Bioactive Conformation of 1-Arylpiperazines at Central Serotonin Receptors

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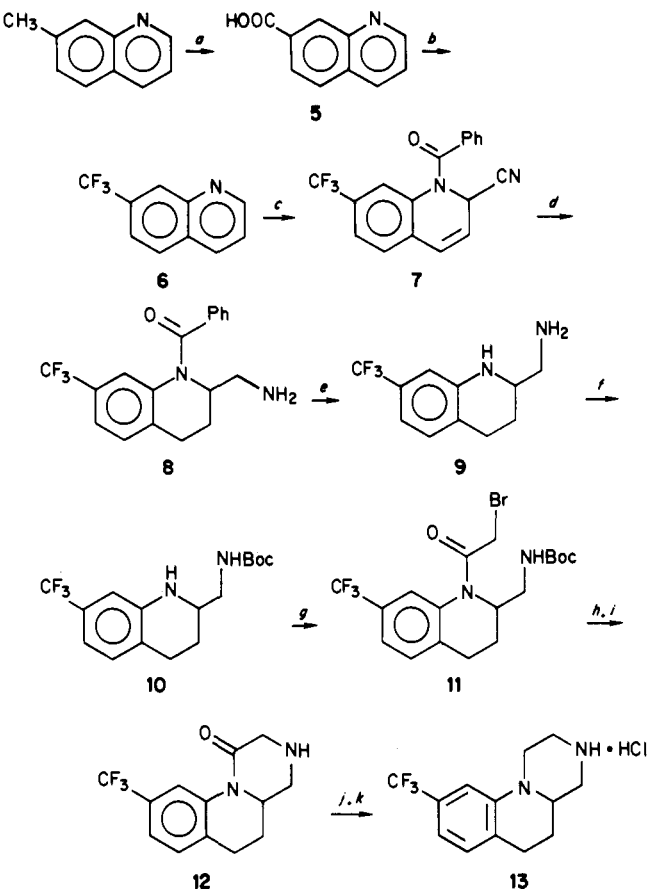
A number of 1-arylpiperazines have been characterized as direct-acting serotonin agonists. Conformational parameters of this class that may affect receptor recognition and binding have been examined through the analysis of X-ray data and synthesis of rigid analogues. Radioligand binding studies indicate that 2,3,4,4a,5,6-hexahydro-9-(trifluoromethyl)-1*H*-pyrazino[1,2-*a*]quinoline (**13**), an arylpiperazine that mimics the X-ray conformation of the serotonin agonist 1-(6-chloropyrazin-2-yl)piperazine (**4**), exhibits high affinity for serotonin receptors, suggesting that the two rings of 1-arylpiperazines are relatively coplanar in the bioactive conformation.

In contrast to the extensive body of information that has been collected with respect to the organization and function of adrenergic neurons, our knowledge of serotoninergic pathways remains, for the most part, rudimentary. This disparity results to a large extent from the paucity of either agonists or antagonists that are potent and selective for serotonin receptors. Historically, such selective compounds have played an essential role in unraveling the complex functions and interactions of neuronal systems. In this regard, 1-arylpiperazines represent a structural class that may provide valuable information for elucidating serotonergic transmission and pharmacology. On the basis of behavioral and pharmacological responses, several of these compounds have been characterized as direct-acting serotonin agonists.[1-3] Biochemical studies provide additional support for this conclusion as these agents reduce serotonin turnover in the central nervous system, an observation that is consistent with direct activation of central serotonin receptors.[4-6] Finally, these molecules specifically and competitively displace [^{3}H]serotonin from synaptic membrane binding sites,[7-9] suggesting that their serotoninmimetic actions result from directly activating serotonin receptors. Some of the more widely studied members of this family are shown in Figure 1 and include 1-(2-quinolinyl)piperazine (**1**),[10,11] 1-(3-chlorophenyl)piperazine (**2**),[12] 1-[3-(trifluoromethyl)phenyl]piperazine (**3**),[8,9] and 1-(6-chloropyrazin-2-yl)piperazine (MK-212) (**4**).[13-15]

As part of our continuing interest in agents that enhance central serotoninergic function, we have investigated certain molecular parameters that affect recognition and binding of arylpiperazines to central serotonin receptors. This report will discuss our efforts to determine the bioactive conformation of 1-arylpiperazines using X-ray analysis of the potent serotoninmimetic **4** and receptor binding data for a structurally rigid analogue 2,3,4,4a,5,6-hexahydro-9-(trifluoromethyl)-1*H*-pyrazino-[1,2-*a*]quinoline (**13**).

Synthesis. The synthesis of **13** is outlined in Scheme I. Quinoline-7-carboxylic acid (**5**), prepared by the procedure of Seibert,[16] was converted in 70% yield to the corresponding (trifluoromethyl)quinoline **6** by heating at 150 °C with SF_4 and HF in a sealed reaction vessel. Addition of cyanide under two-phase Reissert conditions afforded the expected nitrile amide **7**. Simultaneous reduction of the olefin and nitrile was accomplished with Raney Ni catalyst in ethanol saturated with NH_3. Acidic hydrolysis of the benzamide furnished the expected diamine **9**.

Scheme I



[a] CrO_3, H_2SO_4. [b] SF_4, HF, 150 °C. [c] PhCOCl, KCN. [d] H_2, Ra Ni, EtOH/NH_3. [e] H_3O^+. [f] $(t\text{-BuOCO})_2O$, DMF. [g] $BrCH_2COBr$. [h] CF_3COOH, 0 °C. [i] K_2CO_3, DMF. [j] $BH_3 \cdot Me_2S$, THF. [k] HCl.

Acylation of the secondary amine nitrogen in **9** was readily effected with bromoacetyl bromide subsequent to

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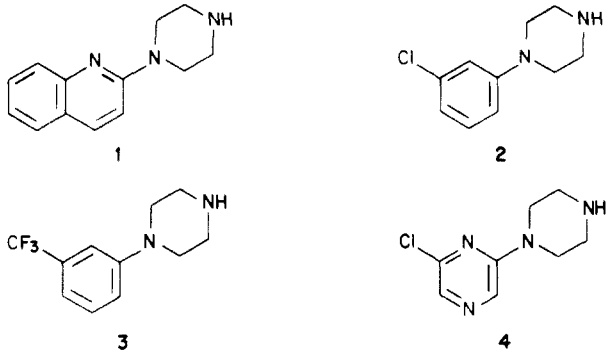
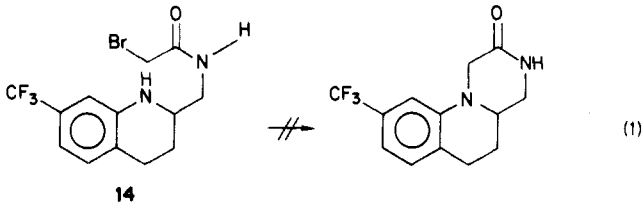


Figure 1. 1-Arylpiperazines that are direct-acting serotonin agonists.

protecting the primary amine as its Boc derivative. Although some cyclization to the corresponding lactam **12** occurred during removal of the protecting group by CF_3-COOH at 0 °C, ring formation was completed by warming the mixture in DMF with K_2CO_3. Reduction of the lactam carbonyl with borane–dimethyl sulfide gave the conformationally rigid arylpiperazine **13**.

More direct routes for generating the tricyclic skeleton were unsuccessful. Treatment of **9** with oxalyl chloride, in an attempt to introduce the requisite carbon atoms and simultaneously form the piperazine ring, produced only intractable polymers. In an alternate approach, bromoacetamide **14** was prepared by acylating **9** with bromoacetyl bromide. This compound failed to cyclize upon heating with *N,N*-diisopropylethylamine for 2 h at 100 °C in DMF (eq 1). Only starting bromoacetamide was recovered. Longer periods of heating or higher temperatures resulted in significant decomposition to unidentified materials. The surprisingly poor nucleophilicity of the aniline nitrogen in **14** was perhaps foreshadowed by the fact that **9** forms only a monohydrochloride salt.

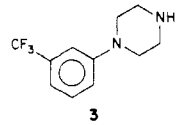
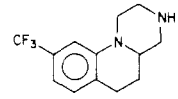
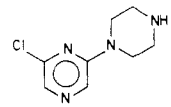


(1)

Biological Results

The intrinsic affinities of **3**, **4**, and **13** for serotonin receptors were determined by displacement of radioligands from membrane binding sites in rat frontal cortex. Two distinct serotonin binding sites have been characterized in this tissue. Those labeled selectively by [^{3}H]serotonin have been designated S1, while the other sites, S2, show higher affinity for [^{3}H]spiperone.[17-21] The physiological role of the S2 receptor has been associated with a variety of serotoninergic effects. They appear to mediate tryptamine-induced clonic seizures[21] and serotonin-induced head twitches[22] in vivo and serotonin-induced contractions in isolated rat caudal arteries in vitro.[23] The physiological function of S1 binding sites appears to be related to serotonin stimulated adenylate cyclase.[22,24] Specific displacement of either [^{3}H]serotonin or [^{3}H]spiperone from rat cortical membranes, therefore, provides an in vitro estimate of the relative affinity for the S1 or S2 receptor, respectively. Data in Table I show that both **3** and **13** block binding of radioligands to the S1 and S2 receptors at nanomolar concentrations. However, **13** shows a higher affinity than its conformationally flexible counterpart in both assays.

Table I. Apparent Affinity Constants for Serotonin Binding Sites[a]

	K_i, nM	
	[^{3}H]serotonin	[^{3}H]spiperone
 **3**	116 ± 40	298 ± 71
 **13**	67 ± 13	136 ± 14
 **4**	3630 ± 588	6000 ± 1580

[a] Values given are the means ± SD of three to nine experiments, each performed in triplicate.

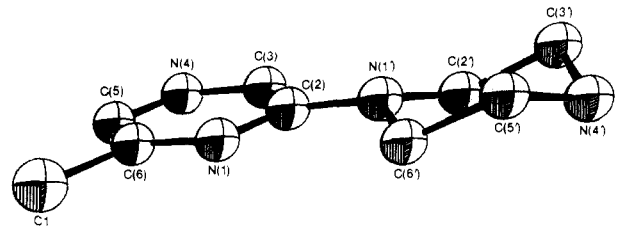


Figure 2. A computer-generated perspective drawing of **4** without hydrogens and without the Cl^- counterion.

Compound **3** has been previously characterized as a serotonin agonist.[8,9,25] In order to validate the comparison of binding data for **3** and **13**, two procedures indicative of central serotoninmimetic action were employed to confirm the agonist properties of **13** in vivo. In the rat, **13** caused arching of the back, spread digits, hindlimb abduction, and straub tail in a dose-dependent manner when administered

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Table II. NMR Parameters for 13·HCl[a]

H	ppm	J^b Hz
H_{1eq}	4.33 dt	13.2, 2.5, 3.0
H_{1ax}	3.25 td	13.2, 2.5, 12.9
H_{2eq}	3.72 dq	2.5, 2.5, 12.8, 2.0
H_{2ax}	3.39 td	3.0, 12.9, 12.8
H_{4eq}	3.62 dt	2.0, 12.2, 2.8
H_{4ax}	3.14 t	12.2, 12.0
H_{4a}	3.54 ddt	2.8, 12.0, 3.0, 9.0
H_{5eq}	2.20 m	3.0, 14.0, 5.0, 5.5
H_{5ax}	1.90 m	9.0, 14.0, 5.0, 11.0
H_{6eq}	2.96 dt	5.0, 5.0, 16.5
H_{6ax}	3.05 ddd	5.5, 11.0, 16.5

[a] Spectrum obtained in D_2O. [b] Estimated error: ±0.4 Hz.

intraperitoneally (ip). All of these postural changes are distinctive features of the serotonergic motor syndrome.[2,3] The tricyclic derivative **13** also elicited head twitches in mice, a standard paradigm for serotoninmimetic action in the central nervous system.[26] At 10 mg/kg ip, **13** produced head twitches in 7 of 10 animals.

Discussion

Previous investigations have shown that **4** is a potent serotonin agonist in vitro and in vivo.[13-15] X-ray crystallographic analysis of this compound was therefore undertaken in an effort to gain insight into the topological features of serotonin receptor binding sites. The resulting structure is shown in Figure 2. The piperazine ring is in a chair conformation with the pyrazine ring occupying an equatorial position. Furthermore, the piperazine and pyrazine rings are coplanar, with a torsion angle between the two rings of 6° (the plane of the piperazine ring was calculated as a least-squares plane through atoms N(1′), C(2′), C(3′), N(4′), C(5′), and C(6′) of **4**). The bond angles around N(1′) are 114.5°, 118.3°, and 119.9°. The bond distance between C(2)–N(1′) is 1.358 Å. The marked flattening of N(1′) and the short C(2)–N(1′) bond distance indicate significant conjugation between the piperazine nitrogen lone pair and the aromatic π orbitals. The shorter C(2)–N(1′) bond distance relative to other *N*-aryl cyclic amines reflects the greater π-acceptor character of pyrazine.

The structure of **4** is in accord with crystal structures of other cyclic N(sp^3)–C(sp^2) compounds.[27] *N*-Arylmorpholines[28] and -piperazines[29] show similar flattening of the pyramidal nitrogen, shortened carbon–nitrogen bond distances, and coplanarity of the rings. All of these features are consistent with significant conjugation. NMR studies provide further evidence that in solution N-substituted piperazines exist in a rapidly interconverting chair conformation with nitrogen substituents occupying an equatorial position.[30]

Although solid-state geometry does not necessarily reflect the most favorable solution conformation, the congruence of the aforementioned crystal structures suggest that resonance energy derived from conjugation may well stabilize a coplanar conformation. It was of interest, then, to construct a rigid, coplanar arylpiperazine in order to test the biological importance of this conformation. Compound **13** was chosen because it was synthetically accessible and because its conformationally flexible counterpart, **3**, exhibits both serotonin agonist properties and high affinity for serotonin receptors.[8,9]

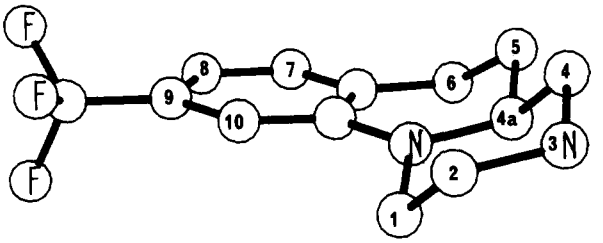

Figure 3. Conformation of **13** with a trans ring junction and chair conformer of the piperazine ring.

Crystals of **13** or its salts which were suitable for X-ray analysis could not be obtained. ^1H NMR studies, however, clearly demonstrated the trans ring junction of **13**. Dispersion at 400 MHz was sufficient to resolve all 11 aliphatic protons of the monohydrochloride of **13**. This resolution combined with decoupling experiments allowed complete assignment of the spectrum. Chemical shifts and coupling constants are listed in Table II. Two stereochemically important features are apparent. Two large spin couplings with the neighboring axial H_4 and H_5 protons establish the axial configuration of H_{4a}. In addition, the distinctive low-field chemical shift of H_{1eq} is consistent with its location near and in the plane of the aromatic ring. This is possible only for the trans-fused piperazine. This analysis, considered in conjunction with previous studies (vida supra), indicates the planar structure of **13** (Figure 3).

Data in Table I demonstrate that **13** exhibits higher affinity for both S1 and S2 serotonin receptors than does **3**. The difference in potency is even more striking when one considers that the K_i values for **13** represent upper limits since **13** is a racemic mixture. The stereoselectivity displayed by both S1 and S2 receptors with respect to ligand binding has been clearly demonstrated.[31-34] On the other hand, because **3** is achiral, the K_i values for this compound indicate true affinities. Thus, taken together, the results of this work provide substantial support for the hypothesis that the coplanar conformation represented by **13** is responsible for the serotoninmimetic effects of 1-arylpiperazines.

Experimental Section

Chemistry. Melting points were determined in open glass capillaries with a Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian EM-390 instrument. Chemical shifts are reported in parts per million with Me_4Si as the internal reference. Elemental analyses indicated were within ±0.4% of the calculated values. TLC analyses were performed on E. Merck 0.25-mm silica gel 60 plates, using the solvent systems indicated.

7-(Trifluoromethyl)quinoline (6). A mixture of quinoline-7-carboxylic acid[16] (67.8 g, 0.39 mol), SF_4 (260.0 g, 2.4 mol), and anhydrous HF (35 mL) was heated in a stainless steel bomb at 150 °C for 15 h. After cooling, the mixture was poured onto ice and neutralized with solid K_2CO_3. The aqueous mixture was extracted with CH_2Cl_2, and the organic extracts were dried ($MgSO_4$). Removal of solvent afforded a solid, which was recrystallized (petroleum ether) to yield 54.5 g (71%) of product: mp 63–64 °C; ^1H NMR ($CDCl_3$) δ 7.52 (1 H, d of d, J = 9, 4 Hz),

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7.70 (1 H, d of d, J = 9, 1.5 Hz), 7.93 (1 H, d, J = 9 Hz), 8.24 (1 H, d, J = 9 Hz), 8.45 (1 H, br s), 9.05 (d of d, J = 4, 1.5 Hz). A sample was converted to the hydrochloride salt, mp 207–209 °C, for analysis. Anal. ($C_{10}H_6F_3N$·HCl) C, H, N.

1-Benzoyl-2-cyano-1,2-dihydro-7-(trifluoromethyl)quinoline (7). To a vigorously stirred mixture of **6** (71.4 g, 0.36 mol), KCN (71.4 g), CH_2Cl_2 (360 mL), and H_2O (180 mL) was slowly added at 0 °C a solution of benzoyl chloride (107.1 g, 0.76 mol) in CH_2Cl_2 (20 mL). After the addition was complete, the reaction was allowed to stir at room temperature for 18 h. The organic layer was then separated, washed with dilute HCl, and then brine, dried ($MgSO_4$), and concentrated. The resulting yellow solid was recrystallized (Et_2O/petroleum ether) to afford 52.6 g (45%) of the desired product: mp 138–139 °C; ^{1}H NMR ($CDCl_3$) δ 6.25 (2 H, m), 6.89 (2 H, m), 7.38 (7 H, m); IR (KBr) 1650 cm^{-1}. Anal. ($C_{18}H_{11}F_3N_2O$) C, H, N.

2-(Aminomethyl)-1-benzoyl-1,2,3,4-tetrahydro-7-(trifluoromethyl)quinoline Hydrochloride (8). A solution of **7** (18 g, 55 mmol) in absolute EtOH (600 mL) was saturated with NH_3 gas at 0 °C. Freshly prepared Raney Ni catalyst (2 g) was added, and the mixture was hydrogenated at 50 psi at room temperature for 18 h. After filtration of the catalyst, the solvent was evaporated. The residue was dissolved in absolute EtOH and acidified with EtOH/HCl. Addition of Et_2O caused the product to crystallize. Filtering and drying yielded 14 g (69%) of the HCl salt: mp 199–202 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.7 (2 H, m), 2.74 (2 H, m), 3.4 (3 H, m), 6.8 (2 H, m), 7.12 (1 H, d, J = 7 Hz), 7.54 (3 H, m), 7.98 (2 H, m), 8.17 (3 H, br s, NH_3^+). Anal. ($C_{18}H_{17}F_3N_2O$·HCl) C, H, N.

2-(Aminomethyl)-1,2,3,4-tetrahydro-7-(trifluoromethyl)quinoline (9). A mixture of **8** (12 g, 32 mmol), 6 N HCl (900 mL), and EtOH (300 mL) was heated at reflux for 18 h. The solvent was removed in vacuo and the residue chromatographed over silica gel, eluting with $CHCl_3$ saturated with NH_3. The product (3.5 g, 47%) was obtained as an oil, which was homogeneous by TLC (5% MeOH/$CHCl_3$ saturated with NH_3); ^{1}H NMR ($CDCl_3$) δ 1.17 (2 H, br s, NH_2), 1.77 (2 H, m), 2.8 (4 H, m), 3.25 (1 H, m), 4.6 (1 H, br s, NH), 6.73 (1 H, s), 6.80 (1 H, d, J = 8 Hz), 7.03 (1 H, d, J = 8 Hz). A sample was converted to the hydrochloride salt, mp 135–138 °C dec for analysis. Anal. ($C_{11}H_{13}F_3N_2$·HCl) C, H, N.

2-[[(*tert*-Butyloxycarbonyl)amino]methyl]-1,2,3,4-tetrahydro-7-(trifluoromethyl)quinoline (10). A solution of **9** (1.93 g, 8.4 mmol) and di-*tert*-butyl dicarbonate (2.01 g, 9.2 mmol) in DMF (5 mL) was stirred at room temperature for 18 h. The reaction mixture was poured into H_2O and extracted with CH_2Cl_2. The organic phase was washed with H_2O and dried (Na_2SO_4). Evaporation of the solvent yielded the product (2.55 g, 92%) as an oil, which was homogeneous by TLC (15% MeOH/$CHCl_3$, silica gel). The crude product was used without further purification.

1-(Bromoacetyl)-2-[[(*tert*-butyloxycarbonyl)amino]methyl]-1,2,3,4-tetrahydro-7-(trifluoromethyl)quinoline (11). Bromoacetyl bromide (1.68 g, 8.3 mmol) was slowly added at 0 °C to a solution of **10** (2.75 g, 8.3 mmol) and *N*,*N*-diisopropylethylamine (1.07 g, 8.3 mmol) in dry THF (30 mL). After 30 min, additional bromoacetyl bromide (1.4 g, 6.9 mmol) and *N*,*N*-diisopropylethylamine (0.84 g, 6.5 mmol) were added, and the reaction mixture was stirred for 1 h. The precipitate was filtered, and the reaction mixture concentrated to dryness. The residue was dissolved in Et_2O and washed with H_2O. The Et_2O solution was dried ($MgSO_4$) and evaporated to dryness. The resulting solid was recrystallized (Et_2O/petroleum ether) to afford 2.0 g (53%) of product: mp 125–127 °C; ^{1}H NMR ($CDCl_3$) δ 1.39 (9 H, s), 2.2–3.4 (6 H, m), 3.96 (2 H, s), 4.78 (1 H, m), 5.07 (1 H, br t), 7.29 (1 H, d, J = 8 Hz), 7.47 (1 H, d, J = 8 Hz), 7.63 (1 H, br s). Anal. ($C_{18}H_{22}BrF_3N_2O_3$) C, H, N.

2,3,4,4a,5,6-Hexahydro-1-oxo-9-(trifluoromethyl)-1*H*-pyrazino[1,2-*a*]quinoline (12). A sample of **11** (2.0 g, 4.4 mmol) was dissolved in CF_3COOH (40 mL) at 0 °C. After 30 min, the CF_3COOH was evaporated, and the residue was dissolved in DMF (20 mL). K_2CO_3 (20 g) was added, and the reaction mixture was stirred at 80 °C for 2 h. The reaction was diluted with EtOAc and washed with H_2O. The organic phase was dried (Na_2SO_4) and concentrated to give the free amine, which was dissolved in 2-PrOH and acidified with EtOH/HCl. Addition of Et_2O caused the salt to crystallize, yielding 520 mg (38%) of the lactam hydrochloride: mp 219–221 °C; ^{1}H NMR (free base, $CDCl_3$) δ 1.79 (1 H, br s, NH), 1.95 (2 H, m), 2.9 (3 H, m), 3.38 (2 H, m), 3.65 (2 H, m), 7.27 (2 H, m), 8.34 (1 H, br s); IR (KBr) 1655 cm^{-1}. Anal. ($C_{13}H_{13}F_3N_2O$·HCl) C, H. N.

2,3,4,4a,5,6-Hexahydro-9-(trifluoromethyl)-1*H*-pyrazino[1,2-*a*]quinoline Hydrochloride (13). A solution of **12** (450 mg, 1.7 mmol) and borane–dimethyl sulfide complex (2.7 mL, 27 mmol) in dry THF (60 mL) was stirred at room temperature under N_2 for 5 h. Methanolic HCl was cautiously added, and the reaction mixture was concentrated. The residue was dissolved in MeOH and reconcentrated. Chromatography over silica gel, eluting with 25% hexane/$CHCl_3$ saturated with NH_3, yielded the free base of the product. This base was dissolved in Et_2O and treated with EtOH/HCl to afford 176 mg (36%) of the HCl salt: mp 201–204 °C; ^{1}H NMR (free base, $CDCl_3$) δ 1.75 (3 H, m), 2.8 (8 H, m), 3.7 (1 H, m), 6.97 (3 H, m). Anal. ($C_{13}H_{15}F_3N_2$·HCl) C, H, N.

X-ray Crystallography. Crystals of the monohydrochloride salt of 4 formed from trifluoroethanol with symmetry *Pbca*. The cell parameters found from preliminary X-ray experiments were a = 13.514 (2) Å, b = 6.870 (1) Å, and c = 22.638 (3) Å for Z = 8. An automatic four-circle diffractometer equipped with Cu radiation (λ = 1.518 Å) was used to measure 1420 unique reflections with $2\theta \leq 114°$. Of these 1074 were observed ($I \geq 3\sigma I$) and corrected for Lorentz and polarization effects. The structure was solved by using a multisolution tangent formula approach and refined by using full-matrix least squares.[35] The function minimized was $\sum\omega(|F_o| - |F_c|)^2$ with $\omega = 1/(\sigma F_o)^2$ to give an unweighted residual value of 0.053. Tables I–III in the supplementary material contain the final fractional coordinates, temperature parameters, bond distances, and bond angles. Figure 2 is a perspective drawing of 4 generated from X-ray coordinates.

Pharmacology. Head Twitch and Serotonin Motor Syndrome. Female Carworth mice weighing 18–22 g were observed under random and blind conditions for twitching of the head at 60 and 180 min after treatment. The mice were observed for 2-min periods. Test compounds were given ip in doses of 40, 10, and 2.5 mg/kg. The compounds were also given to rats, in doses of 20, 10, and 5 mg/kg ip (n = six rats/dose), which were then observed for behavioral characteristics of the serotoninergic motor syndrome for 10 min after dosing. All drugs were dissolved in 0.5–1% methylcellulose. Doses are expressed as the free base.

In Vitro Serotonin Radioligand Binding. S1 receptor binding in rat frontal cortex was measured by the method of Bennett and Snyder[17] using 4 nM [^{3}H]-5HT and 10 μM 5HT to define specific binding. S2 binding was measured as described by Peroutka and Snyder[36] using [^{3}H]spiperone to a final concentration of 0.3 nM and 2 μM LSD to define specific binding.

Three to nine concentrations of each compound were run in triplicate and IC_{50} values determined by linear regression analysis of the log probit data derived from the drug concentration minus percent inhibition of specific radioligand bound relationship. Each drug was examined in at least three separate assays.

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Registry No. 4·HCl, 61655-58-1; **5**, 1078-30-4; **6**, 325-14-4; **6**·HCl, 96430-15-8; **7**, 96430-16-9; **8**·HCl, 96430-17-0; **9**, 96430-18-1; **9**·HCl, 96430-19-2; **10**, 96430-20-5; **11**, 96430-21-6; **12**, 96430-22-7; **12**·HCl, 96430-23-8; **13**, 96430-25-0; **13**·HCl, 96430-24-9.

Supplementary Material Available: Full X-ray data for compound **4** (3 pages). Ordering information is given on any current masthead page.

(35) The following library of crystallographic programs was used: MULTAN 74, University of York, York, England, 1974; XRAY 72, University of Maryland, College Park, MD, 1972; ORTEP-II, Oak Ridge National Laboratory, Oak Ridge, TN, 1970.

(36) Peroutka, S. J.; Snyder, S. H. *J. Pharmacol. Exp. Ther.* **1980**, *215*, 582.