Binding of *O*-Alkyl Derivatives of Serotonin at Human 5-HT1Dβ Receptors

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In humans, 5-HT1D serotonin receptors represent terminal autoreceptors, and there is some evidence that 5-HT1D ligands may be useful in the treatment of migraine. The most widely used 5-HT1D agonist is sumatriptan; however, this agent reportedly displays little selectivity for 5-HT1D versus 5-HT1A receptors. To identify novel serotonergic agents with enhanced 5-HT1D versus 5-HT1A selectivity, we attempted to take advantage of possible differences in the regions of bulk tolerance associated with the 5-position of the 5-HT binding sites for these two populations of receptors. Examination of a series of 5-(alkyloxy)tryptamine derivatives demonstrated that compounds with unbranched alkyl groups of up to eight carbon atoms bind with high affinity at human 5-HT1Dβ receptors (K_i < 5 nM) but demonstrate less than 50-fold selectivity relative to 5-HT1A receptors. Alkyl groups longer than eight carbon atoms impart reduced affinity for 5-HT1A receptors whereas groups longer than nine carbon atoms lead to compounds with reduced affinity at 5-HT1Dβ receptors. 5-(Nonyloxy)tryptamine (**10**) represents a compound with optimal 5-HT1Dβ affinity (K_i = 1 nM) and selectivity (>300-fold). Branching of the alkyl chain, to 5-[(7,7-dimethylheptyl)oxy]tryptamine (**15**), results in an agent with somewhat lower affinity (5-HT1Dβ K_i = 2.3 nM) but with greater (i.e., 400-fold) 5-HT1D versus 5-HT1A selectivity. Replacement of the oxygen atom of **10** with a methylene group (i.e., **20**), replacement of the O-proximate methylene with a carbonyl group (i.e., ester **26**), or cyclization of the aminoethyl moiety to a carbazole (e.g., **34**, **36**) or β-carboline (i.e., **37**), result in reduced affinity and/or selectivity. None of the compounds examined displayed significant selectivity for 5-HT1Dβ versus 5-HT1Dα sites; nevertheless, compounds **10** (recently shown to behave as a 5-HT1D agonist) and **15** represent the most 5-HT1D versus 5-HT1A selective agents reported to date.

Serotonin (5-HT, **1**) receptors have been divided into several major families on the basis of pharmacological properties, sequence data, and second messenger coupling.[1−3] Receptor families having received the most attention are the 5-HT1 (adenylate cyclase coupled), 5-HT2 (phosphoinositol coupled), and 5-HT3 (ion channel) receptors.[1−3] 5-HT1 receptors have been further divided into several subpopulations that include 5-HT1A, 5-HT1B, and 5-HT1D receptors. (Due to greater similarity to the 5-HT2 rather than 5-HT1 family, 5-HT1C receptors were recently renamed 5-HT2C receptors.) Of particular interest to the present investigation are the 5-HT1D receptors. Rodents possess 5-HT1B receptors, which appear to function primarily as autoreceptors. In support of this concept, the synthesis of 5-HT1B receptors at the level of serotonergic terminals has recently been demonstrated.[4] Most other mammal species including humans possess 5-HT1D receptors in corresponding anatomical regions of the brain; thus, these receptors appear to represent species homologs.[1−3] There is evidence that 5-HT1D receptors modulate vascular tone and inhibit neurotransmitter release by acting as terminal autoreceptors.[1−3] Studies with rodents suggest that 5-HT1B receptors may be involved in aggression, depression, and other central actions.[1,5] Thus, by analogy, 5-HT1D receptors may also be involved in similar actions. To date, few 5-HT1D agonists have been identified. Although 5-carbamoyltryptamine (**2**) has been used as a 5-HT1D agonist, it is a nonselective 5-HT1 agent.[6] Sumatriptan (**3**), the most widely used 5-HT1D agonist, is a fairly selective agent which was recently introduced for the treatment of migraine headaches. Although there is some controversy regarding its exact mechanism of action in this regard, 5-HT1D receptors are thought to be involved.[7] Sumatriptan, though fairly selective for 5-HT1D versus most other populations of 5-HT receptors, displays only 10−50-fold selectivity for 5-HT1D versus 5-HT1A receptors. In addition to the difficulty of sumatriptan to penetrate the blood−brain barrier, its lack of selectivity for 5-HT1D versus 5-HT1A receptors detracts from its utility as a tool for 5-HT receptor research.[7] Furthermore, certain of sumatriptan's clinical side effects may be related to its affinity for 5-HT1A receptors.[7] This prompted us to identify a novel agent that binds at 5-HT1D receptors with an affinity comparable to that of sumatriptan, but with greater 5-HT1D versus 5-HT1A selectivity.

While our work was in progress, Weinshank and coworkers identified two populations of human 5-HT1D receptors: 5-HT1Dα and 5-HT1Dβ receptors.[8] 5-HT1Dβ receptors display >90% homology with, and appear to be the human counterpart of, 5-HT1B receptors. 5-HT1Dα and 5-HT1Dβ receptors display >90% homology in their transmembrane domains, and no high-

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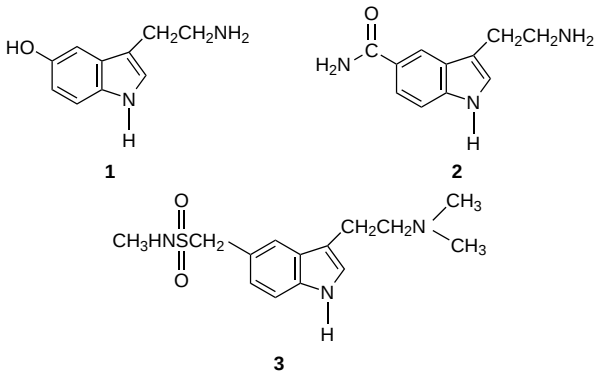


affinity agents have been shown to discriminate between the two subpopulations. Sumatriptan (**3**), for example, binds at the two 5-HT1D receptors with affinities (K_i values) of 3.4 and 7.7 nM, respectively.[8]

The past few years have witnessed the development of several newer 5-HT1D ligands including a series of 5-oxadiazolyltryptamines,[9] 3-amino-6-carbamoyl-1,2,3,4-tetrahydrocarbazole,[10] and several 5-[(3-nitropyrid-2-yl)-amino]indoles;[11] however, none of these agents displays greater 5-HT1D versus 5-HT1A selectivity than sumatriptan. Two structurally novel 5-HT1D antagonists have also been reported: GR127935 and GR133867; these compounds display 50−100-fold 5-HT1D versus 5-HT1A selectivity.[12] Nevertheless, there is still a need for 5-HT1D-selective agonists with greater selectivity than **3**.

Our approach to developing a 5-HT1D versus 5-HT1A selective agent was based on the following observations: (i) because 5-HT binds with high affinity at 5-HT1A and 5-HT1D receptors, those portions of the respective receptors that bind 5-HT likely are similar, (ii) both 5-HT1A and 5-HT1D receptors possess a region of bulk tolerance associated with the aromatic portion of 5-HT, (iii) 5-HT1A receptors allow considerable bulk on the terminal amine whereas 5-HT1D receptors favor smaller amine substituents, preferably primary amines (e.g., refs 13, 14). Given that there is only about 50% sequence homology between the transmembrane portions of 5-HT1A and 5-HT1D receptors,[1−3] we reasoned that the regions of bulk tolerance should not be identical. That is, it might be possible to incorporate at the indole 5-position substituents of varying lengths that, due to potential differences in distant helical environments, will differentially bind with higher affinity at one population of receptors over the other. We recently reported one such agent that binds at 5-HT1D versus 5-HT1A receptors with higher affinity and selectivity than sumatriptan: 5-(nonyloxy)tryptamine (NOT).[15] NOT was also found to be several times more potent than sumatriptan as a 5-HT1D agonist but inactive as a 5-HT1A agonist.[15] We describe now a more detailed investigation of 5-(alkoxy)tryptamines and related analogs and their affinity for 5-HT1D receptors. Although our work was initiated with bovine brain homogenate binding assays (i.e., 5-HT1D receptors), cloned human receptors (i.e., 5-HT1Dβ receptors) were utilized once they became available. As a consequence, the use of the cloned human receptors has allowed us to formulate some limited structure−affinity relationships for the binding of tryptamine analogues at 5-HT1Dβ receptors. Selected compounds were also examined for binding at 5-HT1Dα receptors.

Table 1. Physicochemical Data for *O*-Alkyltryptamines

no.	method[a]	% yield	RS[b]	mp, °C	empirical formula[c]
6	A	27	ME	159−160	$C_{13}H_{18}N_2O\cdot C_2H_2O_4$
7	A	31	ME	145−147	$C_{15}H_{22}N_2O\cdot 0.9C_2H_2O_4$
8	A	22	ME	192−194	$C_{17}H_{26}N_2O\cdot 0.5C_2H_2O_4$[d]
9	A	26	ME	136−139	$C_{18}H_{28}N_2O\cdot C_2H_2O_4$
10	B	29	A	196−198[e]	$C_{19}H_{30}N_2O\cdot HCl$
11	B	95	ME	194−196	$C_{20}H_{32}N_2O\cdot HCl$
12	A	29	ME	190−191	$C_{21}H_{34}N_2O\cdot 0.5C_2H_2O_4$[f]
13	B	70	ME	193−195	$C_{19}H_{30}N_2O\cdot HCl$
14	B	64	ME	196−198[h]	$C_{21}H_{34}N_2O\cdot HCl$[f,g]
15	B	62	ME	173−175	$C_{20}H_{32}N_2O\cdot HCl$[f]
16	B	82	ME	189−191[h]	$C_{20}H_{30}N_2O\cdot HCl$

[a] Method of preparation, see the Experimental Section. [b] Recrystallization solvents: A = EtOAc, M = MeOH, E = anhydrous Et_2O. [c] All compounds analyzed correctly for C, H, N within 0.4%, except where noted. [d] Crystallized with 0.25 mol of H_2O. [e] HCl salt; see the Experimental Section. [f] Crystallized with 0.5 mol of H_2O. [g] H: calcd, 9.65; found, 9.18. [h] Decomposed.

Chemistry

O-Alkyl derivatives **6**−**16** were prepared by either one of two methods (Table 1). In method A,[15] the terminal amine of 5-(benzyloxy)tryptamine was protected with an acetyl group, the benzyl group was removed by hydrogenolysis, and the resultant phenolic hydroxyl group was alkylated using the appropriate alkyl halide. In the final step, the *N*-acetyl-*O*-alkyltryptamine was deprotected under acidic conditions to afford the desired products.

Method B involved protection of the terminal amine of 5-HT (**1**) with a *t*-BOC group, O-alkylation, and subsequent deprotection using acid hydrolysis. Nearly all of the alkyl halides were commercially available; however, those necessary for the preparation of **13**−**16** were synthesized according to literature methods.[16−19]

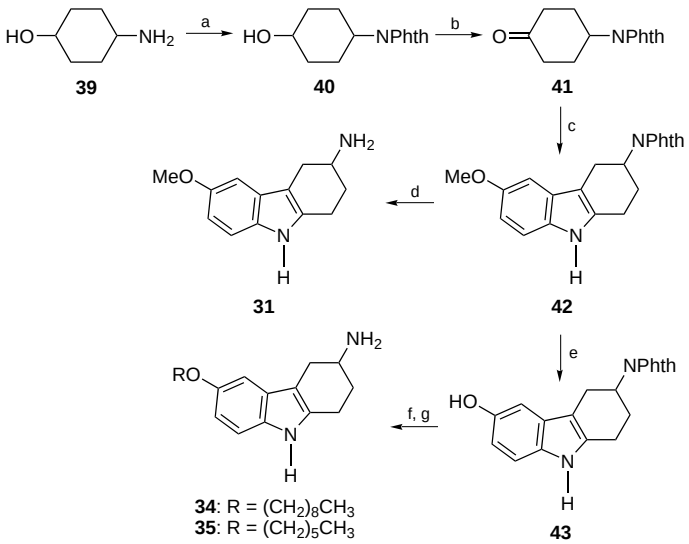
Tryptamines **18** and **19** were obtained from 5-ethylindole using the Speeter−Anthony tryptamine synthesis;[20] the prerequisite 5-ethylindole was prepared by Japp−Klingeman cyclization of 4-ethylaniline. Likewise, the 5-alkyltryptamine **20** was prepared using the Speeter−Anthony method, and the required 5-*n*-decylindole was prepared from 5-*n*-decylaniline using the general indole synthesis of Sugasawa et al.[21]

5-Acetyltryptamine (**21**) was synthesized by a literature method,[22] and the esters **22**−**25** were prepared by acylation of bufotenine as we have previously described.[23] Ester **26** was prepared in an analogous manner. Modification of the terminal amine of **10** by reductive alkylation afforded **27** ($NaCNBH_3/H_2CO$) and **28** [$CH_3(CH_2)_2COCl/LiAlH_4$]. In one instance, an attempt was made to prepare **27** by an Eschweiler−Clarke reaction; rather than obtaining the expected **27**, cyclization occurred to give **37**.

Debenzylation of racemic 5-(benzyloxy)-α-methyltryptamine gave α-methyl-5-HT (**29**).[24] The *O*-alkyl derivative **30** was prepared from the same starting material by method B.

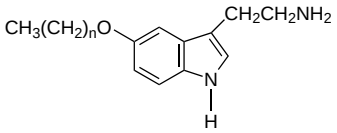
Compounds **31**, **34**, and **35** were prepared from the common intermediate **42** (Scheme 1) which was, in turn, prepared by the general procedure of King et al.[10,25] Fischer cyclization of (4-methoxyphenyl)hydrazine with *N*-phthalimido-4-aminocyclohexanone (**41**) provided **42**, which was N-deprotected to give **31** or O-deprotected to give **43**. Compound **43** was alkylated with 1-bromononane or 1-bromohexane to give **34** and **35**, respectively, after deprotection via hydrazinolysis.

Scheme 1[a]



[a] (a) PhthCOOEt/K_2CO_3/H_2O; (b) PCC/CH_2Cl_2; (c) (*p*-methoxyphenyl)hydrazine/HOAc; (d) H_2N-NH_2/EtOH/$CHCl_3$; (e) BBr_3/$CHCl_3$; (f) RBr/K_2CO_3/acetone; (g) H_2N-NH_2/EtOH/$CHCl_3$.

Table 2. Influence of the 5-Position Alkoxy Substituents on Receptor Binding



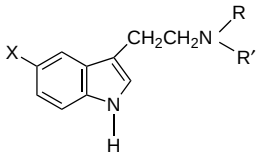
		K_i, nM (SEM)		
no.	*n*	5-HT1A	5-HT1Dβ	selectivity[a]
5	0	3.2(1.1)	3.5(0.9)	1
6	2	88(29)	4.6(1.3)	19
7	4	42(10)	1.6(0.7)	26
8	6	38(5)	1.0(0.1)	38
9	7	48(13)	3.0(1.7)	16
10	8	315(15)	1.0(0.2)	315
11	9	575(45)	35(15)	16
12	10	885(145)	21(7)	44
sumatriptan		330(22)	10(2)	33

[a] 5-HT1A K_i/5-HT1Dβ K_i value; selectivity for 5-HT1Dβ sites.

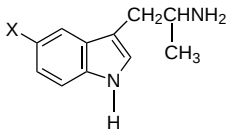
Results and Discussion

***O*-Alkyl Derivatives of Serotonin.** Tryptamine (**4**) binds at 5-HT1D (5-HT1D K_i = 23 nM, 5-HT1Dβ K_i = 36 nM) receptors with modest affinity and with little selectivity over 5-HT1A receptors (K_i = 91 nM). Serotonin (**1**) binds with 10-fold higher affinity but with less selectivity (5-HT1D K_i = 2.2 nM, 5-HT1Dβ K_i = 4.0 nM, 5-HT1A K_i = 1.7 nM). Thus, the presence of the 5-position hydroxyl group enhances affinity both at 5-HT1A and 5-HT1D/5-HT1Dβ receptors, but its presence seems to have a greater effect on 5-HT1A binding. The hydroxy group may participate in hydrogen bond formation with the receptors, but if it does, it likely behaves as a hydrogen bond acceptor because *O*-methyl-5-HT (i.e., **5**; Table 2) binds at 5-HT1Dβ (K_i = 3.5 nM) and 5-HT1A (K_i = 3.2 nM) receptors with an affinity comparable to that of 5-HT. This result is consistent with our previous conclusion for 5-HT1D (bovine homogenate) binding,[14] but is inconsistent with the recent observation by Macor et al.[11] that 5-methoxyindoles bind with lower affinity than their corresponding hydroxy derivatives.

Table 3. Influence of Branching and Amine Substituents on Receptor Affinity



13–16, 27, 28



29, 30

			K_i, nM (SEM)		
no.	X	R/R′	5-HT1A	5-HT1Dβ	select[a]
13	$(CH_3)_2CH(CH_2)_6O$	H/H	1180(360)	14(3)	84
14	$(CH_3)_3C(CH_2)_7O$	H/H	63(12)	2.0(0.2)	32
15	$(CH_3)_3C(CH_2)_6O$	H/H	920(80)	2.3(0.8)	400
16	$(C_6H_{11})(CH_2)_4O$	H/H	800(20)	22(3)	36
27	$CH_3(CH_2)_8O$	Me/Me	575(45)	40(12)	14
28	$CH_3(CH_2)_8O$	H/*n*-Bu	1550(190)	135(22)	11
29	HO			250(20)	
30	$CH_3(CH_2)_8O$			53(8)	

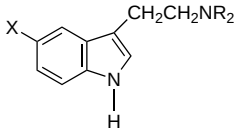
[a] 5-HT1A K_i/5-HT1Dβ K_i value.

Accordingly, we began to probe the previously defined region of bulk tolerance associated with the indole 5-position by examining a series of *O*-alkyl derivatives of 5-HT (Table 2). Indeed, variation of alkyl chain length from *O*-methyl to *O*-*n*-nonyl (i.e., **5**−**10**) had little effect on 5-HT1Dβ affinity, and all derivatives were found to bind with an affinity comparable to that of 5-HT itself. These results support our previous hypothesis concerning a region of bulk tolerance.[14] Furthermore, 5-HT1A receptors also possess a region of bulk tolerance, as reflected by the binding of **6**−**9**, but a region of bulk tolerance whose dimensions are evidently different than that associated with 5-HT1Dβ receptors. *O*-Alkyl substituents longer than *n*-octyloxy (i.e., **9**) are not readily accommodated by 5-HT1A receptors, and the greatest difference is associated with the nonyloxy compound **10**.

As a further probe of these regions of bulk tolerance, we prepared several branched derivatives such as **13**−**16**. The ω-dimethyl and cyclohexyl derivatives **13** and **16** display reduced affinity for 5-HT1Dβ receptors relative to 5-HT (Table 3). It is noteworthy, nonetheless, that both **13** and **16** bind at 5-HT1Dβ receptors with greater affinity and selectivity than tryptamine (**4**). The ω-trimethyl derivative **14** retains 5-HT1Dβ affinity but binds with unexpectedly high affinity for 5-HT1A receptors. However, the ω-trimethyl derivative **15** retains the high 5-HT1Dβ affinity of **14** and displays 400-fold selectivity versus 5-HT1A receptors. As such, **15** is the most 5-HT1Dβ- versus 5-HT1A-selective agent reported to date.

Role of the Ether Oxygen for 5-HT1Dβ Binding. The binding of tryptamine (**4**) at 5-HT1D receptors suggests that the 5-position oxygen atom of 5-HT (**1**) is not critical for binding. Nevertheless, its presence does seem to enhance affinity somewhat. Because the oxygen atom appears to play a more important role for 5-HT1A than for 5-HT1D binding, it was thought that 5-alkyl derivatives of tryptamine might provide a new lead for the development of 5-HT1D-selective agents. We began by comparing the 5-HT1D affinity of *O*-methyl-5-HT (**5**) and its *N*,*N*-dimethyl analogue **17** with that of the corresponding pairs of compounds where the ether oxygen atom had been replaced by a methylene group (i.e., **18** and **19**). Table 4 shows that the ether oxygen

Table 4. Role of the Ether Oxygen on 5-HT Receptor Affinity



			K_i, nM (SEM)		
no.	X	R	5-HT1A	5-HT1D[a]	5-HT1Dβ
5	CH_3O	H	3.2(1.1)	4.1(1.0)	3.5(0.9)
17	CH_3O	Me		20	
18	CH_3CH_2	H	20(6)		7.8(1.8)
19	CH_3CH_2	Me	15(4)		5.5(0.3)
20	$CH_3(CH_2)_8CH_2$	H	2300(200)		275(35)
21	$CH_3C(=O)$	H	1.3(0.3)	9.7(2.1)	7.4(1.4)
22	$CH_3C(=O)O$	Me		31(1)	
23	$CH_3CH_2C(=O)O$	Me	405(6)	17(4)	59(1)
24	$(CH_3)_2CHC(=O)O$	Me		98(17)	52(4)
25	$(CH_3)_3CC(=O)O$	Me		110(20)	63(5)
26	$CH_3(CH_2)_7C(=O)O$	Me	9.3(0.8)		1.1(0.3)

[a] Homogenate binding data.

contributes little to the binding of these compounds (e.g., **5**, 5-HT1Dβ K_i = 3.5 nM; **18**, K_i = 7.8 nM). Thus, we prepared and examined the chain-extended derivative **20** (i.e., the methylene counterpart of **10**); surprisingly, the affinity of **20** is 275-fold lower than that of **10**. It would seem that the oxygen atom plays more of a role in the binding of longer chain compounds (such as **10**) than it does in the binding of simpler compounds such as **18**.

Focusing on the possible requirement of an oxygen atom for optimal binding, we wondered if it was necessary for the oxygen atom to be attached directly to the aromatic nucleus or whether the electron density associated with this general location would be sufficient for binding. Accordingly, we replaced the benzylic methylene group of **18** (K_i = 7.8 nM), or alternatively the ether oxygen atom of **5** (K_i = 3.5 nM), with a carbonyl group; the resulting derivative, **21**, was found to bind at 5-HT1Dβ receptors with comparable affinity (K_i = 7.4 nM). We continued this investigation by examining a series of esters (i.e., derivatives that contained two oxygen atoms; see below).

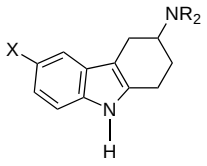
In an earlier investigation we found that *N*,*N*-disubstitution decreases the affinity of tryptamines for 5-HT1D receptors in bovine brain homogenate preparations;[14] see also **5** and **17** (Table 4). However, because the 5-HT1Dβ affinity of **18** and **19** (Table 4) were nearly identical, we continued by examining several additional *N*,*N*-dimethyl derivatives. Compound **22**, for example, is the *N*,*N*-dimethyl ester analogue of **21**. Compounds **22**−**25** bind at 5-HT1Dβ receptors with roughly similar affinity (K_i = 52−63 nM), supporting the concept of a region of bulk tolerance. As with the compounds in Table 2, we extended the length of the alkyl chain to provide ester **26** (i.e., an ester whose chain length is similar to that of **10**). Ester **26** (K_i = 1.1 nM) retained the 5-HT1Dβ affinity of **10**; however, it lacked 5-HT1Dβ versus 5-HT1A selectivity.

The general conclusion is that although the ether oxygen may not be necessary for the binding of shorter chain compounds, its presence seems desirable for optimal 5-HT1Dβ affinity and selectivity.

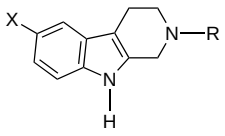
Effect of *N*-Alkyl and α-Alkyl Substituents on 5-HT1Dβ Binding. 5-HT1A receptors allow the presence of relatively small terminal amine groups with no untoward effect on affinity;[13] however, *N*-alkyl derivatives possessing alkyl groups longer than *n*-propyl typically bind with reduced affinity. 5-HT1D receptors seem much more sensitive to the effect of small terminal amine substituents.[14] In order to determine if this is the case for 5-HT1Dβ receptors, we examined the *N*,*N*-dimethyl and *N*-mono-*n*-butyl analogues of **10** (i.e., **27** and **28**, respectively). Both compounds (**27**, K_i = 40 nM; **28**, K_i = 135 nM; Table 3) bind with reduced affinity relative to **10** itself (K_i = 1.0 nM). Although this was not the case with, for example, **18** versus **19**, further work with *N*-alkyl derivatives was abandoned.

α-Methylation of tryptamine derivatives results in a 50−60-fold decrease in 5-HT1D binding.[14] In order to evaluate this effect on 5-HT1Dβ binding, we examined (±)-α-methyl-5-HT and (±)-α-methyl-**10** (**29** and **30**, respectively). Compound **29** (K_i = 250 nM; Table 3) binds with 60-fold lower affinity than 5-HT itself; the α-methyl derivative of **10** (**30**; K_i = 53 nM) also binds with reduced affinity. Thus, consistent with our previous 5-HT1D-derived SAR,[14] substitution α to the terminal amine does not appear optimal for these types of analogues.

Table 5. Binding Affinities of Cyclic Tryptamine Analogues



31–36



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no.	X	R	5-HT1Dβ K_i, nM (SEM)
31	CH_3O	H	342(26)
32	CH_3O	Me	>1000
33	$H_2NC(O)$	H	10[a]
34	$CH_3(CH_2)_8O$	H	172(12)
35	$CH_3(CH_2)_5O$	H	188(31)
36	$CH_3(CH_2)_8CH_2$	H	>1000
37	$CH_3(CH_2)_8O$	Me	>1000

[a] Literature data,[10] reported as pK_D = 8.0 using pig caudate membrane homogenate.

Cyclic Analogues. Methyl substitution at the 2-position of 5-HT reduces 5-HT1D affinity by more than 400-fold.[14] Elaboration of this methyl group to give the cyclic derivatives **31** (K_i = 342 nM) and **32** (K_i > 1000 nM; Table 5) also results in low-affinity compounds. However, King et al.[10] recently reported that carbazole **33** binds at 5-HT1D receptors with high affinity. Compound **33** (pK_D = 8.0), a cyclic analogue of 5-carbamoyltryptamine (**2**; pK_D = 8.8), reportedly retains the affinity of its uncyclized counterpart for pig caudate 5-HT1D receptors. Accordingly, we examine compounds **34** and **37** (carbazole and β-carboline derivatives of **10**) and **35** (a chain-shortened carbazole analogue). The carboline **37** (K_i > 1000 nM) was inactive. The carbazoles **35** (K_i = 188 nM) and **34** (K_i = 172 nM) were found to bind with low affinity. Indeed, **34** binds with >100-fold lower affinity than its corresponding uncyclized derivative **10**. Compound **36**, the methylene counterpart of **34**, is also inactive. At this time, it is not known if these conflicting results reflect differing binding roles of the indole 5-position substituents or differences between porcine versus human 5-HT1D receptors. Nevertheless, the low affinities of our cyclic analogues suggest that the 2-position of the indole nucleus does

Table 6. 5-HT1Dβ versus 5-HT1Dα Binding Data on Selected Compounds

no.	5-HT1Dβ K_i, nM[a]	5-HT1Dα K_i, nM (±SEM)	select
1	4.0	1.7(0.3)	0.4
4	36	61(14)	1.7
5	3.5	5.4(0.6)	1.5
7	1.6	1.5(0.2)	0.9
8	1.0	4.9(2.2)	4.9
10	1.0	1.6(0.3)	1.6
11	65	42(8)	0.7
12	21	69(7)	3.3
13	14	42(9)	3.0
15	2.3	16(6)	7.0
16	22	55(5)	2.5
20	275	210(12)	0.8
27	40	42(1)	1.0
28	135	223(52)	1.7
31	342	1190(337)	3.5
34	172	2350(760)	13.6
35	188	1098(440)	5.8

[a] See text or previous tables for data; included here only for purpose of comparison.

not readily allow substitution and/or that the tryptamine side chain is in the wrong conformation for optimal affinity.

5-HT1Dβ vs 5-HT1Dβ Selectivity. To date, agents are unknown that selectively bind to one population of human 5-HT1D receptors over the other. In order to determine if any of the present compounds might display any selectivity, 16 were selected at random and compared with 5-HT (**1**). Table 6 shows than none of the compounds binds at one of the two populations with more than 15-fold selectivity.

Summary. Sumatriptan (**3**) is a high-affinity 5-HT1D ligand. In order to develop novel compounds with similar affinity for 5-HT1D receptors but with reduced affinity for 5-HT1A receptors, we explored the possibility that substitution on the serotonin oxygen atom with alkyl groups of differing length might impart enhanced selectivity. Small *O*-alkyl groups are tolerated both at 5-HT1A and 5-HT1D receptors. Longer alkyl groups seem to be better tolerated at 5-HT1D relative to 5-HT1A receptors. Of the unbranched *O*-alkyl analogues, the *O*-nonyloxy derivative **10** is optimal in terms of affinity ($K_i = 1$ nM) and selectivity (315-fold). Other structural features were also examined in the present investigation. For example, alkyl branching as with **15**, but not with **13**, **14**, or **16**, can result in enhanced selectivity. Alkyl substitution on the terminal amine, and α-methylation, in the few cases examined, does not result in enhanced affinity or selectivity. Conversion of the *O*-alkyl substituents to esters, as with **22**−**26** results in compounds that bind; however, comparing **26** with **10**, selectivity is reduced. Replacement of the oxygen atom of **10** with a methylene group (i.e., **20**) results in reduced 5-HT1D affinity, as does cyclization of **10** to a carbazole or β-carboline (e.g., **34**, **37**). The most interesting agent described in this study is compound **10**; this prompted its disclosure in an earlier communication in which it was described that **10** behaves as a 5-HT1D agonist with no 5-HT1A agonist properties at the highest doses evaluated.[15]

Experimental Section

Synthesis. Column chromatography was performed on silica gel (grade 62, 60−200 mesh, 150 Å). Merck grade 60 silica gel (230−400 mesh, 60 Å) or MN-silica gel 60 were used for flash chromatography. Melting points, determined on a Thomas-Hoover melting point apparatus, are uncorrected. Proton magnetic resonance spectra were obtained with a GE QE-300, Bruker AC-300, or a Bruker AMX-500 spectrometer; tetramethylsilane was used as an internal standard. Infrared spectra were recorded on a Nicolet 5ZDX FT-IR. High-resolution mass spectra were determined using a VG Analytical ZAB-SE mass spectrometer. Tetrahydrofuran and toluene were dried by distallation with sodium metal. Elemental analyses were performed by Atlantic Microlab Inc. (Norcross, GA), and determined values are within 0.4% of theory except where noted.

3-(2-Aminoethyl)-5-(*n*-pentyloxy)indole Oxalate (7). Method A. A suspension of 5-(benzyloxy)tryptamine (1.9 g, 7.13 mmol) in 10% HCl (30 mL) was treated with NaOAc (20 g), and the solution volume was adjusted to about 80 mL with H_2O. The mixture was allowed to stir at room temperature for 30 min; a few pieces of ice chips were added followed by acetic anhydride (20 mL), and the reaction mixture was allowed to stir for 1 h. The precipitated materials were collected and washed with H_2O (2 × 20 mL), and the solid was recrystallized from CH_2Cl_2/hexane to give 1.6 g (74%) of *N*-acetyl-5-(benzyloxy)tryptamine as a white solid, mp 133−134 °C. A solution of this tryptamine (2.2 g, 7.13 mmol) in absolute EtOH (50 mL) was treated with Raney nickel (4.4 g) in a Parr hydrogenation bottle and hydrogenated at 40 psi overnight. The catalyst was removed by filtration through a Celite pad, and the filtrate was concentrated under reduced pressure to give an oil. The oil was purified by column chromatography using a solvent system of CH_2Cl_2/MeOH (90:10) to give 1.5 g (95%) of *N*-acetyl-5-HT as an oil.

A stirred mixture of *N*-acetyl-5-HT (0.45 g, 2.07 mmol), 1-bromopentane (1.75 g, 11.59 mmol), anhydrous K_2CO_3 (0.94 g, 6.83 mmol), and MeOH (7 mL) in 2-butanone (40 mL) was heated at reflux overnight under N_2. After being allowed to cool to room temperature, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give an oil. A solution of the oil in CH_2Cl_2 (50 mL) was washed successively with 2 N NaOH (1 × 30 mL) and H_2O (1 × 30 mL). The organic portion was dried ($MgSO_4$), and solvent was removed under reduced pressure to give an oil. The oil was purified by column chromatography using a solvent system of CH_2Cl_2/MeOH (90:10) to give 0.53 g of the *O*-alkylated product as an oil. Without further purification, the resulting oil in 2 N HCl (10 mL) was heated at reflux for 20 h. After the reaction mixture was allowed to cool to room temperature, 2 N NaOH (20 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic portions were washed with H_2O (1 × 30 mL) and dried ($MgSO_4$), and the solvent was removed under reduced pressure to give an oil. The resulting oil was purified by column chromatography using a solvent system of CH_2Cl_2/MeOH (90:10). The combined fractions from the column were evaporated under reduced pressure to give 0.16 g (31%) of **7** (free base) as an oil. The oil in anhydrous Et_2O (5 mL) was added to a saturated ethereal solution of oxalic acid. The resultant oxalate salt was collected by filtration, washed with anhydrous Et_2O (2 × 10 mL), and recrystallized from MeOH/Et_2O to give a white solid, mp 145−147 °C. Anal. ($C_{15}H_{22}N_2O \cdot 0.9C_2H_2O_4$) C, H, N.

Compounds **6**, **8**, **9**, and **12** were prepared in a similar manner; see Table 1.

3-(2-Aminoethyl)-5-(*n*-nonyloxy)indole Hydrochloride (10). Method B. Potassium carbonate (3.50 g, 25 mmol) was added in one portion to a solution of *N*-*t*-BOC serotonin (**38**) (3.95 g, 14 mmol) in MeCN (50 mL). Nonyl bromide (2.96 g, 14 mmol) was added via syringe, and the resulting reaction mixture was allowed to stir under reflux conditions for 24 h. After the reaction mixture had reached room temperature, the solid material was removed by filtration and the solvent was evaporated under reduced pressure. The crude product was purified using flash chromatography with 25% EtOAc/hexanes as eluent. The product (4.10 g, 73%) was recovered as a yellow/brown oil which solidifed upon standing, mp 64−65 °C. HRMS (EI): M^+ for $C_{24}H_{38}N_2O_3$, calcd 402.2882, found 402.2861.

A solution of HCl (3 M) in EtOAc (50 mL) was added with vigorous stirring to a solution of the above N-protected

nonyloxy compound (4.00 g, 10 mmol) in EtOAc (10 mL). After the reaction mixture was allowed to stir for 2 h (a white precipitate formed after 5 min), solvent was evaporated under reduced pressure and the product was triturated with anhydrous Et_2O. The solid product was collected by filtration and washed well with anhydrous Et_2O and then EtOAc to yield 2.37 g (70%) of **10**, mp 196−198 °C. A small portion of the product was converted to the hydrogen oxalate salt, mp 149−150 °C (lit.[15] mp 148−150 °C).

Compounds **11** and **13**−**16** were prepared in a similar manner (see Table 1).

3-(2-Aminoethyl)-5-ethylindole Oxalate (18). Solid $NaNO_2$ (3.16 g, 45.8 mmol) was added to a suspension of 4-ethylaniline (5.0 g, 41.3 mmol) and concentrated HCl (17 mL) in H_2O (26 mL) under an ice−H_2O bath. This solution was kept at 0 °C with stirring while ethyl 2-methylacetoacetate (6.6 g, 45.8 mmol) in 95% EtOH (43 mL) was treated at 0 °C with a solution of 50% KOH (16.5 mL) followed at once by ice (85 g). The diazo solution was then added immediately; the reaction mixture was allowed to stir at room temperature for 1 h and was then extracted with Et_2O (2 × 50 mL). The combined Et_2O fractions were washed with H_2O (2 × 50 mL) and dried ($MgSO_4$), and the solvent was removed under reduced pressure to give an oil. Absolute EtOH (33 mL) saturated at 0 °C with anhydrous HCl gas was added to a stirred solution of the oil in absolute EtOH (25 mL) at 0 °C. The solution was heated at reflux for 30 min and then allowed to stir at room temperature for 2 h. The suspension was poured into cold H_2O (200 mL) and was extracted with Et_2O (2 × 200 mL). The combined Et_2O fractions were washed with H_2O (2 × 200 mL) and dried ($MgSO_4$), and the solvent was removed under reduced pressure to give a solid which was recrystallized from CH_2Cl_2/hexane to provide 3.12 g (35%) of a yellow solid, mp 98−99 °C. A suspension of this solid (0.34 g, 1.56 mmol) in 95% EtOH (5 mL) was added to a solution of KOH (0.66 g) in H_2O (2 mL) and heated at reflux for 1 h to give a clear solution. The solution was acidified with glacial acetic acid and poured into cold H_2O (40 mL). The solid was washed well with H_2O (2 × 10 mL) to give 0.29 g (98%) of 5-ethylindole-2-carboxylic acid as a tan solid, mp 180−181 °C.

The mixture of the above acid (0.5 g, 2.64 mmol), freshly distilled quinoline (5 mL), and copper chromite (0.1 g) was immersed in an oil bath and heated at about 240 °C for 3 h under N_2. The cooled brown syrup was poured into Et_2O (50 mL); the solution was decolorized with activated carbon (Darco G-60, 100 mesh), filtered, and washed successively with 2 N HCl (4 × 20 mL) and 2 N NaOH (2 × 20 mL). The solution was washed with H_2O (3 × 20 mL), again decolorized with activated carbon, filtered, and dried ($MgSO_4$). The solvent was removed under reduced pressure to give a yellow oil which as purified [Kugelrohr, bp 73−80 °C (0.35 mmHg)] to give 0.26 g (67.8%) of 5-ethylindole as a colorless oil.

A solution of oxalyl chloride (1.22 g, 9.59 mmol) in anhydrous Et_2O (10 mL) was added over a 5-min period to a solution of 5-ethylindole (1.16 g, 7.99 mmol) in anhydrous Et_2O (20 mL) at 0 °C. The reaction mixture was allowed to stir at room temperature for 1 h. The bright yellow precipitate was collected by filtration, washed with anhydrous Et_2O (2 × 20 mL), and immediately added to concentrated NH_4OH (20 mL) at 0 °C. The basic solution was allowed to stir at room temperature for 4 h, and the solid was collected by filtration, washed with H_2O (3 × 20 mL), air-dried, and recrystallized from acetone to afford 1.4 g 81%) of glyoxylamide as a light yellow solid, mp 230−233 °C. A suspension of the gloxylamide (1.36 g, 6.29 mmol) and $LiAlH_4$ (1.56 g, 40.9 mmol) in dry THF (50 mL) was heated at reflux for 4 days under N_2. After the reaction mixture was allowed to cool to room temperature, excess $LiAlH_4$ was decomposed by the addition of a saturated solution of sodium potassium tartrate (5 mL) at 0 °C. The precipitated material was removed by filtration, and the filtrate was dried ($MgSO_4$). The solvent was removed under reduced pressure to afford an oily product which was dissolved in Et_2O (50 mL) and extracted with 2 N HOAc (3 × 20 mL). The combined acid extracts were basified with 2 N NaOH. The basic solution was extracted with Et_2O (3 × 20 mL), and the combined Et_2O extracts were washed with H_2O (1 × 30 mL). The solution was dried ($MgSO_4$) and evaporated under reduced pressure to give an oil which was purified by column chromatography using a solvent system of CH_2Cl_2/MeOH (9:1). The combined fractions from the column were evaporated under reduced pressure to afford 0.4 g (33.7%) of the desired tryptamine as an oil. The oxalate salt was prepared and recrystallized from MeOH/Et_2O to afford **18** as a white solid, mp 195−197 °C. Anal. ($C_{12}H_{16}N_2 \cdot 0.5C_2H_2O_4$) C, H, N.

3-[2-(*N*,*N*-Dimethylamino)ethyl]-5-ethylindole Oxalate (19). A solution of oxalyl chloride (0.73 g, 5.79 mmol) in anhydrous Et_2O (10 mL) was added over a 5-min period to a solution of 5-ethylindole (0.7 g, 4.82 mmol) in anhydrous Et_2O (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1h. The bright yellow precipitate was collected by filtration, washed with anhydrous Et_2O (2 × 20 mL), and immediately added to a stirred solution of dimethylamine (6 mL, 40% in H_2O) in H_2O (20 mL); stirring at room temperature was allowed to continue overnight. The precipitated material was collected by filtration, washed with H_2O (3 × 20 mL), air-dried, and recrystallized from MeOH/H_2O to afford 0.92 g (78.1%) of the glyoxylamide as a light-yellow solid, mp 177−178 °C. A suspension of the glyoxylamide (1.15 g, 4.71 mmol) and $LiAlH_4$ (1.16 g, 30.6 mmol) in dry THF (50 mL) was heated at reflux for 3 days under N_2. After the reaction mixture was allowed to cool to room temperature, the $LiAlH_4$ was decomposed by the addition of a saturated solution of sodium potassium tartrate (7 mL) at 0 °C. The precipitated material was removed by filtration, and the filtrate was dried ($MgSO_4$). The solvent was removed under reduced pressure to afford an oily product which was purified by column chromatography using a solvent system of CH_2Cl_2/MeOH (9:1). The combined fractions from the column were evaporated under reduced pressure to give an oil that solidified on standing at room temperature. Without further purification, the free base was dissolved in anhydrous Et_2O (10 mL) and added to a saturated ethereal solution of oxalic acid. The resultant oxalate salt was collected by filtration, washed with anhydrous Et_2O (2 × 10 mL), and recrystallized from MeOH/Et_2O to afford 0.52 g (36%) of **19** as white needles, mp 178−179 °C. Anal. ($C_{14}H_{20}N_2 \cdot C_2H_2O_4$) C, H, N.

3-(2-Aminoethyl)-5-*n*-decylindole Hydrochloride (20). A solution of 4-*n*-decylaniline (3 g, 12.9 mmol) in dry toluene (30 mL) was added dropwise to a stirred solution of BCl_3 (1.0 M in CH_2Cl_2, 35 mL) at 0 °C under N_2. The resultant solution was allowed to stir for 5 min, and then chloroacetonitrile (5.1 mL, 79.3 mmol) and $AlCl_3$ (3.5 g, 26.3 mmol) were added in succession in small portions. The mixture was heated at reflux for 6 h and cooled on an ice bath, and HCl (2 N, 18 mL) was added. The suspension was warmed on an oil bath at 70−72 °C for 45 min. NaOH (2 N) was added slowly with stirring to the resultant hydrolyzed product to attain pH 6; during the addition, the temperature was kept below 15 °C with an ice bath. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (4 × 30 mL). The combined organic portions were dried ($MgSO_4$), and solvent was evaporated under reduced pressure to give a brown residue. The crude product was purified by chromatography using a solvent system of EtOAc/hexane (1:9) to afford 0.39 g (9%) of a solid material. $NaBH_4$ (0.093 g, 2.45 mmol) was slowly added to a stirred solution of the solid (0.38 g, 1.22 mmol) in dioxane (3 mL) and H_2O (0.3 mL), and the mixture was heated at reflux for 6 h. The solvents were evaporated under reduced pressure to give an oil. Water (10 mL) was added to the oil, and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined CH_2Cl_2 extracts were dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give 0.28 g of a crude oil which was purified by column chromatography using a solvent system of hexane/$CHCl_3$ (1:1) to afford 0.26 g (82%) of 5-*n*-decylindole, mp 82−84 °C.

A solution of oxalyl chloride (0.15 g, 1.18 mmol) in anhydrous Et_2O (5 mL) was added dropwise to a solution of 5-*n*-decylindole (0.25 g, 0.98 mmol) in anhydrous Et_2O (10 mL) at 0 °C. The reaction mixture was allowed to stir at room temperature for 1 h. The bright yellow precipitate was collected by filtration, washed with hexanes (2 × 20 mL), and immediately added to concentrated NH_4OH (10 mL) at 0 °C.

The basic solution was allowed to stir at room temperature for 4 h, and the solid was collected by filtration, washed with H_2O (3 × 10 mL), air-dried, and recrystallized from methanol to afford 0.20 g (66%) of the glyoxylamide as a light yellow solid, mp 205−208 °C. A solution of the glyoxylamide (0.1 g, 0.31 mmol) and $LiAlH_4$ (0.08 g, 2.06 mmol) in dry THF (15 mL) was heated at reflux for 3 days under N_2. After allowing the reaction mixture to cool to room temperature, excess $LiAlH_4$ was decomposed by the addition of a saturated solution of sodium potassium tartrate (1 mL) at 0 °C. The precipitated material was removed by filtration, and the filtrate was dried ($MgSO_4$). The solvent was removed under reduced pressure to afford an oily product which was purified by column chromatography using a solvent system of CH_2Cl_2/MeOH (9:1). The free base was converted to the hydrochloride salt; recrystallization of the crude salt from MeOH/Et_2O gave 33 mg (30%) of **20** as a white solid, mp 198−200 °C. Anal. ($C_{20}H_{32}N_2$·HCl·0.5H_2O) C, H, N.

3-[2-(*N*,*N*-Dimethylamino)ethyl]-5-[(*n*-octylcarbonyl)-oxy]indole Oxalate (26). A stirred mixture bufotenine hemioxalate (297 mg, 1 mmol), octanoyl chloride (195 mg, 1.2 mmol), and NEt_3 (177 mg, 3 mmol) in dry benzene (15 mL) was heated at reflux for 8 h under N_2. After the reaction mixture was allowed to cool to room temperature, it was filtered, and the filtrate was concentrated under reduced pressure to give an oil. The oil was taken up in CH_2Cl_2 (50 mL) and washed with 0.2 N NaOH (2 × 20 mL) and H_2O (2 × 20 mL). The organic portion was dried ($MgSO_4$), and the solvent was removed under reduced pressure to give an oil which was purified by column chromatography (8:2 CH_2Cl_2/MeOH). The oil in anhydrous Et_2O (5 mL) was added to a saturated ethereal solution of oxalic acid (10 mL). The resultant salt was collected by filtration, washed with anhydrous Et_2O, and recrystallized from MeOH/Et_2O to afford 226 mg (56% yield) of **26** as a white solid, mp 135−137 °C. Anal. ($C_{21}H_{32}N_2O_2$·$C_2H_2O_4$·H_2O) C, H, N.

3-[2-(*N*,*N*-Dimethylamino)ethyl]-5-[(*n*-nonyloxy)indole Oxalate (27). Sodium cyanoborohydride (0.13 g, 2.1 mmol) was added to a stirred solution of **10** (free base; 0.22 g, 0.7 mmol) and CH_2O (37%; 0.21 g, 0.7 mmol) in MeCN (7 mL). Glacial HOAc (0.07 mL) was added, and stirring was allowed to continue; after 2 h, additional HOAc (0.07 mL) was added, and the reaction mixture was allowed to stir for 30 min. The reaction mixture was poured into Et_2O (50 mL). The solution was washed with 1 N KOH (3 × 10 mL) and brine (10 mL), dried (K_2CO_3), and evaporated to dryness under reduced pressure to give 0.24 g of residue. This solid material was purified by column chromatography (silica gel, 60 mesh) using MeOH as eluent to give 0.06 g (25%) of **27** (free base) as an oil. The oxalate salt was prepared and recrystallized from absolute EtOH/anhydrous Et_2O to afford **27** as a white solid, mp 128−131 °C. Anal. ($C_{21}H_{34}N_2O$·$C_2H_2O_4$·0.25 H_2O) C, H, N.

3-[2-(*N*-Butylamino)ethyl]-5-(*n*-nonyloxy)indole Oxalate (28). A solution of butyryl chloride (0.12 g, 1 mmol) in THF (3 mL) was added dropwise to a stirred solution of **10** (free base; 0.33 g, 1 mmol) and Et_3N (0.16 g, 2 mmol) in THF (10 mL) at 0 °C (ice bath). The reaction mixture was allowed to stir overnight at room temperature. The white precipitate (Et_3N·HCl) was removed by filtration and washed well with THF (2 × 5 mL), and the combined filtrate and washings were evaporated under reduced pressure. The oily residue in $CHCl_3$ (10 mL) was washed successively with 5% HCl (20 mL), 5% Na_2CO_3 solution (30 mL), and H_2O (30 mL). The $CHCl_3$ portion was dried ($MgSO_4$), and the solvent was removed under reduced pressure to afford 0.33 g (83%) of a yellow, oily intermediate amide. The compound was promptly used in the next step without further characterization. AlH_3 was prepared by the careful addition of $AlCl_3$ (0.2 g, 1.5 mmol) to a suspension of $LiAlH_4$ (0.2 g, 5.2 mmol) in anhydrous Et_2O (15 mL) at 0 °C, under N_2. The suspension was allowed to stir for 30 min at room temperature, and then a solution of the above amide (0.33 g, 0.9 mmol) in anhydrous Et_2O (10 mL) was added in dropwise manner. The reaction mixture was allowed to stir for 5 h at room temperature. Excess AlH_3 was decomposed by the addition of crushed ice (1 g) and 20% NaOH solution (2 mL) at 0 °C. The mixture was filtered, and the organic portion of the filtrate was washed with H_2O (3 × 15 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford a crude product. The oil was chromatographed on a silica gel column (silica gel, 60 mesh) using a $CHCl_3$:CH_3OH (9:1) mixture as eluent. Treatment of the oil product with a saturated solution of oxalic acid in anhydrous Et_2O gave 0.18 g (45%) of **28**, mp 220−224 °C. Anal. ($C_{23}H_{38}N_2O$·$C_2H_2O_4$) C, H, N.

(±)5-(Nonyloxy)-α-methyltryptamine Hydrochloride (30). A mixture of (±)-5-(benzyloxy)-α-methyltryptamine[24] (0.56 g, 2.0 mmol) and di-*tert*-butyl dicarbonate (0.44 g, 2.0 mmol) in EtOAc (20 mL) was allowed to stir at room temperature for 24 h under N_2 and was then washed with 5% HCl (2 × 30 mL) and H_2O (3 × 3 mL). The organic portion was dried ($MgSO_4$) and evaporated to dryness under reduced pressure to give 0.67 g (88%) of the product as an oil. A solution of the oil (0.76 g, 2.0 mmol) in MeOH (50 mL) containing 10% Pd/C (0.25 g) was hydrogenated in Parr apparatus at 40 psi for 12 h. The reaction mixture was filtered, and the filtrate was evaporated under reduced pressure to give 0.44 g (76%) of (±)-5-hydroxy-*N*-*t*-BOC-α-methyltryptamine as a yellow/brown foam, mp 60−62 °C. A mixture of this protected amine (0.58 g, 2.0 mmol), 1-bromononane (0.62 g, 3.0 mmol), and K_2CO_3 (0.41 g, 3.0 mmol) in MeCN (20 mL) was heated at reflux for 24 h under N_2 with stirring. After the reaction mixture was cooled to room temperature, the solid was removed by filtration and the solvent evaporated under reduced pressure to give 0.47 g of an oily product. The oil was purified by column chromatography (25% EtOAc/hexane) to give 0.34 g (62%) of product as an oil. A solution of 3 N HCl in EtOAc (15 mL) was added to a solution of (±)-5-(nonyloxy)-*N*-*t*-BOC-α-methyltryptamine (0.42, 1.0 mmol) in EtOAc (5 mL). The mixture was allowed to stir for 2 h. The precipitated product was collected by filtration and washed with EtOAc (2 × 15 mL) and Et_2O (2 × 15 mL). An analytical sample was prepared by recrystallization from 1-propanol to give 0.28 g (78%) of **30**, mp 201−202 °C. Anal. ($C_{20}H_{32}N_2O$·HCl·0.5H_2O) C, H, N.

(±)3-Amino-6-methoxy-1,2,3,4-tetrahydrocarbazole (31). Hydrazine hydrate (0.10 g, 1.99 mmol) was added via syringe to a solution of **42** (0.345 g, 1.0 mmol) in $CHCl_3$ (10 mL); absolute EtOH (15 mL) was then added *via* syringe. The reaction mixture was allowed to stir overnight at room temperature, cooled to 0 °C, and filtered, and the solid material was washed with small amounts of cold $CHCl_3$. The combined solvent was removed under reduced pressure to give 0.18 g (83%) of **31** as a yellow solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.6 (br s, 1H), 1.74−1.80 (m, 1H), 2.02−2.06 (m, 1H), 2.41−2.46 (m, 1H), 2.78 (t, J = 6.35 Hz, 2H), 2.98 (ddd, J = 14.9, 5.1, 1.1 Hz, 1H), 3.27−3.29 (m, 1H), 3.84 (s, 3H), 6.76 (dd, J = 8.7, 2.5 Hz, 1H), 6.91 (d, J = 2.5 Hz, 1H), 7.13 (d, J = 8.7 Hz, 1H), 7.85 (s, 1H); HRMS (FAB) MH^+ calculated for $C_{13}H_{16}N_2O$ 217.1341, found 217.1310.

(±)3-(*N*,*N*-Dimethylamino)-6-methoxy-1,2,3,4-tetrahydrocarbazole Oxalate (32). The free base of compound **32** was obtained as a gift from Dr. A. Mooradian (Sterling-Winthrop Research Institute, Rensselaer, NY)[26] and converted to its oxalate salt, mp 195−197 °C (95% EtOH). Anal. ($C_{15}H_{20}N_2O$·$C_2H_2O_4$) C, H, N.

(±)3-Amino-6-(*n*-nonyloxy)-1,2,3,4-tetrahydrocarbazole (34). Potassium carbonate (0.17 g, 1.24 mmol) and 1-bromononae (0.13 g, 0.62 mmol) were added to a solution of **43** (0.21 g, 0.62 mmol) in anhydrous acetone (30 mL). The resulting solution was heated at reflux for 48 h. The solid was removed by filtration and the solvent removed under reduced pressure. The product (0.23 g, 81%) was isolated as a yellow oil. Due to the instability of this compound, the phthalimide group was removed and full characterization was performed only on the free amine. Deprotection was carried out as described for the preparation of **31**. The free amine was isolated in quantitative yield as a white solid: mp 105−107 °C dec; ^{1}H NMR (MeOH-d_4, 500 MHz) δ 0.9 (t, J = 7 Hz, 3H), 1.28−1.40 (m, 10H), 1.45−1.50 (m, 2H), 1.73−1.78 (m, 2H), 1.94−1.97 (m, 1H), 2.18−2.2 (m, 1H), 2.61 (dd, J = 14.8, 8.6 Hz, 1H), 2.86−2.87 (m, 2H), 3.07 (dd, J = 14.5, 5.0 Hz, 1H), 3.48−3.50 (m, 1H), 3.96 (t, J = 6.5 Hz, 2H), 6.69 (dd, J = 8.7,

2.4 Hz, 1H), 6.85 (d, J = 2.4 Hz, 1H), 7.12 (d, J = 8.7 Hz, 1H); HRMS (FAB) MH^+ calculated for $C_{21}H_{32}N_2O$ 329.2593, found 329.2579.

(±)-3-Amino-6-(hexyloxy)-1,2,3,4-tetrahydrocarbazole (35). This compound was prepared following the same procedure used for the preparation of **34**. 1-Bromohexane was used in the place of 1-bromononane. The product was isolated as a white solid in 65% yield: mp 217−219 °C dec; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 0.9 (t, J = 7 Hz, 3H), 1.28−1.32 (m, 6H), 1.40−1.45 (m, 2H), 1.65−1.71 (m, 2H), 1.85−1.93 (m, 1H), 2.12−2.2 (m, 1H), 2.60 (dd, J = 15.0, 8.9 Hz, 1H), 2.78−2.79 (m, 2H), 2.99 (dd, J = 15.0, 5.2 Hz, 1H), 3.36 (br s, 1H), 3.92 (t, J = 6.5 Hz, 2H), 6.64 (dd, J = 8.7, 2.4 Hz, 1H), 6.83 (d, J = 2.4 Hz, 1H), 7.12 (d, J = 8.7 Hz, 1H), 8.01 (s, 1H); HRMS (FAB) MH^+ calculated for $C_{18}H_{26}N_2O$ 287.2123, found 287.2111.

3-Amino-6-*n*-decyl-1,2,3,4-tetrahydrocarbazole Oxalate (36). A solution of $NaNO_2$ (0.6 g, 8.56 mmol) in H_2O (3 mL) was added to a stirred solution of 4-*n*-decylaniline (2 g, 8.56 mmol) in concentrated HCl (8 mL) at −10 °C. The mixture was stirred at 0 °C for 0.1 h and was then added portionwise to a cooled (−10 °C) and stirred solution of $SnCl_2 \cdot 2H_2O$ (7.25 g, 32 mmol) in concentrated HCl (4.8 mL), during which time the temperature was maintained below −5 °C. The resulting cream-colored suspension was warmed to 25 °C, filtered, and washed with Et_2O (3 × 10 mL). The product was recrystallized from absolute EtOH to afford 1.8 g (75%) of (4-decylphenyl)-hydrazine hydrochloride as a white solid, mp 193−195 °C. A solution of *N*-phthalimido-4-aminocyclohexanone[25] (**41**) (0.4 g, 1.64 mmol) in EtOH (10 mL) was added to a stirred solution of this solid (0.47 g, 1.64 mmol) in EtOH (10 mL). The reaction mixture was heated at reflux for 2 h. The precipitate was collected by filtration and recrystallized from methanol to afford 0.60 g (80%) of 6-*n*-decyl-3-phthalimimido-1,2,3,4-tetrahydrocarbazole as a white solid, mp 100−102 °C.

Hydrazine hydrate (7.5 mL) was added to the carbazole (0.5 g, 1.09 mmol) in absolute EtOH (30 mL). The reaction mixture was heated at reflux for 2 h. The solvent was removed under reduced pressure, and the oily residue was dissolved in EtOAc (50 mL), washed successively with 10% $NaHCO_3$ (5 mL) and H_2O (10 mL), and dried $Mg(SO_4)$. The solvent was removed under reduced pressure to give a white solid. An anhydrous Et_2O solution of the amine was treated an with Et_2O solution of oxalic acid to afford the crude salt; recrystallization from MeOH/anhydrous Et_2O gave 93 mg (20%) of **36** as a white solid, mp 205−208 °C. Anal. ($C_{22}H_{34}N_2 \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

6-(*n*-Nonyloxy)-2-methyl-1,2,3,4-tetrahydro-9*H*-pyrido-[3,4-*b*]indole Oxalate (37). Formic acid (88%, 0.14 g, 3.1 mmol), followed by formaldehyde (36%, 0.20 g, 6.7 mmol), was slowly added to 3-(2-aminoethyl)-5-(*n*-nonyloxy)indole (0.36 g, 1 mmol) at 0 °C. The resulting solution was allowed to stir at 80 °C for 24 h, cooled to 0 °C, and acidified with 6 N HCl (1 mL). The mixture was extracted with Et_2O (3 × 10 mL), basified to pH 11 by the addition of 20% aqueous NaOH, and extracted with Et_2O (3 × 10 mL). The pooled ether extracts were washed with H_2O (5 mL) and dried ($MgSO_4$), and solvent was removed under reduced pressure. The resulting residue was purified using column (250 mL volume) chromatography on silica gel (62 mesh), eluting with $CHCl_3$:CH_3OH (9:1), followed by preparation of the oxalate salt, to afford 0.19 g (44%) of **37** as a white solid after recrystallization from absolute EtOH/anhydrous Et_2O: mp 220−224 °C; ^{1}H NMR (DMSO-d_6) δ 0.8−0.9 (t, 3H, CH_3), 1.1−1.5 (m, 12H, CH_2), 1.6−1.8 (m, 2H, CH_2), 2.8−3 (m, 5H, CH_2NCH_3), 3.5 (m, 2H, CH_2), 3.9−4.0 (t, 2H, OCH_2), 4.4 (s, 2H, CH_2), 6.7−6.8 (dd, 1H, Ar), 6.9 (d, 1H, Ar), 7.2−7.3 (d, 1H, Ar). Anal. ($C_{21}H_{32}N_2O \cdot 0.5C_2H_5O_4$) C, H, N.

***N*-*t*-BOC-serotonin (38).** Potassium carbonate (4.1 g, 30 mmol) was added all at one time to a suspension of serotonin creatinine sulfate monohydrate (6.0 g, 15 mmol) in H_2O (75 mL); once the solid material had dissolved, di-*tert*-butyl dicarbonate (3.2 g, 15 mmol) was added via syringe, and the resulting mixture was allowed to stir at room temperature for 24 h. The product was extracted with EtOAc (3 × 75 mL), and the combined organic fraction was washed with H_2O (1 × 50 mL), 5% HCl (1 × 50 mL), and brine (1 × 50 mL). The EtOAc portion was dried ($MgSO_4$) and evaporated to dryness to give 3.8 g (93%) of a yellow/brown foam, mp 52−54 °C. HRMS (EI): M^+ for $C_{15}H_{20}N_2O_3$, calcd 276.1474, found 276−1476.

***N*-Phthalimido-*trans*-4-aminocyclohexanol (40).** Potassium carbonate (8.01 g, 58 mmol) followed by *N*-carbethoxyphthalimide (8.01 g, 37 mmol) was added to a solution of *trans*-4-aminocyclohexanol (**39**) (5.04 g, 33 mmol) in H_2O (75 mL). A white precipitate formed immediately, which after stirring at room temperature for 30 min was collected to give 6.97 g (86%) of **40**, mp 177−178 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.42 (qd, J = 13.5, 3.3 Hz, 2H), 1.71 (dd, J = 12.7, 2 Hz, 2H), 1.79 (s, 1H), 2.08 (dd, J = 12.7, 2 HZ, 2H), 2.32 (qd, J = 13.1, 3.4 Hz, 2H), 3.75 (m, 1H), 4.12 (m, 1H), 7.64−7.82 (m, 4H); HRMS (EI) M^+ calculated for $C_{14}H_{15}NO_3$ 245.1052, found 245.1051.

(±)-*N*-Phthalimido-4-aminocyclohexanone (41). Molecular sieves (4 Å, 15 g), followed by PCC (11.5 g, 53 mmol), was added to a solution of **40** (5.23 g, 21 mmol) in CH_2Cl_2 (100 mL). The reaction became dark green in color and was stirred for 3 h. The entire reaction mixture was transferred to a silica gel column (4 in.) and eluted with EtOAc. The solvent was evaporated under reduced pressure to give 4.85 g (95%) of **41** as a white solid: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.0 (m, 2H), 2.45 (m, 4H), 2.6−2.8 (m, 2H), 4.6 (m, 1H), 7.6−7.9 (m, 4H). Compound **41** was used without further characterization.

(±)-*N*-Phthalimido-3-amino-6-methoxy-1,2,3,4-tetrahydrocarbazole (42). A solution of 1 N NaOH (32 mL, 32 mmol) was added to a solution of (4-methoxyphenyl)hydrazine hydrochloride (5.01 g, 29 mmol) in H_2O (100 mL). A precipitate formed immediately, and the reaction was allowed to stir at room temperature for 15 min. The product was extracted into $CHCl_3$ (3 × 75 mL), and the combined organic portions were dried ($MgSO_4$) and evaporated to dryness under reduced pressure to give the free hydrazine as a yellow solid (2.89 g, 72%). Solid (4-methoxyphenyl)hydrazine (2.89 g, 21 mmol) was added in one portion to a solution of *N*-phthalimido-*trans*-4-aminocyclohexanone (**41**; 5.09 g, 21 mmol) in HOAc (100 mL). The solution was heated at reflux for 2 h and then cooled to room temperature and poured into H_2O (200 mL). The product was extracted into $CHCl_3$, and the combined organic portions were washed with H_2O (100 mL), 1% $NaHCO_3$ (100 mL), and brine (100 mL), then dried ($MgSO_4$), and evaporated to dryness under reduced pressure to give **42** as a yellow solid (6.98 g, 96%), mp 211−213 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.82−3.0 (m, 4H), 3.43−3.52 (m, 2H), 3.82 (s, 3H), 4.62−4.72 (m, 1H), 6.79 (dd, J = 8.8, 2.2 Hz, 1H), 6.86 (d, J = 2.2 Hz, 1H), 7.18 (d, J = 8.8 Hz, 1H), 7.73 (dd, J = 5.5, 2.9 Hz, 2H), 7.76 (s, 1H), 7.86 (dd, J = 5.5, 2.9 Hz, 2H); HRMS (FAB): MH^+ calculated for $C_{21}H_{18}N_2O_3$ 347.1396, found 347.1375.

(±)-*N*-Phthalimido-3-amino-6-hydroxy-1,2,3,4-tetrahydrocarbazole (43). Boron tribromide (3.93 mL of a 1 M solution in CH_2Cl_2, 3.93 mmol) was added under argon to a solution of **42** (0.80 g, 2.31 mmol) in anhydrous CH_2Cl_2 (20 mL) at −78 °C. The reaction mixture was allowed to stir at −78 °C for 2 h and then at room temperature overnight. The dark solution was poured into H_2O (100 mL), and the product was extracted into EtOAc (2 × 100 mL). The combined organic portions were washed with brine, dried ($MgSO_4$), and evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography (using 1:1 hexanes: EtOAc as eluent). Carbazole **43** was obtained as a yellow solid (0.152 g, 20%), mp 270 °C dec. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 2.65−2.92 (m, 4H), 3.1−3.28 (m, 2H), 4.45−4.49 (m, 1H), 6.53 (dd, J = 8.5, 2.2 Hz, 1H), 6.65 (d, J = 2.2 Hz, 1H), 7.06 (d, J = 8.5 Hz, 1H), 7.90 (s, 4H), 8.56 (s, 1H), 10.5 (s, 1H). HRMS (EI): M^+ calculated for $C_{20}H_{16}N_2O_3$ 332.1162, found 332.1144.

Radioligand Binding Assay. The polymerase chain reaction (PCR) was used to amplify and clone human 5-HT1Dα and 5-HT1Dβ subtype genes based upon published sequences. The nucleotide sequences were verified by sequencing the DNA, and then both of the genes were subcloned into expression vectors, pcDNA1/Amp and pRc/CMV (Invitrogen). Expression of each gene was confirmed by the transient transfection of COS-1 cells using the pcDNA1/Amp construct.

Stable cell lines of each receptor subtype were generated by transfecting CHO and/or HEK 293 cells with the pRc/CMV construct using lipofectin-mediated DNA transfection (GIBCO). G418-resistant clones were screened for expression using reverse transcription of RNA followed by PCR. All ligand binding studies were performed on membranes from transiently or stably expressing cells.

Radioligand binding studies were performed using membrane homogenates prepared from cells transfected with the human 5-HT1A, 5-HT1Dα, or 5-HT1Dβ genes as previously described.[27] 5-HT1D binding studies were performed using calf striatum homogenates as previously described.[28] 5-HT1A receptors were labeled with 0.2 nM [^{3}H]-8-OH-DPAT. 5-HT1Dα and -β receptors were labeled with 2 nM [^{3}H]-5-HT. Membrane homogenates, radioligands, and competing drugs were incubated at 37 °C for 30 min, followed by rapid filtration through Schleicher & Schuell glass-fiber filters, and counted in ecoscint cocktail in a Beckman 3801 liquid scintillation counter.

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