2-Substituted Tryptamines: Agents with Selectivity for 5-HT$_6$ Serotonin Receptors[||]

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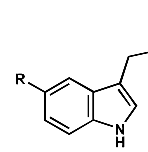
Several 2-alkyl-5-methoxytryptamine analogues were designed and prepared as potential 5-HT$_6$ serotonin agonists. It was found that 5-HT$_6$ receptors accommodate small alkyl substituents at the indole 2-position and that the resulting compounds can bind with affinities comparable to that of serotonin. In particular, 2-ethyl-5-methoxy-*N*,*N*-dimethyltryptamine (**8**) binds with high affinity at human 5-HT$_6$ receptors (K_i = 16 nM) relative to 5-HT (K_i = 75 nM) and was a full agonist, at least as potent (**8:** K_{act} = 3.6 nM) as serotonin (K_{act} = 5.0 nM), in activating adenylate cyclase. Compound **8** displays modest affinity for several other populations of 5-HT receptors, notably h5-HT$_{1A}$ (K_i = 170 nM), h5-HT$_{1D}$ (K_i = 290 nM), and h5-HT$_7$ (K_i = 300 nM) receptors, but is otherwise quite selective. Compound **8** represents the first and most selective 5-HT$_6$ agonist reported to date. Replacing the 2-ethyl substituent with a phenyl group results in a compound that retains 5-HT$_6$ receptor affinity (i.e., **10:** K_i = 20 nM) but lacks agonist character. 2-Substituted tryptamines, then, might allow entry to a novel class of 5-HT$_6$ agonists and antagonists.

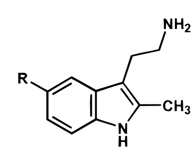
Introduction

Serotonin (5-hydroxytryptamine, 5-HT; **1a**) receptors are classified as belonging to one of several different families: 5-HT$_1$−5-HT$_7$. One of the newest populations identified are the 5-HT$_6$ receptors.[1] 5-HT$_6$ serotonin receptors are members of the G-protein superfamily, are positively coupled to an adenylate cyclase second-messenger system, and are found primarily in the central nervous system.[2] The exact clinical significance of 5-HT$_6$ receptors is unknown at this time. Of interest, however, is that a number of typical and atypical antipsychotic agents and tricyclic antidepressants bind with high affinity at 5-HT$_6$ receptors (i.e., with K_i values of <100 nM).[3−5] In rats prevented from expressing 5-HT$_6$ receptors, the animals behave in a manner that seems to involve an increase in cholinergic function; this has led to speculation that one of the roles of 5-HT$_6$ receptors may be to control cholinergic neurotransmission and that 5-HT$_6$-selective antagonists could be useful in the treatment of anxiety and memory deficits.[6,7] It has been further suggested that GABA-containing neurons in the striatum and glutamate-containing neurons in the hippocampus could be targets of 5-HT actions mediated by 5-HT$_6$ receptors.[8] 5-HT$_6$ ligands might thus be of value in the treatment of anxiety and related disorders. Other studies suggest that 5-HT$_6$ receptors might be involved in motor function, mood-dependent behavior, and early growth processes involving serotonin.[9−11]

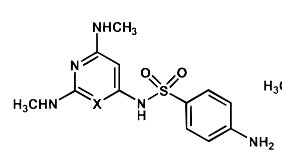
Ro 04-6790 (**2a**) and Ro 63-0563 (**2b**) represent the first 5-HT$_6$-selective antagonists.[12] Several related structures have also been reported including SB-271046 (**3**, R = H).[13] Repeated intracerebroventricular administration of antisense oligonucleotides to rats to prevent expression of 5-HT$_6$ receptors produces a behavioral syndrome that consists of yawning, stretching, and chewing;[6,7] administration of Ro 04-6790 and Ro 63-0563 to naive animals produced a similar effect.[12] [^{3}H]Ro 63-0563 has been developed as a radioligand for binding studies.[12b]



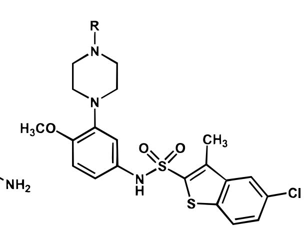
1a R = -OH
1b R = -OCH$_3$
1c R = -H



4 R = -OH
5 R = -OCH$_3$



2a X = N
2b X = CH



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No 5-HT$_6$ -selective agonists have yet been identified. Various indolealkylamines, including the tryptamines

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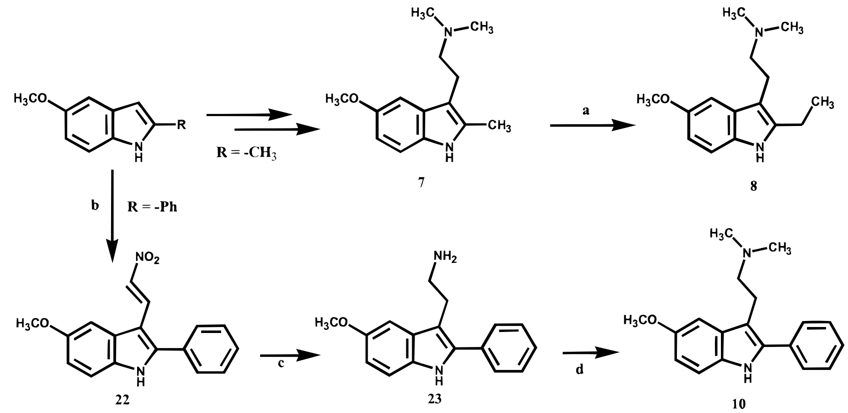
Scheme 1[a]



[a] (a) i. *n*BuLi, THF, −78 °C, ii. CO_2, iii. *t*BuLi, THF, −78 °C, iv. MeI; (b) Me_2N-CH_2CH_2-NO_2, CF_3COOH; (c) $LiAlH_4$, THF, Δ; (d) $NaBH_3CN$, 37% CH_2O, MeCN, HOAc.

5-HT (**1a**) and 5-methoxytryptamine (**1b**), and ergolines, such as (+)lysergic acid diethylamide (LSD) and lisuride, bind with high affinity. In fact, [^{125}I]iodo-LSD and [^{3}H]LSD have been used to label 5-HT_6 receptors. The purpose of our present study was to identify potential agonists with enhanced selectivity for 5-HT_6 receptors that might be useful for investigating this population of receptors and receptor function.

5-HT and 5-methoxytryptamine have been demonstrated to act as 5-HT_6 agonists and produce a potent dose-dependent increase in cAMP levels.[14] Unfortunately, these tryptamines are notoriously nonselective and bind at multiple populations of 5-HT receptors.[15] It has been demonstrated, however, that with appropriate molecular modification tryptamine derivatives can be developed that display enhanced selectivity for different populations of 5-HT receptors.[15]

We began our investigation by exploring the structure−affinity relationships for the binding of tryptamines at 5-HT_6 receptors.[16] We found that O-methylation of 5-HT (**1a:** K_i = 75 nM) to 5-methoxytryptamine (**1b:** K_i = 88 nM) had little effect on affinity and that removal of the hydroxyl group to give tryptamine (**1c:** K_i = 180 nM) only halved affinity.[16] Most other changes led to significant decreases in affinity. For example, lengthening the alkyl chain by one methylene unit, conformational restriction of the side chain as a 1,2,3,4-tetrahydropyrido[3,4-*b*]indole, replacement of the indolic nitrogen atom with an sp^3-hybridized carbon atom, and quaternization of the terminal amine all resulted in a dramatic reduction in affinity (i.e., K_i > 5000 nM). On the other hand, N-monomethylation and N,N-dimethylation resulted in retention or a slight increase in affinity. More importantly, we found that introduction of a 2-methyl substituent was tolerated. That is, 2-methyl 5-HT (**4:** K_i = 46 nM) possessed an affinity at least comparable to that of 5-HT itself. This is particularly noteworthy because, with the exception of 5-HT_3 receptors, 2-methyl substitution is generally thought to reduce the affinity of tryptamines for most populations of 5-HT receptors. Indeed, 2-methyl 5-HT (**4**) is currently considered a 5-HT_3-selective ligand. Interestingly, we have now demonstrated that 2-methyl 5-HT binds at 5-HT_6 receptors (K_i = 46 nM) with much higher affinity than it displays for 5-HT_3 receptors (K_i = 1200 nM).[16] Given that 2-methylation of 5-HT is tolerated by 5-HT_6 receptors and because 2-methyl 5-HT has been previously considered a 5-HT_3-selective agent, this seemed to be a suitable starting point for the exploration of potentially selective 5-HT_6 agents.

Chemistry

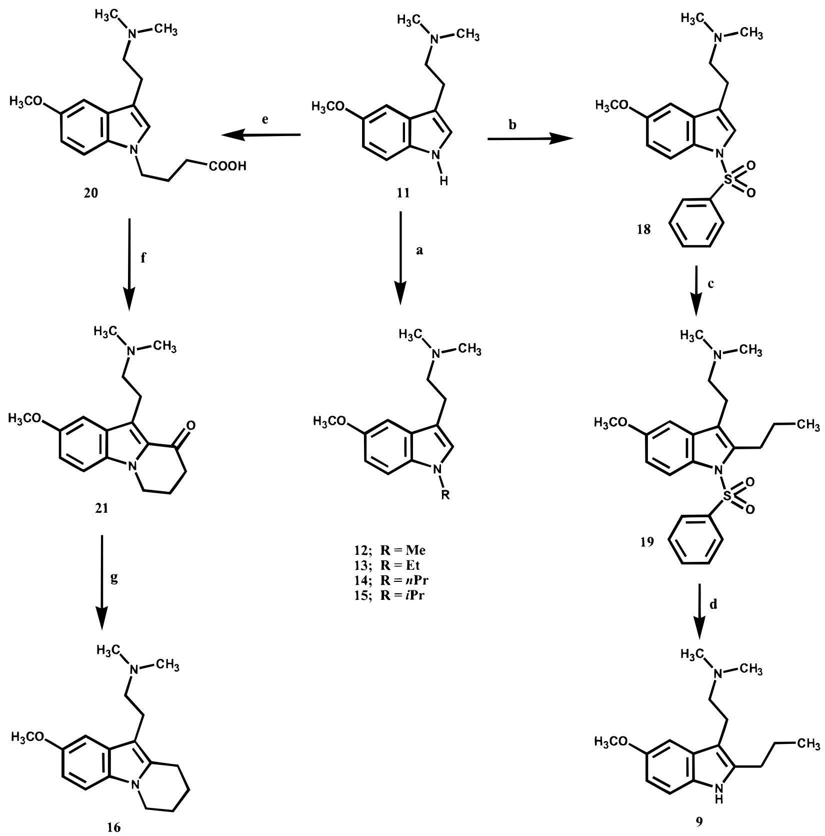
The 2-methyl derivative **7** was prepared via a literature procedure[17] from 2-methylindole using the Speeter−Anthony method, and the 2-ethyl homologue **8** was prepared by treatment of the free base of **7** with *t*BuLi followed by the addition of MeI (Scheme 1). The 2-phenyl derivative **10** was prepared from 5-methoxy-2-phenylindole as shown in Scheme 1. Reaction of 5-methoxy-2-phenylindole with *N*,*N*-dimethylamino-2-nitroethylene afforded the nitrovinyl derivative **22**; compound **22** was reduced to amine **23** using $LiAlH_4$, and the amine was reductively methylated with formaldehyde and sodium cyanoborohydride.

Many of the 5-methoxy-substituted tryptamines were prepared from 5-methoxy-*N*,*N*-dimethyltryptamine (free base of **11**) (Scheme 2). Direct alkylation of **11** (free base) under basic conditions with the appropriate alkyl halide provided the N_1-substituted derivatives **12**−**15**. The procedure is exemplified for compound **15**. The 2-*n*-propyl homologue **9** was also obtained from **11** (Scheme 2). The N_1-position of **11** (free base) was protected with a benzenesulfonyl group, and the resulting compound, **18**, was treated with *n*PrI to give **19**; hydrolysis of the protecting group provided compound **9**. Reaction of the indolyl anion of **11** (free base) with anhydrous γ-butyrolactone afforded the *N*-butyrate **20**. Attempts to cyclize **20** using PPA at 100 °C were unsuccessful and resulted in decomposition; however, substitution of PPE[18] for PPA gave the desired **21,** which was reduced with borane to give the desired **16** (Scheme 2). Compound **17** was synthesized via debenzylation of its known *N*-benzyl derivative.[19]

Results and Discussion

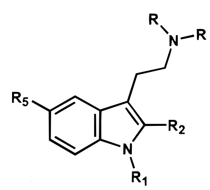
2-Methyl 5-HT (**4**) is currently considered a 5-HT_3-selective ligand; on the other hand, it is known that 5-HT_3 receptors do not readily accommodate a tryptamine 5-methoxy group. For example, 5-methoxytryptamine (**1b**), the *O*-methyl ether of 5-HT (**1a**), is completely devoid of activity at 5-HT_3 receptors.[20] Hence, the first compound that we examined was the simple 2-methyl

Scheme 2[a]



[a] (a) NaH, DMF, rt, and Me_2SO_4, EtBr, *n*PrCl or *i*PrCl; (b) NaH, DMF, $PhSO_2Cl$, rt; (c) BuLi, DME, *n*PrI, −10 °C; (d) Mg, MeOH, rt; (e) γ-butyrolactone; (f) PPE, $CHCl_3$, reflux; (g) B_2H_6/THF, rt.

Table 1. Physicochemical Properties and 5-HT$_6$ Receptor Affinities of Tryptamine Analogues



compd	R	R_5	R_2	R_1	yield (%)	RS[a]	mp (°C)	5-HT$_6$ affinity[b] K_i (nM)	empirical formula[c]
4	H	OH	CH_3	H				46[f]	
5	H	OCH_3	CH_3	H				98	
6	CH_3	H	CH_3	H	88	EtOH−Et_2O	208	300	$C_{13}H_{18}N_2\cdot HCl$
7	CH_3	OCH_3	CH_3	H	92	A	242−245 dec	80	$C_{14}H_{20}N_2O\cdot C_2H_2O_4$
8 (EMDT)	CH_3	OCH_3	C_2H_5	H	16	B−Et_2O	123	52	$C_{15}H_{22}N_2O\cdot C_4H_4O_4$
9	CH_3	OCH_3	nC_3H_7	H	45	A	146−147	185	$C_{16}H_{24}N_2O\cdot C_2H_2O_4$[d]
10	CH_3	OCH_3	C_6H_6	H	25	A	187−188	54	$C_{19}H_{22}N_2O\cdot C_2H_2O_4$
11	CH_3	OCH_3	H	H				78	
12	CH_3	OCH_3	H	CH_3	65	A	181−182	510	$C_{14}H_{20}N_2O\cdot C_2H_2O_4$
13	CH_3	OCH_3	H	C_2H_5	22	A	160−161	240	$C_{15}H_{22}N_2O\cdot 1.5C_2H_2O_4$
14	CH_3	OCH_3	H	nC_3H_7	93	A−Et_2O	104	200	$C_{16}H_{24}N_2O\cdot C_4H_4O_4$
15	CH_3	OCH_3	H	iC_3H_7	49	A−Et_2O	101	130	$C_{16}H_{24}N_2O\cdot C_4H_4O_4$
16	CH_3	OCH_3	$-CH_2CH_2CH_2CH_2-$		75	A	114−115	1030	$C_{17}H_{24}N_2O\cdot 1.15C_2H_2O_4$[e]
17					37	EtOH−Et_2O	224−226	168	$C_{16}H_{22}N_2O\cdot C_2H_2O_4$

[a] Recrystallization solvents: EtOH represents absolute ethanol; Et_2O, anhydrous ether; A, acetone; B, ethyl acetate. [b] K_i values represent replicate determinations and SEM are ±25%; for purpose of comparison, clozapine was determined to possess a K_i = 5.3 (±0.4) nM. [c] All compounds analyzed correctly to within 0.4% of theory for C, H, and N except where noted. [d] Crystallized with 0.7 mol of H_2O. [e] Crystallized with 1 mol of H_2O. [f] K_i value previously reported;[16] included for purpose of comparison.

analogue of 5-methoxytryptamine (**1b:** K_i = 88 nM),[16] namely, 5-methoxy-2-methyltryptamine (**5**). Compound **5** (K_i = 98 nM; Table 1) was found to bind at 5-HT$_6$ receptors with an affinity comparable to that of 5-methoxytryptamine. It was also found that **5** lacks affinity for 5-HT$_3$ receptors (K_i > 10000 nM). Compound **5** might be a useful 5-HT$_6$ ligand; however, given that **5** possesses a primary amine, its utility for future in vivo studies might be hampered by its reduced ability to penetrate the blood−brain barrier and/or due to its potential for rapid metabolism by oxidative deamination. To address these problems, we sought to prepare

Table 2. Binding Profile of Compounds **7**, **8,** and **10**[a]

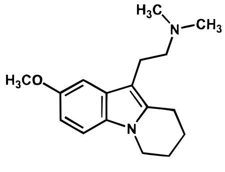
receptor population	K_i, nM (±SEM)			
	7	**8** (EMDT)	**10**	control (agent and K_i)
NET	6380 (±3190)	>10000	>10000	nortriptyline 6.3 ± 1.2
SERT	>10000	>10000	4700 (±1550)	fluoxetine 3.5 ± 0.7
h5-HT_{1A}	200 (±60)	170 (±54)	1470 (±310)	WAY 100,635 0.6 ± 1.5
h5-HT_{1D}	250 (±180)	290 (±70)	6225 (±70)	ergotamine 0.8 ± 0.6
h5-HT_{1E}	1800 (±600)	520 (±180)	>10000	serotonin 0.5 ± 0.15
r5-HT_{2A}	>10000	>10000	470 (±10)	clozapine 9 ± 1
r5-HT_{2C}	4020 (±640)	1810 (±490)	675 (±180)	clozapine 23 ± 5
h5-HT_{5A}	10450 (±2195)	4620 (±650)	5160 (±930)	ergotamine 22 ± 3
h5-HT_7	145 (±34)	300 (±60)	155 (±35)	clozapine 9 ± 2
h5-HT_6	60 (13)	16 (±4)	20 (±5)	clozapine 10 ± 3

[a] Compounds displayed K_i values of >10000 nM at the following populations of receptors: histamine, NMDA, PCP, acetylcholine, opiate, and vasopressin receptors; see Experimental Section for specific subpopulations examined. K_i values were >10000 nM for compounds **7** and **8** at hD_1, rD_2, rD_3, rD_4, and hD_5 receptors and >10000 nM for **10** at hD_1, rD_2, and rD_4 receptors; although **10** produced 70% inhibition at 10000 nM at rD_3 and hD_5 receptors, it was not further evaluated. NET and SERT represent the norepinephrine and serotonin transporters. K_i values for all three compounds at the dopamine transporter were >10000 nM.

several related derivatives that were somewhat more lipophilic and/or that might be less prone to metabolism.

One approach to enhancing lipophilicity and hindering metabolism was to add *N*,*N*-dimethyl substituents to the terminal amine; a second approach to enhancing lipophilicity was to homologate the 2-position substituent. 2-Methyl-*N*,*N*-dimethyltryptamine (2-methyl DMT, **6**: $K_i = 300$ nM), an *N*,*N*-dimethyl analogue of **5** lacking the 5-methoxy group, binds with severalfold lower affinity than **5** itself. Reintroduction of the 5-methoxy group, affording 2-methyl-5-methoxy DMT (**7**: $K_i = 80$ nM), enhanced affinity. Homologation of the 2-methyl substituent to an ethyl group (i.e., **8**: $K_i = 52$ nM) resulted in a slight increase in affinity and in a compound with affinity at least comparable to that of 5-HT itself. Further homologation of the ethyl substituent to a 2-*n*-propyl group (i.e., **9**: $K_i = 185$ nM) reversed this trend. To explore the possibility of bulk tolerance, we examined the 2-phenyl derivative **10** ($K_i = 54$ nM) and found it to bind with an affinity comparable to that of **8**.

Another attempt to enhance lipophilicity was to incorporate small alkyl substituents at the indole N_1-position. The idea was to subsequently incorporate a 2-alkyl substituent into whatever N_1-substituted analogue retained high 5-HT_6 receptor affinity. N_1-Methylation of 5-methoxy DMT (**11**: $K_i = 78$ nM) decreased 5-HT_6 receptor affinity of the resulting compound by >6-fold (**12**: $K_i = 510$ nM). Homologation of the N_1-methyl group to an ethyl group (i.e., **13**: $K_i = 240$ nM) or *n*-propyl group (i.e., **14**: $K_i = 200$ nM) doubled affinity, but the compounds did not bind as well as **11**. Branching of **13** to the isopropyl derivative **15** ($K_i = 130$ nM) resulted in a further slight enhancement of affinity. However, none of these compounds displayed significantly enhanced affinity. Compound **16** ($K_i = 1030$ nM), which may be viewed as a cyclic 1,2-disubstituted analogue of **11,** was also prepared for evaluation and was found to bind with reduced affinity.



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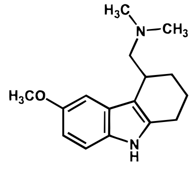

17

In a final attempt to enhance lipophilicity in the 2-substituted DMT series, the propyl group of **9** was tethered to the DMT side chain to afford **17**; compound **17** ($K_i = 168$ nM) was found to bind at 5-HT_6 receptors with about 3-fold lower affinity than **8**. Although compound **17** possesses an asymmetric center and can exist as a pair of optical isomers, no attempt was made to examine the individual isomers because structurally related agents have been shown to bind at 5-HT_{1D} receptors,[21,22] and it was anticipated that the isomers of **17** might lack the desired selectivity.

Binding Profile. Compounds **7**, **8,** and **10** were selected for examination of detailed binding profiles. All three agents were examined at more than 30 different receptor populations and produced <50% inhibition of binding at a concentration of 10000 nM at most of these populations. Where >50% displacement was observed, K_i values were determined (Table 2). For these studies, K_i values were redetermined for **7**, **8,** and **10**. Compounds **8** and **10** bind at human 5-HT_6 receptors with comparable affinity ($K_i = 16$ and 20 nM, respectively) and with an affinity similar to that of clozapine; compound **7** binds with severalfold lower affinity ($K_i = 60$ nM). Although **7** and **8** appear relatively selective, they also bind at h5-HT_{1A}, h5-HT_{1D}, h5-HT_{1E}, and h5-HT_7 receptors, yet compound **8**, in particular, still displays 10-fold selectivity over 5-HT_{1A} receptors and nearly 20-fold selectivity over h5-HT_{1D} and h5-HT_7 receptors. Compound **10** is more selective and displays 735-fold selectivity over h5-HT_{1A} receptors and >300-fold selectivity over h5-HT_{1D} receptors.

Functional Studies. Compounds **7**, **8**, and **10** were examined for their ability to activate adenylate cyclase. Whereas compounds **7** and **8** behaved as full agonists ($K_{act} = 7.9 \pm 5.0$ and 3.6 ± 1.3 nM, respectively) relative to 5-HT ($K_{act} = 5.0 \pm 3.0$ nM), compound **10** showed no agonist activity (see Figure 1). Compound **10** inhibited 5-HT-stimulated adenylate cyclase at 10000 nM suggesting that it is an antagonist.

Summary

Molecular manipulation of a tryptamine template revealed that 2-methyl substitution was tolerated by 5-HT_6 receptors.[16] Because 2-methyl 5-HT was previously considered to be a 5-HT_3-selective ligand and by taking advantage of the fact that 5-HT_3 receptors do not readily accommodate a 5-methoxy group, a series of

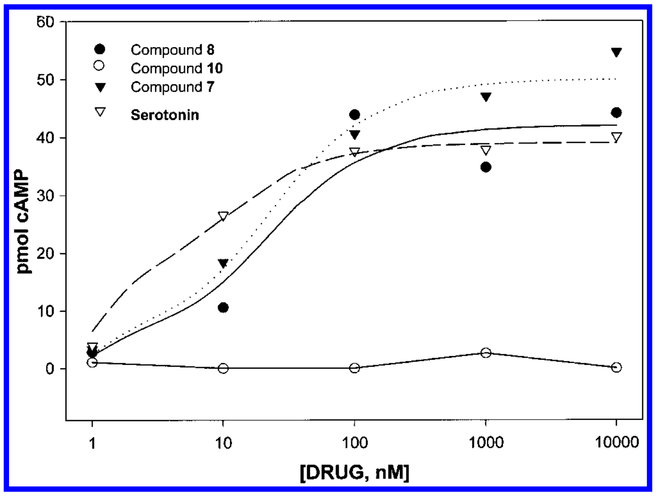

Figure 1. Typical dose−response curves for the effects of compounds **7**, **8**, and **10** as 5-HT_6 agonists in an adenylate cyclase assay; serotonin was used as control. Each compound was examined at five concentrations.

2-alkyl-5-methoxytryptamines was synthesized for evaluation at 5-HT_6 receptors. Several compounds were identified with affinities at least comparable to that of 5-HT itself (K_i = 75 nM). In particular, 2-ethyl-5-methoxy-*N*,*N*-dimethyltryptamine (EMDT; **8**) possessed high affinity (K_i = 16 nM) and displayed reasonable selectivity for 5-HT_6 versus other receptors examined. In functional studies, EMDT (**8**) was demonstrated to behave as a 5-HT_6 agonist (K_{act} = 3.6 nM) with a potency at least equivalent to that of 5-HT (K_{act} = 5.0 nM). EMDT is the most selective 5-HT_6 agonist reported to date. Also of interest is the 2-phenyl derivative **10** (MPDT: K_i = 20 nM), which possesses a somewhat different binding profile than **8**; compound **10** lacks agonist activity up to concentrations of 10000 nM and may represent a novel 5-HT_6 antagonist. Indeed, when examined at the single concentration of 10000 nM, **10** behaved an antagonist. Hence, with the appropriate substituents, 2-substituted tryptamines may provide entry to new 5-HT_6-selective agonists and antagonists.

Experimental Section

Synthesis. Melting points, determined with a Thomas-Hoover melting point apparatus, are uncorrected. Proton magnetic resonance spectra were obtained with a GE QE-300 or Varian Gemini 300 spectrometer; and tetramethylsilane was used as an internal standard. Infrared spectra were recorded on a Nicolet 5ZDX FT-IR. Elemental analysis was performed by Atlantic Microlab Inc. and determined values are within 0.4% of theory. Flash chromatography was performed on silica gel (Merck grade 60, 230−400 mesh 60 Å). Certain compounds were previously reported in the literature but due to difficulty in either preparing or purifying the reported salt, a different salt was prepared. Specifically, compounds **7**,[17] **10**,[23] and **12**[24] are known as their HCl salts but were isolated as their monooxalate salts in the present investigation. Compound **6**, prepared earlier as a maleate salt,[25] was isolated as its HCl salt. All four of these compounds analyzed correctly for C, H, and N.

2-Ethyl-5-methoxy-*N*,*N*-dimethyltryptamine Maleate (8). A 2.5 M solution of *n*BuLi (1.75 mL, 4.38 mmol) was added in a dropwise manner to a stirred solution of **7**[17] (free base) (1.00 g, 4.33 mmol) in dry THF (7 mL) at −78 °C under N_2. After stirring the reaction mixture for 5 min, the cooling bath was removed and CO_2 gas was passed into the solution for 10 min. The solvent was removed at 0 °C under reduced pressure to give a transparent solid. The flask was flushed with N_2 and dry THF (7 mL) was added. The reaction mixture was degassed at −150 °C under reduced pressure of 1 mmHg, then allowed to warm to −78 °C; 1.7 M *t*BuLi (2.8 mL, 4.8 mmol) was added to give a bright yellow solution. The cooling bath was replaced by an ice-salt bath and the reaction was kept at −20 °C for 45 min, then cooled to −78 °C, and MeI (0.3 mL, 4.81 mmol) was added in a dropwise manner. The solution was kept at −78 °C for 3 h. The reaction mixture was acidified with a saturated ethereal solution of HCl. Anhydrous Et_2O was added to the resulting suspension and the supernatant was decanted. The residue was heated at 100 °C under reduced pressure for 20 min. The resulting residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH; 12:1) to give 0.17 g of a bright yellow oil (16%): ^1H NMR ($CDCl_3$) δ 8.06 (s, 1H), 7.14 (d, 1H, J = 8.67 Hz), 6.98 (s, 1H), 6.76 (dd, 1H, J = 2.34, 8.73 Hz), 3.84 (s, 3H), 2.91−2.87 (m, 2H), 2.71 (q, 2H, J = 7.38 Hz), 2.57−2.52 (m, 2H), 2.38 (s, 6H), 1.25 (t, 3H, J = 7.38 Hz). The maleate salt was prepared and recrystallized from an EtOAc/Et_2O mixture: mp 123 °C. Anal. ($C_{15}H_{22}N_2O{\cdot}C_4H_4O_4$) C, H, N.

5-Methoxy-2-*n*-propyl-*N*,*N*-dimethyltryptamine Oxalate (9). Magnesium turnings (840 mg) and NH_4Cl (77 mg, 1.44 mmol) were added to a solution of **19** (free base) (259 mg, 0.65 mmol) in MeOH (17 mL) and the mixture was allowed to stir at room temperature for 1 h. Saturated NH_4Cl solution was added and the reaction mixture was extracted with CH_2Cl_2. The organic portion was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH; 9:1) to give 75 mg (45%) of a bright yellow oil: ^1H NMR ($CDCl_3$) δ 7.71 (brs, 1H), 7.16 (d, 1H, J = 8.67 Hz), 6.99 (d, 1H, J = 2.43 Hz), 6.77 (dd, 1H, J = 2.25, 8.73 Hz), 3.85 (s, 3H), 2.89−2.83 (m, 2H), 2.69 (t, 2H, J = 7.56 Hz), 2.53−2.47 (m, 2H), 2.36 (s, 6H), 1.68 (tq, 2 H, J = 7.28, 7.56 Hz), 0.98 (t, 3H, J = 7.28 Hz). The oxalate salt was prepared and recrystallized from acetone: mp 146−147 °C. Anal. ($C_{16}H_{24}N_2O{\cdot}C_2H_2O_4{\cdot}0.7H_2O$) C, H, N.

5-Methoxy-2-phenyl-*N*,*N*-dimethyltryptamine Oxalate (10). 5-Methoxy-2-phenylindole[26] (3 g, 13.44 mmol) was added to a stirred ice-cooled solution of 1-dimethylamino-2-nitroethylene (1.56, 13.44 mmol) in trifluoroacetic acid (8 mL). The resulting mixture was allowed to stir under N_2 at room temperature for 30 min and was then poured into ice/water. The solution was extracted with EtOAc and the organic portion was washed consecutively with saturated $NaHCO_3$ solution, H_2O, then brine. The organic portion was dried ($MgSO_4$) and solvent was removed under reduced pressure. The residue was recrystallized from CH_2Cl_2/hexane to give 2.36 g (60%) of **22** as a red powder: ^1H NMR (acetone-d_6) δ 8.82 (brs, 1H), 8.32 (d, 1H, J = 13.44 Hz), 7.94 (d, 1H, J = 13.35 Hz), 7.69−7.41 (m, 7H), 6.98−6.94 (m, 1H), 3.92 (s, 3H); IR (KBr) 1606, 1475, 1251 cm^{-1}. A solution of **22** (2.00 g, 6.75 mmol) in dry THF (20 mL) was added in a dropwise manner to a cooled (0 °C) suspension of $LiAlH_4$ (1.54 g, 40.5 mmol) in dry THF (40 mL) under N_2. The reaction mixture was heated at reflux for 1 h and then allowed to stand at room-temperature overnight. The resulting mixture was quenched with H_2O then 15% NaOH solution. Celite was added and the solution was filtered. The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH; 9:1) to give 1.00 g (55%) of the primary amine **23**[23] as an oil: ^1H NMR ($CDCl_3$) δ 8.19 (brs, 1H), 7.59−7.58 (m, 2H), 7.49−7.44 (m, 2H), 7.39−7.34 (m, 1H), 7.28−7.25 (m, 1H), 7.09 (d, 1H, J = 2.37 Hz), 6.88 (dd, 1H, J = 2.24, 8.75 Hz), 3.89 (s, 3H), 3.04 (brs, 4H); IR (KBr) 3397, 3347 cm^{-1}. Sodium cyanoborohydride (510 mg, 8.12 mmol) was added to a solution of primary amine **23** (700 mg, 2.63 mmol) and 37% aqueous CH_2O in MeCN (10 mL) at room temperature. The resulting mixture was adjusted to pH 5 with HOAc and was allowed to stir at room-temperature overnight. A 15% solution of NaOH was added to neutralize the mixture and the mixture was extracted with CH_2Cl_2. The combined organic portion was washed with saturated $NaHCO_3$ solution and brine. The organic portion was dried ($MgSO_4$) and solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH; 9:1) to give 195 mg (25%) of **10** (free base) as a white powder: ^{1}H NMR ($CDCl_3$) δ 8.05 (brs, 1H), 7.56−7.53 (m, 2H), 7.49−7.44 (m, 2H), 7.39−7.34 (m, 1H), 7.29−7.25 (m, 1H), 7.11 (d, 1H, J = 2.25 Hz), 6.87 (dd, 1H, J = 2.52, 8.73 Hz), 3.89 (s, 3H), 3.13−3.08 (m, 2H), 2.72−2.66 (m, 2H), 2.39 (s, 6H). Although the HCl salt has been previously reported,[23] difficulties in its purification led to isolation of the product as its oxalate salt: mp 187−188 °C after recrystallization from acetone. Anal. ($C_{19}H_{22}N_2O$·$C_2H_2O_4$) C, H, N.

5-Methoxy-1-(2-propyl)-*N*,*N*-dimethyltryptamine Maleate (15). A mixture of 5-methoxy-*N*,*N*-dimethyltryptamine (**11**; free base) (500 mg, 2.29 mmol) and 60% NaH (100 mg, 2.52 mmol) was heated at 100 °C under N_2 until evolution of H_2 gas ceased. The resultant mass was dissolved in anhydrous DMF (3 mL) and 2-bromopropane (0.25 mL, 2.84 mmol) was added to the solution at 0 °C. The reaction mixture was allowed to stir at room temperature for 3 h. Brine was added and the reaction mixture was extracted with CH_2Cl_2. The organic portion was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH; 10:1) to give 294 mg of a bright yellow oil (49%): ^{1}H NMR ($CDCl_3$) δ 7.23 (d, 1H, J = 8.94 Hz), 7.04 (d, 1H, J = 2.46 Hz), 7.01 (s, 1H), 6.86 (dd, 1H, J = 2.46, 8.88 Hz), 4.59−4.54 (m, 1H), 3.86 (s, 3H), 2.95−2.89 (m, 2H), 2.66−2.61 (m, 2H), 2.36 (s, 6H), 1.48 (d, 6H, J = 6.72 Hz). The maleate salt was prepared and recrystallized from an acetone/Et_2O mixture: mp 101−102 °C. Anal. ($C_{16}H_{24}N_2O$·$C_4H_4O_4$) C, H, N.

^{1}H NMR data for compounds **13** and **14** are as follows: **13** ($CDCl_3$) δ 7.22 (d, 1H, J = 9.0 Hz), 7.06 (d, 1H, J = 2.5 Hz), 6.95 (s, 1H), 6.88 (dd, 1H, J = 2.5, 6.0 Hz), 4.10 (q, 2H, J = 7.5 Hz), 3.88 (s, 3H), 3.01−2.97 (m, 2H), 2.76−2.73 (m, 2H), 2.45 (s, 6H), 1.44 (t, 3H, J = 7.5 Hz); **14** ($CDCl_3$) δ 7.19 (d, 1H, J = 8.85 Hz), 7.04 (d, 1H, J = 2.37 Hz), 6.90 (s, 1H), 6.87−6.83 (m, 1H), 3.98 (t, 2 H, J = 7.08 Hz), 3.86 (s, 3H), 2.93−2.87 (m, 2H), 2.64−2.59 (m, 2H), 2.35 (s, 6H), 1.82 (q, 3H, J = 7.2 Hz), 0.91 (t, 2H, J = 7.4 Hz).

6,7,8,9-Tetrahydro-2-methoxy-10-(*N*,*N*-dimethylaminoethyl)pyrido[1,2-*a*]indole Oxalate (16). A solution of 1.0 M borane/THF (2 mL, 2 mmol) was added in a dropwise manner to ice-bath cooled **21** (290 mg, 1.01 mmol) under N_2. The reaction mixture was allowed to stir at room temperature for 2 h. Acetone (3 mL) was added, and the reaction mixture was heated at reflux for 1 h to quench the unreacted borane reagent. The solvent was removed under reduced pressure. A 15% solution of NaOH was added and the mixture was extracted with CH_2Cl_2, and the CH_2Cl_2 portion was washed with H_2O, then brine. Solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc; 4:1) to give 207 mg (75%) of a light yellow oil: ^{1}H NMR (DMSO-d_6) δ 7.34 (d, 1 H, J = 8.85 Hz), 7.21 (s, 1H), 7.11 (s, 1H), 4.08 (t, 2H, J = 6.65 Hz), 3.79 (s, 3H), 3.40−3.35 (m, 2H), 3.30−3.25 (m, 2H), 3.06−3.01 (m, 2H), 2.83 (s, 6H), 1.76−1.69 (m, 2H), 1.40−1.31 (m, 2H). A small portion was converted to its oxalate salt: mp 114−115 °C. Anal. ($C_{17}H_{24}N_2O$·$1.15C_2H_2O_4$·H_2O) C, H, N.

4-(Dimethylaminomethyl)-6-methoxy-1,2,3,4-tetrahydrocarbazole Oxalate (17). Sodium metal (1.0 g) was added portionwise over a 30-min period to a stirred solution of 4-(dimethylaminomethyl)-9-benzyl-6-methoxy-1,2,3,4-tetrahydrocarbazole hydrochloride[19] (4.0 g, 0.01 mol) in liquid NH_3 (300 mL). NH_4Cl (3.0 g) was added until the blue color of the mixture dissipated. The NH_3 was evaporated, H_2O (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic portion was washed with H_2O (50 mL), brine (50 mL), dried ($MgSO_4$) and evaporated to give an oil. The oil was purified by column chromatography ($CHCl_3$/MeOH; 9:1) and converted to an oxalate salt. The oxalate salt was recrystallized from anhydrous Et_2O/absolute EtOH to give 1.8 g (37%) of the desired target as a white powder: mp 224−226 °C; ^{1}H NMR ($CDCl_3$, free base) δ 8.10 (s, 1H, NH), 7.20 (t, 1H, ArH), 6.90 (d, 1H, ArH), 6.70 (dd, 1H, ArH), 3.80 (s, 3H, OCH_3), 3.40 (t, 1H, CH), 3.15 (d, 1H, CH), 3.00 (t, 1H, CH), 2.82 (s, 6H, 2× CH_3), 2.63−2.73 (m, 2H, CH_2), 2.33 (m, 1H, CH), 1.8−2.0 (m, 3H, CH_2-CH). Anal. ($C_{16}H_{22}N_2O$·$C_2H_2O_4$) C, H, N.

1-Benzenesulfonyl-5-methoxy-*N*,*N*-dimethyltryptamine Oxalate (18). A mixture of 5-methoxy-*N*,*N*-dimethyltryptamine (**11**; free base) (4.35 g, 19.93 mmol) and 60% NaH (0.87 g, 21.75 mmol) was heated at 100 °C under N_2 until evolution of H_2 gas ceased. The resultant mass was dissolved in anhydrous DMF (21 mL) and benzenesulfonyl chloride (2.8 mL, 21.94 mmol) was added in a dropwise manner at 0 °C. The reaction mixture was allowed to stir at room-temperature overnight. Saturated $NaHCO_3$ solution was added and the mixture was extracted with CH_2Cl_2. The organic portion was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH; 9:1) to give 4.39 g of an oil (61%): ^{1}H NMR ($CDCl_3$) δ 7.89−7.87 (m, 1H), 7.83 (d, 2H, J = 8.0 Hz), 7.51 (t, 1H, J = 7.8 Hz), 7.34 (s, 1H), 6.93−6.92 (m, 2H), 3.82 (s, 3H), 2.80 (t, 2H, J = 7.8 Hz), 2.59 (t, 2H, J = 7.8 Hz), 2.33 (s, 6H); IR ($CHCl_3$) 1357, 1115 cm^{-1}. The oxalate salt was prepared and recrystallized from an acetone/Et_2O mixture: mp 224−226 °C. Anal. ($C_{19}H_{22}N_2O_3S$·$C_2H_2O_4$) C, H, N.

1-Benzenesulfonyl-5-methoxy-2-*n*-propyl-*N*,*N*-dimethyltryptamine Oxalate (19). A 2.5 M solution of *n*BuLi (1.4 mL, 3.5 mmol) was added in a dropwise manner to a stirred solution of **18** (free base) (1.00 g, 2.79 mmol) in DME (4 mL) at −10 °C under N_2. The resulting solution was allowed to stir for an additional 10 min at −10 °C, and then *n*PrI (0.35 mL, 3.59 mmol) was added. The reaction mixture was allowed to stir for 1 h at −10 °C. Saturated $NaHCO_3$ solution was added and the reaction mixture was extracted with CH_2Cl_2. The organic portion was washed with brine and dried ($MgSO_4$); the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH; 30:1) to give 0.19 g (17%) of a bright yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.06 (d, 1H, J = 8.79 Hz), 7.62 (d, 2H, J = 8.22 Hz), 7.51−7.46 (m, 1H), 7.38−7.33 (m, 2H), 6.95 (brs, 1H), 6.89−6.85 (m, 1H), 3.85 (s, 3H), 2.96−2.89 (m, 4H), 2.63−2.57 (m, 2H), 2.48 (s, 6H), 1.73 (q, 2H, J = 7.51 Hz), 1.00 (t, 3H, J = 7.51 Hz); IR ($CHCl_3$) 1355 cm^{-1}. The oxalate salt was prepared and recrystallized from acetone: mp 175−176 °C. Anal. ($C_{22}H_{28}N_2O_3S$·$C_2H_2O_4$) C, H, N.

6,7,8,9-Tetrahydro-2-methoxy-10-(*N*,*N*-dimethylaminoethyl)pyrido[1,2-*a*]indol-9-one Oxalate (21). A mixture of 5-methoxy-*N*,*N*-dimethyltryptamine (**11**; free base) (2.00 g, 9.17 mmol) and 60% NaH (0.41 g, 10.1 mmol) was heated at 100 °C under N_2 until evolution of H_2 gas ceased. The resultant mass was dissolved in anhydrous DMF (25 mL) and anhydrous γ-butyrolactone (1.4 mL, 18.2 mmol) was added in a dropwise manner at room temperature. The reaction mixture was heated at reflux for 20 h, cooled to 0 °C, and acidified by the addition of a saturated ethereal solution of HCl. Additional Et_2O was added to the resulting suspension and the supernatant was decanted. The residue was dissolved in PPE (52.5 mL) and $CHCl_3$ (100 mL) and the reaction mixture was heated at reflux for 3 h under N_2. The resulting mixture was neutralized by the addition of 15% NaOH solution, at ice-bath temperature, and extracted with CH_2Cl_2. The organic portion was dried ($MgSO_4$) and solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH; 20:1) to give 0.52 g (20%) of **21** (free base) as a yellow oil: ^{1}H NMR (DMSO-d_6) δ 7.35 (d, 1H, J = 8.79 Hz), 7.18 (s, 1H), 6.88 (d, 1H, J = 8.85 Hz), 4.06 (t, 2H, J = 6.60 Hz), 3.80 (s, 3H), 3.42−3.36 (m, 2H), 3.17−3.12 (m, 2H), 2.85 (s, 6H), 2.66−2.62 (m, 2H); IR ($CHCl_3$) 1648 cm^{-1}. A small sample was converted to the oxalate salt: mp 191−192 °C dec. Anal. ($C_{19}H_{24}N_2O_6$·$1.6C_2H_2O_4$) C, H, N.

5-HT$_6$ Radioligand Binding Assay. The binding assay employed human 5-HT$_6$ receptors stably transfected to HEK 293 human embryonic kidney cells with [^{3}H]lysergic acid diethylamide (70 Ci/mmol; DuPont NEN) as radioligand. All assays were conducted in triplicate using polypropylene 1 mL/well plates (Anachemia). The radioligand was diluted in incubation buffer in borosilicate glass vials and protected from light. Competing agents (1 mM stock solutions) were dissolved in DMSO or saline and stored at −20 °C in 1.2-mL polypropylene tubes (ElKay). Dilutions of compounds were made using incubation buffer in 96-well polypropylene plates and mixed by multichannel pipetting >25 times. Serial dilutions (1 in 4) started at a final concentration of 10000 nM. Final concentrations >10000 nM were individually prepared from the 1 mM stock solution. Nonspecific binding was defined by 100 μM serotonin creatinine sulfate (Research Biochemicals) prepared fresh in incubation buffer at the time of each determination and protected from light. Reactions volumes were as follows: 200 μL of incubation buffer (50 mM Tris, 0.5 mM EDTA, 10 mM $MgCl_2$), pH 7.4 at 22 °C, 100 μL of test agent or serotonin (100 μM) or buffer (for total binding), 100 μL of [^{3}H]lysergic acid diethylamide (2 nM final concentration), and 100 μL of membrane preparation (15 μg of protein). The incubation was initiated by the addition of membrane homogenate and the plates were vortexed (Baxter S/P multitube mixer). The plates were incubated, with protection from light, by shaking (Gyrotop water bath/shaker model G76, speed 2) at 37 °C for 60 min. The binding reaction was stopped by filtration. The samples were filtered under vacuum over 96-well glass fiber filters (Packard Unifilter GF/B), presoaked in 0.3% PEI in 50 mM Tris buffer (4 °C, pH 7.4) for at least 1 h, and then washed six times with 1 mL of cold 50 mM Tris buffer (pH 7.4) using the Packard Filtermate 196 harvester. The Unifilter plates were dried overnight in a 37 °C dry incubator. The Unifilter bottoms were sealed and 35 μL of Packard MicroScint-0 was added. The plates were allowed to equilibrate for 1 h and were then sealed using a Packard TopSeal P with the Packard Plate Micromate 496. Plates were counted in a Packard TopCount 4.1 by liquid scintillation spectrometry. Each well was counted for 3 min. The test agents were initially assayed at 1000 and 100 nM. If the compound was active (defined as causing at least 80% inhibition of [^{3}H]lysergic acid diethylamide binding at 1000 nM), it was further tested for determination of a K_i value. The range of concentrations was chosen such that the middle concentration would produce approximately 50% inhibition.

Receptor Screen. Assays for the following receptors were performed by the NIMH Psychoactive Drug Screening Program: (1) serotonin receptors: h5-HT_{1A}, h5-HT_{1B}, h5-HT_{1D}, h5-HT_{1E}, r5-HT_{2A}, r5-HT_{2C}, h5-HT_6, h5-HT_7; (2) dopamine receptors: hD_1, rD_2, rD_3, rD_4, hD_5; (3) muscarinic acetylcholine receptors: hm_1, hm_2, hm_3, hm_4, hm_5; (4) nicotinic acetylcholine receptors: α2/β2, α2/β4, α3/β2, α3/β4, α4/β2, α4/β2, α4/β4; (5) vasopressin receptors: hV1, hV2, hV3; (6) opiate receptors: hμ, hδ, rκ; (7) transporters: hSERT, hNET, rDAT; (8) rNMDA; (9) rPCP; and (10) rH1-histamine. Detailed on-line protocols for the binding assays are described at: http://meds20785.cwru.edu/myweb/protocol.htm. For screening purposes, the ability of 10 μM of each compound (dissolved in 10% DMSO) was incubated with the appropriate receptor preparation and percent inhibition determined for duplicate determinations each performed in duplicate. Where >50% inhibition of specific binding was measured, K_i determinations were then measured by competition binding assays in which concentrations from 1 to 100000 nM were incubated in duplicate. For each K_i value the data represent the mean ± SD of computer-derived estimates for $N = 4$ separate determinations. h5-HT_6 receptor assays were performed exactly as previously described.[3,4]

Adenylate Cyclase Assay. h5-HT_6 receptors stably expressed in HEK-293 cells were grown in 24-well plates to near-confluency and 18 h prior to assay the medium was replaced with DMEM containing dialyzed 10% fetal calf serum. For the assay, the medium was aspirated and replaced with fresh DMEM without serum and incubated with various concentrations of test agent in a total volume of 0.5 mL for 15 min. The assay was terminated by aspiration and the addition of 10% trichloroacetic acid (TCA). The TCA extract was used for cAMP determinations. Data represent the mean of $N = 4$ separate determinations.

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