (relative proportions depending upon the compound), in 35-55% yields. All new compounds described had correct CHN analysis (± 0.4%) and spectral data (mono- and bidimensional ^1H and C^{13} NMR spectra) supported their structural assignment.
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(*Received in Belgium* 7 *March* 1996; *accepted* 23 *April* 1996)