Pergamon

Bioorganic & Medicinal Chemistry Letters 11 (2001) 793–795

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

A Novel Fluorinated Tryptamine with Highly Potent Serotonin 5-HT_{1A} Receptor Agonist Properties

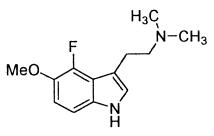
Uroš Laban, Deborah Kurrasch-Orbaugh, Danuta Marona-Lewicka and David E. Nichols*

Department of Medicinal Chemistry and Molecular Pharmacology, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, IN 47907-1333, USA

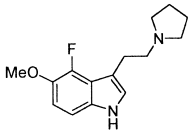
Received 4 December 2000; accepted 23 January 2001

Abstract—Synthesis and biological evaluation of a novel fluorinated tryptamine analogue are described. This new compound 1-(4-fluoro-5-methoxyindol-3-yl)pyrrolidine (**2**) was found to be a potent serotonin 5-HT_{1A} agonist.

Recently[1] we reported on several fluorinated tryptamines. One of them, 4-fluoro-5-methoxy-*N*,*N*-dimethyltryptamine **1**, proved to be a potent serotonin 5-HT_{1A} agonist. Substitution with the 4-fluorine markedly increased 5-HT_{1A} selectivity over 5-$HT_{2A/2C}$ receptors. In view of widespread interest in the function of 5-HT_{1A} receptors in the central nervous system,[2] and the relative paucity of agonists for this receptor, it was decided to explore further the structure–activity requirements of **1**. An earlier paper by McKenna et al.[3] had compared a variety of *N*-substituted tryptamines at both the 5-HT_{1A} and 5-$HT_{2A/2C}$ receptors. We noted that the compound with the greatest potency at the 5-HT_{1A} receptor possessed the *N*,*N*-dialkyl substituents constrained into a pyrrolidine ring. Thus, herein we describe the synthetic route and the potent 5-HT_{1A} agonist properties of 1-(4-fluoro-5-methoxyindol-3-yl)pyrrolidine **2**, as well as an improved synthesis of its *N*,*N*-dimethyl congener. These compounds, although somewhat less readily accessible than the standard 5-HT_{1A} receptor agonist, 8-hydroxy-2-(*N*,*N*-dipropylamino)tetralin, are an order of magnitude more potent, thereby representing new pharmacological probes to study the functions of this receptor.



1



2

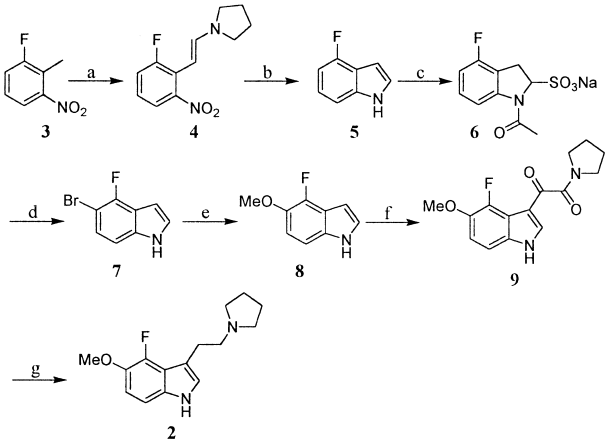
*Corresponding author. Tel.: +1-765-494-1461; fax: +1-765-494-1414; e-mail: drdave@pharmacy.purdue.edu

In our recent report,[1] we obtained compound **1** as a minor product from the synthesis of 6-fluoro-5-methoxy-*N*,*N*-dimethyltryptamine. Clearly, a more efficient approach was required, both for resynthesis of **1**, as well as for preparation of any additional congeners such as **2**. Our initial synthetic strategy was an attempt to functionalize the 4-position of N_1-TIPS-5-methoxy gramine through lithiation and, with a few subsequent transformations, obtain the final product.[4] This methodology failed because attempted lithiation at the 4-position only afforded product where the triisopropylsilyl group had rearranged from N_1 to C_2. The successful approach is shown below. Indole **5** was synthesized in high yield via the Leimgruber–Batcho method,[5] converting the corresponding toluene (**3**) to the styrene (**4**) followed by catalytic reduction. Preparation of the bisulfite adduct, followed by *N*-acetylation (**6**) allowed for the introduction of bromine at the 5-position with concurrent removal of the protecting groups (**7**).[6] A modification of the Ullmann ether synthesis, employed earlier in our group,[7] was utilized to displace the bromine with the methoxy functionality (**8**). It was necessary, however, to perform this reaction under elevated pressure and temperature to achieve a moderate yield. After chromatography, some unreacted starting material may be recovered and recycled. Classical Speeter–Anthony tryptamine synthesis[8] leads to the glyoxylamide (**9**) and with subsequent LAH reduction the final product **2** was obtained. Long reflux times and the higher boiling dioxane are necessary for this reaction to proceed to completion (Scheme 1).

Table 1 shows the results of radioligand competition studies at the 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} serotonin

0960-894X/01/$ - see front matter
PII: S0960-894X(01)00062-2

receptor subtypes. Substitution of the dimethyl functionality in **1** with a pyrrolidyl (**2**) results in a doubling of 5-HT_{1A} affinity, as well as an increased selectivity for 5-HT_{1A}/5-HT_2 binding. Compound **2** is more potent than the standard 5-HT_{1A} agonist 8-hydroxy-2-(*N*,*N*-dipropylamino)tetralin (8-OH-DPAT) at this site and has potency nearly comparable to the partial ergoline LY293284.[9] An agonist effect at serotonin 5-HT_{2A} sites is believed responsible for the hallucinogenic properties[10] of various drugs, while stimulation of 5-HT_{1A} sites results in anxiolytic effects.[2]



Scheme 1. (a) $(CH_3)_2NCH(OCH_3)_2$, pyrrolidine, DMF, reflux 3 h, 77%; (b) H_2, Pd/C, 84%; (c) (i) $NaHSO_3$, rt, 24 h; (ii) Ac_2O, 3 h, reflux 50%; (d) (i) Br_2, H_2O, 0 °C; (ii) 5 N aq NaOH, 75%; (e) NaOMe, CuI, CH_3CO_2Et, 5 h, sealed tube, 140 °C, 70%; (f) (i) $(CO)_2Cl_2$, Et_2O, 0.5 h, 0 °C; (ii) pyrrolidine, 24 h, rt, 72%. (g) LAH, dioxane, 24 h, 90 °C, 69%.

Table 1. Results of radioligand competition studies at [^{125}I] DOI-labeled cloned rat 5-HT_{2A}, rat 5-HT_{2C}, and [^{3}H]8-OH-DPAT-labeled human 5-HT_{1A} receptors (K_i values ± SEM in nanomolar)

Compd	5-HT_{2A}[a]	5-HT_{2C}	5-HT_{1A}
1	122 ± 14.2	55 ± 9.4	0.23 ± 0.03
2	130 ± 3.2	140 ± 8.4	0.12 ± 0.012
8-OH DPAT			0.83 ± 0.093[b]
LY293284			0.053 ± 0.012

[a]Values are means of three experiments, standard deviation is given in parentheses.
[b]K_D value.

Table 2. Data from substitution tests in LSD-trained rats

Drug	Dose μmol/kg	N[a]	% D[b]	% SDL[c]	ED_{50} (95% C.I.) μmol/kg
LSD		15			0.026 (0.014–0.045)
2	0.125	10	10	11	
	0.25	15	*53*	57	N.S.[d]
	0.5	10	*60*	75	
	1.0	9	*78*	67	

[a]Number of animals tested at each dose.
[b]Percentage of animals that failed to emit 50 responses within 5 min.
[c]Percentage of animals tested that selected the training drug appropriate lever.
[d]No substitution occurred.

The behavioral effects of drugs acting at 5-$HT_{1A/2A}$ receptors may be quantified using the two lever drug discrimination procedure (DD).[11] In these experiments we employed two hallucinogenic training drugs, LSD and DOI (2,5-dimethoxy-4-iodoamphetamine),[1] and the 5-HT_{1A} agonist LY293284.[1] Animals were trained on a food-reinforced FR50 schedule. Drug discrimination data for hallucinogen-like activity are shown in Tables 2 and 3. The fluorotryptamine **2** fails to substitute in either LSD- or DOI-trained rats, consistent with its low affinity for 5-HT_{2A} receptors, whereas in LY293284-trained rats (Table 4) full substitution occurs at doses of 1 μmol/kg. This latter result is indicative of in vivo full agonism of compound **2** at the serotonin 5-HT_{1A} receptor subtype, an observation we have previously made for compound **1**.[1]

Compound **2** (at 0.046 mg/kg and higher) induced a pronounced serotonin syndrome (i.e., flat body posture and forepaw treading) that affected response rates, causing behavioral disruption. These effects are characteristic of agonist stimulation of the 5-HT_{1A} receptor in rats.

In conclusion, we have shown that 4-fluoro-5-methoxytryptamines possess potent 5-HT_{1A} activity. Although compound **2** represents a further potency enhancement over the *N*,*N*-dimethyl analogue **1**, more potent congeners may exist. More importantly, general pharmacological studies of agonist effects at the 5-HT_{1A} receptor are almost exclusively carried out with the single agent 8-OH-DPAT. The new molecules reported herein offer pharmacologists the opportunity to employ an agonist from a different chemical class that possesses enhanced potency and potentially enhanced selectivity. Further characterization of compound **2**, particularly for affinity at other receptor types, is currently underway.

Table 3. Data from substitution tests in DOI-trained rats

Drug	Dose μmol/kg	N	% D	% SDL	ED_{50} (95% C.I.) μmol/kg
DOI		10			0.29 (0.19–0.43)
2	0.125	9	22	0	
	0.25	10	30	29	N.S.
	0.50	9	*50*	50	

Table 4. Data from substitution tests in LY293284-trained rats

Drug	Dose μmol/kg	N	% D	% SDL	ED_{50} (95% C.I.) μmol/kg
LY293284		10			0.031 (0.02–0.05)
8-OH-DPAT		10			0.099 (0.06–0.20)
2	0.063	8	0	25	
	0.125	10	10	66.6	0.091[a]
	0.250	8	12.5	100	(0.064–0.12)
	0.50	9	*66.6*	100	
	1.0	10	*90*	100	

[a]Only the three lower doses were used to calculate the ED_{50} because the higher doses produced greater than 50% disruption of responding.

Acknowledgements

The authors are grateful to Mr. Stewart Frescas for many helpful suggestions. This work was supported by NIH grant DA02189.

References

1. Blair, J. B.; Kurrasch-Orbaugh, D.; Marona-Lewicka, D.; Cumbay, M. G.; Watts, V. J.; Barker, E. L.; Nichols, D. E. *J. Med. Chem.* **2000**, *43*, 4701.
2. (a) De Vry, J. *Psychopharmacology* **1995**, *121*, 1. (b) Olivier, B.; Soudijn, W.; van Wijngaarden, I. *Prog. Drug Res.* **1999**, *52*, 103.
3. McKenna, D. J.; Repke, D. B.; Lo, L.; Peroukta, S. J. *Neuropharmacology* **1990**, *3*, 193.
4. Iwao, M. *Heterocycles* **1993**, *36*, 29.
5. (a) Nichols, D. E.; Lloyd, D. H. *J. Org. Chem.* **1986**, *51*, 4294. (b) Batcho, A. D.; Leimgruber, W. *Org. Synth.* **1984**, *63*, 214. (c) Bentov, M.; Pelchowitz, Z.; Levy, A. *Israel J. Chem.* **1964**, *2*, 25. (d) Kruse, L. *Heterocycles* **1981**, *16*, 1119.
6. (a) Russel, H. F.; Harris, B. J.; Hood, D. B.; Thompson, E. G.; Watkins, A. D.; Williams, A. D. *Org. Prep. Proc. Int.* **1985**, 391. (b) Thesing, J.; Semler, G.; Mohr, G. *Chem. Ber.* **1962**, 2205.
7. Nichols, D. E.; Frescas, S. P.; Lee, S. *Synth. Commun.* **1995**, *25*, 2775.
8. Speeter, M. E.; Anthony, W. C. *J. Am. Chem. Soc.* **1954**, *76*, 6208.
9. Foreman, M. M.; Fuller, R. W.; Rasmussen, K.; Nelson, D. L.; Calligaro, D. O.; Zhang, L.; Barret, J. E.; Booher, R. N.; Pajet, C. J.; Flaugh, M. E. *J. Pharmacol. Exp. Ther.* **1994**, *270*, 1270.
10. Fiorella, D.; Rabin, R. A.; Winter, J. C. *Psychopharmacology* **1995**, *121*, 347.
11. (a) Oberlender, R.; Nichols, D. E. *Psychopharmacology (Berl)* **1988**, *95*, 71. (b) Monte, A. P.; Marona-Lewicka, D.; Cozzi, N. V.; Nichols, D. E. *J. Med. Chem.* **1993**, *36*, 3700. (c) Nichols, D. E.; Frescas, S.; Marona-Lewicka, D.; Huang, X.; Roth, B. L.; Gudelsky, G. A.; Nash, J. F. *J. Med. Chem.* **1994**, *37*, 4346.