6.93 (m, 2 H), 6.28 (d, 1 H, J = 1 Hz), 6.2 (d, 1 H, J = 1 Hz), 4.3 (br d, 1 H, J = 12 Hz), 3.13 (m, 1 H), 3.0 (d, 1 H, J = 17 Hz), 2.85 (d, 1 H, J = 17 Hz), 2.78 (br d, 1 H, J = 11 Hz), 2.55 (dd, 5 H, J = 5, 9 Hz), 2.48 (m, 1 H), 2.23 (br dd, 1 H, J = 3, 12 Hz), 1.5–1.8 (cm, 9 H), 1.35 (s, 3 H), 1.25 (s, 3 H), 1.18 (dd, 3 H, J = 2, 7 Hz); IR ($CDCl_3$) ν 2800–3300 br, 1660, 1620, 1570, 1510, 1430 cm^{-1}. Anal. ($C_{28}H_{37}FN_2O_3 \cdot 0.5H_2O$) C, H, N.

8-[4-(4-Fluorophenyl)-1-methylbutyl]-1,2,3,4-tetrahydro-10-hydroxy-*N*-methyl-5-oxo-5*H*-[1]benzopyrano[4,3-*c*]-pyridine-2-acetamide (37). A solution of **14** (2.2 g, 4.67 mmol) in acetic acid (100 mL) over $Pd(OH)_2$ catalyst (2.1 g) was hydrogenated at 1 atm of H_2 pressure at ambient temperature for 16 h. The solution was then filtered through a pad of Celite (10 g), washed with glacial acetic acid (150 mL), and concentrated in vacuo. After azeotropic drying with toluene (2 × 25 mL) the residue was partitioned between $CHCl_3$ (250 mL) and saturated aqueous $NaHCO_3$(250 mL). The organic extract was separated, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 2.1 g (98%) of an oil.

The material prepared above (2.1 g, 4.67 mmol) was dissolved in DMF (50 mL) and triethylamine (5 mL, 36 mmol, 7.7 equiv), and 2-chloro-*N*-methylacetamide (1.5 g, 14 mmol, 3 equiv) was added. The reaction mixture was stirred at ambient temperature for 48 h and then concentrated in vacuo. The residue was diluted with H_2O (100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with saturated NaCl (300 mL), dried over $MgSO_4$, and filtered. After solvent removal, purification by silica gel chromatography with ethyl acetate afforded a yellow solid which after recrystallization from ethyl acetate and hexanes afforded 1.1 g (52%) of an off-white solid: mp 165–168 °C; ^1H NMR ($CDCl_3$) δ 7.5 (br d, 1 H, J = 5 Hz), 7.05 (m, 2 H), 6.9 (m, 2 H), 6.63 (d, 2 H, J = 10 Hz), 4.1 (s, 2 H), 3.3 (s, 2 H), 2.8 (m, 3 H), 2.6–2.8 (cm, 5 H), 2.5 (m, 2 H), 1.45–1.6 (cm, 5 H), 1.2 (d, 3 H, J = 7 Hz). Anal. ($C_{26}H_{29}FN_2O_4 \cdot 0.25H_2O$) C, H, N.

2-{5-[4-(4-Fluorophenyl)-1-methylbutyl]-2,6-dihydroxyphenyl}-4-(1-hydroxy-1-methylethyl)-3,6-dihydro-2*H*-pyridin-1-yl}-*N*-methylacetamide (7). To a solution of MeMgBr (3.0 M, 1.37 mL, 4.1 mmol, 10 equiv) in ether cooled to 0 °C was added a solution of **34** (179 mg, 0.4 mmol) in toluene (20 mL). The reaction mixture was stirred at ambient temperature under nitrogen for 16 h. The reaction was quenched with saturated aqueous ammonium chloride (25 mL), and the layers were separated. The organic extract was washed with saturated NaCl (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford after silica gel chromatography with 5% MeOH/$CHCl_3$ 190 mg (98%) of a white solid: mp 203–204 °C; ^1H NMR ($CDCl_3$–CD_3OD) δ 7.07 (m, 2 H), 6.9 (m, 2 H), 6.2 (s, 2 H), 3.08 (s, 2 H), 3.0 (br s, 2 H), 2.8 (s, 3 H), 2.75 (t, 2 H, J = 6 Hz), 2.43–2.55 (cm, 6 H), 1.3 (m, 4 H), 1.2 (s, 6 H), 1.18 (d, 3 H, J = 6 Hz); IR (KBr) ν 3000–3600 br, 2900, 1650, 1620, 1510, 1430 cm^{-1}. Anal. ($C_{28}H_{37}FN_2O_4$) C, H, N.

Acknowledgment. We thank Dr. Cheuk-Man Lee and William B. Arnold for providing us with a supply of intermediate **3**.

Benzofuran Bioisosteres of Hallucinogenic Tryptamines

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The benzofuran analogues of the hallucinogens 5-methoxy-*N*,*N*-dimethyltryptamine and 5-methoxy-α-methyltryptamine were synthesized and evaluated for affinity at the serotonin 5-HT_2 and 5-HT_{1A} receptors in rat brain homogenate, labeled with [^{125}I]-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane ([^{125}I]DOI) and [^{3}H]-8-hydroxy-2-(*N*,*N*-di-*n*-propylamino)tetralin ([^{3}H]-8-OH-DPAT), respectively. At the 5-HT_2 receptor, the benzofurans had slightly decreased affinities, approximately one-third and one-sixth those of the indoles, for the primary amines and the tertiary amines, respectively. The benzofurans also had lower affinity at the 5-HT_{1A} receptor, but decreased only about 20–30% from that of the indole isosteres. Thus, the 5-HT_{1A} receptor is less discriminating with respect to preference for an indole versus a benzofuran, although all of the compounds did have higher affinities for the 5-HT_2 receptor than for the 5-HT_{1A} receptor. It is suggested that benzofurans may be useful in the design of serotonin receptor ligands.

We recently reported on the biological activity of compounds **1a** and **1b**, which proved to possess high LSD-like potency in an animal behavioral model, as well as high affinity for the agonist-labeled state of the serotonin 5-HT_2 receptor.[1] In view of the similar biological activity of the indole **2**,[2] one could speculate that the 2,3-dihydrofuran ring of **1** served as a bioisosteric replacement of the pyrrole ring of the indole.

A logical question which presented itself was whether a fully aromatic benzofuran might itself also be a bioisostere for an indole. Although benzo[*b*]thiophenes have been investigated as analogues of indoles,[3] only a few early reports seem to exist relevant to the use of benzofurans to replace indoles.[4–7] Furthermore, the chemical properties

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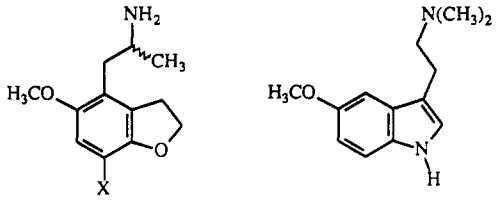
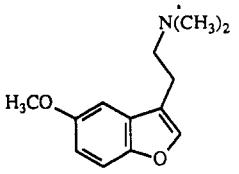


1a X = H
1b X = Br

2



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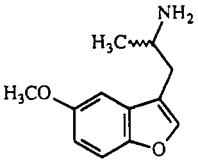


4

and reactivities of indole and benzo[*b*]thiophene are more similar to each other than to benzofuran, suggesting that the latter system might resemble an indole to a lesser degree than benzo[*b*]thiophene.

This report describes the synthesis of compounds **3** and **4** and their affinities for the serotonin 5-HT_2 and 5-HT_{1A} receptors, binding sites where compounds **1a**, **1b**, and **2** are known to have high affinity.[1,2]

Chemistry

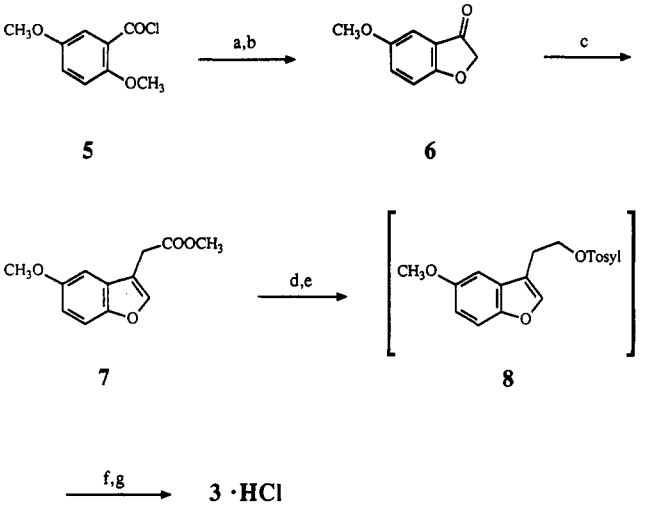
The syntheses were initiated with the facile preparation of benzofuran-3-ones described by Jung and Abrecht.[8] Thus, treatment of acid chloride **5** with diazomethane (Scheme I), followed by reaction of the resulting diazo ketone with acetic acid led to the desired 5-methoxybenzofuran-3-one (**6**) in modest yield. Reaction of this ketone with appropriate Wittig reagents readily affords 3-substituted benzofurans. Thus, **7** was prepared from **6**, the ester was reduced to the primary alcohol, this was O-tosylated, and tosylate **8** was then treated with dimethylamine to afford **3**, which was isolated as its hydrochloride salt. Although Jung and Abrecht[8] accomplished a similar transformation with 7-methoxy-3-benzofuranone in two steps using the Wittig reagent from the analogous *N*,*N*-dimethylamide, the preparation and use of that reagent proved more troublesome than the ester.

Extensive attempts were then made to prepare the enantiomers of **4**. Initial efforts were directed toward an asymmetric synthesis involving the use of commercially-available N-protected (*R*)- or (*S*)-2-aminopropanol or 3-bromo-2-methylpropanol. However, efforts to prepare appropriate Wittig reagents were unsuccessful. The racemic material was finally prepared as shown in Scheme II. The key step involved displacement of the hydroxy groups of **10** by phthalimide under Mitsunobu conditions.[9]

Pharmacology

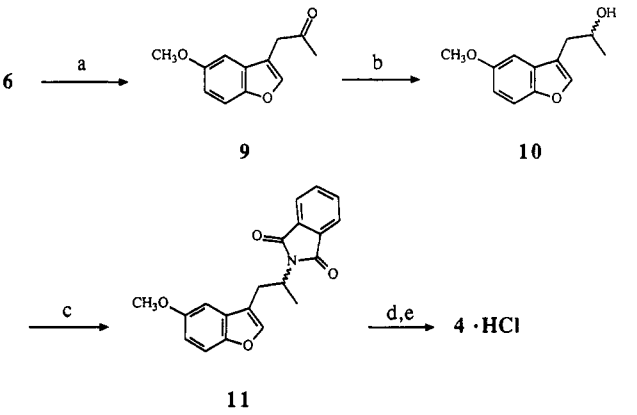
The affinities of compounds **3** and **4** were measured for

Scheme I[a]



[a] Reagents: (a) CH_2N_2; (b) AcOH; (c) $(Ph)_3P{=}CHCOOCH_3$, xylene, reflux; (d) $LiAlH_4$, THF; (e) tosyl chloride, pyridine; (f) $(CH_3)_2NH$; (g) HCl.

Scheme II[a]



[a] Reagents: (a) $(Ph)_3P{=}CHCOCH_3$, xylene, reflux; (b) $LiAlH_4$, THF; (c) phthalimide, $(Ph)_3P$, DEAD; (d) H_2NNH_2, EtOH, reflux; (e) HCl.

the [^{125}I]-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane ([^{125}I]DOI)-labeled 5-HT_2 receptor in rat frontal cortex homogenate. Affinity for this receptor shows a high correlation with hallucinogenic potency in humans[10] and with animal models of hallucinogenic activity.[11] Affinities were also measured of **2**–**4** and (±)-α-methyl-5-methoxytryptamine for the [^{3}H]-8-hydroxy-2-(*N*,*N*-di-*n*-propylamino)-tetralin ([^{3}H]-8-OH-DPAT)-labeled serotonin 5-HT_{1A} receptor in rat hippocampal homogenate.

Results and Discussion

The measured affinities of **3** and **4** for the 5-HT_2 receptor labeled by [^{125}I]DOI were 95.0 ± 8.1 and 27.1 ± 3.5 nM, respectively. Hill coefficients were not significantly different from unity. In our earlier work,[1] using a different agonist label for this 5-HT_2 receptor, compound **2** had a K_I = 15 nM, and the more potent *S*-(+) isomer of 5-methoxy-α-methyltryptamine, the indole biostere of **4**, had

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a K_I = 4.2 nM. If one anticipates an approximate doubling of affinity for the more active enantiomer of **4**, this suggests that it has about one-third the affinity of its indole bioisostere. Compound **3** has about one-sixth the affinity of the indole bioisostere **2**.

The measured affinities of **2**–**4** and (±)-α-methyl-5-methoxytryptamine for the 5-HT_{1A} receptor labeled by [^{3}H]-8-OH-DPAT were 69 ± 8.1, 101 ± 9.5, 779 ± 63, and 445 ± 68 nM, respectively. Again, Hill coefficients were not significantly different from unity. Thus, **3** has nearly equal affinity for both the 5-HT receptors labeled in this study, while **4** has a nearly 30-fold greater affinity for the 5-HT_2 receptor than for the 5-HT_{1A} receptor. Comparison of the affinities of **2** versus **3** and **4** versus α-methyl-5-methoxytryptamine shows that the replacement of the indole nitrogen with the benzofuran oxygen leads to a nearly 2-fold loss of affinity at the 5-HT_{1A} receptor. Thus, while all these compounds generally have higher affinity for the 5-HT_2 receptor, changing the indole to a benzofuran has a larger detrimental effect on binding at that site, relatively speaking, than it does at the 5-HT_{1A} receptor.

A related example has been examined by McKenna et al.[12] *N*-methyl-*N*-isopropyltryptamine was compared with its benzofuran bioisostere. In that report, both the indole and the benzofuran had low affinity (760 and 5000 nM, respectively) for the 5-HT_{1A} site. Affinity of *N*-methyl-*N*-isopropyltryptamine for the 5-HT_2 receptor was 20-fold better (38 nM), but that of the benzofuran isostere was still more than 1 order of magnitude lower than this.

Although the benzofuran examined by McKenna et al.[12] lacked the 5-methoxy group, a function which increases affinity for both the 5-HT_{1A} and 5-HT_2 receptors, their results are consistent with the present ones in that in all cases the benzofurans had lower affinity than did the corresponding indoles. In addition, both in the work of McKenna et al.[12] and in the present study, *N*,*N*-dimethylation had a rather modest effect both on 5-HT_{1A} and on 5-HT_2 affinity. However, the addition of an α-methyl to the side chain either in the tryptamines or in the benzofuran analogues dramatically attenuates affinity for the 5-HT_{1A} receptor, but not for the 5-HT_2 receptor. Thus, one may conclude that the 5-HT_{1A} receptor is less tolerant of side-chain modification.

In an early study, the benzofuran isostere of serotonin was examined by Pinder et al.[7] for a contractile effect in the rate stomach fundus. In that work, the benzofuran was less potent than the corresponding benzo[*b*]thiophene, and both were considerably less potent than serotonin itself.

From these results, it appears that the benzofuran nucleus can serve as a bioisostere for an indole. However, based on our previous study,[1] 2,3-dihydrobenzofuran may be a better bioisostere, although the side chain of **1** originates from the phenyl ring and not from the 5-membered heterocyclic ring as in **3** and **4**. Reduction of the 2,3-bond of **3** or **4** would introduce a new stereocenter (at C3) into the molecule; the effect of this is unknown at present. In view of the present interest in the pharmacology of serotonin, benzofuran and 2,3-dihydrobenzofuran bioisosteres are clearly worthy of further study as serotonin agonists and antagonists.

Experimental Section

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. ^{1}H NMR spectra (500 MHz) were obtained with a Varian VXR-500S NMR instrument in $CDCl_3$ unless otherwise noted. Chemical shifts are reported in δ values (parts per million) relative to an internal reference of $CHCl_3$ (δ 7.24). Abbreviations used in the NMR analysis are as follows: br s = broad singlet, d = doublet, dd = doublet of doublets, dq = doublet of quartets, m = multiplet, q = quartet, s = singlet, t = triplet. Chemical ionization mass spectra were obtained with a Finnegan 4000 spectrometer. Elemental analyses were performed by Galbraith Laboratories (Knoxville, TN) and were within ±0.4% of the calculated values unless otherwise noted.

5-Methoxybenzofuran-3-one (6). An etheral solution of diazomethane was prepared via standard procedures from Diazald (11.8 g, 55.2 mmol) in 100 mL of ether and KOH (6.0 g, 107.2 mmol) in a mixture of 10 mL of water, 20 mL of ether, and 35 mL of 2-(2-ethoxyethoxy)ethanol. To the diazomethane solution was added 2,5-dimethoxybenzoyl chloride (3.0 g, 15.0 mmol), and the resulting mixture was stirred at room temperature for 45 min (no more gas evolution was observed). After evaporation of the solvent under reduced pressure, the yellow oil was dissolved in 30 mL of glacial acetic acid and stirred for 30 min at room temperature. The solvent was removed under reduced pressure, and the residue was dried under high vacuum overnight. The residue was crystallized from ether to give 1.58 g (64%) of product as slightly yellow crystals: mp 85–87 °C (lit.[13] mp 88 °C); IR ($CHCl_3$) 3000, 1715, 1495, 1280, 1000 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25 (1 H, d, *J* = 7.9 Hz), 7.15 (1 H, d, *J* = 7.9 Hz), 7.02 (1 H, t, *J* = 7.9 Hz), 4.68 (2 H, s), 3.75 (3 H, s).

Methyl 2-(5-Methoxybenzofuran-3-yl)acetate (7). A solution of **6** (3.28 g, 20 mmol) and methyl (triphenylphosphoranylidene)acetate (Aldrich; 7.30 g, 22 mmol) in xylene (250 mL) was heated at reflux for 48 h under nitrogen. The solvent was removed, and the residue was applied to a silica gel column and eluted with 10% ethyl acetate–benzene. The initial band contained methyl (5-methoxy-3-benzofuranyl)acetate (**7**) (2.52 g, 57%) as an oil: IR (film) 2952, 1739, 1479, 1264 cm^{-1}; MS *m*/*e* 220 (M^+, 100); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (1 H, s), 7.37 (1 H, d, *J* = 9 Hz), 7.00 (1 H, d, *J* = 2 Hz), 6.91 (1 H, dd, *J* = 2 Hz, 9 Hz), 3.84 (3 H, s), 3.73 (3 H, s), 3.68 (3 H, s). The second band eluted from the column contained unreacted **6** (1.2 g).

***N*,*N*-Dimethyl-2-(5-methoxybenzofuran-3-yl)ethanamine Hydrochloride (3).** A solution of **7** (2.20 g, 10 mmol) in 50 mL of dry tetrahydrofuran was added dropwise to a suspension of lithium aluminum hydride (1 g, 26 mmol) in 100 mL of tetrahydrofuran at room temperature. The reaction mixture was heated at reflux for 1 h. After the mixture was cooled to 0 °C, 15 mL of tetrahydrofuran containing 1 mL of water was added dropwise. Then, 15 g of anhydrous sodium sulfate was added, and the mixture was stirred for 1 h. The precipitate was removed by filtration and washed several times with tetrahydrofuran. Evaporation of the solvent under reduced pressure gave 2-(5-methoxybenzofuran-3-yl)ethanol as a colorless oil (1.89 g, 98%) homogeneous on TLC: IR (film) 3383, 2940, 1601, 1476, 1450, 1263, 1220, 1182, 1097, 796 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (1 H, s), 7.37 (1 H, d, *J* = 9 Hz), 7.00 (1 H, d, *J* = 2 Hz), 6.91 (1 H, dd, *J* = 2, 9 Hz), 3.92 (2 H, q, *J* = 6 Hz, 12 Hz), 3.85 (3 H, s), 2.93 (2 H, t, *J* = 6 Hz).

The product was not purified but was dissolved in 50 mL of dry pyridine and treated with *p*-toluenesulfonyl chloride (3.8 g, 20 mmol). The mixture was left overnight at room temperature and then was poured on ice, extracted with dichloromethane (3 × 50 mL), washed with water (2 × 50 mL) and brine, and dried (Na_2SO_4). Evaporation of the solvent gave a yellow crystalline product which was dried under high vacuum for 2 h. The residue, which was homogeneous on TLC, was then dissolved in acetonitrile (100 mL), and 10 g of dimethylamine was added at 0 °C. The mixture was stirred overnight at room temperature, and then the solvent was removed under reduced pressure. The mixture was treated with 20 mL of concentrated HCl and extracted with ether (2 × 50 mL). The acidic aqueous phase was made strongly alkaline with sodium hydroxide, and the amine was extracted into methylene chloride (3 × 75 mL). The extract was washed with

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water and dried (Na_2SO_4). Evaporation of the solvent gave 1.68 g (76%) of **3**. The amine was distilled three times in a Kugelrohr apparatus at 100 °C (0.09 mmHg) to give 1.2 g (54%) of the free base as a colorless liquid: IR 2940, 2856, 2816, 2766, 1600, 1476, 1177, 1070, 1028, 919 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (1 H, s), 7.35 (1 H, d, J = 9 Hz), 7.00 (1 H, d, J = 2 Hz), 6.89 (1 H, dd, J = 2, 9 Hz), 3.86 (s, 3 H), 2.82 (2 H, t, J = 7 Hz), 2.62 (2 H, t, J = 7 Hz), 2.34 (6 H, s); MS m/e 219 (M^+, 0.5). The HCl salt was prepared by bubbling HCl gas into a solution of the amine in methylene chloride. The solid was collected by filtration and recrystallized from MeOH–ether, mp 166–167 °C. Anal. ($C_{13}H_{18}ClNO_2$) C, H, N.

1-(5-Methoxybenzofuran-3-yl)-2-propanone (9). A solution of **6** (2.0 g, 12.2 mmol) and 1-(triphenylphosphoranylidene)-2-propanone (Aldrich; 7.0 g, 21.2 mmol) was heated at reflux in xylene (100 mL) for 72 h. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography over silica gel using hexane–10% ethyl acetate. The major band contained the desired ketone **9** (1.73 g, 71%) as an oil, which was sublimed at 40 °C (0.2 mm) to form slightly yellow crystals: mp 45–46 °C (lit.[13] mp 46–47 °C); IR ($CDCl_3$) 1720 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.60 (1 H, s), 7.39 (1 H, d, J = 9.7 Hz), 6.95 (1 H, d, J = 2.5 Hz), 6.92 (1 H, dd, J = 9.7, 2.5 Hz), 3.82 (3 H, s), 3.70 (2 H, s), 2.18 (3 H, s).

1-(5-Methoxybenzofuran-3-yl)-2-propanol (10). To a suspension of 0.38 g (10 mmol) of lithium aluminum hydride in anhydrous THF was added, dropwise, a solution of **9** (2.04 g, 10 mmol) in 50 mL of THF. The mixture was stirred at reflux under nitrogen for 30 min. The reaction was cooled to 0 °C (ice bath), and 2 mL of water was added dropwise. The mixture was diluted with 200 mL of THF and dried ($MgSO_4$). Filtration through Celite and evaporation of the solvent gave 2.02 g (98%) of slightly yellow oil: IR (neat) 3620 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.4 (1 H, s), 7.39 (1 H, d, J = 9.7 Hz), 6.93 (1 H, d, J = 2.5 Hz), 6.89 (1 H, dd, J = 9.7, 2.5 Hz), 4.13 (1 H, m), 3.86 (3 H, s), 2.80 (2 H, t, J = 7.3 Hz), 1.13 (3 H, d, J = 7.3 Hz). Anal. ($C_{12}H_{14}O_3$) C, H.

***N*-[1-(5-Methoxybenzofuran-3-yl)-2-propyl]phthalimide (11).** To a mixture of alcohol **10** (1.21 g, 5.9 mmol), phthalimide (0.84 g, 5.9 mmol), and triphenylphosphine (1.52 g, 5.9 mmol) in 200 mL of anhydrous THF was added dropwise diethyl azodicarboxylate (1.03 g, 5.9 mmol). The orange solution was stirred under nitrogen at room temperature for 1 h. The solvent was removed under reduced pressure at 40 °C. The yellow crystalline residue was subjected to flash chromatography over silica gel and elution with dichloromethane followed by solvent removal to give 1.6 g (82.5%) of crystalline product. Recrystallization from ether afforded a white fine crystalline product: mp 112–113 °C; IR ($CDCl_3$) 1750 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.15 (4 H, m), 7.49 (1 H, s), 7.39 (1 H, d, J = 9.7 Hz), 6.95 (1 H, d, J = 2.5 Hz), 6.92 (1 H, dd, J = 9.7, 2.5 Hz), 4.75 (1 H, m), 3.85 (1 H, s), 3.48 (1 H, dd, J = 17.5, 7.5 Hz), 3.25 (1 H, dd, J = 17.5, 7.5 Hz), 1.52 (3 H, d, J = 7.5 Hz); MS m/e 331 (M^+, 100). Anal. ($C_{20}H_{17}NO_4$) C, H, N.

(*R*,*S*)-1-(5-Methoxybenzofuran-3-yl)-2-aminopropane Hydrochloride (4). A solution of **11** (1 g, 3.02 mmol) in 50 mL of absolute ethanol was heated at reflux with hydrazine hydrate (0.151 g, 3.02 mmol) for 3 h. The white solid was filtered out and washed on the filter with methylene chloride. Evaporation of the filtrate gave a solid, which was partitioned between dilute HCl and ether. The water phase was separated, basified with NaOH, and then extracted with methylene chloride. Evaporation of the organic extract gave 0.30 g of an oil which was purified with a chromatotron (silica, 1:3 hexane–ethyl acetate) under an ammonia atmosphere to obtain 201 mg (51%) of free base. The HCl salt, prepared by bubbling HCl gas into a solution of free base in ether, was recrystallized from MeOH–ether: mp 151–152 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.42 (1 H, s, broad), 7.56 (1 H, s), 7.33 (1 H, d, J = 8.8 Hz), 7.08 (1 H, s), 6.86 (1 H, dd, J = 2.0, 7.9 Hz), 3.7 (1 H, m), 3.80 (1 H, m), 3.21 (1 H, m), 1.43 (3 H, s, J = 3.9 Hz). Anal. ($C_{12}H_{16}ClNO_2$) C, H, N.

Pharmacology Methods. Radioligand Binding Studies. The ability of the test drugs to displace either 0.1 nM [^{125}I]DOI or 1.0 nM [^{3}H]-8-OH-DPAT was examined. The procedure of Johnson et al.[2] was followed with minor modifications. Briefly, [^{125}I]DOI and [^{3}H]-8-OH-DPAT were purchased fron New England Nuclear (Boston, MA) at specific activities of 2000 and 169.9 Ci/mmol, respectively. The frontal cortex and hippocampal regions from 10–20 male Sprague–Dawley rats (175–199 g, Harlan Laboratories, Indianapolis, IN) were removed, separated, pooled, and homogenized using a Brinkman Polytron (setting 6 for 2 × 20 s) in either 4 or 8 volumes, respectively, of 0.32 M sucrose. The homogenates were centrifuged for 10 min at 36500g, and the resulting pellets were resuspended in the same volumes of sucrose. Aliquots of tissue were frozen separately and stored at −70 °C for up to 1 month.

For each experiment, a tissue aliquot was thawed and diluted 1:25 with 50 mM Tris-HCl (pH = 7.4). An incubation at 37 °C for 10 min preceded two centrifugations at 36500g for 10 min, with an intermittent wash with Tris. The final pellet was resuspended in 50 mM Tris-HCl containing 10 mM $MgCl_2$, 0.5 mM Na_2EDTA, 0.1% Na ascorbate, and 10 μM pargyline HCl (pH = 7.4). In experiments with [^{3}H]-8-OH-DPAT, the same buffer without $MgCl_2$ was used. The tissue was preincubated for 10 min at 37 °C and then cooled in an ice bath until assay.

Incubations were commenced by the addition of 200–400 μg of protein to test tubes, giving a final volume of 1 mL. Tubes were allowed to equilibrate for either 10 or 15 min at 37 °C for [^{3}H]-8-OH-DPAT and [^{125}I]DOI, respectively, before filtering through Whatman GF/C filters using a cell harvester (Brandel, Gaithersburg, MD) followed by two 5-mL washes using ice-cold Tris buffer. Specific binding was defined as that displaceable with 1 μM cinanserin in [^{125}I]DOI experiments and with 10 μM 5-HT in [^{3}H]-8-OH-DPAT experiments. Filters were air-dried before counting at an efficiency of 34 or 79% for [^{3}H] and [^{125}I], respectively.

Data were analyzed using the computer programs EBDA and Ligand as described by McPherson.[14] Under these conditions, saturation experiments indicated [^{125}I]DOI bound to a single site (Hill coefficient = 0.94 ± 0.03) in rat frontal cortex with a K_D of 1.03 ± 0.12 nM and a B_{max} of 11.0 ± 0.9 fmol/mg of protein, from three separate experiments. Similarly, saturation experiments indicated that [^{3}H]-8-OH-DPAT bound to a single site (Hill coefficient = 1.00 ± 0.01) in rat hippocampus with a K_D of 2.50 ± 0.23 nM and a B_{max} of 119 ± 8 fmol/mg of protein, from three separate experiments. Displacement results are reported as the mean ± SEM from three separate experiments, each run in triplicate with 8–10 different concentrations of the displacing ligand.

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Registry No. **3**, 140853-58-3; **3**·HCl, 140853-53-8; (±)-**4**, 140853-59-4; (±)-**4**·HCl, 140853-54-9; **5**, 17918-14-8; **6**, 39581-55-0; **7**, 118610-60-9; **9**, 56798-52-8; (±)-**10**, 140853-56-1; (±)-**11**, 140853-57-2; $Ph_3P{=}CHCOOCH_3$, 2605-67-6; $Ph_3P{=}CHCOCH_3$, 1439-36-7; 2-(5-methoxybenzoylfuran-3-yl)ethanol, 140853-55-0.

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