A Structure–Affinity Study of the Binding of 4-Substituted Analogues of 1-(2,5-Dimethoxyphenyl)-2-aminopropane at 5-HT_2 Serotonin Receptors

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With [^{3}H]ketanserin as the radioligand, structure–affinity relationships (SAFIRs) for binding at central 5-HT_2 serotonin receptors (rat frontal cortex) were examined for a series of 27 4-substituted 1-(2,5-dimethoxyphenyl)-2-aminopropane derivatives (2,5-DMAs). The affinity (K_i values) ranged over a span of several orders of magnitude. It appears that the lipophilic character of the 4-position substituent plays a major role in determining the affinity of these agents for 5-HT_2 receptors, 2,5-DMAs with polar 4-substituents (e.g. OH, NH_2, COOH) display a very low affinity (K_i > 25 000 nM) for these receptors, whereas those with lipophilic functions display a significantly higher affinity. The results of these studies prompted us to synthesize and evaluate examples of newer lipophilic derivatives and several of these (e.g. *n*-hexyl, *n*-octyl) bind with very high (K_i values = 2.5 and 3 nM, respectively) affinities at central 5-HT_2 sites. Although, 2,5-DMAs are generally considered to be 5-HT_2 agonists, preliminary studies with isolated rat thoracic aorta suggest that some of the more lipophilic derivatives (e.g. the *n*-hexyl and *n*-octyl derivatives) are 5-HT_2 antagonists.

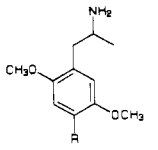
Central serotonin (5-HT) receptors can be categorized as belonging to one of three major classes: 5-HT_1, 5-HT_2, and 5-HT_3.[1,2] Serotonin itself is nonselective and binds at each of these neurotransmitter sites. One of the goals of our work is to develop site-selective 5-HT agonists and antagonists and, to this extent, we have demonstrated that certain 4-substituted 1-(2,5-dimethoxyphenyl)-2-aminopropane (i.e., 2,5-DMA) derivatives bind at 5-HT_2 receptor sites.[3] We have also found that the affinity and selectivity of these agents are significantly influenced by the nature of the 4-substituent. For example, 2,5-DMA (**1a**) binds at 5-HT_2 sites with little selectivity and with rather low affinity (K_i = 5200 nM), whereas its 4-bromo derivative DOB (**1g**) binds selectively and with considerably greater affinity (K_i = 40 nM).[1,4] Indeed, [^{3}H]DOB is now commercially available as a radioligand for use in binding studies. In order to determine the influence of the 4-substituents on binding at 5-HT_2 sites, several years ago we conducted a Hansch analysis on a series of 13 derivatives of 2,5-DMA that varied in structure only at the 4-position.[5] Preliminary results suggested that lipophilic substituents are important for affinity. We have now prepared and examined a total of 27 4-substituted derivatives of 2,5-DMA with a broader range of substituents in order to further challenge this hypothesis. We report here the synthesis and 5-HT_2 binding data for the new compounds and the structure–affinity relationships (SAFIR) for the entire series. We have also found that some of the new, more lipophilic 2,5-DMA derivatives act as 5-HT_2 antagonists.

Chemistry

A total of 27 2,5-DMA derivatives were examined in the present study; some of these compounds (i.e., **1a–e,g–k,m–o**) are the 13 included in the original study and their syntheses have been previously reported.[6,7] The 4-chloro derivative **1f** was synthesized according to the method of Coutts and Malicky.[8] Amine **1t** was prepared by catalytic reduction of the corresponding 4-nitro compound by a literature procedure.[8]

Compounds **1p–s** were all prepared in a similar manner, i.e., Friedel–Crafts acylation of *N*-trifluoroacetyl-2,5-DMA (**2**) followed by catalytic reduction and deprotection. For example, acylation of **2** with hexanoyl chloride in the presence of $TiCl_4$ afforded ketone **3a**, which was subse-

Table I. Structures and 5-HT_2 Binding Data for 1-(2,5-Dimethoxyphenyl)-2-aminopropanes[a]



	R	K_i, nM		R	K_i, nM
1a	H	5200	**1o**	Am	7 (1)
1b	OMe	1250	**1p**	Hex	2.5 (0.4)
1c	OEt	2200	**1q**	Oct	3.0 (0.2)
1d	NO_2	300	**1r**	Ph-Pr	10 (1)
1e	F	1100	**1s**	Bz	7.0 (0.8)
1f	Cl	218 (18)	**1t**	NH_2	26000 (900)
1g	Br	41 (5)	**1u**	CN	2400 (180)
1h	I	19	**1v**	COOPr	2460 (90)
1i	Me	100	**1w**	COOBu	1530 (125)
1j	Et	100	**1x**	COEt	735 (75)
1k	Pr	69	**1y**	CONHPr	7550 (675)
1l	*i*-Pr	76 (9)	**1z**	OH	>50000
1m	Bu	58 (6)	**1aa**	COOH	>50000
1n	*t*-Bu	19 (3)	ketanserin		1.2 (0.2)

[a] Affinities (K_i values) for [^{3}H]ketanserin-labeled 5-HT_2 sites. Some of the K_i values were reported earlier;[3,4] K_i values are followed by ±SEM only for those data not previously published. SEM not determined for **1z** and **1aa**.

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quently reduced to **4a** and deprotected to give **1p**. Nitrile **1u** was prepared by treatment of an *N*-phthalimido-protected 4-bromo derivative of 2,5-DMA (i.e., **5**) with cuprous cyanide followed by deprotection with hydrazine. Esters **1v** and **1w** were obtained by esterification of acid **1aa**, and amide **1y** was obtained by treatment of **1v** with *n*-propylamine. Although 4-OH analogue **1z** has been mentioned in the literature on several ocassions (e.g. see ref 9), there is no evidence of its preparation or characterization. Attempts to prepare **1z** via hydrolysis of the diazonium salt generated from *N*-acetyl **1t** were unsuccessful. However, **1z** was prepared in low yield by Baeyer–Villiger oxidation of the 4-formyl derivative of **5** followed by deprotection.

Results

Radioligand binding data for the entire set of 27 4-substituted 2,5-DMA analogues are shown in Table I; K_i values range from 2.5 to >50 000 nM. Substitution at the 4-position by polar/hydrophilic substituents such as NH_2, OH, and COOH (i.e., **1t,z,aa**, respectively) result in compounds with a lower affinity (K_i > 25 000 nM) for 5-HT_2 sites than that of the 4-unsubstituted 2,5-DMA itself (**1a**, K_i = 5200 nM). Compounds with hydrophobic substituents display high affinity for 5-HT_2 sites. The 4-amyl (K_i = 7 nM), 4-hexyl (K_i = 2.5 nM), 4-octyl (K_i = 3 nM), 4-[3-(phenyl)propyl] (K_i = 10 nM), and 4-benzyl (K_i = 7 nM) derivatives of 2,5-DMA (i.e., derivatives **1o–s**, respectively) all possess affinities (K_i values) for the 5-HT_2 sites of 10 nM or less (Table I). Surprisingly, esters **1v** and **1w**, though fairly lipophilic (4-substituent π values = 1.07 and 1.62, respectively),[10] display a low affinity for 5-HT_2 sites.

Evaluation of 2,5-DMA Analogues as Potential Antagonists. Overall, it seems that affinity is explained primarily by the lipophilicity of the 4-substituent.[11] But, previous studies have shown that certain of these compounds behave as agonists whereas others do not (see ref 12 for a review). For example, using rats trained to discriminate DOM from saline, ED_{50} values for stimulus generalization are significantly correlated with 5-HT_2 affinity. However, some of the compounds included in the present study (e.g., **1n** and **1o**) possess a high affinity for the 5-HT_2 sites but do not result in stimulus generalization. If the lipophilic contribution of the 4-substituent is predictive of affinity and if all agents with high affinity are not necessarily agonists, the possibility exists that some of these agents might serve as antagonists (or at least as partial agonists). We examined this possibility in an isolated tissue assay. In rat thoracic aorta, serotonin receptors

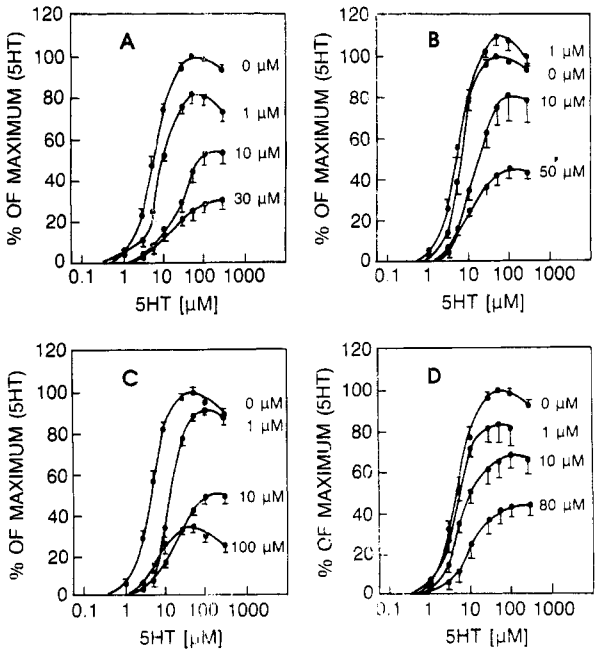

Figure 1. Antagonism of 5-HT-induced contractions of rat thoracic aorta by the 4-benzyl (**1s**; A), 4-hexyl (**1p**; B), 4-phenylpropyl (**1r**; C), and 4-octyl (**1q**; D) derivatives of 2,5-DMA.[30]

appear to be of the 5-HT_2 type.[13,14] As with central 5-HT_2 sites, 5-HT activates phosphoinositol turnover in rat aorta[15] and the physiological consequences of this 5-HT_2 receptor activation appear related to tissue contraction.[14] It has been proposed that aortic receptors provide an appropriate model system for studying 5-HT_2 receptor interactions;[14,15] for example, racemic DOB (**1g**; K_i = 41 nM) is a potent full agonist in this system and (*R*)-(−)-DOB (K_i = 24 nM)[16] is approximately twice as potent as its racemate.[17] In the present study, we examined four agents suspected of being potential antagonists (i.e., **1p–s**). Preliminary evaluations (data not shown) revealed no consistent agonist activity. In contrast, increasing concentrations of all four compounds shifted the concentration–response curves of 5-HT to the right and resulted in depressed maximal responses (Figure 1). Thus, all four compounds displayed antagonist character; however, it appears that the antagonism may be of a noncompetitive nature. Because the 5-HT_2 antagonist ketanserin (pA_2 = 8.5) seems to produce a competitive antagonism,[14] the present data might reflect differences between central and peripheral 5-HT_2 receptors or differences in the nature of the interactions. Nevertheless, it is clear that **1p–s** behave as antagonists, not agonists, in this preparation.

Discussion

Our preliminary studies suggested that the 5-HT_2 receptor affinity of 2,5-DMA analogues is related to the lipophilicity of the 4-substituent and that as lipophilicity

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(11) A quantitative structure–activity relationship analysis of the binding data shown in Table I has been conducted. There is a significant correlation between 5-HT_2 affinity (K_i values) and the lipophilicity (π values) of the 4-position substituents (n = 25, r = 0.858; the 4-OH and 4-COOH derivatives **1z** and **1aa**, respectively, could not be included in the analysis due to their low affinity and lack of specific K_i values). If esters **1v** and **1w** are neglected, for reasons discussed in the text, the correlation between affinity and π values is still significant (n = 23, r = 0.903). For more detail, see: Glennon, R. A.; Seggel, M. R. In *Probing Bioactive Mechanisms*; Magee, P. S., Henry, D., Block, J., Eds.; American Chemical Society: Washington, DC, 1989; pp 264–280.
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increases, affinity increases.[5] Although the initial series of compounds was small (n = 13), the results in Table I are consistent with these preliminary findings in that those compounds with the highest affinity are those with lipophilic 4-substituents. On the other hand, esters **1v** and **1w**, which are also quite lipophilic, possess a relatively low affinity. This low affinity might be explained by the adjacency of the 4-position carbonyl group to the 5-position methoxy group (i.e., a possible alteration in substituent orientation might result from an electrostatic repulsion between the two oxygen atoms), or it may be a result of partial hydrolysis under the conditions of the binding assay to the low-affinity 4-COOH derivative **1aa**. Preliminary data showed that acid **1aa** was of low affinity (i.e., K_i > 5000 nM); however, subsequent examination of this agent at higher concentrations revealed that the acid displays minimal affinity even at concentrations of up to 50000 nM. Hansch analysis of the binding data show that there is a significant correlation between affinity and the lipophilicity of the 4-position substituent.[11]

Other than for our preliminary studies, an analysis of the role of the 4-position substituents of these types of agents on 5-HT_2 receptor affinities has not been previously reported. However, we have demonstrated that the hallucinogenic potencies of phenylalkylamines are significantly correlated with their affinities for 5-HT_2 receptors and that such agents are most likely acting as 5-HT_2 agonists.[4] In 1975, Barfknecht and co-workers[18] reported that the octanol/water partition coefficients of phenylalkylamines may be an important, though not necessarily exclusive, determinant of their hallucinogenic potency. Using a somewhat larger data set, we later reported that the overall lipophilicity of these agents might be important, but that (a) by itself, lipophilicity could not account for the potencies of all of these agents, and (b) that the overall lipophilicities of these agents might simply reflect the large lipophilic contribution of the 4-position substituents of the more potent agents.[19] Furthermore, we provided evidence for a direct receptor interaction of the 4-position substituents.[19] Shulgin and Dyer[20] also found, for a limited set of 4-substituted 2,5-DMAs, that hallucinogenic potency could be explained on the basis of the lipophilicity of the 4-position substituent. Several other studies (e.g. ref 21–24) have also addressed the possible relationships between the activities of related agents and serotonin receptor interactions; however, because the 5-HT receptors involved in those studies may not be of the 5-HT_2 type, the significance of these results is unknown.

This study represents the first comprehensive investigation of the structure–affinity requirements for the binding of 4-substituted phenylalkylamine derivatives at 5-HT_2 receptors. It was determined that the lipophilic character of the 4-position substituents of the 2,5-DMAs appears to be important in determining their affinity for central 5-HT_2 receptors. It might be hypothesized that the receptors possess a hydrophobic area in this region that can accommodate these 4-substituents. The nature of this hydrophobic site needs to be investigated in greater detail, as does its ramifications for receptor selectivity. Nevertheless, it is apparent that not all agents with high affinity for these sites behave as agonists. For example, in rat thoracic aorta, DOB (**1g**) is a potent 5-HT_2 agonist[17] whereas compounds **1p–s** act as antagonists. Furthermore, the affinities of some of these agents at [^{3}H]ketanserin-labeled 5-HT_2 sites rivals that of the currently most popular 5-HT_2 antagonist ketanserin (K_i = 1.2 nM) and are several orders of magnitude greater than that of serotonin ($K_i \cong$ 500 nM).[1] Thus, the possibility exists for the development of an entirely new structural class of 5-HT_2 antagonists. Because [^{3}H]ketanserin binds at neurotransmitter sites other than 5-HT sites[1] and because it apparently binds to a tetrabenazine-sensitive site in brain and in the periphery,[15b] a new structural class of 5-HT_2 antagonists may not share some of these disadvantages of ketanserin.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Microanalysis were performed by Atlantic Microlab (Atlanta, GA) and determined values are within 0.4% of theoretical values. Proton NMR spectra were recorded on a JEOL FX90Q spectrometer, operating at 90 MHz and using tetramethylsilane as an internal standard. Infrared spectra were obtained on a Nicolet 5ZDX FT-IR spectrophotometer. All spectral data are consistent with the assigned structures. The 4-isopropyl compound **1l** as its HCl salt, was a gift from Drs. F. Benington and R. D. Morin (Neurosciences Program, Department of Psychiatry, University of Alabama, Birmingham, AL).

1-(2,5-Dimethoxy-4-hexylphenyl)-2-aminopropane Hydrochloride (1p). A suspension of **4a** (0.15 g, 0.4 mmol) in 15% aqueous NaOH (5 mL), H_2O (5 mL), and MeOH (10 mL) was heated at reflux for 2.5 h. The solution was allowed to cool to room temperature and was extracted with Et_2O (3 × 20 mL). The combined extracts were dried (Na_2SO_4) and ethereal HCl (ca. 20 mL) was added. After removal of the solvent under reduced pressure, the residue was recrystallized from EtOH/Et_2O to give 0.09 g (71%) of the title compound: mp 133–135 °C. Anal. ($C_{17}H_{29}NO_2$·HCl) C, H, N.

1-(2,5-Dimethoxy-4-octylphenyl)-2-aminopropane Hydrochloride (1q). Compound **1q** was prepared from **4b** in a manner similar to that used for **1p**. The residue was recrystallized from EtOH/Et_2O to give 78% of compound **1q**: mp 138–140 °C. Anal. ($C_{19}H_{33}NO_2$·HCl) C, H, N.

1-[2,5-Dimethoxy-4-(3-phenylpropyl)phenyl]-2-aminopropane Hydrochloride (1r). Compound **1r** was prepared from **4c** in a manner similar to that used for **1p**. Excess HCl and solvent were removed in vacuo and the residue was recrystallized from EtOH/Et_2O to give 81% of the title compound: mp 160–162 °C. Anal. ($C_{20}H_{27}NO_2$·HCl) C, H, N.

1-(4-Benzyl-2,5-dimethoxyphenyl)-2-aminopropane Hydrochloride (1s). Compound **1s** was prepared from **4d** in a manner similar to that used for **1p**. Removal of the EtOH under reduced pressure left a white solid which was recrystallized from EtOH/Et_2O, yielding 85% of the title compound: mp 181–183 °C. Anal. ($C_{18}H_{23}NO_2$·HCl), C, H, N.

1-(4-Cyano-2,5-dimethoxyphenyl)-2-aminopropane Hydrochloride (1u). The title compound was prepared by using the general procedure described by Cheng and Castagnoli.[25] Cuprous cyanide (0.61 g, 1.8 mmol) and **5** (0.63 g, 1.57 mmol) were heated at reflux in DMF (10 mL) for 5 h. After cooling, the reaction mixture was poured into a solution of $FeCl_3$·H_2O (0.48 g) in aqueous HCl (0.12 mL of concentrated HCl in 0.72 mL of H_2O). The mixture was heated to 60 °C and allowed to cool. After dilution with H_2O (50 mL) and extraction with CH_2Cl_2 (3 × 25

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mL), the extract was washed with 5% HCl (2 × 25 mL) and dried ($MgSO_4$). Evaporation of the solvent and recrystallization of the residue from 95% EtOH yielded 0.45 g (82%) of *N*-phthaloyl-1-(4-cyano-2,5-dimethoxyphenyl)-2-aminopropane (**6**): mp 154–156 °C. Deprotection of the amine was accomplished by heating a solution of **6** (0.35 g, 1.0 mmol) and hydrazine (97%, 110 μL) at reflux in absolute EtOH (5 mL) for 2 h. After cooling the solution, the precipitate was removed by filtration. The filter cake was washed thoroughly with absolute EtOH (30 mL), and the combined filtrates were concentrated in vacuo. The residue was suspended in H_2O (15 mL) and the suspension was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extract was washed with aqueous Na_2CO_3 (10% w/v, 3 × 15 mL). The organic phase was dried (Na_2SO_4) and evaporated. The oily residue was dissolved in absolute EtOH (5 mL) and layered with ethereal HCl. The resulting product was recrystallized from EtOH/Et_2O to give 0.15 g (58%) of the title compound: mp 236–238 °C. Anal. ($C_{12}H_{16}N_2O_2$·HCl) C, H, N.

***n*-Propyl 2,5-Dimethoxy-4-(2-aminopropyl)benzoate Hydrogen Oxalate (1v).** The title compound was prepared by following the procedure for the synthesis of *n*-butyl ester **1w**. Thus, a mixture of 1-propanol (300 mg, 5.0 mmol), concentrated H_2SO_4 (50 mg, 0.5 mmol), and **1aa** (150 mg, 0.5 mmol) in benzene, after heating at reflux and extraction, gave 80 mg (60%) of the propyl ester: mp 85–90 °C. The hydrogen oxalate salt was prepared as for **1w**: mp 169–170 °C. Anal. ($C_{15}H_{23}NO_4$·($CO_2H)_2$) C, H, N.

***n*-Butyl 2,5-Dimethoxy-4-(2-aminopropyl)benzoate Hydrogen Oxalate (1w).** 1-Butanol (650 mg, 10.0 mmol) and concentrated H_2SO_4 (100 mg, 1.0 mmol) were added to a suspension of **1aa** (as the free base; 0.24 g, 1.0 mmol) in benzene (30 mL). The reaction mixture was then heated under reflux for 5 h with continuous removal of H_2O into a Dean–Stark trap. After cooling, the reaction mixture was extracted with H_2O (2 × 50 mL). The aqueous extract was made alkaline (pH 10) with a 10% Na_2CO_3 solution and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with H_2O (2 × 50 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the oily residue was dried under high vacuum (0.15 mmHg) for 1 h. Upon standing at 0 °C, the oil solidified to give 150 mg (54%) of the title compound: mp 75–80 °C.

A solution of the ester (100 mg) in anhydrous Et_2O (10 mL) was added to a saturated solution of oxalic acid in anhydrous Et_2O (10 mL). The precipitate was collected by filtration, air dried, and recrystallized from 2-PrOH/Et_2O to afford the hydrogen oxalate salt: mp 149–150 °C. Anal. ($C_{16}H_{25}NO_4$·($CO_2H)_2$·$^1/_2H_2O$) C, H, N.

1-(2,5-Dimethoxy-4-propionylphenyl)-2-aminopropane Hydrochloride (1x). A mixture of **7** (200 mg, 0.58 mmol), 15% NaOH (2 mL), H_2O (8 mL), and MeOH (5 mL) was heated at reflux for 2.5 h. The solution was allowed to cool to room temperature, combined with H_2O (20 mL), and extracted with Et_2O (4 × 15 mL). The hydrochloride salt was prepared by adding ethereal HCl to the dried ($MgSO_4$) extract. Removal of the solvent under reduced pressure left a yellow oil, which solidified under high vacuum. Recrystallization from EtOH/Et_2O, followed by recrystallization from 1-PrOH/Et_2O, gave 90 mg (54%) of the title compound: mp 164–166 °C. Anal. ($C_{14}H_{21}NO_3$·HCl) C, H, N.

***N*-*n*-Propyl-2,5-dimethoxy-4-(2-aminopropyl)benzamide Hydrogen Oxalate (1y).** A solution of *n*-propyl 2,5-dimethoxy-4-(2-aminopropyl)benzoate (**1v**; 120 mg, 0.43 mmol) in *n*-propylamine (5 mL) was heated under reflux for 5 h. Excess *n*-propylamine was removed in vacuo and the resulting solid residue was washed with Et_2O to yield 60 mg (56%) of the amide as a pale, buff solid: mp 110–115 °C. A solution of the amide (50 mg) in absolute EtOH (1 mL) was added to a solution of oxalic acid in anhydrous Et_2O (5 mL). The oxalate salt was collected by filtration and recrystallized from 2-PrOH/Et_2O: mp 183–184 °C. Anal. ($C_{15}H_{24}N_2O_3$·($CO_2H)_2$) C, H, N.

1-(2,5-Dimethoxy-4-hydroxyphenyl)-2-aminopropane Hydrogen Oxalate (1z). To a solution of *N*-phthaloyl-1-(2,5-dimethoxy-4-formylphenyl)-2-aminopropane[26] (0.5 g, 1.42 mmol) in $CHCl_3$ (25 mL) was added 0.42 g (2.07 mmol) of 85% 3-chloroperoxybenzoic acid. The solution was then stirred at room temperature for 21 h. The residue remaining after removal of the solvent under reduced pressure was dissolved in Et_2O (50 mL). This solution was washed with 4% $NaHSO_3$ (2 × 25 mL). The washed ethereal solution was evaporated to dryness under reduced pressure and the residue was dissolved in absolute EtOH (50 mL). HCl (g) was bubbled through the ethanolic solution for 60 s. The flask was sealed and allowed to stand at room temperature for 18 h. The solvent was removed under reduced pressure and the remaining HCl was chased with 95% EtOH. The residue was chromatographed on silica gel (10 g, 12 mm i.d.) and eluted with EtOAc. Crystallization from EtOH/H_2O yielded 0.57 g of a waxy material, which was used without further purification. A solution of the hydroxy compound (0.34 g) and anhydrous hydrazine (110 μL) in absolute EtOH (5 mL) was heated at reflux for 3 h and then stirred at room temperature for an additional 14 h. After the solvent was removed under reduced pressure, the residue was washed with 5% HCl (20 mL), and the mixture was filtered. The filtrate was made alkaline with 15% NaOH and extracted with $CHCl_3$ (3 × 15 mL). The organic portion was dried (Na_2SO_4), evaporated to dryness, and the residue was dissolved in a minimal amount of absolute EtOH and was added dropwise to a saturated ethereal solution of oxalic acid. The precipitate was recrystallized from EtOH/Et_2O to yield 25 mg (5.8%) of the title compound, mp 205–210 °C dec. Anal. ($C_{13}H_{17}NO_3$·($COOH)_2$) C, H, N.

1-(4-Carboxy-2,5-dimethoxyphenyl)-2-aminopropane Hydrochloride (1aa). A solution of **1g** (as the free base; 1.4 g, 5.0 mmol) in anhydrous Et_2O (20 mL) was added dropwise to a stirred solution of *n*-butyllithium (1.3 g, 20 mmol; 12.5 mL of 1.6 M solution) in anhydrous Et_2O (20 mL) at 0 °C. The reaction mixture was then stirred at room temperature for 2 h, after which the mixture was poured over solid CO_2 (50 g). The solvent was removed under reduced pressure and the residue was washed with Et_2O. The residue was dissolved in water (50 mL) and washed with $CHCl_3$ (2 × 30 mL). The aqueous solution was acidified with concentrated HCl and washed with $CHCl_3$ (2 × 30 mL). The aqueous portion was evaporated under reduced pressure to give a solid residue, which was recrystallized twice from MeCN to afford 0.25 g (30%) of a very light tan amorphous solid: mp 194–196 °C (lit.[27] mp 196–198 °C).

***N*-(Trifluoroacetyl)-1-(2,5-dimethoxyphenyl)-2-aminopropane (2).** Trifluoroacetic anhydride (20 mL) was slowly added to 1-(2,5-dimethoxyphenyl)-2-aminopropane (**1a**; 2.7 g, 13.8 mmol) while cooling in an ice bath. The reaction mixture was allowed to warm to room temperature, was stirred for 2 h, and was poured over crushed ice (200 g). The white precipitate was collected by filtration and was washed with a large volume of cold H_2O. Recrystallization from EtOH/H_2O afforded 3.0 g (74%) of the title compound as a flocculent, white solid: mp 101–103 °C. Anal. ($C_{13}H_{16}F_3NO_3$) C, H, N.

***N*-(Trifluoroacetyl)-1-(2,5-dimethoxy-4-hexanoylphenyl)-2-aminopropane (3a).** Titanium tetrachloride (1.4 mL, 12.8 mmol) was added dropwise, under a N_2 atmosphere, to a solution of **2** (2.0 g, 6.9 mmol) in CH_2Cl_2 (60 mL) cooled to ca. −30 °C. Hexanoyl chloride (1.28 g, 9.5 mmol) in CH_2Cl_2 (5 mL) was then added dropwise while the reaction mixture was maintained at ca. −30 °C. The mixture was stirred at ca. −30 °C for an additional 30 min and was allowed to warm to room temperature. Stirring was continued for 3 days and the reaction mixture was cautiously poured over 300 g of crushed ice. After vigorous stirring, the layers were separated. The aqueous portion was further extracted with CH_2Cl_2 (3 × 200 mL). The extract was washed successively with H_2O (200 mL), 5% HCl (100 mL), (200 mL), saturated aqueous $NaHCO_3$ (200 mL), and saturated aqueous NaCl (100 mL). After drying of the extract (Na_2SO_4), the solvent was removed under reduced pressure. Recrystallization from EtOH/H_2O afforded 1.33 g (49%) of **3a**: mp 105–107 °C. Anal. ($C_{19}H_{26}F_3NO_4$) C, H, N.

***N*-(Trifluoroacetyl)-1-(2,5-dimethoxy-4-octanoylphenyl)-2-aminopropane (3b).** The title compound was prepared in 52% yield in a manner similar to that used for the

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synthesis of **3a**; recrystallization from EtOH/H_2O afforded the product as an off-white solid: mp 104–105 °C. Anal. ($C_{21}H_{30}F_3NO_4$) C, H, N.

***N*-(Trifluoroacetyl)-1-(4-benzoyl-2,5-dimethoxyphenyl)-2-aminopropane (3c).** Compound **3c** was prepared in a manner similar to that used for the synthesis of **3a**. Recrystallization from EtOH/H_2O gave 48% of the title compound: mp 134–136 °C. Anal. ($C_{20}H_{20}F_3NO_4$) C, H, N.

***N*-(Trifluoroacetyl)-1-(2,5-dimethoxy-4-hydrocinnamoylphenyl)-2-aminopropane (3d).** Compound **3d** was prepared by using the same method used for the preparation of **3a**. The material remaining after removal of the solvent under reduced pressure was recrystallized from EtOH/H_2O to give 1.3 g (44%) of the title compound: mp 131–133 °C. Anal. ($C_{22}H_{24}F_3NO_4$) C, H, N.

***N*-(Trifluoroacetyl)-1-(2,5-dimethoxy-4-hexylphenyl)-2-aminopropane (4a).** A solution of **3a** (0.22 g, 0.6 mmol) in glacial acetic acid (60 mL) containing ca. 0.3 mL of 60% aqueous $HClO_4$ was hydrogenated over 0.1 g of 10% Pd/C for ca. 6 h. The catalyst was removed by filtration and washed with CH_2Cl_2 (25 mL). After addition of H_2O (150 mL) to the filtrate, the product was extracted with CH_2Cl_2 (4 × 75 mL). The organic portion was washed with H_2O (200 mL), saturated aqueous $NaHCO_3$ (200 mL), and again with H_2O (200 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was recrystallized from EtOH/H_2O, yielding 0.15 g (66%) of compound **4a**: mp 119.5–120.5 °C. Anal. ($C_{19}H_{28}F_3NO_3$) C, H, N.

***N*-(Trifluoroacetyl)-1-(2,5-dimethoxy-4-octylphenyl)-2-aminopropane (4b).** The title compound was prepared by using the procedure described for **4a**. Recrystallization of the residue from 95% EtOH gave 56% of the title compound: mp 109–111 °C. Anal. ($C_{21}H_{32}F_3NO_3$) C, H, N.

***N*-(Trifluoroacetyl)-1-(4-benzyl-2,5-dimethoxyphenyl)-2-aminopropane (4c).** The title compound was prepared with the procedure used for the synthesis of **4a**. Recrystallization from EtOH/H_2O gave 61% of **4c**: mp 147–149 °C. Anal. ($C_{20}H_{22}F_3NO_3$) C, H, N.

***N*-(Trifluoroacetyl)-1-[2,5-dimethoxy-4-(3-phenylpropyl)phenyl]-2-aminopropane (4d).** The title compound was prepared by using the procedure described for the synthesis of **4a**. The residue was recrystallized from EtOH/H_2O to give 63% of **4d**: mp 125–126.5 °C. Anal. ($C_{22}H_{26}F_3NO_3$) C, H, N.

***N*-Phthaloyl-1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane (5).** A solution of 48% HBr (0.80 g) in glacial acetic acid (10 mL) was added to a stirred solution of *N*-phthaloyl-1-(2,5-dimethoxyphenyl)-2-aminopropane[23] (1.5 g, 4.0 mmol) in glacial acetic acid (10 mL) at 0 °C. A solution of Br_2 (0.8 g, 4.2 mmol) in glacial acetic acid (10 mL) was then added dropwise. The reaction mixture was then allowed to stir at room temperature for 3 h. The solvent was removed under reduced pressure and the residue was recrystallized from 95% EtOH to give the title compound as a white, crystalline solid in quantitative yield: mp 111–112 °C. Anal. ($C_{19}H_{18}BrNO_4$) C, H, Br.

***N*-(Trifluoroacetyl)-1-(2,5-dimethoxy-4-propionylphenyl)-2-aminopropane (7).** Titanium tetrachloride (1.4 mL, 12.8 mmol) was added dropwise under a N_2 atmosphere to a solution of **2** (2.0 g, 6.9 mmol) in CH_2Cl_2 (70 mL) cooled to ca. −30 °C. Propionyl chloride (0.88 g, 9.5 mmol) in CH_2Cl_2 (5 mL) was added dropwise to the dark brown solution while the reaction mixture was maintained at ca. −30 °C. The mixture was stirred at ca. −30 °C for an additional 30 min and was allowed to warm to room temperature. Stirring was continued for 3 days and the reaction mixture was cautiously poured over 300 g of crushed ice. The deep red dissipated upon vigorous mixing. After separating the layers, the aqueous portion was extracted with CH_2Cl_2 (4 × 175 mL) and the organic portion was washed successively with H_2O (200 mL), 5% HCl (100 mL), H_2O (200 mL), saturated aqueous $NaHCO_3$ (200 mL), and saturated aqueous NaCl (200 mL). After drying (Na_2SO_4), the solvent was removed under reduced pressure. Recrystallization from EtOH/H_2O gave 1.63 g (68%) of **7**: mp 143–145 °C. Anal. ($C_{16}H_{20}F_3NO_4$) C, H, N.

Radioligand Binding Studies. Radioligand binding assays were conducted in essentially the same manner as previously reported.[28] Briefly, Taconic Farms male Sprague–Dawley rats (ca. 220 g) were decapitated and the brains were immediately placed in ice-cold 0.9% saline. Dissecting over ice, the frontal corticies were removed with the anterior border of the corpus callosum as a landmark. Tissue was either used immediately or stored at −30 °C until needed (no differences were noted between preparations). Membrane homogenates were prepared in a 50 mM Tris HCl buffer (pH 7.4 at 37 °C) containing 10 mM $MgSO_4$ and 0.5 mM Na_2EDTA. Assays were performed in 2.0 mL of this same buffer to which was added to 0.1% ascorbate and 10 μM pargyline; membranes (3-mg wet weight) were added last. Displacement experiments at 11 concentrations of nonlabeled drug were performed in triplicate with tritiated ketanserin (90.4 Ci/mmol) (New England Nuclear). Specific binding was defined with 1 μM cinanserin. Solutions of all test compounds were made fresh daily. Following incubation at 37 °C for 15 min, membranes were rapidly filtered over glass-fiber filters that had been presoaked in 0.1% polyethyleneimine, followed by a 10-mL wash with ice-cold buffer. Following a 6-h equilibration in Scintiverse (Fisher), samples were counted in a Beckman 3801 counter with an efficiency of 45%. IC50 values were determined and K_i values were calculated with the Cheng–Prusoff equation.[29]

Isolated Tissue Studies. The isolated tissue studies with rat aorta were performed as previously described in detail.[14,17] In brief, using male Sprague–Dawley rats (250–300 g), 4-mm rings of rat thoracic aorta were dissected and suspended between two stainless steel hooks connected to a force displacement transducer. The organ bath was continuously bubbled with 95% O_2/5% CO_2 in a Krebs-bicarbonate buffer maintained at 37 °C. Resting tension was set at 2.5 g and, after a 1-h equilibration period, concentration–response studies were performed as previously described.[14] The aortic segments were incubated with varying concentrations of antagonist for 10 min at 37 °C prior to titration with graded concentrations of 5-HT. All results represent the mean, ± standard error of the mean, of five or six individual experiments.

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(30) EC_{50} (±SEM) values were calculated for 5-HT by using logit–log transformations of the cummulative concentration–response curves and linear least-squares regression analysis. The Student's *t* test for unpaired samples was used for evaluation of significant differences ($p < 0.05$*). For each compound, concentrations (and μM EC_{50} values of 5-HT) are as follows: **1s**, 0 μM (6.3 ± 0.8), 1 μM (7.7 ± 1.7), 10 μM (20.5 ± 3.8*), 30 μM (12.4 ± 1.8*); **1p**, 0 μM (5.8 ± 0.5), 1 μM (5.4 ± 1.3), 10 μM (12.8 ± 0.8*), 50 μM (9.5 ± 1.4*); **1r**, 0 μM (4.8 ± 0.6), 1 μM (13.8 ± 2.4*), 10 μM (18.2 ± 0.4*), 100 μM (8.4 ± 2.2); **1q**, 0 μM (5.4 ± 0.9), 1 μM (4.1 ± 0.8), 10 μM (7.4 ± 0.9), 80 μM (9.8 ± 3.2).