

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

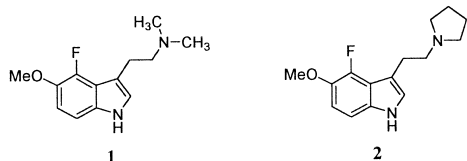
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Abstract—Synthesis and biological evaluation of a novel fluorinated tryptamine analogue are described. This new compound 1-(4-fluoro-5-methoxyindol-3-yl)pyrrolidine (**2**) was found to be a potent serotonin 5-HT_{1A} agonist. © 2001 Elsevier Science Ltd. All rights reserved.

Recently¹ 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.

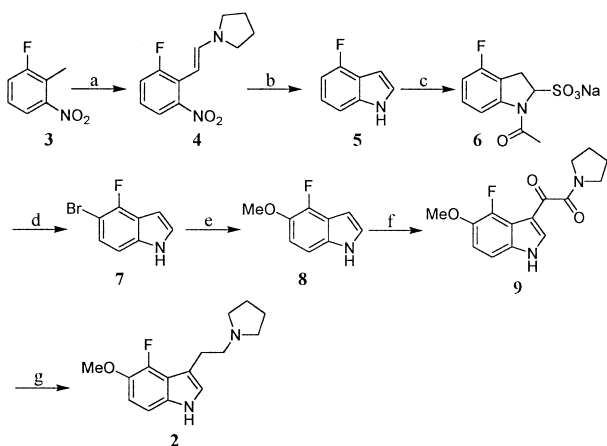


In our recent report,¹ we obtained compound **1** as a minor product from the synthesis of 6-fluoro-5-methoxy-*N,N*-dimethyltryptamine. Clearly, a more efficient approach was required, both for resynthesis of **1**, as well as for preparation of any additional congeners such as **2**. Our initial synthetic 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 synthesis⁸ 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

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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-HT₂ 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 properties¹⁰ of various drugs, while stimulation of 5-HT_{1A} sites results in anxiolytic effects.²



Scheme 1. (a) (CH₃)₂NCH(OCH₃)₂, pyrrolidine, DMF, reflux 3 h, 77%; (b) H₂, Pd/C, 84%; (c) (i) NaHSO₃, rt, 24 h; (ii) Ac₂O, 3 h, reflux 50%; (d) (i) Br₂, H₂O, 0 °C; (ii) 5 N aq NaOH, 75%; (e) NaOMe, CuI, CH₃CO₂Et, 5 h, sealed tube, 140 °C, 70%; (f) (i) (CO)₂Cl₂, Et₂O, 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 [¹²⁵I] DOI-labeled cloned rat 5-HT_{2A}, rat 5-HT_{2C}, and [³H]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

^aValues 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	N.S. ^d
	0.25	15	53	57	
	0.5	10	60	75	
	1.0	9	78	67	

^aNumber of animals tested at each dose.

^bPercentage of animals that failed to emit 50 responses within 5 min.

^cPercentage of animals tested that selected the training drug appropriate lever.

^dNo 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	N.S.
	0.25	10	30	29	
	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	0.091 ^a (0.064–0.12)
	0.125	10	10	66.6	
	0.250	8	12.5	100	
	0.50	9	66.6	100	
	1.0	10	90	100	

^aOnly the three lower doses were used to calculate the ED₅₀ because the higher doses produced greater than 50% disruption of responding.

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