N-Arylsulfonylindole Derivatives as Serotonin 5-HT$_6$ Receptor Ligands

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A series of N_1-arylsulfonyltryptamines were found to be potent ligands of the human serotonin 5-HT$_6$ receptor with the 5-methoxy-1-benzenesulfonyl analogue (**19**) having the highest affinity. Additionally, it was discovered that a group such as 3-(3-methoxybenzyl)-1,2,4-oxadiazol-5-yl in the 2-position of the indole ring (**43**) can replace the arylsulfonyl substituent in the 1-position with no loss of affinity. This suggested that the binding conformation of the aminoethyl side chain at this receptor was toward the 4-position of the indole ring and was supported by the fact that the 4-(aminoethyl)indoles (**45**) also displayed high affinity, as did the conformationally rigid 1,3,4,5-tetrahydrobenz[*c,d*]indole (**49**). Molecular modeling showed that **19**, **43**, and **45** all had low-energy conformers that overlaid well onto **49**. Both **19** and **49** had good selectivity over other serotonin receptors tested, with **49** also showing excellent selectivity over all dopamine receptors. In a functional adenylate cyclase stimulation assay, **19** and **49** had no agonist activity, whereas **45** behaved as a partial agonist. Finally, it was shown that **19** had good activity in the 5-HT$_{2A}$ centrally mediated mescaline-induced head twitch assay, which implies that it is brain-penetrant.

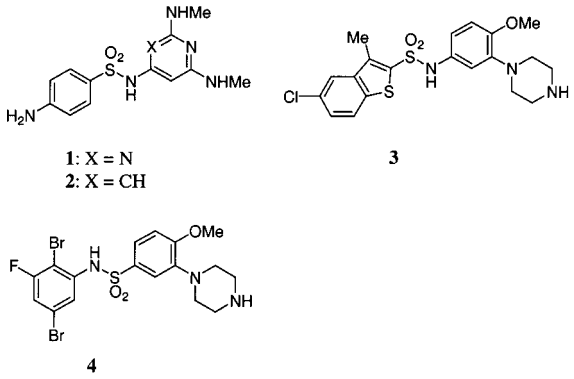
Introduction

The serotonin (5-HT) receptors have been subdivided into seven main classes (5-HT$_{1-7}$).[1] The cloned rat 5-HT$_6$ receptor was found to consist of a polypeptide chain of 437 or 436 amino acids with little homology to other 5-HT receptors,[2,3] while the cloned human 5-HT$_6$ receptor contains 440 amino acids and shares 96% homology with the rat receptor within the transmembrane region.[4] Hybridization studies and northern blots in the rat indicate that the density of 5-HT$_6$ receptor mRNA is highest in the olfactory tubercule, followed by the striatum, nucleus accumbens, dentate gyrus, and CA1, CA2, and CA3 regions of the hippocampus.[2,3,5] The 5-HT$_6$ receptor mRNA seems to be present almost exclusively in the brain since very little was detected in peripheral tissues. Interestingly, several atypical antipsychotic drugs (e.g., clozapine and loxapine), as well as tricyclic antidepressants (e.g., amoxipine and clomiprimine), bind with high affinity to the 5-HT$_6$ receptor, which may indeed play a role in their mechanisms of action.[6]

Recent studies in rats treated with 5-HT$_6$ receptor antisense oligonucleotides (AOs) have shown that they elicit a yawning, stretching, and chewing behavioral syndrome which was dose-dependently antagonized by the muscarinic antagonist atropine, implying that 5-HT$_6$ receptors may control cholinergic transmission.[7] In addition, treatment with AOs significantly inhibited the increase in 5-HT release from the prefrontal cortex produced by conditioned fear stress, suggesting that 5-HT$_6$ receptors may be involved in certain anxiety disorders.[8]

To further elucidate the functional role of 5-HT$_6$ receptors, potent and selective ligands are required.

Chart 1



Recently, the benzenesulfonamides Ro 04−6790 (**1**, Chart 1) and Ro 63-0563 (**2**), and the benzo[*b*]thiophenesulfonamide SB-271046 (**3**), have been reported as selective 5-HT$_6$ receptor antagonists.[9,10] This has enabled some in vivo investigations of the function of the 5-HT$_6$ receptor to be performed. Thus, Ro 04-6790 was shown to inhibit the rotational behavior of 6-hydroxydopamine (6-OHDA) lesioned rats induced by treatment with the muscarinic antagonists scopolamine and atropine, supporting the experiments with AOs that the 5-HT$_6$ receptor is involved in the control of acetylcholine neurotransmission.[11] The same compound also produced a stretching behavior in rats that appears to be mediated by an increase in cholinergic transmission in the CNS.[12]

In vivo microdialysis studies in the freely moving rat have shown that administration of SB-271046 produced a significant increase in extracellular levels of both glutamate and aspartate within the frontal cortex, suggesting that 5-HT$_6$ receptor antagonists may have therapeutic utility in the treatment of cognitive dysfunction.[13] SB-271046 and Ro 04-6790 also produced

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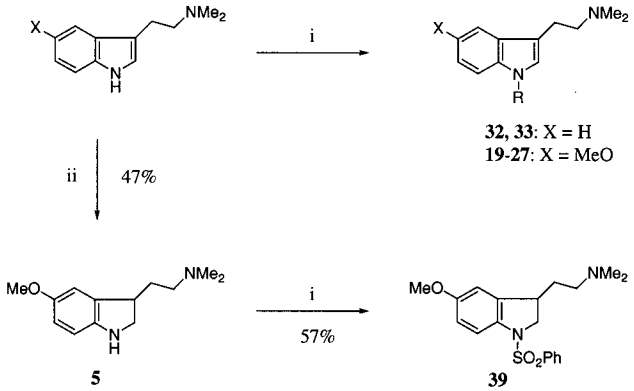
Scheme 1[a]



[a] Reagents: (i) RCl, Bu_4NHSO_4, NaOH(aq), CH_2Cl_2; (ii) H_2, 10% Pd/C, 5 N HCl(aq).

potent anticonvulsant activity in the rat maximal electroshock seizure threshold (MEST) test, although the magnitude is modest in comparison to known antiepileptic drugs.[14]

During the preparation of this paper, Bromidge et al.[15] published on a series of analogues of SB-271046 in which the sulfonamide linker group has been reversed, leading to the identification of SB-357134 (**4**), while others have reported on N_1-(benzenesulfonyl)-tryptamines as novel 5-HT_6 receptor antagonists.[16−18] Through the screening of our in-house sample collection, we independently discovered that *N*-(arylsulfonyl)indole derivatives were potent, selective 5-HT_6 receptor ligands and in this paper we report on our own work in this area.

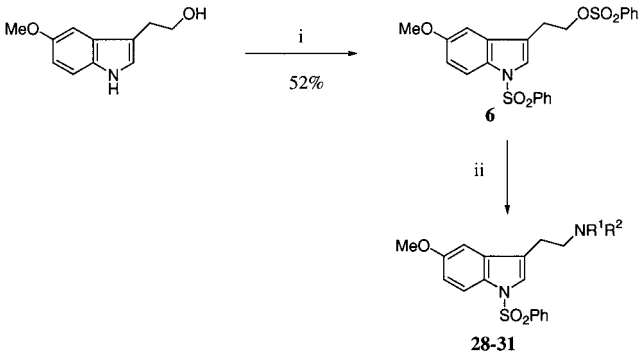
Chemistry

The 1-substituted *N*,*N*-dimethyl-5-methoxytryptamines (**19**−**27**, **32**, and **33**) were prepared by treating *N*,*N*-dimethyl-5-methoxytryptamine with the appropriate sulfonyl chloride or carboxylic acid chloride in a two-phase reaction medium of aqueous sodium hydroxide and dichloromethane with tetrabutylammonium hydrogen sulfate as a phase transfer catalyst (Scheme 1). The indoline analogue (**39**) was synthesized by hydrogenation over palladium of *N*,*N*-dimethyl-5-methoxytryptamine to give **5**, followed by treatment with benzenesulfonyl chloride under the previously described conditions.

Changes to the dimethylamino group were achieved by doubly benzenesulfonylating 5-methoxytryptol, followed by displacement of the *O*-benzenesulfonyl group of **6** by treatment with the appropriate amine in the presence of potassium carbonate to give compounds **28**−**31** (Scheme 2).

In the case of the 5-cyano-substituted analogue (**38**), the corresponding tryptamine[19] was dimethylated first by reductive alkylation, with formaldehyde and sodium cyanoborohydride, before reaction with benzenesulfonyl chloride (Scheme 3). The 5-methoxy-2-methyl derivative (**40**) was prepared via the 1-unsubstituted analogue (**41**) by similar chemistry. The derivative with an ethyl ester group in the 2-position of the indole (**42**) was prepared in an analogous fashion from the corresponding tryptamine.[20] This was then converted to the oxadiazole (**43**) by reaction with sodium hydride and 3-methoxybenzeneacetamide oxime.[21] The aminoethyl derivative

Scheme 2[a]



[a] Reagents: (i) $PhSO_2Cl$, Bu_4NHSO_4, NaOH(aq), CH_2Cl_2; (ii) R^1R^2NH, K_2CO_3, *i*-PrOH.

(**18**) was synthesized by protecting the free amino group of the corresponding tryptamine with a Boc group before reaction with benzenesulfonyl chloride as before to give **7**. The Boc group was then removed with trifluoroacetic acid.

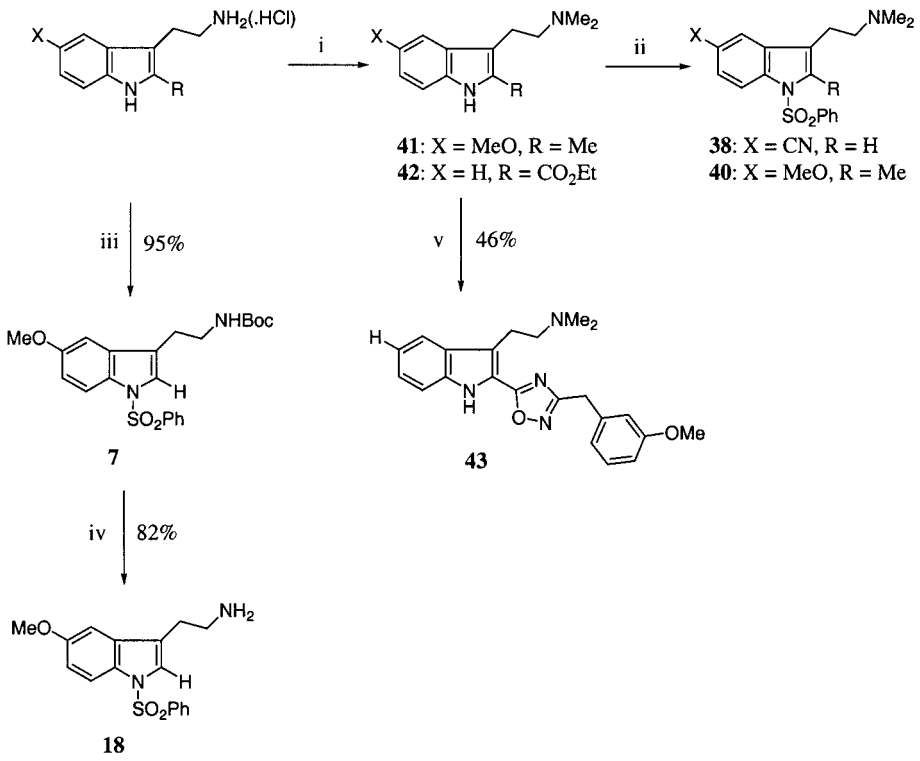
The 5-hydroxy-substituted analogue (**35**) was prepared by dimethylating 5-(benzyloxy)tryptamine hydrochloride, which was then reacted with benzenesulfonyl chloride to give the 5-benzyloxy analogue (**34**) (Scheme 4). The benzyl group was then removed by hydrogenation over palladium hydroxide to give **35**. The other 5-hydroxy analogues (**36** and **37**) were prepared in a similar manner from [2-(5-benzyloxy-1*H*-indol-3-yl)-ethyl]dimethylamine[22] by treatment with either benzoyl chloride or di-*tert*-butyl dicarbonate followed by hydrogenation over palladium on carbon.

The 4-(aminoethyl)indole analogues[23] were prepared from methylindole-4-carboxylate[24] as shown in Scheme 5. Thus, treatment with benzenesulfonyl chloride in the presence of potassium carbonate was followed by reduction of the ester functionality of **10** to the corresponding alcohol with DIBALH. Oxidation to the aldehyde (**11**) with manganese dioxide followed by treatment in nitromethane with ammonium acetate gave the nitroalkene (**12**). This was then reduced to the aminoethyl analogue (**44**) by use of zinc−mercury amalgam. Dimethylation of the amino group was carried out by reductive alkylation as described above to give **45**. The 2-benzoyl derivative (**47**) was prepared by lithiation of **45** with *tert*-butyllithium, followed by addition of benzaldehyde and subsequent oxidation with manganese oxide. Finally, the benzenesulfonyl group was removed by sodium hydroxide to give **48**.

The 4-(aminopropyl)indole (**46**) was synthesized by a Wittig reaction on the aldehyde (**11**) with (carboethoxymethylene)triphenylphosphorane, followed by hydrogenation of the alkene (**13**) over palladium. The resulting ester (**14**) was converted to the dimethylamide (**15**) by reaction with trimethylaluminum and dimethylamine hydrochloride, and the amide was then reduced with lithium aluminum hydride to give **46**.

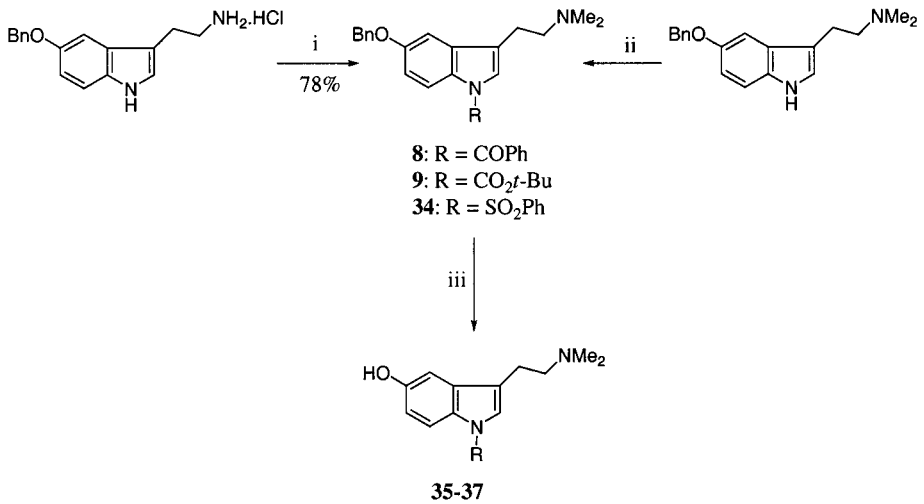
The tetrahydrobenz[*cd*]indole derivatives were synthesized from (±)-4-amino-3,4-dihydro-1-[(4-methylbenzyl)sulfonyl]-1,3,4,5-tetrahydrobenz[*cd*]indol-5(1*H*)-one hydrochloride[25] (**16**) by reduction of the ketone with sodium borohydride to give a 9:1 mixture of trans/cis amino alcohols (**17**) (Scheme 6). The mixture was then dimethylated by reductive alkylation, and the trans

Scheme 3[a]



[a] Reagents: (i) (a) NaOMe, MeOH; (b) CH_2O(aq), $NaCNBH_3$, AcOH; (ii) $PhSO_2Cl$, Bu_4NHSO_4, NaOH(aq), CH_2Cl_2; (iii) (a) Boc_2O, CH_2Cl_2, RT, 25 h; (b) $PhSO_2Cl$, NaOH, Bu_4NHSO_4, CH_2Cl_2, RT, 30 min; (iv) CF_3CO_2H, CH_2Cl_2, RT, 3 h; (v) 3-methoxybenzeneacetamide oxime, NaH, THF, −78 °C to reflux, 3 h.

Scheme 4[a]



[a] Reagents: (i) (a) NaOMe, MeOH, CH_2O(aq), $NaCNBH_3$, AcOH, RT, 4 h; (b) $PhSO_2Cl$, Bu_4NHSO_4, NaOH(aq), CH_2Cl_2, RT, 30 min; (ii) PhCOCl or Boc_2O, Et_3N, DMAP, 0 °C to RT, 3−18 h; (iii) H_2, 10% Pd/C or 20% $Pd(OH)_2$, (4 N HCl), EtOH, 35−45 psi, 3−7 h.

isomer (**49**) was separated from the cis isomer by column chromatography. Finally the hydroxyl group was methylated in low yield by use of sodium hydride and methyl 3-bromopropionate in the presence of benzyltrimethylammonium chloride to give **50**.

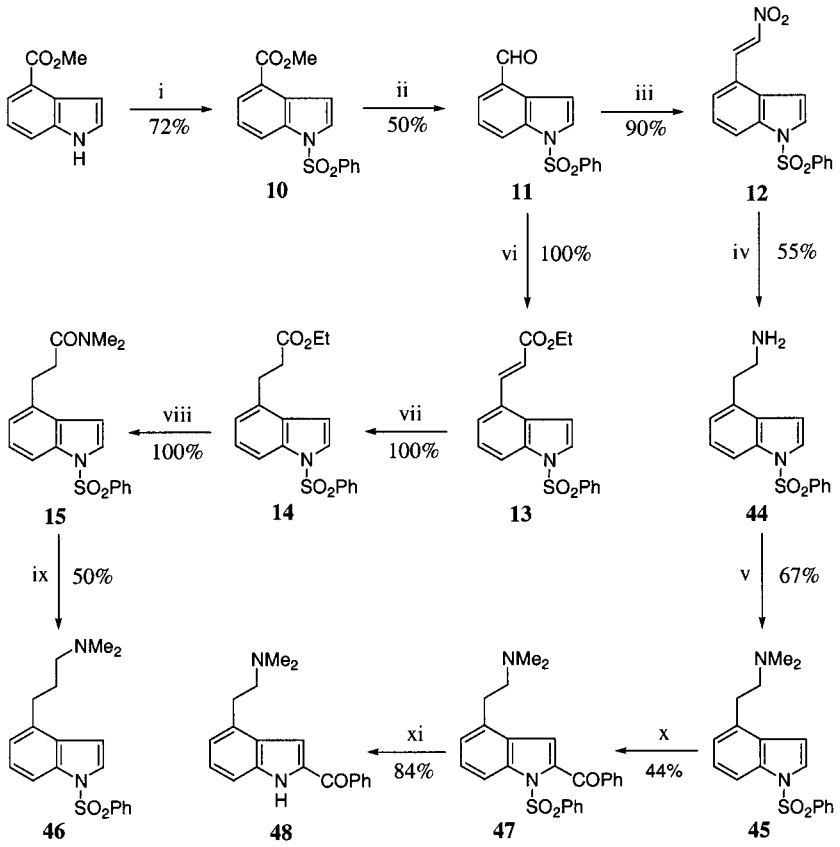
Results and Discussion

The compounds in Tables 1−3 were evaluated for their affinity to cloned human 5-HT$_6$ receptors stably expressed in HeLa cells.

It can be seen from Table 1 that monosubstitution of the aromatic ring of the benzenesulfonyl group of **19** by chlorine in either the *o*-, *m*-, or *p*-position (**20**−**22**) was slightly detrimental to affinity, as was substitution in the *p*-position by methyl (**23**) or methoxy (**24**). The fact that substitution of the phenyl ring by either electron-withdrawing or electron-donating groups did not improve affinity over the unsubstituted compound (**19**) was also found by Glennon and co-workers.[16] Replacement of the phenyl ring by the bulkier 2-naphthyl group (**25**) or by a 2-thiophene (**26**) gave compounds with only slightly reduced affinity, and the sulfonyl moiety could be replaced by a carbonyl group as in **27** with 11-fold loss in affinity.

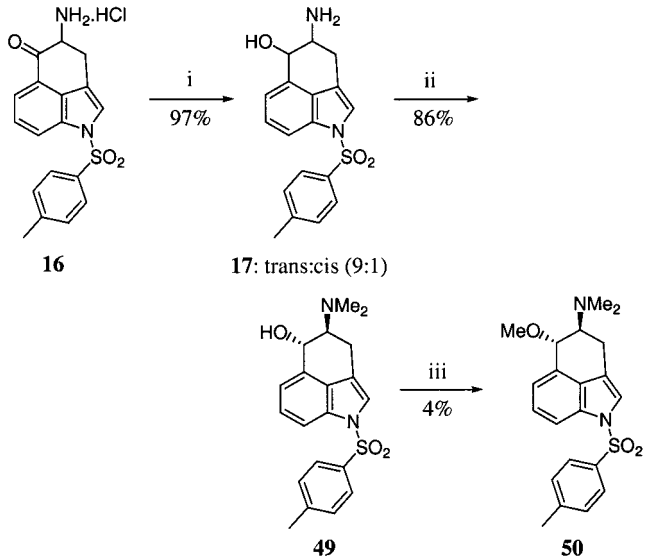
Removal of the two methyl groups on the side-chain amino functionality to give the primary amine (**18**) led

Scheme 5[a]



[a] Reagents: (i) $PhSO_2Cl$, K_2CO_3, butan-2-one, reflux, 10 h; (ii) (a) DIBALH, Et_2O, −70 °C, 3 h; (b) MnO_2, CH_2Cl_2, RT, 15 h; (iii) $MeNO_2$, NH4OAc, reflux, 2 h; (iv) Zn/Hg, MeOH, concd HCl, 0 °C to RT, 2.5 h; (v) CH_2O(aq), $NaCNBH_3$, AcOH, MeOH, 0 °C to RT, 1 h; (vi) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, reflux, 3 h; (vii) H2, 10% Pd/C, EtOAc−EtOH, 4 h; (viii) Me_3Al, $Me_2NH{-}HCl$, benzene, reflux, 18 h; (ix) $LiAlH_4$, THF, RT, 5 h; (x) (a) t-BuLi, THF, −78 to 0 °C, 1.5 h; (b) PhCHO, THF, −78 °C to RT, 3 h; (c) MnO_2, CH_2Cl_2; (xi) 2 N NaOH(aq), MeOH, 80° C, 30 min.

Scheme 6[a]



[a] Reagents: (i) $NaBH_4$, EtOH, −2 °C, 100 min; (ii) H_2, 10% Pd/C, CH_2O(aq), AcOH, EtOH, 30 psi, 65 h; (iii) NaH, $BrCH_2CH_2CO_2Me$, $BnNMe_3Cl$, THF−DMF, RT, 18.5 h.

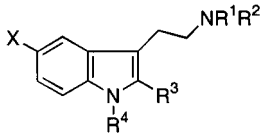
to a 17-fold decrease in affinity (cf. **18** and **19**). Interestingly, replacement of the dimethylamino group with larger heterocycloalkyl groups such as pyrrolidine (**28**) led to a 19-fold decrease in affinity, and the six-membered ring compounds (**29**−**31**) were a further order of magnitude down in 5-HT_6 receptor affinity.

Some other substituents at the 5-position of the indole ring were also explored. Thus, it was found that having no C-5 substituent at all gave compounds with similar affinity (cf. **19** and **32**), whereas the hydroxyl (**35**) and cyano (**38**) groups led to an 8- and 14-fold reduction, respectively. Larger groups such as a benzyloxy group (**34**) led to a further decrease (140-fold) in affinity, which is significantly different from that reported by Glennon and co-workers.[17] However, with a 5-hydroxyl group an N_1-benzoyl substituent was not so detrimental (cf. **27** and **36**). The compounds with a *tert*-butoxycarbonyl substituent (**37**) or a methylsulfonyl group (**33**) on the indole nitrogen were significantly less well tolerated.

While reduction of the indole to the indoline to give **39** also led to a significant reduction (27-fold) in affinity, addition of a 2-methyl substituent on the indole ring (**40**) was only marginally detrimental (5-fold). Removal of the *N*-benzenesulfonyl group from **40** to give **41** was, however, less well tolerated,[26,27] although introduction of an ethyl ester (**42**) in the 2-position, in the absence of N-1 substitution, recovered some of this affinity, and further elaboration of the carboxy functionality to 3-methoxybenzyloxadiazole (**43**) led to a compound with comparable affinity to the original lead (**19**).

These latter results suggested that the ethylamine side chain may bind to the 5-HT_6 receptor in a conformation in which the amino group is pointing away from the 2-position of the indole and toward the 4-position, similar to the conformationally constrained ergot alka-

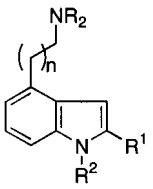
Table 1. 5-HT$_6$ Binding Affinity of Substituted Tryptamines



compd	X	NR^1R^2	R^3	R^4	K_i (nM) h5-HT$_6$[a]
18	MeO	NH_2	H	$PhSO_2$	40 (34, 47)
19	MeO	NMe_2	H	$PhSO_2$	2.3 (1.7, 3.2)
20	MeO	NMe_2	H	2-$ClC_6H_4SO_2$	11 (7.8, 15)
21	MeO	NMe_2	H	3-$ClC_6H_4SO_2$	7.9 (6.2, 10)
22	MeO	NMe_2	H	4-$ClC_6H_4SO_2$	17 (19, 21)
23	MeO	NMe_2	H	4-$MeC_6H_4SO_2$	45 (40, 50)
24	MeO	NMe_2	H	4-$MeOC_6H_4SO_2$	26 (23, 30)
25	MeO	NMe_2	H	2-naphthyl-SO_2	9.8 (7.8, 12)
26	MeO	NMe_2	H	2-thienyl-SO_2	8.3 (7.1, 9.8)
27	MeO	NMe_2	H	PhCO	25 (22, 27)
28	MeO	pyrrolidinyl	H	$PhSO_2$	44 (40, 48)
29	MeO	piperidinyl	H	$PhSO_2$	350 (280, 430)
30	MeO	4-methyl-piperazinyl	H	$PhSO_2$	490 (410, 590)
31	MeO	morpholinyl	H	$PhSO_2$	1700 (1400, 2100)
32	H	NMe_2	H	$PhSO_2$	2.9 (2.1, 3.9)
33	H	NMe_2	H	$MeSO_2$	620 (420, 910)
34	BnO	NMe_2	H	$PhSO_2$	320 (280, 370)
35	HO	NMe_2	H	$PhSO_2$	19 (18, 21)
36	HO	NMe_2	H	PhCO	54 (37, 78)
37	HO	NMe_2	H	*t*-BuOCO	370 (300, 470)
38	NC	NMe_2	H	$PhSO_2$	33 (13, 45)
39[b]	MeO	NMe_2	H	$PhSO_2$	63 (51, 78)
40	MeO	NMe_2	Me	$PhSO_2$	12 (10, 13)
41	MeO	NMe_2	Me	H	89 (69, 110)
42	H	NMe_2	CO_2Et	H	20 (13, 33)
43	H	NMe_2	ox[c]	H	1.3 (1.2, 1.5)

[a] Displacement of [^{3}H]-5-HT binding to cloned h5-HT$_6$ receptors stably expressed in HeLa cells. The figures are the geometric mean of at least three independent determinations performed in duplicate. The values in parentheses are the upper and lower limits derived as a result of the SEM. In each case the radioligand concentration used was approximately at the K_D for the receptor. Clozapine was used as a control [K_i 13 (11, 15) nM]. [b] This is an indoline. [c] 3-(3-methoxybenzyl)-1,2,4-oxadiazol-5-yl.

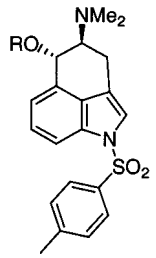
Table 2. 5-HT$_6$ Binding Affinity of 4-(Aminoalkyl)Indoles



compd	n	R	R^1	R^2	K_i (nM) h5-HT$_6$[a]
44	1	H	H	$PhSO_2$	2.4 (1.7, 3.4)
45	1	Me	H	$PhSO_2$	1.5 (1.0, 2.3)
46	2	Me	H	$PhSO_2$	7.9 (6.3, 11)
47	1	Me	COPh	$PhSO_2$	3.0 (2.0, 4.5)
48	1	Me	COPh	H	260 (240, 290)

[a] See corresponding footnote in Table 1.

Table 3. 5-HT$_6$ Binding Affinity of 1,3,4,5-Tetrahydrobenz[*cd*]indoles



compd	R	K_i (nM) h5-HT$_6$[a]
49	H	7.2 (6.0, 8.7)
50	Me	130 (120, 150)

[a] See corresponding footnote in Table 1.

loids and LSD, which has a high affinity for 5-HT$_6$ receptors. This theory was further supported by the fact that the 4-[(dimethylamino)ethyl]indole analogue (**45**) displayed comparable affinity for the h5-HT$_6$ receptor as the corresponding *N*,*N*-dimethyltryptamine (**32**) (Table 2). Interestingly, the primary amine (**44**) had similar affinity to **45**, in contrast to the tryptamines (**18** and **19**). Increasing the length of the side chain by one carbon atom, as in **46**, lowered the affinity by about 5-fold. A large substituent in the 2-position such as a benzoyl group was well tolerated in the presence of the N-1 benzenesulfonyl group (**47**) but not in its absence (**48**).

Additional support for this proposed binding conformation of the basic amino group was gained from the conformationally rigid 5-hydroxy-1,3,4,5-tetrahydrobenz[*cd*]indole (**49**). This compound in fact displayed 6-fold better affinity than its nearest reported acyclic analogue (**23**), although some of this may be due to an additional hydrogen-bonding interaction of the hydroxyl group since its methylation to give **50** led to a 18-fold reduction in affinity (Table 3). This preferred binding conformation at the 5-HT$_6$ receptor has also recently been postulated by Glennon et al.[26] and contrasts with the proposed binding mode of tryptamine derivatives at 5-HT$_{1D}$ receptors, for example.[28]

For some of the higher affinity compounds, the binding affinities at other serotonin receptors, as well as dopamine receptors, were measured (Table 4). It can

Table 4. BindingAffinity at Other Serotonin and Dopamine Receptors

	K_i[a] (nM)									
compd	h5-HT_{1A}	h5-HT_{1B}	h5-HT_{1D}	h5-HT_{1F}	5-HT_2	r5-HT_{5A}	h5-HT_7	hD_2	hD_3	hD_4
19	1100 (1200, 1100)	2200	720	2500	65 (95, 44)	>5000	1900	210 (190, 230)	80 (65, 98)	>3200
32	520	2300	510	770	84	4000	3700	62 (50, 76)	23 (19, 28)	>3200
36	620	420	180	29	200	4500	1600 (1500, 1700)	>2200[b]	3500[b]	>3900[b]
42	1800	910 (1100, 760)	330 (340, 320)	2000	130	4200[b]	510 (420, 630)	59 (53, 67)	110 (90, 120)	1600 (1000, 2400)
44	140 (200, 100)	6.5 (7.4, 5.6)	4.5 (5.1, 3.9)	47	4.8 (5.5, 4.2)	1200	29 (21, 42)	>1700	940 (780, 1140)	>3200
45	170 (210, 130)	11 (14, 8)	9.3 (12, 7.6)	3.9	18 (19, 17)	3400	460	1600	300 (220, 400)	>3200
47	480	190	98	570	6.6	1600	1300 (1000, 1800)	750 (640, 880)	66 (52, 84)	>3200
49	>5600	3100	3900[b]		320	>6400	>5800	>1700	3700 (3400, 4100)	>3200

[a] The figures are the geometric mean of at least three independent determinations performed in duplicate. The values in parentheses are the upper and lower limits derived as a result of the SEM. Where these limits are not quoted, only two independent determinations were performed. Receptors and radioligands used in the binding assays were as follows: 5-HT_{1A} (human cloned receptors in HeLa cells, [^{3}H]-5-HT); 5-HT_{1B} (human cloned receptors in CHO cells, [^{3}H]-5-HT); 5-HT_{1D} (human cloned receptors in CHO cells, [^{3}H]-5-HT); 5-HT_{1F} (human cloned receptors in CHO cells, [^{3}H]-5-HT); 5-HT_2 (rat cortical membranes, [^{3}H]DOB); 5-HT_{5A} (rat cloned 5-HT_{5A} receptors in HEK 293 cells); [^{3}H]LSD; 5-HT_7 (human cloned 5-HT_7 receptors in CHO cells, [^{3}H]-5-HT); dopamine D_2 (human cloned dopamine D_2 receptors in CHO cells, [^{3}H]spiperone); dopamine D_3 (human cloned dopamine D_3 receptors in HEK 293 cells, [^{3}H]spiperone); dopamine D_4 (human cloned dopamine D_4 receptors in HEK 293 cells, [^{3}H]spiperone). For the 5-HT assays, nonspecific binding was defined with 10 μM 5-HT, and for the dopamine assays, with 10 μM apomorphine. [b] This value is from a single determination.

be seen that the 1-(benzenesulfonyl)tryptamines (**19** and **32)** had >100-fold selectivity over all other serotonin receptors tested, apart from the 5-HT_2 receptor,[29] for which they had 28- and 29-fold selectivity, respectively. They also showed some affinity for hD_2 and hD_3 receptors with **32**, which lacks the 5-methoxy substituent, having particularly low selectivity against these receptors. The 1-benzoyl-5-hydroxytryptamine (**36)** was not so selective against the serotonin receptors, although it did have high selectivity over all the dopamine receptors tested. The 2-(carboxyethyl)tryptamine (**42**) was also not very selective over some of the serotonin receptors, and moreover, it displayed fairly high affinity at hD_2 and hD_3 receptors. The 4-(aminoethyl)indoles (**44** and **45**) both showed high affinity at several other serotonin receptors, although this series seemed to have better selectivity over the dopamine receptors. This high affinity for 5-HT_{1D} receptors, for example, may be explained by the compounds binding in the reverse orientation to the tryptamines in which the 3- and 4-positions of the indole ring are interchanged. The 2-benzoyl-substituted analogue (**47)** still had high affinity for 5-HT_2 receptors as well as some affinity for hD_3, 5-HT_{1B}, and 5-HT_{1D} receptors. Finally, the tetrahydrobenzindole (**49)** showed excellent selectivity over all the serotonin and dopamine receptors tested, with the lowest selectivity being against the 5-HT_2 receptor (44-fold).

Molecular modeling overlays with SQ[30] were performed of the rigid **49** with the 3- and 4-(aminoethyl)-indoles (**19** and **45)**, in which the sulfurs were forced to be coincident but the remainder of the molecule was left to find the best fit. It was found that, for both **19** and **45**, a low-energy conformer (within 2 kcal/mol of the global minima) overlaid well onto **49** with the basic N atoms being in close proximity (Figure 1). An overlay of **49** and the competitor compounds **1** and **3** using the same criteria again showed a reasonably good match, suggesting that these compounds may all bind in the same way to the 5-HT_6 receptor (Figure 2). This is different than the binding mode proposed by Glennon and co-workers[16] for **2** since the pyridine ring of **2** is overlaid onto the six-membered ring of the indole of **19**, leaving the basic amino groups of the two structures some distance away from each other. However, we believe that a positively charged N atom has an important interaction with Asp^{106} in transmembrane region III of the receptor[31] and thus should be in the same region of space for all compounds. Finally, to gain some insight into the binding mode of **43**, which does not have a phenylsulfonyl group, this was overlaid onto the other compounds, stipulating that the basic N atom should be matched by another heavy atom. The energy of the conformation depicted is only 0.6 kcal/mol above that of the global minimum for this compound and shows that the phenyl ring of the methoxybenzyl substituent on the oxadiazole of **43** overlays well onto the phenyl rings of the benzenesulfonyl group in the other compounds (Figure 3). This is achieved by the indole ring being displaced somewhat from the position that it occupies for the other compounds, with the six-membered ring of the indole occupying some of the same space as the methoxy substituent of **19** and the hydroxyl group of **49**.

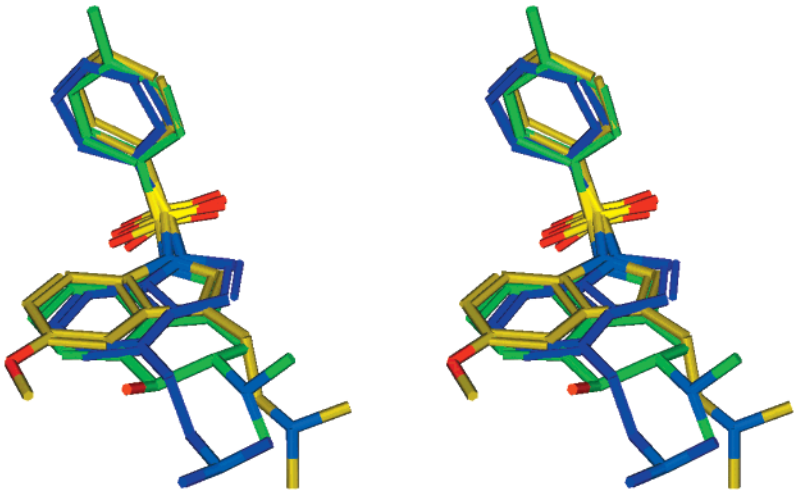


Figure 1. Overlay of **19** (yellow) and **45** (blue) onto **49** (green).

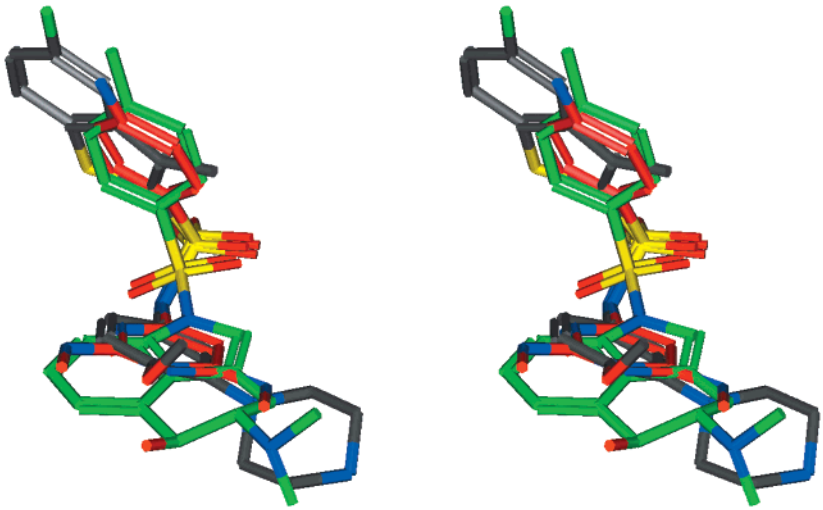


Figure 2. Overlay of Ro 04-6790 (**1**) (red) and SB-271046 (**3**) (black) onto **49** (green).

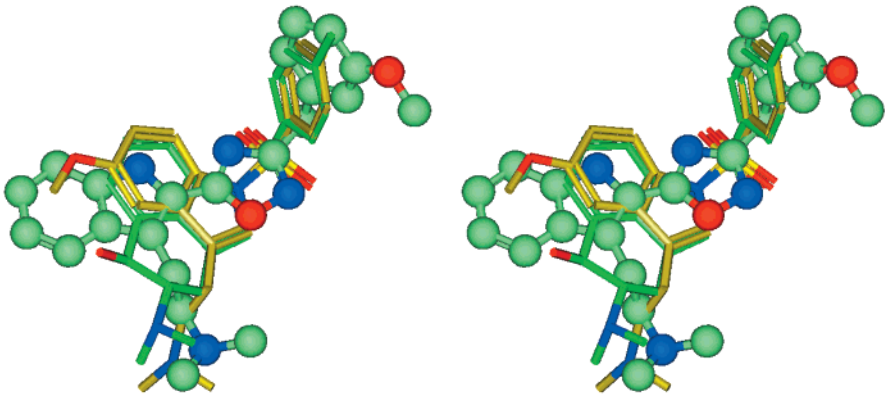


Figure 3. Overlay of **43** (green ball-and-sticks) onto **19** (yellow) and **49** (green).

Most of the compounds in Table 4 were also examined for their ability to stimulate adenylate cyclase in the rat 5-HT$_6$ receptor cell line. It was found that compounds **19**, **36**, **42**, **47**, and **49** had no agonist activity at 10 μM, whereas **32** and **45** behaved as partial agonists, giving 59% and 49%, respectively, of the response seen with 5-HT (Figure 4). Additionally, **19** and **42** completely inhibited the 5-HT-stimulated adenylate cyclase at the single concentration of 1 μM, suggesting that they were antagonists, although it cannot be ruled out that they may be inverse agonists.

To determine whether these compounds penetrate the brain and interact with receptors, advantage was taken of the fact that compound **19** has some affinity for 5-HT$_2$ receptors. In rodents, activation of 5-HT$_2$ receptors by agonists such as mescaline[32] and DOI [1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane] elicits a head twitch response that is blocked by selective 5-HT$_{2A}$ receptor antagonists such as MDL 100,907.[33] In this model, pretreatment with **19** also significantly and dose-dependently reduced mescaline-induced head twitches with an ID$_{50}$ of 11.3 $\pm$ 0.6 mg/kg ip (Figure 5). Given

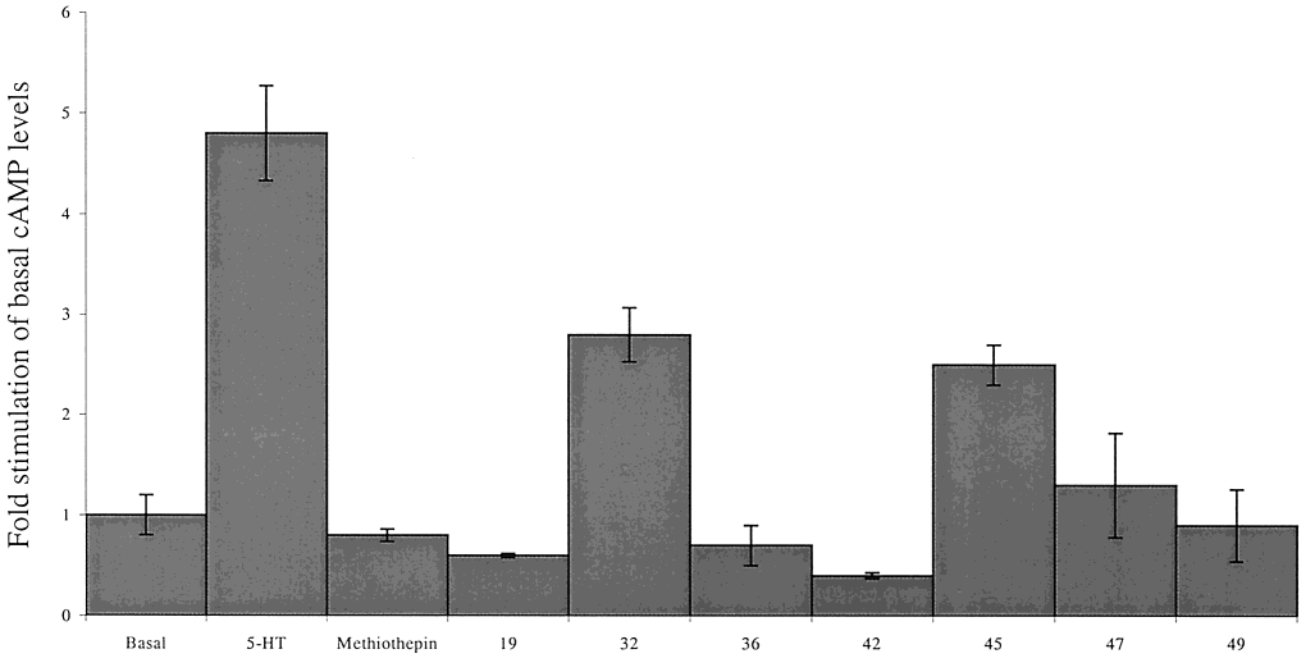


Figure 4. Stimulation of cAMP levels following treatment with 10 μM compound.

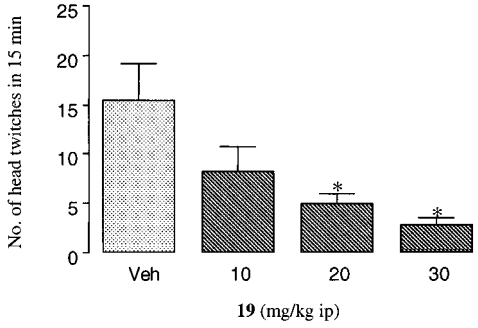


Figure 5. Effect of **19** on mescaline-induced head twitches in the rat. Results are expressed as the mean ± SEM number of head twitches recorded in 15 min (n = 6 rats/dose). Data were analyzed by analysis of variance followed by Dunnett's t test; *P < 0.05 compared to vehicle-pretreated rats.

that **19** has reasonble affinity for 5-HT_2 receptors, the simplest explanation for this effect is that **19** acts as a 5-HT_{2A} receptor antagonist in vivo. In addition, plasma and brain tissue were analyzed following dosing of **19** to rats at 3 mg/kg i.p. The mean plasma concentrations after 30 min in the plasma and brain were 86 ± 35 and 637 ± 220 ng/mL, respectively, giving a brain:plasma ratio of 7.4.

Thus, in conclusion, the present work has significantly extended the structure−activity relationships of the *N*-arylsulfonyltryptamines for binding at the 5-HT_6 receptor and led to the discovery that a suitable substituent at the 2-position of the indole ring can replace the arylsulfonyl group. Additionally, further delineation of the binding conformation has been achieved through the finding that 4-(aminoethyl)indoles and the conformationally rigid 1,3,4,5-tetrahydrobenz[*c,d*]indoles also bound with high affinity to this receptor.

Experimental Section

General Methods. Melting points were obtained on a Reichert Thermovar hot stage and are uncorrected. Proton NMR spectra were obtained on either a Bruker AM360 or a Bruker AC250 spectrometer. Mass spectra were recorded on a Quattro operating in an electrospray (ES) mode or a VB70−250 instrument operating in the electron impact (EI) or chemical ionization (CI) mode as indicated. (Note that only the strongest peaks from the mass spectra are reported below.) Elemental analysis for carbon, hydrogen, and nitrogen was performed by Butterworth Laboratories Ltd. High-performance liquid chromatography (HPLC) analysis was performed on a Hewlett-Packard HP1090 instrument with a Spherisorb S5 ODS2 column, eluted with acetonitrile/water (containing 0.2% triethylamine and made to pH 3 with orthophosphoric acid). Analytical thin-layer chromatography (TLC) was conducted on precoated silica gel 60 F_{254} plates (Merck). Visualization of the plates was accomplished by using UV light and/or iodine and/or aqueous potassium permanganate solution. Chromatography was conducted on silica gel 60, 220−440 mesh (Fluka) under low pressure. Solutions were evaporated on a Büchi rotary evaporator under reduced pressure. All starting materials were obtained from commercial sources and used as received unless otherwise indicated.

***N,N*-Dimethyl-2-(5-methoxy-2,3-dihydro-1*H*-indol-3-yl)-ethylamine (5).** A mixture of *N,N*-dimethyl-2-(5-methoxy-1*H*-indol-3-yl)ethylamine (0.200 g, 0.939 mmol) and palladium on carbon (10%, 200 mg) in 5 M aqueous HCl (50 mL) was hydrogenated at 50 psi overnight. The catalyst was removed by filtration, and the filtrate was extracted with dichloromethane (3 × 25 mL). The combined organic extracts were evaporated and the residue was purified by flash chromatography (silica gel, CH_2Cl_2−MeOH−NH_3(aq) 92:8:0.8) to give 94 mg (47%) of **5**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.71 (1H, m), 1.99 (1H, m), 2.26 (6H, s), 2.37 (2H, m), 3.20 (1H, t, J = 8.0 Hz), 3.27 (1H, m), 3.68 (1H, t, J = 8.0 Hz), 3.75 (3H, s), 6.60−6.61 (2H, m), 6.73 (1H, m).

Benzenesulfonic Acid 2-(1-Benzenesulfonyl-5-methoxy-1*H*-indol-3-yl)ethyl Ester (6). To a stirred two-phase mixture of 5-methoxytryptophol (0.150 g, 0.785 mmol) and tetrabutylammonium hydrogen sulfate (27 mg, 0.0785 mmol) in 50% aqueous NaOH (3 mL) and dichloromethane (30 mL) was added benzenesulfonyl chloride (0.25 mL, 1.96 mmol) dropwise over 5 min. The mixture was stirred for 20 min, more benzenesulfonyl chloride (0.10 mL, 0.784 mmol) was added dropwise, and the mixture was stirred for a further hour. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (silica gel, 50−100% EtOAc−hexane) to afford 0.095 g (37%)

of 2-(1-benzenesulfonyl-5-methoxy-1*H*-indol-3-yl)ethanol and 0.191 g (52%) of **6**: ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.98 (2H, t, J = 6.1 Hz), 3.71 (3H, s), 4.30 (2H, t, J = 6.2 Hz), 6.92 (1H, dd, J = 8.9 and 2.5 Hz), 6.95 (1H, d, J = 2.2 Hz), 7.47 (2H, t, J = 7.8 Hz), 7.53−7.59 (3H, m), 7.63−7.67 (4H, m), 7.77 (1H, d, J = 8.9 Hz), 7.89 (2H, m); MS (ES$^+$) m/z 510 [M + K]$^+$, 494 [M + Na]$^+$, 489 [M + NH$_4$]$^+$, 472 [M + H]$^+$.

1-(Benzenesulfonyl)-3-[2-[(tert-butyloxycarbonyl)amino]ethyl]-5-methoxy-1*H*-indole (7). To a stirred solution of 5-methoxytryptamine (3.5 g, 18.4 mmol) in dichloromethane (100 mL) was added dropwise a solution of di-*tert*-butyl dicarbonate (4.02 g, 18.4 mmol) in dichloromethane (25 mL) over 5 min. The resulting pale brown solution was allowed to stand at room temperature for 25 h, then the solvents were evaporated to leave a thick oil.

To a stirred two-phase mixture of a solution of the above 3-[2-[(*tert*-butyloxycarbonyl)amino]ethyl]-5-methoxy-1*H*-indole in dichloromethane (200 mL) and 50% aqueous NaOH (50 mL) was added tetrabutylammonium hydrogen sulfate (611 mg, 1.8 mmol), and the mixture was stirred for 10 min. Benzenesulfonyl chloride (3.52 mL, 27.6 mmol) was added dropwise via syringe and the mixture was vigorously stirred for 30 min. The mixture was diluted with diethyl ether (500 mL), washed with water (100 mL) and then brine (2 × 70 mL), dried (MgSO$_4$), and concentrated. Flash chromatography of the residue (silica gel, 10% Et$_2$O−CH$_2$Cl$_2$) followed by trituration with hexane−diethyl ether (10:1; 100 mL) afforded 7.55 g (95%) of **7** as a white solid: ^{1}H NMR (360 MHz, CDCl$_3$) δ 1.45 (9H, s), 2.82 (2H, t, J = 6.8 Hz), 3.36−3.44 (2H, m), 3.82 (3H, s), 4.55 (1H, br s), 6.90−6.96 (2H, m), 7.32 (1H, s), 7.38−7.45 (2H, m), 7.48−7.54 (1H, m), 7.80−7.84 (2H, m), 7.88 (1H, d, J = 8.8 Hz).

[5-Benzyloxy-3-[2-(dimethylamino)ethyl]-1*H*-indol-1-yl]phenylmethanone (8). Benzoyl chloride (217 mL, 1.9 mmol) was added to a stirred solution of [2-(5-benzyloxy-1*H*-indol-3-yl)ethyl]dimethylamine (500 mg, 1.7 mmol), triethylamine (473 mL, 3.4 mmol), and 4-(dimethylamino)pyridine (20 mg, 0.2 mmol) in anhydrous dichloromethane (5 mL) at 0 °C. The mixture was allowed to warm slowly to ambient temperature and then stirred at this temperature overnight. The reaction was quenched with saturated aqueous NaHCO$_3$ and then extracted three times with dichloromethane. The combined extracts were dried (Na$_2$SO$_4$) and evaporated. The residue was purified by flash chromatography (silica gel, CH$_2$-Cl$_2$–MeOH−NH$_3$(aq) 80:8:1) to give 327 mg (48%) of **8** as a thick oil: ^{1}H NMR (250 MHz, CDCl$_3$) δ 2.30 (6H, s), 2.52−2.60 (2H, m), 2.78−2.84 (2H, m), 5.16 (2H, s), 7.06−7.10 (3H, m), 7.30−7.64 (10H, m), 8.28 (0.5H, s), 8.32 (0.5H, s).

Benzyloxy-3-[2-(dimethylamino)ethyl]-1*H*-indole-1-carboxylic Acid tert-Butyl Ester (9). Di-*tert*-butyl dicarbonate (408 mg, 1.9 mmol) was added to a stirred solution of [2-(5-benzyloxy-1*H*-indol-3-yl)ethyl]dimethylamine (500 mg, 1.7 mmol), triethylamine (473 mL, 3.4 mmol), and 4-(dimethylamino)pyridine (20 mg, 0.2 mmol) in anhydrous dichloromethane (5 mL) at 0 °C. The reaction was allowed to warm slowly to ambient temperature. After 3 h the mixture was poured into saturated aqueous NaHCO$_3$ and extracted three times with dichloromethane. The combined extracts were dried (Na$_2$SO$_4$) and evaporated. The residue was purified by flash chromatography (silica gel, CH$_2$Cl$_2$−MeOH−NH$_3$(aq) 80:8:1) to give 630 mg (95%) of **9** as a thick oil: ^{1}H NMR (360 MHz, CDCl$_3$) δ 1.65 (9H, s), 2.33 (6H, s), 2.58−2.62 (2H, m), 2.79−2.83 (2H, m), 5.12 (2H, s), 6.99 (1H, dd, J = 9.0 and 2.5 Hz), 7.06 (1H, d, J = 2.5 Hz), 7.29−7.48 (6H, m), 8.0 (1H, br d).

Methyl 1-(Benzenesulfonyl)-1*H*-indole-4-carboxylate (10). A mixture of methyl indole-4-carboxylate[24] (5.0 g, 28.5 mmol), benzenesulfonyl chloride (10.1 g, 57.1 mmol), and anhydrous potassium carbonate (15.78 g, 114 mmol) in butan-2-one (150 mL) was heated at reflux under nitrogen for 15 h. Additional benzenesulfonyl chloride (10.1 g) and anhydrous potassium carbonate (10.1 g) were added, and heating at reflux was continued for 5 h. After cooling, the mixture was diluted with water (300 mL) and extracted with diethyl ether (3 × 300 mL). The combined organic extracts were dried (MgSO$_4$) and evaporated. Recrystallization from ethanol gave 6.35 g (72%) of **10** as a white solid: ^{1}H NMR (360 MHz, CDCl$_3$) δ 3.94 (3H, s), 7.33−7.56 (5H, m), 7.69 (1H, d, J = 3.7 Hz), 7.84−7.87 (2H, m), 7.96 (1H, dd, J = 8.1 and 0.7 Hz), 8.21 (1H, d, J = 8.3 Hz); MS (CI) m/z 316 [M + H]$^+$.

1-(Benzenesulfonyl)-1*H*-indole-4-carboxaldehyde (11). To a cooled (−70 °C) and stirred solution of **10** (4.5 g, 14.3 mmol) in anhydrous diethyl ether (50 mL) was added diisobutylaluminum hydride (1 M in toluene; 37 mL) over 30 min, under a nitrogen atmosphere. After the mixture was stirred at −70 °C for 3 h, excess diisobutylaluminum hydride was destroyed by the dropwise addition of methanol (3 mL) and the mixture was allowed to warm to room temperature. 5% Aqueous citric acid (100 mL) was added and the mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic phases were dried (MgSO$_4$) and evaporated. Flash chromatography of the residue (silica gel, 50% EtOAc−hexane) gave 2.6 g (63%) of the intermediate 1-(benzenesulfonyl)-1*H*-indole-4-methanol as a thick colorless oil. To a solution of the above alcohol (2.5 g) in anhydrous dichloromethane (200 mL) was added activated manganese(IV) oxide (9 g), and the resulting mixture was stirred for 15 h at room temperature under a nitrogen atmosphere. The manganese residues were removed by filtration and washed with chloroform, and the filtrates were evaporated to give 1.96 g (79%) of **11** as a white solid: ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.42−7.56 (5H, m), 7.72−7.77 (2H, m), 7.86−7.90 (2H, m), 8.28 (1H, d, J = 8.25 Hz); 10.18 (1H, s); MS (EI$^+$) m/z 285 (M$^+$). (Found, m/z 285.0444; $C_{15}H_{11}NO_3S$ requires m/z 285.0460).

1-(Benzenesulfonyl)-4-(2-nitrovinyl)-1*H*-indole (12). To a solution of **11** (1.9 g, 6.6 mmol) in nitromethane (12 mL) was added ammonium acetate (205 mg, 2.7 mmol), and the resulting mixture was heated at reflux for 2 h. After cooling, water (50 mL) was added and the mixture was extracted with ethyl acetate (2 × 100 mL). The combined organic phases were washed with brine (30 mL), dried (MgSO$_4$), and evaporated. Flash chromatography (silica gel, 75% CH$_2$Cl$_2$−hexane) of the residue gave 1.95 g (90%) of **12** as a pale yellow solid: ^{1}H NMR (250 MHz, CDCl$_3$) δ 6.89 (1H, dd, J = 3.7 and 0.9 Hz), 7.34−7.62 (5H, m), 7.65 (1H, d, J = 13.7 Hz), 7.75 (1H, d, J = 3.7 Hz), 7.87−7.92 (2H, m), 8.14 (1H, d, J = 8.2 Hz), 8.27 (1H, d, J = 13.7 Hz); MS (EI$^+$) m/z 329 [M + H]$^+$.

3-[1-(Benzenesulfonyl)-1*H*-indol-4-yl]acrylic Acid Ethyl Ester (13). A solution of **11** (2.0 g, 7 mmol) and (carbethoxymethylene)triphenylphosphorane (2.69 g, 7.7 mmol) in anhydrous dichloromethane (50 mL) was heated at reflux for 3 h under nitrogen. After cooling, the reaction was evaporated and purified by dry flash chromatography (silica gel, CH$_2$Cl$_2$) to give 2.49 g (100%) of **13** as a colorless solid: ^{1}H NMR (360 MHz, CDCl$_3$) δ 1.34 (3H, t, J = 7.2 Hz), 4.27 (2H, q, J = 7.2 Hz), 6.51 (1H, d, J = 17.2 Hz), 6.94 (1H, d, J = 0.7 Hz), 7.32 (1H, t, J = 7.9 Hz), 7.43−7.67 (4H, m), 7.67 (1H, d, J = 3.6 Hz), 7.68−7.89 (2H, m), 7.94−8.03 (2H, m).

3-[1-(Benzenesulfonyl)-1*H*-indol-4-yl]propionic Acid Ethyl Ester (14). A mixture of **13** (2.48 g, 6.98 mmol) in ethyl acetate−ethanol (4:1; 75 mL) was hydrogenated over 10% Pd−C (500 mg) under an atmosphere of hydrogen. After 4 h the catalyst was removed by filtration, and the solvents were evaporated to obtain 2.47 g (100%) of **14** as a colorless oil that crystallized on standing: ^{1}H NMR (360 MHz, CDCl$_3$) δ 1.10 (3H, t, J = 6.8 Hz), 2.57 (2H, t, J = 7.5 Hz), 3.06 (2H, t, J = 7.5 Hz), 4.02 (2H, q, J = 7.2 Hz), 6.66 (1H, d, J = 0.7 Hz), 6.98 (1H, d, J = 7.5 Hz), 7.14−7.18 (1H, m), 7.34−7.38 (2H, m), 7.43−7.48 (1H, m), 7.50 (1H, d, J = 4.0 Hz), 7.77−7.82 (3H, m).

***N*,*N*-Dimethyl-3-[1-(benzenesulfonyl)-1*H*-indol-4-yl]propionamide (15).** Trimethylaluminum (2 M solution in hexanes, 1.4 mL, 2.8 mmol) was added to a suspension of dimethylamine hydrochloride (228 mg, 2.8 mmol) in benzene (10 mL). The reaction was stirred for 1 h before a solution of **14** (0.5 g, 1.4 mmol) in benzene (10 mL) was added dropwise. The reaction was heated at reflux for 18 h, allowed to cool, and then quenched by the addition of 2 N aqueous HCl (5 mL).

The mixture was partitioned between water and ethyl acetate. The organic phase was washed with brine, dried ($MgSO_4$), and evaporated to leave 527 mg (100%) of **15** as an oil that subsequently crystallized: ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.63 (2H, t, J = 7.5 Hz), 2.79 (2H, br s), 3.16 (2H, t, J = 8.5 Hz), 6.74 (1H, d, J = 0.7 Hz), 6.08 (1H, d, J = 7.5 Hz), 7.21−7.27 (1H, m), 7.41−7.58 (4H, m), 7.84−7.90 (3H, m).

4-Amino-1-(4-methyl)benzenesulfonyl-1,3,4,5-tetrahydrobenz[*cd*]indol-5-ol (17).[25] To a solution of sodium borohydride (1 g) in absolute ethanol (75 mL) was added dropwise via cannula a suspension of (±)-4-amino-3,4-dihydro-1-[(methylphenyl)sulfonyl]benz[*cd*]indol-5(1*H*)one hydrochloride (**16**)[25] (4.55 g) in absolute ethanol (150 mL) over 15 min, keeping the internal temperature below 3 °C. The resulting mixture was stirred at −2 °C for 1 h 40 min under nitrogen before it was carefully acidified with 2 N aqueous HCl (28 mL). The ethanol was evaporated and the residue was basified with 2 N aqueous NaOH (35 mL). The products were extracted with ethyl acetate (3 × 150 mL) and the combined organic phases were washed with brine (50 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue (silica gel, CH_2Cl_2−EtOH−NH_3(aq) 170:28:3) gave 3.99 g (97%) of **17** as a 90:10 mixture of trans and cis isomers: MS m/z 342 (M^+).

2-[1-(Benzenesulfonyl)-5-methoxy-1*H*-indol-3-yl]ethylamine Hydrochloride (18). A solution of **7** (2.1 g) in a mixture of dichloromethane and trifluoroacetic acid (1:1; 60 mL) was allowed to stand at room temperature for 3 h. The solvents were removed under vacuum and the residue was azeotroped with toluene−methanol (5:1; 100 mL). The residue was dissolved in 4 N aqueous NaOH (50 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic solutions were washed with brine (1 × 50 mL), dried (Na_2SO_4), and concentrated. The hydrochloride salt was prepared and recrystallized from acetonitrile to give 1.53 g (82%) of **18**: mp 117−120 °C; ^{1}H NMR (360 MHz, D_2O) δ 3.01 (2H, t, J = 7.6 Hz), 3.29 (2H, t, J = 7.6 Hz), 3.78 (3H, s), 6.89 (1H, dd, J = 9.0 and 2.3 Hz), 6.89 (1H, dd, J = 9.0 and 2.3 Hz), 7.00 (1H, d, J = 2.3 Hz), 7.41 (2H, t, J = 8.1 Hz), 7.54 (1H, t, J = 7.5 Hz), 7.56 (1H, s), 7.74 (1H, d, J = 9.0 Hz), 7.81 (2H, d, J = 7.5 Hz); MS (ES) m/z 331 [M + H]$^+$. Anal. [$C_{17}H_{18}N_2O_3S$·1.0HCl·0.6H_2O] C, H, N.

***N,N*-Dimethyl-2-[1-(benzenesulfonyl)-5-methoxy-1*H*-indol-3-yl]ethylamine (19).** To a stirred two-phase mixture of 5-methoxy-*N*,*N*-dimethyltryptamine (2 g, 9.16 mmol) and tetrabutylammonium hydrogen sulfate (311 mg, 0.916 mmol) in dichloromethane (120 mL) and 50% aqueous NaOH (30 mL) was added benzenesulfonyl chloride (2.43 g, 13.7 mmol) over 30 min. The mixture was stirred at room temperature for 20 min and then diluted with ethyl acetate (250 mL) and water (125 mL). The organic phase was decanted off, washed with brine (2 × 65 mL), dried ($MgSO_4$), and evaporated. Flash chromatography (silica gel, CH_2Cl_2−MeOH−NH_3(aq) 95:5:0.5) of the residue afforded 3.166 g (96%) of **19** as a thick oil that solidified on standing. The hydrogen chloride salt was prepared: mp 200−215 °C (EtOH); ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.81 (6H, s), 3.06−3.16 (2H, m), 3.16−3.28 (2H, m), 3.28−3.36 (2H, m), 3.80 (3H, s), 6.98 (1H, dd, J = 9.0 and 2.5 Hz), 7.26 (1H, d, J = 2.5 Hz), 7.58 (2H, t, J = 7.5 Hz), 7.65−7.72 (2H, m), 7.82 (1H, d, J = 9.0 Hz), 7.92 (2H, dd, J = 8.6 and 1.3 Hz), 10.82 (1H, br s); MS (ES$^+$) m/z 359 [M + H]$^+$. Anal. [$C_{19}H_{22}N_2SO_3$·HCl] C, H, N.

Compounds **20**−**26** were prepared with the appropriate sulfonyl chloride by a procedure similar to that described for **19**.

***N,N*-Dimethyl-2-[1-(2-chlorobenzenesulfonyl)-5-methoxy-1*H*-indol-3-yl]ethylamine (20).** Yield 43%. Hydrochloride salt: mp 185−188 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.84 (6H, s), 3.14 (2H, m), 3.37 (2H, m), 3.81 (3H, s), 6.93 (1H, dd, J = 9.0 and 2.4 Hz), 7.31 (1H, d, J = 2.4 Hz), 7.54 (1H, d, J = 9.0 Hz), 7.63 (1H, td), 7.68 (1H, dd), 7.74 (1H, td), 7.78 (1H, s), 8.14 (1H, dd, J = 7.9 and 1.5 Hz), 10.45 (1H, br s); MS (ES$^+$) m/z 395/393 [M + H]$^+$. Anal. [$C_{19}H_{21}ClN_2O_3S$·HCl] C, H, N.

***N,N*-Dimethyl-2-[1-(3-chlorobenzenesulfonyl)-5-methoxy-1*H*-indol-3-yl]ethylamine (21).** Yield 67%. Hydrochloride salt: mp 191−194 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.81 (6H, s), 3.09 (2H, m), 3.34 (2H, m), 3.80 (3H, s), 7.00 (1H, dd, J = 9.0 and 2.5 Hz), 7.26 (1H, d, J = 2.4 Hz), 7.61 (1H, t, J = 8.0 Hz), 7.73 (1H, s), 7.77 (1H, dt), 7.84 (1H, d, J = 9.1 Hz), 7.89 (1H, dt), 7.97 (1H, t, J = 1.9 Hz), 10.59 (1H, br s); MS (ES$^+$) m/z 395/393 [M + H]$^+$. Anal. [$C_{19}H_{21}ClN_2O_3S$·HCl] C, H, N.

***N,N*-Dimethyl-2-[1-(4-chlorobenzenesulfonyl)-5-methoxy-1*H*-indol-3-yl]ethylamine (22).** Yield 39%. Hydrochloride salt: mp 222−224 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.82 (6H, s), 3.09 (2H, m), 3.35 (2H, m), 3.81 (3H, s), 6.99 (1H, dd, J = 9.0 and 2.5 Hz), 7.27 (1H, d, J = 2.4 Hz), 7.67 (2H, d, J = 8.8 Hz), 7.70 (1H, s), 7.82 (1H, d, J = 9.0 Hz), 7.94 (2H, d, J = 8.7 Hz), 10.65 (1H, br s); MS (ES$^+$) m/z 395/393 [M + H]$^+$. Anal. [$C_{19}H_{21}ClN_2O_3S$·HCl·0.2H_2O] C, H, N.

***N,N*-Dimethyl-2-[5-methoxy-1-(4-methylbenzenesulfonyl)-1*H*-indol-3-yl]ethylamine (23).** Yield 72%. Hydrochloride salt: mp 214−215 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.32 (3H, s), 2.81 (6H, s), 3.08 (2H, m), 3.37 (2H, m), 3.79 (3H, s), 6.97 (1H, dd, J = 9.0 and 2.5 Hz), 7.23 (1H, d, J = 2.4 Hz), 7.37 (2H, d, J = 8.1 Hz), 7.67 (1H, s), 7.79 (2H, d, J = 8.4 Hz), 7.80 (1H, d, J = 9.1 Hz), 10.60 (1H, br s); MS (ES$^+$) m/z 373 [M + H]$^+$. Anal. [$C_{20}H_{24}N_2O_3S$·HCl·0.4H_2O] C, H, N.

***N,N*-Dimethyl-2-[5-methoxy-1-(4-methoxybenzenesulfonyl)-1*H*-indol-3-yl]ethylamine (24).** Yield 61%. Hydrochloride salt: mp 152−155 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.82 (6H, s), 3.08 (2H, m), 3.34 (2H, m), 3.80 (3H, s), 3.81 (3H, s), 6.98 (1H, dd, J = 9.0 and 2.5 Hz), 7.08 (2H, d, J = 9.0 Hz), 7.24 (1H, d, J = 2.4 Hz), 7.67 (1H, s), 7.81 (1H, d, J = 9.0 Hz), 7.86 (2H, d, J = 9.1 Hz), 10.55 (1H, br s); MS (ES$^+$) m/z 389 [M + H]$^+$. Anal. [$C_{20}H_{24}N_2O_4S$·HCl] C, H, N.

***N,N*-Dimethyl-2-[5-methoxy-1-(2-naphthalenesulfonyl)-1*H*-indol-3-yl]ethylamine (25).** Yield 56%. Hydrochloride salt: mp 191−193 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.81 (6H, s), 3.09 (2H, m), 3.35 (2H, m), 3.78 (3H, s), 6.98 (1H, dd, J = 9.0 and 2.4 Hz), 7.23 (1H, d, J = 2.4 Hz), 7.72 (2H, m), 7.78 (1H, s), 7.81 (1H, dd, J = 8.8 and 1.9 Hz), 7.90 (1H, d, J = 9.1 Hz), 8.01 (1H, d, J = 7.7 Hz), 8.08 (1H, d, J = 8.8 Hz), 8.21 (1H, d), 8.76 (1H, s), 10.60 (1H, br s); MS (ES$^+$) m/z 409 (MH^+). Anal. [$C_{23}H_{24}N_2O_3S$·HCl] C, H, N.

***N,N*-Dimethyl-2-[5-methoxy-1-(2-thiophenesulfonyl)-1*H*-indol-3-yl]ethylamine (26).** Yield 25%. Oxalate salt: mp 215−220 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.78 (6H, s), 3.03 (2H, m), 3.29 (2H, m), 3.81 (3H, s), 7.16 (1H, m), 7.20 (1H, d, J = 2.3 Hz), 7.61 (1H, s), 7.81 (1H, d, J = 9.2 Hz), 7.83 (1H, m), 8.01 (1H, dd, J = 5.1 and 1.3 Hz); MS (ES$^+$) m/z 365 [M + H]$^+$. Anal. [$C_{17}H_{20}N_2O_3S_2$·$C_2H_2O_4$] C, H, N.

***N,N*-Dimethyl-2-(1-benzoyl-5-methoxy-1*H*-indol-3-yl)-ethylamine (27).** By a procedure similar to that described for **19** but with benzoyl chloride instead of benzenesulfonyl chloride, **27** was prepared in 53% yield as a white solid. Oxalate salt: mp 199−201 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.78 (6H, s), 3.05 (2H, m), 3.27 (2H, m), 3.86 (3H, s), 7.02 (1H, dd, J = 9.0 and 2.4 Hz), 7.28 (1H, d, J = 2.4 Hz), 7.32 (1H, s), 7.61 (2H, t, J = 7.0 Hz), 7.70 (1H, t, J = 7.3 Hz), 7.75 (2H, d, J = 6.9 Hz), 8.19 (1H, d, J = 9.0 Hz); MS (ES$^+$) m/z 323 [M + H]$^+$. Anal. [$C_{20}H_{22}N_2O_2$·$C_2H_2O_4$] C, H, N.

1-Benzenesulfonyl-5-methoxy-3-[(2-pyrrolidin-1-yl)-ethyl]-1*H*-indole (28). To a stirred mixture of **6** (0.191 g, 0.405 mmol) and anhydrous potassium carbonate (0.112 g, 0.810 mmol) in anhydrous 2-propanol (10 mL) under nitrogen was added a solution of pyrrolidine (0.17 mL, 2.03 mmol) in anhydrous 2-propanol (3 mL). The mixture was heated at reflux for 4 h, and the solvents were then evaporated. The residue was partitioned between dichloromethane and water, and the aqueous layer was extracted further with dichloromethane. The combined organic extracts were washed with brine (2 × 25 mL), dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (silica gel, CH_2Cl_2−MeOH−NH_3(aq) 95:5:0.5) to give 0.102 g (65%) of **28**. The oxalate salt was prepared in EtOH−Et_2O as a white solid: mp 217−220 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.94 (4H, s), 3.03

(2H, m), 3.27 (4H, s), 3.40 (2H, m), 3.79 (3H, s), 6.98 (1H, dd, J = 9.0 and 2.3 Hz), 7.17 (1H, d, J = 2.3 Hz), 7.58 (2H, t, J = 8.0 Hz), 7.69 (2H, m), 7.82 (1H, d, J = 9.0 Hz), 7.92 (2H, d, J = 7.9 Hz); MS (ES$^+$) m/z 385 [M + H]$^+$. Anal. [$C_{21}H_{24}N_2O_3S\cdot C_2H_2O_4$] C, H, N.

Compounds **29**−**31** were prepared with the appropriate amine by a method similar to that described for **28**.

1-Benzenesulfonyl-5-methoxy-3-[(2-piperidin-1-yl)ethyl]-1*H*-indole (29). Yield 90%. Oxalate salt: mp 231−234 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.55 (2H, m), 1.75 (4H, m), 3.04 (2H, m), 3.15 (4H, s), 3.27 (2H, m), 3.79 (3H, s), 6.98 (1H, dd, J = 9.0 and 2.4 Hz), 7.15 (1H, d, J = 2.4 Hz), 7.58 (2H, t, J = 8.0 Hz), 7.68 (2H, m), 7.82 (1H, d, J = 9.0 Hz), 7.91 (2H, d, J = 7.7 Hz); MS (ES$^+$) m/z 399 [M + H]$^+$. Anal. [$C_{22}H_{26}N_2O_3S\cdot C_2H_2O_4\cdot 0.3H_2O$] C, H, N.

1-Benzenesulfonyl-5-methoxy-3-[(2-piperazin-1-yl)ethyl]-1*H*-indole (30). Yield 76%. Oxalate salt: mp 230−232 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.70 (3H, s), 2.82 (8H, br s), 3.09 (4H, br s), 3.78 (3H, s), 6.96 (1H, dd, J = 9.0 Hz), 7.08 (1H, d), 7.57 (2H, t, J = 7.5 Hz), 7.60 (1H, s), 7.68 (1H, t, J = 7.5 Hz), 7.81 (1H, d, J = 9.0 Hz), 7.90 (2H, d, J = 7.6 Hz); MS (ES$^+$) m/z 414 [M + H]$^+$. Anal. [$C_{22}H_{27}N_3O_3S\cdot 4C_2H_2O_4\cdot 2H_2O$] C, H, N.

1-[2-(5-Methoxy-1-phenylsulfonyl-1*H*-indol-3-yl)ethyl]-morpholine (31). Oxalate salt: mp 215−220 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.91 (8H, br s), 3.03 (4H, br s), 3.78 (3H, s), 6.97 (1H, d, J = 9.1 Hz), 7.11 (1H, s), 7.57 (2H, t, J = 7.8 Hz), 7.64 (1H, s), 7.68 (1H, t), 7.81 (1H, d, J = 9.0 Hz), 7.90 (2H, d, J = 7.8 Hz); MS (ES$^+$) m/z 401 [M + H]$^+$. Anal. [$C_{21}H_{24}N_2O_4S\cdot C_2H_2O_4\cdot 0.3H_2O$] C, H, N.

Compounds **32** and **33** were prepared from the appropriate tryptamine compounds and the corresponding sulfonyl chloride following a method similar to that described for **19**.

***N*,*N*-Dimethyl-2-(1-benzenesulfonyl-1*H*-indol-3-yl)ethylamine (32).** Oxalate salt: mp 196−198 °C (EtOH−Et_2O); ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.77 (6H, s), 3.00−3.08 (2H, m), 3.26−3.34 (2H, m), 7.29 (1H, t, J = 7.3 Hz), 7.38 (1H, t, J = 7.3 Hz), 7.61 (2H, t, J = 8.0 Hz), 7.64−7.72 (2H, m), 7.74 (1H, s), 7.91−7.97 (3H, m); MS (CI) m/z 329 [M + H]$^+$. Anal. [$C_{18}H_{20}N_2O_2S\cdot C_2H_2O_4$] C, H, N.

***N*,*N*-Dimethyl-2-(1-methylsulfonyl-1*H*-indol-3-yl)ethylamine (33).** Oxalate salt: mp 191−193 °C (EtOH−Et_2O); ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.79 (6H, s), 3.05−3.14 (2H, m), 3.28−3.36 (2H, m), 3.37 (3H, s), 7.30−7.44 (2H, m), 7.52 (1H, s), 7.75 (1H, d, J = 7.3 Hz), 7.83 (1H, d, J = 8.1 Hz); MS (CI) m/z 267 [M + H]$^+$. Anal. [$C_{13}H_{18}N_2O_2S\cdot 1.1(C_2H_2O_4)$] C, H, N.

***N*,*N*-Dimethyl-2-(1-benzenesulfonyl-5-benzyloxy-1*H*-indol-3-yl)ethylamine (34).** To a stirred solution of 5-benzyloxytryptamine hydrochloride (2.29 g, 7.56 mmol) in methanol (100 mL) was added sodium methoxide (30% w/v in methanol; 1.44 mL) followed by glacial acetic acid (1.70 mL, 30.2 mmol) and sodium cyanoborohydride (950 mg, 15.1 mmol). A solution of formaldehyde (38% w/v aqueous solution; 1.43 mL) in methanol (25 mL) was then added dropwise over 20 min, and the resulting solution was stirred at room temperature for 4 h. Aqueous NaOH (4 N, 60 mL) was added and the methanol was removed under vacuum. The aqueous residue was extracted with diethyl ether (2 × 250 mL) and the combined organic phases were washed with brine (2 × 50 mL), dried (Na_2SO_4), and concentrated. The residue was dissolved in dichloromethane (120 mL), and 50% aqueous NaOH (40 mL) was added followed by tetrabutylammonium hydrogen sulfate (258 mg). The mixture was vigorously stirred, benzenesulfonyl chloride (1.45 mL) in dichloromethane (10 mL) was added dropwise over 3 min, and stirring was continued for 30 min. Water (120 mL) and diethyl ether (200 mL) were added and the organic phase was decanted off, washed with brine (2 × 50 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue (silica gel, CH_2Cl_2−MeOH−NH_3(aq) 95:5:0.5) afforded 2.57 g (78%) of **34** as a colorless thick oil. The oxalate salt was prepared: mp 212−215 °C (EtOH); ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.77 (6H, s), 2.98−3.06 (2H, m), 3.22−3.30 (2H, m), 5.12 (2H, s), 7.06 (1H, dd, J = 9.0 and 2.4 Hz), 7.28−7.48 (6H, m), 7.58 (2H, t, J = 8.0 Hz), 7.64−7.72 (2H, m), 7.82 (1H, d, J = 9.0 Hz), 7.90−7.94 (2H, m); MS (ES) m/z 435 [M + H]$^+$. Anal. [$C_{25}H_{26}N_2O_3S\cdot C_2H_2O_4$] C, H, N.

***N*,*N*-Dimethyl-2-(1-benzenesulfonyl-5-hydroxy-1*H*-indol-3-yl)ethylamine (35).** A solution of **34** (2.25 g, 4.6 mmol) in absolute ethanol (100 mL) was hydrogenated at 40 psi over 20% palladium hydroxide (600 mg) for 4.5 h. Additional catalyst (1.6 g) was then added and hydrogenation was resumed at 45 psi for 2.5 h. The catalyst was removed by filtration, washed with a mixture of dichloromethane−methanol−ammonia (80:20:2; 3 × 70 mL), and the filtrate was evaporated. The residue was purified by flash chromatography (silica gel, CH_2Cl_2−MeOH−NH_3(aq) 95:5:0.5) to give **35** as a crystalline solid after trituration with diethyl ether (30 mL): mp 185−188 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.18 (6H, s), 2.47 (2H, t, J = 7.6 Hz), 2.67 (2H, t, J = 7.6 Hz), 6.78 (1H, dd, J = 8.8 and 2.2 Hz), 6.82 (1H, d, J = 2.2 Hz), 7.48 (1H, s), 7.55 (2H, t, J = 8.0 Hz), 7.62−7.68 (1H, m), 7.69 (1H, d, J = 8.7 Hz), 7.84−7.90 (2H, m), 9.32 (1H, br s); MS (ES) m/z 345 [M + H]$^+$. Anal. [$C_{18}H_{20}N_2O_3$] C, H, N.

[3-[2-(Dimethylamino)ethyl]-5-hydroxy-1*H*-indol-1-yl]-phenylmethanone (36). A solution of **8** (300 mg, 0.75 mmol) and 4 N aqueous HCl (190 mL, 0.76 mmol) in ethanol (10 mL) was hydrogenated over 10% palladium on carbon (100 mg) at 35 psi for 3 h. The catalyst was removed by filtration and the filtrate was evaporated. The residue was partitioned between dichloromethane and saturated aqueous $NaHCO_3$, and the aqueous layer was further extracted twice with dichloromethane. The combined extracts were dried (K_2CO_3) and evaporated. The residue was purified by flash chromatography (silica gel, CH_2Cl_2−MeOH−NH_3(aq) 80:8:1) to give 120 mg (52%) of **36** as a colorless solid: mp 154−156 °C. ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.40 (6H, s), 2.70−2.75 (2H, m), 2.83−2.88 (2H, m), 6.86−6.90 (2H, m), 7.04 (1H, s), 7.49−7.61 (3H, m), 7.68−7.71 (2H, m), 8.17 (0.5H, s), 8.20 (0.5H, s); MS (CI$^+$) m/z 309 [M + H]$^+$. Anal. [$C_{19}H_{20}N_2O_2\cdot 0.2H_2O$] C, H, N.

3-[2-(Dimethylamino)ethyl]-5-hydroxy-1*H*-indole-1-carboxylic Acid tert-Butyl Ester (37). This was prepared from **9** following a procedure similar to that described for **36** in 50% yield as a colorless solid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.64 (9H, s), 2.45 (6H, s), 2.73−2.80 (2H, m), 2.88−2.93 (2H, m), 6.82−6.85 (1H, m), 6.96 (1H, br s), 7.33 (1H, br s), 7.92 (1H, m); MS (CI$^+$) m/z 305 [M + H]$^+$. Anal. [$C_{17}H_{24}N_2O_3\cdot 0.8H_2O$] C, H, N.

***N*,*N*-Dimethyl-2-(1-benzenesulfonyl-5-cyano-1*H*-indol-3-yl)ethylamine (38).** To a stirred solution of 3-(2-aminoethyl)-5-cyano-1*H*-indole hydrochloride[19] (0.1208 g, 0.545 mmol) in methanol (25 mL) was added a 30% (w/v) solution of sodium methoxide in methanol (0.1 mL, 0.545 mmol), then acetic acid (0.125 mL, 2.18 mmol), followed by sodium cyanoborohydride (68 mg, 1.09 mmol). A 38% (w/v) aqueous solution of formaldehyde (0.103 mL, 1.31 mmol) in methanol (10 mL) was then added dropwise over 30 min. The mixture was stirred for 3.5 h, then 4 N aqueous NaOH (25 mL) was added, and the methanol was evaporated. The aqueous residue was extracted with diethyl ether (3 × 25 mL), and the combined organic extracts were washed with brine (2 × 20 mL), dried (Na_2SO_4), and evaporated to give crude *N*,*N*-dimethyl 2-(5-cyano-1*H*-indol-3-yl)ethylamine.

To this crude product was added dichloromethane (30 mL), 50% aqueous NaOH (2 mL), and tetrabutylammonium hydrogen sulfate (19 mg, 0.0545 mmol). Benzenesulfonyl chloride (0.104 mL, 0.817 mmol) was then added dropwise over 3 min while the mixture was stirred magnetically, and the mixture was stirred for an additional 30 min. Ethyl acetate (50 mL) and water (25 mL) was then added, and the organic layer was washed with brine (2 × 25 mL), dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (silica gel, CH_2Cl_2−MeOH−NH_3(aq) 95:5:0.5) to yield 0.132 g (66%) of **38**. The oxalate salt was prepared in EtOH−Et_2O as a white solid: mp 213−220 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.78 (6H, s), 3.10 (2H, m), 3.31 (2H, m), 7.63 (2H, t, J = 7.5 Hz), 7.74 (1H, t, J = 7.5 Hz), 7.78 (1H, dd, J = 8.6 and 1.4 Hz), 7.98 (1H, s), 8.03 (2H, d, J = 7.4 Hz), 8.11 (1H, d, J = 8.4 Hz),

8.31 (1H, s); MS (ES^+) *m/z* 354 $[M + H]^+$. Anal. $[C_{19}H_{19}N_3O_2S \cdot C_2H_2O_4]$ C, H, N.

***N,N*-Dimethyl-2-(1-benzenesulfonyl-5-methoxy-2,3-dihydro-1*H*-indol-3-yl)ethylamine (39).** This was prepared in 57% yield from **5** by a procedure similar to that described for **19**. Oxalate salt: mp 183−185 °C; ^1H NMR (360 MHz, DMSO-d_6) δ 1.47 (1H, m), 1.94 (1H, m), 2.68 (6H, s), 2.96 (2H, m), 3.14 (1H, m), 3.63 (1H, m), 3.71 (3H, s), 4.06 (1H, m), 6.82 (2H, m), 7.42 (1H, d, J = 9.4 Hz), 7.57 (2H, t, J = 7.3 Hz), 7.68 (1H, t), 7.78 (2H, d, J = 7.6 Hz); MS (ES^+) *m/z* 361 $[M + H]^+$. Anal. $[C_{19}H_{24}N_2O_3S \cdot C_2H_2O_4 \cdot 0.7H_2O]$ C, H, N.

***N,N*-Dimethyl-2-(1-benzenesulfonyl-5-methoxy-2-methyl-1*H*-indol-3-yl)ethylamine (40).** This was prepared from **41** by a procedure similar to that described for **19**. Oxalate salt: mp 194−196 °C; ^1H NMR (360 MHz, DMSO-d_6) δ 2.54 (3H, s), 2.76 (6H, s), 2.98 (2H, m), 3.44 (2H, m), 3.80 (3H, s), 6.92 (1H, dd, J = 9.0 and 2.5 Hz), 7.09 (1H, d, J = 2.5 Hz), 7.56 (2H, t, J = 7.5 Hz), 7.67 (1H, t, J = 7.5 Hz), 7.77 (2H, d, J = 7.4 Hz), 7.94 (1H, d, J = 9.1 Hz); MS (ES^+) *m/z* 373 $[M + H]^+$. Anal. $[C_{20}H_{24}N_2O_3S \cdot C_2H_2O_4 \cdot 0.4H_2O]$ C, H, N.

***N,N*-Dimethyl-2-(1-benzenesulfonyl-5-methoxy-2-methyl-1*H*-indol-3-yl)ethylamine (41).** To a stirred solution of 2-(5-methoxy-2-methyl-1*H*-indol-3-yl)ethylamine hydrochloride[34] (1.6 g, 6.55 mmol) in methanol (100 mL) was added a 30% (w/v) solution of sodium methoxide in methanol (1.24 mL, 6.55 mmol), then acetic acid (1.50 mL, 26.2 mmol), followed by sodium cyanoborohydride (0.82 g, 13.1 mmol). A 38% (w/v) aqueous solution of formaldehyde (1.24 mL, 15.7 mmol) in methanol (30 mL) was then added dropwise over 40 min, and the mixture was stirred overnight. Aqueous NaOH (4 N, 50 mL) was then added, the methanol was evaporated, and the aqueous residue was extracted with ethyl acetate. The organic extract was washed with brine (50 mL), dried (Na_2SO_4), and evaporated to give 1.215 g (80%) of **41**. The oxalate salt was prepared in ethanol−diethyl ether: mp 212−215 °C; ^1H NMR (360 MHz, DMSO-d_6) δ 2.32 (3H, s), 2.82 (6H, s), 2.95 (2H, m), 3.09 (2H, m), 3.76 (3H, s), 6.64 (1H, dd, J = 8.7, 2.3 Hz), 6.99 (1H, d, J = 2.3 Hz), 7.13 (1H, d, J = 8.7 Hz); MS (ES^+) *m/z* 233 $[M + H]^+$. Anal. $[C_{14}H_{20}N_2O \cdot C_2H_2O_4]$ C, H, N.

***N,N*-Dimethyl-3-(2-aminoethyl)-1*H*-indole-2-carboxylic Acid Ethyl Ester (42).** To a solution of 3-(2-aminoethyl)-indole-2-carboxylic acid, ethyl ester[20] (2.0 g, 8.61 mmol) in anhydrous methanol (50 mL) was added sodium cyanoborohydride (1.19 g, 18.9 mmol) and glacial acetic acid (2.46 mL, 43.1 mmol). A 38% aqueous solution of formaldehyde (1.88 mL, 25.8 mmol) in anhydrous methanol (25 mL) was then added dropwise under nitrogen, and the mixture was stirred at room temperature for 2 h and then quenched with aqueous K_2CO_3 solution (20 mL). The methanol was evaporated and residue was partitioned between ethyl acetate and water. The aqueous layer was extracted twice more with ethyl acetate, and the combined organic extracts were washed twice with brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (silica gel, 3−10% MeOH−CH_2Cl_2) to afford 800 mg (36%) of **42** as a white solid. The hydrochloride salt was prepared in EtOAc−Et_2O to give a colorless solid: mp 248−250 °C; ^1H NMR (360 MHz, DMSO-d_6) δ 1.39 (3H, t, J = 7.1 Hz), 2.86 (6H, s), 3.19 (2H, m), 3.49 (2H, m), 4.38 (2H, q, J = 7.1 Hz), 7.12 (1H, t, J = 7.2 Hz), 7.30 (1H, t, J = 7.1 Hz), 7.45 (1H, d, J = 8.3 Hz), 7.83 (1H, d, J = 8.1 Hz), 10.82 (1H, br s), 11.76 (1H, s); MS (CI^+) *m/z* 261 $[M + H]^+$. Anal. $[C_{15}H_{20}N_2O_2 \cdot HCl]$ C, H, N.

***N,N*-Dimethyl-2-[2-[3-(3-methoxybenzyl)-1,2,4-oxadiazol-5-yl]-1*H*-indol-3-yl]ethylamine (43).** To a stirred solution of 3-methoxybenzeneacetamide oxime[21] (1.24 g, 6.90 mmol) in anhydrous THF (60 mL) at −78 °C under nitrogen was added sodium hydride (60% dispersion in oil, 258 mg, 6.44 mmol). The mixture was then allowed to warm to room temperature over 15 min before a solution of **42** (600 mg, 2.30 mmol) in anhydrous THF (20 mL) was added dropwise. The mixture was stirred at room temperature for 1 h and then at reflux for a further 2 h. After cooling, aqueous NH_4Cl (10 mL) was added and the THF was evaporated. The residual aqueous phase was partitioned between ethyl acetate and water. The aqueous layer was further extracted twice with ethyl acetate and the combined organic extracts were washed with brine twice, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (silica gel, 3−10% MeOH−CH_2Cl_2) to yield 395 mg (46%) of **43** as a white solid. The hydrochloride salt was prepared in ethyl acetate−diethyl ether: mp 248−249 °C; ^1H NMR (360 MHz, DMSO-d_6) δ 2.78 (6H, s), 3.22 (2H, m), 3.55 (2H, m), 3.75 (3H, s), 4.18 (2H, s), 6.86 (1H, m), 6.95 (1H, d, J = 8.3 Hz), 6.97 (1H, s), 7.16 (1H, t, J = 7.3 Hz), 7.28 (1H, t, J = 8.3 Hz), 7.33 (1H, t, J = 7.3 Hz), 7.48 (1H, d, J = 8.3 Hz), 7.85 (1H, d, J = 8.1 Hz), 10.55 (1H, br s), 12.28 (1H, s); MS (CI^+) *m/z* 377 $[M + H]^+$. Anal. $[C_{22}H_{24}N_4O_2 \cdot HCl]$ C, H, N.

2-[1-(Benzenesulfonyl)-1*H*-indol-4-yl]ethylamine (44). Zinc amalgam was prepared by mixing zinc dust (6 g) and mercury(II) chloride (600 mg) in a mixture of water (6 mL) and concentrated hydrochloric acid (300 μL) and stirring at room temperature for 10 min. The aqueous phase was decanted off and the amalgam was then covered with methanol.

To a cooled (0 °C) and stirred solution of **12** (1.9 g) in a mixture of methanol (35 mL) and concentrated hydrochloric acid (20 mL) was added portionwise, over 30 min, the zinc amalgam prepared above. The mixture was stirred at 0 °C for a further 30 min and at room temperature for 2 h before the solvent was decanted off and evaporated under vacuum. The remaining residue was partitioned between 1 M aqueous ammonia (50 mL) and diethyl ether (75 mL) and the aqueous phase was re-extracted with diethyl ether (2 × 75 mL). The combined ethereal solutions were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue (silica gel, CH_2Cl_2−MeOH−NH_3(aq) 40:8:1) gave 950 mg (55%) of **44** as a thick colorless oil: ^1H NMR (250 MHz, $CDCl_3$) δ 3.06 (4H, s), 6.78 (1H, d), 7.04 (1H, d), 7.20 (1H, t), 7.36−7.60 (4H, m), 7.86 (3H, d); MS (EI) *m/z* 301 $[M + H]^+$. Anal. $[C_{16}H_{16}N_2O_2S \cdot C_2H_2O_4]$ C, H, N.

***N,N*-Dimethyl-2-[1-(benzenesulfonyl)-1*H*-indol-4-yl]ethylamine (45).** A solution of aqueous formaldehyde (38% w/v; 790 μL) in methanol (10 mL) was added dropwise to a cooled (0 °C) and stirred mixture of **44** (750 mg), sodium cyanoborohydride (345 mg), and glacial acetic acid (715 μL) in methanol (30 mL). The mixture was then allowed to warm to room temperature and it was stirred for 1 h before saturated aqueous K_2CO_3 (20 mL) was added and the methanol was removed under vacuum. The remaining residue was diluted with water (20 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic solutions were washed with brine (30 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue (silica gel, 10% MeOH−CH_2Cl_2) gave 550 mg (67%) of **45** as a colorless thick oil. The oxalate salt was prepared and recrystallized from 2-propanol−ether: mp 192−195 °C; ^1H NMR (360 MHz, D_2O) δ 2.89 (6H, s), 3.22−3.28 (2H, m), 3.37−3.43 (2H, m), 6.91 (1H, d, J = 3.9 Hz), 7.19 (1H, d, J = 7.5 Hz), 7.35 (1H, t, J = 8.2 Hz), 7.45−7.50 (2H, m), 7.60 (1H, t, J = 7.6 Hz), 7.77 (1H, d, J = 3.8 Hz), 7.89−7.93 (3H, m); MS (EI) *m/z* 329 $[M + H]^+$. Anal. $[C_{18}H_{20}N_2O_2S \cdot C_2H_2O_4 \cdot 0.2H_2O]$ C, H, N.

***N,N*-Dimethyl-3-[1-(benzenesulfonyl)-1*H*-indol-4-yl]propylamine (46).** A solution of **15** (527 mg, 1.4 mmol) in THF (15 mL) was treated dropwise with lithium aluminum hydride (1.0 M solution in THF, 1.4 mL) while the mixture was stirred under a nitrogen atmosphere. The reaction was stirred for 5 h and then quenched with water (1 mL). The reaction was filtered through a glass fiber pad, and the filtrate was evaporated. The residue was partitioned between 2 N aqueous NaOH and ethyl acetate. The organic phase was dried (Na_2SO_4), evaporated, and purified by flash chromatography (silica gel, CH_2Cl_2−MeOH−NH_3(aq) 95:5:0.5) to give 275 mg (50%) of **46** as an oil. The oxalate salt was prepared in diethyl ether: mp 142−144 °C; ^1H NMR (250 MHz, DMSO-d_6) δ 1.8−2.0 (2H, m), 2.67 (6H, s), 2.78−2.84 (2H, m), 2.98−3.04 (2H, m), 6.97 (1H, d, J = 3.75 Hz), 7.11 (1H, d, J = 7 Hz), 7.29 (1H, t, J = 7.5 Hz), 7.11 (1H, d, J = 7 Hz), 7.29 (1H, t, J = 7.5 Hz), 7.57−7.73 (3H, m), 7.79−7.85 (2H, m), 7.98−9.01 (2H, m); MS

(ES$^+$) *m/z* 343 [M + H]$^+$. Anal. [$C_{19}H_{20}N_2O_3S$·1.3($C_2H_2O_4$)] C, H, N.

***N,N*-Dimethyl-2-[1-(benzenesulfonyl)-2-benzoyl-1*H*-indol-4-yl]ethylamine (47).** To a cooled (−78 °C) and stirred solution of **45** (1.16 g, 3.6 mmol) in anhydrous tetrahydrofuran (8 mL) was added dropwise, under nitrogen, *tert*-butyllithium (1.7 M solution in pentane, 25 mL). The resulting solution was stirred at −78 °C for 30 min and then it was allowed to warm to 0 °C over 1 h. After being recooled to −78 °C, a solution of freshly distilled benzaldehyde (415 mg, 3.9 mmol) in anhydrous tetrahydrofuran (4 mL) was added and the mixture was allowed to warm to room temperature over 3 h. The reaction was quenched by addition of water (20 mL) and extracted with ethyl acetate (2 × 75 mL). The combined extracts were dried ($MgSO_4$) and evaporated. Flash chromatography (silica gel, 10% EtOH−CH_2Cl_2 to CH_2Cl_2−MeOH−NH_3(aq) 60:8:1) of the residue gave 720 mg of [1-(benzenesulfonyl)-4-[2-(dimethylamino)ethyl]-1*H*-indol-2-yl]phenylmethanol as a white solid.

To a solution of the above alcohol (350 mg) in anhydrous dichloromethane (20 mL) was added activated manganese(IV) oxide (250 mg), and the resulting mixture was stirred vigorously at room temperature for 30 min. The manganese residues were removed by filtration and washed with dichloromethane, and the filtrates were evaporated. Flash chromatography of the residual oil (silica gel, 10% EtOH−CH_2Cl_2 to CH_2Cl_2−MeOH−NH_3(aq) 60:8:1) gave 330 mg (44% over two steps) of **47** as a yellow oil. The oxalate salt was prepared and recrystallized from 2-propanol−diethyl ether: mp 154−156 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.73 (6H, s), 3.16 (4H, s), 7.26 (1H, d, J = 7.4 Hz), 7.46−7.51 (2H, m), 7.59−7.68 (4H, m), 7.72−7.78 (2H, m), 7.93−8.03 (5H, m); MS (CI$^+$) *m/z* 433 [M + H]$^+$, 293 [M − SO_2Ph + 2H]$^+$. Anal. [$C_{25}H_{24}N_2O_3S$·$C_2H_2O_4$·0.2H_2O] C, H, N.

***N,N*-Dimethyl-2-[2-benzoyl-1*H*-indol-4-yl]ethylamine (48).** To a solution of **47** (280 mg, 0.648 mmol) in methanol (5 mL) was added 2 N aqueous NaOH (1 mL), and the solution was stirred at 80 °C under nitrogen for 30 min. The solvent was then evaporated and the residue was purified by flash chromatography (silica gel, 10% EtOH−CH_2Cl_2 and then CH_2Cl_2−EtOH−NH_3(aq) 60:8:1) to afford 160 mg (84%) of **48** as a yellow oil. The oxalate salt was prepared: mp 243−245 °C (MeOH−*i*-PrOH−Et_2O); ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.51 (6H, s), 2.93 (2H, m), 3.13 (2H, m), 6.97 (1H, d, J = 6.2 Hz), 7.23 (1H, s), 7.26 (1H, t, J = 7.1 Hz), 7.38 (1H, d, J = 8.3 Hz), 7.61 (2H, t, J = 7.7 Hz), 7.70 (1H, t, J = 7.4 Hz), 7.96 (2H, d, J = 7.1 Hz), 12.01 (1H, s); MS (CI$^+$) *m/z* 294 [M + H]$^+$. Anal. [$C_{21}H_{22}N_2O_5$·0.5($C_2H_2O_4$)] C, H, N.

trans-4-(Dimethylamino)-1-(4-methylbenzenesulfonyl)-1,3,4,5-tetrahydrobenz[*cd*]indol-5-ol (49).[25] A solution of **17** (3.97 g, 11.59 mmol) in absolute ethanol (150 mL), aqueous formaldehyde (38% w/v; 9.2 mL) and glacial acetic acid (92 mL) was hydrogenated at 30 psi over 10% palladium on carbon (1.56 g) for 65 h. The catalyst was removed by filtration and washed with absolute ethanol, and the filtrate was evaporated. The residue was dissolved in dichloromethane (40 mL) and washed with 10% aqueous $NaHCO_3$ (100 mL). The aqueous layer was extracted with dichloromethane (2 × 120 mL), and the combined organic phases were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue (silica gel, CH_2Cl_2−EtOH−NH_3(aq) 85:15:0 to 70:9:1) gave 3.68 g (86%) of **49** together with 400 mg of the corresponding cis isomer. The oxalate salt was prepared from ethanol−diethyl ether: mp 123−126 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.32 (3H, s), 2.78 (6H, s), 2.96−3.12 (1H, m), 3.16−3.26 (1H, m), 3.38−3.54 (1H, m), 5.14 (1H, d, J = 9.3 Hz), 7.30 (1H, d, J = 7.4 Hz), 7.36−7.44 (3H, m), 7.55 (1H, s), 7.76 (1H, d, J = 8.1 Hz), 7.86 (2H, d, J = 8.4 Hz); MS (EI) 371 *m/z* [M + H]$^+$. Anal. [$C_{20}H_{22}N_2O_3S$·$C_2H_2O_4$] C, H, N.

4-(Dimethylamino)-5-methoxy-1-(4-methylbenzenesulfonyl)-1,3,4,5-tetrahydrobenz[*cd*]indole (50). To a solution of **49** (700 mg, 1.89 mmol) in anhydrous THF (10 mL) and anhydrous DMF (3 mL) was added sodium hydride (60% dispersion in oil; 91 mg), followed, after 10 min, by benzyltrimethylammonium chloride (35 mg) and methyl 3-bromopropionate. After the mixture was stirred at room temperature for 2.5 h, additional sodium hydride was added and stirring was continued for 16 h. Water (50 mL) was added and products were extracted with dichloromethane (3 × 50 mL) and then dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (silica gel, 5% EtOH−CH_2Cl_2) gave 30 mg (4%) of **50**. The oxalate salt was prepared and crystallized from 2-propanol: mp 133−136 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.31 (3H, s), 2.52 (6H, s), 3.08 (2H, d, J = 5.6 Hz), 3.48−3.56 (4H, m and s), 4.89 (1H, d, J = 6.5 Hz), 7.29 (1H, d, J = 7.3 Hz), 7.34−7.42 (3H, m), 7.52 (1H, s), 7.80 (1H, d, J = 8.1 Hz), 7.86 (2H, d, J = 8.4 Hz); MS *m/z* 384 (M$^+$). Anal. [$C_{21}H_{24}N_2O_3S$·$C_2H_2O_4$] C, H, N.

Molecular Modeling Methods. Structures of compounds **19**, **45**, **49**, **1,** and **3** were sketched and then converted to sets of 26 diverse conformations of each molecule by use of the torsional enumeration program "et".[35] Each conformation was subjected to energy minimization with the macromodel batchmin engine with the MMFFs force field and default minimization conditions. After minimization, conformations were checked for uniqueness by alignment on all heavy atoms. Only the lower-energy conformer of any pair in which the RMS superposition error was less than 0.1 Å, together with conformers that had no equivalent conformer by this definition, were considered further. Alignment points (SQ points) were added to each conformer, with the point corresponding to the sulfur atom of the sulfonamide in each molecule being marked as "essential" points, required to be matched by another atom of the same physicochemical type (percent type of essential point). The SQ program[30] was then used to align all conformers of each molecule on all conformers of each of the other molecules, the best 50 ensemble alignments according to their overall SQ score (the sum of all pairwise SQ scores in the ensemble) being kept for further study. The overall SQ scores for these ensembles were quite similar, ranging from 1029 to 1035. The molecular mechanics energy associated with each ensemble was calculated by summing the energies calculated for the conformer of each molecule present in that ensemble. A preferred ensemble (score 1032.6, the ninth highest score) was selected on the basis of its low total energy (338.95 kcal/mol) with respect to the lowest total found for any ensemble (337.28 kcal/mol) and the presence of no conformation in the ensemble with an energy of greater than 1.66 kcal/mol higher than the lowest-energy conformation found for that molecule, together with the observation that this ensemble was oriented in such a way as to present similar groups (aromatic rings, basic nitrogen atoms) in similar volumes of space. This preferred ensemble was then reassigned SQ points on all heavy atoms of all molecules in the ensemble, this time marking the basic nitrogen of compound **19** as essential by physicochemical type (percent). Conformations of compound **43** were then generated with et as before to provide 26 diverse conformations, which were then subjected to the same minimization conditions as had been used previously. SQ was then used to superimpose this molecule on the preferred ensemble of the other five molecules previously generated, with the top-scoring superposition having an SQ score of 391 and requiring a conformer of compound **43** only 0.61 kcal/mol higher in energy than the best minimum found for any conformer of **43** (79.91 kcal/mol MMFFs energy).

5-HT$_6$ Receptor Binding Assay. HeLa cells stably transfected with the human 5-HT$_6$ receptor (obtained from Dr. D. Sibley, HIH) were grown to confluency in DMEM medium supplemented with 10% fetal calf serum, 100 units/mL penicillin, and 100 μg/mL streptomycin before being harvested, pelleted in phosphate-buffered saline (pH 7.4), and stored at −70 °C. On the day of assay the pellets were thawed and resuspended in 10 mL of assay buffer (50 mM Tris buffer containing 0.03% ascorbic acid, pH 7.6 at room temperature), homogenized in a Polytron (setting 5, 10 s), and centrifuged at 3000 rpm at 4 °C for 10 min. The resulting pellet was then resuspended in the same 50 mM Tris buffer to give a washed wet weight:volume ratio of 3 mg:100 μL. All assays were carried out in duplicate. Membranes, [^{3}H]-LSD (69.9 mCi/

mmol, DuPont NEN) and test compounds were prepared in assay buffer. A 100 μL aliquot of membrane suspension (3 mg wet weight of tissue) was incubated at 37 °C in a shaking water bath in the presence of [^{3}H]-LSD (1 nM) with or without competing compound to give a final volume of 500 μL. 5-HT (10 μM) was used to define nonspecific binding. The reaction was initiated by the addition of the membrane suspension and was terminated after 60 min by rapid filtration through Whatman GF/C filters, which had been presoaked in 0.3% poly(ethylenimine)/0.5% Triton X100, using a Brandel cell harvester. Each assay tube was washed twice with approximately 4 mL of 50 mM Tris buffer, pH 7.6 at room temperature. The filter-bound radioactivity was then determined by scintillation spectrometry at approximately 40% efficiency. Data were fitted to a one-site curve-fitting equation by RS Client to yield IC_{50} values (the concentration that inhibits specific binding by 50%). Apparent K_i values were estimated from the Cheng−Prusoff equation where the apparent K_i values are the IC_{50} values corrected for ligand concentration as follows: $IC_{50}/(1 + [L]/[K_d])$, where [L] is the ligand concentration and K_d is the ligand dissociation constant.

Adenylate Cyclase Assay. CHO cells expressing the rat 5-HT_6 receptor were grown in Iscoves medium containing 10% FCS, 2 mM L-glutamine, 50 IU/mL penicillin, and 50 μg/mL streptomycin. The cells were plated into 24-well tissue culture plates 24 h prior to being used. Following this recovery period the medium was removed and the cells were washed with 1 mL of warm (37 °C) DMEM containing 1 mM of the phosphodiesterase inhibitor, 3-isobutyl-1-methylxanthine (IBMX). Warm DMEM (1 mL) containing 1 mM IBMX and 10 μM of the appropriate compound (where required) was added to each well, and the cells were placed back in the incubator for 60 min to allow cAMP to accumulate. The medium was then removed and the cells were washed with 1 mL of ice-cold PBS. The cells were then killed by the addition of 200 μL of ice-cold 5% TCA. The cells were then scraped into labeled eppendorf vials and extracted three times with 1 mL of water-saturated ether to remove the TCA. Following ether extraction, the samples were dried and dissolved in 300 μL of cAMP assay buffer from the Amersham Biotrak [^{3}H]-cAMP assay kit (product number TRK432). The amount of cAMP present in each sample was then determined with the reagents and protocol supplied with the kit.

Mescaline-Induced Head Twitch Assay. Male Sprague-Dawley rats (220−270 g; Bantin and Kingman, Hull, U.K.) were pretreated with either **19** (10−30 mg/kg ip) or vehicle [25% poly(ethylene glycol) in water, pH = 6; 1 mL/kg] 30 min prior to administration of mescaline (20 mg/kg iv). Rats were immediately placed into individual Perspex observation boxes and the number of head twitches was recorded for the following 15 min. Pretreatment with **19** dose-dependently reduced mescaline-induced head twitches with an $ID_{50} = 11.3 \pm 0.6$ mg/kg ip.

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References

(1) Hoyer, D.; Clarke, D. E.; Fozard, J. R.; Hartig, P. R.; Martin, G. R.; Mylecharane, E.; Saxena, P. R.; Humphrey, P. P. A. International Union of Pharmacology Classification of Receptors for 5-Hydroxytryptamine (Serotonin). *Pharmacol. Rev.* **1994**, *46*, 157−204.

(2) Monsma, F. J.; Shen, Y.; Ward, R. P.; Hamblin, W.; Sibley, D. R. Cloning and Expression of a Novel Serotonin Receptor with High Affinity for Tricyclic Psychotropic Drugs. *Mol. Pharmacol.* **1993**, *43*, 320−327.

(3) Ruat, M.; Traiffort, E.; Arrang, J.-M.; Tardivel-Lacombe, J.; Diaz, J.; Leurs, R.; Swartz, J.-C. A Novel Serotonin (5-HT_6) Receptor: Molecular Cloning, Localisation and Stimulation of cAMP Accumulation. *Biochem. Biophys. Res. Commun.* **1993**, *193*, 269−276.

(4) Kohnen, R.; Metcalf, M. A.; Khan, N.; Druck, T.; Huebner, K.; Lachowicz, J. E.; Meltzer, H.; Sibley, D. R.; Roth, B. L.; Hamblin, M. W. Cloning, Characterization, and Chromosomal Localization of a Human 5-HT_6 Serotonin Receptor. *J. Neurochem.* **1996**, *66*, 47−56.

(5) Ward, R. P.; Hamblin, M. W.; Lachowicz, J. E.; Hoffman, B. J.; Sibley, D. R.; Dorsa, D. M. Localization of Serotonin Subtype 6 Receptor Messenger RNA in the Rat Brain by in situ Hybridization Histochemistry. *Neuroscience* **1995**, *64*, 1105−1111.

(6) Branchek, T. A. Blackburn, T. P. 5-HT_6 Receptors as Emerging Targets for Drug Discovery. *Annu. Rev. Pharmacol. Toxicol.* **2000**, *40*, 319−334.

(7) Bourson, A.; Borroni, E.; Austin, R. H.; Monsma, F. J.; Sleight, A. J. Determination of the Role of the 5-ht_6 Receptor in the Rat Brain: A Study Using Antisense Oligonucleotides. *J. Pharmacol. Exp. Ther.* **1995**, *274*, 173−180.

(8) Yoshioka, M.; Matsumoto, M.; Togashi, H.; Mori, K.; Saito, H. Central Distribution and Function of 5-HT_6 Receptor Subtype in the Rat Brain. *Life Sci.* **1998**, *62*, 1473−1477.

(9) Sleight, A. J.; Boess, F. G.; Bös, M.; Levet-Trafit, B.; Riemer, C.; Bourson, A. Characterization of Ro 04-6790 and Ro 63-0563: Potent and Selective Antagonists at Human and Rat 5-HT_6 Receptors. *Br. J. Pharmacol.* **1998**, *124*, 556−562.

(10) Bromidge, S. M.; Brown, A. M.; Clarke, S. E.; Dodgson, K.; Gager, T.; Grassam, H. L.; Jeffrey, P. M.; Joiner, G. F.; King, F. D.; Middlemiss, D. N.; Moss, S. F.; Newman, H.; Riley, G.; Routledge, C.; Wyman, P. 5-Chloro-*N*-(4-methoxy-3-piperazin-1-ylphenyl)-3-methyl-2-benzothiophenesulfonamide (SB-271046): A Potent, Selective, and Orally Bioavailable 5-HT_6 Receptor Antagonist. *J. Med. Chem.* **1999**, *42*, 202−205.

(11) Bourson, A.; Boess, F. G.; Bös, M.; Sleight, A. J. Involvement of 5-HT_6 Receptors in Nigro-striatal Function in Rodents. *Br. J. Pharmacol.* **1998**, *125*, 1562−1566.

(12) Bentley, J. C.; Bourson, A.; Boess, F. G.; Fone, K. C. F.; Marsden, C. A.; Petit, N.; Sleight, A. J. Investigation of Stretching Behaviour Induced by the Selective 5-HT_6 Receptor Antagonist, Ro 04-6790, in Rats. *Br. J. Pharmacol.* **1999**, *126*, 1537−1542.

(13) Dawson, L. A.; Nguyen, H. Q.; Li, P. In vivo Effects of the 5-HT_6 Antagonist SB-271046 on Striatal and Frontal Cortex Extracellular Concentrations of Noradrenaline, Dopamine, 5-HT, Glutamate and Aspartate. *Br. J. Pharmacol.* **2000**, *130*, 23−26.

(14) Routledge, C.; Bromidge, S. M.; Moss, S. F.; Price, G. W.; Hirst, W.; Newman, H.; Riley, G.; Gager, T.; Stean, T.; Upton, N.; Clarke, S. E.; Brown, A. M.; Middlemiss, D. N. Characterization of SB-271046: A Potent, Selective and Orally Active 5-HT_6 Receptor Antagonist. *Br. J. Pharmacol.* **2000**, *130*, 1606−1612.

(15) Bromidge, S. M.; Clarke, S. E.; Gager, T.; Griffith, K.; Jeffrey, P.; Jennings, A. J.; Joiner, G. F.; King, F. D.; Lovell, P. J.; Moss, S. F.; Newman, H.; Riley, G.; Rogers, D.; Routledge, C.; Serafinowska, H.; Smith, D. R. Phenyl Benzenesulfonamides are Novel and Selective 5-HT_6 Antagonists: Identification of *N*-(2,5-Dibromo-3-fluorophenyl)-4-methoxy-3-piperazin-1-ylbenzenesulfonamide (SB-357134). *Bioorg. Med. Chem. Lett.* **2001**, *11*, 55−58.

(16) Tsai, Y.; Dukat, M.; Slassi, A.; MacLean, N.; Demchyshyn, L.; Savage, J. E.; Roth, B. L.; Hufesein, S.; Lee, M.; Glennon, R. A. N_1-(Benzenesulfonyl)tryptamines as Novel 5-HT_6 Antagonists. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2295−2299.

(17) Lee, M.; Rangisetty, J. B.; Dukat, M.; Slassi, A.; Maclean, N.; Lee, D. K. H.; Glennon, R. A. 5-HT_6 Serotonin Receptor Binding Affinities of N_1-Benzenesulfonyl and Related Tryptamines. *Med. Chem. Res.* **2000**, *10*, 230−242.

(18) Slassi, A.; Edwards, L.; O'Brien, A.; Xin, T.; Tehim, A. Preparation of 1-(Arylsulfonyl)-3-(tetrahydropyridinyl)indoles as 5-HT_6 Receptor Inhibitors. U.S. Patent 6,133,287, 2000.

(19) Castro, J. L.; Baker, R.; Guiblin, A. R.; Hobbs, S. C.; Jenkins, M. R.; Russell, M. G. N.; Beer, M. S.; Stanton, J. A.; Scholey, K.; Hargreaves, R. J.; Graham, M. I.; Matassa, V. G. Synthesis and Biological Activity of 3-[2-(Dimethylamino)ethyl]-5-[(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)methyl]-1*H*-indole and Analogues: Agonists for the 5-HT_{1D} Receptor. *J. Med. Chem.* **1994**, *37*, 3023−3032.

(20) Szantay, C.; Szabo, L.; Kalaus, G. A New Route to Tryptamines. *Synthesis* **1974**, 354−356.

(21) Street, L. J.; Baker, R.; Castro, J. L.; Chambers, M. S.; Guiblin, A. R.; Hobbs, S. C.; Matassa, V. G.; Reeve, A. J.; Beer, M. S.; Middlemiss, D. N.; Noble, A. J.; Stanton, J. A.; Scholey, K.; Hargreaves, R. J. Synthesis and Serotonergic Activity of 5-(Oxadiazolyl)tryptamines: Potent Agonists for 5-HT_{1D} Receptors. *J. Med. Chem.* **1993**, *36*, 1529−1538.

(22) Barf, T. A.; de Boer, P.; Wikstroem, H.; Peroutka, S. J.; Svensson, K. A.; Ennis, M. D.; Ghazal, N. B.; McGuire, J. C.; Smith, M. W. 5-HT_{1D} Receptor Agonist Properties of Novel 2-[5-[[(Trifluoromethyl)sulfonyl]oxy]indolyl]ethylamines and Their Use as Synthetic Intermediates. *J. Med. Chem.* **1996**, *39*, 4717−4726.

(23) There is one example in the literature of the preparation of a 4-aminoethyl-1-arylsulfonylindole. See Cannon, J. G.; Lee, T.; Ilhan, M.; Koons, J.; Long J. P. 6-Hydroxy-4-[2-(di-*n*-propylamino)ethyl]indole: Synthesis and Dopaminergic Actions. *J. Med. Chem.* **1984**, *27*, 386−389.

(24) Kozikowski, A. P.; Ishida, H.; Chen, Y.-Y. New Synthesis and Some Selected Reactions of the Potential Ergot Alkaloid Precursor Indole-4-carboxaldehyde. *J. Org. Chem.* **1980**, *45*, 3350−3352.

(25) Bowman, R. E.; Evans, D. D.; Guyett, J.; Nagy, H.; Weale, J.; Weyell, D. J. 1,3,4,5-Tetrahydrobenz[*cd*]indoles and Related Compounds. Part III. *J. Chem. Soc., Perkin Trans. 1* **1973**, 438−442.

(26) Glennon, R. A.; Bondarev, M.; Roth, B. 5-HT$_6$ Serotonin Receptor Binding of Indolealkylamines: A Preliminary Structure−Affinity Investigation. *Med. Chem. Res.* **1999**, *9*, 108−117.

(27) Glennon, R. A.; Lee, M.; Rangisetty, J. B.; Dukat, M.; Roth, B. L.; Savage, J. E.; McBride, A.; Rauser, L.; Hufeisen, S.; Lee, D. K. H. 2-Substituted Tryptamines: Agents with Selectivity for 5-HT$_6$ Serotonin Receptors. *J. Med. Chem.* **2000**, *43*, 1011−1018.

(28) King, F. D.; Brown, A. M.; Gaster, L. M.; Kaumann, A. J.; Medhurst, A. D.; Parker, S. G.; Parsons, A. A.; Patch, T. L.; Raval, P. (±)-3-Amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole: A Conformationally Restricted Analogue of 5-Carboxamidotryptamine with Selectivity for the Serotonin 5-HT$_{1D}$ Receptor. *J. Med. Chem.* **1993**, *36*, 1918−1919.

(29) Since cloned human 5-HT$_2$ receptors were unavailable at the time of this work, binding was performed on rat cortical membranes, which are primarily composed of 5-HT$_{2A}$ receptors.

(30) Miller, M. D.; Sheridan, R. P.; Kearsley, S. K. SQ: A Program for Rapidly Producing Pharmacophorically Relevant Molecular Superpositions. *J. Med. Chem.* **1999**, *42*, 1505−1514.

(31) Boess, F. G.; Monsma, F. J., Jr.; Sleight, A. J. Identification of Residues in Transmembrane Regions III and VI that Contribute to the Ligand Binding Site of the Serotonin 5-HT$_6$ Receptor. *J. Neurochem.* **1998**, *71*, 2169−2177.

(32) Appel, J. B.; Callahan, P. M. Involvement of 5-HT Receptor Subtypes in the Discriminative Stimulus Properties of Mescaline. *Eur. J. Pharmacol.* **1989**, *159*, 41−46.

(33) Schreiber, R.; Brocco, M.; Audinot, V.; Gobert, A.; Veiga, S.; Millan, M. J. (1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane)-Induced Head-Twitches in the Rat are Mediated by 5-Hydroxytryptamine (5-HT)$_{2A}$ Receptors: Modulation by Novel 5-HT$_{2A/2C}$ Antagonists, D$_1$ antagonists and 5-HT$_{1A}$ Agonists. *J. Pharmacol. Exp. Ther.* **1995**, *273*, 101−112.

(34) Spadoni, G.; Stankov, B.; Duranti, A.; Biella, G.; Lucini, V.; Salvatori, A.; Fraschini, F. 2-Substituted 5-Methoxy-*N*-acyltryptamines: Synthesis, Binding Affinity for the Melatonin Receptor, and Evaluation of the Biological Activity. *J. Med. Chem.* **1993**, *36*, 4069−4074.

(35) B. P. Feuston, M. D. Miller, J. C. Culbertson, R. B. Nachbar, and S. K. Kearsley, unpublished results.

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