1-[4-(3-Phenylalkyl)phenyl]-2-aminopropanes as 5-HT$_{2A}$ Partial Agonists

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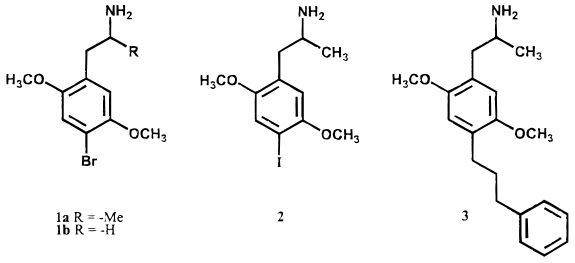
Phenylalkylamines such as 1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane (DOB; **1a**) and its corresponding iodo derivative DOI (**2**) are commonly used 5-HT$_2$ serotonin agonists. Previous studies have established that the 2,5-dimethoxy substitution pattern found in these compounds is optimal for high affinity at 5-HT$_{2A}$ receptors and that substituents at the 4-position can modulate affinity over a wide range. We have previously shown, however, that when the 4-position is substituted with a 3-phenylpropyl substituent (i.e., **3**), the compound binds with an affinity comparable to that of **1a** but that it possesses 5-HT$_{2A}$ antagonist character. The present study examined the structure−affinity relationships of **3**, and the results were very much unexpected. That is, the 2,5-dimethoxy substitution pattern of **3** is not required for high affinity. Either of the two methoxy groups can be removed without untoward effect on affinity, and relocation of the methoxy substituents actually enhances affinity by as much as an order of magnitude. None of the compounds displayed more than 20-fold selectivity for 5-HT$_{2A}$ over 5-HT$_{2C}$ receptors. In addition, several were demonstrated to act as 5-HT$_{2A}$ partial agonists. As such, the results of this study suggest that the structure−affinity relationships of phenylalkylamines as 5-HT$_{2A}$ ligands now be reinvestigated in greater detail.

The 5-HT$_2$ family of serotonin (5-HT) receptors has been implicated in cardiovascular function, thermoregulation, schizophrenia, depression, anxiety, and eating disorders (reviewed in refs 1−3). Considerable literature exists on the search for, and development of, novel 5-HT$_2$ agents—in particular, of novel 5-HT$_2$ antagonists (reviewed in refs 3 and 4). Perhaps one reason there has been less emphasis on 5-HT$_2$ agonists is that agents with demonstrated 5-HT$_2$ agonist character have been shown to be hallucinogenic in humans.[5] Phenylalkylamines such as 1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane (DOB; **1a**) and 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI; **2**) represent well-established 5-HT$_2$ receptor ligands, and [^{3}H]DOB and [^{125}I]DOI have been introduced as radioligands to label 5-HT$_2$ receptors. Both DOB and DOI are considered 5-HT$_2$ agonists,[2] and both are psychoactive in humans.[6] The structure−affinity relationships for the binding of these agents at 5-HT$_2$ receptors have been investigated in some detail.[2,7,8] For example, it has been reported that the presence of the 2,5-dimethoxy pattern is optimal for 5-HT$_2$ binding, and that removal of either of the methoxy groups of DOB results in a dramatic decrease in affinity.[9]

During the course of our investigations with phenylalkylamines, we prepared the 4-(3-phenylpropyl) derivative **3**.[7] Compound **3** was found to bind at 5-HT$_{2A}$ receptors with high affinity (K_i = 10 nM) and with an affinity comparable to that of *R*(−)DOB (K_i = 24 nM).[7,10] Interestingly however, unlike DOB, compound **3** was found to act as a 5-HT$_{2A}$ antagonist in a phosphoinositide hydrolysis assay.[10] As such, compound **3** represented the first example of a DOB-like phenylalkylamine with 5-HT$_2$ antagonist character. It has been proposed that although 5-HT$_{2A}$ agonists and antagonists might share a common amine binding site (i.e., an aspartate moiety in transmembrane helix III), they otherwise appear to utilize different receptor binding features (reviewed in ref 11). The possibility exists, then, that **3** binds at 5-HT$_{2A}$ receptors in a somewhat different fashion than DOB (**1a**). If such is the case, the structure−affinity requirements of **3** might be different than those of DOB. This prompted the present investigation. The purpose of this study, then, was to examine the structure−affinity requirements for the binding of **3**-type compounds at 5-HT$_{2A}$ receptors. Because few compounds display selectivity for 5-HT$_{2A}$ versus 5-HT$_{2C}$ receptors, 5-HT$_{2C}$ binding data were also obtained.



Chemistry

Compound **3** was prepared as previously reported.[7] Compounds **4**−**6** (Scheme 1) were prepared in a similar

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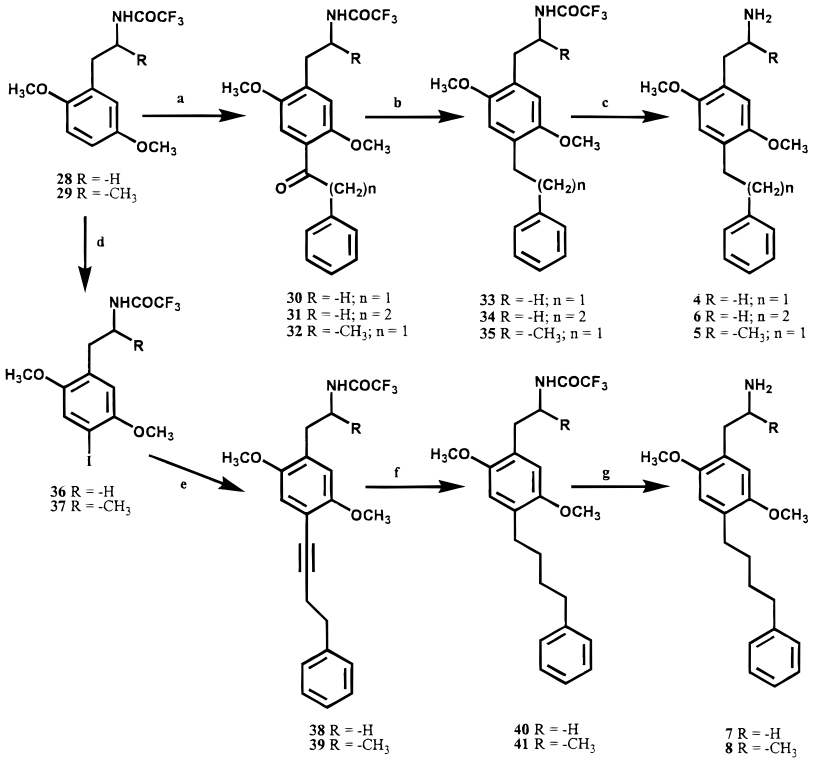
Scheme 1[a]

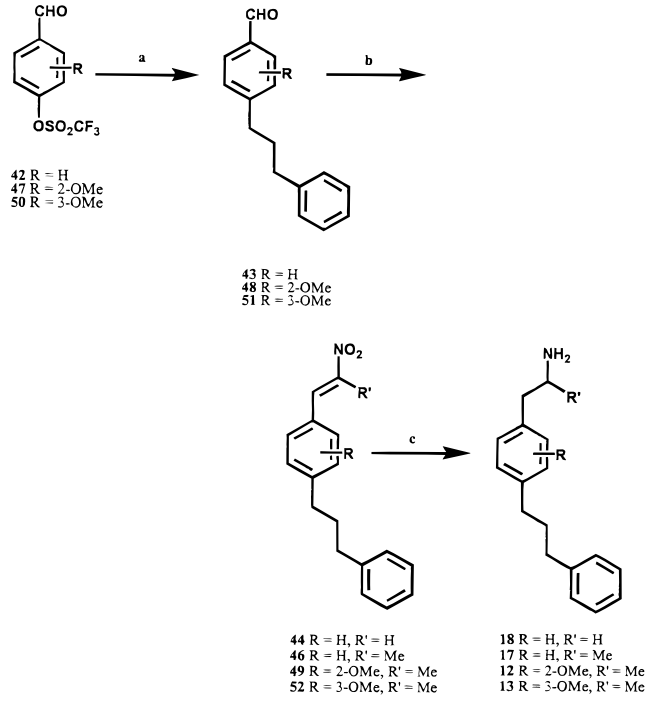


[a] Reagents and conditions: (a) phenylacetyl chloride or hydrocinnamoyl chloride, $TiCl_4$, CH_2Cl_2; (b) H_2, 10% Pd/C, HOAc, 70% $HClO_4$, (c) 15% NaOH, MeOH; (d) ICl, NaI, HOAc, NaOH; (e) 4-(phenyl)butyn-1-yl cuprate, pyridine; (f) H_2, 10% Pd/C, MeOH; (g) 15% NaOH, MeOH.

manner. That is, beginning with the *N*-trifluoroacetyl-protected phenylalkylamines **28** and **29**, Friedel−Crafts acylation provided the 4-acyl analogues **30**−**32**. Acylations of this type have been shown to occurs exclusively at the 4-position.[12] Catalytic reduction of the ketone and subsequent deprotection afforded compounds **4**−**6**. Compounds **7** and **8** were prepared in a somewhat different manner (Scheme 1). The phenylalkylamines **28** and **29** were iodinated to give **36** and **37**, respectively. We have previously reported the synthesis of **37**.[13] The iodo derivatives were reacted with 4-(phenyl)butyn-1-yl cuprate to give the corresponding alkynes **38** and **39**, which were then catalytically reduced to **40** and **41**, respectively. Deprotection afforded compounds **7** and **8**. Compounds **9** and **10**, chloro and methoxy analogues of **3**, were obtained using a reaction similar to that used for the preparation of **4** except that a Wolff−Kishner reduction was used to reduce the intermediate ketone leading to **9**.

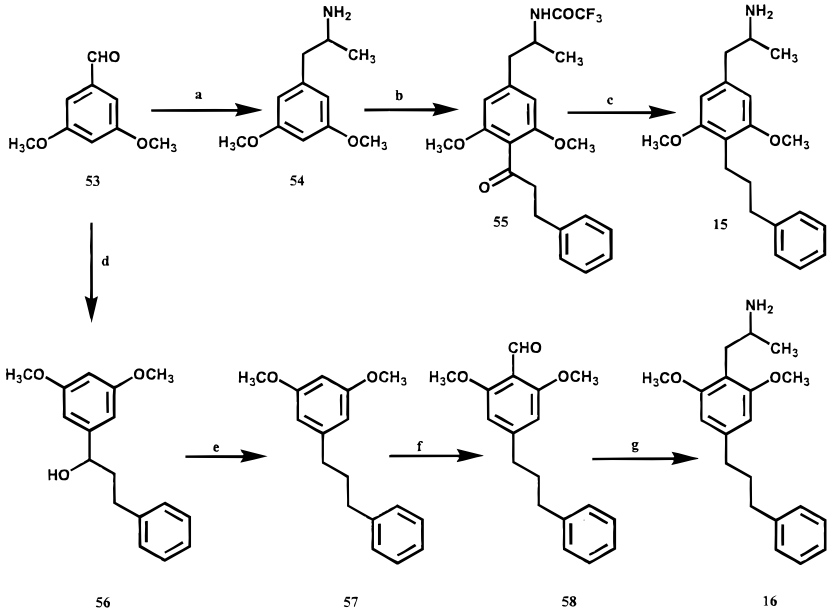
Compounds **12**, **13**, **17**, and **18** were prepared via a common route (Scheme 2) employing a Suzuki-type reaction[14] with the appropriately substituted triflates (i.e., **42**, **47**, or **50**) as starting material. Reaction of the triflates with 9-(3-phenylpropyl)-9-BBN (**45**) and 1,1′-bis(diphenylphosphinoferrocene)Pd afforded phenylpropylbenzaldehydes **43**, **48**, and **51**. The benzaldehyde derivatives were converted to their nitrostyrenes and reduced with $LiAlH_4$ to the required amines. Compound **14** was obtained by introduction of a 3-(3-phenylpropyl) group to 1,2-dimethoxybenzene, followed by formylation and elaboration to the amine as described above. In contrast, compound **15** was prepared directly from the preformed phenylisopropylamine **54** by an acylation−reduction reaction (Scheme 3). Compound **54** was obtained from 3,5-dimethoxybenzaldehyde (**53**) via a literature procedure.[15] Compound **53** was also used to obtain the phenylpropyl derivative **57** which was subsequently formylated and elaborated to the desired amine **16** (Scheme 3).

Scheme 2[a]



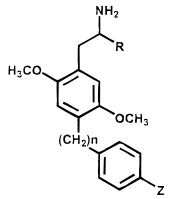
[a] Reagents and conditions: (a) **45**, 1,1′-bis(diphenylphosphinoferrocene)Pd, THF, NaOH; (b) CH_3NO_2 or $C_2H_5NO_2$, NH_4OAc, Δ; (c) $LiAlH_4$, THF, Δ.

Scheme 3[a]



[a] Reagents and conditions: (a) *i.* $C_2H_5NO_2$, NH_4OAc, Δ; *ii.* $LiAlH_4$, THF, Δ; (b) *i.* $(CF_3CO)_2O$, CH_2Cl_2; *ii.* hydrocinnamoyl chloride, $TiCl_4$, CH_2Cl_2; (c) *i.* H_2, 10% Pd/C, 70% $HClO_4$, HOAc; *ii.* 15% NaOH, MeOH; (d) Mg, $PhCH_2CH_2Br$, Et_2O; (e) TMSCl, MeCN, NaI, Et_2O; (f) nBuLi, DMF, THF; (g) *i.* $C_2H_5NO_2$, NH_4OAc, Δ; *ii.* $LiAlH_4$, THF, Δ.

Table 1. 5-HT_{2A} and 5-HT_{2C} Serotonin Receptor Binding Data for Derivatives of **3**



	n	R	Z	receptor affinity; K_i, nM (SEM) 5-HT_{2A}	5-HT_{2C}	5-HT_{2A} selectivity[a]
4	2	-H	-H	37 (3)	76 (6)	2.0
5	2	-Me	-H	95 (5)	140 (20)	1.5
6	3	-H	-H	150 (15)	28 (2)	0.2
3	3	-Me	-H	30 (3)	50 (1)	1.7
7	4	-H	-H	115 (45)	25 (6)	0.2
8	4	-Me	-H	8 (1)	6 (1)	0.8
9	3	-Me	-Cl	12 (3)	16 (1)	1.3
10	3	-Me	-OMe	28 (3)	24 (1)	0.9

[a] Selectivity represented by 5-HT_{2C} K_i value/5-HT_{2A} K_i value.

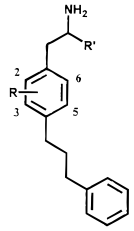
Results and Discussion

5-HT_{2A} Receptor Binding. The study began by examining the role of chain length and the necessity of the α-methyl group on the 5-HT_{2A} affinity of **3** (K_i = 30 nM) (Table 1). Shortening the propyl chain to an ethyl chain (i.e., **5**) reduced affinity by about 3-fold whereas lengthening the chain to a *n*-butyl group (i.e., **8**) enhanced affinity by about the same amount. The α-methyl substituent seems to have a different effect depending upon chain length. That is, demethylation of **5** (i.e., **4**) resulted in a 3-fold increase in affinity, whereas demethylation of **3** (i.e., **6**) and demethylation of **8** (i.e., **7**) decreased affinity by nearly 5-fold and 15-fold, respectively. Because the longer chain compound **8** displayed slightly higher affinity than **3**, it was thought that adding some lipophilic character to **3** in the form of a lipophilic chloro group (i.e., compound **9**) might enhance affinity whereas introduction of a methoxy group (i.e., compound **10**) might have no effect. These compounds would additionally assist in exploring the influence of varied electronic character of the terminal phenyl ring on 5-HT_2 binding. Both **9** (K_i = 12 nM) and **10** (K_i = 28 nM) were found to bind with an affinity comparable to that of **3**. All of the changes shown in Table 1 had minimal effect on 5-HT_{2A} receptor affinity.

Of major interest was the role of the 2,5-dimethoxy groups of **3** on 5-HT_{2A} affinity because this substitution pattern is generally considered optimal for high affinity. Interestingly, removal of either the 5-methoxy group (i.e., **12**; K_i = 8 nM) or removal of the 2-methoxy group (i.e., **13**; K_i = 17 nM) resulted in retention of affinity (Table 2). Even relocation of the two methoxy groups to the 2,3-, 3,5-, and 2,6-positions (i.e., compounds **14**−**16**; K_i = 4 nM, 4 nM, and 3 nM, respectively) was tolerated. In fact, the latter three compounds displayed approximately 10-fold higher affinity than **3** itself. Furthermore, removal of the two methoxy groups (i.e., **17**; K_i = 78 nM) only halved affinity, whereas the desmethoxy analogue of **6** (i.e., **18**; K_i = 60 nM) displayed twice the affinity of its parent (**6**, K_i = 150 nM). Apparently, the presence and location of the methoxy groups are not as important for the binding of **3** as they appear to be for DOB (**1a**)-type compounds.

Because most of the structure−affinity relationships for DOB-type compounds were originally formulated a decade ago on the basis of rat brain-homogenate binding data, and because the present investigation employed cloned 5-HT_{2A} receptors, the affinities of some known DOB analogues were reinvestigated. Table 3 shows that DOB (**1a**; K_i = 32 nM) binds with high affinity at these 5-HT_{2A} receptors and that removal of the α-methyl group (i.e., **1b**; K_i = 16 nM) has little effect on affinity. Removal of the 4-bromo group of **1a** and **1b**, as in **19** and **20**, reduces affinity by about 150- to 200-fold,

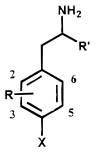
Table 2. 5-HT_{2A} and 5-HT_{2C} Serotonin Receptor Binding Data for Methoxy-Modified Derivatives of **3**



	R	R′	receptor affinity; K_i, nM (SEM) 5-HT_{2A}	5-HT_{2C}	5-HT_{2A} selectivity[a]
3	2,5-Di-OMe	-Me	30 (3)	50 (1)	1.7
12	2-OMe	-Me	8 (1)	89 (1)	11.1
13	5-OMe[b]	-Me	17 (1)	135 (6)	7.9
14	2,3-Di-OMe	-Me	4 (1)	79 (8)	19.8
15	3,5-Di-OMe	-Me	4 (1)	40 (2)	10.0
16	2,6-Di-OMe	-Me	3 (1)	39 (2)	13.0
17	H	-Me	78 (6)	530 (19)	6.8
18	H	-H	60 (6)	525 (65)	8.9

[a] Selectivity represented by 5-HT_{2C} K_i value/5-HT_{2A} K_i value. [b] The 5-methoxy derivative actually represents the 3-methoxy-substituted compound; the present terminology is used for ease of discussion.

Table 3. 5-HT_{2A} and 5-HT_{2C} Serotonin Receptor Binding Data for Simple Monomethoxy, Dimethoxy, and Nonmethoxy Phenylalkylamine Analogues



	R	R′	X	receptor affinity; K_i, nM (SEM) 5-HT_{2A}	5-HT_{2C}
1a	2,5-Di-OMe	-Me	Br	32 (4)	64 (12)
1b	2,5-Di-OMe	-H	-Br	16 (1)	190 (90)
19	2,5-Di-OMe	-Me	-H	4 720 (1,150)	>10 000
20	2,5-Di-OMe	-H	-H	3 000 (410)	5 520 (390)
21	2-OMe	-Me	-H	>10 000	>10 000
22	5-OMe[a]	-Me	-H	>10 000	>10 000
23	2,3-Di-OMe	-Me	-H	4 280 (460)	>10 000
24	3,5-Di-OMe	-Me	-H	>10 000	>10 000
25	3,5-Di-OMe	-Me	-Br	210 (45)	570 (110)
26	2,6-Di-OMe	-Me	-H	>10 000	>10 000
27	H	-Me	-H	>10 000	>10 000

[a] The 5-methoxy derivative actually represents the 3-methoxy-substituted compound; the present terminology is used for ease of discussion.

respectively. Removal of either of the methoxy groups reduces the affinity of **19**; that is, the two individual monomethoxy derivatives (i.e., **21** and **22)** lack affinity for 5-HT_{2A} receptors. Relocation of the 2,5-dimethoxy groups to the 3,5- or 2,6-positions (i.e., **24**, **26**; K_i >10 000 nM), and removal of both methoxy groups (i.e., **27**; K_i >10 000 nM), essentially abolishes affinity. We previously reported that **27** binds with a K_i = 43 000 nM.[9] Reincorporation of a 4-bromo group (i.e., **25**) enhances the affinity of **24**. In general, these results are qualitatively similar to what we have previously reported: (a) monomethoxy phenylalkylamine derivatives lack affinity, (b) dimethoxy derivatives lack affinity or bind only with low affinity, and (c) substitution at the 4-position of 2,5-dimethoxy derivatives modulates affinity.[2,7] What is remarkable about the present results is the influence of the 4-(3-phenylpropyl) group on 5-HT_{2A} affinity. Incorporation of this group enhances the affinity of the monomethoxy-, dimethoxy-, and even the unsubstituted phenylalkylamines. In particular, each of the following conversions enhances affinity by more than 1000-fold: **21** → **12** (1,250-fold), **23** → **14** (1070-fold), **24** → **15** (2500-fold), and **26** → **16** (>3000-fold). For the 4-(3-phenylpropyl) series, 2,5-dimethoxy substitution cannot be considered optimal. Monomethoxy derivative **12**, and dimethoxy derivatives **14**−**16**, bind with K_i values of <10 nM. Even the nonmethoxy analogues **17** and **18** bind with affinities not much less than that of **3**.

5-HT_{2C} Receptor Binding. For those compounds examined in the present study, the structure−affinity requirements for 5-HT_{2C} binding are not very different from those for 5-HT_{2A} binding. Consequently, none of the compounds displayed dramatic selectivity for one population over the other. Compound **3** binds at 5-HT_{2C} receptors with high affinity (K_i = 50 nM) and with <2-fold selectivity for 5-HT_{2A} receptors (Table 1). Shortening the propyl chain by a single methylene group (i.e., **5**) decreases affinity by about 3-fold, whereas lengthening the chain by a methylene group (i.e., **8**) enhances affinity by about 8-fold. Removal of the α-methyl group has relatively little effect on 5-HT_{2C} affinity. The only change that seems to have less effect on 5-HT_{2C} binding than on 5-HT_{2A} binding is the influence of the methoxy groups. For example, although removal of one of the methoxy groups of **3** has little effect on 5-HT_{2C} affinity, relocation of the 2,5-methoxy groups to the 2,3-, 3,5-, or 2,6-positions does not show the affinity-enhancing effect that it did at 5-HT_{2A} receptors. Consequently, compounds **14**−**16** display about 10- to 20-fold selectivity for 5-HT_{2A} receptors. Nevertheless, selectivity is not remarkable.

PI Hydrolysis. Several compounds were examined for their 5-HT_{2A} functional activity in a PI hydrolysis assay, and all showed agonist actions. Compounds examined (followed by apparent intrinsic activity) include the following: **3** (0.71 ± 0.08), **12** (0.63 ± 0.04), **13** (0.90 ± 0.02), **15** (1.09 ± 0.02), and **17** (0.48 ± 0.08). That is, these compounds behaved either as partial or full agonists relative to 5-HT. Because we had previously demonstrated that **3** can act as an antagonist, this effect was examined in greater detail. Several concentrations of **3** were examined (Figure 1); 100 nM **3** was without significant agonist activity, and even 1 μM **3** produced only about 25% of the maximal 5-HT effect. However, at a concentration of 10 μM, **3** produced 71% of the maximal agonist effect. It would appear, then, that **3** is a 5-HT_{2A} partial agonist. However, 10 μM **3** plus 10 μM ketanserin (a 5-HT_2 antagonist that reduces the effect of 10 μM 5-HT to basal levels; data not shown), still produced 30% of the maximal possible effect (Figure 1). These results suggest that **3** is producing its effect by a combination of a 5-HT_2 mechanism plus some other ketanserin-insensitive mechanism. Because **15** appeared to be a full agonist, it too was examined in the absence and presence of ketanserin (Figure 2). At first glance, it would seem that **15** is a full agonist; that is, 10 μM **15** produced an effect comparable to that produced by 10 μM 5-HT. However, 10 μM **15** plus 10 μM ketanserin produced 43% of the maximal possible effect.

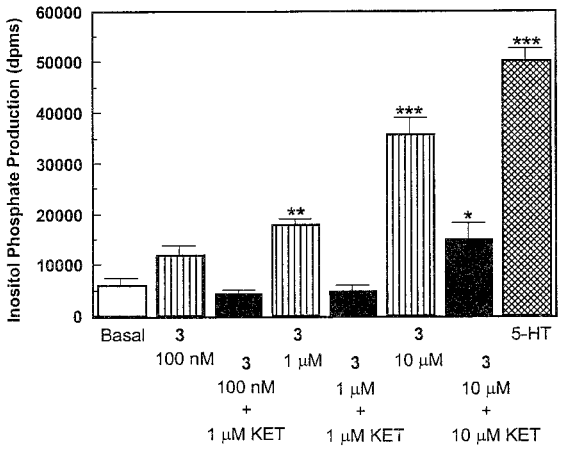


Figure 1. Effect (±SEM) of compound **3**, alone and in combination with the 5-HT_2 antagonist ketanserin (KET), on PI turnover. Basal = basal level; 5-HT = 10 μM 5-HT. The response to 5-HT was completely blocked by 10 μM ketanserin (data not shown). *p < 0.05; **p < 0.01; ***p < 0.001 relative to Basal (Student's t-test).

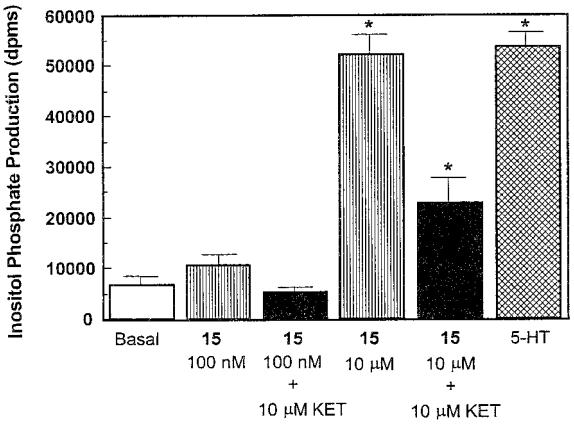


Figure 2. Effect (±SEM) of compound **15**, alone and in combination with the 5-HT_2 antagonist ketanserin (KET), on PI turnover. Basal = basal level; 5-HT = 10 μM 5-HT. The response to 5-HT was completely blocked by 10 μM ketanserin (data not shown). *p < 0.001 relative to Basal (Student's t-test).

Like **3**, **15** seems to be producing its agonist effects via more than one mechanism. Compounds **3** and **15** might best be classified as partial agonists in this assay.

Summary. Although 2,5-dimethoxy substitution is common to DOB (**1a**) and DOI-type 5-HT_2 agonists and is thought to be an important factor for high affinity, the present study provides the first evidence that this dimethoxy pattern is not required for binding at this receptor population. 1-[2,5-Dimethoxy-4-(3-phenylpropyl)phenyl]-2-aminopropane (**3**; K_i = 30 nM) binds at 5-HT_{2A} receptors with an affinity comparable to that of DOB (K_i = 32 nM). However, unlike what is seen with DOB,[9] removal of either one of the two methoxy groups has little effect on 5-HT_{2A} affinity. In fact, removal of either of the two methoxy groups actually enhances affinity. In addition, the location of these methoxy groups is seemingly unimportant for binding. That is, the 2,3-, 3,5-, and 2,6-dimethoxy analogues of **3** bind with up to 10 times the affinity of **3**. Even removal of both methoxy groups has little effect on affinity. Stereochemistry (i.e., optical isomerism and regioisomerism) may play a role in the binding of some of these compounds; although this remains to be investigated in detail, it is unlikely that stereochemical differences by themselves can account for the observed variation in 5-HT_{2A} affinity. None of the investigated compounds displayed >20-fold selectivity for 5-HT_{2A} versus 5-HT_{2C} receptors. Several of the compounds were examined in a 5-HT_{2A} PI hydrolysis assay and were found to behave as partial agonists. It now can be concluded that when a 4-(3-phenylpropyl) substituent is present, the resulting phenylalkylamine derivatives defy currently established DOB-like structure−affinity relationships for 5-HT_{2A} binding. The same may be true of certain other 4-alkyl- or 4-(arylalkyl)-substituted derivatives, but this remains to be determined. In retrospect, because the presence of 2,5-dimethoxy substitution now has been demonstrated to result in compounds that retain 5-HT_2 agonist character, the structure−activity relationships of phenylalkylamines require reinvestigation.

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. Unless otherwise stated, amine salts were obtained and purified by the following standard methods: (a) hydrochlorides: by the dropwise addition of a saturated, anhydrous solution of ethereal HCl into a cold solution of the free base in anhydrous ether until addition of ethereal HCl did not produce further precipitate; (b) oxalates: by the dropwise addition of a solution of an excess of oxalic acid in anhydrous ether into a cold solution of the free base in anhydrous ether. Addition was terminated when oxalic acid failed to produce more precipitate. Thin-layer chromatography (TLC) was performed using silica gel-coated GHIF plates (250 μm, 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). Most compounds shown in Table 3 were available from previous studies or were resynthesized using methods we had reported earlier and, with the exception of **27** sulfate, were used as their HCl salts.

2-[2,5-Dimethoxy-4-(2-phenylethyl)phenyl]-1-aminoethane HCl (4). A solution of **33** (0.18 g, 0.47 mmol) in MeOH (15 mL) and 15% NaOH (15 mL) was heated at reflux for 2 h. The MeOH was removed under reduced pressure, and the basic solution was cooled to room temperature and extracted with Et_2O (3 × 30 mL). The ethereal solution was dried ($MgSO_4$) and evaporated under reduced pressure. The HCl salt was formed and recrystallized from 2-PrOH to give 0.07 g (46%) of **4** as a white powder; mp 197−198 °C. ^{1}H NMR (D_2O): δ 2.86−2.89 (m, 6H, CH_2), 3.13 (t, 2H, CH_2), 3.66 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 6.72 (s, 1H, Ar−H), 6.85 (s, 1H, Ar−H), 7.14−7.28 (m, 5H, Ar−H); IR (KBr pellet): 2962 (NH^+) cm^{-1}. Anal. Calcd. for ($C_{18}H_{24}ClNO_2$) C, H, N.

(±)1-[2,5-Dimethoxy-4-(2-phenylethyl)phenyl]-2-aminopropane HCl (5). Compound **5** was prepared in 47% overall yield from **35** in the same manner used for the preparation of **4**. The HCl salt was recrystallized from 2-PrOH to give 0.10 g of **5**; mp 165−167 °C. ^{1}H NMR (D_2O): δ 1.20 (d, 3H, CH_3), 2.79−2.84 (m, 6H, CH_2), 3.50−3.57 (m, 1H, CH), 3.64 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 6.70 (s, 1H, Ar−H), 6.81 (s, 1H, Ar−H), 7.12−7.24 (m, 5H, Ar−H); IR (KBr pellet): 2892 (NH^+) cm^{-1}. Anal. Calcd. for ($C_{19}H_{26}ClNO_2$) C, H, N.

2-[2,5-Dimethoxy-4-(3-phenylpropyl)phenyl]-1-aminoethane HCl (6). Compound **6** was prepared from **34** in the same manner used for the synthesis of **4**. The HCl salt was recrystallized from 2-PrOH to give 0.08 g (45%) of the desired

compound as a white powder; mp 155−156 °C. ^{1}H NMR (D_2O): δ 1.80 (t, 2H, CH_2), 2.52−2.61 (m, 4H, CH_2CH_2), 2.87−2.88 (m, 2H, CH_2), 3.13 (t, 2H, CH_2), 3.71 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 6.81−6.85 (m, 2H, Ar−H), 7.15−7.29 (m, 5H, Ar−H); IR (KBr pellet): 2955 (NH^+) cm^{-1}. Anal. Calcd. for ($C_{19}H_{26}ClNO_2$) C, H, N.

2-[2,5-Dimethoxy-4-(4-phenylbutyl)phenyl]-1-aminoethane HCl (7). A solution of **40** (0.20 g, 0.49 mmol) in 15% NaOH (15 mL) and MeOH (10 mL) was heated at reflux for 2 h. The MeOH was removed under reduced pressure and the aqueous solution was extracted with Et_2O (4 × 50 mL). The ethereal solution was dried ($MgSO_4$), and solvent was removed under reduced pressure. The oil was dissolved in anhydrous Et_2O and ethereal HCl was added to form the salt, which was recrystallized from 2-PrOH to give 0.08 g (47%) of **7** as a white powder; mp 172−174 °C. ^{1}H NMR (D_2O): δ 1.30−1.45 (m, 4H, CH_2CH_2), 2.30−2.40 (m, 4H, CH_2CH_2), 2.79 (t, 2H, CH_2), 3.04 (t, 2H, CH_2), 3.48 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 6.48 (s, 1H, Ar−H), 6.72 (s, 1H, Ar−H), 6.91−7.03 (m, 5H, Ar−H); IR (KBr pellet): 2936 (NH^+) cm^{-1}. Anal. Calcd. for ($C_{20}H_{28}ClNO_2$) C, H, N.

(±)1-[2,5-Dimethoxy-4-(4-phenylbutyl)phenyl]-2-aminopropane HCl (8). Compound **8** was obtained from **41** in the same manner used for the synthesis of **7**. The resulting crude solid material was recrystallized from absolute EtOH to give 0.40 g (18%) of the desired compound; mp 111−113 °C. ^{1}H NMR ($CDCl_3$): δ 2.93 (t, 2H, CH_2), 3.57 (t, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.32 (s, 2H, CH_2), 6.76 (s, 1H, Ar−H), 6.99 (bs, 1H, NH), 7.21−7.31 (m, 6H, Ar−H); IR (film): 3314 (NH), 1709 (C═O, amide), 1671 (C═O, ketone) cm^{-1}. Anal. Calcd. for ($C_{20}H_{20}F_3NO_4$) C, H, N.

(±)1-[2,5-Dimethoxy-4-(3-(4-chloro)phenylpropyl)phenyl]-2-aminopropane HCl (9). Compound **9** was prepared from **29**[13] in a manner similar to that of compound **4**, except that a Wolff−Kishner reduction was used to reduce the intermediate ketone. Acylation of **29** with 3-(4-chlorophenyl)-propionyl chloride afforded (±)*N*-trifluoroacetyl-1-[2,5-dimethoxy-4-(3-(4-chloro)phenylpropionyl)phenyl]-2-aminopropane in 68% yield; mp 160−163 °C after recrystallization from aqueous EtOH. This compound (1.16 g, 2.54 mmol) in diethylene glycol (10 mL) was added to a preheated (150 °C) solution of KOH (4.2 g) and 97% hydrazine (7.3 mL) in diethylene glycol (18 mL). The stirred mixture was heated at this temperature for 2 h; H_2O (10 mL) and MeOH (10 mL) were added, and the reaction mixture was heated at reflux overnight. Once cool, the reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL); the organic solvent was removed under reduced pressure, and the oily product was purified by distillation (bp 90 °C, 0.05 mmHg) to give 0.52 g (59%) of the target compound as its free base. The product was converted to its HCl salt, **9**; mp 164−166 °C after recrystallization from an absolute EtOH/anhydrous Et_2O mixture. ^{1}H NMR (DMSO-d_6): δ 1.10 (d, 3H, CH_3), 1.85 (m, 2H, CH_2), 2.70 (m, 6H, CH_2), 3.51 (m, 1H, CH), 3.70 (s, 6H, OCH_3), 6.80 (s, 2H, ArH), 7.25 (m, 4H, ArH), 8.10 (bs, 3H, NH^+); IR (KBr pellet): 2931 (NH^+) cm^{-1}. Anal. Calcd. for ($C_{20}H_{27}Cl_2NO_2$) C, H, N.

(±)1-[2,5-Dimethoxy-4-(3-(4-methoxy)phenylpropyl)-phenyl]-2-aminopropane HCl (10). Compound **10** was prepared from **29**[13] in the same manner used for the synthesis of **4**. Acylation of **29** with 3-(4-methoxyphenyl)propionyl chloride afforded (±)*N*-trifluoroacetyl-1-[2,5-dimethoxy-4-(3-(4-methoxy)phenylpropionyl)phenyl]-2-aminopropane (**11**) in 16% yield after distillation; bp 105−110 °C (0.05 mmHg). Catalytic reduction of **11** and removal of the protecting group afforded an 85% yield of the target compound (free base) as a yellow oil. A sample was converted to the HCl salt; mp 158−160 °C after recrystallization from an absolute EtOH/anhydrous Et_2O mixture. ^{1}H NMR (DMSO-d_6): δ 1.35 (d, 3H, CH_3), 1.85 (m, 2H, CH_2), 2.60 (t, 4H, CH_2), 2.95 (m, 2H, CH_2), 3.65 (m, 1H, CH), 4.80 (s, 9H, OCH_3), 6.60 (s, 1H, ArH), 6.70 (s, 1H, ArH), 6.82 (d, 2H, ArH), 7.10 (d, 2H, ArH), 8.30 (bs, 3H, NH^+); IR (KBr pellet): 2935 (NH^+) cm^{-1}. Anal. Calcd. for ($C_{21}H_{30}ClNO_3$) C, H, N.

(±)1-[2-Methoxy-4-(3-phenylpropyl)phenyl]-2-aminopropane HCl (12). Compound **12** was prepared from **49** in the same manner as **18**. The crude free amine was converted immediately to the HCl salt using ethereal HCl. The white solid was recrystallized from 2-PrOH to give 0.19 g (45%) of **12**; mp 134−136 °C. ^{1}H NMR (D_2O): δ 1.17 (d, 3H, CH_3), 1.77−1.85 (m, 2H, CH_2), 2.47−2.53 (m, 4H, CH_2, CH_2), 2.79 (d, 2H, CH_2), 3.49−3.55 (m, 1H, CH), 3.70 (s, 3H, OCH_3), 6.69 (d, 1H, Ar−H), 6.75 (s, 1H, Ar−H), 7.02 (d, 1H, Ar−H), 7.10−7.25 (m, 5H, Ar−H); IR (KBr pellet): 2922 (NH^+) cm^{-1}. Anal. Calcd. for ($C_{19}H_{26}ClNO$) C, H, N.

(±)1-[3-Methoxy-4-(3-phenylpropyl)phenyl]-2-aminopropane HCl (13). Compound **13** was prepared from **52** using the same procedure used for the synthesis of **18.** The HCl salt was obtained and recrystallized from 2-PrOH/anhydrous Et_2O to give 0.17 g (23%) of **13**; mp 107−109 °C. ^{1}H NMR (D_2O): δ 1.12 (d, 3H, CH_3), 1.65 (quintet, 2H, CH_2), 2.34−2.40 (m, 4H, CH_2, CH_2), 2.66 (dd, 1H, CH_2), 2.89 (dd, 1H, CH_2-b), 3.43 (m, 1H, CH), 3.60 (s, 3H, OCH_3), 6.59 (d, 1H, Ar−H), 6.74 (s, 1H, Ar−H), 6.83 (d, 1H, Ar−H), 7.03 (m, 5H, Ar−H); IR (KBr pellet): 2939.6 (NH^+) cm^{-1}. Anal. Calcd. for ($C_{19}H_{26}ClNO$) C, H, N.

(±)1-[2,3-Dimethoxy-4-(3-phenylpropyl)phenyl]-2-aminopropane Hemioxalate (14). At 0 °C and under N_2, dry THF (5 mL) was added to $LiAlH_4$ (0.14 g, 3.67 mmol), followed by the addition of nitropropene **59** (0.29 g, 0.85 mmol) in dry THF (7 mL). The reaction mixture was heated at reflux for 1 h, then cooled to 0 °C. Excess $LiAlH_4$ was decomposed by the addition of H_2O (0.2 mL), 10% NaOH (0.2 mL), and H_2O (1 mL). The salts were removed by filtration, and the filtrate was diluted with Et_2O (25 mL) and dried ($MgSO_4$); removal of the solvents under reduced pressure gave a clear oil. Preparation of the HCl salt was unsuccessful. The oxalate salt was prepared and recrystallized from 2-PrOH to give 0.05 g (16%) of **14**; mp 228−230 °C. ^{1}H NMR (DMSO-d_6): δ 1.01 (d, 3H, CH_3), 1.77−1.88 (m, 2H, CH_2), 2.53−2.72 (m, 6H, CH_2, CH_2, CH_2), 3.13−3.21 (m, 1H, CH), 3.65 (bs, 3H, NH_3^+), 3.71 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 6.86−6.90 (m, 2H, Ar−H), 7.17−7.31 (m, 5H, Ar−H); IR (KBr pellet): 2946 (NH^+) cm^{-1}. Anal. Calcd. for ($C_{20}H_{27}NO_2 \cdot 0.5C_2H_2O_4$) C, H, N.

(±)1-[3,5-Dimethoxy-4-(3-phenylpropyl)phenyl]-2-aminopropane HCl (15). A solution of **62** (0.43 g, 1.05 mmol) in MeOH (15 mL) and 15% NaOH (10 mL) was heated at reflux for 1 h. After cooling the reaction mixture to room temperature, MeOH was removed under reduced pressure. The aqueous solution was extracted with Et_2O (3 × 50 mL), the organic portion was dried ($MgSO_4$), and solvent was removed under reduced pressure to give an oil. The HCl salt was prepared and recrystallized from 2-PrOH to give 0.27 g (73%) of **15**; mp 158−160 °C. ^{1}H NMR (D_2O): δ 1.20 (d, 3H, CH_3), 1.64−1.71 (m, 2H, CH_2), 2.48−2.54 (m, 4H, CH_2, CH_2), 2.74 (dd, 1H, CH_2), 2.87 (dd, 1H, CH_2), 3.48−3.55 (m, 1H, CH), 3.67 (s, 6H, $(OCH_3)_2$), 6.50 (s, 2H, Ar−H), 7.08−7.20 (m, 5H, Ar−H); IR (KBr pellet): 2940 (NH^+) cm^{-1}. Anal. Calcd. for ($C_{20}H_{28}ClNO_2$) C, H, N.

(±)1-[2,6-Dimethoxy-4-(3-phenylpropyl)phenyl]-2-aminopropane HCl (16). At 0 °C under N_2, dry THF (5 mL) was added to $LiAlH_4$ (0.21 g, 5.53 mmol), followed by the addition of nitropropene **64** (0.50 g, 1.46 mmol) in dry THF (8 mL). The reaction mixture was heated at reflux under N_2 for 1 h, then cooled to 0 °C (ice bath). Excess $LiAlH_4$ was decomposed by the addition of H_2O (0.2 mL), 10% NaOH (0.2 mL), and H_2O (1 mL). The reaction mixture was filtered and washed with Et_2O (3 × 25 mL). The ethereal solution was dried ($MgSO_4$) and concentrated under reduced pressure to give 0.41 g (90%) of a colorless oil. The HCl salt was prepared and recrystallized from 2-PrOH/anhydrous Et_2O to give 0.26 g (51%) of **16** as a white powder; mp 160−162 °C. ^{1}H NMR (D_2O): δ 1.16 (d, 3H, CH_3), 1.65−1.75 (m, 2H, CH_2), 2.33−2.41 (m, 4H, CH_2, CH_2), 2.80 (d, 2H, CH_2), 3.42−3.49 (m, 1H, CH), 3.57 (s, 6H, $[OCH_3]_2$), 6.24 (s, 2H, Ar−H), 6.95−7.08 (m, 5H, Ar−H); IR (KBr pellet): 2936 (NH^+) cm^{-1}. Anal. Calcd. for ($C_{20}H_{28}ClNO_2$) C, H, N.

(±)1-[4-(3-Phenylpropyl)phenyl]-2-aminopropane HCl (17). At 0 °C and under N_2, **46** (1.50 g, 5.33 mmol) in dry THF (25 mL) was added in a dropwise manner to a suspension of $LiAlH_4$ (0.73 g, 19.24 mmol) in dry THF (25 mL). The reaction mixture was heated at reflux for 1 h then cooled to 0 °C (ice bath). Excess $LiAlH_4$ was decomposed by the dropwise addition of H_2O (1 mL), 15% NaOH (1 mL), and H_2O (3 mL). The reaction mixture was filtered, and the solids were washed with excess CH_2Cl_2. After drying ($MgSO_4$), the organic portion was evaporated under reduced pressure to give 1.10 g (81%) of an oil. The HCl salt was prepared and recrystallized from 2-PrOH/anhydrous Et_2O to give 0.36 g (23%) of **17**; mp 123−125 °C. ^{1}H NMR (D_2O): δ 1.14 (d, 3H, CH_3), 1.67−1.77 (m, 2H, CH_2), 2.38−2.47 (m, 4H, CH_2, CH_2), 2.72 (dd, 1H, CH_2-a), 2.90 (dd, 1H, CH_2), 3.41−3.48 (m, 1H, CH), 6.98−7.20 (m, 9H, Ar−H); IR (KBr pellet): 2939 (NH^+) cm.$^{-1}$ Anal. Calcd. for ($C_{18}H_{24}$-ClN) C, H, N.

2-[4-(3-Phenylpropyl)phenyl]-1-aminoethane Hemifumarate (18). A solution of **44** (0.55 g, 2.06 mmol) in dry THF (20 mL) was added in a dropwise manner to a stirred suspension of $LiAlH_4$ (0.30 g, 7.90 mmol) in THF (10 mL) at 0 °C under an N_2 atmosphere. The reaction mixture was heated at reflux for 1.5 h then cooled to 0 °C; excess $LiAlH_4$ was decomposed by the successive addition of H_2O (0.4 mL), 15% NaOH (0.4 mL), and H_2O (1 mL). The lithium salts were collected by filtration and washed with Et_2O. The filtrate was dried ($MgSO_4$) and evaporated under vacuum to afford a brown oil. Attempts to prepare the HCl, oxalate, or maleate salts failed. Preparation of the fumarate salt yielded a solid material which was recrystallized from 2-PrOH to give 0.14 g (19%) of **18**; mp 179−181 °C. ^{1}H NMR (CD_3OD): δ 1.76−1.81 (m, 2H, CH_2), 2.47−2.52 (m, 4H, CH_2, CH_2), 2.78 (t, 2H, CH_2), 3.01 (t, 2H, CH_2) 6.54 (s, 1H, CH= (for 2 CH= of the fumarate)), 7.00−7.18 (m, 9H, Ar−H); IR (KBr pellet): 2936 (NH^+) cm^{-1}. Anal. Calcd. for ($C_{17}H_{21}N\cdot 0.5C_4H_4O_4$) C, H, N.

(±)1-(4-Bromo-3,5-dimethoxyphenyl)-2-aminopropane HCl (25). At 0 °C, $LiAlH_4$ (0.07 g, 1.84 mmol) was added to $AlCl_3$ (0.10 g, 0.75 mmol) in anhydrous Et_2O (2 mL) under an N_2 atmosphere. Nitropropene **65** (0.20 g, 0.66 mmol) in a dry THF (2 mL)/anhydrous Et_2O (6 mL) solution was added to the alane mixture in a dropwise manner. The reaction mixture was heated at reflux under N_2 for 1 h and was then cooled over ice. Decomposition of the alane was accomplished by the addition of H_2O (1 mL). Solids were removed by filtration and washed with Et_2O. The combined ethereal solution was dried ($MgSO_4$), and solvent was evaporated to give a colorless oil. The HCl salt was prepared by the addition of ethereal HCl solution to the oil in anhydrous Et_2O. The salt was recrystallized from 2-PrOH/anhydrous Et_2O to give a beige-colored powder (0.008 g, 4%); mp 222−224 °C (lit.[16] mp 221−222 °C).

***N*-Trifluoroacetyl-2-(2,5-dimethoxyphenyl)-1-aminoethane (28)**. At 0 °C, trifluoroacetic anhydride (2.4 mL, 17.03 mmol) was added in a dropwise manner to the free base of 2-(2,5-dimethoxyphenyl)-1-aminoethane (1.26 g, 6.59 mmol) with stirring. The reaction mixture was poured onto crushed ice (50 g) and a white solid was formed. The solid was collected by filtration to give 1.77 g (92%) of the desired compound **28**; mp 56−57 °C. ^{1}H NMR ($CDCl_3$): δ 2.89 (t, 2H, CH_2), 3.55 (t, 2H, CH_2), 3.76 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 6.71−6.82 (m, 3H, Ar−H), 7.17 (bs, 1H, NH); IR (film): 3327 (NH), 1731 (C=O, carbonyl), 1715 (C=O, amide) cm^{-1}.

***N*-Trifluoroacetyl-2-(2,5-dimethoxy-4-(phenylacetyl)-phenyl)-1-aminoethane (30)**. At −30 °C (dry ice/acetone) and under a nitrogen atmosphere, titanium(IV) chloride (2.6 mL, 23.71 mmol) was added in a dropwise manner to a stirred solution of **28** (1.60 g, 5.77 mmol) in dry CH_2Cl_2 (30 mL) followed by the addition of phenylacetyl chloride (1.0 mL, 7.56 mmol) in dry CH_2Cl_2 (20 mL). The reaction mixture was allowed to stir at −30 °C for 30 min and then warmed to room temperature where stirring continued under N_2 for an additional 2 d. The reaction mixture was poured onto crushed ice (100 g) and placed in a refrigerator overnight. The layers were separated, and the aqueous portion was washed with CH_2Cl_2 (4 × 50 mL). The combined organic portions were extracted with H_2O (3 × 30 mL), 5% HCl (3 × 30 mL), H_2O (3 × 30 mL), saturated $NaHCO_3$ (3 × 30 mL), saturated NaCl (3 × 30 mL), and dried ($MgSO_4$). Solvent was removed under reduced pressure, and the residual solid was recrystallized from absolute EtOH to give 0.40 g (18%) of the desired compound; mp 111−113 °C. ^{1}H NMR ($CDCl_3$): δ 2.93 (t, 2H, CH_2), 3.57 (t, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.32 (s, 2H, CH_2), 6.76 (s, 1H, Ar−H), 6.99 (bs, 1H, NH), 7.21−7.31 (m, 6H, Ar−H); IR (film): 3314 (NH), 1709 (C=O, amide), 1671 (C=O, ketone) cm^{-1}. Anal. Calcd. for ($C_{20}H_{20}F_3NO_4$) C, H, N.

***N*-Trifluoroacetyl-2-(2,5-dimethoxy-4-hydrocinnamoylphenyl)-1-aminoethane (31)**. Compound **31** was prepared from **28** and hydrocinnamoyl chloride in the same manner used for the preparation of **30**. The resulting crude solid (1.39 g) was recrystallized from absolute EtOH to give 0.41 g (31%) of the desired compound as an off-white crystalline solid; mp 102−104 °C. ^{1}H NMR ($CDCl_3$): δ 2.97 (t, 4H, CH_2CH_2), 3.32 (t, 2H, CH_2), 3.59 (t, 2H, CH_2), 3.85 (s, 6H, $(OCH_3)_2$), 6.76 (s, 1H, Ar−H), 7.00 (bs, 1H, NH), 7.23−7.30 (m, 6H, Ar−H); IR (film): 3333 (NH), 1715 (C=O, amide), 1665 (C=O, ketone) cm^{-1}. Anal. Calcd. for ($C_{21}H_{22}F_3NO_4$) C, H, N.

(±)*N*-Trifluoroacetyl-1-[2,5-dimethoxy-4-(phenylacetyl)-phenyl]-2-aminopropane (32). Compound **32** was prepared from **29**[13] and phenylacetyl chloride in the same manner used for the synthesis of **30**. The resulting solid was recrystallized from absolute EtOH to give a 60% yield of the desired compound; mp 146−148 °C. ^{1}H NMR ($CDCl_3$): δ 1.29 (d, 3H, CH_3), 2.80−2.97 (m, 2H, CH_2), 3.85 (s, 6H, $(OCH_3)_2$), 4.14−4.17 (m, 1H, CH), 4.32 (s, 2H, CH_2), 6.76 (s, 1H, Ar−H), 7.21−7.31 (m, 7H, Ar−H, NH); IR (film): 3295 (NH), 1693 (C=O, amide), 1673 (C=O, ketone) cm^{-1}. Anal. Calcd. for ($C_{21}H_{22}F_3$-NO_4) C, H, N.

***N*-Trifluoroacetyl-2-[2,5-dimethoxy-4-(2-phenylethyl)-phenyl]-1-aminoethane (33)**. A solution of **30** (0.30 g, 0.76 mmol) in HOAc (70 mL) and 70% $HClO_4$ (0.3 mL) was hydrogenated over 10% Pd/C (0.15 g, 1.43 mmol) for 6 h at 60 psi. Catalyst was removed by filtration, and the reaction mixture was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic phase was extracted with H_2O (3 × 30 mL), saturated $NaHCO_3$ (3 × 30 mL), and H_2O (3 × 30 mL). The organic portion was dried ($MgSO_4$) and solvent was removed under reduced pressure. The resulting solid was recrystallized from absolute EtOH to give 0.23 g (79%) of **33** as a white powder; mp 95−96 °C. ^{1}H NMR ($CDCl_3$): δ 3.16−3.20 (m, 6H, CH_2), 3.83 (t, 2H, CH_2), 4.02 (s, 3H, OCH_3), 4.07 (s, 3H, OCH_3), 6.89 (s, 1H, Ar−H), 6.96 (s, 1H, Ar−H), 7.48−7.60 (m, 5H, Ar−H), 7.68 (bs, 1H, NH); IR (film): 3320 (NH), 1703 (C=O) cm^{-1}. Anal. Calcd. for ($C_{20}H_{22}F_3$-NO_3) C, H, N.

***N*-Trifluoroacetyl-2-[2,5-dimethoxy-4-(3-phenylpropyl)-phenyl]-1-aminoethane (34)**. Compound **34** was prepared from **31** in the same manner used for the synthesis of **33**. The product was isolated as a yellow oil which solidified upon standing (0.89 g). The solid was purified by column chromatography using silica gel (grade 62, 60−200 mesh, 150 Å) (eluted, 5:1, hexanes/EtOAc) to give 0.25 g (43%) of **34**; mp 95−98 °C. ^{1}H NMR ($CDCl_3$): δ 1.89−1.94 (m, 2H, CH_2), 2.62−2.70 (m, 4H, CH_2CH_2), 2.87 (t, 2H, CH_2), 3.56−3.58 (m, 2H, CH_2), 3.77 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 6.63 (s, 1H, Ar−H), 6.69 (s, 1H, Ar−H), 7.18−7.31 (m, 6H, Ar−H, NH); IR (film): 3339 (NH), 1709 (C=O) cm^{-1}. The product was used in the preparation of **6** without further characterization.

(±)*N*-Trifluoroacetyl-1-[2,5-dimethoxy-4-(2-phenylethyl)phenyl]-2-aminopropane (35). Compound **35** was prepared from **32** in the same manner used for the preparation of **33**. The resulting white solid was recrystallized from absolute EtOH to give a 47% yield of the desired compound; mp 127−129 °C. ^{1}H NMR ($CDCl_3$): δ 1.27 (d, 3H, CH_3), 2.80−2.91 (m, 6H, CH_2), 3.73 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.09−4.15 (m, 1H, CH), 6.56 (s, 1H, Ar−H), 6.62 (s, 1H, Ar−H), 7.16−7.27 (m, 5H, Ar−H), 7.54 (bs, 1H, NH); IR (film):

3314 (NH), 1703 (C=O) cm^{-1}. Anal. Calcd. for ($C_{21}H_{24}F_3NO_3$) C, H, N.

***N*-Trifluoroacetyl-2-(2,5-dimethoxy-4-iodophenyl)-1-aminoethane (36)**. At room temperature, a solution of iodine monochloride (0.2 mL, 3.84 mmol) in HOAc (3 mL) was added to a solution of NaI (0.08 g, 0.52 mmol) in 0.1 N NaOH (0.3 mL) and HOAc (3 mL). After stirring the solution for 5 min, a solution of *N*-trifluoroacetyl-2-(2,5-dimethoxyphenyl)-1-aminoethane (**28**) (0.75 g, 2.71 mmol) in HOAc (14 mL) was added to the reaction mixture. Stirring was allowed to continue overnight, and the reaction mixture was poured onto crushed ice (50 g). The gray solid was collected by filtration and washed with H_2O (30 mL), 1% $Na_2S_2O_3$/1% KI (50 mL), and H_2O (30 mL), then recrystallized from absolute EtOH to give 0.63 g (58%) of the title compound as shiney, white crystals; mp 132−134 °C (lit.[17] mp 137 °C). ^{1}H NMR ($CDCl_3$): δ 2.88 (t, 2H, CH_2), 3.55 (t, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 6.63 (s, 1H, Ar−H), 6.92 (bs, 1H, NH), 7.27 (s, 1H, Ar−H); IR (film): 3327 (NH), 1703 (C=O) cm^{-1}.

***N*-Trifluoroacetyl-2-[2,5-dimethoxy-4-(4-phenyl-1-butynyl)phenyl]-1-aminoethane (38)**. *N*-Trifluoroacetyl-2-(2,5-dimethoxy-4-iodophenyl)-1-aminoethane (**36**) (0.55 g, 1.36 mmol) and 4-(phenyl)butyn-1-yl cuprate (0.46 g, 2.39 mmol) were dissolved in dry pyridine (12 mL), and the reaction mixture was heated no higher than 120 °C under a nitrogen atmosphere overnight. [Preparation of cuprate: At room temperature and under a nitrogen atmosphere, H_2O (30 mL) was added to a solution of $CuSO_4$ (1.78 g, 7.11 mmol) in ammonium hydroxide (7.5 mL), followed by the addition of hydroxylamine hydrochloride (0.99 g, 14.22 mmol). The reaction mixture was cooled on ice for 5 min, followed by the addition of a solution of 4-(phenyl)-1-butyne (1.0 mL, 7.11 mmol) in absolute EtOH (40 mL). The reaction mixture was allowed to stir at room temperature under a nitrogen atmosphere for 2 h. The yellow solid was collected by filtration, washed with H_2O (30 mL), absolute EtOH (20 mL), and Et_2O (20 mL), and dried under high vacuum to yield 1.10 g (80%) of the desired compound; mp 187−189 °C (decomp). The product was used in the preparation of **38** and **39** without further characterization.] The reaction mixture was allowed to cool to room temperature, diluted with H_2O (50 mL), and extracted with Et_2O (4 × 50 mL). The ethereal solution was dried ($MgSO_4$) and evaporated under reduced pressure to give a crude solid which was purified by column chromatography using silica gel (grade 62, 60−200 mesh, 150 Å) (eluted, 5:1, hexanes/EtOAc) to give a solid (0.47 g). Recrystallization from absolute EtOH gave 0.36 g (65%) of **38**; mp 93−95 °C. ^{1}H NMR ($CDCl_3$): δ 2.77 (t, 2H, CH_2), 2.74−2.99 (m, 4H, CH_2CH_2), 3.53−3.59 (m, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.65 (s, 1H, Ar−H), 6.87 (s, 1H, Ar−H), 6.98 (bs, 1H, NH), 7.27−7.32 (m, 5H, Ar−H); IR (film): 3320 (NH), 2351 (C∞C), 1734 (C=O) cm^{-1}. Anal. Calcd. for ($C_{22}H_{22}F_3NO_3$) C, H, N.

(±)*N*-Trifluoroacetyl-1-[2,5-dimethoxy-4-(4-phenyl-1-butynyl)phenyl]-2-aminopropane (39). 4-(Phenyl)butyn-1-yl cuprate (see write-up for compound **38**) (0.57 g, 2.95 mmol) was added to a solution of *N*-trifluoroacetyl-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (**37**)[13] (0.60 g, 14.38 mmol) in dry pyridine (14 mL) and heated overnight under N_2 on an oil bath no higher than 120 °C. The reaction mixture was cooled to room temperature and extracted between H_2O and Et_2O. The ethereal portion was dried ($MgSO_4$) and evaporated under reduced pressure to give a brown oil. The oil was purified twice by column chromatography using silica gel (grade 62, 60−200 mesh, 150 Å) (eluted, 5:1, hexanes/EtOAc) and the resulting solid was recrystallized from EtOAc/hexanes to give 0.30 g (50%) of the desired compound as white cottony crystals; mp 146−147 °C. ^{1}H NMR ($CDCl_3$): δ 1.27 (d, 3H, CH_3), 2.74−2.88 (m, 4H, CH_2CH_2), 2.95−3.00 (m, 2H, CH_2), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.09−4.18 (m, 1H, CH), 6.64 (s, 1H, Ar−H), 6.88, (s, 1H, Ar−H), 7.26−7.33 (m, 6H, Ar−H, NH); IR (film): 2359 (C≡C), 1694 (C=O) cm^{-1}. The product was used in the preparation of **41** without further characterization.

***N*-Trifluoracetyl-2-[2,5-dimethoxy-4-(4-phenylbutyl)-phenyl]-1-aminoethane (40)**. A solution of **38** (0.35 g, 0.86 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 crude solid (0.43 g). The solid was purified by column chromatography using silica gel (grade 62, 60−200 mesh, 150 Å) (eluted, 5:1, hexanes/EtOAc) to yield 0.23 g (65%) of **40**; mp 78−80 °C. ^{1}H NMR ($CDCl_3$): δ 1.60−1.69 (m, 4H, CH_2CH_2), 2.59−2.67 (m, 4H, CH_2CH_2), 2.85−2.89 (m, 2H, CH_2), 3.56 (t, 2H, CH_2), 3.76 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 6.62 (s, 1H, Ar−H), 6.68 (s, 1H, Ar−H), 7.17−7.30 (m, 5H, Ar−H); IR (film): 3308 (NH), 1709 (C=O) cm^{-1}. Anal. Calcd. for ($C_{22}H_{26}F_3NO_3$) C, H, N.

(±)*N*-Trifluoroacetyl-1-[2,5-dimethoxy-4-(4-phenylbutyl)phenyl]-2-aminopropane (41). Compound **41** was prepared from **39** in the same manner used for the preparation of **40** to give a white solid. The solid was purified by radial chromatography on a Chromatotron (TLC grade 7749) (eluted, 10:1, hexanes/EtOAc) and recrystallized from EtOAc/hexanes to give 0.13 g (46%) of **41**; mp 119−121 °C. ^{1}H NMR ($CDCl_3$): δ 1.26 (d, 3H, J = 7 Hz, CH_3), 1.59−1.69 (m, 4H, CH_2CH_2), 2.59−2.65 (4H, CH_2CH_2), 2.76−2.84 (m, 2H, CH_2), 3.76 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.05−4.14 (m, 1H, CH), 6.60 (s, 1H, Ar−H), 6.67 (s, 1H, Ar−H), 7.17−7.30 (m, 5H, Ar−H), 7.52 (bs, 1H, NH); IR (film): 1693 (C=O) cm^{-1}. The product was used in the preparation of **8** without further characterization.

4-(3-Phenylpropyl)benzaldehyde (43). Trifluoromethanesulfonic anhydride (3.10 mL, 18.43 mmol) in CH_2Cl_2 (10 mL) was added in a dropwise manner to a solution of 4-hydroxybenzaldehyde (2.00 g, 16.38 mmol) in CH_2Cl_2 (20 mL) and pyridine (5 mL) under N_2 at 0 °C. The reaction mixture was allowed to warm to room temperature where stirring continued for 20 min. Solvent was removed under reduced pressure, and the resulting residue was placed under high vacuum for 1 h. The residue was distilled using a Kugelrohr apparatus to give 2.56 g (61%) of a clear oil (**42**) at 0.06 mmHg (oven temp: 85−90 °C). ^{1}H NMR ($CDCl_3$): δ 7.48 (d, 2H, Ar−H), 8.02 (d, 2H, Ar−H), 10.06 (s, 1H, CHO); IR (film): 1709 (C=O) cm^{-1}. Under a nitrogen atmosphere, 9-phenylpropyl-9-BBN (**45**) (8.52 mmol) was added to a stirred solution of triflate **42** (2.00 g, 7.89 mmol), THF (34 mL), 3 M NaOH (7.7 mL), and 1,1′-bis-(diphenylphosphinoferrocene)Pd (163 mg, 0.20 mmol). Upon addition, the reaction mixture turned from red to dark brown. The reaction mixture was heated at reflux for 1.5 h. After allowing the reaction mixture to cool to room temperature, the solvents were removed under reduced pressure. The dark residue was extracted between Et_2O and H_2O. The ethereal solution was dried ($MgSO_4$) and evaporated under reduced pressure to give **43** as a brown oil. Kugelrohr distillation gave 1.67 g (94%) of a clear oil at 0.05 mmHg (oven temp.: 70−75 °C). ^{1}H NMR ($CDCl_3$): δ 1.95−2.05 (m, 2H, CH_2), 2.65−2.76 (m, 4H, CH_2, CH_2), 7.81 (d, 2H, Ar−H), 7.18−7.36 (m 7H, Ar−H), 9.98 (s, 1H, CHO); IR (film): 1703 (C=O) cm^{-1}. The product, **43**, was used in the preparation of **44** and **46** without further characterization.

2-[4-(3-Phenylpropyl)phenyl]-1-nitroethene (44). A mixture of 4-(3-phenylpropyl)benzaldehyde (**43**) (1.00 g, 4.46 mmol) and ammonium acetate (0.30 g, 3.89 mmol) in nitromethane (25 mL) was heated at reflux under N_2 for 2.5 h. Solvent was removed under reduced pressure to give a yellow oil which crystallized upon standing. The solid was recrystallized from absolute EtOH to give **44** as yellow leaflets (0.59 g, 49%); mp 83−85 °C. ^{1}H NMR ($CDCl_3$): δ 1.92−2.03 (m, 2H, CH_2), 2.64−2.72 (m, 4H, CH_2, CH_2), 7.17−7.32 (m, 7H, Ar−H), 7.47 (d, 2H, Ar−H), 7.58 (d, 1H, CH=), 8.00 (d, 1H, CH=); IR (film): 1494 (N=O) cm^{-1}. The product was used without further characterization in the synthesis of **18**.

9-(3-Phenylpropyl)-9-BBN (45). At 0 °C and N_2, allylbenzene (735 μL, 5.55 mmol) was added in a dropwise manner to a stirred mixture of 9-BBN (0.5 M in THF) (11.2 mL, 5.55 mmol). The reaction mixture was brought to room temperature where stirring continued for 2 h. Thin-layer chromatography indicated a complete reaction, and the product was used in subsequent reactions without further purification or characterization.

1-[4-(3-Phenylpropyl)phenyl]-2-nitropropene (46). A solution of 4-(3-phenylpropyl)benzaldehyde (**43**) (1.60 g, 7.13 mmol) and ammonium acetate (0.44 g, 5.71 mmol) in nitroethane (30 mL) was heated at reflux under N_2 for 3 h. After allowing the reaction mixture to cool to room temperature, the solvent was removed under reduced pressure, and the yellow residue was purified by column chromatography (silica gel, grade 62, mesh 60−120 Å) (eluted hexanes/EtOAc, 5:1) to give 1.59 g (79%) of **46**. ^{1}H NMR ($CDCl_3$): δ 1.96−2.04 (m, 2H, CH_2), 2.47 (s, 3H, CH_3), 2.65−2.73 (m, 4H, CH_2, CH_2), 7.18−7.39 (m, 9H, Ar−H), 8.09 (s, 1H, CH=); IR (film): 1522 (N=O) cm^{-1}. The product was used in the preparation of **17** without further characterization.

2-Methoxy-4-(trifluoromethanesulfonyl)benzaldehyde (47). Compound **47** was prepared from 4-hydroxy-2-methoxybenzaldehyde in the same manner used for the preparation of **42**. Purification by column chromatography (silica gel, grade 62, mesh 60−120 Å) (eluted hexanes/EtOAc, 5:1) gave 0.97 g (44%) of **47**. ^{1}H NMR ($CDCl_3$): δ 3.98 (s, 3H, OCH_3), 6.91 (s, 1H, Ar−H), 6.96 (d, 1H, Ar−H), 7.93 (d, 1H, Ar−H), 10.43 (s, 1H, CHO); IR (film): 1681 (C=O) cm^{-1}. The product was used in the synthesis of **48** without further characterization.

2-Methoxy-4-(3-phenylpropyl)benzaldehyde (48). Compound **48** was prepared from **47** in the same manner used for the synthesis of **43** to give a crude product. Kugelrohr distillation gave a colorless oil (0.60 g, 84%) at 0.06 mmHg (oven temp.: 185−195 °C). ^{1}H NMR ($CDCl_3$): δ 1.94−2.04 (m, 2H, CH_2), 2.65−2.72 (m, 4H, CH_2, CH_2), 3.92 (s, 3H, OCH_3), 6.77 (s, 1H, Ar−H), 6.86 (d, 1H, Ar−H), 7.21−7.33 (m, 5H, Ar−H), 7.76 (d, 1H, Ar−H), 10.41 (s, 1H, CHO); IR (film): 1681 (C=O) cm^1. The product was used in the preparation of **49** without further characterization.

1-[2-Methoxy-4-(3-phenylpropyl)phenyl]-2-nitropropene (49). Compound **49** was prepared from **48** in the same manner as **44** to give a dark-yellow oil. Purification by column chromatography (silica gel, grade 62, mesh 60−120 Å) (eluted hexanes/EtOAc, 5:1) gave 0.43 g (61%) of **49** as a pale-yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.41 (s, 3H, CH_3), 2.67−2.72 (m, 4H, CH_2, CH_2), 3.88 (s, 3H, OCH_3), 6.76 (s, 1H, Ar−H), 6.85 (d, 1H, Ar−H), 7.20−7.31 (m, 6H, Ar−H), 8.31 (s, 1H, CH=); IR (film): 1525 (N=O) cm^{-1}. The product was used in the preparation of **12** without further characterization.

3-Methoxy-4-(trifluoromethanesulfonyl)benzaldehyde (**50**). Compound **50** was prepared from 3-methoxy-4-hydroxybenzaldehyde in the same manner as compound **42** to afford a dark-colored solid material. The crude product was purified by Kugelrohr distillation to yield a colorless oil (1.51 g, 27%) which was homogeneous to thin-layer chromatography. ^{1}H NMR ($CDCl_3$): δ 4.01 (s, 3H, OCH_3), 7.41−7.58 (m, 3H, Ar−H), 9.99 (s, 1H, CHO); IR: 1706 (C=O) cm^{-1}. The product was used in the synthesis of **51** without further purification.

3-Methoxy-4-(3-phenylpropyl)benzaldehyde (51). This compound was prepared from **50** in the same manner as **43** to yield a dark oil. The oil was dissolved in a small amount of Et_2O (5 mL) and combined with a saturated solution of $NaHSO_3$ (50 mL). After 30 min of vigorous stirring, the mixture was extracted with Et_2O (3 × 25 mL). The aqueous portion was made basic with 15% NaOH and re-extracted with Et_2O (3 × 25 mL). The ether portion was dried ($MgSO_4$), and the solvent was removed under reduced pressure to yield the product (0.56 g) as a clear oil. The solvent of the original ether portion was removed under reduced pressure. The resulting oil was purified by Kugelrohr distillation to give a colorless oil (0.73 g) at 0.04 mmHg (oven temp.: 170−180 °C). Total yield is 99%. ^{1}H NMR ($CDCl_3$): δ 1.66−1.97 (m, 2H, CH_2), 2.65−2.75 (m, 4H, CH_2, CH_2), 3.88 (s, 3H, OCH_3), 7.19−7.40 (m, 8H, Ar−H), 9.93 (s, 1H, CHO); IR (film): 1687 (C=O) cm^{-1}. The product was used in the synthesis of **52** without further purification.

1-[3-Methoxy-4-(3-phenylpropyl)phenyl]-2-nitropropene (52). Compound **52** was prepared from **51** using the same procedure employed in the synthesis of **44.** The product was purified by column chromatography (silica gel, grade 62, mesh 60−120 Å) (eluted hexanes/EtOAc, 5:1) to give 0.75 g (56%) of **52** as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.91−1.98 (m, 2H, CH_2), 2.47 (s, 3H, CH_3), 2.65−2.71 (m, 4H, CH_2, CH_2), 3.84 (s, 3H, OCH_3), 6.86 (s, 1H, Ar−H), 6.98 (d, 1H, Ar−H), 7.18−7.31 (m, 6H, Ar−H), 8.07 (s, 1H, CH=); IR (film): 1518 (N=O) cm^{-1}. The product was used in the preparation of **13** without further characterization.

(±)*N*-Trifluoroacetyl-1-[3,5-dimethoxy-4-(1-oxo-3-phenylpropyl)phenyl]-2-aminopropane (55). At −30 °C (dry ice/acetone) under N_2, titanium(IV) chloride (1.20 mL, 10.94 mmol) was added in a dropwise manner to a stirred solution of the acetamide **63** (1.50 g, 5.15 mmol) in dry CH_2Cl_2 (50 mL), followed by the addition of hydrocinnamoyl chloride (1.20 mL, 8.08 mmol) in dry CH_2Cl_2 (40 mL). The reaction mixture was allowed to stir at −30 °C for 30 min and was then allowed to warm to room temperature where stirring continued for 2 d. The reaction mixture was poured over crushed ice (10 g) to hydrolyze any remaining acid chloride. The layers were separated, and the aqueous portion was washed with CH_2Cl_2 (3 × 50 mL). The combined CH_2Cl_2 portions were successively washed with H_2O (3 × 50 mL), 3 M HCl (3 × 50 mL), H_2O (3 × 50 mL), saturated $NaHCO_3$ (3 × 50 mL), and saturated NaCl (3 × 50 mL). The organic portion was dried ($MgSO_4$), and solvent was removed under reduced pressure to give a solid. Kugelrohr distillation removed impurities (0.09 mmHg, oven temp: 225 °C). The residual solid was recrystallized from absolute EtOH to give 1.11 g (51%) of ketone **55**; mp 118−120 °C. ^{1}H NMR ($CDCl_3$): δ 1.24 (d, 3H, CH_3), 2.78 (dd, 1H, CH_2), 2.89 (dd, 1H, CH_2), 2.99−3.09 (m, 4H, CH_2, CH_2), 3.75 (s, 6H, $(OCH_3)_2$), 4.25−4.35 (m, 1H, CH), 6.10 (bs, 1H, NH), 6.32 (s, 2H, Ar−H), 7.18−7.27 (m, 5H, Ar−H); IR (film): 1720 (ketone C=O), 1702 (amide C=O) cm^{-1}. The product was used without further characterization in the synthesis of **62**.

1-(3,5-Dimethoxyphenyl)-3-phenylpropane (57). Cleaned, oven-dried Mg turnings (1.19 g, 48.95 mmol) and a few crystals of iodine were placed in a three-neck round-bottom flask with anhydrous Et_2O (5 mL). A small portion (5 mL) of a solution of 1-bromo-2-phenylethane (3.20 mL, 23.43 mmol) in anhydrous Et_2O (15 mL) was added, and the Grignard reaction began with the disappearance of the brown iodine color. The remainder of the bromo compound was added. After bubbling ceased, the reaction mixture was heated at reflux on an oil bath for 1 h, then allowed to cool to room temperature. At 0 °C and under N_2, the Grignard reagent was added via syringe to a solution of 3,5-dimethoxybenzaldehyde (**53**) (3.00 g, 18.05 mmol) in anhydrous Et_2O (12 mL). The reaction mixture was allowed to stir at 0 °C for 30 min, then at room temperature for 30 min, whereupon the reaction was quenched by the addition of 30% H_2SO_4 (15 mL), and the mixture was extracted between H_2O and Et_2O. The ethereal portion was dried ($MgSO_4$) and evaporated under reduced pressure to give an oil. Purification by column chromatography (silica gel, grade 62, 60−120 mesh, 150 Å) (eluted, hexanes/EtOAc, 10:1) gave 3.50 g (71%) of the desired propanol **56**. Further purification of the impure fractions by radial chromatography on a Chromatotron (silica gel, grade 7769) (eluted, hexanes/EtOAc, 10:1) gave 0.58 g of **56** (83% total yield). ^{1}H NMR ($CDCl_3$): δ 1.88 (bs, 1H, OH), 1.94−2.17 (m, 2H, CH_2), 2.62−2.89 (m, 2H, CH_2), 3.78 (s, 6H, $(OCH_3)_2$), 4.61 (dd, 1H, CH), 6.37 (t, 1H, Ar−H), 6.51 (d, 2H, Ar−H), 7.16−7.30 (m, 5H, Ar−H); IR (film): 3433 (OH) cm^{-1}. Chlorotrimethylsilane (5.00 mL, 39.40 mmol), sodium iodide (5.93 g, 39.56 mmol), and dry MeCN (2.61 mL, 49.97 mmol) were combined and allowed to stir at room temperature under an N_2 atmosphere for 15 min. A solution of propanol **56** (1.79 g, 6.57 mmol) in anhydrous Et_2O (4.5 mL) and hexanes (3.5 mL) was added. The reaction mixture was allowed to stir at room temperature for 24 h and was then quenched with H_2O, extracted between Et_2O and H_2O, and the ethereal portion was dried over $MgSO_4$. Filtration and removal of the solvent gave 6 g of a dark oil. Purification by column chromatography (silica gel, grade 62, 60−120 mesh, 150 Å) (eluted, hexanes/EtOAc, 10:1) gave 1.31 g (78%) of the desired **57** as a reddish oil. ^{1}H NMR ($CDCl_3$): δ 1.90−2.00 (m, 2H, CH_2), 2.57−2.68 (m, 4H, CH_2, CH_2), 3.78 (s, 6H, $(OCH_3)_2$), 6.31

(s, 1H, Ar−H), 6.35 (s, 2H, Ar−H), 7.18−7.28 (m, 5H, Ar−H); IR (film): 2937 (aromatic) cm^{-1}. The product was used without further characterization for the preparation of **58**.

2,6-Dimethoxy-4-(3-phenylpropyl)benzaldehyde (58). At −10 °C and under an N_2 atmosphere, *n*-butyllithium (2.5 M in hexanes) (3.0 mL, 7.5 mmol) was added to **57** (0.96 g, 3.75 mmol) in dry THF (8 mL). The red reaction mixture was stirred under a nitrogen atmosphere at −10 °C for 2 h; DMF (0.60 mL, 6.32 mmol) in dry THF (2 mL) was added. The reaction mixture, which turned from red to colorless, was allowed to stir at room temperature for 2 h. The reaction was quenched by the addition of 30% H_2SO_4 (4 mL) and extracted between H_2O and Et_2O; the ethereal portion was washed with saturated NaCl solution and dried ($MgSO_4$), and solvent was evaporated under reduced pressure to give 1.10 g of a yellow oil. Purification by column chromatography (silica gel, grade 62, 60−120 mesh, 150 Å) (eluted, hexanes/EtOAc, 5:1) gave 0.79 g (74%) of the desired aldehyde **58**. ^1H NMR ($CDCl_3$): δ 1.93−2.04 (m, 2H, CH_2), 2.62−2.71 (m, 4H, CH_2, CH_2), 3.88 (s, 6H, $(OCH_3)_2$), 6.38 (s, 2H, Ar−H), 7.18−7.33 (m, 5H, Ar−H), 10.45 (s, 1H, CHO); IR (film): 1684 (CHO) cm^{-1}. Compound **58** was used for the preparation of **64**.

1-[2,3-Dimethoxy-4-(3-phenylpropyl)phenyl]-2-nitropropene (59). Aldehyde **61** (0.50 g, 1.76 mmol) was combined with ammonium acetate (0.08 g, 1.04 mmol) in nitroethane (10 mL), and the reaction mixture was heated at reflux under N_2. After 3 h, the solvent was removed under reduced pressure to give a yellow oil. Purification by column chromatography on silica gel (grade 62, 60−120 mesh, 150 Å) (eluted, 100:1, hexanes/EtOAc) gave 0.05 g of product. Purification of the impure fractions by radial chromatography on a Chromatotron (silica gel, grade 7769) (eluted, 100:1, hexanes/EtOAc) gave an additional 0.25 g of the nitropropene (**59**), for a total yield of 0.30 g (50%), as a yellow oil. ^1H NMR ($CDCl_3$): δ 1.90−2.00 (m, 2H, CH_2), 2.41 (s, 3H, CH_3), 2.67−2.74 (m, 4H, CH_2, CH_2), 3.84 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.96−7.03 (m, 2H, Ar−H), 7.20−7.33 (m, 5H, Ar−H), 8.24 (s, 1H, CH=); IR (film): 1522 (N=O) cm^{-1}. The product was used in the preparation of **14** without further characterization.

1,2-Dimethoxy-3-(3-phenylpropyl)benzene (60). At 0 °C under N_2, *n*-butyllithium (2.5 M in hexanes) (27.0 mL, 67.5 mmol) was added to 1,2-dimethoxybenzene (9.0 g, 65.1 mmol) in dry THF (40 mL). The reaction mixture was allowed to stir at 0 °C for 1.5 h. 3-Phenyl-1-bromopropane (13.0 g, 65.1 mmol) in THF (35 mL) was added in a dropwise manner at 0 °C, and the reaction mixture was heated at reflux for 3 h. After the solution had cooled to room temperature, stirring was continued overnight under N_2. The reaction was quenched with 3 M HCl, and the layers were separated. The organic portion was washed with brine. The aqueous portion was washed with Et_2O, the combined organic portions were dried ($MgSO_4$), and solvent was removed to give a brown oil which had three components as determined by thin-layer chromatography. The product was partially purified by column chromatography using silica gel (grade 62, 60−200 mesh, 150 Å) (eluted, 15:1, hexanes/EtOAc), then further purified using radial chromatography on a Chromatotron (silica gel, grade 7769) (eluted, 15:1, hexanes/EtOAc) to give 5.6 g (34%) of **60** as a colorless oil which was used in the preparation of **61**. (Yield is 80% based on recovered 1,2-dimethoxybenzene.) ^1H NMR ($CDCl_3$): δ 1.88−1.98 (m, 2H, CH_2), 2.65−2.70 (m, 4H, CH_2, CH_2), 3.78 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 6.76−6.78 (m, 2H, Ar−H). 6.98 (t, 1H, Ar−H), 7.17−7.30 (m, 5H, Ar−H); IR (film): 2940 (aromatic) cm^{-1}.

2,3-Dimethoxy-4-(3-phenylpropyl)benzaldehyde (61). At 0 °C and under a nitrogen atmosphere, TMEDA (1.54 mL, 10.20 mmol) was added to *n*-butyllithium (2.5 M in hexanes) (4.0 mL, 10.00 mmol) and allowed to stir for 5 min. 1,2-Dimethoxy-3-(3-phenypropyl)benzene (**60**) (2.50 g, 9.75 mmol) in dry THF (25 mL) was added to the reaction mixture, and stirring was continued for 0.5 h. DMF (2.30 mL, 29.70 mmol) was added, and stirring was continued at 0 °C for an additional 1 h, then at room temperature for 4 h. The reaction was quenched by the addition of 3 M HCl. Et_2O (25 mL) was added, and the layers were separated. The organic portion was washed with brine, and the aqueous portion was washed with Et_2O. The combined organic portions were dried ($MgSO_4$) and evaporated to give 3.0 g of a yellow oil. Purification by column chromatography on silica gel (grade 62, 60−120 mesh, 150 Å) (eluted, 40:3, hexanes/EtOAc) gave 0.24 g of **61**. Further purification of the crude material by radial chromatography on a Chromatotron (silica gel, grade 7769) gave another 0.31 g, for a total of 0.55 g (20%), of the desired compound as a clear oil. ^1H NMR ($CDCl_3$): δ 1.89−1.99 (m, 2H, CH_2), 2.68−2.72 (m, 4H, CH_2, CH_2), 3.84 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 7.01 (d, 1H, Ar−H), 7.19−7.32 (m, 5H, Ar−H), 7.51 (d, 1H, Ar−H), 10.34 (s, 1H, CHO); IR (film): 1686 (C=O) cm^{-1}. The aldehyde was used without further identification in the preparation of **59**.

(±)*N*-Trifluoroacetyl-1-[3,5-Dimethoxy-4-(3-phenylpropyl)phenyl]-2-aminopropane (62). A suspension of the amine-protected ketone **55** (0.70 g, 1.65 mmol), HOAc (60 mL), perchloric acid (70%, 0.30 mL), and 10% palladium on carbon (0.35 g) was shaken at room temperature on a Parr hydrogenator at 45 psi for 6 h. The catalyst was removed by filtration, and the filtrate was diluted with H_2O (75 mL). The aqueous solution was extracted with Et_2O (3 × 50 mL). The ethereal solution was washed with saturated $NaHCO_3$ solution (3 × 50 mL), dried ($MgSO_4$), and evaporated under reduced pressure. (Heptane and hexanes were used to remove acetic acid azeotropically.) The resulting white solid (0.79 g) was recrystallized from absolute EtOH to give 0.44 g (65%) of the desired material; mp 124−125 °C. ^1H NMR ($CDCl_3$): δ 1.24 (d, 3H, CH_3), 1.74−1.85 (m, 2H, CH_2), 2.62−2.69 (m, 2H, CH_2), 2.69−2.84 (m, 2H, CH_2), 3.78 (s, 6H, $(OCH_3)_2$), 4.36−4.26 (m, 1H, CH), 6.12 (bs, 1H, NH), 6.30 (s, 2H, Ar−H), 7.19−7.30 (m, 5H, Ar−H); IR (film): 1696 (C=O) cm^{-1}.

(±)*N*-Trifluoroacetyl-1-(3,5-dimethoxyphenyl)-2-aminopropane (63). At 0 °C under N_2, trifluoroacetic anhydride (2.10 mL, 14.90 mmol) in CH_2Cl_2 (10 mL) was added in a dropwise manner to a solution of 1-(3,5-dimethoxyphenyl)-2-aminopropane (**54**)[15] (2.31 g, 11.83 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was brought to room temperature where stirring was continued for another 15 min. Solvent was removed under reduced pressure to give a yellow oil which solidified upon the addition of crushed ice (0.5 g). The solid was collected by filtration and recrystallized from absolute EtOH to give white feathery crystals of the trifluoroacetamide (1.55 g, 33%); mp 111−113 °C. ^1H NMR ($CDCl_3$): δ 1.23 (d, 3H, CH_3), 2.74 (dd, 1H, CH_2), 2.83 (dd, 1H, CH_2), 3.78 (s, 6H, $(OCH_3)_2$), 4.24−4.33 (m, 1H, CH), 6.17 (bs, 1H, NH), 6.31 (d, 2H, Ar−H), 6.36 (t, 1H, Ar−H); IR (film): 1696 (C=O) cm^{-1}. Compound **63** was used in the preparation of **55**.

1-[2,6-Dimethoxy-4-(3-phenylpropyl)phenyl]-2-nitropropene (64). 2,6-Dimethoxy-4-(3-phenylpropyl)benzaldehyde (**58**) (0.70 g, 2.46 mmol) and ammonium acetate (0.15 g, 1.95 mmol) were dissolved in nitroethane (6.2 mL), and the reaction mixture was heated at reflux for 1 h. The solvents were removed under reduced pressure to give a brown oil. The oil was purified by radial chromatography on a Chromatotron (silica gel, grade 7749) (eluted, 10:1, hexanes/EtOAc) to give 0.57 g (68%) of a nitropropene **64** as a yellow oil. ^1H NMR ($CDCl_3$): δ 1.94−2.04 (m, 2H, CH_2), 2.10 (s, 3H, CH_3), 2.64−2.72 (m, 4H, CH_2, CH_2), 3.82 (s, 6H, $(OCH_3)_2$), 6.40 (s, 2H, Ar−H), 7.19−7.31 (m, 5H, Ar−H), 7.95 (s, 1H, CH=); IR (film): 1518 (N=O) cm^{-1}. The product was used without further characterization in the synthesis of **16**.

(±)1-(4-Bromo-3,5-dimethoxyphenyl)-2-nitropropene (65). A solution of 4-bromo-3,5-dimethoxybenzaldehyde (0.30 g, 1.22 mmol) and NH_4OAc (0.08 g, 1.04 mmol) in nitroethane (3 mL) was heated at reflux for 5 h under an N_2 atmosphere. Solvent was removed under reduced pressure to give a semisolid material. Purification by column chromatography (silica gel, grade 62, 60−120 mesh, 150 Å) (eluted, hexanes/EtOAc, 20:1) gave 0.21 g (57%) of the desired nitrostyrene; mp 108−110 °C (lit.[16] mp 121−121.5 °C). ^1H NMR ($CDCl_3$): δ 2.47 (s, 3H, CH_3), 3.93 (s, 6H, $(OCH_3)_2$), 6.60 (s, 2H, Ar−H), 8.04 (s, 1H, CH=); IR (film): 1522 (N=O) cm^{-1}.

B. Radioligand Binding Assays. The binding assays were conducted according to published procedures.[18] 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 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: $K_i = IC_{50}/(1 + [D]/K_D)$.[19] The results reflect a minimum of three assays.

C. PI Hydrolysis Assay. Inositol phosphate (IP) production was measured as previously described,[20] with minor modifications. Briefly, NIH-3T3 cells stably transfected with rat 5HT_{2A} receptors were washed with phosphate-buffered saline (PBS) and labeled with 0.25 μCi/well of *myo*-[^{3}H]inositol (New England Nuclear) in inositol free/serum-free DMEM (GIBCO) for 18 h at 37 °C. After labeling, cells were washed with PBS and preincubated in inositol-free/serum-free DMEM with 10 mM LiCl and 10 μM pargyline (assay medium) for 10 min at 37 °C. When antagonists were used, they were added during the 10 min preincubation period. Agonists were added to each well and incubation continued for an additional 30 min. Assay medium was removed and cells were lysed in 200 μL of stop solution (1 M KOH/18 mM sodium borate/3.8 mM EDTA) and neutralized by adding 200 μL of 7.5% HCl. The contents of each well were extracted with 3 volumes of $CHCl_3$/MeOH (1:2), centrifuged 5 min at 10 000*g*, and the upper layer loaded onto a 1 mL AG1-X8 resin (100−200 mesh, Bio-Rad) column. Columns were washed with 10 mL of 5 mM myo-inositol and 10 mL of 5 mM sodium borate/60 mM sodium formate. Total IPs were eluted with 3 mL of 0.1 M formic acid/1 M ammonium formate. Radioactivity was measured by liquid scintillation counting in Ecoscint cocktail. Assays were performed in triplicate.

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Supporting Information Available: Elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Hoyer, D.; Clarke, D. E.; Fozard, J. R.; Hartig, P. R.; Martin, G. R.; Mylecharane, E. J.; Saxena, P. R.; Humphrey, P. P. A. International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (serotonin). *Pharmacol. Rev.* **1994**, *46*, 157−203.

(2) Glennon, R. A.; Dukat, M. Serotonin receptor subtypes. In *Psychopharmacology: The Fourth Generation of Progess*; Bloom, F. E., Kupfer, D. J., Eds.; Raven Press: Ltd., New York, 1995; pp 415−429. Updated CD Version: Glennon, R. A.; Dukat, M.; Westkaemper, R. B. *Psychopharmacology*; Watson, S. J., Ed.: Lippincott-Raven: New York, 1998.

(3) Van Wijngaarden, I.; Soudijn, W. 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptor ligands. In *Serotonin Receptors and their Ligands*; Olivier, B., van Wijngaarden, I., Soudijn, W., Eds.; Elsevier: Amsterdam, 1997; pp 161−197.

(4) Glennon, R. A.; Dukat, M. Novel serotonergic agents: 5-HT_2 − Update 1997. *ID Res. Alerts* **1997**, *2*, 107−113.

(5) Glennon, R. A.; Titeler, M.; McKenney, J. D. Evidence for 5-HT_2 involvement in the mechanism of action of hallucinogenic agents. *Life Sci.* **1984**, *35*, 2505−2511.

(6) Shulgin, A.; Shulgin, A. PIHKAL, Transform Press: Berlkley, CA, 1991.

(7) Seggel, M. R.; Yousif, M. Y.; Lyon, R. A.; Titeler, M.; Roth, B. L.; Suba, E. A.; Glennon, R. A. A structure−affinity study of the binding of 4-substituted analogues of 1-(2,5-dimethoxyphenyl)-2-aminopropane at 5-HT_2 serotonin receptors. *J. Med. Chem.* **1990**, *33*, 1032−1036.

(8) Nelson, D. L.; Lucaites, V. L.; Wainscott, D. B.; Glennon, R. A. Comparisons of hallucinogenic phenylisopropylamine binding affinities at cloned human 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors. *Naunyn-Schmeideberg's Arch. Pharmacol.* **1999**, *359*, 1−6.

(9) Glennon, R. A.; McKenney, J. D.; Lyon, R. A.; Titeler, M. 5-HT_1 and 5-HT_2 binding characteristics of 1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane analogues. *J. Med. Chem.* **1986**, *29*, 194−199.

(10) Glennon, R. A.; Teitler, M.; Sanders-Bush, E. Hallucinogens and serotonergic mechanisms. *NIDA Res. Monogr.* **1992**, *119*, 131−135.

(11) Roth, B. L.; Willins, D. L.; Kristiansen, K.; Kroeze, W. K. 5-Hydroxytryptamine$_2$-family receptors (5-hydroxytryptamine$_{2A}$, 5-hydroxytryptamine$_{2B}$, 5-hydroxytryptamine$_{2C}$): Where structure meets function. *Pharmacol. Ther.* **1998**, *79*, 231−257.

(12) Standridge, R. T.; Howell, H. G.; Tilson, H. A.; Chamberlain, J. H.; Holava, H. M.; Gylys, J. A.; Partyka, R. A.; Shulgin, A. T. Phenylalkylamines with potential psychotherapeutic utility. 2. Nuclear substituted 2-amino-1-phenylbutanes. *J. Med. Chem.* **1980**, *23*, 154−162 and references therein.

(13) Glennon, R. A.; Seggel, M. R.; Soine, W. H.; Herrick-Davis, K.; Lyon, R. A.; Titeler, M. [^{125}I]-1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane: An iodinated radioligand that specifically labels the agonist high-affinity state of 5-HT_2 serotonin receptors. *J. Med. Chem.* **1988**, *31*, 5−7.

(14) Oh-e, T.; Miyaura, N.; Suzuki, A. Palladium-catalyzed cross-coupling reaction of organoboron compounds with organic triflates. *J. Org. Chem.* **1993**, *58*, 2201−2208.

(15) Ho, B. T.; McIsaac, W. M.; An, R.; Tansey, L. W.; Walker, K. E.; Englert, L. F., Jr.; Noel, M. B. Analogues of α-methylphenethylamine (amphetamine). I. Synthesis and pharmacological activity of some methoxy and/or methyl analogues. *J. Am. Chem. Soc.* **1970**, *13*, 26−30.

(16) Barfknecht, C. F.; Nichols, D. E. Potential Psychotomimetics. Bromomethoxyamphetamines. *J. Med. Chem.* **1971**, *14*, 370−372.

(17) Nichols, D. E.; Frescas, S.; Marona-Lewicka, D.; Huang, X.; Roth, B. L.; Gudelsky, G. A.; Nash, J. F. 1-(2,5-Dimethoxy-4-trifluoromethyl)phenyl)-2-aminopropane: A Potent Serotonin 5-$HT_{2A/2C}$ Agonist. *J. Med. Chem.* **1994**, *37*, 4346−4351.

(18) Metwally, K. A.; Dukat, M.; Egan, C. T.; Smith, C.; DuPre, A.; Gauthier, C. B.; Herrick-Davis, K.; Teitler, M.; Glennon, R. A. Spiperone: influence of spiro ring substituents on 5-HT_{2A} serotonin receptor binding. *J. Med. Chem.* **1998**, *41*, 5084−5093.

(19) Cheng, Y.-C.; Prusoff, W. H. Relationship between inhibitory constant (K_i) and the concentration of inhibitor which causes 50% inhibition (IC50) of an enzyme reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099−3108.

(20) Herrick-Davis, K.; Egan, C. T.; Teitler, M. Activating mutations of the serotonin 5-HT_{2C} receptor. *J. Neurochem.* **1997**, *69*, 1138−1144.

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