***N*-(1-LONG ALKYL-2-PYRROLIDINYL)METHYL]BENZAMIDES WITH POTENT SEROTONIN 5-HT_{1A} RECEPTOR AFFINITIES**

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A series of *N*-(2-pyrrolidinylmethyl)-2-methoxy-5-sulfamoylbenzamide derivatives bearing a long alkyl chain at the 1-position of the pyrrolidine ring was synthesized and found to possess high affinities for serotonin 5-HT_{1A} receptors.

KEYWORDS benzamide; 5-HT_{1A} receptor; long alkyl substituent; pyrrolidine; sulpiride

During the past decade there has been a marked increase in research on serotonin 5-HT_{1A} receptors, as summarized in recent reviews.¹⁾ To date, several different chemical classes of agents such as aminotetraline, arylpiperazine, and indole derivatives have been reported to interact potently with serotonin 5-HT_{1A} receptors.¹⁾

In the course of the studies on sulpiride analogues previously reported,²⁾ we found that high affinities for serotonin 5-HT_{1A} receptors resided in *N*-(1-long alkyl-2-pyrrolidinyl) methyl]-2-methoxy-5-sulfamoylbenzamides retaining significant dopamine D₂ receptor affinities. The present paper describes the synthesis of the benzamides and the results of serotonin 5-HT_{1A} receptor binding assay *in vitro*.

Chemistry

The synthesis of the new benzamides (4a-7b) was carried out by use of an approach similar to that employed for the synthesis of the benzamides (1a-3b) reported previously (Chart 1).²⁾ The coupling reaction of the known 2-methoxy-5-sulfamoylbenzoic acid (8) with the enantiomers of the 1-alkyl-2-(aminomethyl)pyrrolidines (9a-12b) was performed by a mixed anhydride method as follows. Isobutyl chloroformate was added to a mixture of the acid (8) and *N*-methylmorpholine (NMM) in DMF and THF (−10°C, 30 min). The resulting mixture was treated with the enantiomers of the amines (9a-12b) to yield the benzamides (4a-7b) (−10°C→rt, 2h).

Chart 1

The requisite enantiomers of the 1-alkyl-2-(aminomethyl) pyrrolidines (9a-12b) were prepared by the following synthetic sequence according to the procedure reported in the previous paper²: (i) *N*-alkylation of 2-pyrrolidinone, (ii) treatment with nitromethane in the presence of dimethyl sulfate and sodium methoxide, (iii) reduction (H₂, Raney Ni), and (iv) resolution of the racemic amines through the formation of their L- and D-ditartrate salts. The absolute configuration of the resolved amines was established by comparison in optical rotation with the amines derived from L-prolinamide by a stereoconservative method.

The chemical data of (+)-(*R*)-*N*-(1-nonyl-2-pyrrolidinyl) methyl]-2-methoxy-5-sulfamoylbenzamide (5b) are representative: mp 115-117 °C (IPA/IPE); [α]_D²⁴ + 53.5° (c=1.0, MeOH); ee>98%; MS *m/z*: 439 (M⁺); ¹H-NMR (CDCl₃, 400 MHz) δ: 0.85 (3H, t, *J*=7Hz), 1.1-2.0 (18 H), 2.1-2.3 (2H, m), 2.5-2.8 (2H, m), 3.1-3.4 (2H, m), 3.7-3.8 (1H, m), 4.0 (3H, s), 5.7 (2H, brs), 7.04 (1H, d, *J*=9Hz), 8.01 (1H, dd, *J*=2Hz, 9Hz), 8.3 (1H, brs), 8.75 (1H, d, *J*=2Hz); Anal. Calcd for C₂₂H₃₇N₃O₄S: C, 60.11; H, 8.48; N, 9.56. Found: C, 60.03; H, 8.34; N, 9.52.

Results

The enantiomeric benzamides were evaluated for their abilities to displace [³H]-8-OH-DPAT from serotonin 5-HT_{1A} binding sites in rat hippocampal membranes *in vitro* and to displace [³H]-spiperone from dopamine D₂ binding sites in rat striatal membranes *in vitro* (Table I). It is well known that the 1-ethyl substituted benzamide (sulpiride) interacts potently and selectively with dopamine D₂ receptors. In our experiments, both enantiomers of the 1-ethyl benzamides (1a, 1b) were virtually devoid of 5-HT_{1A} receptor affinities (*K*_i=36000 and 18000 nM for 1a and 1b, respectively). However, it is of particular interest to note that the serotonin 5-HT_{1A} receptor binding affinities gradually increased as the chain length of the *N*-alkyl function on the pyrrolidine nitrogen atom was made greater in both enantiomers series as shown in Table I. Thus, the 1-hexyl-substituted benzamides (3a, 3b) showed moderate affinities to the 5-HT_{1A} receptors (*K*_i of 3a and 3b were 370 and 430 nM, respectively) and the 1-nonyl derivatives (5a, 5b) exhibited high affinities in the 5-HT_{1A} receptor binding (*K*_i of 5a and 5b were 81 and 16 nM, respectively). Substitution with further long alkyl function, dodecyl group (7a, 7b), resulted in lower affinities than the nonyl substitution in each absolute configuration. Correlation between the 5-HT_{1A} receptor binding affinities and the chain length showed a parabolic relationship, with nonyl group producing the most potent compounds for each enantiomer series. These results indicate that the steric bulk and/or lipophilicity of the long alkyl substituent may greatly contribute to the increased 5-HT_{1A} receptor binding affinities rather than the stereochemistry, although there are some small differences in affinity between the enantiomers. Comparing the 5-HT_{1A} receptor affinities with the D₂ receptor affinities, these 1-long alkylated benzamides (3a, 4a-7b) were found to be more potent at 5-HT_{1A} receptor binding sites than at D₂ receptor binding sites, as shown in Table I (D₂/5-HT_{1A} ratio >1).

In the case studied, the nonyl substituted *R*-enantiomer 5b was ranked as having the highest affinities for 5-HT_{1A} receptors and was 3 orders of magnitude more potent than sulpiride, binding with significant affinities to D₂ receptor sites (*K*_i=92 nM). Such compounds, which act on 5-HT_{1A} receptors more potently

than D₂ receptors, will represent a new class of substituted benzamides family and may have unique therapeutic potential (anxiolytics, neuroleptics, antidepressant). Extensive biochemical and pharmacological studies on the compounds with both 5-HT_{1A} and D₂ receptor affinities are ongoing.

TABLE I. Affinities of Benzamides to 5-HT_{1A} and D₂ Receptors

Compd. ^{a)}	n	Isomer	K_i ^{b)} (nM)		D ₂ /5-HT _{1A} ratio
			5-HT _{1A} ^{c)}	D ₂ ^{d)}	
1a	2	S	36000	29	<0.01
1b	2	R	18000	2700	0.15
2a	4	S	1200	51	0.04
2b	4	R	4500	230	0.05
3a	6	S	370	1400	3.8
3b	6	R	430	59	0.14
4a	8	S	120	310	2.6
4b	8	R	47	120	2.6
5a	9	S	81	180	2.2
5b	9	R	16	92	5.8
6a	10	S	120	230	1.9
6b	10	R	21	80	3.8
7a	12	S	1600	1700	1.1
7b	12	R	68	130	1.9

- a) All compounds gave satisfactory IR, ¹H-NMR, MS, and elemental analysis. The enantiomeric purities of all compounds were confirmed to be >98 % ee by HPLC(column; CHIRALPAK AD DAICEL Chemical Industries, Ltd.).
- b) Each value is the mean from triplicate assays in a single experiment.
- c) Binding studies were conducted according to the method of M.D.Hall et al.³⁾
- d) [³H]-spiperone binding.⁴⁾

REFERENCES AND NOTES

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All test compounds inhibited the specific binding of [³H]-8-OH-DPAT in a concentration-dependent manner. The maximum effect of each compound was 100 %.

- 4) D₂ receptor affinities of compounds 1a-3b have previously been reported.²⁾ The newly synthesized compounds 4a-7b were evaluated according to a previously described method.²⁾

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