Effect of Ring Fluorination on the Pharmacology of Hallucinogenic Tryptamines

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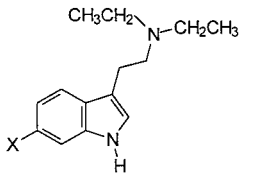
A series of fluorinated analogues of the hallucinogenic tryptamines *N*,*N*-diethyltryptamine (DET), 4-hydroxy-*N*,*N*-dimethyltryptamine (4-OH-DMT, psilocin), and 5-methoxy-DMT was synthesized to investigate possible explanations for the inactivity of 6-fluoro-DET as a hallucinogen and to determine the effects of fluorination on the molecular recognition and activation of these compounds at serotonin receptor subtypes. The target compounds were evaluated using in vivo behavioral assays for hallucinogen-like and 5-HT_{1A} agonist activity and in vitro radioligand competition assays for their affinity at 5-HT_{2A}, 5-HT_{2C}, and 5-HT_{1A} receptor sites. Functional activity at the 5-HT_{2A} receptor was determined for all compounds. In addition, for some compounds functional activity was determined at the 5-HT_{1A} receptor. Hallucinogen-like activity, evaluated in the two-lever drug discrimination paradigm using LSD-trained rats, was attenuated or abolished for all of the fluorinated analogues. One of the tryptamines, 4-fluoro-5-methoxy-DMT (**6**), displayed high 5-HT_{1A} agonist activity, with potency greater than that of the 5-HT_{1A} agonist 8-OH-DPAT. The ED_{50} of **6** in the two-lever drug discrimination paradigm using rats trained to discriminate the 5-HT_{1A} agonist LY293284 was 0.17 μmol/kg, and the K_i at [^{3}H]8-OH-DPAT-labeled 5-HT_{1A} receptors was 0.23 nM. The results indicate that fluorination of hallucinogenic tryptamines generally has little effect on 5-$HT_{2A/2C}$ receptor affinity or intrinsic activity. Affinity at the 5-HT_{1A} receptor was reduced, however, in all but one example, and all of the compounds tested were full agonists but with reduced functional potency at this serotonin receptor subtype. The one notable exception was 4-fluoro-5-methoxy-DMT (**6**), which had markedly enhanced 5-HT_{1A} receptor affinity and functional potency. Although it is generally considered that hallucinogenic activity results from 5-HT_{2A} receptor activation, the present results suggest a possible role for involvement of the 5-HT_{1A} receptor with tryptamines.

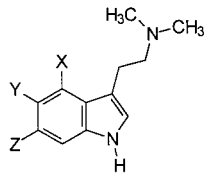
Introduction[1]

Fluorine can dramatically change the properties of biologically active compounds and can influence the metabolism and distribution of drug molecules in the body. Substitution of fluorine at various positions of the aromatic ring of the neurotransmitter norepinephrine produces large differences in biological activity.[2] Fluorinated melatonin analogues have enhanced activity at the pituitary melatonin receptor and increased biological half-life.[3] Phenol acidity is significantly increased in fluorinated tyramine, dopamine, and serotonin analogues.[4,5] Also, the *p*-fluorophenyl group is optimal for the neuroleptic activity of butyrophenones such as haloperidol.[6]

In 1963 Kalir and Szara[7] reported that 6-fluoro-*N*,*N*-diethyltryptamine (6F-DET, **1b**) was inactive as a hallucinogen in humans. Although autonomic symptoms similar to the parent compound **1a** were observed, along with some mood changes, **1b** did not produce the perceptual and visual disturbances characteristic of **1a** and other hallucinogens. Although these authors originally attributed this inactivity to the inability of **1b** to be metabolized to an "active" metabolite, **1c**, this idea was not fully accepted. Furthermore, a report in 1963 indicated that the homologous **2a** was devoid of hallucinogenic activity.[8] The biological activities of tryptamines **1c** and **2a** should be similar, considering the only change in structure is the alkyl group on the side chain amine. Thus, the concept of 6-hydroxytryptamines being active hallucinogenic metabolites was abandoned. Although lacking hallucinogenic activity, **1b** did prove useful as an "active placebo" in clinical trials due to its autonomic effects.[9]



1a X = H; DET
1b X = F; 6F-DET
1c X = OH



2a X = Y = H; Z = OH
2b X = OH; Y = Z = H; Psilocin
2c X = Z = H; Y = OCH_3

We hypothesized that the lack of hallucinogenic activity of 6F-DET (**1b**) might be attributed to a change in affinity, intrinsic activity, and/or selectivity at one or more serotonin receptor subtypes. The potent hal-

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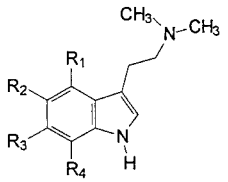
lucinogens **2b**,**c** seemed to be additional logical starting points in the evaluation of fluorinated analogues of hallucinogenic tryptamines.

Although the fluorine atom has generally been considered to have a van der Waals radius similar to that of a hydrogen atom, it has more recently been recognized that it is much larger, at 1.47 Å, and nearly comparable in size to an oxygen atom at 1.52 Å.[10] Thus, F and O, not H, are more nearly isosteric. Of course, F has very different electronic properties from H and is much more electronegative than O.[11] Fluorine can increase the lipophilicity of a molecule to allow better partitioning into membranes and facilitate hydrophobic interactions with a target receptor. Fluorine could also mimic a hydroxy through a dipole−dipole interaction. Theoretical calculations estimate the strength of a hydrogen bond with fluorine to be between 1.48 and 3.53 kcal/mol,[12,13] weaker than a hydrogen bond to oxygen (5−10 kcal/mol).[12] Although the fluorine substituent must be isolated from an aqueous environment (such as in the receptor interior) in order to be involved in a hydrogen-bonding interaction, within the constraints of a hydrophobic receptor pocket a fluorine hydrogen bond may in some situations be favorable.

To test the hypothesis that the lack of activity of 6-fluoro-DET (**1b**) might be attributed to loss of 5-HT_{2A} affinity or efficacy, and also to determine the effects of fluorination on the molecular recognition of other potent hallucinogenic tryptamines at serotonin receptor subtypes, compounds **1a** and **2b**,**c** were compared with the fluorinated analogues **1b** and **3**−**6**. We present here the synthesis and pharmacological assessment of compounds **1a**,**b**, **2b**,**c**, and **3**−**6**.



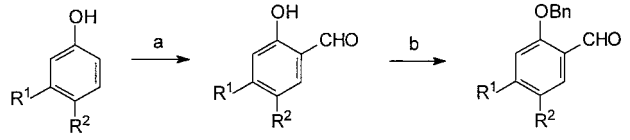
3 R_1 = OH; R_2 = H; R_3 = F; R_4 = H
4 R_1 = OH; R_2 = R_3 = H; R_4 = F
5 R_1 = H; R_2 = OCH_3; R_3 = F; R_4 = H
6 R_1 = F; R_2 = OCH_3; R_3 = R_4 = H

Chemistry

Although **1b** has been previously prepared,[7,14] compounds **3**−**6** had not. The requisite indoles required for **1b**, **3**, and **4** were synthesized using the Hemetsberger azide pyrolysis reaction.[15,16]

The compound 6-fluoropsilocin (**3**) had been a target for our laboratory for many years, but the necessary 6-fluoro-4-benzyloxyindole was not readily accessible by previously known synthetic methods until the development of the Hemetsberger reaction. Since ortho-formylated phenols were required for the syntheses of the indoles for **3** and **4**, the first step in the syntheses of these derivatives involved ortho-specific formylations of *m*- and *p*-fluorophenol. Formylation of free phenols frequently results in low yields, poor regioselectivity, and/or para-formylation as the major result. In addition, formylations using metal catalysts generally require high pressure. Aldred et al.[17] recently reported the successful ortho-formylation of magnesium bis(phenoxides). Starting phenols **7a,b** were therefore formylated to yield the salicylaldehydes **8a,b** (Scheme 1), following the procedure of Aldred et al.[17] Protection of the phenol functionalities with a benzyl group then yielded **9a,b**.

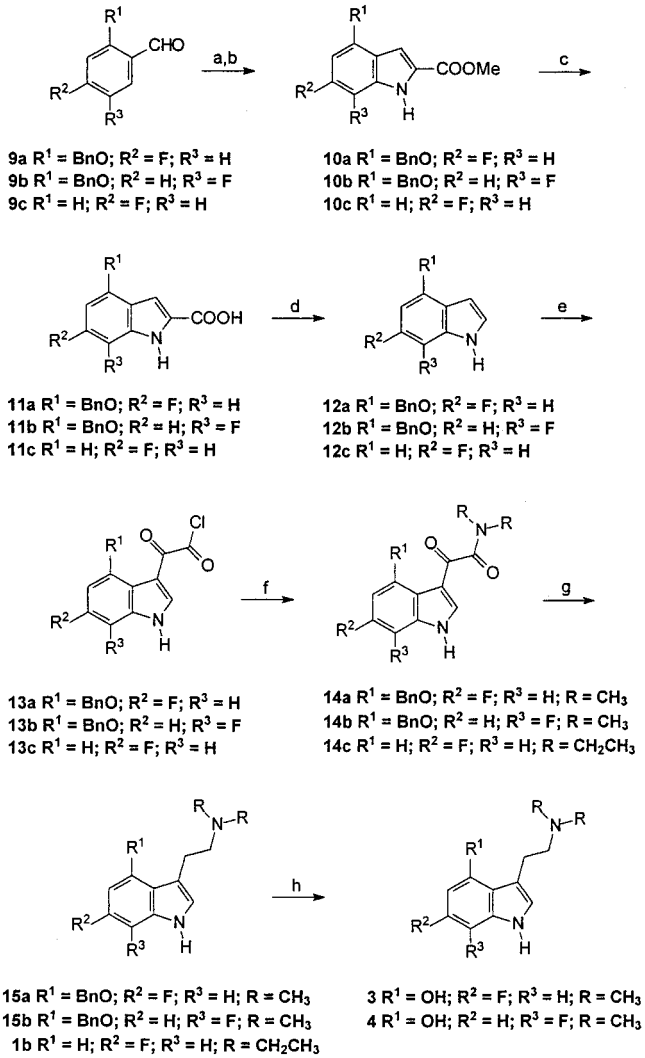
Scheme 1[a]



7a R^1 = F; R^2 = H
7b R^1 = H; R^2 = F
8a R^1 = F; R^2 = H
8b R^1 = H; R^2 = F
9a R^1 = F; R^2 = H
9b R^1 = H; R^2 = F

[a] (a) Mg, $(CH_2O)_n$, MeOH/toluene, Δ; (b) BnCl, K_2CO_3, DMF, Δ.

Scheme 2[a]



9a R^1 = BnO; R^2 = F; R^3 = H
9b R^1 = BnO; R^2 = H; R^3 = F
9c R^1 = H; R^2 = F; R^3 = H
10a R^1 = BnO; R^2 = F; R^3 = H
10b R^1 = BnO; R^2 = H; R^3 = F
10c R^1 = H; R^2 = F; R^3 = H
11a R^1 = BnO; R^2 = F; R^3 = H
11b R^1 = BnO; R^2 = H; R^3 = F
11c R^1 = H; R^2 = F; R^3 = H
12a R^1 = BnO; R^2 = F; R^3 = H
12b R^1 = BnO; R^2 = H; R^3 = F
12c R^1 = H; R^2 = F; R^3 = H
13a R^1 = BnO; R^2 = F; R^3 = H
13b R^1 = BnO; R^2 = H; R^3 = F
13c R^1 = H; R^2 = F; R^3 = H
14a R^1 = BnO; R^2 = F; R^3 = H; R = CH_3
14b R^1 = BnO; R^2 = H; R^3 = F; R = CH_3
14c R^1 = H; R^2 = F; R^3 = H; R = CH_2CH_3
15a R^1 = BnO; R^2 = F; R^3 = H; R = CH_3
15b R^1 = BnO; R^2 = H; R^3 = F; R = CH_3
1b R^1 = H; R^2 = F; R^3 = H; R = CH_2CH_3
3 R^1 = OH; R^2 = F; R^3 = H; R = CH_3
4 R^1 = OH; R^2 = H; R^3 = F; R = CH_3

[a] (a) $N_3CH_2C(O)OCH_3$, NaOMe, MeOH, −20 °C; (b) xylenes, reflux; (c) aq NaOH, Δ; (d) Cu^0, *N*-methylpyrrolidinone, 240 °C; (e) $(COCl)_2$, ether, 0 °C; (f) $(CH_3)_2NH$ *or* Et_2NH, ether; (g) LAH, THF, reflux; (h) H_2, Pd/C, EtOH.

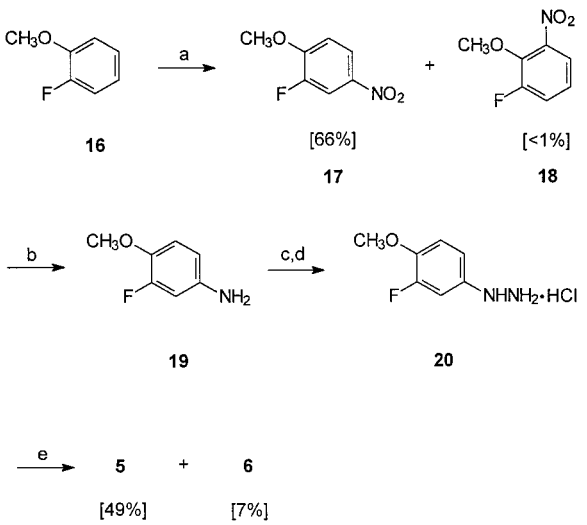
The methyl indole-2-carboxylates **10a**−**c** were formed from the respective benzaldehydes **9a**−**c** by condensation with methyl azidoacetate[18] (Scheme 2) followed by thermal cyclization of the intermediate azidocinnamates.[18,19] The esters were then hydrolyzed, followed by decarboxylation at high temperature to afford **12a**−**c** in excellent yields. The decarboxylation method was improved using *N*-methylpyrrolidinone as the solvent (rather than quinoline), which has the advantage of more easy removal of *N*-methylpyrrolidinone in the workup as opposed to the difficulty in removing quino-

Table 1. Results of the Drug Discrimination Studies in LSD-, DOI-, and LY293284-Trained Rats

	LSD-trained rats			DOI-trained rats			LY293284-trained rats		
drug	ED_{50} (μmol/kg)	95% CI	n[a]	ED_{50} (μmol/kg)	95% CI	n	ED_{50} (μmol/kg)	95% CI	n
LSD	0.037	0.02−0.06	13−16	0.014	0.005−0.04	11	NT[b]		
DOI	0.27	0.15−0.47	14−18	0.30	0.19−0.47	11	NT[b]		
LY293284[c]	NS[e]						0.031	0.02−0.05	10
DPAT[d]	NS[e]						0.099	0.06−0.20	10
1a	2.53	1.12−5.71	8−12				NT[b]		
1b	40% @ 8.0[f]	NS[e]	9−10	33% @ 8.0[f]	NS[e]	8	NT[b]		
2b	1.01	0.69−1.46	9−11	NT[b]			NT[b]		
4	63% @ 8.0[f]	PS[g]	10−15	NT[b]			NT[b]		
2c	1.49[h]	0.88−2.53	9−17	NT[b]			NT[b]		
5	4.72	3.02−7.36	8−11	50% @ 4.0[f]	NS[e]	6−12	NT[b]		
6	22% @ 2.0[f]	NS[e]	8−10	66% @ 1.0[f]	PS[g]	6	0.17	0.13−0.20	13−14

[a] Number of animals tested at each dose. [b] Not tested in this assay. [c] Ref 45. [d] DPAT = 8-OH-DPAT. [e] NS = no substitution. [f] Maximum percentage of rats responding on the training drug lever at the given dose. [g] PS = partial substitution. [h] Tests carried out 15 min after injection.

Scheme 3[a]



[a] (a) $NaNO_2$, 66% H_2SO_4, cat. HNO_3; (b) H_2, Pd/C, EtOH; (c) $NaNO_2$, aq HCl, 0 °C; (d) $SnCl_2$, concd HCl, −5 °C; (e) $(MeO)_2CH(CH_2)_3N(CH_3)_2$, 25% aq AcOH, Δ.

line. In addition, the decarboxylation was performed with a constant stream of nitrogen bubbling through the solution to flush out carbon dioxide. Increases in yields up to 15% were obtained by this decarboxylation method in the syntheses of indoles **12a−c.** The glyoxalylamides **14a−c** were prepared by acylation of **12a−c** with oxalyl chloride followed by treatment with diethyl- or dimethylamine, according to the method of Speeter and Anthony.[20] Reduction of **14a−c** with $LiAlH_4$ then afforded the tryptamines **15a,b** and final compound **1b**. Removal of the benzyl protecting group in compounds **15a,b** by catalytic hydrogenation then yielded **3** and **4**.

The remaining fluorinated derivatives **5** and **6** were obtained via Fischer indole cyclization. The required 4-(*N*,*N*-dimethylamino)butanal dimethylacetal was prepared according to a literature procedure.[21] Scheme 3 outlines the syntheses of **5** and **6**. *o*-Fluorophenol[22] was O-methylated to afford **16**. Modification of the procedure of Schofield et al.[23] by nitration of **16** in 66% H_2SO_4 with 1 equiv of $NaNO_2$ and catalytic HNO_3 resulted in a 66% yield of the para-nitrated product **17**. The ortho-isomer **18** could be detected in the ^1H NMR spectrum, in an estimated yield of less than 1%.

Anisidine **19** was prepared by catalytic reduction of **17**, and by modifying the procedure of Street et al.,[24] subsequent diazotization of the aniline followed by reduction with stannous chloride yielded the hydrazine **20**. This fluorinated hydrazine was then treated with 4-(*N*,*N*-dimethylamino)butanal dimethylacetal,[25] to produce a 56% overall yield of **5** and **6**, with the 6-fluoro isomer **5** as the major product.

Pharmacology

The fluorinated tryptamines **1b** and **3−6** were evaluated in the two-lever drug discrimination (DD) behavioral assay to assess hallucinogen-like activity in LSD- and DOI-trained rats and 5-HT_{1A} agonist activity in LY293284-trained rats (Table 1). Details of the DD methodology have been described elsewhere.[26−30] Briefly, rats were trained to discriminate the effects of intraperitoneal (ip) injections of the training drug from saline. For those compounds that completely substituted for LSD, potencies were measured using ED_{50} values with 95% confidence intervals (CI). Additionally, **1b** and **3−6** were tested for their ability to compete in radioligand binding at the cloned rat 5-HT_{2A} and 5-HT_{2C} and human 5-HT_{1A} serotonin receptor subtypes (Table 2). Finally, compounds were examined for their functional effects by determining the potency to stimulate phosphoinositide hydrolysis mediated by the 5-HT_{2A} receptor and the ability to inhibit forskolin-stimulated cAMP formation mediated by the 5-HT_{1A} receptor.

Results and Discussion

The DD paradigm is routinely used in our laboratory as an initial behavioral screen for evaluating serotonergic activity at the 5-HT_{1A} and 5-HT_2 receptor subtypes.[26−30] This method has been used extensively to model human hallucinogenic effects by studying the LSD- or DOI-like discriminative stimulus properties produced in animals[28,30] that are mediated primarily by agonist interaction with 5-HT_2 receptors.[31−33]

Table 1 shows the results of the DD studies in LSD-, DOI-, and LY293284-trained rats, and Table 2 presents the results of the radioligand competition and 5-HT_{2A} functional assays. First of all, the behavioral data are consistent with the reported clinical effects for the hallucinogen **1a**, which fully substituted in LSD-trained rats, whereas its clinically inactive 6-fluoro analogue[7] **1b** did not substitute. It is evident that fluorination of the tryptamines at the 4-, 5-, 6-, or 7-position attenuates

Table 2. Results of Radioligand Competition Studies at [^{125}I]DOI-Labeled Rat 5-HT$_{2A}$ and 5-HT$_{2C}$ Receptors and [^{3}H]8-OH-DPAT-Labeled Human 5-HT$_{1A}$ Receptors (K_i values), PI Hydrolysis Studies at the 5-HT$_{2A}$ Receptor (EC_{50} values), and Ability to Inhibit Forskolin-Stimulated cAMP Production via the 5-HT$_{1A}$ Receptor[a]

	5-HT$_{2A}$			5-HT$_{2C}$	5-HT$_{1A}$	
compd	$K_i \pm$ SEM (nM)	$EC_{50} \pm$ SEM (nM)[b]	% intrinsic activity (SEM)	$K_i \pm$ SEM (nM)	$K_i \pm$ SEM (nM)	$EC_{50} \pm$ SEM (nM)[c]
1a	133 ± 15.1	5370 ± 1470	82 ± 7.0	104 ± 18.7	47 ± 3.6	680 ± 33
1b	145 ± 17.0	33900 ± 3340	63% @ 100 μM	210 ± 37.9	256 ± 49.6	3700 ± 630
2b	25 ± 4.7	2310 ± 290	52 ± 5.6	10 ± 1.4	49 ± 5.5	NT[d]
2c	42 ± 9.9	2390 ± 890	99 ± 9.0	16 ± 1.8	1.7 ± 0.08	22 ± 6.7
3	13 ± 4.0	2600 ± 650	85 ± 7.6	7.4 ± 2.2	114 ± 12.8	NT
4	13 ± 0.8	4920 ± 1100	76 ± 7.3	5.4 ± 1.0	120 ± 7.4	NT
5	33 ± 3.3	7900 ± 2920	110 ± 6.0	19 ± 3.2	84.5 ± 12.5	NT
6	122 ± 14.2	18100 ± 3800	88 ± 7.0	55 ± 9.4	0.23 ± 0.03	0.93 ± 0.21
LY293284					0.088 ± 0.020	0.13 ± 0.02
8-OH-DPAT					K_D 0.88	5.82 ± 1.37

[a] The intrinsic activity at the 5-HT$_{2A}$ receptor is the percentage response given by the compound, compared with the response produced by 10 μM serotonin. For each assay, $n = 3-5$. [b] EC_{50} value for stimulating PI turnover; 5-HT $EC_{50} = 130 \pm 6.9$ nM. [c] EC_{50} value for inhibition of 50 μM forskolin-stimulated cAMP accumulation; 5-HT $EC_{50} = 160 \pm 36$ nM. All tested compounds were full agonists. [d] NT= not tested. [^{3}H]8-OH-DPAT $K_D = 0.88$ nM; [^{125}I]DOI at the 5-HT$_{2A}$ receptor $K_D = 0.85$ nM; [^{125}I]DOI at the 5-HT$_{2C}$ receptor $K_D = 0.80$ nM.

or abolishes hallucinogen-like activity. Of all the fluorinated derivatives, the LSD cue generalized only to 6-fluoro-5-methoxy-DMT (**5**) with an ED_{50} of 4.72 μmol/kg, about one-third the potency of its nonfluorinated congener **2c**. The substitution of **5** in LSD-trained rats, but not in DOI-trained animals, is interesting because both **2c** and **5** have virtually identical 5-HT$_{2A/2C}$ affinity and intrinsic activity at the 5-HT$_{2A}$ receptor and it has generally been considered that hallucinogenic activity is mediated by activation of 5-HT$_{2A}$ receptors.[31] The most obvious difference between **2c** and **5** is the 40-fold lower affinity of **5** at the 5-HT$_{1A}$ receptor. These data may suggest a role for the 5-HT$_{1A}$ receptor in the LSD cue. One possibility is that activation of the 5-HT$_{2A}$ receptor may be a necessary, but not sufficient, condition or an enabling pharmacological mechanism, which can be potentiated or modulated by interactions at other receptors, for example, the 5-HT$_{1A}$ receptor.[34]

An interesting discovery was made in the behavioral evaluation of compound **6**. Although this analogue did not substitute for LSD, it produced a marked "serotonin syndrome" characteristic of 5-HT$_{1A}$ agonist activity, which included flat body posture, lower lip retraction (LLR), and forepaw treading.[35] This derivative also produced hypothermia in rats. Activation of central 5-HT$_{1A}$ receptors produces hypothermia in laboratory animals, whereas systemic administration of 5-HT$_2$ agonists evokes a hyperthermic response. We therefore decided to characterize more extensively the 5-HT$_{1A}$ receptor effects of these fluorinated tryptamines.

Drug discrimination studies in LY293284-trained rats, which model 5-HT$_{1A}$ agonist activity, confirmed these observations (Table 1), where 4-fluoro-5-methoxy-DMT (**6**) fully substituted for the training drug with an ED_{50} comparable to that of the 5-HT$_{1A}$ agonist 8-OH-DPAT. The high 5-HT$_{1A}$ activity of **6** was unexpected since 4-oxygenation (i.e. psilocin, **2b**) produces selectivity for 5-HT$_{2A}$ receptors[31] and fluorine can sometimes be considered a bioisosteric replacement for an oxygen atom.

The radioligand competition studies (Table 2) were interesting but provided no simple explanations. In general, 6-fluorination has only a minor effect on *affinity* at the 5-HT$_{2A}$ or 5-HT$_{2C}$ receptors in any of the series: **1a** vs **1b**, **2b** vs **3**, or **2c** vs **5**. Indeed, the drug discrimination data suggest that compound **5** might possess LSD-like effects in humans, but with lower potency than **2c**. Thus, our initial hypothesis that activity of **1b** might be lost due to a decrease in 5-HT$_{2A}$ receptor *affinity* was not borne out. Fluorination at the 7-position of psilocin similarly had little effect on either 5-HT$_{2A}$ or 5-HT$_{2C}$ affinity: e.g. compare **2b** and **4**. On the other hand, the potency of fluorinated compounds to stimulate phosphoinositide (PI) turnover was decreased in all cases except for **3**. Whereas the EC_{50} values of **4** and **5** to effect phosphoinositide turnover were increased only 2−3-fold when compared with their nonfluorinated parents, the functional potency of **1b** was more dramatically decreased. In addition, **1a** was a nearly full (82%) agonist, whereas **1b** produced only 63% of the maximal response at 100 μM. Thus, although the 5-HT$_{2A}$ affinity of **1b** was comparable to that of **1a**, its intrinsic activity and functional potency were significantly reduced.

Fluorination did have a more marked effect on 5-HT$_{1A}$ receptor affinity, however. Fluorination at the 6-position of **1a** (6F-DET, **1b**) resulted in a 5-fold decrease in receptor binding affinity. Likewise, fluorination at the 6-position of psilocin (6F-psilocin, **3**) caused about a 2-fold decrease in receptor affinity. Similarly, 6-fluorinated **5** had 50-fold lower affinity than the parent **2c**. By contrast, fluorination at the 4-position of **2c** (4F-5MeO-DMT, **6**), led to a 7.5-fold *increase* in 5-HT$_{1A}$ affinity. In addition, **6** was a full agonist, about 30 times more potent than **2c** and about 6 times more potent than the standard 5-HT$_{1A}$ agonist, 8-OH-DPAT. Although we did not examine functional effects of the psilocin analogues **2b**, **3**, and **4**, both **1a**,**b** were full agonists at the 5-HT$_{1A}$ receptor (data not shown). Fluorination of **1a** led to about a 5-fold decrease both in 5-HT$_{1A}$ affinity and in functional potency (Table 2).

With respect to our original motivation to understand why 6-fluorination abolished the hallucinogenic activity of DET (**1a**) what can be concluded? First, although 5-HT$_{2A}$ receptor affinity is not significantly altered by 6-fluorination, the ability to activate the receptor is dramatically reduced as measured using PI turnover. Second, although a role for the 5-HT$_{2C}$ receptor in the process of hallucinogenesis is still somewhat controversial, 6-fluorination did reduce affinity at that site by about 2-fold. Finally, 6-fluorination reduced affinity and ability to activate the 5-HT$_{1A}$ receptor by about 5-fold.

Although tryptamine hallucinogens have significant affinity and agonist activity at 5-HT_{1A} receptors, the pharmacological relevance of that observation is not presently clear. Studies of possible functional interactions between 5-HT_{1A} and 5-HT_{2A} receptors have not led to unambiguous conclusions. In some cases there appeared to be little interaction, whereas in others there was synergism, and in yet others functional antagonism was observed. For example, using rats trained to discriminate DOI, administration of the 5-HT_{1A} agonist 8-OH-DPAT, up to doses that completely suppressed responding, produced only a slight blockade of the DOI training dose stimulus.[36] Most studies have reported that 5-HT_{1A} *antagonists* potentiated 5-HT_{2A}-mediated behaviors. For example, Darmani and Reeves[37] found that the 5-HT_{1A} antagonist (*S*)-(−)-UH 301 produced the head-twitch in mice, a response believed to be mediated by the 5-HT_{2A} receptor. These workers reasoned that disinhibition of pulse-modulating 5-HT_{1A} somatodendritic autoreceptors led to indirect release of 5-HT that consequently stimulated 5-HT_{2A} receptors. Further studies with the 5-HT_{1A} antagonist WAY 100,635[38] and the nonselective 5-HT_{1A} antagonist pindolol[39] gave results consistent with this hypothesis, that 5-HT_{1A} *antagonists* enhanced 5-HT_{2A} function through disinhibition of somatodendritic 5-HT_{1A} autoreceptors. In a similar vein, Strassman has shown that pretreatment with pindolol potentiated the behavioral effects of the hallucinogen *N*,*N*-dimethyltryptamine (DMT) in humans.[40]

By contrast, in the control of sexual behavior, bilateral injection of 8-OH-DPAT into the VMN of the hypothalamus inhibited lordosis in proestrous rats, whereas DOI blocked the lordosis-inhibiting effect of 8-OH-DPAT, demonstrating a functional antagonism between activation of the 5-HT_{1A} and 5-HT_{2A} receptors.[41] Similarly, the DOI-induced head-twitch response in rats was abolished by administration of the 5-HT_{1A} agonist 8-OH-DPAT.[42] Nevertheless, Glennon[43] has reported that a small dose of 8-OH-DPAT could potentiate stimulus generalization in rats trained to discriminate DOM. Our results would also suggest that stimulation of 5-HT_{1A} receptors might potentiate 5-HT_{2A}-mediated discriminative stimulus effects. In any case, it seems possible that intrinsic 5-HT_{1A} agonist activity might modulate behavioral effects mediated by the 5-HT_{2A} receptor in rats. In summary, the loss of hallucinogenic activity in **1b** could be the result of one or more of the above explanations.

The underlying basis for the observed pharmacological effects of a fluorine atom in the tryptamines is not apparent. It is clear from the present data that the effects are highly dependent both on the location of the fluorine atom as well as on the other substituents that are present. An interesting possibility does arise from the ability of fluorine to participate in a hydrogen-bonding interaction with the receptor. Fluorine hydrogen bonds can vary in strength from 1.48 to 3.53 kcal/mol,[12,13] up to approximately one-half the strength of an oxygen hydrogen bond. A fluorine hydrogen bond may therefore contribute significantly to the molecular recognition of certain tryptamines at serotonin receptor subtypes. In order for a fluorine hydrogen bond to form, the fluorine substituent must be directed optimally toward a hydrogen bond donor in the receptor−ligand recognition domain.

Kuipers et al.[44] modeled the 5-HT_{1A} receptor based on the three-dimensional structure of bacteriorhodopsin and evaluated the possible binding orientations of tryptamines and ergolines. In that model, the hydrogen bonds to the 5-methoxy and indole N(1)H are preserved, as well as the ionic interaction with the side chain amine. Since the three-dimensional structure of the receptor is not known, it is difficult to ascertain toward which transmembrane helix the fluorine might be directed. Most likely, however, a hydrogen bond donor in this model would need to reside in transmembrane domain 5, 6, or 7. One of these hydrogen-bonding interactions could explain the increased affinity of **6** at the 5-HT_{1A} receptor.

On the other hand, **6** may be rotated ∼180° in the ligand-binding pocket because it is not known in which *orientation* tryptamines bind to serotonin receptors. There is also controversy concerning the orientation of ligand binding to the 5-HT_2 receptor subtype.[45,46] These arguments could also apply to **1b**, where the formation of a receptor−fluorine hydrogen bond could force an unfavorable reorientation of the indole nucleus in the ligand-binding domain.

One of the most interesting findings of this study, however, was our discovery that 4-fluorination of 5-methoxy-DMT results in a selective, potent ligand for the 5-HT_{1A} receptor. To our knowledge, **6** is the first example of a simple fluorinated tryptamine with high selectivity and functional activity at the 5-HT_{1A} receptor.

Experimental Section

Chemistry. Starting materials, solvents, and reagents were purchased commercially, except where noted. All ^{1}H NMR spectra were recorded on a Bruker ARX 300-MHz instrument. Chemical shifts are reported in δ values (parts per million, ppm) relative to an internal standard of tetramethylsilane (TMS) in $CDCl_3$, except where noted. Melting points were determined with a Thomas-Hoover Meltemp apparatus and are uncorrected. Analytical thin-layer chomatography (TLC) was performed on Baker-Flex silica gel 1B2-F plastic plates. Chemical ionization mass spectra (CIMS) were determined on a Finnigan 4000 quadrupole mass spectrometer, using isobutane as the reagent gas and are reported as *m*/*e* (relative intensity). Elemental analyses were obtained from the Purdue Microanalysis Laboratory and are within ±0.4% of the calculated values. All reactions were performed under an inert atmosphere of nitrogen or argon. THF was distilled over Na^0 metal.

General Procedure for the Preparation of 2-Benzyloxybenzaldehydes 9a,b. Benzyl chloride (0.011 mol) was added dropwise into a reaction flask containing the appropriate salicylaldehyde (0.010 mol) and potassium carbonate (0.016 mol) in DMF (5 mL). After reflux for 2.5 h, the reaction mixture was poured into 50 mL of cold water and extracted with ether (3 × 30 mL). The organic extract was washed with 10% aqueous NaOH and brine, dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel with methylene chloride as the eluent to afford the respective 2-benzyloxybenzaldehydes.

2-Benzyloxy-4-fluorobenzaldehyde (9a). This compound was obtained as a solid in 91% yield from 4-fluorosalicylaldehyde (**8a**):[17] mp 31 °C; ^{1}H NMR δ 10.41 (s, 1, CHO), 8.06 (t, 1, ArH, J = 8.1 Hz), 7.39 (m, 5, benzyl-ArH), 6,73 (m, 2, ArH), 5.15 (s, 2, CH_2); CIMS 231 (MH^+). Anal. ($C_{14}H_{11}FO_2$) C, H.

2-Benzyloxy-5-fluorobenzaldehyde (9b). This compound was obtained as a solid in 91% yield from 5-fluorosalicylalde-

hyde (**8b**):[17] mp 46 °C; ^{1}H NMR δ 10.51 (s, 1, CHO), 7.55 (dd, 1, ArH, J = 3.0 and 9.0 Hz), 7.42 (m, 5, benzyl-ArH), 7.26 (m, 1, ArH), 7.05 (dd, 1, ArH, J = 3.0 and 9.0 Hz), 5.27 (s, 2, CH_2); CIMS 231 (MH^+). Anal. ($C_{14}H_{11}FO_2$) C, H.

General Procedure for the Preparation of Methyl Indole-2-carboxylates 10a−c.[15,16] Dry methanol (85 mL) and sodium (0.19 mol) were added to a three-neck flask equipped with mechanical stirrer, dropping funnel, low-temperature thermometer, and nitrogen line. The resulting solution was cooled in a dry ice/CH_3CN bath to −20 °C. A solution of the appropriate benzaldehyde (0.041 mol) and methyl azidoacetate[15] (0.19 mol) in dry MeOH (42 mL) was added dropwise over 30 min. The mixture was allowed to stir for an additional 2−3 h at −8 °C. The heterogeneous mixture was then poured over ice, allowed to warm to 5−10 °C, filtered, and the precipitate was washed on the funnel with water. The yellow solid was dried briefly on the funnel with suction and collected to provide the azidocinnamate. The solid was immediately dissolved in xylenes (200 mL) and the solution was washed twice with brine, followed by drying over $MgSO_4$. The resulting solution was added dropwise to a flask of xylenes (450 mL) at reflux and the solution was held at reflux until TLC indicated the reaction was complete (3−6 h). The mixture was then cooled in a ice/NaCl bath and the resulting precipitate was collected by filtration to afford the respective methyl indole-2-carboxylate, which was purified by column chromatography with CH_2Cl_2 as eluent.

Methyl 4-Benzyloxy-6-fluoroindole-2-carboxylate (10a). This compound was obtained from **14a** as a white solid in 54% yield: mp 228−229 °C; ^{1}H NMR (DMSO-d_6) δ 12.04 (br s, 1, NH), 7.42 (m, 5, benzyl-ArH), 7.12 (s, 1, ArH-3), 6.74 (d, 1, ArH, J = 9.0 Hz), 6.61 (d, 1, ArH, J = 9.0 Hz), 5.24 (s, 2, CH_2), 3.81 (s, 3, $COOCH_3$); CIMS 300 (MH^+). Anal. ($C_{17}H_{14}FNO_3$) C, H, N.

Methyl 4-Benzyloxy-7-fluoroindole-2-carboxylate (10b). This compound was obtained from **14b** as a white solid in 43% yield: mp 179 °C; ^{1}H NMR (DMSO-d_6) δ 12.48 (br s, 1, NH), 7.42 (m, 5, benzyl-ArH), 7.19 (d, 1, ArH, J = 3.0 Hz), 6.99 (dd, 1, ArH, J = 6.0 and 12 Hz), 6.54 (dd, 1, ArH, J = 3.0 and 9.0 Hz), 5.20 (s, 2, CH_2), 3.75 (s, 3, $COOCH_3$); CIMS 300 (MH^+). Anal. ($C_{17}H_{14}FNO_3$) C, H, N.

Methyl 6-Fluoroindole-2-carboxylate (10c). This compound was obtained as a white solid in 48% yield from 4-fluorobenzaldehyde: mp 156 °C; ^{1}H NMR δ 8.96 (br s, 1 NH), 7.64 (m, 1, ArH-5), 7.23 (s, 1, ArH-3), 7.10 (d, 1, ArH-4, J = 9.4 Hz), 6.95 (t, 1, ArH-7, J = 8.5 Hz), 3.98 (s, 3, $COOCH_3$); CIMS 194 (MH^+). Anal. ($C_{10}H_8FNO_2$) C, H, N.

General Procedure for the Preparation of Indole-2-carboxylic Acids 11a−c. The appropriate indole-2-carboxylate (4.87 mmol) was added to a solution of aqueous 2 N NaOH (100 mL). The suspension was stirred at 80−90 °C until solution and was then held at reflux 1−2 h. The solution was cooled and acidified with aqueous 3 N HCl, the resulting precipitate was collected by filtration, washed on the filter with water, and dried under vacuum to provide the indole-2-carboxylic acid.

4-Benzyloxy-6-fluoroindole-2-carboxylic Acid (11a). This compound was obtained in 97% yield as a white solid: mp 218−220 °C dec; ^{1}H NMR (DMSO-d_6) δ12.88 (br s, 1, COOH), 11.87 (br s, 1, NH), 7.40 (m, 5, benzyl-ArH), 7.24 (s, 1, ArH-3), 6.73 (d, 1, ArH, J = 9.0 Hz), 6.58 (d, 1, ArH, J = 12 Hz), 5.24 (s, 2, CH_2); CIMS 286 (MH^+). Anal. ($C_{16}H_{12}FNO_3$) C, H, N.

4-Benzyloxy-7-fluoroindole-2-carboxylic Acid (11b). This compound was obtained in 94% yield as a white solid: mp 193 °C; ^{1}H NMR (DMSO-d_6) δ 13.02 (br s, 1, COOH), 12.28 (br s, 1, NH), 7.41 (m, 5, benzyl-ArH), 7.12 (t, 1, ArH, J = 3.0 Hz), 6.95 (dd, 1, ArH, J = 12 and 12 Hz), 6.52 (dd, 1, ArH, J = 3.0 and 9.0 Hz), 5.20 (s, 2, CH_2); CIMS 286 (MH^+). Anal. ($C_{16}H_{12}FNO_3$) C, H, N.

6-Fluoroindole-2-carboxylic Acid (11c). This compound was obtained in 88% yield as a white solid: mp 244 °C (lit.[47] mp 246 °C); ^{1}H NMR (DMSO-d_6) δ 12.10 (br s, 1, COOH), 10.98 (br s, 1, NH), 6.81 (dd, 1, ArH), J = 5.6 and 8.9 Hz), 6.28 (m, 2, ArH), 6.09 (td, 1, ArH, J = 9.6 and 1.8 Hz); CIMS 179 (MH^+).

General Procedure for the Preparation of Fluorinated Indoles 12a−c. The appropriate indole-2-carboxylic acid (40.5 mmol), copper powder (4 equiv, 162 mmol) and *N*-methylpyrrolidinone (500 mL) were heated at reflux (240−250 °C). A continuous stream of nitrogen or argon was bubbled slowly through the reaction mixture via a metal tube, while maintaining reflux for 6 h. The mixture was cooled, filtered through Celite, and the filter cake was washed with ether. The filtrate and ether washings were combined, diluted with water (1.8 L), and extracted four times with ether. The organic extract was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by column chromatography over silica gel with CH_2Cl_2 as eluent to give the respective fluoroindole.

4-Benzyloxy-6-fluoroindole (12a). This compound was obtained as a white solid in 81% yield: mp 83−84 °C; ^{1}H NMR δ 8.12 (br s, 1, NH), 7.42 (m, 5, benzyl-ArH), 7.08 (t, 1, ArH, J = 3.0 Hz), 6.73 (d, 1, ArH, J = 9.0 Hz), 6.68 (t, 1, ArH, J = 3.0 Hz), 6.41 (d, 1, ArH, J = 12 Hz), 5.20 (s, 2, CH_2); CIMS 242 (MH^+). Anal. ($C_{15}H_{12}FNO_3$) C, H, N.

4-Benzyloxy-7-fluoroindole (12b). This material was obtained as a white solid in 83% yield: mp 58 °C; ^{1}H NMR δ 8.30 (br s, 1, NH), 7.42 (m, 5, benzyl-ArH), 7.16 (t, 1, ArH, J = 2.0 Hz), 6.77 (m, 2, ArH), 6.43 (dd, 1, ArH, J = 3.0 and 9.0 Hz), 5.20 (s, 2, CH_2); CIMS 242 (MH^+). Anal. ($C_{14}H_{12}FNO$) C, H, N.

6-Fluoroindole (12c).[14] This compound was obtained as colorless needles in 89% yield: mp 64.5 °C (lit.[14] mp 75−76 °C); ^{1}H NMR δ 8.15 (br s, 1, NH), 7.55 (dd, 1, ArH, J = 5.5 and 9.2 Hz), 7.19 (t, 1, ArH, J = 2.8), 7.08 (dd 1, ArH, J = 9.2 and 2.8 Hz), 6.89 (td, 1, ArH, J = 2.8 and 5.5), 6.54 (d, 1, ArH, J = 2.8 Hz); CIMS 136 (MH^+).

6-Fluoroindol-3-ylglyoxalyl Chloride (13c).[14] A solution of oxalyl chloride (1.6 mL, 18.4 mmol) in anhydrous ether (20 mL) was added dropwise over 15 min to a 0 °C solution of **17c** (1.91 g, 14.1 mmol) in anhydrous ether (50 mL). After stirring at room temperature for 5 h, the reaction mixture was filtered and the precipitate was washed on the filter with cold ether. The filtrate was concentrated to precipitate additional glyoxyl chloride, which was also removed by filtration and washed with cold ether. The combined crude 6-fluoro-3-indoleglyoxalyl chloride (**13c**) was obtained as an orange solid (2.95 g) that was used in the next step without further purification.

***N,N*-Diethyl-6-fluoroindol-3-ylglyoxalylamide (14c).**[14] A solution of diethylamine (2.60 mL, 24.9 mmol) in anhydrous ether (20 mL) was added dropwise to a suspension of crude **13c** (1.91 g, 14.1 mmol) in anhydrous ether (100 mL) in a three-neck flask equipped with mechanical stirrer, condenser, and dropping funnel. The crude product was collected by flitration and was washed on the filter with water, and dried under vacuum to provide **19c** as a white solid (2.06 g, 55.4%). An analytical sample was recrystallized from acetone to give colorless crystals: mp 178 °C (lit.[14] mp 189 °C); ^{1}H NMR (acetone-d_6) δ 11.30 (br s, 1, NH), 8.23 (dd, ArH, J = 5.8 and 8.6 Hz), 8.07 (s, 1, ArH-2), 7.31 (dd, 1, ArH, J = 2.3 and 10 Hz), 7.09 (td, 1, ArH, J = 8.7 and 2.3 Hz), 3.50 (q, 2, CH_2, J = 7.8 Hz), 3.35 (q, 2, CH_2, J = 7.8 Hz), 1.21 (t, 3, CH_3, J = 7.8 Hz), 1.15 (t, 3, CH_3, J = 7.8 Hz); CIMS 263 (MH^+).

General Procedure for the Preparation of *N,N*-Dimethylindol-3-ylglyoxalylamides 14a,b.[20] A solution of oxalyl chloride (18.4 mmol) in anhydrous ether (20 mL) was added dropwise over 15 min to a 0 °C solution of the appropriate indole (14.1 mmol) in anhydrous ether (50 mL). The reaction solution was stirred at room temperature for 5 h. In the same reaction flask, fitted with a dry ice/acetone condenser, gas inlet, and mechanical stirrer, dimethylamine gas was bubbled in until the reaction mixture had turned from yellow to white (pH = 8−9 on moist pH paper). The solid that formed was filtered, washed with water, and recrystallized from acetone to provide the respective *N,N*-dimethylindol-3-ylglyoxalylamide.

***N,N*-Dimethyl-4-benzyloxy-6-fluoroindol-3-ylglyoxalylamide (14a).** This compound was obtained in 68% yield from 4-benzyloxy-6-fluoroindole (**17a**) as colorless crystals: mp 222 °C; ^{1}H NMR (acetone-d_6) δ 12.75 (s, 1, NH), 8.03 (s, 1, ArH), 7.47 (m, 5, benzyl-ArH), 6.87 (d, 1, ArH, J = 9.0 Hz), 6.59 (d, 1, ArH, J = 12 Hz), 5.33 (s, 2, CH_2), 2.98 (s, 3, CH_3), 2.93 (s, 3, CH_3); CIMS 341 (MH^+). Anal. ($C_{19}H_{17}FN_2O_3$) C, H, N.

***N,N*-Dimethyl-4-benzyloxy-7-fluoroindol-3-ylglyoxalylamide (14b).** This compound was obtained from **17b** in 38% yield as colorless crystals: mp 211 °C; ^{1}H NMR (DMSO-d_6) δ 12.80 (br s, 1, NH), 8.09 (s, 1, ArH-2), 7.42 (m, 5, benzyl-ArH), 6.96 (t, 1, ArH, J = 9.0 Hz), 6.58 (dd, 1, ArH, J = 3.3 and 9.0 Hz), 5.22 (s, 2, CH_2), 2.90 (s, 3, CH_3), 2.86 (s, 3, CH_3); CIMS 341 (MH^+). Anal. ($C_{19}H_{17}FN_2O_3$) C, H, N.

General Procedure for the Preparation of *N,N*-Dialkyltryptamines 1b and 15a,b. A solution of the appropriate *N,N*-dialkyl-3-indoleglyoxylamide in dry THF was added dropwise to a slurry of $LiAlH_4$ (5 equiv) in dry THF at reflux. The mixture was held at reflux for 6−51 h until TLC indicated the reaction was complete. The mixture was then cooled, quenched with water, filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was taken up into ether, washed with aqueous 1 N NaOH and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The product was purified either by sublimation or recrystallization from ethyl acetate.

6-Fluoro-*N,N*-diethyltryptamine (1b).[7,14] The reflux time was 6 h. This amine was obtained in 67% yield as a white solid (sublimation): mp 59−60 °C (lit.[7] mp 69−70 °C); ^{1}H NMR δ 8.02 (br s 1, NH), 7.51 (dd, 1, ArH, J = 5.5 and 8.8 Hz), 7.04 (dd, 1, ArH, J = 2.2 and 9.9), 7.01 (d, 1, ArH, J = 2.2, 6.89 (td, 1, ArH, J = 2.2 and 9.9 Hz), 2.91 (m, 2, CH_2), 2.79 (m, 2, CH_2), 2.67 (q, 4, CH_2, J = 6.9), 1.10 (t, 6, CH_3, J = 7.5 Hz); CIMS 235 (MH^+). The fumarate salt was prepared (1:1 base:acid) and recrystallized (EtOH/EtOAc): mp 134 °C; ^{1}H NMR (DMSO-d_6) δ 10.98 (s, 1, NH), 7.54 (dd, 1, ArH, J = 6.0 and 9.0 Hz), 7.21 (d, 1, ArH, J = 3.0 Hz), 7.10 (dd, 1, ArH, J = 3.0 and 9.0 Hz), 6.84 (td, 1, ArH, J = 3.0 and 12 Hz), 6.51 (s, 2, fumarate-H), 2.93 (m, 8, CH_2), 1.11 (t, 6, CH_3, J = 9.0 Hz); CIMS 235 (MH^+). Anal. ($C_{18}H_{23}FN_2O_4$) C, H, N.

4-Benzyloxy-6-fluoro-*N,N*-dimethyltryptamine (15a). The reflux time was 49 h. This tryptamine was obtained in 87% yield as a white solid (recrystallized from EtOAc): mp 131 °C; ^{1}H NMR (CD_3OD) δ 7.41 (m, 5, benzyl-ArH), 6.87 (s, 1, ArH-2), 6.63 (dd, 1, ArH-5, J = 2.1 and 9.0 Hz), 6.39 (dd, 1, ArH-7, J = 3.0 and 12 Hz), 3.10 (s, 2, CH_2), 2.95 (m, 2, CH_2), 2.60 (m, 2, CH_2), 2.10 (s, 6, CH_3); CIMS 313 (MH^+). Anal. ($C_{19}H_{21}FN_2O$) C, H, N.

4-Benzyloxy-7-fluoro-*N,N*-dimethyltryptamine (15b). The reflux time was 51 h. This tryptamine was obtained in 88% yield as a white solid (recrystallized from EtOAc): mp 155 °C; ^{1}H NMR δ 8.25 (br s, 1, NH), 7.39 (m, 5, benzyl-ArH), 6.92 (d, 1, ArH-2, J = 1.7 Hz), 6.72 (dd, 1, ArH, J = 9.0 and 11 Hz), 6.36 (dd, 1, ArH, J = 8.5 and 3.1 Hz), 5.15 (s, 2, CH_2), 3.03 (t, 2, CH_2, J = 7.5 Hz), 2.58 (t, 2, CH_2, J = 7.6 Hz), 2.15 (s, 6, CH_3); CIMS 313 (MH^+). Anal. ($C_{19}H_{21}FN_2O$) C, H, N.

General Procedure for the Preparation of Fluorinated Analogues of Psilocin (3 and 4). The appropriate benzyloxytryptamine (3.20 mmol) was hydrogenated at 50 psig in 95% EtOH (250 mL) over 10% Pd/C (340 mg) for 4 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to give a solid which was purified by sublimation to afford the respective hydroxytryptamine.

6-Fluoro-4-hydroxy-*N,N*-dimethyltryptamine (3). This compound was obtained in quantitative yield as a white solid: mp 178 °C dec; ^{1}H NMR (CD_3OD) δ 6.83 (s, 1, ArH), 6.46 (dd, 1, ArH, J = 3.0 and 9.0 Hz), 6.10 (dd, 1, ArH, J = 3.0 and 12 Hz), 2.98 (t, 2, CH_2, J = 6.0 Hz), 2.75 (t, 2, CH_2, J = 6.0 Hz), 2.37 (s, 6, CH_3); CIMS 223 (MH^+). Anal. ($C_{12}H_{15}FN_2O$) C, H, N. The fumarate salt was prepared (2:1 base:acid) and recrystallized (EtOH/EtOAc): mp 226 °C dec; ^{1}H NMR (DMSO-d_6) δ 10.69 (br s, 2, NH), 6.92 (d, 2, ArH, J = 2.0 Hz), 6.49 (dd, 2, ArH, J = 2.0 and 10 Hz), 6.50 (s, 2, fumarate-H), 6.13 (dd, 2, ArH, J = 3.0 and 12 Hz), 2.89 (t, 4, CH_2, J = 6.0 Hz), 2.70 (t, 4, CH_2, J = 6.0 Hz), 2.34 (s, 12, CH_3); CIMS 223 (MH^+). Anal. ($C_{28}H_{34}F_2N_4O_6$) C, H, N.

7-Fluoro-4-hydroxy-*N,N*-dimethyltryptamine (4). This compound was obtained in 98% yield as a white solid: mp 170 °C dec; ^{1}H NMR δ 8.03 (br s, 1, NH), 6.88 (d, 1, ArH-2, J = 2.0 Hz), 6.75 (dd, 1, ArH, J = 8.4 and 10 Hz), 6.40 (dd, 1, ArH, J = 3.7 and 8.5 Hz), 2.94 (m, 2, CH_2), 2.69 (m, 2, CH_2), 2.38 (s, 6, CH_3); CIMS 223 (MH^+). Anal. ($C_{12}H_{15}FN_2O$) C, H, N. The fumarate salt was prepared (2:1 base:acid) and recrystallized (EtOH/EtOAc): mp 220 °C dec; ^{1}H NMR (DMSO-d_6) δ 11.09 (br s, 2, NH), 7.02 (d, 2, ArH, J = 1.9 Hz), 6.62 (dd, 2, ArH, J = 8.3 and 11 Hz), 6.49 (s, 2, fumarate-H), 6.16 (dd, 2, ArH, J = 3.4 and 8.0 Hz), 1.85 (t, 4, CH_2, J = 7.0 Hz), 2.75 (t, 4, CH_2, J = 7.0 Hz), 2.37 (s, 12, CH_3); CIMS 223 (MH^+). Anal. ($C_{28}H_{34}F_2N_4O_6$) C, H, N.

2-Fluoro-4-nitroanisole (17). Nitric acid (2.6 mL) was added to a stirred mixture of 2-fluoroanisole[48] (5.01 g, 39.7 mmol), sulfuric acid (96%, 675 mL) and water (250 mL) at 0 °C. A solution of sodium nitrite (2.71 g, 39.2 mmol) in water (50 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 3 h, then diluted with 3000 mL of water and placed in the refrigerator overnight. The precipitate that formed (containing the ortho-nitrated product **18** in less than 1% yield as detected by ^{1}H NMR) was collected by filtration and purified by column chromatography over silica gel with CH_2Cl_2 as eluent to obtain pure **23** in 66% yield (4.08 g) as a white solid: mp 95−96 °C (lit.[48] mp 104−104.5 °C); ^{1}H NMR δ 8.08 (m, 1, ArH), 7.99 (dd, 1, ArH, J = 11 and 2.7 Hz), 7.04 (t, 1, ArH, J = 8.6 Hz), 4.01 (s, 3, OCH_3); CIMS 172 (MH^+).

3-Fluoro-4-methoxyaniline (19). A solution of **17** (9.20 g, 53.8 mmol) in 95% ethanol (200 mL) was hydrogenated at 45 psig for 16 h over 10% Pd/C (1.50 g). The catalyst was removed by filtration, washed with ethanol, and the filtrate was evaporated under reduced pressure to provide **19** (7.52 g, 99%) as a solid: mp 75 °C (lit.[49] mp 83−83.5 °C); ^{1}H NMR δ 6.80 (t, 1, ArH, J = 9.0 Hz), 6.49 (dd, 1, ArH, J = 13 and 2.6 Hz), 6.39 (m, 1, ArH), 3.82 (s, 3, OCH_3), 3.50 (br s, 2, NH_2); CIMS 142 (MH^+).

3-Fluoro-4-methoxyphenylhydrazine Hydrochloride (20). A solution of sodium nitrite (2.58 g, 37.4 mmol) in water (8 mL) was added dropwise to a solution of 2-fluoro-4-methoxyaniline (**19**) (5.28 g, 37.4 mmol) in aqueous 2.35 N HCl at 0 °C. The solution was stirred for 10 min and then slowly added dropwise to a rapidly stirred mixture of $SnCl_2 \cdot 2H_2O$ (33.74 g, 149.5 mmol) in concentrated HCl (140 mL) at 0 °C. The reaction was allowed to warm to room temperature, stirred for 15 min, and filtered. The collected precipitate was washed on the filter with several large portions of ether and dried under vacuum to give **20** (4.73 g, 66%), which was used in the next step without further purification: mp > 100 °C dec; ^{1}H NMR (DMSO-d_6) δ 10.20 (br s, 3, NH_3+), 8.15 (br s, 1, NH), 7.10 (t, 1, ArH, J = 9.2 Hz), 6.97 (dd, 1, ArH, J = 13 and 2.6 Hz), 6.97 (m, 1, ArH), 3.80 (s, 3, OCH_3).

6-Fluoro- and 4-Fluoro-5-methoxy-*N,N*-dimethyltryptamine (5 and 6). To a heated (80 °C) solution of hydrazine **20** (530 mg, 2.75 mmol) in 24% aqueous acetic acid (40 mL) was added 4-(*N,N*-dimethylamino)butanal dimethylacetal[21] (710 mg, 4.40 mmol) and the reaction was stirred at 85 °C for 28 h. After cooling, the solution was basified to pH 10−11 with concentrated ammonium hydroxide and was then extracted with ether (3 × 30 mL). The organic extract was dried (Na_2SO_4), evaporated under reduced pressure, and the residue was purified by centrifugal radial chromatography (chromatotron, Harrison Research, Palo Alto, CA), on a 4-mm silica gel plate, eluting with 5% MeOH/CH_2Cl_2 under an atmosphere of nitrogen and ammonia to afford 6-fluoro-5-methoxy-*N,N*-dimethyltryptamine (**5**) (318 mg, 49%): mp 73 °C; ^{1}H NMR δ 7.99 (br s, 1, NH), 7.09 (m, 2, ArH), 6.98 (s, 1, ArH), 3.93 (s, 3, OCH_3), 2.90 (t, 2, CH_2, J = 9.0 Hz), 2.62 (t, 2, CH_2, J = 9.0 Hz), 2.38 (s, 6, NCH_3); CIMS 237 (MH^+). Anal. ($C_{13}H_{17}FN_2O$) C, H, N. Characterized as the fumarate salt (2:1 base:acid) and recrystallized (EtOH/EtOAc): mp 208 °C; ^{1}H NMR

(DMSO-d_6) δ 10.73 (br s, 2, NH), 7.15 (m, 6, ArH), 6.50 (s, 2, fumarate-H), 3.83 (s, 6, OCH_3), 2.85 (m, 4, CH_2), 2.75 (m, 4, CH_2), 2.40 (s, 12, NCH_3); CIMS 237 (MH^+). Anal. ($C_{30}H_{38}F_2N_4O_6$) C, H, N.

Continued elution afforded 4-fluoro-5-methoxy-*N*,*N*-dimethyltryptamine (**6**) (45 mg, 7.0%): mp 75 °C; ^{1}H NMR δ 7.94 (br s, 1, NH), 6.96 (m, 3, ArH), 3.93 (s, 3, OCH_3), 3.02 (t, 2, CH_2, J = 9.0 Hz), 2.67 (t, 2, CH_2, J = 9.0 Hz), 2.37 (s, 6, NCH_3). Also characterized as the fumarate salt (2:1 base:acid): mp 185 °C; ^{1}H NMR (DMSO-d_6) δ 10.89 (br s, 2, NH), 7.13 (d, 2, ArH, J = 2.1 Hz), 7.06 (d, 2, ArH, J = 8.7 Hz), 6.93 (t, 2, ArH, J = 8.4 Hz), 6.50 (s, 2, fumarate-H) 3.80 (s, 6, OCH_3), 2.90 (t, 4, CH_2, J = 7.8 Hz), 2.65 (t, 4, CH_2, J = 7.8 Hz), 2.30 (s, 12, NCH_3); CIMS 237 (MH^+). Anal. ($C_{30}H_{38}F_2N_4O_6$) C, H, N.

Pharmacology Methods. 1. Drug Discrimination Studies. Male Sprague−Dawley rats (Harlan Laboratories, Indianapolis, IN) weighing 200−220 g at the beginning of the drug discrimination study were divided into groups and trained to discriminate LSD tartrate (n = 18), DOI hydrochloride (n = 12), or the 5-HT_{1A} agonist LY 293284[50] (n = 14) from saline. None of the rats had previously received drugs or behavioral training. Water was freely available in the individual home cages and a rationed amount of supplemental feed (Purina Lab Blox) was made available after experimental sessions so as to maintain approximately 80% of free-feeding weight. Lights were on from 07:00 to 19:00. The laboratory and animal facility temperature was 22−24 °C and the relative humidity was 40−50%. Experiments were performed between 09:00 and 17:00 each day, Monday−Friday.

The animal protocols used in the present experiments were consistent with current NIH principles of animal care and were approved by the Purdue University Animal Care and Use Committee.

Six standard operant chambers (model E10-10RF, Coulbourn Instruments, Lehigh Valley, PA) consisted of modular test cages enclosed within sound-attenuated cubicles with fans for ventilation and background white noise. A white house light was centered near the top of the front panel of the cage, which was also equipped with two response levers, separated by a food hopper (combination dipper pellet trough, model E14-06, module size 1/2), all positioned 2.5 cm above the floor. Solid state logic in an adjacent room, interfaced through a Med Associates (Lafayette, IN) interface to a PC microcomputer, controlled reinforcement and data acquisition with a locally written program.

A fixed ratio (FR) 50 schedule of food reinforcement (Noyes 45 mg dustless pellets) in a two-lever paradigm was used. The drug discrimination procedure details have been described elsewhere.[26−30,35] Training sessions lasted 15 min and were conducted at the same time each day. Levers were cleaned between animals with 10% ethanol solution to avoid olfactory cues.[51] Animals were trained to an FR50 until an accuracy of at least 85% (number of correct presses × 100/number of total presses) was attained for 8 of 10 consecutive sessions (approximately 40−60 sessions). Once criterion performance was attained, test sessions were interspersed between training sessions, either one or two times per week. At least one drug and one saline session separated each test session. Rats were required to maintain the 85% correct responding criterion on training days in order to be tested. In addition, test data were discarded when the accuracy criterion of 85% was not achieved on the two training sessions following a test session. Test drugs were administered ip 30 min prior to the sessions; test sessions were run under conditions of extinction, with rats removed from the operant chamber when 50 presses were emitted on one lever. A minimum of three different doses were used for each tested compound, and a least eight rats were tested at each dose. If 50 presses on one lever were not completed within 5 min, the session was ended and scored as a disruption. Treatments were randomized at the beginning of the study.

The training drugs, dosages, and sources used in the drug discrimination studies were as follows: (+)-lysergic acid diethylamide tartrate (LSD; 0.08 mg/kg, 186 nmol/kg; NIDA), 2,5-dimethoxy-4-iodoamphetamine (DOI; 0.4 mg/kg, 1.12 μmol/kg; synthesized in our laboratory), and LY 293284 (0.025 mg/kg, 75 nmol/kg; a generous gift of the Eli Lilly Laboratories, Indianapolis, IN). All training drugs were dissolved in 0.9% saline and were injected ip in a volume of 1 mL/kg, 15 or 30 min before the session. Because many tryptamines have a short half-life, if a tested compound did not produce a minimum of 59% generalization when administered 30 min before test sessions, it was tested again using a 15-min preinjection time.

2. Data Analysis. Data from the drug discrimination study were scored in a quantal fashion, with the lever on which the rat first emitted 50 presses in a test session scored as the "selected" lever. The percentage of rats selecting the drug lever (%SDL) for each dose of test compound was determined. The degree of substitution was determined by the maximum %SDL for all doses of the test drug. "No substitution" is defined as 59% SDL or less, and "partial" substitution is 60−79% SDL. If the drug was one that completely substituted for the training drug (at least one dose resulted in a %SDL = 80% or higher) the method of Litchfield and Wilcoxon[52] was used to determine the ED_{50} and 95% confidence interval (95% CI). If the percentage of rats disrupted (%D) was 50% or higher, the ED_{50} value was not determined, even if the %SDL of nondisrupted animals was higher than 80%.

3. Radioligand Competition Assays. Radioligands [^{3}H]8-OH-DPAT (124 Ci/mmol) and [^{125}I]DOI (2200 Ci/mmol) were purchased from New England Nuclear (Boston, MA). Mianserin was purchased from Sigma Chemical Corp. (St. Louis, MO), and serotonin creatinine sulfate and cinanserin were purchased from Research Biochemicals Inc. (Natick, MA).

NIH3T3 fibroblast cells expressing either the rat 5-HT_{2A} or 5-HT_{2C} receptor were a generous gift of Dr. David Julius. CHO cells stably transfected with the human 5-HT_{1A} receptor were a gift from Pharmacia & Upjohn, Inc., Kalamazoo, MI.

Cells were maintained in minimum essential medium containing 10% dialyzed fetal bovine serum (Gibco-BRL, Grand Island, NY) and supplemented with L-glutamine (1%), Pen/Strep (1%), and either Geneticin (157 units; NIH3T3 cells) or Hygromycin B (45 units; CHO cells). The cells were cultured at 37 °C in a humidified atmosphere of 95% air and 5% CO_2. Confluent cell monolayers were washed with sterile filtered phosphate-buffered saline and incubated in serum free Opti-MEM (Gibco-BRL, Grand Island, NY) for 5 h. After this incubation, the cells were harvested by centrifugation (15000g, 20 min) and placed immediately in a −80 °C freezer until the assays were performed.

For saturation binding assays, 0.25−12 nM [^{3}H]8-OH-DPAT (for 5-HT_{1A}) or 0.125−5.0 nM [^{125}I]DOI (for 5-$HT_{2A/2C}$) was used. The total volume of the assay was 250 μL. Nonspecific binding was defined as the binding measured in the presence of 10 μM cinanserin (5-HT_{2A} cells), 10 μM mianserin (5-HT_{2C} cells), or 10 μM serotonin (5-HT_{1A} cells). Competition experiments were carried out in a total volume of 500 μL with either 0.80 nM [^{3}H]8-OH-DPAT or 0.20 nM [^{125}I]DOI. Previously harvested cells were resuspended and added to each well containing assay buffer (50 mM Tris, 0.5 mM EDTA, 10 mM $MgCl_2$, pH 7.4), radioligand, and test compound (or in the case of the saturation isotherm assays, cinanserin, mianserin, or serotonin). The incubation was carried out at 25 °C for 60 min and then terminated by rapid filtration through GF/B unifilters that had been pretreated with 0.3% polyethylenimine for 30 min, using a prechilled Packard 96-well harvester (Packard Instrument Corp.). The filters were washed using chilled buffer (10 mM Tris, 154 mM NaCl, pH 7.4) and dried overnight. The following day, Microscint-O (Packard Instrument Corp.) was added and radioactivity was determined using a TopCount (Packard) scintillation counter. Data analysis was performed by nonlinear regression using the program GraphPad Prism (GraphPad Software, San Diego, CA) to analyze the saturation and competition binding curves. K_i values were calculated using the Cheng−Prusoff equation. Each assay was run in duplicate with 10 drug concentrations and assays were repeated 3−5 times (n = 3−5).

4. Phosphoinositol Hydrolysis Studies. Accumulation of inositol phosphates was determined using a modified version of a previously published protocol.[53] [^{3}H]*myo*-Inositol (22.3 Ci/mmol) was purchased from New England Nuclear. Briefly, confluent cells in 48-well cluster plates were labeled for 18−20 h in CRML-1066 medium (Gibco-BRL, Grand Island, NY) containing 1.0 μCi/mL [^{3}H]*myo*-inositol. After pretreating the cells with 10 μM pargyline and 10 mM LiCl for 15 min, agonists were added to the cells for 30 min at 37 °C and placed back into the incubator. The assay was terminated by aspirating the medium and adding 300 μL of 10 mM formic acid. After incubation for 16 h at 4 °C, the [^{3}H]inositol phosphates were separated from the cellular debris on Dowex-1 ion-exchange columns and eluted with 1.0 M ammonium formate and 0.10 M formic acid. The vials were counted using a TriCarb scintillation counter (Packard Instrument Corp.). All assays were repeated 3−4 times.

5. Inhibition of Forskolin-Stimulated cAMP Production. CHO h5-HT$_{1A}$ cells were grown to confluence in 48-well cluster plates. Cells were preincubated for 10 min in 200 μL of assay buffer (EBSS containing 0.02% ascorbic acid and 2% bovine calf serum). Following incubation cells were placed on ice and drugs were added. Cyclic AMP accumulation was determined using 50 μM forskolin in the absence or presence of increasing concentrations of 5-HT$_{1A}$ receptor agonists. Incubations were carried out for 15 min at 37 °C and the medium was decanted. The cells were lysed with ice cold 3% TCA and stored at 4 °C until assay.

Cyclic AMP was quantified using a competitive binding assay as described by Watts and Neve[54] with minor modifications. Duplicate samples of the cell lysate (15 μL) were added to reaction tubes containing cyclic AMP assay buffer (100 mM Tris/HCl, pH 7.4, 100 mM NaCl, 5 mM EDTA). [^{3}H]Cyclic AMP (2 nM final concentration) was added to each well. Binding protein (ca. 150 μg in 200 μL of cyclic AMP buffer) was then added to each well. The reaction tubes were incubated on ice for 2 h. The tubes were then harvested as described for the radioreceptor binding assays. Cyclic AMP concentrations from each sample were estimated in duplicate from a standard curve ranging from 0.1 to 300 pmol cyclic AMP/tube. Assays were repeated 3−4 times.

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