1-[2-Methoxy-5-(3-phenylpropyl)]-2-aminopropane Unexpectedly Shows 5-HT_{2A} Serotonin Receptor Affinity and Antagonist Character

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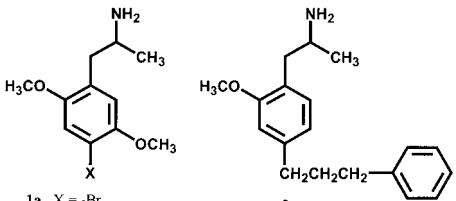
Certain phenylethylamines, such as 1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane (DOB; **1a**), are high-affinity 5-HT_2 agonists. Previous structure−affinity studies have concluded that both the 2,5-dimethoxy substitution pattern and the nature of substituents at the 4-position are important determinants of high affinity. We recently demonstrated that replacement of the bromo group of DOB with a 3-(phenyl)propyl substituent results in retention of affinity and that, counter to established structure−affinity relationships, the 2,5-dimethoxy substitution pattern is no longer a requirement for the binding. The present investigation extends these findings by examining a series of analogues, **3**, lacking a 5-methoxy group. It was additionally found that shifting the phenylalkyl substituent from the 4- to the 5-position (e.g., **4i**) also results in retention of affinity. For example, 1-(2-methoxy-5-(3-phenylpropyl)-2-aminopropane (**6**; the α-methyl derivative of **4i**) binds at 5-HT_{2A} receptors with high affinity (K_i = 13 nM) and possesses 5-HT_{2A} antagonist character. Thus, not only is the 2,5-dimethoxy substitution pattern not a requirement for the binding of certain phenylethylamines at 5-HT_{2A} receptors, the presence of a 4-position substituent (previously thought to serve as a modulator of affinity of DOB-like agents) is also not required. Striking differences in the 5-HT_{2A} binding requirements of the present compounds as compared to DOB-like agents suggest multiple substituent-dependent modes of binding.

The 5-HT_2 family of serotonin (5-HT) receptors is reportedly involved in cardiovascular function and in a wide array of central disorders including schizophrenia, depression, anxiety, migraine, hallucinations, and eating disorders (reviewed[1−4]). An extensive body of literature is available on novel 5-HT_2 antagonists (reviewed[2−4]). A few 5-HT_2 agonists are also available.[2,4] Although 5-HT itself is a prototypical 5-HT_2 agonist, it lacks selectivity and is, consequently, of limited utility. For the past 15 to 20 years, phenylethylamines such as 1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane (DOB; **1a**) and related analogues such as its 4-iodo (DOI; **1b**) and 4-methyl (DOM; **1c**) counterparts have been regarded as 5-HT_2 (now 5-HT_{2A})[1] serotonin receptor agonists[2] and have seen broad application in pharmacological investigations.



Structure−affinity relationships have been formulated for DOB-like phenylethylamines,[2,5] and the 2,5-dimethoxy substitution pattern found in these ligands was thought, until recently, to be important for 5-HT_2 binding. The nature of the 4-position substituent is also thought to be a major determinant of binding, and has been shown to modulate affinity over a very broad (>10000-fold) range.[2,5] When the 4-position substituent is -H or a polar group (e.g., -OH, -COOH) the compounds bind with little (i.e., micromolar) to no affinity, whereas halogen and small alkyl functions, e.g., C_1−C_6, impart markedly enhanced affinity (e.g., refs 5 and 6). DOB (**1a**), for example, binds at 5-HT_{2A} receptors with high affinity (K_i = 32 nM).[7] It has been further shown, however, that when alkyl chain length exceeds that of a *n*-propyl group, agonist potency declines although affinity is retained.[2,8]

Recently, we found that 1-(2,5-dimethoxy-4-(3-phenylpropyl)phenyl)-2-aminopropane (**1d**; K_i = 30 nM) binds at 5-HT_{2A} receptors with an affinity comparable to that of DOB (**1a**) but that it behaves, at best, as a partial agonist.[7] More interestingly, we found that with the 4-(3-phenylpropyl) substituent present, the structure−affinity relationships of **1d**-like compounds significantly deviate from established structure−affinity requirements of DOB-like phenylethylamines. That is, the presence of the 2,5-dimethoxy substitution pattern is no longer a requirement for high affinity. For example, removal of the 5-methoxy group of **1d**, rather

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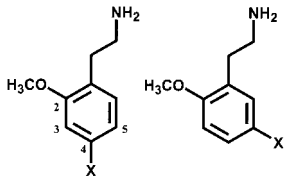
than reducing or abolishing affinity as might have been expected, actually enhanced affinity by severalfold (i.e., 2; 5-HT_{2A} K_i = 8 nM).[7]

Because the 2-methoxy analogue 2 binds with higher affinity than **1d**, we embarked on a structure−affinity investigation focusing on a series of aryl-substituted (2-methoxyphenyl)-1-aminoethanes. We have already demonstrated that the presence of a methyl group α to the amine has little effect on 5-HT_{2A} affinity.[7] Hence, our initial studies were conducted using derivatives of **3**. Because phenylethylamines are typically prone to rapid metabolism in vivo, our intent was to prepare an α-methyl analogue (i.e., a phenylisopropylamine) of one of the more interesting compounds identified in this study for use in future in vivo investigations. The present study began with a determination of the affinity of (2-methoxyphenyl)-1-aminoethane (**3a**; i.e., **3**, X = H). The 4-position of **3a** was modified using several substituents shown to influence the affinity of **1d**-type compounds.[7] During the course of this investigation it became apparent that moving a 4-position substituent to the 5-position impacted 5-HT_{2A} binding. To further study this effect, because 4-position substituents have been previously thought to be a requirement for binding, substituents used to explore the 4-position of **3** were introduced to the 5-position to obtain a series of analogues **4**. Due to a paucity of compounds with selectivity for 5-HT_{2A} vs 5-HT_{2C} receptors, the 5-HT_{2C} receptor affinities of the present compounds were also determined.



3 4

Chemistry

The reported phenylethylamines **3** and **4** (Table 1) were prepared from the appropriate 4- or 5-substituted 2-methoxybenzaldehydes via a Henry reaction to give the corresponding nitrostyrenes, followed by reduction of the nitrostyrenes with $LiAlH_4$ or, where halogen was present, with AlH_3 (Scheme 1). The requisite benzaldehydes, which generally were not characterized, were prepared by one of several methods.

Method A. The benzaldehydes required for preparation of **3d**, **3e**, **3g**, **4i**, **4j**, **4k**, and **4l**, were obtained using a Suzuki cross-coupling reaction between triflates (i.e., **10** and **11**) or commercially available 5-bromo-2-methoxybenzaldehyde (**9**) with the appropriate 9-phenylalkyl-9-borabicyclo[3.3.1]nonane[7] in the presence of palladium catalyst. In the case of **3j** and **4n**, the intermediate aldehydes were obtained by cross-coupling of **10** or 5-bromo-2-methoxybenzaldehyde (**9**), respectively, with phenylboronic acid. The triflates **10** and **11** were synthesized from 4-hydroxy-2-methoxybenzaldehyde (**7**) or 5-hydroxy-2-methoxybenzaldehyde (**8**),[9] respectively, in the presence of triflic anhydride and pyridine. Preparation of the aldehydes is exemplified in the Experimental Section for **12b** (used in the synthesis of **3d**) and **12h** (used in the synthesis of **3j**); a typical conversion of the aldehyde to the corresponding phenylethylamine is described for **3d**. The physicochemical properties of the target amines, and the method of preparation used for the synthesis of their intermediate aldehydes, is shown in Table 1. Compounds **3b**, **3c**, **4g**, and **4h** were prepared in a similar manner.

Table 1. Physiochemical Data for Phenylalkylamines

	method[a]	yield (%)	mp (°C)[b]	empirical formula[c]
3b	A	41	168−169	$C_{16}H_{19}NO{\cdot}C_2H_2O_4$
3c	A	44	167−169	$C_{17}H_{21}NO{\cdot}C_2H_2O_4$[e]
3d	A	55	161−163	$C_{18}H_{23}NO{\cdot}C_2H_2O_4$[d]
3e	A	24	163−165	$C_{19}H_{25}NO{\cdot}C_2H_2O_4$[e]
3f	−	41	138−140	$C_{20}H_{27}NO{\cdot}C_2H_2O_4$[f]
3g	A	33	161−163	$C_{18}H_{28}NO{\cdot}0.9C_2H_2O_4$
3h	B	72	161−163	$C_{17}H_{21}NO_2{\cdot}C_2H_2O_4$
3i	C	28	167−169	$C_{20}H_{23}NO{\cdot}C_2H_2O_4$[e]
3j	A	29	189−191	$C_{15}H_{17}NO{\cdot}C_2H_2O_4$[e]
4a	−	48	189−190[h]	
4b	−	56	175−177	$C_9H_{11}BrNO{\cdot}C_2H_2O_4$[g]
4c	−	46	206−208	$C_9H_{12}INO{\cdot}C_2H_2O_4$
4d	B	62	187−189[i]	
4e	B	57	165−167	$C_{17}H_{21}NO_2{\cdot}C_2H_2O_4$
4f	B	22	196−197	$C_{17}H_{20}BrNO_2{\cdot}0.5C_2H_2O_4$
4g	A	46	175−177	$C_{16}H_{19}NO{\cdot}C_2H_2O_4$[e]
4h	A	52	178−180	$C_{17}H_{21}NO{\cdot}C_2H_2O_4$[e]
4i	A	66	169−171	$C_{18}H_{23}NO{\cdot}C_2H_2O_4$[g]
4j	A	19	181−183	$C_{19}H_{25}NO{\cdot}C_2H_2O_4$
4k	—[j]	61	144−146	$C_{20}H_{27}NO{\cdot}C_2H_2O_4$[d]
4l	A	32	181−183	$C_{18}H_{29}NO{\cdot}C_2H_2O_4$
4m	C	32	182−184	$C_{20}H_{23}NO{\cdot}C_2H_2O_4$[g]
4n	A	29	209−210	$C_{15}H_{27}NO{\cdot}C_2H_2O_4$[e]

[a] Method of preparation of the requisite aldehyde precursor (see Experimental Section). [b] All compounds were recrystallized from MeOH/anhydrous Et_2O. [c] All compounds analyzed correctly for C, H, N within 0.4% of theory. [d] Crystallized with 0.75 mol of H_2O. [e] Crystallized with 0.25 mol of H_2O. [f] Crystallized with 1 mol of H_2O. [g] Crystallized with 0.5 mol of H_2O. [h] Lit.[10] mp 186 °C. [i] Lit.[10] mp 189 °C. [j] Prepared in the same manner as **3g**.

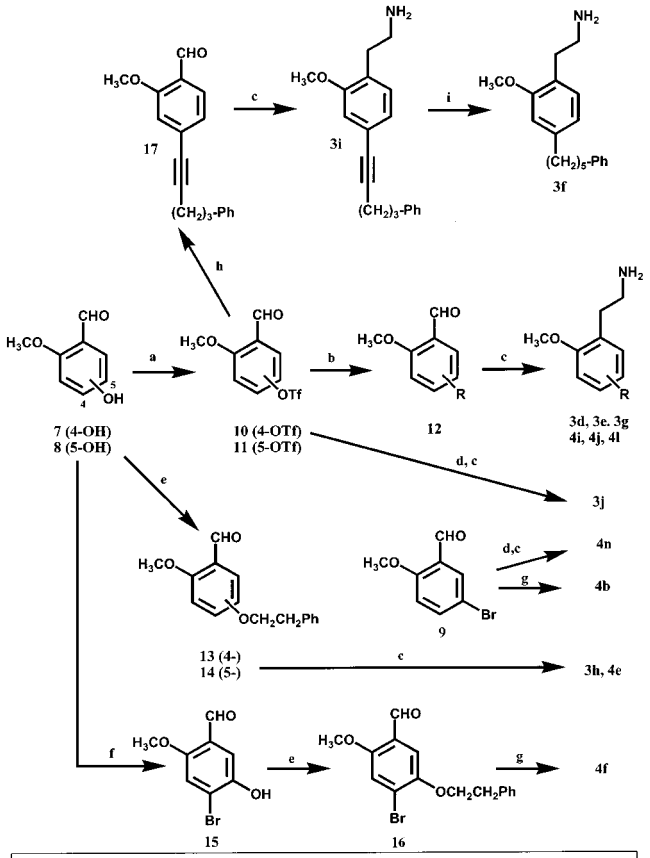
Method B. Phenylalkylamines **3h** and **4e** were obtained from 4-(2-phenylethoxy)-2-methoxybenzaldehyde (**13**) and 5-(2-phenylethoxy)-2-methoxybenzaldehyde (**14**), respectively. The required aldehydes were prepared by alkylating 4-hydroxy-2-methoxybenzaldehyde (**7**) and 5-hydroxy-2-methoxybenzaldehyde (**8**) with 2-bromo-1-ethylbenzene using Adogen-464 as a phase transfer catalyst (Scheme 1). The above method was adopted for the preparation of 5-(2-phenylethoxy)-4-bromo-2-methoxybenzaldehyde (**16**) used in synthesis of **4f**. Synthesis of **16** began with bromination of 5-hydroxy-2-methoxybenzaldehyde (**8**) using Br_2 and $SnCl_4$ to afford **15**. Compound **15** was also prepared by selective O-demethylation of 2,5-dimethoxy-4-bromobenzaldehyde followed by alkylation with 2-bromo-1-ethylbenzene to give the desired aldehyde.

Method C. The intermediate aldehyde, **17**, for the synthesis of **3i** was obtained by Sonogashira cross-coupling of **10** with 5-phenyl-1-pentyne in the presence of a catalytic amount of palladium catalyst and copper iodide. Compound **4m** was prepared in like manner (Table 1).

The phenylethylamine **3f** was prepared by catalytic reduction of alkyne **3i** using Pd/C as catalyst (Scheme 1). Compounds **4a**[10] and **4d**[10] were synthesized according to literature methods, and amine **4c** was synthesized by the iodination of 2-(2-methoxyphenyl)-1-aminoethane (**3a**) with iodine and silver sulfate.

Compound **6** was prepared in a manner similar to that which we have previously reported for several

Scheme 1[a]

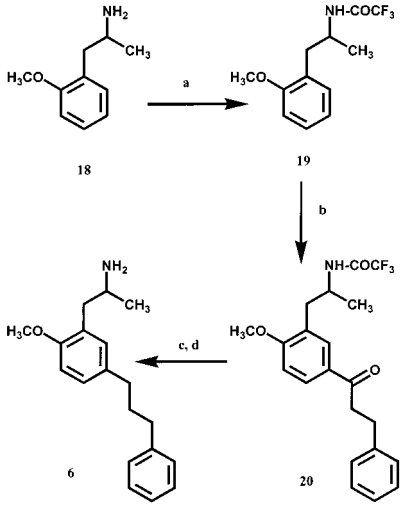


3d: R = 4-$(CH_2)_3$Ph; **3e**: R = 4-$(CH_2)_4$Ph, **3g**: R = 4-$(CH_2)_3$-cC_6H_{11}; **3h**: R = 4-OCH_2CH_2Ph; **3j**: R = 4-Ph; 4b: R = -Br; **4e**: R = 5-OCH_2CH_2Ph; **4f**: R = 4-Br, 5-OCH_2CH_2Ph; **4i**: R = 5-$(CH_2)_3$Ph; **4j**: R = 5-$(CH_2)_4$Ph; **4l**: R = 5-$(CH_2)_3$-cC_6H_{11}; **4n**: R = 5-Ph.

[a] Reagents: (a) triflic anhydride, pyridine; (b) Suzuki; (c) (i) $MeNO_2$, (ii) $LiAlH_4$; (d) phenylboronic acid, LiCl, Na_2CO_3, Pd-$(PPh_3)_4$; (e) 2-Br-1-ethylbenzene, Adogen-464; (f) $SnCl_2$, Br_2; (g) (i) $MeNO_2$, (ii) AlH_3; (h) 5-phenyl-1-pentyne, CuI, Et_3N, $PdCl_2$dppf; (i) H_2, 10% Pd/C.

structurally related compounds.[7] 1-(2-Methoxyphenyl)-2-aminopropane (**18**) was protected by acylation of the amine with trifluoroacetic anhydride to afford acetamide **19**. The acetamide was acylated with hydrocinnamoyl chloride under Friedel−Crafts conditions to afford the ketone **20**. Compound **20** was subjected to hydrogenolytic conditions, and the product, **21**, was deprotected to give the target compound **6** (Scheme 2).

Scheme 2[a]



[a] Reagents: (a) $(CF_3CO)_2O$; (b) $TiCl_4$, hydrocinnamoyl chloride; (c) H_2, 10% Pd/C; (d)15% NaOH.

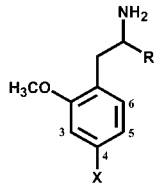
Results and Discussion

5-HT_{2A} Radioligand Binding Studies. The monosubstituted methoxy compound **3a** (K_i > 10000 nM) showed little affinity for 5-HT_{2A} receptors (Table 2). As expected on the basis of our earlier findings,[7] introduction of a 4-(3-phenylpropyl) substituent (**3d**; K_i = 18 nM) enhanced affinity by >500-fold, and its affinity was similar to that of its phenylisopropylamine counterpart 2 (K_i = 8 nM).[7] Shortening the alkyl chain of **3d** (i.e., **3b** and **3c**; K_i = 23 and 46 nM, respectively) had relatively little effect on affinity, whereas chain lengthening of **3d** to the 4-(4-phenylbutyl) and 4-(5-phenylpentyl) analogues **3e** and **3f** (K_i = 59 and 72 nM, respectively) reduced affinity by 3- to 4-fold. The phenyl ring of **3d** was reduced to a cyclohexyl ring (**3g**; K_i = 438 nM) and resulted in about a 20-fold decrease in affinity, whereas replacement of the benzylic methylene of **3d** with an ether oxygen (**3h**; K_i = 172 nM), or introduction of unsaturation in the form of alkyne **3i** (K_i = 295 nM), reduced affinity by an order of magnitude or more. Finally, the 4-(3-propylphenyl) substituent of **3d** was replaced by a 4-phenyl group to give **3j** (K_i = 6720 nM) to result in a compound with significantly reduced affinity.

On the basis that **1d** presents a 5-oxygenated substituent whereas the inactive **3a** does not, it was of interest to determine the influence of 5-position substituents on the binding of **3a** (Table 3). Introduction of a 5-methoxy group (i.e., **5**; K_i = 2820 nM) resulted in measurable affinity. O-Demethylation of **5** (**4a**; K_i = 5960 nM) halved affinity, whereas replacement by a bromo or iodo group (K_i = 1000 nM and 700 nM for **4b** and **4c**, respectively) only doubled or tripled affinity. Ether analogues **4d** and **4e** (K_i = 345 and 600 nM, respectively) displayed somewhat enhanced, yet still relatively modest, affinity. Most of these modifications seemed to have a rather minimal influence on binding. Attempting to rely on DOB-like structure−affinity requirements, a 4-bromo group was added to **4e**; the resulting compound, **4f** (K_i = 91 nM), showed a 6-fold increase in affinity. It might be noted that we have previously shown that introduction of a 4-bromo group enhances the affinity of 1-(2,5-dimethoxyphenyl)-2-aminopropane (i.e., **1**, X = −H) and 2-(2,5-dimethoxyphenyl)-1-aminoethane (**5**) by >150-fold.[7] It appears that bromination of the ether analogue **4e** does not follow DOB-like SAR.

Taking a lead from the detrimental influence of the oxygen ether in the **3**-series compounds (i.e., comparing ether **3h** and its methylene counterpart **3d**), we replaced the ether oxygen atom of **4e** with a methylene group to give **4i**. Compound **4i** (K_i = 20 nM), which binds with enhanced affinity, is a positional isomer of **3d** (K_i = 18 nM) and both bind with comparable affinity. Consequently, we explored the effect of several other substituents that we had examined in the 4-substituted series. In contrast to what was observed in the 4-substituted series, shortening of the alkyl chain of **4i** by one or two

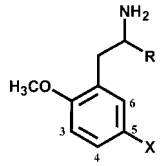
Table 2. Influence of 4-Position Substituents on the Binding of (2-Methoxyphenyl)-1-aminoethane (**3a**)



	X	R	5-HT$_{2A}$[a] K_i, nM (SEM)	5-HT$_{2A}$[b] K_i, nM (SEM)	5-HT$_{2C}$ K_i, nM (SEM)	2C/2A ratio[c]
3a	-H	-H	>10000	>10000	>10000	–
3b	-CH$_2$-Ph	-H	23 (4)	–[d]	93 (12)	4
3c	-(CH$_2$)$_2$-Ph	-H	46 (12)	–	170 (12)	4
3d	-(CH$_2$)$_3$-Ph	-H	18 (6)	12 (3)	295 (23)	16
2[e]	-(CH$_2$)$_3$-Ph	-Me	8	–	89	11
3e	-(CH$_2$)$_4$-Ph	-H	59 (13)	42 (19)	68 (6)	1
3f	-(CH$_2$)$_5$-Ph	-H	72 (27)	18 (2)	19 (5)	<1
3g	-(CH$_2$)$_3$-*c*C$_6$H$_{11}$	-H	438 (140)	250 (95)	116 (17)	<1
3h	-O-CH$_2$CH$_2$-Ph	-H	172 (40)	110(23)	810 (140)	5
3i	-C≡C-(CH$_2$)$_3$-Ph	-H	295 (133)	240 (16)	70 (18)	<1
3j	-Ph	-H	6720 (1818)	4900 (840)	1520 (346)	<1

[a] 5-HT$_{2A}$ sites labeled using [^{3}H]ketanserin. [b] 5-HT$_{2A}$ sites labeled using [^{3}H]DOB. [c] 2C/2A ratio = selectivity for 5-HT$_{2A}$ receptors (i.e., 5-HT$_{2C}$ K_i ÷ 5-HT$_{2A}$ K_i value). [d] Binding data not obtained. [e] Data for compound 2 were previously reported[7] and are included only for comparison.

Table 3. Influence of 5-Position Substituents on the Binding of (2-Methoxyphenyl)-1-aminoethane (**3a**)



	X	R	5-HT$_{2A}$[a] K_i, nM (SEM)	5-HT$_{2A}$[b] K_i, nM (SEM)	5-HT$_{2C}$ K_i, nM (SEM)	2C/2A ratio[c]
3a	-H	-H	>10000	>10000	>10000	–
5	-OCH$_3$	-H	2820 (240)	–[d]	6400 (600)	2
4a	-OH	-H	5960 (1546)	1330 (255)	4860 (260)	1
4b	-Br	-H	1000 (270)	208 (85)	960 (125)	1
4c	-I	-H	700 (110)	211 (55)	1640 (10)	2
4d	-O-CH$_2$-Ph	-H	345 (52)	255 (9)	410 (68)	1
4e	-O-(CH$_2$)$_2$-Ph	-H	600 (54)	440 (160)	1790 (52)	3
4f	-O-(CH$_2$)$_2$-Ph; 4-Br	-H	91 (9)	35 (12)	115 (30)	1
4g	-CH$_2$-Ph	-H	176 (33)	–	230 (7)	1
4h	-(CH$_2$)$_2$-Ph	-H	240 (14)	–	435 (30)	2
4i	-(CH$_2$)$_3$-Ph	-H	20 (3)	30 (11)	220 (50)	11
6	-(CH$_2$)$_3$-Ph	-Me	13 (2)	19 (7)	110 (10)	8
4j	-(CH$_2$)$_4$-Ph	-H	89 (31)	67 (20)	71 (11)	1
4k	-(CH$_2$)$_5$-Ph	-H	110 (20)	–	150 (10)	1
4l	-(CH$_2$)$_3$-*c*C$_6$H$_{11}$	-H	380 (150)	760 (89)	198 (37)	<1
4m	-C≡C-(CH$_2$)$_3$-Ph	-H	295 (35)	–	205 (10)	<1
4n	-Ph	-H	3460 (995)	1520 (390)	2870 (80)	1

[a] 5-HT$_{2A}$ sites labeled using [^{3}H]ketanserin. [b] 5-HT$_{2A}$ sites labeled using [^{3}H]DOB. [c] 2C/2A ratio = selectivity for 5-HT$_{2A}$ receptors (i.e., 5-HT$_{2C}$ K_i ÷ 5-HT$_{2A}$ K_i value). [d] Binding data not obtained.

methylene units (i.e., **4h** and **4g**; K_i = 240 and 176 nM, respectively) decreased affinity by approximately 10-fold. Parallel structural changes in the longer chain analogues, however, seemed to result in roughly parallel changes in affinity when the **3**-series and **4**-series compounds were compared. That is, compared to the 3-phenylpropyl compounds **3d** (K_i = 18 nM) and **4i** (K_i = 20 nM), extension of the alkyl chain by one methylene group (i.e., **3e**; **4j**) decreased affinity by about 3- to 4-fold, further extension by an additional methylene (i.e., **3f**; **4k**) had little effect, replacement of the benzylic methylene by an ether oxygen (i.e., **3h**; **4e**) decreased affinity by about 10- to 30-fold, reduction of the phenyl ring to a cyclohexyl ring (i.e., **3g**; **4l**) decreased affinity by 20-fold, and introduction of an ethynyl group (i.e., **3i**; **4m**) reduced affinity by 15-fold. Replacement of the entire group by a phenyl group (i.e., **3j**; **4n**) decreased affinity by >100-fold.

The significance of these parallel shifts is not fully understood, but suggest that the longer chain members of the two series might bind in such a manner that they orient themselves in a roughly similar fashion, or that their binding is influenced in a similar topographical manner by receptor amino acid residues. Of particular interest were the regioisomers **3d** and **4i** which bind with nearly identical affinities. The structures of **3d** and **4i** were modeled using SYBYL, and conformational searches identified the lowest energy conformers (3.58 and 3.45 kcal/mol for **3d** and **4i**, respectively). To determine if **3d** and **4i** could bind at the receptor in such

a manner that they interact with common amine and aromatic binding sites, the lowest energy conformers from each of the sets were superimposed using MULTIFIT. A good superimposition was achieved (rms = 0.050). Calculated energies of the conformers obtained from the superimposition study (3.73 and 3.66 kcal/mol, respectively) were not very different from their starting energies. Calculated distances between the amine nitrogen atom and the phenylethylamine centroid (C1) were 5.13 and 5.17 Å for **3d** and **4i**, respectively, and the distances between the amine and the distant aromatic centroid (C2) were 9.26 Å for **3d** and 9.25 Å for **4i**. The calculated C1−C2 distances were 6.49 and 6.56 Å, respectively. It would seem possible then, at least in theory, for the terminal amine and the distant phenyl ring of both compounds to avail themselves of common contact points on the receptor structure.

As originally planned, we synthesized an α-methyl or phenylisopropylamine analogue of one of the phenylethylamines. Specifically, we selected **4i**, the highest affinity member of the series, and prepared its α-methyl analogue **6**. Compound **6**, a positional isomer of 2, was found to bind with an affinity (K_i = 13 nM; Table 3) similar to that of its desmethyl counterpart (**4i**; K_i = 20 nM) and comparable to that of 2 (K_i = 8 nM; Table 2).

5-HT$_{2C}$ Radioligand Binding Studies. Most of the compounds in Tables 2 and 3 bind at 5-HT$_{2C}$ receptors with an affinity comparable to, up to about 10-fold lower than, what they display at 5-HT$_{2A}$ receptors. With the exception of **3d** (16-fold 5-HT$_{2A}$ selective), none of the compounds displayed >11-fold selectivity for one population over the other. Given the high amino acid sequence homology between 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors,[11] this lack of selectivity is not surprising.

Functional Activity. 5-HT$_2$ agonists typically bind with higher affinity at sites labeled by a 5-HT$_2$ agonist (e.g., [^{3}H]DOB, [^{125}I]DOI) than at sites labeled by a 5-HT$_2$ antagonist (e.g., [^{3}H]ketanserin), whereas antagonists typically bind with similar affinity regardless of the type of radioligand employed. Hence, a comparison of affinities at the differently labeled sites serves as a preliminary indicator of functional activity. Most of the compounds in Tables 2 and 3 failed to show markedly higher affinity for agonist-labeled (i.e., [^{3}H]-DOB-labeled) sites as compared to antagonist-labeled (i.e., [^{3}H]ketanserin-labeled) sites suggesting that they might be 5-HT$_2$ antagonists. In particular, **6** binds with nearly equal affinity at agonist-labeled 5-HT$_{2A}$ sites (K_i = 19 nM) and antagonist-labeled 5-HT$_{2A}$ sites (K_i = 13 nM). The α-methyl analogue **6** was selected for examination in a PI hydrolysis assay to obtain further evidence for possible 5-HT$_{2A}$ antagonist activity. Serotonin (5-HT) stimulated PI turnover and accumulation of total [^{3}H]-IPs in A7r5 cells was measured in a concentration-dependent manner. The potency of 5-HT (EC_{50} = 329 ± 38 nM; n = 4) and its intrinsic activity (IA = 1.0) compare well with results previously reported by Doyle et al.[12] At a concentration of 10 μM, compound **6** was found to produce little more than baseline effects in this assay. Compound **6** was evaluated as an antagonist, and was found to antagonize 5-HT-induced accumulation of total [^{3}H]-IPs in a concentration-dependent manner (Figure 1) with an equilibrium dissociation constant, K_i, of 244 ± 45 nM (n = 3). A known

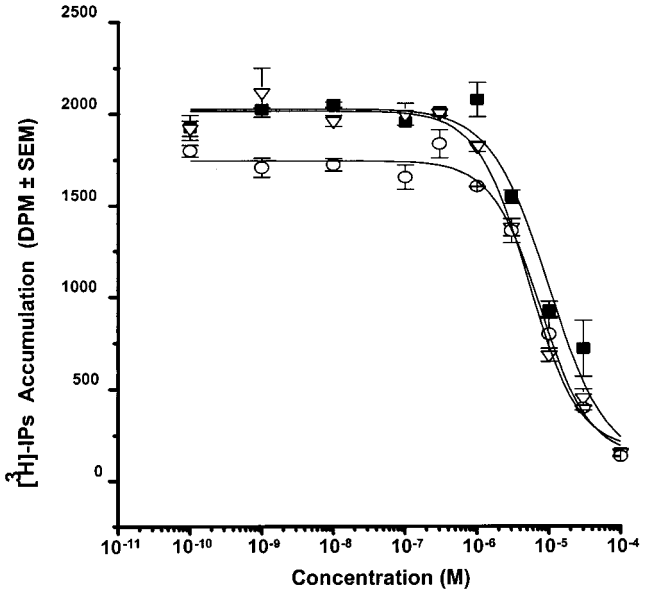


Figure 1. Inhibition of 5-HT-induced PI turnover by **6** in A7r5 cells. The figure depicts results from three separate experiments (mean ± SEM), each conducted in duplicate. The concentration of 5-HT was 10 μM in these experiments.

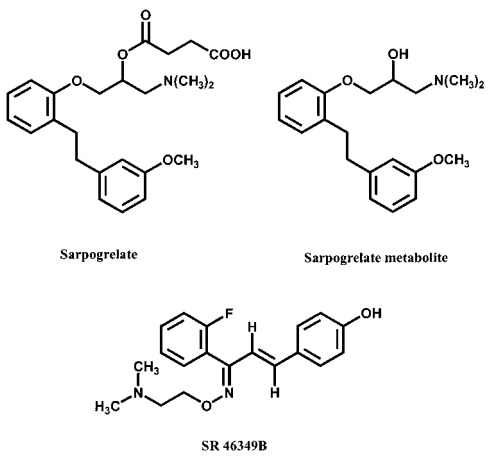


Figure 2. Structures of sarpogrelate and one of its metabolites and of *trans*-4-([3*Z*]3-(2-dimethylaminoethyl)oxyimino-3-(2-fluorophenyl)propen-1-yl]phenol (SR 46349B).

antagonist of 5-HT-induced PI turnover, RS-102221, was used as control (K_i = 34 ± 7 nM; n = 3; data not shown). It would appear, then, that compound **6** possesses 5-HT$_{2A}$ antagonist character.

Compound **6** bears a remote structural similarity to certain other 5-HT$_2$ antagonists, in particular sarpogrelate and SR 46349B (Figure 2). Sarpogrelate (IC_{50} ca. 150 nM) possesses a nonessential ester function and its hydroxy metabolite binds at 5-HT$_2$ receptors with enhanced affinity (IC_{50} = 12.5 nM).[13] Although newer sarpogrelate analogues have been reported with even higher affinity, they have in common a 2-(2-phenylethyl)phenoxypropylamine moiety; that is, they are phenoxypropylamines, not phenylethylamines.[14] SR 46349B (5-HT$_{2A}$ IC_{50} = 5.8 nM; 5-HT$_{2C}$ IC_{50} = 120 nM)[15,16] is another example of a nonphenylethylamine 5-HT$_2$ antagonist containing two phenyl rings separated by an alkyl chain. Although each of these agents is structurally distinct, there is insufficient evidence to eliminate the possibility that compounds such as **6**, the sarpogrelate analogues, and SR 46349B might somehow bind in

Table 4. Calculated Distances for Selected Atoms in the MULTIFIT Superimposition of **3d**, **4i**, and SR 46349B

	energy[a] (kcal/mol)	energy after MULTIFIT (kcal/mol)	distances (Å)[b]		
			N−C1	N−C2	C1−C2
3d	3.58	3.63	5.16	10.04	6.68
4i	3.45	4.37	5.19	10.03	6.70
SR 46349B	9.79	9.97	5.16	10.11	6.76

[a] Energy of lowest energy conformer prior to performing MULTIFIT. [b] C1 for **3d** and **4i** is defined as the aromatic centroid of the phenylethylamine ring whereas C2 is the centroid of the distant phenyl ring. For SR 46349B, C1 is the centroid of the fluorine-containing ring whereas C2 is the centroid of the hydroxyl-containing ring; N is the dimethylamino nitrogen atom.

a similar fashion at 5-HT_2 receptors. To explore this a bit further, we identified the lowest energy conformer of SR 46349B (9.79 kcal/mol). Using MULTIFIT, this conformer was superimposed on **3d** and **4i**. The calculated interatom (i.e., amine and aryl centroid) distances are shown in Table 4. Using FIT ATOMS, superimposition of SR 46349B with **3d** or **4i** gave rms values of 0.037 and 0.044, respectively. Thus, there exists a reasonable possibility that the 3-(phenyl)propyl-substituted phenylethylamines could bind at 5-HT_2 receptors in a manner that mimics SR 46349B. These are fairly flexible molecules, and a number of low energy conformations exist. Nevertheless, the ability to mimic the general structure of known 5-HT_2 antagonists, such as SR 46349B, might provide one explanation for the shift in functional activity of certain phenylalkylamines from agonist to antagonist when the 3-(phenyl)propyl substituent is present.

Summary. The purpose of the present investigation was not to develop novel 5-HT_2 antagonists; indeed, numerous high-affinity and potent 5-HT_2 antagonists already are known.[4] Rather, the intended purpose of this study was to redefine the structure−affinity requirements for the binding of simple phenylethylamines at 5-HT_2 receptors. Phenylethylamines such as DOB (**1a**) and DOI (**1b**) are widely used 5-HT_2 agonists, and it has nearly become dogma that the presence of 2,5-dimethoxy substitution is a critical requirement for high-affinity binding. In contrast to established structure−activity requirements, we have recently demonstrated that the 2,5-dimethoxy substitution pattern can no longer be considered a requirement for phenylethylamines to bind with high affinity at 5-HT_{2A} receptors or to produce 5-HT_2 agonist action.[7] The present study extends these findings and provides further evidence in support of this concept. Compounds such as **4i** and **6** are quite unusual in that they unexpectedly bind at 5-HT_{2A} receptors. Not only do these compounds lack the 2,5-dimethoxy substitution pattern, they are the first simple phenylethylamines to bind at 5-HT_{2A} receptors with low nanomolar affinity even though they lack a 4-position substituent. Moreover, the binding data obtained using [^{3}H]DOB as radioligand indicates that many of these compounds should act as 5-HT_{2A} antagonists; this was verified for compound **6** using a functional assay. Although the antagonist potency of **6** is unremarkable, what *is* remarkable is that it binds at 5-HT_{2A} receptors with high affinity and that it is not a 5-HT_{2A} agonist. The present findings, coupled with the results of an earlier study,[7] argue that when a phenylalkyl substituent is present, structure−affinity relationships established for the binding of phenylethylamines at 5-HT_2 receptors are no longer valid. It might be noted, however, that those compounds violating these previously established relationships seem to lack activity as full agonists. Thus, the possibility exists that agonist phenylethylamines and partial agonist (or antagonist) phenylethylamines are binding at 5-HT_{2A} receptors in a different manner. Furthermore, modeling studies with **3d** and **4i** indicate that it is energetically feasible for the two compounds to assume conformations that result in nearly identical amine-to-centroid distances, and that these structures can assume conformations similar to that of a known 5-HT_2 antagonist. Nevertheless, continued effort is required to definitively establish whether these novel compounds bind at 5-HT_2 receptors in a manner similar to, or different than, that of DOB-like agonists.

Experimental Section

A. Synthesis. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Proton magnetic resonance (^{1}H NMR) spectra were obtained with a Varian Gemini 300 spectrometer, using tetramethylsilane as an internal standard. Infrared spectra were recorded on a Nicolet 5ZDX FT-infrared spectrometer. Elemental analysis was performed by Atlantic Microlab, Inc., and determined values are within 0.4% of theory. Thin-layer chromatography (TLC) was performed using silica gel-coated GHIF plates (250 μ, 2.5 × 10 cm, Analtech, Inc., Newark, DE). Dry THF was obtained by distillation over sodium metal and benzophenone. Dry CH_2Cl_2 was obtained by distillation over phosphorus pentoxide (P_2O_5).

2-(2-Methoxy-4-(3-phenylpropyl)phenyl)-1-aminoethane Oxalate (3d). A solution of **12b** (0.30 g, 1.10 mmol), NH_4OAc (0.09 g, 1.16 mmol), and $MeNO_2$ (10 mL) was heated at reflux under a N_2 atmosphere for 3 h. The solvent was removed under reduced pressure. The resultant residue was extracted with CH_2Cl_2 (2 ×15 mL), washed with H_2O (30 mL), and dried ($MgSO_4$), and the solvent was removed under reduced pressure to give an oil. The oil in dry THF (20 mL) was added in a dropwise manner to a suspension of $LiAlH_4$ (0.10 g, 2.64 mmol) in dry THF (20 mL). The reaction mixture was heated at reflux for 5 h under a N_2 atmosphere, then cooled to 0 °C. The hydride reagent was decomposed by addition of H_2O (1 mL) and 15% NaOH (1 mL). The resulting white solid was collected by filtration and washed with dry THF (25 mL). The solvent was evaporated under reduced pressure to give a yellow oil. The oil was purified by column chromatography (CH_2Cl_2/MeOH, 9:1) and converted to an oxalate salt which was recrystallized from MeOH/anhydrous Et_2O to give 0.24 g (55%) of **3d** as a white solid: mp 161−163 °C. ^{1}H NMR (DMSO-d_6) δ: 8.3 (s, 3H, NH_3^+), 7.4−7.6 (m, 5H, ArH), 7.1 (d, 1H, ArH), 6.9 (s, 1H, ArH), 6.8 (d, 1H, ArH), 3.7 (s, 3H, OCH3), 2.9 (t, 2H, CH_2), 2.7 (t, 2H, CH_2), 2.5 (m, 4H, 2 × CH_2), 1.9 (t, 2H, CH_2). Anal. ($C_{18}H_{23}NO{\cdot}C_2H_2O_4{\cdot}0.75\ H_2O$) C, H, N.

2-(2-Methoxy-4-(5-phenylpentyl)phenyl)-1-aminoethane Oxalate (3f). A solution of **3i** (0.20 g, 0.68 mmol) in MeOH (50 mL) was hydrogenated over 10% Pd/C (0.15 g, 1.43 mmol) for 3 h at 40 psi. The reaction mixture was filtered, and the solvent was removed under reduced pressure to give a white solid, which was then converted to an oxalate salt. The oxalate salt was recrystallized from MeOH/anhydrous Et_2O to give 0.10 g (41%) of the title compound: mp 138−140 °C. ^{1}H NMR (CD_3OD) δ: 6.8−7.2 (m,5H,ArH) 6.4−6.6 (m, 3H, ArH), 3.80 (s, 3H, OCH_3), 2.9 (t, 2H, CH_2), 2.7 (t, 2H, CH_2), 2.3 (m,4H, $2CH_2$) 1.8 (m, 4H, $2CH_2$). Anal. ($C_{20}H_{27}NO{\cdot}C_2H_2O_4{\cdot}H_2O$) C,H,N.

2-(2-Methoxy-4-(2-phenylethoxy)phenyl)-1-aminoethane Oxalate (3h). The title compound was prepared as described for **3d** using **13** as a starting material. The oxalate

salt (0.80 g, 72%) was obtained as white solid after recrystallization from MeOH/anhydrous Et_2O: mp 161−163 °C. ^1H NMR ($CDCl_3$, free base) δ: 7.2−7.3 (m, 5H, ArH), 7.0 (d, 1H, ArH), 6.4 (d, 1H,ArH), 4.1 (t, 2H, CH_2), 3.7 (s, 3H, OCH_3), 3.0 (t, 2H, CH_2), 2.7−2.9 (m, 4H, $2CH_2$). Anal. ($C_{17}H_{21}NO_2 \cdot C_2H_2O_4$) C, H, N.

2-(2-Methoxy-4-(5-phenyl-1-pentnyl)phenyl)-1-aminoethane Oxalate (3i). Compound **3i** was prepared in 28% yield as described for **3d** using **17** as starting material. Compound **3i** was obtained as white solid: mp 167−169 °C (MeOH/anhydrous Et_2O). ^1H NMR (CD_3OD) δ: 6.6−7.2 (m, 5H, ArH) 6.1−6.3 (m, 3H, ArH), 3.90 (s, 3H, OCH_3), 2.9 (t, 2H, CH_2), 2.7 (t, 2H, CH_2), 2.4−2.6 (m, 6H, $3CH_2$). Anal. (C_{20} $H_{23}NO \cdot C_2H_2O_4 \cdot 0.25$ H_2O) C, H, N.

2-(2-Methoxy-5-bromophenyl)-1-aminoethane Oxalate (4b). A solution of 5-bromo-2-methoxybenzaldehyde (**9**) (0.25 g, 1.16 mmol), NH_4OAc (0.10 g, 1.29 mmol), and $MeNO_2$ (10 mL) was heated at reflux under a N_2 atmosphere for 4 h. The solvent was removed under reduced pressure, and the residue was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic portion was washed with H_2O (20 mL) and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The resultant solid was recrystallized from 2-PrOH: mp 121−123 °C. ^1H NMR ($CDCl_3$) δ: 8.2 (d, 1H, CH), 7.9 (d, 1H, CH), 6.8−7.6 (m, 3H, ArH), 3.97 (s, 3H, OCH_3). A slurry of $AlCl_3$ (0.10 g, 0.80 mmol) in dry THF (10 mL) was cooled in an ice bath, and $LiAlH_4$ (0.06 g, 1.60 mmol) was slowly added under a N_2 atmosphere. A solution of above intermediate nitrostyrene (0.20 g, 0.75 mmol) in dry THF (15 mL) was added in a dropwise manner to the above solution at 0 °C. The mixture was allowed to stir overnight at room temperature. The reaction mixture was cooled in an ice bath, and excess alane was destroyed by successive addition of H_2O (1 mL), 10% NaOH (1 mL). The resulting white solid was collected by filtration and washed with dry THF (25 mL). The solvent was evaporated under reduced pressure to give a yellow oil. The oil was purified by column chromatography (CH_2Cl_2/MeOH, 10:1) and converted to an oxalate salt. The oxalate salt was recrystallized from MeOH/anhydrous Et_2O to give 0.14 g (56%) of the title compound: mp 175−177 °C. ^1H NMR ($CDCl_3$, free base) δ: 7.2−7.3 (m, 2H, ArH), 6.7 (d, 1H, ArH), 3.78 (s, 3H, OCH_3), 2.9 (t, 2H,CH_2), 2.72 (t, 2H, CH_2), 2.58 (s, 2H, NH_2). Anal. ($C_9H_{11}BrNO \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

2-(2-Methoxy-5-iodophenyl)-1-aminoethane Oxalate (4c). Following the general method of Sy,[17] 2-(2-methoxyphenyl)ethylamine (1.00 g, 6.61 mmol) was added to a mixture of I_2 (3.35 g, 13.22 mmol) and Ag_2SO_4 (4.12 g, 13.22 mmol) in absolute EtOH (50 mL) at room temperature. The mixture was allowed to stir for 20 h and was filtered. The filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with 5% NaOH solution (40 mL) then with H_2O (50 mL). The organic portion was dried ($MgSO_4$) and evaporated to dryness. The residue was purified by column chromatography (CH_2Cl_2/MeOH, 20:1) to give an oil, and the oil was treated with oxalic acid. The oxalate salt was recrystallized from MeOH/anhydrous Et_2O to give 1.10 g (46%) of **4c**: mp 206−208 °C.[1] H NMR ($CDCl_3$, free base) δ: 7.3−7.4 (m, 2H, ArH), 6.5 (d, 1H, ArH), 3.71 (s, 3H, OCH_3), 2.85 (t, 2H,CH_2), 2.66 (t, 2H, CH_2), 2.01 (s, 2H, NH_2). Anal. (C_9 H_{12} $INO \cdot C_2H_2O_4$) C, H, N.

(±)1-[2-Methoxy-5-(3-phenylpropyl)phenyl]-2-aminopropane Hydrochloride (6). A mixture of **20** (0.45 g, 1.14 mmol), AcOH (45 mL), $HClO_4$ (70%, 0.20 mL), and 10% Pd/C (0.20 g) was shaken on a Parr hydrogenator under 45 psi of hydrogen at room temperature for 5.5 h. The reaction mixture was filtered; the filtrate was diluted by the addition of H_2O (30 mL), and the solution was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic portion was extracted with saturated $NaHCO_3$ (3 × 40 mL) and dried ($MgSO_4$). Evaporation and azeotropic removal of the residual AcOH with hexanes gave 0.43 g (99%) of **21** as a white solid: mp 65−67 °C. ^1H NMR ($CDCl_3$): δ 1.25 (d, 3H, CH_3), 1.89−1.97 (m, 2H, CH_2), 2.58 (t, 2H, CH_2), 2.64 (t, 2H, CH_2), 2.83 (d, 2H, CH_2), 3.84 (s, 3H, OCH_3), 4.06−4.15 (m, 1H, CH), 6.81 (d, 1H, ArH), 6.93 (d, 1H, ArH), 7.05 (dd, 1H, ArH), 7.16−7.31 (m, 5H, Ar−H), 7.44 (bs, 1H, NH). Aqueous 15% NaOH (20 mL) was added to a solution of **21** (0.41 g, 1.08 mmol) in MeOH (20 mL), and the reaction mixture was heated at reflux for 2 h then allowed to cool to room temperature. The MeOH was removed under reduced pressure, and the aqueous portion was extracted with Et_2O (3 × 50 mL). The combined organic portion was dried ($MgSO_4$), and solvent was evaporated under reduced pressure to give a clear oil. The oil was triturated with ethereal HCl to give 0.15 g (43%) of the salt as a white powder: mp 86−88 °C. ^1H NMR (D_2O) δ: 1.08 (d, 3H, CH_3), 1.65−1.69 (m, 2H, CH_2), 2.31 (t, 2H, CH_2), 2.40 (t, 2H, CH_2), 2.64 (dd, 1H, CH_2), 2.81 (dd, 1H, CH_2), 3.42−3.48 (m, 1H, CH), 3.62 (s, 3H, OCH_3), 6.64 (d, 1H, ArH,), 6.78−6.80 (m, 2H, ArH), 7.01−7.16 (m, 5H, ArH). Anal. ($C_{19}H_{26}ClNO \cdot HCl \cdot 0.25$ H_2O) C, H, N.

2-Methoxy-4-(trifluoromethanesulfonyloxy)benzaldehyde (10). Trifluoromethanesulfonic anhydride (1.50 mL, 8.88 mmol) in CH_2Cl_2 (25 mL) was added in a dropwise manner to a solution of 4-hydroxy-2-methoxybenzaldehyde (**7**) (1.18 g, 7.76 mmol) in CH_2Cl_2 (25 mL) and pyridine (1 mL) at 0 °C under a N_2 atmosphere. The reaction mixture was brought to room temperature and allowed to stir for 2 h. The solvents were removed under reduced pressure to give a semisolid material. Purification by column chromatography (hexanes/EtOAc, 5:1) gave 1.10 g (47%) of **10**. ^1H NMR ($CDCl_3$) δ: 3.98 (s, 3H, OCH_3), 6.91 (s,1H, ArH), 6.96 (d, 1H, ArH) 7.93 (d, 1H, ArH), 10.43 (s, 1H, CHO).

2-Methoxy-5-(trifluoromethanesulfonyloxy)benzaldehyde (11). Compound **11** was obtained as a semisolid material in 86% yield by reaction of 5-hydroxy-2-methoxybenzaldehyde (**8**)[9] with trifluoromethanesulfonic anhydride in manner similar to that described for **10**. ^1H NMR ($CDCl_3$) δ: 3.98(s, 3H, OCH_3), 6.92 (s, 1H, ArH), 6.96 (d, 1H, ArH), 7.94 (d, 1H, ArH), 10.43 (s, 1H, CHO).

Method A. 2-Methoxy-4-(3-phenylpropyl)benzaldehyde (12b). A solution of 9-phenyl-propyl-9-BBN (prepared from allylbenzene and 9-BBN at room temperature for 3 h)[7] (3.70 mmol) was added to a mixture of **10** (0.80 g, 2.82 mmol), THF (20 mL), 3 M NaOH (3 mL), and $PdCl_2$(dppf) (0.08 g, 0.08 mmol) under a N_2 atmosphere and heated at reflux for 6 h. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The remaining residue was extracted between EtOAc (4 × 25 mL) and H_2O. The organic portion was dried ($MgSO_4$), and the solvent was removed under reduced pressure to give a yellow oil. Kugelrohr distillation of the oil gave a colorless oil (0.60 g, 84%) at 0.06 mmHg (oven temp: 185−195 °C). ^1H NMR ($CDCl_3$) δ: 10.41 (s, 1H, CHO), 7.75 (d, 1H, ArH), 7.20−7.30 (m, 5H, ArH), 6.81 (s, 1H, ArH), 6.70 (s, 1H, ArH), 3.90 (s, 3H, OCH_3), 2.65−2.72 (m, 4H, CH_2-CH_2), 1.94−2.04 (m, 2H, CH_2). Aldehyde **12b** was used in the preparation of **3d**.

2-Methoxy-4-phenylbenzaldehyde (12h). Phenylboronic acid (0.30 g, 2.46 mmol) was added to a mixture of **10** (0.50 g, 1.76 mmol), THF (20 mL), LiCl (0.01 g), 2 M Na_2CO_3 solution (2.0 mL), and $Pd(PPh_3)_4$ (0.03 g) under N_2 atmosphere and heated at reflux for 10 h. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The remaining residue was extracted between EtOAc (4 × 25 mL) and H_2O. The organic portion was dried ($MgSO_4$), and the solvent was removed under reduced pressure to give an oil. The oil was purified by column chromatography (hexanes/EtOAc, 40:1) to give 0.30 g (79%) of the title compound. ^1H NMR ($CDCl_3$) δ: 10.48 (s, 1H, CHO), 7.88 (d, 1H, ArH), 7.4−7.6 (m, 5H, ArH), 7.1−7.2 (s, 2H, ArH), 3.99 (s, 3H, OCH_3). Aldehyde **12h** was used in the synthesis of **3h**.

Method B. 2-Methoxy-4-(2-phenylethoxy)benzaldehyde (13). Following the general procedure of Leeson et al.,[18] NaOH (0.32 g, 8.00 mmol) in H_2O (25 mL) was added to a stirred suspension of 4-hydroxy-2-methoxybenzaldehyde (**7**) (1.00 g, 6.57 mmol), 2-bromo-1-ethylbenzene (1.30 g, 7.00 mmol), and Adogen-464 (1.00 g) in CH_2Cl_2 (25 mL) at room temperature. After 8 h, the organic portion was removed, washed with H_2O (25 mL) and saturated NaCl solution, and dried ($MgSO_4$), and the solvent was evaporated under reduced

pressure to give 1.20 g (69%) of **13** as an oil. ^{1}H NMR ($CDCl_3$) δ: 10.30 (s, 1H, CHO), 7.6 (d, 1H, ArH), 7.0−7.5 (m, 5H, ArH), 6.4 (d, 1H, ArH), 6.3 (s, 1H, ArH), 4.1 (t, 2H, CH_2), 3.7 (s,3H, OCH_3), 3.4 (t, 2H,CH_2). Compound **13** was used without further characterization in the synthesis of **3h**.

4-Bromo-5-hydroxy-2-methoxybenzaldehyde (15): Method I. According to a procedure described by Ulrich et al.,[9] concentrated H_2SO_4 (20 mL) was slowly added to 4-bromo-2,5-dimethoxybenzaldehyde[19] (2.5 g, 10.20 mmol) with ice cooling, and the mixture was heated at 50−55 °C for 48 h. The reaction mixture was poured into ice, and precipitated oil was extracted with Et_2O (4 × 25 mL). The Et_2O solution was extracted with 5% NaOH solution (75 mL), and the aqueous portion was acidified with dilute HCl and then extracted with Et_2O (4 × 30 mL). The combined Et_2O portions were dried ($MgSO_4$), and evaporation of the solvent gave 1.3 g (55%) of **15**. ^{1}H NMR ($CDCl_3$) δ: 10.35 (s, 1H, CHO). 7.45 (s, 1H, ArH), 7.1 (s, 1H, ArH), 3.88 (s, 3H, OCH_3).

Method II. Anhydrous $SnCl_4$ (3.65 g, 14.00 mmol) was slowly added to a solution of 5-hydroxy-2-methoxybenzaldehyde (**8**)[9] (2.00 g, 13.15 mmol) in CH_2Cl_2 (50 mL); this was followed by the dropwise addition of Br_2 (2.40 g, 15.01 mmol) over a 30-min period. The resulting solution was heated at reflux for 2 h and allowed to stir at room temperature overnight. The suspension was poured onto ice, and the layers were separated. The organic portion was washed with 10% $NaHCO_3$ and H_2O and dried ($MgSO_4$), and the solvent was removed under vacuum to give 1.80 g (59%) of **15**. The products obtained by the two methods were identical by thin-layer chromatography and NMR spectrometry. Compound **15** was used in the preparation of **16** following the procedure described for the synthesis of **13**; aldehyde **16** was used without further characterization in the synthesis of **4f** (Table 1).

Method C. 2-Methoxy-4-(5-phenyl-1-pentynyl)benzaldehyde (17). 5-Phenyl-1-pentyne (0.30 g, 2.00 mmol) was added to a mixture of **10** (0.50 g, 1.76 mmol), CuI (0.01 g), Et_3N (5 mL), $PdCl_2$ dppf (0.01 g, 0.08 mmol), and MeCN (10 mL) under N_2 atmosphere and heated at reflux for 5 h. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The remaining residue was extracted between EtOAc (4 × 50 mL) and H_2O. The organic layer was dried ($MgSO_4$), and the solvent was removed under reduced pressure to give an oil. The oil was purified by flash chromatography (hexanes/EtOAc, 15:1) to give 0.43 g (87%) of the title compound. ^{1}H NMR ($CDCl_3$) δ: 10.5 (s, 1H, CHO), 7.3 (d, 1H, ArH), 7.1−7.3 (m, 5H, ArH), 7.1 (m, 2H, ArH), 3.9 (s. 3H, OCH_3), 2.8 (t, 2H, CH_2), 2.4 (t, 2H, CH_2), 1.9 (m, 2H, CH_2).

(±)*N*-Trifluoroacetyl-1-(2-methoxyphenyl)-2-aminopropane (19). Trifluoroacetic anhydride (1.15 mL, 8.16 mmol) was added all at once to a solution of 1-(2-methoxy-phenyl)-2-aminopropane (**18**) (1.30 g, 7.86 mmol) in dry benzene (10 mL). The reaction mixture was heated at reflux for 2 h, then was allowed to cool to room temperature. The solvents were removed under reduced pressure, and the residue was extracted between Et_2O and 15% NaOH. The ethereal portion was dried ($MgSO_4$) and evaporated under reduced pressure to give a white solid. Recrystallization from absolute EtOH/H_2O gave 1.38 g (67%) of the desired compound: mp 71−73 °C. ^{1}H NMR ($CDCl_3$) δ: 1.26 (d, 3H, CH_3), 2.86 (d, 2H, CH_2), 3.86 (s, 3H, OCH_3), 4.12−4.16 (m, 1H, CH), 6.89−6.96 (m, 2H, ArH), 7.12 (dd, 1H, ArH), 7.26 (dt, 1H, ArH), 7.38 (bs, 1H, NH). The product was used in the preparation of **20** without further characterization.

(±)*N*-Trifluoroacetyl-1-[2-methoxy-5-(3-phenyl-1-propionyl)phenyl]-2-aminopropane (20). At −30 °C (dry ice/acetone) and under a N_2 atmosphere, titanium chloride (1.50 mL, 13.68 mmol) was added to a stirred solution of **19** (1.35 g, 5.17 mmol) in dry CH_2Cl_2 (25 mL), followed by the addition of hydrocinnamoyl chloride (1.30 mL, 8.75 mmol) in dry CH_2Cl_2 (25 mL). The reaction mixture was allowed to warm to room temperature where stirring continued under N_2 for 3 d. The reaction was quenched by pouring the mixture over ice/H_2O (10 g) and stirring for 15 min. The layers were separated. The CH_2Cl_2 portion was washed with H_2O (3 × 25 mL). The aqueous portion was washed with CH_2Cl_2 (3 × 25 mL). The combined organic portions were washed with 5% HCl, H_2O, saturated $NaHCO_3$, saturated NaCl (3 × 25 mL each), then dried ($MgSO_4$). Solvent was removed under reduced pressure to give 0.9 g of a beige solid. Recrystallization from absolute EtOH gave 0.48 g (24%) of the desired compound: mp 94−96 °C. ^{1}H NMR ($CDCl_3$) δ: 1.26 (d, 3H, CH_3), 2.88 (d, 2H, CH_2), 3.05 (t, 2H, CH_2), 3.24 (t, 2H, CH_2), 3.92 (s, 3H, OCH_3), 4.15−4.25 (m, 1H, CH), 6.92 (d, 1H, ArH), 7.20−7.33 (m, 5H, ArH), 7.76 (d, 1H, ArH), 7.89 (dd, 1H, ArH). The product was used in the preparation of **6** without further characterization.

B. Molecular Modeling. The structures of **3d** and **4i** were constructed from standard bond lengths and angles using the SKETCH MOLECULE command in version 6.6 of SYBYL. The structures were energy minimized with the Tripos force field, and charges were calculated using the Gasteiger−Huckel algorithm as implemented in SYBYL. A conformational search was performed using the SYSTEMATIC SEARCH command; rotatable bonds of the phenylpropyl tail were rotated in 30° increments including the starting conformation. The results were analyzed with the SEARCH routine of the SYBYL program. The conformational searches identified >300 conformers with total energies ranging from 3.58 to 18.11 kcal/mol and from 4.04 to 15.73 kcal/mol for **3d** and **4i**, respectively.

The lowest energy conformer in each series was further energy minimized (3.58 and 3.45 kcal/mol, respectively), and superimpositions were performed with the MULTIFIT command using the two aromatic centroids and terminal amine of each compound. The energies were recalculated for each of the individual conformers of the superimposed structure.

The same process was used to construct the structure of SR 46439B and to search for the lowest energy conformations (allowing flexibility only for the rotatable bonds between the two aromatic rings); 171 conformers were identified with energies ranging from 10.16 to 38.12 kcal/mol. Further energy minimization identified a conformer with an energy of 9.79 kcal/mol. MULTIFIT was used to compare this conformer with the lowest energy conformers of **3d** and **4i**.

C. Radioligand Binding Assays. The binding assays were conducted according to published procedures.[7] Briefly, NIH-3T3 cells stably transfected with rat 5-HT_{2A} receptors (generously donated by Dr. David Julius) and A-9 cells stably transfected with rat 5-HT_{2C} receptors (generously donated by Dr. Beth Hoffman) were grown to confluence, suspended in 50 mM TRIS−HCl and centrifuged at 12,000 × *g* for 30 min. The pellet was resuspended in buffer and centrifuged for an additional 20 min. Assay buffer used in the experiments consisted of 50 mM TRIS−HCl, 0.5 mM EDTA, 10 mM $MgCl_2$, and 0.1% ascorbate (pH 7.4). After resuspension in assay buffer, 1 mL membrane aliquots (~10 μg of protein measured by bicinchoninic assay) were added to each tube containing 1 mL of assay buffer with either 0.5 nM [^{3}H]ketanserin (5-HT_{2A}) or 2.0 nM [^{3}H]mesulergine (5-HT_{2C}) and competing test agent. Ketanserin (10 μM, 5-HT_{2A}) and mesulergine (1 μM, 5-HT_{2C}) were used to determine nonspecific binding. Competition experiments were performed in triplicate in a 2.0 mL volume. Membranes were incubated for 30 min at 37 °C, then filtered on Schleicher and Schuell (Keene, NH) glass fiber filters (presoaked in 0.1% polyethyleneimine), and washed with 10 mL of buffer. The filters were counted in an Ecoscint liquid scintillation counter at 40% efficiency. Competition experiments were plotted and analyzed using Graphpad Prism. K_i values were determined from the Cheng−Prusoff equation[20]: $K_i = IC_{50}/(1 + [D]/K_D)$. The results reflect a minimum of three assays.

D. PI Hydrolysis Assay. Rat vascular smooth muscle cells (A7r5; from ATCC, Rockville, MD) were maintained and cultured by standard procedures as previously described.[21] In brief, the cells were grown in Dulbecco's Modified Eagle Medium (DMEM) containing 4.5 g/L glucose and 110 mg/L sodium pyruvate, supplemented with 2 mM L-glutamine, 10 mg/mL gentamicin sulfate and 10% fetal bovine serum. The cells were subcultured at 5−7-day intervals using 0.05%

trypsin/ 0.53 mM EDTA and were used within 10 passages after thawing the frozen cells obtained form the vendor.

Previously published procedures were utilized to measure [^{3}H]inositol phosphates ([^{3}H]-IPs) produced by agonist-activation of phospholipase C in the A7r5 cells.[17,22] In brief, cells grown to confluence in 24-well uncoated plastic plates were exposed for 24−30 h to 1.0−1.5 mCi [^{3}H]myoinositol (18.3 Ci/mmol; Amersham Life Sciences Corp., Arlington Heights, IL) in 0.5 mL of DMEM (serum-free, containing unlabeled myoinositol), corresponding to a specific activity of 37.5 mCi/mmol [^{3}H]myoinositol in the labeling medium. This permitted the labeling of the cell membrane inositol lipid pool with [^{3}H]-myoinositol. Cells were then rinsed once with DMEM/F-12 containing 10 mM LiCl and then incubated with agonist in the same medium for 1 h at 37 °C (triplicate determinations for each concentration). Antagonist effects were determined by adding the antagonist (or the solvent ethanol as a control[23]) for 20 min prior to the 1 h incubation with agonist (serotonin; 5HT) After aspirating the medium, cells were lysed with 1 mL of cold (4 °C) 0.1 M formic acid. The chromatographic separation of radiolabeled components on an AG- 1-X8 column was performed exactly as previously described.[21,22] The total [^{3}H]-IPs eluted with 4 mL of 1.2 M ammonium formate (containing 0.1 M formic acid) was mixed with 15 mL of Ecolume scintillation fluid (ICN Biomedicals, Costa Mesa, CA) and counted on a β-counter at ∼50% efficiency. RS-102221 (8-[5-(2,4-dimethoxy-5−4-trifluoromethylphenylsulfonamido)phenyl-5-oxopentyl]-1,3,8-triazaspiro[4.5]decane-2,4-dione hydrochloride), used as control, was purchased from Tocris Cookson (St. Louis, MO).

E. Data Analysis. The PI turnover functional data were analyzed by the sigmoidal fit function of the Origin Scientific Graphics software (Microcal Software, Northampton, MA) to determine agonist potency (EC_{50}) and intrinsic activity (IA) values. The logistical equation employed for curve fitting was

$$\frac{A_1 - A_2}{1 + (x/x_0)^p} + A_2$$

x_0 = EC_{50} or IC_{50}; p = power; A_1 = minimal Y value; A_2 = maximal Y value. The apparent intrinsic activity (IA) of the agonists was defined relative to the maximal response to the natural full agonist (5-HT) (IA set to 1.0 for full agonist; i.e., 100% activity). Data from functional assays where various antagonist concentrations were used against a single concentration of 5-HT (10 μM) were analyzed using the equation of Cheng−Prusoff.[20] The Cheng−Prusoff equation is as follows: $K_i = IC_{50}/(1 + L/\text{agonist } EC_{50})$, where IC_{50} is the compound concentration causing 50% inhibition of the functional response, L is the agonist concentration used in the PI experiments, and EC_{50} the potency of the agonist used (5-HT).

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