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 substituents 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 such 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. 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, and both are psychoactive in humans. The structure-affinity relationships for the binding of these agents at 5-HT$_2$ receptors have been investigated in some detail. 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.

During the course of our investigations with phenylalkylamines, we prepared the 4-(3-phenylpropyl) derivative 3. 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). Interestingly however, unlike DOB, compound 3 was found to act as a 5-HT$_{2A}$ antagonist in a phosphoinositide hydrolysis assay. As such, compound 3 represented the first example of a DOB-like phenylalkylamine with 5-HT$_{2A}$ 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 may bind to 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. Compounds 4–6 (Scheme 1) were prepared in a similar...
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 occur 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 reaction14 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 LiAlH₄ 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).
Results and Discussion

5-HT\textsubscript{2A} Receptor Binding. The study began by examining the role of chain length and the necessity of the \(\alpha\)-methyl group on the 5-HT\textsubscript{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 an \(n\)-butyl group (i.e., 8) enhanced affinity by about the same amount. The \(R\)-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\textsubscript{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\textsubscript{2A} receptor affinity.

Of major interest was the role of the 2,5-dimethoxy groups of 3 on 5-HT\textsubscript{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\textsubscript{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\textsubscript{2A} receptors and that removal of the \(\alpha\)-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-HT2A and 5-HT2C Serotonin Receptor Binding Data for Methoxy-Modified Derivatives of 3

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>5-HT2A affinity; Kᵢ, nM (SEM)</th>
<th>5-HT2C affinity; Kᵢ, nM (SEM)</th>
<th>5-HT2A selectivity&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
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<tbody>
<tr>
<td>3</td>
<td>-Me</td>
<td>30 (3)</td>
<td>50 (1)</td>
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<tr>
<td>12</td>
<td>-Me</td>
<td>8 (1)</td>
<td>69 (1)</td>
<td>11.1</td>
</tr>
<tr>
<td>13</td>
<td>-Me</td>
<td>17 (1)</td>
<td>135 (6)</td>
<td>7.9</td>
</tr>
<tr>
<td>14</td>
<td>-Me</td>
<td>4 (1)</td>
<td>79 (8)</td>
<td>19.8</td>
</tr>
<tr>
<td>15</td>
<td>-Me</td>
<td>4 (1)</td>
<td>40 (2)</td>
<td>10.0</td>
</tr>
<tr>
<td>16</td>
<td>-Me</td>
<td>3 (1)</td>
<td>39 (2)</td>
<td>13.0</td>
</tr>
<tr>
<td>17</td>
<td>-Me</td>
<td>78 (6)</td>
<td>530 (19)</td>
<td>6.8</td>
</tr>
<tr>
<td>18</td>
<td>-Me</td>
<td>60 (6)</td>
<td>525 (65)</td>
<td>8.9</td>
</tr>
</tbody>
</table>

<sup>a</sup> Selectivity represented by 5-HT<sub>2C</sub> Kᵢ value/5-HT<sub>2A</sub> Kᵢ value.

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

Table 3. 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> Serotonin Receptor Binding Data for Simple Monomethoxy, Dimethoxy, and Nonmethoxy Phenylalkylamine Analogues

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>X</th>
<th>receptor affinity; Kᵢ, nM (SEM)</th>
<th>5-HT&lt;sub&gt;2A&lt;/sub&gt; affinity; Kᵢ, nM (SEM)</th>
<th>5-HT&lt;sub&gt;2C&lt;/sub&gt; affinity; Kᵢ, nM (SEM)</th>
<th>5-HT&lt;sub&gt;2A&lt;/sub&gt; selectivity&lt;sup&gt;a&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>1a</td>
<td>-Me</td>
<td>Br</td>
<td>32 (4)</td>
<td>64 (12)</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>-H</td>
<td>Br</td>
<td>16 (1)</td>
<td>190 (90)</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>-Me</td>
<td>H</td>
<td>4 720 (1,150)</td>
<td>&gt;10 000</td>
<td>&gt;10 000</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>-Me</td>
<td>H</td>
<td>3 000 (410)</td>
<td>5 520 (390)</td>
<td>&gt;10 000</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>-Me</td>
<td>H</td>
<td>&gt;10 000</td>
<td>&gt;10 000</td>
<td>&gt;10 000</td>
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<td>-Me</td>
<td>H</td>
<td>&gt;10 000</td>
<td>&gt;10 000</td>
<td>&gt;10 000</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>-Me</td>
<td>H</td>
<td>4 280 (460)</td>
<td>&gt;10 000</td>
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<td></td>
</tr>
<tr>
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<td>-Me</td>
<td>H</td>
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<td>&gt;10 000</td>
<td>&gt;10 000</td>
<td></td>
</tr>
<tr>
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<td>-Me</td>
<td>Br</td>
<td>210 (45)</td>
<td>570 (110)</td>
<td>&gt;10 000</td>
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<td></td>
</tr>
<tr>
<td>27</td>
<td>-H</td>
<td>H</td>
<td>&gt;10 000</td>
<td>&gt;10 000</td>
<td>&gt;10 000</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> 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<sub>2A</sub> receptors. Relocation of the 2,5-dimethoxy groups to the 3,5- or 2,6-positions (i.e., 24, 26, Kᵢ >10 000 nM), and removal of both methoxy groups (i.e., 27; Kᵢ >10 000 nM), essentially abolishes affinity. We previously reported that 27 binds with a Kᵢ = 43 000 nM. 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. What is remarkable about the present results is the influence of the 4-(3-phenylpropyl) group on 5-HT<sub>2A</sub> 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 Kᵢ values of <10 nM. Even the nonmethoxy analogues 17 and 18 bind with affinities not much less than that of 3.

5-HT<sub>2C</sub> Receptor Binding. For those compounds examined in the present study, the structure–affinity requirements for 5-HT<sub>2C</sub> binding are not very different from those for 5-HT<sub>2A</sub> binding. Consequently, none of the compounds displayed dramatic selectivity for one population over the other. Compound 3 binds at 5-HT<sub>2C</sub> receptors with high affinity (Kᵢ = 50 nM) and with <2-fold selectivity for 5-HT<sub>2A</sub> 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<sub>2C</sub> affinity. The only change that seems to have less effect on 5-HT<sub>2C</sub> binding than on 5-HT<sub>2A</sub> 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<sub>2C</sub> 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<sub>2A</sub> receptors. Consequently, compounds 14–16 display about 10- to 20-fold selectivity for 5-HT<sub>2A</sub> receptors. Nevertheless, selectivity is not remarkable.

PI Hydrolysis. Several compounds were examined for their 5-HT<sub>2A</sub> 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<sub>2A</sub> partial agonist. However, 10 μM 3 plus 10 μM ketanserin (a 5-HT<sub>2</sub> 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<sub>2</sub> 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.
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-HT₂A affinity. None of the investigated compounds displayed >20-fold selectivity for 5-HT₂A versus 5-HT₂C receptors. Several of the compounds were examined in a 5-HT₂A 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-HT₂A binding. The same may be true of certain other 4-alkyl- or 4-(aryalkyl)-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-HT₂ 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 (¹H NMR) spectra were obtained with a Varian Gemini 300 spectrometer, using tetramethylsilane as an internal standard. Infrared spectra were recorded on a Nicolet 52DX FT-infrared spectrometer. Elemental analysis was performed by Atlantic Microlab, Inc., and determine 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 X 10 cm, Analtech, Inc., Newark, DE). Dry THF was obtained by distillation over sodium metal and benzophenone. Dry CH₂Cl₂ was obtained by distillation over phosphorus pentoxide (P₂O₅). 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.

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-HT₂ 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; Kᵢ = 30 nM) binds at 5-HT₂A receptors with an affinity comparable to that of DOB (Kᵢ = 32 nM). However, unlike what is seen with DOB,⁹ removal of either one of the two methoxy groups has little effect on 5-HT₂A 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. Stereoechemistry (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-HT₂A affinity. None of the investigated compounds displayed >20-fold selectivity for 5-HT₂A versus 5-HT₂C receptors. Several of the compounds were examined in a 5-HT₂A 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-HT₂A binding. The same may be true of certain other 4-alkyl- or 4-(aryalkyl)-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-HT₂ agonist character, the structure–activity relationships of phenylalkylamines require reinvestigation.

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compound as a white powder; mp 155–156 °C. 1H NMR (D2O): \( \delta \) 1.80 (t, 2H, CH2), 2.52–2.61 (m, 4H, CH2CH2), 2.87–2.88 (m, 2H, CH2), 3.13 (t, 2H, CH2), 3.71 (s, 3H, OCH3), 3.74 (s, 3H, OCH3), 6.81–6.85 (m, 2H, Ar–H), 7.15–7.29 (m, 5H, Ar–H); IR (KBr pellet): 2955 (NH–) cm\(^{-1}\). Anal. Calc. for (C19H26ClNO2) C, H, N.

2-[[2,5-Dimethoxy-4-(3-chlorophenyl)phenyl]-2-aminopropane hemioxalate (14)]. At 0 °C and under N2, dry THF (5 mL) was added to LiAlH4 (0.14 g, 3.67 mmol), followed by the addition of nitropine (0.5 g, 1.46 mmol) in dry THF (7 mL). The reaction mixture was heated for 1 h at reflux, then cooled to 0 °C. Excess LiAlH4 was decomposed by the addition of H2O (0.2 mL), 10% NaOH (0.2 mL), and H2O (1 mL). The salts were removed by filtration, and the filtrate was diluted with Et2O (25 mL) and dried (MgSO4). The aqueous solution was extracted with Et2O (3 × 50 mL). The organic product was dried under reduced pressure. The aqueous solution was extracted with Et2O (3 × 50 mL), the organic portion was dried (MgSO4), and the solvent was removed under reduced pressure to give an oil. The HCl salt was prepared and recrystallized from 2-PrOH to give 0.05 g (59%) of the desired compound; mp 160–163 °C after recrystallization from aqueous EtOH. This compound (1.16 g, 2.54 mmol) in diethylene glycol (18 mL) was heated at this temperature for 50 mL). The stirred mixture was heated at this temperature for 1 h, then cooled to 0 °C. Excess LiAlH4 was decomposed by the addition of H2O (0.2 mL), 10% NaOH (0.2 mL), and H2O (1 mL). The MeOH was removed under reduced pressure to give an oil. The mixture was heated at reflux overnight. Once cool, the reaction mixture was heated at reflux for 1 h, then cooled to 0 °C (ice bath). Excess LiAlH4 was decomposed by the addition of H2O (0.2 mL), 10% NaOH (0.2 mL), and H2O (1 mL). The salts were removed by filtration, and the filtrate was diluted with Et2O (25 mL) and dried (MgSO4). The mixture was heated at reflux for 2 h. The MeOH was removed under reduced pressure and the aqueous solution was extracted with Et2O (4 × 50 mL). The ethereal solution was dried (MgSO4), and the solvent was removed under reduced pressure. The oil was dissolved in anhydrous Et2O and etheral HCl was added to form the salt, which was recrystallized from 2-PrOH to give 0.08 g (47%) of the desired compound; mp 172–174 °C. 1H NMR (CDCl3): \( \delta \) 2.39 (t, 2H, CH2), 3.57 (t, 2H, CH2), 3.81 (s, 3H, OCH3), 3.88 (s, 3H, OCH3), 4.32 (s, 2H, CH2), 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), 2.60 (t, 4H, CH2), 2.95 (m, 2H, CH2), 3.65 (m, 1H, Ar–CH), 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. Calc. for (C20H28ClNO2) 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 etheral HCl. The white solid was recrystallized from 2-PrOH to give 0.19 g (45%) of the desired compound; mp 134–136 °C. 1H NMR (D2O): \( \delta \) 1.17 (d, 3H, CH3), 1.77–1.85 (m, 2H, CH2), 2.47–2.53 (m, 4H, CH2, CH2), 2.72 (d, 2H, CH2), 3.49–3.55 (m, 5H, CH2), 3.70 (s, 3H, OCH3), 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. Calc. for (C21H24ClNO) 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 Et2O to give 0.17 g (23%) of the desired compound; mp 107–109 °C. 1H NMR (D2O): \( \delta \) 1.12 (d, 3H, CH3), 1.65 (quintet, 2H, CH2), 2.34–2.40 (m, 4H, CH2, CH2), 2.66 (dd, 1H, CH2), 2.89 (dd, 1H, CH2), 3.43 (m, 1H, CH), 3.60 (s, 3H, OCH3), 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. Calc. for (C21H25NO) C, H, N.

1-[3,5-Dimethyl-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 Et2O (3 × 50 mL), the organic portion was dried (MgSO4), and the 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 the desired compound; mp 158–160 °C. 1H NMR (D2O): \( \delta \) 1.20 (d, 3H, CH3), 1.64–1.71 (m, 2H, CH2), 2.48–2.54 (m, 4H, CH2, CH2), 2.74 (dd, 1H, CH), 2.87 (dd, 1H, CH), 3.54–3.55 (m, 5H, CH2), 3.65 (bs, 3H, NH2), 3.71 (s, 3H, OCH3), 3.75 (s, 3H, OCH3), 6.86–6.90 (m, 2H, Ar–H), 7.17–7.31 (m, 5H, Ar–H); IR (KBr pellet): 2946 (NH–) cm\(^{-1}\). Anal. Calc. for (C20H27ClNO) C, H, N.

1-[2,5-Dimethoxy-4-(3-phenylpropyl)phenyl]-2-aminopropane HCl (16). At 0 °C under N2, dry THF (5 mL) was added to LiAlH4 (0.21 g, 5.53 mmol), followed by the addition of nitropine (0.5 g, 1.46 mmol) in dry THF (8 mL). The reaction mixture was heated at reflux under N2 for 1 h, then cooled to 0 °C (ice bath). Excess LiAlH4 was decomposed by the addition of H2O (0.2 mL), 10% NaOH (0.2 mL), and H2O (1 mL). The reaction mixture was filtered and washed with Et2O (3 × 25 mL). The ethereal solution was dried (MgSO4) and concentrated under reduced pressure to give 0.43 g (90%) of a colorless oil. The HCl salt was prepared and recrystallized from 2-PrOH/anhydrous Et2O to give 0.26 g (51%) of the desired compound; mp 160–162 °C. 1H NMR (D2O): \( \delta \) 1.16 (d, 3H, CH3), 1.65–1.75 (m, 2H, CH2), 2.33–2.41 (m, 4H, CH2, CH2), 2.80 (d, 2H, CH2), 3.42–3.49 (m, 1H, CH), 3.57 (s, 3H, OCH3), 6.24 (s, 2H, Ar–H), 6.95–7.08 (m, 5H, Ar–H); IR (KBr pellet): 2936 (NH–) cm\(^{-1}\). Anal. Calc. for (C19H24ClNO) C, H, N.
which was recrystallized from 2-PrOH to give 0.14 g (19%) of
failed. Preparation of the fumarate salt yielded a solid material
7.18 (m, 9H, Ar
CH2), 2.47
H, CH2), 2.72 (dd, 1H, CH2-3a), 2.90 (dd, 1H, CH3), 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 (C18H24Cl4F2N)·HCl: 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 LiAlH4 (0.30 g, 7.90 mmol) in dry THF (10 mL) at 0 °C under an N2 atmosphere. The reaction mixture was heated at reflux for 1.5 h then cooled to 0 °C; excess LiAlH4 was decomposed by the successive addition of H2O (0.4 mL), 15% NaOH (1 mL), and H2O (3 mL). The reaction mixture was filtered, and the solids were washed with anhydrous CH2Cl2 to give the alane, which was decomposed by the addition of AlCl3 (0.10 g, 0.75 mmol) in anhydrous Et2O (2 mL) under N2. The alane mixture in a dropwise manner. The reaction mixture was allowed to stir at –30 °C for 30 min and then warmed to room temperature where stirring continued under N2 for an additional 2 h. 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 CH2Cl2 (4 × 50 mL). The combined organic portions were extracted with H2O (3 × 30 mL), 5% HCl (3 × 30 mL), NaHCO3 (3 × 30 mL), saturated NaCl (3 × 30 mL), and dried (MgSO4). 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. 1H NMR (CDCl3): δ 2.93 (2H, CH2), 3.57 (2H, CH3), 3.81 (3H, OCH3), 3.88 (3H, OCH3), 4.32 (2H, NH2), 6.76 (1H, Ar–H), 6.99 (3H, 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 (C20H32F2NO4)·C, H, N.

N-Trifluoroacetyl-2-(2,5-dimethoxy-4-hydrocinnamoyl)-1-aminooethane (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. 1H NMR (CDCl3): δ 2.97 (4H, CH2CH2), 3.12 (2H, CH2), 3.59 (2H, CH2), 3.85 (8H, OCH3), 6.76 (1H, 1H, Ar–H), 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 (C21H26F2NO4)·C, H, N.

Compound 32 was prepared from 29 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. 1H NMR (CDCl3): δ 1.29 (3H, CH3), 2.80–2.97 (m, 2H, CH2), 3.85 (6H, OCH3), 4.14–4.17 (1H, CH), 4.32 (3H, CH3), 6.76 (1H, Ar–H), 7.21–7.31 (m, 7H, Ar–H); IR (film): 3295 (NH), 1693 (C=O, amide), 1673 (C=O, ketone) cm–1. Anal. Calcd. for (C20H22F3NO4)·C, H, N.

N-Trifluoroacetyl-2-(2,5-dimethoxy-4-(2-phenylethyl)-phenyl)-1-aminopropane (32). Compound 32 was prepared from 29 and phenylacetyl chloride in the same manner used for the preparation of 30. The resulting solid was recrystallized from absolute EtOH to give a 60% yield of the desired compound; mp 146–148 °C. 1H NMR (CDCl3): δ 1.29 (3H, CH3), 2.80–2.97 (m, 2H, CH2), 3.85 (6H, OCH3), 4.14–4.17 (1H, CH), 4.32 (3H, CH3), 6.76 (1H, Ar–H), 7.21–7.31 (m, 7H, Ar–H); IR (film): 3295 (NH), 1693 (C=O, amide), 1673 (C=O, ketone) cm–1. Anal. Calcd. for (C20H22F3NO4)·C, H, N.

Compound 33 was prepared from 20, 22, and phenylacetyl chloride in the same manner used for the preparation of 30. The resulting solid 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. 1H NMR (CDCl3): δ 1.29 (3H, CH3), 2.80–2.97 (m, 2H, CH2), 3.85 (6H, OCH3), 4.14–4.17 (1H, CH), 4.32 (3H, CH3), 6.76 (1H, Ar–H), 7.21–7.31 (m, 7H, Ar–H); IR (film): 3333 (NH), 1715 (C=O, amide), 1665 (C=O, ketone) cm–1. Anal. Calcd. for (C21H26F2NO4)·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-dimethoxy-4-iodophenyl)-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 H2O (30 mL), 1% Na2S2O3/1% KI (50 mL), and H2O (30 mL), then recrystallized from EtOH to give 0.63 g (58%) of the title compound as white, white crystals; mp 132–134 °C (lit.13 mp 137 °C). 1H NMR (CDCl3): ä 2.78 (t, 2H, CH3), 3.55 (2H, CH2), 3.81 (3H, OCH3), 3.82 (3H, OCH3), 6.63 (s, 1H, Ar–H), 6.92 (bs, 1H, NH), 7.27 (s, 1H, Ar–H); IR (film): 3237 (NH), 1703 (C=O) cm–1.

N-Trifluoroacetyl-2-(2,5-dimethoxy-4-(4-phenylbutyl)-1-aminopropanoate (38). N-Trifluoroacetyl-2-(2,5-dimethoxy-4-iodophenyl)-1-aminoethane (36) (0.55 g, 1.36 mmol) and 4-(phenylbutyn-1-yl) cuprate (0.46 g, 2.39 mmol) were dissolved in dry pyridine (12 mL), and the reaction mixture was heated at reflux for 45 min. The reaction mixture was cooled to room temperature, diluted with H2O (50 mL), 1% Na2S2O3/1% KI (50 mL), and H2O (30 mL). The ethereal solution was washed with H2O (30 mL), absolute EtOAc (20 mL), and Et2O (20 mL), and dried under high vacuum to yield 1.10 g (80%) of the desired compound; mp 187–189 °C (dec). The product was used in the preparation of 38 and 39 without further characterization. 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 H2O (30 mL), absolute EtOAc (20 mL), and Et2O (20 mL), and dried under high vacuum to yield 1.27 g (100%) of the desired compound; mp 187–189 °C. 1H NMR (CDCl3): 134 °C (lit.13 mp 137 °C). 1H NMR (CDCl3): 2.78 (t, 2H, CH3), 3.55 (2H, CH2), 3.81 (3H, OCH3), 3.82 (3H, OCH3), 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-1-(2,5-dimethoxy-4-(4-phenylbutynyl)-1-aminopropanoate (40). A solution of 38 (0.5 g, 2.95 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 (6%) of 40; mp 78–80 °C. 1H NMR (CDCl3): 1.60–1.69 (m, 4H, CH2=CH2), 2.59–2.67 (4H, CH2=CH2), 2.63 (s, 3H, OCH3), 3.56 (2H, CH2), 3.76 (s, 3H, OCH3), 6.78 (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 (C22H26F3NO3)C, H, N.
1-[4-(3-Phenylpropyl)phenyl]-2-nitropropane (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 nitromethane (30 mL) was heated at reflux under N2 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. 1H NMR (CDCl3): δ 1.96–2.04 (m, 2H, CH₂), 2.47 (s, 3H, CH₃), 2.65–2.73 (m, 4H, CH₂, CH₃), 2.61–2.75 (m, 4H, CH₂, CH₃), 3.84 (s, 3H, OCH₃), 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.

2-Methoxy-4-(trifluoromethanesulfonyl)benzaldehyde (48). The product was used in the preparation of 52 without further characterization.

2-Methoxy-4-(3-phenylpropyl)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 0.43 g (61%) of 49 without further characterization.

1-[4-(3-Phenylpropyl)phenyl]-2-nitropropane (49). Compound 49 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). 1H NMR (CDCl3): δ 2.49–2.54 (m, 2H, CH₂), 2.67–2.70 (m, 2H, CH₂, CH₃), 2.89 (s, 3H, OCH₃), 6.75 (s, 1H, Ar–H), 6.85(1H, Ar–H), 7.70–7.73 (m, 3H, Ar–H), 8.18 (s, 1H, CHO); IR (film): 1651 (C=O) cm⁻¹. The product was used in the preparation of 49 without further characterization.

1-(2-Methoxy-4-(3-phenylpropyl)phenyl)-2-nitropropane (50). Compound 50 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 51 as a pale-yellow oil. 1H NMR (CDCl3): δ 2.43 (s, 3H, CH₃), 2.67–2.72 (m, 4H, CH₂, CH₃), 3.88 (s, 3H, OCH₃), 6.76 (s, 1H, Ar–H), 6.85 (1H, Ar–H), 7.70–7.71 (m, 6H, Ar–H), 8.31 (s, 1H, CH=); IR (film): 1525 (N=O cm⁻¹). The product was used in the preparation of 50 without further characterization.

1-(2-Methoxy-4-(3-phenylpropyl)phenyl)-2-nitropropane (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 Et₂O (5 mL) and combined with a saturated solution of NaHSO₃ (50 mL). After 30 min of vigorous stirring, the reaction mixture was heated at reflux on an oil bath for 1 h, then allowed to cool to room temperature, the impure fractions by radial chromatography on a Chromatotron (silica gel, grade 7769) (eluted, hexanes/EtOAc, 10:1) gave 0.56 g of 52 (63% total yield). 1H NMR (CDCl3): δ 1.88 (bs, 1H, CH=), 2.17 (s, 2H, CH₂), 2.52 (s, 3H, CH₃), 4.31 (d, 1H, CH), 6.52 (d, 1H, CH), 7.29–3.09 (m, 9H, CH₃, CH₂), 7.55 (s, 6H, O(CH₃)₂), 4.25–4.35 (m, 1H, CH), 6.10 (bs, 1H, NH), 6.32 (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-Trimesitylene (52). 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 a few crystals of the acetamide (1.20 mL, 10.94 mmol) and a few crystals of the acetamide (30 mL). The mixture was heated at reflux on an oil bath for 1 h, then allowed to cool to room temperature. At 0 °C and under N₂, the Grignard reagent was added via syringe to a solution of 3,5-dimethoxybenzaldehyde (53) (3.00 g, 18.05 mmol) in anhydrous Et₂O (15 mL). The reaction mixture was stirred at 0 °C for 30 min, then at room temperature for 30 min, whereupon the reaction was quenched by adding 30% H₂SO₄ (5 mL). The mixture was extracted between Et₂O and H₂O. The ethereal portion was dried (MgSO₄) and evaporated under reduced pressure to give a colorless 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 product 56. Further purification of the impure fractions by radial chromatography on a Chromatotron (silica gel, grade 7169) (eluted, hexanes/EtOAc, 10:1) gave 0.56 g of 56 (83% total yield). 1H NMR (CDCl3): δ 0.88 (bs, 1H, CH=), 2.17 (s, 2H, CH₂), 2.52 (d, 1H, CH), 6.52 (d, 1H, CH), 7.29–3.09 (m, 9H, CH₃, CH₂), 7.55 (s, 6H, O(CH₃)₂), 4.25–4.35 (m, 1H, CH), 6.10 (bs, 1H, NH), 6.32 (2H, Ar–H), 7.18–7.27 (m, 5H, Ar–H); IR (film): 3433 (OH) cm⁻¹. Chlorotrimethylsilane (5.00 mL, 39.40 mmol), sodium iodide (5.95 g, 39.56 mmol), and dry MeCN (2.61 mL, 49.97 mmol) were combined and allowed to stir at room temperature under an N₂ atmosphere for 15 min. A solution of propenol (56) (1.79 g, 6.57 mmol) in anhydrous Et₂O (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 H₂O, extracted between Et₂O and H₂O. The ethereal portion was dried over MgSO₄. 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. 1H NMR (CDCl3): δ 1.88–2.00 (m, 2H, CH₂), 2.57–2.68 (m, 4H, CH₂, CH₃), 3.78 (3s, 6H, O(CH₃)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 N₂ atmosphere, n-butylithium (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% H₂SO₄ (4 mL) and extracted between H₂O and Et₂O; the ethereal portion was washed with saturated NaCl solution and dried (MgSO₄), and solvent was evaporated under reduced pressure to give 1.10 g of a yellow oil. Purification by column chromatography on silica gel (grade 7769) (eluted, 100:1, hexanes/EtOAc) gave another 0.39 g of the desired aldehyde 58. Further purification of the crude material by radial chromatography on a Chromatotron (silica gel, grade 7769) gave another 0.31 g of the desired aldehyde 58. IR (film): 1522 (N—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.

1-(3,5-Dimethoxy-4-(3-phenylpropyl)phenyl)-2-nitropropene (59). A suspension of the product (0.70 g, 1.22 mmol) and NH₄OAc (0.08 g, 1.04 mmol) in nitroethane (3 mL) was heated at reflux for 5 h under an N₂ atmosphere. At 0 °C under N₂, trifluoroacetic anhydride (2.10 mL, 14.90 mmol) in CHCl₃ (10 mL) was added in a dropwise manner to a solution of 1-(4-bromo-3,5-dimethoxyphenyl)-2-nitropropene (54) (2.31 g, 11.83 mmol) in CHCl₃ (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 as a colorless solid. The product was used without further characterization for the preparation of 14.

1,2-Dimethoxy-3-(3-phenylpropyl)benzene (60). At 0 °C under N₂, n-butylithium (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 N₂. 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 EtO₂, the combined organic portions were dried (MgSO₄), and solvent was removed to give a yellow oil which had three components as determined by thin-layer chromatography. The product was partially purified by column chromatography using silica gel (grade 62–120 mesh, 150 Å) (eluted, 100:1, hexanes/EtOAc) to give 5.6 g of a colorless oil which was used in the preparation of 61. (Yield is 80% based on recovered 1,2-dimethoxybenzene.) IR (film): 1.88–1.98 (m, 2H, CH₂), 2.65–2.70 (m, 4H, CH₂, CH₃), 3.78 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 6.76–6.78 (m, 2H, Ar—H). IR (film): 2940 (aromatic) cm⁻¹.

2,3-Dimethoxy-4-(3-phenylpropyl)benzaldehyde (61). At 0 °C and under a nitrogen atmosphere, TEMEDA (1.54 mL, 10.20 mmol) was added to n-butylithium (2.5 M in hexanes) (4.0 mL, 10.00 mmol), and aldehyde was reduced under pressure to give 5.1 g of a colorless oil which was used in the preparation of 61. (Yield is 80% based on recovered 1,2-dimethoxybenzene.) IR (film): 1.88–1.98 (m, 2H, CH₂), 2.65–2.70 (m, 4H, CH₂, CH₃), 3.78 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 6.76–6.78 (m, 2H, Ar—H). IR (film): 1522 (N—O) cm⁻¹; IR (film): 2940 (aromatic) cm⁻¹.

2,6-Dimethoxy-4-(3-phenylpropyl)benzaldehyde (58). At −10 °C and under an N₂ atmosphere, n-butylithium (2.5 M in hexanes) (4.0 mL, 10.00 mmol), and aldehyde was reduced under pressure to give 5.1 g of a colorless oil which was used in the preparation of 61. (Yield is 80% based on recovered 1,2-dimethoxybenzene.) IR (film): 1.88–1.98 (m, 2H, CH₂), 2.65–2.70 (m, 4H, CH₂, CH₃), 3.78 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 6.76–6.78 (m, 2H, Ar—H). IR (film): 2940 (aromatic) cm⁻¹. The product was used without further characterization in the synthesis of 16.

1-(4-Bromo-3,5-dimethoxyphenyl)-2-nitropropane (65). A solution of 4-bromo-3,5-dimethoxybenzaldehyde (0.30 g, 1.22 mmol) and NH₄OAc (0.08 g, 1.04 mmol) in nitroethane (3 mL) was heated at reflux for 5 h under N₂ atmosphere. Solvent was removed under reduced pressure to give a semisolid material. Purification by column chromatography on silica gel (grade 62, 60–120 mesh, 150 Å) (eluted, hexanes/EtOAc 2:1) gave 0.41 g (57%) of the desired nitrostyrene; mp 108–110 °C (lit. mp 121–125 °C). IR (film): 1522 (N—O) cm⁻¹; IR (film): 2940 (aromatic) cm⁻¹.
References


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