Brief Articles

N-Methyl-5-*tert*-butyltryptamine: A Novel, Highly Potent 5-HT$_{1D}$ Receptor Agonist

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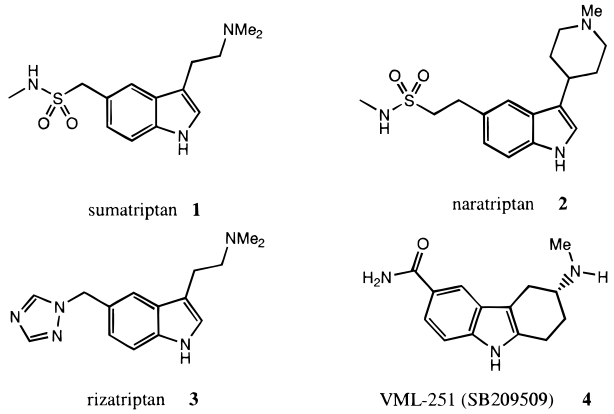
It has been observed that reported 5-HT$_{1D}$ receptor agonists have at least one heteroatom (N, O, or S) on the 5-substituent of the indole. This has led to the hypothesis that a 5-substituent capable of participating in hydrogen bonding is critical for conveying high affinity. This article describes the synthesis and biological evaluation of a new series of 5-alkyltryptamine analogues, which does not have a heteroatom in the 5-substituent group. In contrast to the hypothesis, 5-alkyltryptamines all exhibit high binding affinities for the human 5-HT$_{1D}$ receptor. The size of the lipophilic alkyl group at the 5-position of the indole has significant impact on the 5-HT$_{1D}$ binding affinity. Compounds with a *tert*-butyl group at the 5-position such as **9d**, **10**, and **11** were identified. These analogues display high binding affinity (K_i < 1 nM) and moderate receptor selectivity in comparison with known antimigraine agents such as sumatriptan, naratriptan, rizatriptan, and VML-251.

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter widely distributed in the brain and peripheral tissues and is involved in the regulation of various physiological functions such as mood, appetite, pain, sexual behavior, body temperature, and blood pressure.[1] Recent advances in the molecular cloning of seven serotonin receptor families (5-HT$_1$, 5-HT$_2$, 5-HT$_3$, 5-HT$_4$, 5-HT$_5$, 5-HT$_6$, and 5-HT$_7$) have provided a plethora of medicinally important targets for drug discovery research. Among the 5-HT receptor families, the 5-HT$_1$ receptor family appears to be the most complex and has been further subclassified into the 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_{1E}$, and 5-HT$_{1F}$ subtypes.[2]

Sumatriptan (**1**) is the first 5-HT$_1$ receptor agonist approved for the clinical treatment of migraine headaches.[3] Although there is some debate surrounding its exact mechanism of action,[4] 5-HT$_{1D}$ receptor activation has been proposed to be involved in mediating its therapeutic effects.[5] Sumatriptan has high binding affinity at the human 5-HT$_{1D}$ receptor (K_i = 4.4 nM) and varying selectivity relative to other 5-HT$_1$ receptor subtypes (Table 3). Further, some of the side effects for sumatriptan have been postulated to be mediated by activation of other 5-HT$_1$ receptors including the 5-HT$_{1A}$ and 5-HT$_{1B}$ subtypes.[5,6]

The clinical efficacy of sumatriptan in the treatment of migraine,[7] regardless of its specific mechanism of action, has created tremendous interest among academic laboratories as well as pharmaceutical companies. Second-generation 5-HT$_{1D}$ receptor agonists have been developed in recent years,[8] and many compounds including naratriptan (**2**),[9] rizatriptan (**3**),[10,8c] VML-251 (**4**)[11] (Chart 1), and zolmitriptan[12] have entered late-stage clinical trials.

Chart 1



All compounds in Chart 1 bind with high affinity (K_i = 2.0−5.4 nM, Table 3) to the human 5-HT$_{1D}$ receptor. A simple comparison of the 5-HT$_{1D}$ receptor agonists **1**−**4** would suggest that the key groups required for binding and efficacy are a basic amine, an indole nucleus, and a 5-substituent capable of participating in hydrogen-bonding interactions as an acceptor and/or donor. Among these key groups, the 5-substituent seems to be the focus of the structure−activity relationship (SAR) studies for improving affinity and selectivity at the 5-HT$_{1D}$ receptor.[8−12] It would appear that a 5-substituent capable of participating in hydrogen bonding is critical for imparting high affinity. This apparent

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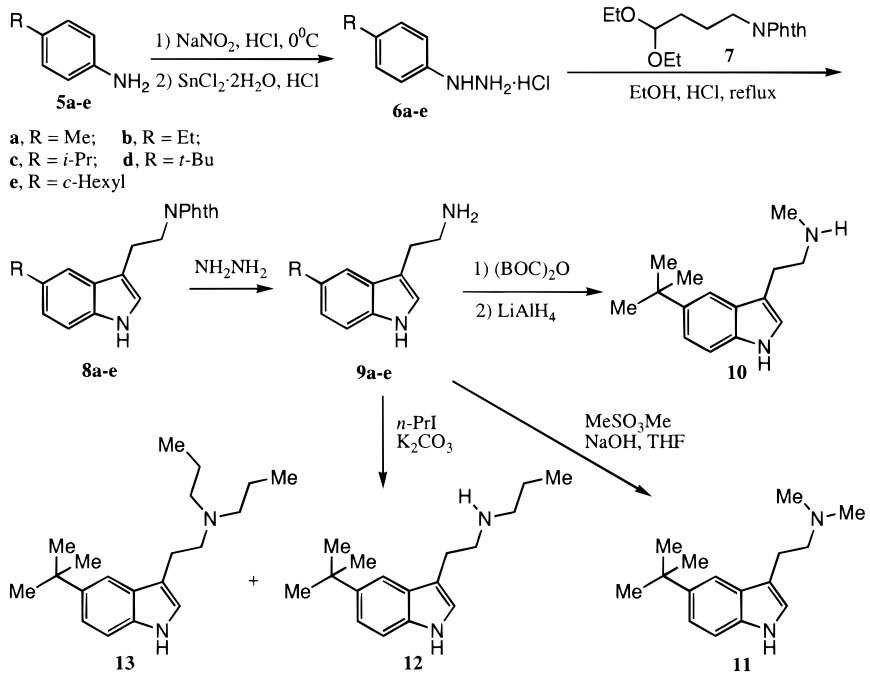
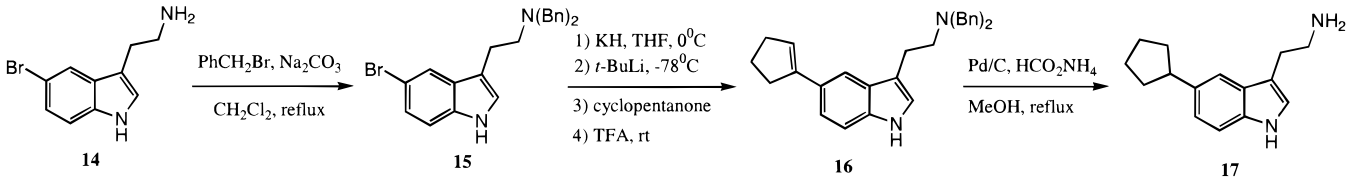
Scheme 1



Scheme 2



requirement has been supported by the fact that virtually all 5-HT_{1D} receptor agonists reported in the literature have at least one heteroatom (N, O, or S) in the 5-substituent group.[13] We now report on the binding properties of compound **10** which has a non-heteroatom-containing *tert*-butyl group on the 5-position of indole. This compound possesses very high binding affinity for the human 5-HT_{1D} receptor and displays comparable selectivity versus human 5-HT_{1A} and 5-HT_{1B} receptors to those known clinical candidates **1**−**4**. The chemical synthesis, SAR studies, radioligand binding, and functional data for this new class of compouunds are also reported.

Chemistry

Starting from the readily available 4-alkylanilines **5a**−**e**, the preparation of 5-alkyltryptamine analogues is presented in Scheme 1. Treatment of **5a**−**e** with $NaNO_2$ in acid followed by reduction of the intermediate diazonium salts with $SnCl_2{\cdot}2H_2O$ gave the hydrazine hydrochloride salts **6a**−**e**.[14] Fisher indolization of **6a**−**e** with 4-phthalimidobutanal diethyl acetal (**7**) in the presence of a catalytic amount of concentrated HCl, in refluxing EtOH, provided 5-alkyltryptamine derivatives **8a**−**e** after purification by silica gel flash chromatography.[15] Removal of phthaloyl group from **8a**−**e** by use of hydrazine gave rise to the targeted 5-alkyltryptamine analogues **9a**−**e**.[16]

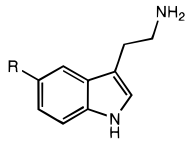
N-Methyl-5-*tert*-butyltryptamine (MBT, **10**) was prepared by introduction of a BOC group on the basic nitrogen of **9d** using $(BOC)_2O$ and NaOH, followed by $LiAlH_4$ reduction of the resulting *tert*-butyl carbamate.[17] Di-*N*-alkylation of **9d** with methyl methanesulfonate in the presence of NaOH afforded *N*,*N*-dimethyl analogue **11**. Direct *N*-alkylation of **9d** with 1-iodopropane using K_2CO_3 gave both monoalkylated and dialkylated analogues **12** and **13**, which were readily separated by silica gel flash chromatography.

Due to the unavailability of 4-cyclopentylphenylalanine, 5-cyclopentyltryptamine (**17**) was synthesized using a different route shown in Scheme 2. Treatment of 5-bromotryptamine (**14**) with benzyl bromide in the presence of Na_2CO_3 in refluxing CH_2Cl_2 gave rise to *N*,*N*-di-benzylated intermediate **15**, which was converted to the cyclopenten-1-yltryptamine derivative **16** following the chemistry developed by Rapoport et al.[18] Debenzylation of **16** accompanied by hydrogenation of the double bond for the cyclopentenyl ring was accomplished using catalytic transfer hydrogenation conditions (Pd/C, HCO_2NH_4) in refluxing methanol[19] to afford analogue **17** in low overall yield.

Pharmacology

The in vitro receptor affinities of compounds were evaluated by radioligand binding assays using cell lines expressing the human 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} receptors described previously.[20] The binding data are expressed in K_i values. The forskolin-stimulated adenylate cyclase assays were performed with cell lines expressing the human 5-HT_{1D} receptor to evaluate the agonist potency as previously reported.[21]

Table 1. Binding of 5-Alkyltryptamines at the Cloned Human 5-HT_{1D} Receptor



compd	R	5-HT_{1D} ($K_i \pm$ SEM, nM)
9a	Me	6.4 ± 1.8
9b	Et	3.7 ± 1.5
9c	*i*-Pr	1.1 ± 0.2
9d	*t*-Bu	0.6 ± 0.2
17	*c*-pentyl	1.7 ± 0.5
9e	*c*-hexyl	3.4 ± 0.8
5-HT	OH	2.0 ± 0.2

Results and Discussion

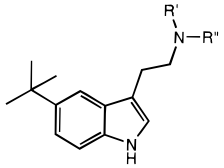
As seen in Table 1, 5-alkyltryptamines all exhibit high binding affinities for the human 5-HT_{1D} receptor (K_i < 7 nM). However, the size of the lipophilic alkyl group at the 5-position of the indole has significant impact on the 5-HT_{1D} binding affinity. Increasing the size of the 5-alkyl substituent resulted in an increased affinity for the human 5-HT_{1D} receptor. For example, compound **9a** with a small methyl substituent has the lowest affinity for the 5-HT_{1D} receptor (K_i = 6.4 nM). The binding affinity increased to K_i = 1.1 and 0.6 nM when the methyl group (**9a**) was replaced by the isopropyl group (**9c**) and *tert*-butyl group (**9d**), respectively. This presents an increase of 6- and 11-fold for the 5-HT_{1D} binding affinity. Cycloalkyl groups, e.g., cyclopentyl (**17**) and cyclohexyl (**9e**), can still be accommodated with slight loss of the affinity (<6-fold).

It was very intriguing that the C-5 alkyl-substituent analogues **9c**, **9d**, and **9e** have higher binding affinity for the 5-HT_{1D} receptor than does serotonin (5-HT) itself. This has led us to propose that *the hydrogen-bonding substituent at the indole C-5 position is not essential for the high 5-HT_{1D} binding affinity*. Further, we believe that the *5-HT_{1D} receptor has a hydrophobic pocket in the proximity of the 5-position of sertonin*. The binding affinity of the derivatives is dictated by the ability of the C-5 alkyl group to fit into the hydrophobic pocket, which is dependent on the size of alkyl group. It is apparent from the SAR studies shown in Table 1 that the *tert*-butyl group is the optimal substituent which is among those examined at the indole C-5 position.

After identifying *tert*-butyl as an optimal group, substitution of alkyl groups on the basic nitrogen was explored. Introduction of a methyl group on the nitrogen gives rise to a secondary amine analogue **10**, which has similar affinity as the parent compound (**9d**). Introduction of an additional methyl group results in a similarly potent tertiary amine analogue **11**. Substitution of a larger group such as propyl on the nitrogen (**12**, **13**) is detrimental to the 5-HT_{1D} receptor binding affinity. *N*-Methyl-5-*tert*-butyltryptamine (MBT) (**10**) was identified as a new lead compound in this series with a K_i = 0.45 nM, which is one of the highest affinity compounds reported for the human 5-HT_{1D} receptor.

Table 3 compares the binding affinity for the 5-HT_{1D} receptor and selectivity versus the 5-HT_{1A} and 5-HT_{1B} receptors of our lead compound **10** with the clinical candidates **1**−**4**. As shown in Table 3, *N*-methyl-5-*tert*-butyltryptamine (**10**) has highest binding affinity for the 5-HT_{1D} receptor and is 5 times more potent than naratriptan (**2**) which is the most potent among the clinical candidates **1**−**4**. As far as the selectivity against the 5-HT_{1A} receptor, compound **10** shows similar selectivity as VML-251 (**4**) but has slightly lower selectivity as compared to sumatriptan (**1**), naratriptan (**2**), and rizatriptan (**3**). Although none of the 5-HT_{1D} receptor agonists in the current study demonstrate as good selectivity versus the 5-HT_{1B} receptor, the *N*-methyl-5-*tert*-butyltryptamine (**10**) remains the most selective (4-fold).

Table 2. Binding of 5-*tert*-Butyltryptamines at the Cloned Human 5-HT_{1D} Receptor



compd	R′	R″	5-HT_{1D} ($K_i \pm$ SEM, nM)
9d	H	H	0.61 ± 0.15
10	Me	H	0.45 ± 0.12
11	Me	Me	0.44 ± 0.05
12	*n*-propyl	H	6.2 ± 0.8
13	*n*-propyl	*n*-propyl	10.8 ± 0.9

Table 3. Binding and Selectivity Comparison of MBT (**10**) with Known Compounds

	K_i (nM)		
compd	5-HT_{1D}	5-HT_{1A} (5-HT_{1A}/5-HT_{1D})	5-HT_{1B} (5-HT_{1B}/5-HT_{1D})
sumatriptan, **1**	4.4 ± 0	230 ± 1.0 (52)	9.6 ± 0 (2)
naratriptan, **2**	2.3 ± 0.2	45 ± 0.7 (20)	3.3 ± 0.4 (1)
rizatriptan, **3**	4.3 ± 0.8	140 ± 8.0 (33)	10.1 ± 0.7 (3)
VML-251, **4**	4.4 ± 0.4	62 ± 8.6 (14)	10.3 ± 1.9 (2)
MBT, **10**	0.45 ± 0.1	6.1 ± 0.7 (14)	1.9 ± 0 (4)

Table 4. 5-HT1D Receptor Intrinsic Activity Comparison

compd	EC_{50} (nM)	E_{MAX} (% of 5-HT)
sumatripatan, **1**	4.3 ± 0.1	93
naratriptan, **2**	1.6 ± 0.7	100
rizatriptan, **3**	3.0 ± 0.5	97
MBT, **10**	0.22 ± 0.2	100

To determine the functional properties at the human 5-HT_{1D} receptor, compound **10** and some known 5-HT_{1D} receptor agonists were evaluated for their ability to inhibit forskolin-stimulated adenylate cyclase in a cell line expressing the human 5-HT_{1D} receptor.[21] The intrinsic activity including EC_{50} and E_{MAX} of these derivatives are provided in Table 4. MBT (**10**) did not display any antagonist properties. Like these known compounds such as sumatriptan, naratriptan, and rizatriptan, MBT (**10**) was found to be a full 5-HT_{1D} receptor agonist (E_{MAX} = 100% of 5-HT). More importantly, **10** displays high agonist potency at the 5-HT_{1D} receptor, and the EC_{50} of **10** is about 7 times more potent than that of naratriptan (**2**) as shown in Table 4.

In summary, we have identified a novel series of 5-HT_{1D} receptor agonists, which have only lipophilic alkyl groups at the indole C-5 position. This finding indicates the hydrogen-bonding substituent at the C-5 position of the indole is not required for high-affinity binding as previously suggested and further suggests

the existence of a hydrophobic binding region near the indole 5-position. This discovery should assist future SAR studies in discovering more potent and selective 5-HT_{1D} receptor agonists. The lead compound **10** generated from this limited SAR study displays one of the highest binding affinities for the human 5-HT_{1D} receptor. It displays comparable selectivity versus 5-HT_{1A} and 5-HT_{1B} receptors with the known clinical candidates. Functionally, **10** behaves as a potent agonist at the human 5-HT_{1D} receptor.

Experimental Section

Unless otherwise indicated all common reagents and anhydrous solvents were used as obtained from commerical suppliers without further purification. 5-Methyltryptamine (**9a**) was obtained from Aldrich Chemical Company, Inc. Air-sensitive reactions were run under a positive pressure of dry nitrogen. Melting points were determined on a Hoover-Thomas Uni-Melt capillary melting point apparatus and are uncorrected. Routine ^{1}H NMR spectra were recorded on a 300-MHz spectrometer. Chemical shifts are reported in parts per million downfield (δ) from tetramethylsilane in the form: chemical shift (multiplicity, coupling constant, number of protons). Mass spectra were recorded using field desorption (FD) ionization on a Varian MAT 731 mass spectrometer. Elemental analyses were carried out by the Physical Chemistry Research department of the Lilly Research Laboratories.

5-Ethyltryptamine (9b).[13] To a stirred solution of 4-ethylaniline (**5b**) (5.06 g, 41.7 mmol) in 40 mL of concentrated hydrogen chloride solution at 0 °C was slowly added a solution of $NaNO_2$ (3.17 g, 45.9 mmol) in 30 mL of water. The mixture was stirred for ca. 10 min upon completion of the addition. The reaction mixture was transferred in dropwise fashion to a solution of $SnCl_2 \cdot H_2O$ (29.20 g, 129.4 mmol) in 40 mL of concentrated hydrogen chloride solution at room temperature. A white paste was slowly formed upon stirring. After 1 h, the white precipitate was collected by filtration and washed with water. Upon drying, the crude 4-ethylphenylhydrazine hydrochloride (**6b**) (7.14 g, 41.3 mmol) was obtained in 99% yield.

Compound **7** was prepared by treating 4-aminobutyraldehyde diethyl acetal (8.33 g, 90% pure, 46.5 mmol) with *N*-carbethoxyphthalmide (10.73 g, 48.95 mmol) in water (75 mL) in the presence of $NaHCO_3$ (3.93 g, 46.82 mmol) for 2 h at room temperature. The reaction mixture was extracted with CH_2Cl_2 (100 mL × 3). The combined organic layers were washed with 5% $NaHCO_3$ solution, dried over K_2CO_3, filtered, and concentrated to give relatively pure **7** (13.2 g, 45.3 mmol) as a colorless oil in 97% yield.

A mixture of compound **6b** (3.05 g, 17.7 mmol) and **7** (5.14 g, 17.64 mmol) in 140 mL of EtOH was heated to 60 °C for 1 h in the presence of a small amount of water (0.12 mL). After addition of 1 mL of concentrated HCl solution, the mixture was heated to reflux for 14 h. The volatiles were removed by evaporation. The residue was redissolved in CH_2Cl_2 (150 mL) and saturated Na_2CO_3 (100 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried, filtered, and concentrated. The residue was purified by flash chromatography using a 7:3 mixture of hexanes and ethyl acetate to give compound **8b** (2.70 g, 8.5 mmol) in 48% yield.

Compound **8b** (2.70 g, 8.5 mmol) was then treated with hydrazine hydrate (8 mL) in the presence of 80 mL of EtOH and 20 mL of H_2O at room temperature for 15 h. The volatiles were removed by reduced pressure, and the residue was extracted with CH_2Cl_2 (80 mL × 3). The combined organic layers were washed with H_2O, dried, filtered, and then concentrated to a residue that was purified by flash chromatography using 15% methanol, 1% NH_4OH in CH_2Cl_2 to give **9b** (1.50 g, 8.0 mmol) in 94% yield. HCl salt of **9b** was prepared; mp 252 °C dec. ^{1}H NMR ($CDCl_3$) for free base: 1.30 (t, J = 7.5 Hz, 3H), 1.49 (br s, 2H), 2.76 (q, J = 7.5 Hz, 2H), 2.90 (t, J = 7.4 Hz, 2H), 3.03 (t, J = 7.4 Hz, 2H), 7.02 (d, J = 1.8 Hz, 1H), 7.06 (dd, J = 9.0, 1.8 Hz, 1H), 7.30 (d, J = 9.0 Hz, 1H), 7.42 (s, 1H), 7.98 (br s, 1H). MS for HCl salt: 189 ($M^+ + 1$). Anal. for oxalate salt: ($C_{12}H_{17}N_2Cl$) C, H, N.

5-Isopropyltryptamine (9c).[22] Compound **9c** was prepared by the method described for **9b**. Thus, a mixture of 4-isopropylphenylhydrazine hydrochloride (**6c**) (1.0 g, 5.37 mmol) and compound **7** (1.5 g, 5.11 mmol) in 50 mL of EtOH was heated to 70 °C for 2 h in the presence of water (0.10 mL). After addition of 0.5 mL of concentrated HCl solution, the mixture was heated to reflux for 14 h. After the usual workup, compound **8c** was obtained as a crude mixture, which was used for next step without further purification.

The crude mixture was then treated with hydrazine hydrate (6 mL) in the presence of 80 mL of EtOH and 20 mL of H_2O at room temperature for 15 h. The volatiles were removed by reduced pressure, and the residue was extracted with CH_2Cl_2 (80 mL × 3). The combined organic layers were washed with H_2O, dried, filtered, and then concentrated to a residue that was purified by flash chromatography using 15% methanol, 1% NH_4OH in CH_2Cl_2 to give **9c** (310 mg, 1.30 mmol) in 25% overall yield. HCl salt of **9c** was prepared; mp 181−184 °C dec. ^{1}H NMR ($CDCl_3$) for free base: 1.30 (d, J = 7.0 Hz, 6H), 1.45 (br s, 2H), 2.90 (t, J = 7.1 Hz, 2H), 3.02 (m, 3H), 7.00 (s, 1H), 7.09 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.42 (s, 1H), 8.00 (br s, 1H). MS for HCl salt: 203 ($M^+ + 1$). Anal. for HCl salt: ($C_{13}H_{19}N_2Cl$) C, H, N.

5-*tert*-Butyltryptamine (9d). Compound **9d** was prepared by the method described for **9b**. Thus, a mixture of 4-*tert*-butylphenylhydrazine hydrochloride (**6d**) (2.97 g, 14.8 mmol) and compound **7** (4.11 g, 14.1 mmol) in 110 mL of EtOH was heated to 70 °C for 2 h in the presence of a small amount of water (0.20 mL). After addition of 1 mL of concentrated HCl solution, the mixture was heated to reflux for 14 h. After usual workup, compound **8d** was obtained in a crude mixture, which was used for next step without further purification.

The above crude residue was then treated with hydrazine hydrate (12 mL) in the presence of 160 mL of EtOH and 40 mL of H_2O at room temperature for 14 h. After workup, the residue was purified by flash chromatography using 10% methanol, 1% NH_4OH in CH_2Cl_2 to give **9d** (1.59 g, 7.3 mmol) in 52% overall yield. Hydrochloride salt of **9d** was prepared; mp 246−248 °C. ^{1}H NMR ($CDCl_3$) for free base: 1.20 (s, 9H), 2.92 (q, J = 7.0 Hz, 2H), 3.05 (t, J = 7.0 Hz, 2H), 7.02 (s, 1H), 7.30 (s, 2H), 7.58 (s, 1H), 7.97 (br s, 1H). MS for hydrochloride salt: 217 ($M^+ + 1$). Anal. for oxalate salt: ($C_{14}H_{21}N_2Cl$) C, H, N.

5-Cyclophenyltryptamine (17). To a stirred solution of 5-bromotryptamine (**14**) (2.68 g, 11.2 mmol) in 20 mL of CH_2Cl_2 were added Na_2CO_3 (3.00 g, 28.3 mmol), H_2O (10 mL), and benzyl bromide (3.99 g, 23.3 mmol). The mixture was heated to reflux for 3 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (30 mL × 3). The combined organic layers were washed with water, dried, filtered, and concentrated to a residue that was purified by flash chromatography using a 4:1 mixture of hexanes and ethyl acetate to give *N*,*N*-dibenzyl-5-bromotryptamine (**15**) (3.36 g, 8.0 mmol) in 71% yield.

Compound **15** (1.72 g, 4.1 mmol) in 10 mL of THF was then added to a suspension of KH (1.00 g, 20%, 5.0 mmol) in 10 mL of THF at 0 °C. After stirred at 0 °C for 15 min, the mixture was cooled to −78 °C. *t*-BuLi (1.7 M, 6.2 mL, 10.54 mmol) was then added dropwise. After 20 min of stirring, cyclopentanone (1.14 g, 13.57 mmol) was introduced via syringe. The reaction mixture was slowly warmed to room temperature. Cold H_3PO_4 solution (1M, 15 mL) was added. The organic layer was separated, and the aqueous layer was extracted wiith diethyl ether. The combined organic layers were washed with water, dried, filtered, and concentrated. The residue was then redissolved in CH_2Cl_2 (25 mL). After addition of 1 mL of trifluoroacetic acid, the mixture was stirred at 0 °C for 3 h. Dichloromethane (20 mL) and 1 N NaOH solution (20 mL) were added. The organic layer was separated, washed with water, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography using a 5:1 mixture of

hexanes and ethyl acetate to give the tryptamine analogue **16** (129 mg, 0.32 mmol) in 8% overall yield from **15**.

To a solution of **16** (91 mg, 0.22 mmol) in 10 mL of methanol were added Pd/C (5%, 30 mg), and HCO_2NH_4 (100 mg, 1.59 mmol). The mixture was heated to reflux for 30 min. The mixture was filtered through a pad of Celite and rinsed with methanol. The filtrate was concentrated, and the residue was purified by flash chromatography using 10% methanol, 1% NH_4OH in CH_2Cl_2 to afford 5-cyclopentyltryptamine (**17**) (41 mg, 0.18 mmol) in 82% yield. Hydrobromide salt of **17** was prepared; mp 155−157 °C. ^{1}H NMR (CD_3OD) for free base: 0.90 (m, 4H), 1.06 (m, 2H), 1.28 (m, 2H), 2.12 (m, 4H), 2.27 (m, 1H), 6.21 (dd, J = 9.8, 1.8 Hz, 1H), 6.22 (s, 1H), 6.45 (d, J = 9.8 Hz, 1H), 6.59 (d, J = 1.8 Hz, 1H). MS for free base: 228 (M^+). HRMS for hydrobromide: calcd for $C_{15}H_{21}N_2$, 229.1705; found, 229.1699.

5-Cyclohexyltryptamine (9e). Compound **9e** was prepared by the method described for **9b**. First, 4-cyclohexylaniline (**5e**) (15.2 g, 86.7 mmol) was converted to 4-cyclohexylphenylhydrazine hydrochloride (**6e**) (13.3 g, 58.7 mmol) in 68% yield.

Then, the Fisher indole cyclization was carried out by heating a mixture of compound **6e** (4.08 g, 18.0 mmol) and **7** (5.24 g, 18.0 mmol) at 60 °C for 30 min in the presence of EtOH (140 mL) and water (0.12 mL). After the usual workup and flash chromatography using a 25:25:1 mixture of hexanes, CH_2Cl_2, and methanol, compound **8e** (24.5 g, 12.1 mmol) was obtained in 67% yield.

Compound **8e** (4.48 g, 12.0 mmol) was then treated with hydrazine hydrate (12.0 mL) in the presence of 160 mL of EtOH and 40 mL of H_2O at room temperature for 15 h. After workup, the residue was purified by flash chromatography using 10% methanol, 1% NH_4OH in CH_2Cl_2 to give **9e** (2.80 g, 11.6 mmol) in 96% yield. Hydrochloride salt of **9e** was prepared; mp 227−229 °C. ^{1}H NMR ($CDCl_3$) for free base: 1.20 (br m, 7H), 1.90 (br m, 5H), 2.60 (m, 1H), 2.90 (t, J = 6.8 Hz, 2H), 3.03 (t, J = 6.8 Hz, 2H), 7.01 (d, J = 1.5 Hz, 1H), 7.09 (dd, J = 8.4, 1.5 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.43 (s, 1H), 8.00 (br s, 1H). MS for free base: 242 (M^+). Anal. for the hydrochloride salt: ($C_{16}H_{23}N_2Cl$) C, H, N.

***N*-Methyl-5-*tert*-butyltryptamine (10).** To a stirred solution of 5-*tert*-butyltryptamine (**9d**) (358 mg, 1.65 mmol) in 15 mL of THF were added $(BOC)_2O$ (378 mg, 1.73 mmol) and 2 N NaOH solution (0.83 mL, 1.66 mmol). The mixture was stirred at room temperature for 1 h. CH_2Cl_2 (50 mL) and water (50 mL) were added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (30 mL × 3). The combined organic layers were dried, filtered, and concentrated to a residue that was used for the next step without further purification.

To a stirred suspension of $LiAlH_4$ (235 mg, 6.2 mmol) in 15 mL of THF was added dropwise a solution of the residue from the previous step in 8 mL of THF at 0 °C under nitrogen. The mixture was warmed to room temperature and stirred for 30 min. It was then heated to reflux for 3 h. Upon cooling, $Na_2SO_4 \cdot 10H_2O$ was slowly added to quench excess $LiAlH_4$. The suspension sat still for 30 min and then was filtered. The filtrate was evaporated, and the residue was purified by flash chromatography using 15% methanol, 1% NH_4OH in CH_2Cl_2 to afford compound **10** (264 mg, 1.15 mmol) in 70% overall yield. Hydrochloride salt of **10** was prepared; mp 221−223 °C. ^{1}H NMR ($CDCl_3$) for free base: 1.36 (br s, 1H), 1.40 (s, 9H), 2.43 (s, 3H), 2.96 (m, 4H), 7.01 (d, J = 1.5 Hz, 1H), 7.30 (m, 2H), 7.61 (s, 1H), 7.96 (br s, 1H). MS for free base: 230 (M^+). Anal. for the hydrochloride salt: ($C_{15}H_{23}N_2Cl$), C, H, N.

***N*,*N*-Dimethyl-5-*tert*-butyltryptamine (11).** To a stirred solution of **9d** (381 mg, 1.76 mmol) in 20 mL of THF were added 2 N NaOH (7.1 mL, 14.2 mmol) and methyl methanesulfonate (403 mg, 3.66 mmol). The mixture was stirred at room temperature for 6 h. Dichloromethane (50 mL) and water (20 mL) were added. The organic layer was separated, washed with water, dried, filtered, and then concentrated. Purification of the residue by flash chromatography using 10% methanol, 1% NH_4OH in CH_2Cl_2 to give *N*,*N*-dimethyl-5-*tert*-butyltryptamine (**11**) (45 mg, 0.18 mmol) in 10% yield. Hydrobromide salt of **11** was prepared; mp 184−186 °C. ^{1}H NMR ($CDCl_3$) for free base: 1.40 (s, 9H), 2.38 (s, 6H), 2.65 (m, 2H), 2.97 (m, 2H), 6.98 (br s, 1H), 7.28 (m, 2H), 7.59 (s, 1H), 8.07 (br s, 1H). MS for free base: 244 (M^+). HRMS for hydrobromide: calcd for $C_{16}H_{25}N_2$, 245.2018; found, 245.2030.

***N*-*n*-Propyl-5-*tert*-butyltryptamine (12) and *N*,*N*-Di-*n*-propyl-5-*tert*-butyltryptamine (13).** To a stirred solution of **9d** (396 mg, 1.83 mmol) in 9 mL of CH_3CN were added K_2CO_3 (758 mg, 5.49 mmol) and *n*-PrI (933 mg, 5.49 mmol). The mixture was stirred at room temperature for 4 h. Dichloromethane (60 mL) and water (30 mL) were added. The organic layer was separated, washed with water, dried, filtered, and concentrated. The residue was purified by flash chromatography using 7% methanol, 1% NH_4OH in CH_2Cl_2 to give both monoalkylated product **12** (12.6 mg, 0.05 mmol, 3%) and dialkylated product **13** (410 mg, 1.37 mmol, 75%).

Hydrochloride salt of **12** was prepared. ^{1}H NMR ($CDCl_3$) for free base: 0.90 (t, J = 7.0 Hz, 3H), 1.40 (s, 9H), 1.50 (m, 3H), 2.62 (t, J = 7.0 Hz, 2H), 2.98 (m, 4H), 7.02 (d, J = 1.5 Hz, 1H), 7.31 (m, 2H), 7.62 (s, 1H), 8.00 (br s, 1H). MS for free base: 258 (M^+). HRMS for hydrochloride: calcd for $C_{17}H_{27}N_2$, 259.2174; found, 259.2176.

Hydrochloride salt of **13** was prepared; mp 234−236 °C. ^{1}H NMR ($CDCl_3$) for free base: 0.98 (t, J = 7.1 Hz, 6H), 1.45 (s, 9H), 1.60 (m, 4H), 2.60 (t, J = 7.1 Hz, 4H), 2.93 (m, 4H), 6.98 (d, J = 1.5 Hz, 1H), 7.32 (m, 2H), 7.63 (s, 1H), 8.18 (br s, 1H. MS for free base: 300 (M^+). Anal. for the hydrochloride salt: ($C_{20}H_{33}N_2Cl$) C, H, N.

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