

# A Novel Fluorinated Tryptamine with Highly Potent Serotonin 5-HT<sub>1A</sub> Receptor Agonist Properties

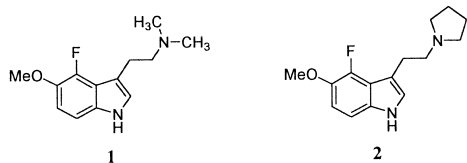
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**Abstract**—Synthesis and biological evaluation of a novel fluorinated tryptamine analogue are described. This new compound 1-(4-fluoro-5-methoxyindol-3-yl)pyrrolidine (**2**) was found to be a potent serotonin 5-HT<sub>1A</sub> agonist. © 2001 Elsevier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

Recently<sup>1</sup> 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<sub>1A</sub> agonist. Substitution with the 4-fluorine markedly increased 5-HT<sub>1A</sub> selectivity over 5-HT<sub>2A/2C</sub> receptors. In view of widespread interest in the function of 5-HT<sub>1A</sub> receptors in the central nervous system,<sup>2</sup> 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.<sup>3</sup> had compared a variety of *N*-substituted tryptamines at both the 5-HT<sub>1A</sub> and 5-HT<sub>2A/2C</sub> receptors. We noted that the compound with the greatest potency at the 5-HT<sub>1A</sub> receptor possessed the *N,N*-dialkyl substituents constrained into a pyrrolidine ring. Thus, herein we describe the synthetic route and the potent 5-HT<sub>1A</sub> 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<sub>1A</sub> 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.

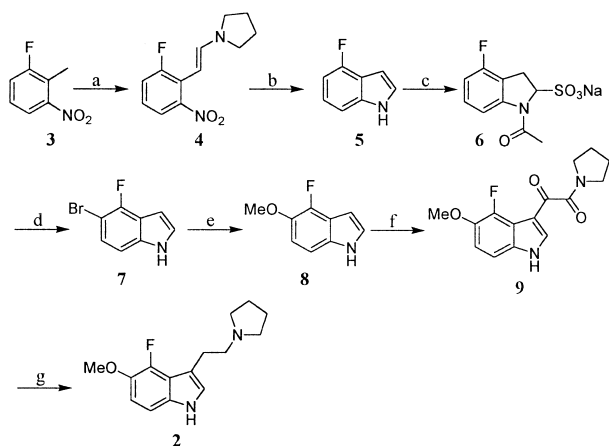


In our recent report,<sup>1</sup> we obtained compound **1** as a minor product from the synthesis of 6-fluoro-5-methoxy-*N,N*-dimethyltryptamine. Clearly, a more efficient approach was required, both for resynthesis of **1**, as well as for preparation of any additional congeners such as **2**. Our initial synthetic strategy was an attempt to functionalize the 4-position of *N*<sub>1</sub>-TIPS-5-methoxy gramine through lithiation and, with a few subsequent transformations, obtain the final product.<sup>4</sup> This methodology failed because attempted lithiation at the 4-position only afforded product where the triisopropylsilyl group had rearranged from N<sub>1</sub> to C<sub>2</sub>. The successful approach is shown below. Indole **5** was synthesized in high yield via the Leimgruber–Batcho method,<sup>5</sup> 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**).<sup>6</sup> A modification of the Ullmann ether synthesis, employed earlier in our group,<sup>7</sup> 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<sup>8</sup> 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<sub>1A</sub>, 5-HT<sub>2A</sub>, and 5-HT<sub>2C</sub> 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<sub>1A</sub> affinity, as well as an increased selectivity for 5-HT<sub>1A</sub>/5-HT<sub>2</sub> binding. Compound **2** is more potent than the standard 5-HT<sub>1A</sub> agonist 8-hydroxy-2-(*N,N*-dipropylamino)tetralin (8-OH-DPAT) at this site and has potency nearly comparable to the partial ergoline LY293284.<sup>9</sup> An agonist effect at serotonin 5-HT<sub>2A</sub> sites is believed responsible for the hallucinogenic properties<sup>10</sup> of various drugs, while stimulation of 5-HT<sub>1A</sub> sites results in anxiolytic effects.<sup>2</sup>



**Scheme 1.** (a) (CH<sub>3</sub>)<sub>2</sub>NCH(OCH<sub>3</sub>)<sub>2</sub>, pyrrolidine, DMF, reflux 3 h, 77%; (b) H<sub>2</sub>, Pd/C, 84%; (c) (i) NaHSO<sub>3</sub>, rt, 24 h; (ii) Ac<sub>2</sub>O, 3 h, reflux 50%; (d) (i) Br<sub>2</sub>, H<sub>2</sub>O, 0 °C; (ii) 5 N aq NaOH, 75%; (e) NaOMe, CuI, CH<sub>3</sub>CO<sub>2</sub>Et, 5 h, sealed tube, 140 °C, 70%; (f) (i) (CO)<sub>2</sub>Cl<sub>2</sub>, Et<sub>2</sub>O, 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 [<sup>125</sup>I] DOI-labeled cloned rat 5-HT<sub>2A</sub>, rat 5-HT<sub>2C</sub>, and [<sup>3</sup>H]8-OH-DPAT-labeled human 5-HT<sub>1A</sub> receptors (*K<sub>i</sub>* values ± SEM in nanomolar)

Compd	5-HT <sub>2A</sub> <sup>a</sup>	5-HT <sub>2C</sub>	5-HT <sub>1A</sub>
<b>1</b>	122 ± 14.2	55 ± 9.4	0.23 ± 0.03
<b>2</b>	130 ± 3.2	140 ± 8.4	0.12 ± 0.012
8-OH DPAT			0.83 ± 0.093 <sup>b</sup>
LY293284			0.053 ± 0.012

<sup>a</sup>Values are means of three experiments, standard deviation is given in parentheses.

<sup>b</sup>*K<sub>D</sub>* value.

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

Drug	Dose μmol/kg	N <sup>a</sup>	% D <sup>b</sup>	% SDL <sup>c</sup>	ED <sub>50</sub> (95% C.I.) μmol/kg
LSD		15			0.026 (0.014–0.045)
<b>2</b>	0.125	10	10	11	N.S. <sup>d</sup>
	0.25	15	53	57	
	0.5	10	60	75	
	1.0	9	78	67	

<sup>a</sup>Number of animals tested at each dose.

<sup>b</sup>Percentage of animals that failed to emit 50 responses within 5 min.

<sup>c</sup>Percentage of animals tested that selected the training drug appropriate lever.

<sup>d</sup>No substitution occurred.

The behavioral effects of drugs acting at 5-HT<sub>1A/2A</sub> receptors may be quantified using the two lever drug discrimination procedure (DD).<sup>11</sup> In these experiments we employed two hallucinogenic training drugs, LSD and DOI (2,5-dimethoxy-4-iodoamphetamine),<sup>1</sup> and the 5-HT<sub>1A</sub> agonist LY293284.<sup>1</sup> 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<sub>2A</sub> 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<sub>1A</sub> receptor subtype, an observation we have previously made for compound **1**.<sup>1</sup>

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<sub>1A</sub> receptor in rats.

In conclusion, we have shown that 4-fluoro-5-methoxytryptamines possess potent 5-HT<sub>1A</sub> 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<sub>1A</sub> 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 <sub>50</sub> (95% C.I.) μmol/kg
DOI		10			0.29 (0.19–0.43)
<b>2</b>	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 <sub>50</sub> (95% C.I.) μmol/kg
LY293284		10			0.031 (0.02–0.05)
8-OH-DPAT		10			0.099 (0.06–0.20)
<b>2</b>	0.063	8	0	25	0.091 <sup>a</sup> (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	

<sup>a</sup>Only the three lower doses were used to calculate the ED<sub>50</sub> because the higher doses produced greater than 50% disruption of responding.

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