

# 'Hybrid' benzofuran–benzopyran congeners as rigid analogs of hallucinogenic phenethylamines

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**Abstract**—Phenylalkylamines that possess conformationally rigidified furanyl moieties in place of alkoxy arene ring substituents have been shown previously to possess the highest affinities and agonist functional potencies at the serotonin 5-HT<sub>2A</sub> receptor among this chemical class. Further, affinity declines when both furanyl rings are expanded to the larger dipyranyl ring system. The present paper reports the synthesis and pharmacological evaluation of a series of 'hybrid' benzofuranyl–benzopyranyl phenylalkylamines to probe further the sizes of the binding pockets within the serotonin 5-HT<sub>2A</sub> agonist binding site. Thus, **4(a–b)**, **5(a–b)**, and **6** were prepared as homologs of the parent compound, 8-bromo-1-(2,3,6,7-tetrahydrobenzo[1,2-*b*:4,5-*b'*]difuran-4-yl)-2-aminopropane **2**, and their affinity, functional potency, and intrinsic activity were assessed using cells stably expressing the rat 5-HT<sub>2A</sub> receptor. The behavioral pharmacology of these new analogs was also evaluated in the two-lever drug discrimination paradigm. Although all of the hybrid isomers had similar, nanomolar range receptor affinities, those with the smaller furanyl ring at the arene 2-position (**4a–b**) displayed a 4- to 15-fold greater functional potency than those with the larger pyranyl ring at that position (**5a–b**). When the furan ring of the more potent agonist **4b** was aromatized to give **6**, a receptor affinity similar to the parent difuranyl compound **2** was attained, along with a functional potency equivalent to **2**, **4a**, and **4b**. In drug discrimination experiments using rats trained to discriminate LSD from saline, **4b** was more than two times more potent than **5b**, with the latter having a potency similar to the classic hallucinogenic amphetamine **1** (DOB).

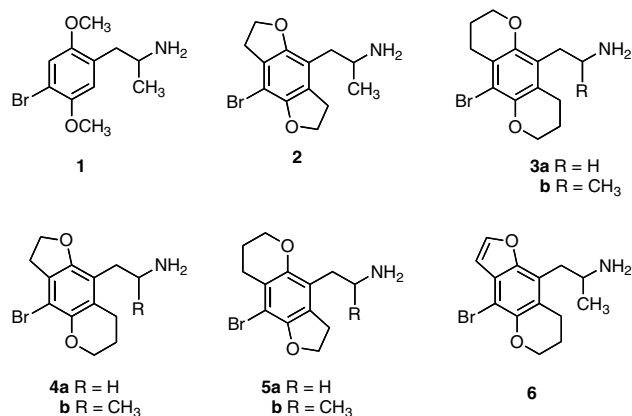
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## 1. Introduction

Agonist activity at the serotonin 5-HT<sub>2A</sub> receptor appears to be essential for the observed psychopharmacology of psychedelic agents such as LSD, mescaline, psilocin, and 5-MeO-DMT, compounds that exert unique and dramatic effects on certain aspects of consciousness.<sup>1</sup> A key aspect to understanding the unusual effects of psychedelics is the study of the receptor–ligand interaction at the molecular level and how it modulates second messenger generation subsequent to receptor activation.

Recently, we have been particularly interested in experimental validation of our h5-HT<sub>2A</sub> receptor homology model.<sup>2</sup> This model has proven to have predictive power in designing simple conformationally constrained phen-

ethylamine agonists for this receptor,<sup>3,4</sup> and we have been interested in extending it to provide a more comprehensive description of the key amino acid residues involved in receptor binding and activation.<sup>5</sup> As a member of the type A G-protein coupled receptor (GPCR) family, we



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reasoned that understanding this receptor would provide general concepts that might extend across the GPCR field.

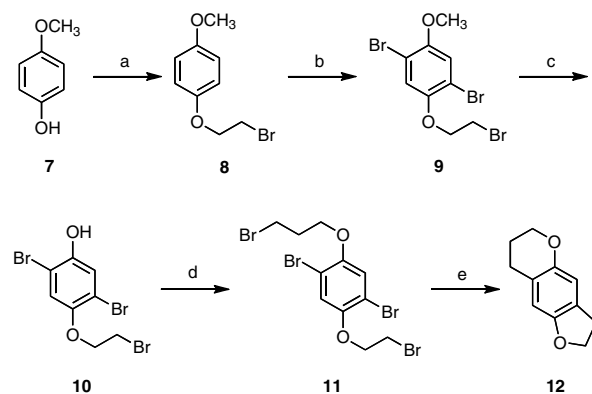
We previously discovered that constraining the 2- and 5-methoxy groups of prototypical, substituted phenethylamine ligands such as 2,5-dimethoxy-4-bromoamphetamine (DOB) **1** into rigid heterocycles gave highly potent compounds such as **2**.<sup>6</sup> These findings clearly demonstrated that the methoxy groups adopted particular orientations upon binding to the 5-HT<sub>2A</sub> receptor, presumably to direct their unshared electron pairs toward polar complementary residues within the agonist binding site, most likely serine residues S239 and S159.<sup>2,5</sup> We also had found that expanding the two heterocyclic rings to two, six-membered dihydropyran moieties, as in **3**, led to an almost 10-fold decrease in activity, both in vitro and in vivo.<sup>7</sup> The most reasonable explanation for these findings was that the receptor space around one, or both, of the oxygen atoms was sterically constricted.

This present study extends that earlier work, where now the activity of the two isomeric pyrano/furano ‘hybrid’ analogues (**4a–b** vs **5a–b**) is examined to determine which, if either, of the oxygen atoms lies within a more constrained steric area. Our virtual docking experiments place the 2-oxygen atom downward in the binding cavity, whereas the 5-oxygen atom is projected upward toward the extracellular face of the receptor.<sup>3,5,8</sup> These observations suggest that the oxygen atom that is more deeply embedded in the receptor might be the one that has greater steric restriction around it. The present experiments tested that hypothesis, and compared compounds **4a** and **4b** with **5a** and **5b**, respectively, for affinity and functional potency at the 5-HT<sub>2A</sub> receptor. We also examined **4b** and **5b** for an LSD-like behavioral effect in rats. Because the lipophilic properties of these latter two compounds are virtually identical, any difference in activity would be related to pharmacodynamic, rather than pharmacokinetic effects. In addition, because it was known that aromatization of the furan rings in **2** greatly enhanced activity,<sup>9</sup> we aromatized the furan ring of **4b** to afford **6** and examined the effect on receptor affinity and potency.

## 2. Results

### 2.1. Chemistry

It was envisioned that all target molecules **4–6** could be prepared readily from their common tricyclic intermediate **12** (Scheme 1). This asymmetric pyrano/furano hybrid ring system required that the precursors of each oxygen heterocycle (the respective bromoethyl and bromopropyl ether moieties) be constructed independently, as outlined in the scheme. Initially, *para*-methoxy phenol **7** was alkylated with dibromoethane to provide diether **8**. (Our early attempts to build the larger pyran ring first, by alkylating with 1,3-dibromopropane, proved to be considerably less efficient.) Following dibromination of **8**, the aromatic methyl ether of **9** was selectively cleaved using *B*-bromo-9-BBN.<sup>10,11</sup> This



**Scheme 1.** Reagents and conditions: (a) 1,2-dibromoethane, K<sub>2</sub>CO<sub>3</sub>, acetone, reflux; (b) Br<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, Fe; (c) *B*-bromo-9-BBN, CH<sub>2</sub>Cl<sub>2</sub>, reflux 14 days; (d) 1,3-dibromopropane, K<sub>2</sub>CO<sub>3</sub>, acetone, reflux; (e) *n*-butyllithium, THF, 0 °C.

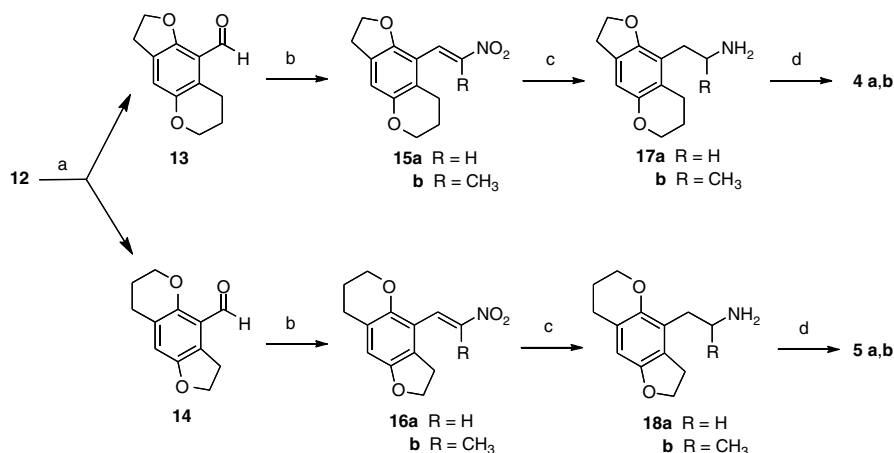
mild demethylating agent was found to be highly effective, whereas the more reactive traditional reagents, HBr, BBr<sub>3</sub> and BCl<sub>3</sub>, were all found to cleave both of the ether moieties of **9**. Due to the moderately unstable nature of phenol **10**, after isolation, it was immediately alkylated with 1,3-dibromopropane to afford the desired diether **11**. Finally, the simultaneous tandem ring-closure of **11** to yield key tricyclic intermediate **12** was readily achieved using *n*-butyllithium.

With **12** in hand, formylation using dichloromethyl methyl ether in the presence of a tin(IV) catalyst produced regioisomers **13** and **14** (Scheme 2). Separation of these isomers by selective recrystallization and flash column chromatography<sup>12</sup> gave **13** and **14** in a 5:1 ratio, respectively. Both aldehydes were then carried through the parallel sequence of reactions shown in Scheme 2. Thus, following condensation of the aldehydes with nitromethane or nitroethane, the resulting nitroalkenes **15** and **16** were fully reduced in the presence of LiAlH<sub>4</sub> to afford primary amines **17** and **18**. Target compounds **4a–b** and **5a–b** were then produced in good yield by brominating the remaining aromatic positions of **17** and **18**, respectively.

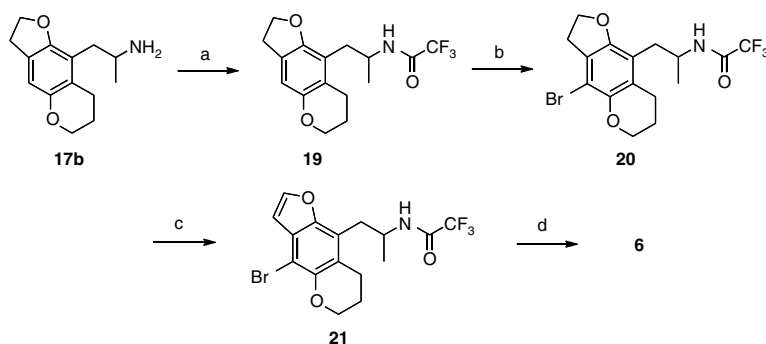
Aromatization of the furan ring of **4b** was accomplished using a method analogous to that employed by Parker et al.<sup>9</sup> As shown in Scheme 3, dihydrofuran **17b** was protected as its *N*-trifluoroacetamide **19**, brominated to provide **20**, and then oxidized using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to afford the protected intermediate **21**. Deprotection in strong base gave **6**, the final target molecule. The relatively minor amounts of **14** obtained from the formylation reaction in Scheme 2 precluded a parallel synthesis of aromatized **5b**; fortunately, **4b** proved to be the more potent isomer, and its oxidized analog **6** sufficiently demonstrated the effects of aromatization of the furan ring.

### 2.2. Pharmacology

All new target compounds were assessed for their affinity at the rat 5-HT<sub>2A</sub> receptor, using displacement of



**Scheme 2.** Reagents and conditions: (a) dichloromethyl methyl ether,  $\text{SnCl}_4$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ ; (b)  $\text{RCH}_2\text{NO}_2$ , ammonium acetate,  $80^\circ\text{C}$ ; (c)  $\text{LiAlH}_4$ , THF, reflux; (d)  $\text{Br}_2$ ,  $\text{AcOH}$ .



**Scheme 3.** Reagents and conditions: (a) ethyl trifluoroacetate,  $\text{Et}_3\text{N}$ , THF, reflux; (b)  $\text{AcOH}$ ,  $\text{Br}_2$ , dioxane; (c) DDQ, toluene, reflux; (d) 5 M  $\text{KOH}$ ,  $\text{MeOH}$ .

$[\text{^3H}]$ ketanserin. In addition, functional potency and intrinsic activity were determined using the inositol phosphate accumulation assay.<sup>13</sup> The affinities and potencies of the new compounds were compared with the prototype dimethoxy compound, DOB **1**, and its rigidified difurano and dipyrano analogs, **2** and **3**, respectively. These data are presented in Table 1, along with the  $\text{clogP}$  values of all compounds. Behavioral pharmacology for new compounds **4b** and **5b** was assessed using the two-lever drug discrimination paradigm,<sup>14–18</sup> and those results are presented in Table 2, along with the comparative data for **1**.

As seen in Table 1, the two new hybrid congeners, **4** and **5**, as well as the dipyrano compounds **3**,<sup>7</sup> had approximately 4- to 5-fold lower affinity than the difurano analog **2**, suggesting that the smaller furan rings are better tolerated by the receptor than the larger pyran rings. There was no significant difference in receptor affinity between **4** and **5**. As we had previously observed with the aromatization of **2**,<sup>9,19</sup> oxidation of the dihydrofuran ring of **4b** to give **6** increased receptor affinity nearly 4-fold (compare  $K_i$  values of **4b** and **6**).

When functional potency was examined (see  $\text{EC}_{50}$  values in Table 1), **4b** had about 4-fold higher potency in stimulating inositol phosphate accumulation, compared to

**Table 1.** Analysis of biological activity at the rat 5-HT<sub>2A</sub> receptor

Drug	$\text{clogP}$	5-HT <sub>2A</sub> $K_i$ , nM (SEM)	$n$	$\text{EC}_{50}$ , nM (SEM)	Intrinsic activity % 5-HT (SEM)	$n$
<b>1</b>	2.45	13 (6.0)	2	22 (3.8)	73 (5)	3
<b>2</b>	2.65	1.0 (0.12)	5	13 (1.9)	88 (4)	3
<b>3a</b>	3.46	4.5 (0.76)	3	241 (46)	61 (9)	3
<b>3b</b>	3.77	3.1 (0.55)	4	258 (45)	72 (2)	3
<b>4a</b>	2.90	11 (1.4)	3	9.4 (1.2)	61 (6)	3
<b>4b</b>	3.21	3.6 (0.73)	6	19 (1.9)	86 (7)	5
<b>5a</b>	2.90	8.4 (0.35)	3	146 (30)	64 (12)	3
<b>5b</b>	3.21	5.3 (0.57)	7	78 (11)	74 (8)	4
<b>6</b>	3.77	1.0 (0.12)	5	13 (1.9)	102 (6)	3

$K_i$  values for  $[\text{^3H}]$ ketanserin competition displacement assays in NIH-3T3 cells expressing the rat 5-HT<sub>2A</sub> receptor and functional potency for stimulating inositol phosphate accumulation in the same cells.

**5b**, and was nearly as potent as the difuranyl compound **2**. Surprisingly, although the receptor affinities were nearly the same for the dipyranyl compound **3b** and the smaller hybrid compound **4b**, the latter was functionally more than an order of magnitude more potent than **3b** in stimulating inositol phosphate accumulation. Further, aromatization of the furan ring of **4b** to give **6** had virtually no effect on potency, although receptor affinity was enhanced. Comparison of **3a** with **3b**, **4a** with **4b**, and **5a** with **5b** also shows that the addition

**Table 2.** Results from substitution tests in LSD-trained rats

Drug	Dose		N	% D	% SDL	ED <sub>50</sub> (95% CL)	
	mg/kg	μmol/kg				mg/kg	μmol/kg
<b>1</b>	0.25	0.80	13	46	29	0.35	1.06
	0.38	1.21	10	40	50	(0.27–0.46)	(0.82–1.36)
	0.50	1.61	14	36	89		
<b>4b</b>	0.09	0.25	12	0	33	0.14	0.38
	0.17	0.50	11	0	54	(0.08–0.23)	(0.24–0.60)
	0.35	1.00	12	0	83		
<b>5b</b>	0.17	0.50	12	17	10	0.40	1.16
	0.35	1.00	12	0	41	(0.26–0.61)	(0.77–1.75)
	0.69	2.00	10	0	80		

All drugs were injected 30 min before tests. *N*, number of rats used for tests. % D, the percentage of rats with disrupted behavior. % SDL, the percentage of rats that selected the drug-appropriate lever. If the drug was one that completely substituted for the training drug, the method of Litchfield and Wilcoxon<sup>20</sup> was used to determine the ED<sub>50</sub> and 95% confidence interval (95% CL).

of the alpha methyl slightly enhances intrinsic activity in this series, confirming the earlier conclusions drawn by Parrish et al.<sup>8</sup>

The drug discrimination (DD) paradigm routinely has been used in our laboratory as a screen for evaluating the behavioral activity and hallucinogenic potential of newly synthesized molecules.<sup>14–16</sup> This assay system models human hallucinogenic effects by examining the LSD-like discriminative stimulus properties produced in animals.<sup>17,18</sup> Thus, compounds **1**, **4b**, and **5b** were evaluated in the two-lever DD assay using a group of rats trained to discriminate the effects of ip injections of saline from those of D-lysergic acid *N,N*-diethylamide (LSD) tartrate (0.08 mg/kg; 186 nmol/kg) (Table 2). As can be seen in Table 2, **4b** has nearly three times the in vivo potency of **5b**, whereas the ED<sub>50</sub>s for **1** and **5b** are not significantly different from each other.

### 3. Discussion

Previously, we demonstrated that when the two methoxy groups of **1** are constrained into dihydrofuran rings, as in **2**, both receptor affinity and functional potency are significantly increased.<sup>9</sup> In a prior study, we also had shown that expansion of both furan rings to the larger, six-membered pyrans led to a nearly 10-fold loss of affinity and in vivo behavioral activity, although compounds **3** were still significantly more potent than the flexible prototype **1**.<sup>7</sup> In this report, new compounds **4–6** further support those earlier observations and confirm the proper orientation of the arene oxygen lone pair electrons for optimal activity at the 5-HT<sub>2A</sub> receptor.

On the basis of virtual docking studies, we have hypothesized that the 5-HT<sub>2A</sub> receptor has less steric tolerance around the oxygen moiety that projects downward into the receptor than the one projected toward the extracellular face of the receptor.<sup>2</sup> Those virtual docking studies are supported by our recent mutagenesis experiments and indicate that the 5-oxygen of **1** projects upward, toward the extracellular face of the receptor, whereas the 2-oxygen projects downward into the receptor binding cavity.<sup>5</sup> In the present study, a comparison of the activities of **4** and **5** further supports this hypothesis.

Although this conclusion is not as evident in the affinity data, it is clearly apparent when functional potency is assessed. Indeed, because affinity simply measures how tightly the ligand binds to the receptor, measures of functional potency better reflect general complementarity between the agonist and the receptor.

Intrinsic activity also is increased slightly by addition of the alpha-methyl to the side chain (compare **3a** with **3b**, **4a** with **4b**, and **5a** with **5b**). We previously reported a similar result for other substituted hallucinogenic phenalkylamines.<sup>8</sup> Although there is no definitive explanation for this observation, our virtual docking studies<sup>8</sup> prompt us to speculate that the alpha-methyl may have favorable van der Waals interactions with a residue in transmembrane helix 6. Although aromatization of the furan rings of **2** leads to the most potent simple phenethylamine type agonists presently known,<sup>9,19</sup> aromatization of the furan ring of **4b** to **6** had a slight, albeit non-significant, effect on intrinsic activity. It should be noted, however, that this aromatization did increase receptor affinity nearly 4-fold.

Of the new compounds reported here, those with the smaller *O*-heterocycle (furan) at the 2-position of the aryl ring (**4a**, **4b**, and **6**) clearly have higher affinities and functional potencies than those with the smaller *O*-heterocycle (furan) at the 5-position (**5a** and **5b**). These findings support our primary current hypothesis that the 5-HT<sub>2A</sub> receptor is more tolerant of steric bulk in the region that interacts with the 5-oxygen function.

Data from the in vivo behavioral studies using the drug discrimination paradigm, where rats are trained to discriminate LSD from saline, are also consistent with these conclusions. Thus, analog **4b**, which had a 4-fold higher functional potency than **5b**, proved to be nearly three times more potent than **5b** in this in vivo assay. Because **4** and **5** have essentially identical pharmacokinetic properties (compare clog *P* values in Table 1), as well as similar affinities and intrinsic activities, the in vivo potency seems to be primarily attributable to the functional potency of the ligand, and thus to a highly complementary agonist–receptor interaction. Nonetheless, **5b**, where the 2-oxygen is incorporated into a pyran ring and the 5-oxygen into a furan ring, still produced a



discriminative stimulus effect similar to that of **1**. It should be noted that the loss of potency of **5b**, when compared with **4b**, was not as dramatic as was observed earlier for compounds **3**, where both oxygen atoms are incorporated into larger pyran rings.<sup>7</sup>

The high potency and intrinsic activity of compounds with an extended aromatic system, that is, **6**, suggests that they are also closely complementary to the agonist binding site of the receptor. Because the endogenous agonist ligand, serotonin, is based on a bicyclic aromatic indole nucleus, we speculate that the aromatic furan rings better mimic the indole system and provide a more extensive  $\pi$ – $\pi$  stacking partner for an aromatic residue within the receptor. Furthermore, the differences in hydrophobicity between **4b**, **5b**, and **6** are most likely so small as to not contribute significantly to the different in vivo activities of these agents; rather, the primary factors influencing activity and potency in this class appear to be the steric–electronic effects of the heterocyclic moieties of the 2 and 5 positions.

In conclusion, we have demonstrated that the different regioisomeric *O*-heterocycles in this homologous series of phenethylamines are not equally well accommodated by the receptor. In particular, we have shown that the steric space around the 2-oxygen appears to be more constrained than around the 5-position, as seen when comparing the potencies of **4b** with **5b**. Future structure–activity relationship work probing the extent of these different spatial size constraints is warranted and is currently underway in our laboratories.

## 4. Experimental

### 4.1. Chemistry

All reactions were carried out under an inert atmosphere unless otherwise indicated. Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed using Baker-flex silica gel plastic-backed plates with fluorescent indicator, developing with  $\text{CH}_2\text{Cl}_2$ , and visualizing under UV light.  $^1\text{H}$  NMR spectra were obtained using a 300 MHz Bruker AC-300 or a 300 MHz Bruker ARX-300 NMR spectrometer with TMS as the internal standard. Abbreviations used in NMR analyses are as follows: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, and Ar = aromatic. GC–MS analyses were obtained using a Varian 3800 GC coupled to a Varian Saturn 2000 ion trap MS. Infrared spectra were recorded on a Midac Prospect FT-IR spectrometer. Elemental analyses were performed by Quantitative Technologies, Inc. (QTI) of Whitehouse, NJ, USA, and reported values are within  $\pm 0.4\%$  of the calculated values. High-resolution mass spectrometry was performed with a Perkin-Elmer Voyager matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometer located in the Biophysics Instrumentation Facility at the University of Wisconsin-Madison Biophysics Instrumentation

Facility. All solvents (acetone, diethyl ether,  $\text{CH}_2\text{Cl}_2$ , THF, ethyl acetate, hexanes, acetic acid, and toluene) were obtained from Fisher Scientific and used as received. Most inorganic reagents, along with 4-methoxyphenol, 1,3-dibromopropane, 1,2-dibromoethane, 1.0 M *B*-bromo-9-BBN in  $\text{CH}_2\text{Cl}_2$ , dichloromethyl methyl ether, DDQ, ethyl trifluoroacetate, nitromethane, and nitroethane were used as received from Sigma–Aldrich.

### 4.2. Synthesis of 13

**4.2.1. 1-(2-Bromoethoxy)-4-methoxybenzene (8)**<sup>21</sup>. A solution of **7** (10.1 g, 81.3 mmol) dissolved in acetone (100 mL) was added over a 12 h period to a mixture of 1,2-dibromoethane (35 mL, 0.41 mol), finely powdered  $\text{K}_2\text{CO}_3$  (35 g, 0.25 mol) and acetone (300 mL) at reflux. The reaction was held at reflux for 125 h before the  $\text{K}_2\text{CO}_3$  was removed by filtration. After solvent removal in vacuo, the remaining residue was combined with  $\text{CH}_2\text{Cl}_2$ , washed with 2.5 M NaOH, 1 M HCl, and brine, and dried over anhydrous  $\text{MgSO}_4$ . Evaporation of the volatiles in vacuo yielded an orange solid that was treated with a 10%  $\text{CH}_2\text{Cl}_2$ –90% hexanes solution (100 mL) to precipitate the dimeric material present. Following filtration, the filtrate was evaporated in vacuo and recrystallized from EtOAc/hexanes to yield 8.42 g (44.8%) of **8** as translucent sheet-like crystals (mp 50–51 °C) with a  $^1\text{H}$  NMR spectrum identical to that reported by Pomilio and Tettamanzi.<sup>21</sup> Low-resolution ESIMS,  $m/z$  (rel intensity) 136, 151, 178.

**4.2.2. 1,4-Dibromo-2-(2-bromoethoxy)-5-methoxybenzene (9)**. Bromine (21.8 g, 0.137 mol) in  $\text{CH}_2\text{Cl}_2$  (50 mL) was added dropwise to a mixture of **8** (14.9 g, 64.6 mmol) dissolved in  $\text{CH}_2\text{Cl}_2$  (500 mL) with a catalytic amount of Fe filings. The reaction continued for 24 h before the mixture was washed with 3 M NaOH, 3 M HCl, and brine. The organic phase was dried over  $\text{MgSO}_4$  and the solvent was removed in vacuo to give an orange solid that was recrystallized from EtOAc/hexanes to yield 21.5 g (85.3%) of **9** as off-white crystals: mp 64–65 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.66 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{Br}$ ,  $J = 6.4$  Hz), 3.87 (s, 3,  $\text{ArOCH}_3$ ), 4.30 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{Br}$ ,  $J = 6.4$  Hz), 7.11 (s, 1,  $\text{ArH}$ ), 7.17 (s, 1,  $\text{ArH}$ ). Low-resolution EIMS,  $m/z$  386/388/390 ( $\text{M}^+$ ), 309, 281. Anal. Calcd for  $\text{C}_9\text{H}_9\text{Br}_3\text{O}_2$ : C, 27.80; H, 2.31. Found: C, 27.69; H, 2.08.

**4.2.3. 2,5-Dibromo-4-(2-bromoethoxy)phenol (10)**. A 1.0 M *B*-Br-9-BBN (522 mL, 0.522 mol) was added dropwise to a solution of **9** (45.0 g, 0.116 mol) in  $\text{CH}_2\text{Cl}_2$  (1 L). The reaction continued for 14 days before the volatiles were removed in vacuo to give a yellow colored oil (that emitted white fumes). The oil was stirred under  $\text{N}_2$  for 2 h until the white fumes subsided, and the oil was taken up in  $\text{Et}_2\text{O}$  (500 mL) and brought to 0 °C. Ethanolamine (37.9 mL, 1.2 equiv relative to *B*-Br-9-BBN) was added to precipitate the *B*-Br-9-BBN adduct, and this solid was removed by filtration, washing thoroughly with  $\text{Et}_2\text{O}$ . Solvent was removed from the filtrate in vacuo to yield a yellow oil that was taken up in  $\text{CH}_2\text{Cl}_2$  and washed with 3 M HCl and 3 M NaOH. The basic extracts were acidified with 12 M HCl, and the solution

was extracted with  $\text{CH}_2\text{Cl}_2$ . The organic fractions were combined, washed once with brine, dried over  $\text{MgSO}_4$ , and solvent removal in vacuo gave a yellow oil. The crude oil was purified by dry column flash chromatography<sup>22</sup> on silica gel (eluting with  $\text{CH}_2\text{Cl}_2$ ) to yield 29.5 g (73.7%) of **10** as a fine white powder: mp 106–107 °C. IR (NaCl,  $\text{cm}^{-1}$ ) 3437, 3054, 2986, 1266.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.65 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{Br}$ ,  $J = 6.4$  Hz), 4.27 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{Br}$ ,  $J = 6.4$  Hz), 5.29 (s, 1,  $\text{ArOH}$ ), 7.07 (s, 1,  $\text{ArH}$ ), 7.28 (s, 1,  $\text{ArH}$ ). Low-resolution EIMS,  $m/z$  372/374/376 ( $\text{M}^+$ ), 295, 267. Anal. Calcd for  $\text{C}_8\text{H}_7\text{Br}_3\text{O}_2$ : C, 25.63; H, 1.86. Found: C, 25.80; H, 1.64.

**4.2.4. 1,4-Dibromo-2-(2-bromoethoxy)-5-(3-bromo-propoxy)benzene (11).** In a manner analogous to the preparation of **8**, **10** (17.5 g, 46.6 mmol) was alkylated with 1,3-dibromopropane to give 18.3 g (79.0%) of **11** as white needle-like crystals: mp 67–68 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.34 (p, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2\text{Br}$ ), 3.64 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2\text{Br}$ ), superimposed upon 3.67 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{Br}$ ), 4.10 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2\text{Br}$ ,  $J = 5.7$  Hz), 4.27 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{Br}$ ,  $J = 6.3$  Hz), 7.17 (s, 1,  $\text{ArH}$ ), 7.28 (s, 1,  $\text{ArH}$ ). Low-resolution EIMS,  $m/z$  492/494/496 ( $\text{M}^+$ ), 107. Anal. Calcd for  $\text{C}_{11}\text{H}_{12}\text{Br}_4\text{O}_2$ : C, 26.65; H, 2.42. Found: C, 26.85; H, 2.20.

**4.2.5. 3,6,7,8-Tetrahydro-2H-furo[2,3-g]chromene (12).** Diether **11** (17.6 g, 35.5 mmol) was dissolved in anhydrous THF (75 mL) and cooled to 0 °C before the dropwise addition of 10 M *n*-butyllithium in hexanes (10.9 mL, 109 mmol). The reaction was held at 0 °C for 4 h before being quenched with  $\text{H}_2\text{O}$  (10 mL). Solvent removal in vacuo gave a red oil that was taken up in  $\text{Et}_2\text{O}$  and washed with  $\text{H}_2\text{O}$  and brine. The organic phase was dried over  $\text{MgSO}_4$  and the solvent was removed in vacuo to afford a red oil that was recrystallized from EtOAc/hexanes to yield 4.3 g (69%) of **12** as orange crystals: mp 75–76 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.96 (p, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ,  $J = 5.2$ , 6.3 Hz), 2.72 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ,  $J = 6.3$  Hz), 3.12 (t, 2,  $\text{ArOCH}_2\text{CH}_2$ ,  $J = 8.5$  Hz), 4.12 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ,  $J = 5.2$  Hz), 4.56 (t, 2,  $\text{ArOCH}_2\text{CH}_2$ ,  $J = 8.5$  Hz), 6.46 (s, 1,  $\text{ArH}$ ), and 6.65 (s, 1,  $\text{ArH}$ ). Low-resolution EIMS,  $m/z$  (rel intensity) 176/178 ( $\text{M}^+$ , 94/100). Anal. Calcd for  $\text{C}_{11}\text{H}_{12}\text{O}_2$ : C, 74.98; H, 6.86. Found: C, 74.65; H, 6.96.

**4.2.6. 3,6,7,8-Tetrahydro-2H-furo[2,3-g]chromene-9-carbaldehyde (13) and 3,6,7,8-tetrahydro-2H-furo[2,3-g]chromene-4-carbaldehyde (14).** A solution of **12** (8.29 g, 47.1 mmol) dissolved in  $\text{CH}_2\text{Cl}_2$  (200 mL) was stirred and cooled to 0 °C. The solution was charged with  $\text{SnCl}_4$  (6.07 mL, 51.8 mmol) and the reaction was held at 0 °C for 15 min before the slow addition of dichloromethyl methyl ether (5.9 mL, 52 mmol). The reaction was halted after 4 h by the addition of  $\text{H}_2\text{O}$  (50 mL). The reaction mixture was partitioned and the organic phase was set aside. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$ , and the organic fractions were combined and washed with 3 M HCl and once with brine. The organic phase was dried over  $\text{MgSO}_4$  and the solvent was removed under reduced pressure to give a dark red oil (10.29 g) that contained the two regioisomers **13** and **14**. The oil was recrystallized from

EtOAc/hexanes to afford 3.91 g (40.6%) of pure **13**. The remaining oil, containing both **13** and **14**, was subjected to silica gel flash chromatography (eluting with 95%  $\text{CH}_2\text{Cl}_2$ /5% hexane) to afford **14**, the first to elute, as a yellow solid: mp 72–73 °C. IR (NaCl,  $\text{cm}^{-1}$ ) 3053, 2986, 1265.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.96 (p, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ), 2.79 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ,  $J = 6.5$  Hz), 3.45 (t, 2,  $\text{ArOCH}_2\text{CH}_2$ ,  $J = 8.8$  Hz), 4.22 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ,  $J = 5.2$  Hz), 4.55 (t, 2,  $\text{ArOCH}_2\text{CH}_2$ ,  $J = 8.8$  Hz), 6.70 (s, 1,  $\text{ArH}$ ), 10.47 (s, 1,  $\text{ArCHO}$ ). Low-resolution EIMS,  $m/z$  (rel intensity) 204 ( $\text{M}^+$ , 100). Anal. Calcd for  $\text{C}_{12}\text{H}_{12}\text{O}_3$ : C, 70.57; H, 5.92. Found: C, 70.36; H, 6.08.

The second to elute, **13**, was isolated as a bright yellow solid: mp 71–72 °C. IR (NaCl,  $\text{cm}^{-1}$ ) 3054, 2986, 1264.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.96 (p, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ), 3.11 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ), superimposed upon 3.17 (t, 2,  $\text{ArOCH}_2\text{CH}_2$ ,  $J = 8.7$  Hz), 4.11 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ,  $J = 5.1$  Hz), 4.65 (t, 2,  $\text{ArOCH}_2\text{CH}_2$ ,  $J = 8.4$  Hz), 6.92 (s, 1,  $\text{ArH}$ ), 10.37 (s, 1,  $\text{ArCHO}$ ). Low-resolution EIMS,  $m/z$  (rel intensity) 204 ( $\text{M}^+$ , 100). Anal. Calcd for  $\text{C}_{12}\text{H}_{12}\text{O}_3$ : C, 70.57; H, 5.92. Found: C, 70.47; H, 5.98.

### 4.3. Synthesis of 4a and 5a

**4.3.1. 9-[(E)-2-Nitroethenyl]-3,6,7,8-tetrahydro-2H-furo[2,3-g]chromene (15a).** Aldehyde **13** (1.37 g, 6.69 mmol) and ammonium acetate (0.539 g, 7.00 mmol) were dissolved in nitromethane (12 mL) and heated to 90 °C for 2.5 h. Volatiles were removed in vacuo to give an orange solid that was dissolved in  $\text{CH}_2\text{Cl}_2$  and washed with 3 M HCl,  $\text{H}_2\text{O}$ , and once with brine. The organic phase was dried using  $\text{MgSO}_4$  and the solvent was removed in vacuo, leaving 1.61 g (97.3%) of a dark orange solid that was recrystallized from MeOH to afford 1.36 g (82.6%) of **15a** as an orange crystalline solid: mp 130–131 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.04 (p, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ), 2.87 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ,  $J = 6.9$  Hz), 3.18 (t, 2,  $\text{ArOCH}_2\text{CH}_2$ ,  $J = 8.4$  Hz), 4.09 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ,  $J = 5.1$  Hz), 4.67 (t, 2,  $\text{ArOCH}_2\text{CH}_2$ ,  $J = 8.7$  Hz), 6.80 (s, 1,  $\text{ArH}$ ), 8.11 (s, 2,  $\text{ArCH}=\text{CH}$ ). Low-resolution EIMS,  $m/z$  (rel intensity) 247 ( $\text{M}^+$ , 100). Anal. Calcd for  $\text{C}_{13}\text{H}_{13}\text{NO}_4$ : C, 63.15; H, 5.30; N, 5.66. Found: C, 62.88; H, 5.40; N, 5.57.

**4.3.2. 4-[(E)-2-Nitroethenyl]-3,6,7,8-tetrahydro-2H-furo[2,3-g]chromene (16a).** Similar to the preparation of **15a**, aldehyde **14** (0.127 g, 1.65 mmol) was condensed to give 0.301 g (73.8%) of **16a** as fluffy bright orange colored crystals: mp 139–140 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.01 (p, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ), 2.77 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ), 3.31 (t, 2,  $\text{ArOCH}_2\text{CH}_2$ ), 4.26 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ), 4.58 (t, 2,  $\text{ArOCH}_2\text{CH}_2$ ), 6.61 (s, 1,  $\text{ArH}$ ), 7.94 (d, 1,  $\text{ArCH}=\text{CH}$ ), 8.01 (d, 1,  $\text{ArCH}=\text{CH}$ ). Low-resolution EIMS,  $m/z$  (rel intensity) 247 ( $\text{M}^+$ , 100). Anal. Calcd for  $\text{C}_{13}\text{H}_{13}\text{NO}_4$ : C, 63.15; H, 5.30; N, 5.66. Found: C, 63.08; H, 5.22; N, 5.51.

**4.3.3. 2-(3,6,7,8-Tetrahydro-2H-furo[2,3-g]chromen-9-yl)ethanamine (17a).** A dry reaction flask was purged with  $\text{N}_2$ , charged with anhydrous THF (100 mL), and

cooled to 0 °C before the dropwise introduction of 1 M LiAlH<sub>4</sub> (in THF) (25.0 mL, 25.0 mmol). Once the addition was complete, **15a** (2.41 g, 9.76 mmol) was dissolved in anhydrous THF (25 mL) and added to the suspension over a 30 min period. The flask was held at reflux for 4 h before the reaction was quenched with the addition of 2.5 M NaOH (15 mL). Celite was added to the flask and the mixture was filtered, washing thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. The yellow colored filtrate was concentrated under vacuum, dissolved in CH<sub>2</sub>Cl<sub>2</sub> and washed with 3 M HCl. The aqueous extracts were combined and cooled to 0 °C and made basic with the addition of 5 M NaOH. The basic solution was extracted with CH<sub>2</sub>Cl<sub>2</sub>, and the organic fractions were washed with brine. The organic phase was dried over MgSO<sub>4</sub> and the volatiles were removed in vacuo to yield **17a** as a yellow oil. This free amine was converted to its hydrochloride salt by dissolving the oil in Et<sub>2</sub>O and adding 1.1 equivalents of 1 M HCl in anhydrous EtOH to the flask. The salt was recrystallized from EtOH/Et<sub>2</sub>O to afford 0.934 g (37.4%) of **17a·HCl** as a white crystalline solid: mp 279–280 °C. <sup>1</sup>H NMR (free base in CDCl<sub>3</sub>) δ 1.11 (br s, 2, NH<sub>2</sub>), 1.96 (p, 2, ArOCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.69 (t, 2, ArCH<sub>2</sub>CH<sub>2</sub>, *J* = 6.6 Hz), superimposed onto 2.69 (t, 2, ArOCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, *J* = 7.2 Hz), 2.85 (t, 2, ArCH<sub>2</sub>CH<sub>2</sub>, *J* = 6.6 Hz), 3.12 (t, 2, ArOCH<sub>2</sub>CH<sub>2</sub>, *J* = 8.4 Hz), 4.06 (t, 2, ArOCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, *J* = 5.1 Hz), 4.45 (t, 2, ArOCH<sub>2</sub>CH<sub>2</sub>, *J* = 8.4 Hz), 6.56 (s, 1, ArH). Low-resolution ESIMS, *m/z* (rel intensity) 220 (M+H, 67), 203 ((M+H)–NH<sub>3</sub>, 100). Anal. Calcd for C<sub>13</sub>H<sub>17</sub>NO<sub>2</sub>·HCl: C, 61.06; H, 7.09; N, 5.47. Found: C, 60.91; H, 7.05; N, 5.44.

**4.3.4. 2-(3,6,7,8-Tetrahydro-2H-furo[2,3-g]chromen-4-yl)ethanamine (18a).** Similar to the preparation of **17a**, **16a** (0.572 g, 2.31 mmol) was reduced to give 0.408 g (68.9%) of **18a** as pale yellow oil which was converted to its hydrochloride salt **18a·HCl** with the addition of 1 M HCl in anhydrous EtOH: mp 272 °C. <sup>1</sup>H NMR (free base in CDCl<sub>3</sub>) δ 1.27 (br s, 2, NH<sub>2</sub>), 1.93 (p, 2, ArOCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.65 (t, 2, ArCH<sub>2</sub>CH<sub>2</sub>) superimposed onto 2.70 (t, 2, ArOCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.87 (t, 2, ArCH<sub>2</sub>CH<sub>2</sub>), 3.11 (t, 2, ArOCH<sub>2</sub>CH<sub>2</sub>), 4.10 (t, 2, ArOCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 4.49 (t, 2, ArOCH<sub>2</sub>CH<sub>2</sub>), 6.34 (s, 1, ArH). Low-resolution ESIMS, *m/z* (rel intensity) 220 (M+H, 100), 203 ((M+H)–NH<sub>3</sub>, 49), 175. High resolution MALDI-TOF *m/z* calculated for C<sub>13</sub>H<sub>18</sub>NO<sub>2</sub> (M+H) 220.1346. Found 220.1332.

**4.3.5. 2-(4-Bromo-3,6,7,8-tetrahydro-2H-furo[2,3-g]chromen-9-yl)ethanamine (4a).** A 0.776 M Br<sub>2</sub> solution in HOAc (0.75 mL, 0.58 mmol) was added dropwise to a solution of **17a·HCl** (0.333 g, 0.520 mmol) dissolved in glacial AcOH (10 mL). The reaction continued for 3.5 h before the volatiles were removed in vacuo. The white solid that remained was taken up in 3 M HCl and washed with Et<sub>2</sub>O. The aqueous phase was made basic with the addition of 5 M NaOH and the basic solution was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic extracts were combined, washed once with brine, dried over MgSO<sub>4</sub>, and the volatiles were removed in vacuo to give 0.144 g (93.0%) of **4a** as a pale yellow oil. The free amine was converted to its hydrochloride salt with

the addition of 1.1 equivalents of 1 M HCl in anhydrous EtOH, and recrystallization from EtOH/Et<sub>2</sub>O afforded **4a·HCl** as a white, crystalline solid: mp >300 °C. <sup>1</sup>H NMR (free base in CDCl<sub>3</sub>) δ 1.09 (br s, 2, NH<sub>2</sub>), 1.98 (p, 2, ArOCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.63 (t, 2, ArCH<sub>2</sub>CH<sub>2</sub>, *J* = 7.2 Hz), 2.73 (t, 2, ArOCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, *J* = 6.3 Hz), 2.83 (q, 2, ArCH<sub>2</sub>CH<sub>2</sub>), 3.18 (t, 2, ArOCH<sub>2</sub>CH<sub>2</sub>, *J* = 8.1 Hz), 4.17 (t, 2, ArOCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, *J* = 5.1 Hz), 4.51 (t, 2, ArOCH<sub>2</sub>CH<sub>2</sub>, *J* = 8.4 Hz). Low-resolution ESIMS, *m/z* (rel intensity) 298/300 (M+H, 71/66), 281/283 ((M+H)–NH<sub>3</sub>, 100/96). Anal. Calcd for C<sub>13</sub>H<sub>16</sub>BrNO<sub>2</sub>·HCl: C, 46.66; H, 5.12; N, 4.18. Found: C, 46.48; H, 4.96; N, 4.07.

**4.3.6. 2-(9-Bromo-3,6,7,8-tetrahydro-2H-furo[2,3-g]chromen-4-yl)ethanamine (5a).** In a manner analogous to that reported for the preparation of **4a**, **18a·HCl** (0.051 g, 0.20 mmol) was brominated to yield 0.051 g (86%) of **5a** as a pale yellow oil that was taken up in Et<sub>2</sub>O and converted to its hydrochloride salt **5a·HCl** with the addition of 1 M HCl in anhydrous EtOH: mp >300 °C. <sup>1</sup>H NMR (free base in CDCl<sub>3</sub>) δ 1.24 (br s, 2, NH<sub>2</sub>), 1.98 (p, 2, ArOCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.65 (t, 2, ArCH<sub>2</sub>CH<sub>2</sub>) superimposed onto 2.71 (t, 2, ArOCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.86 (t, 2, ArCH<sub>2</sub>CH<sub>2</sub>), 3.24 (t, 2, ArOCH<sub>2</sub>CH<sub>2</sub>), 4.06 (t, 2, ArOCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 4.60 (t, 2, ArOCH<sub>2</sub>CH<sub>2</sub>). Low-resolution ESIMS, *m/z* (rel intensity) 298/300 (M+H, 100/96), 281/283 ((M+H)–NH<sub>3</sub>, 69/67). Anal. Calcd for C<sub>13</sub>H<sub>16</sub>BrNO<sub>2</sub>·HCl: C, 46.66; H, 5.12; N, 4.18. Found: C, 46.73; H, 5.07; N, 4.02.

#### 4.4. Synthesis of 4b and 5b

**4.4.1. 9-[(1E)-2-Nitroprop-1-en-1-yl]-3,6,7,8-tetrahydro-2H-furo[2,3-g]chromene (15b).** In a manner analogous to that used in the preparation of **15a**, aldehyde **13** (3.50 g, 17.1 mmol) was condensed with nitroethane to give 2.90 g (64.7%) of **15b** as orange needle-like crystals: mp 88–89 °C. IR (NaCl, cm<sup>–1</sup>) 3054, 2986, 1422, 1264. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.96 (p, 2, ArOCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.16 (s, 3, CH<sub>3</sub>), 2.63 (t, 2, ArOCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, *J* = 6.4 Hz), 3.19 (t, 2, ArOCH<sub>2</sub>CH<sub>2</sub>, *J* = 8.4 Hz), 4.11 (t, 2, ArOCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, *J* = 5.2 Hz), 4.55 (t, 2, ArOCH<sub>2</sub>CH<sub>2</sub>, *J* = 8.5 Hz), 6.76 (s, 1, ArH), 7.84 (s, 1, ArCH=C). Low-resolution EIMS, *m/z* 262 (M<sup>+</sup>), 244 (M–OH). Anal. Calcd for C<sub>14</sub>H<sub>15</sub>NO<sub>4</sub>: C, 64.35; H, 5.78; N, 5.36. Found: C, 64.07; H, 5.64; N, 5.29.

**4.4.2. 4-[(1E)-2-Nitroprop-1-en-1-yl]-3,6,7,8-tetrahydro-2H-furo[2,3-g]chromene (16b).** Aldehyde **14** (0.623 g, 3.05 mmol) and benzylamine (0.399 mL, 3.66 mmol) were dissolved in benzene (50 mL) and refluxed for 2 h with a Dean-Stark trap attached. After cooling to room temperature, the solvent was removed in vacuo to give a yellow oil that was combined with nitroethane (40 mL) and AcOH (0.55 mL, 9.2 mmol) and stirred for 48 h. The volatiles were removed in vacuo, leaving behind a yellow oil that was taken up in Et<sub>2</sub>O and washed with 1 M HCl, H<sub>2</sub>O, and once with brine. The organic phase was dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure to give a bright yellow oil that was recrystallized from MeOH to afford **16b** as an orange crystalline solid: mp 103–104 °C. IR (NaCl, cm<sup>–1</sup>)

3054, 2986, 1422, 1264.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.98 (p, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ), 2.16 (s, 3,  $\text{CH}_3$ ), 2.77 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ,  $J = 6.6$  Hz), 3.01 (t, 2,  $\text{ArOCH}_2\text{CH}_2$ ,  $J = 8.7$  Hz), 4.15 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ,  $J = 5.1$  Hz), 4.53 (t, 2,  $\text{ArOCH}_2\text{CH}_2$ ,  $J = 8.4$  Hz), 6.55 (s, 1,  $\text{ArH}$ ), 7.92 (s, 1,  $\text{ArCH}=\text{C}$ ). Low-resolution EIMS,  $m/z$  261 ( $\text{M}^+$ ), 244 ( $\text{M}-\text{OH}$ ). Anal. Calcd for  $\text{C}_{14}\text{H}_{15}\text{NO}_4$ : C, 64.35; H, 5.78; N, 5.36. Found: C, 64.23; H, 6.03; N, 5.25.

**4.4.3. 1-(3,6,7,8-Tetrahydro-2H-furo[2,3-g]chromen-9-yl)propan-2-amine (17b).** In a manner analogous to that used in the preparation of **17a** and **18a**, **15b** (2.01 g, 7.69 mmol) was reduced to afford 1.70 g (94.9%) of **17b** as the free amine. The hydrochloride salt **17b-HCl** was formed by the addition 1 M HCl in anhydrous EtOH, and the solid was recrystallized from MeOH/EtOAc: mp 255–256 °C.  $^1\text{H}$  NMR (free base in  $\text{CDCl}_3$ )  $\delta$  1.15 (d, 3,  $\text{ArCH}_2\text{CHCH}_3$ ,  $J = 6.3$  Hz), 1.62 (br s, 2,  $\text{NH}_2$ ), 1.98 (p, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ), 2.58 (d, 2,  $\text{ArCH}_2\text{CHCH}_3$ ,  $J = 6.9$  Hz), superimposed upon 2.59 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ), 2.71 (m, 1,  $\text{ArCH}_2\text{CHCH}_3$ ,  $J = 6.6$  Hz), 3.14 (t, 2,  $\text{ArOCH}_2\text{CH}_2$ ), 4.08 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ,  $J = 5.1$  Hz), 4.47 (t, 2,  $\text{ArOCH}_2\text{CH}_2$ ,  $J = 8.7$  Hz), 6.58 (s, 1,  $\text{ArH}$ ). Low-resolution ESIMS,  $m/z$  (rel intensity) 234 ( $\text{M}+\text{H}$ , 64), 217 ( $(\text{M}+\text{H})-\text{NH}_3$ , 100). Anal. Calcd for  $\text{C}_{14}\text{H}_{19}\text{NO}_2\cdot\text{HCl}$ : C, 62.33; H, 7.47; N, 5.19. Found: C, 62.10; H, 7.34; N, 5.11.

**4.4.4. 1-(3,6,7,8-Tetrahydro-2H-furo[2,3-g]chromen-4-yl)propan-2-amine (18b).** In a method analogous to that used for the preparation of **17a**, **17b**, and **18a**, **16b** (0.200 g, 0.765 mmol) was reduced to yield 0.142 g (79.7%) of **18b** as the free amine that was converted to its hydrochloride salt by the addition 1 M HCl in anhydrous EtOH: mp 270–271 °C.  $^1\text{H}$  NMR (free base in  $\text{CDCl}_3$ )  $\delta$  1.21 (d, 3,  $\text{ArCH}_2\text{CHCH}_3$ ,  $J = 6.3$  Hz), 1.95 (p, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ,  $J = 5.1$ , 6.3 Hz), 2.55 (br s, 2,  $\text{NH}_2$ ), superimposed upon 2.65 (d, 2,  $\text{ArCH}_2\text{CHCH}_3$ ,  $J = 6.9$  Hz), 2.74 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ,  $J = 6.6$  Hz), 3.11 (m, 2,  $\text{ArOCH}_2\text{CH}_2$ ), 3.40 (m, 1,  $\text{ArCH}_2\text{CHCH}_3$ ), 4.12 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ,  $J = 5.1$  Hz), 4.49 (t, 2,  $\text{ArOCH}_2\text{CH}_2$ ,  $J = 8.4$  Hz), 6.37 (s, 1,  $\text{ArH}$ ). Low-resolution ESIMS,  $m/z$  (rel intensity) 234 ( $\text{M}+\text{H}$ , 100), 217 ( $(\text{M}+\text{H})-\text{NH}_3$ , 77). Anal. Calcd for  $\text{C}_{14}\text{H}_{19}\text{NO}_2\cdot\text{HCl}$ : C, 62.33; H, 7.47; N, 5.19. Found: C, 61.98; H, 7.66; N, 5.11.

**4.4.5. 1-(4-Bromo-3,6,7,8-tetrahydro-2H-furo[2,3-g]chromen-9-yl)propan-2-amine (4b).** In a manner similar to the preparation of **4a** and **5a**, amine **17b** (0.818 g, 3.51 mmol) was brominated to give 0.441 g (63.9%) of **4b** as a yellow oil that was converted to its hydrochloride salt by the addition of 1 M HCl in anhydrous EtOH: mp 269–270 °C.  $^1\text{H}$  NMR (free base in  $\text{CDCl}_3$ )  $\delta$  1.13 (d, 3,  $\text{ArCH}_2\text{CHCH}_3$ ), 1.48 (br s, 2,  $\text{NH}_2$ ), 1.99 (p, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ), 2.52 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ), superimposed upon 2.53 (d, 2,  $\text{ArCH}_2\text{CHCH}_3$ ), 2.74 (m, 1,  $\text{ArCH}_2\text{CHCH}_3$ ), 3.18 (t, 2,  $\text{ArOCH}_2\text{CH}_2$ ,  $J = 8.4$  Hz), 4.18 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ,  $J = 5.1$  Hz), 4.51 (t, 2,  $\text{ArOCH}_2\text{CH}_2$ ,  $J = 9.3$  Hz). Low-resolution ESIMS,  $m/z$  (rel intensity) 312/314 ( $\text{M}+\text{H}$ , 91/84). Anal. Calcd for

$\text{C}_{14}\text{H}_{18}\text{BrNO}_2\cdot\text{HCl}$ : C, 48.23; H, 5.49; N, 4.02. Found: C, 47.85; H, 5.21; N, 4.10.

**4.4.6. 1-(9-Bromo-3,6,7,8-tetrahydro-2H-furo[2,3-g]chromen-4-yl)propan-2-amine (5b).** In a manner analogous to that used for the preparation of **4a**, **4b**, and **5a**, amine **18b** (0.183 g, 7.84 mmol) was brominated to give 0.156 g (63.8%) of **5b** that was converted to its hydrochloride salt by the addition of 1 M HCl in anhydrous EtOH: mp 277–278 °C.  $^1\text{H}$  NMR (free base in  $\text{CDCl}_3$ )  $\delta$  1.21 (d, 3,  $\text{ArCH}_2\text{CHCH}_3$ ), 1.95 (p, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ), 2.55 (br s, 2,  $\text{NH}_2$ ), superimposed upon 2.65 (d, 2,  $\text{ArCH}_2\text{CHCH}_3$ ), 2.73 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ), 3.11 (m, 2,  $\text{ArOCH}_2\text{CH}_2$ ), 3.40 (m, 1,  $\text{ArCH}_2\text{CHCH}_3$ ), 4.12 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ), 4.48 (m, 2,  $\text{ArOCH}_2\text{CH}_2$ ). Low-resolution ESIMS,  $m/z$  (rel intensity) 312/314 ( $\text{M}+\text{H}$ , 100/95). Anal. Calcd for  $\text{C}_{14}\text{H}_{18}\text{BrNO}_2\cdot\text{HCl}$ : C, 48.23; H, 5.49; N, 4.02. Found: C, 48.37; H, 5.47; N, 3.92.

## 4.5. Synthesis of 6

**4.5.1. 2,2,2-Trifluoro-N-[1-methyl-2-(3,6,7,8-tetrahydro-2H-furo[2,3-g]chromen-9-yl)ethyl]acetamide (19).** Compound **17b** (1.52 g, 6.51 mmol) was dissolved in anhydrous THF (250 mL) and cooled to 0 °C before the addition of ethyl trifluoroacetate (1.71 mL, 14.3 mmol) and triethylamine (0.953 mL, 6.84 mmol). The reaction continued at 0 °C for 30 min before being brought to reflux for 24 h. The volatiles were removed in vacuo, leaving behind a light orange solid that was taken up in  $\text{CH}_2\text{Cl}_2$ , washed with 3 M HCl, and once with brine. The organic phase was dried over  $\text{MgSO}_4$  and the solvent was removed in vacuo to afford 1.58 g (73.9%) of a pale orange solid that was recrystallized from EtOAc to give 1.27 g (59.3%) of **19** as fluffy white crystals: mp 156–157 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.32 (d, 3,  $\text{ArCH}_2\text{CHCH}_3$ ,  $J = 6.6$  Hz), 2.01 (p, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ), 2.67 (m, 2,  $\text{ArCH}_2\text{CHCH}_3$ ), superimposed upon 2.71 (m, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ), 3.71 (t, 2,  $\text{ArOCH}_2\text{CH}_2$ ,  $J = 8.1$  Hz), 4.02 (m, 1,  $\text{ArCH}_2\text{CHCH}_3$ ), superimposed upon 4.05 (m, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ), 4.50 (t, 2,  $\text{ArOCH}_2\text{CH}_2$ ,  $J = 8.7$  Hz), 6.61 (s, 1,  $\text{ArH}$ ), 7.64 (br s, 1,  $\text{NH}$ ). Low-resolution ESIMS,  $m/z$  (rel intensity) 328 ( $\text{M}-\text{H}$ , 100). High-resolution MALDI-TOF  $m/z$  calculated for  $\text{C}_{16}\text{H}_{19}\text{F}_3\text{NO}_3$  ( $\text{M}+\text{H}$ ) 330.1323. Found 330.1312.

**4.5.2. N-[2-(4-Bromo-3,6,7,8-tetrahydro-2H-furo[2,3-g]chromen-9-yl)-1-methylethyl]-2,2,2-trifluoroacetamide (20).** Amide **19** (0.538 g, 1.63 mmol) was dissolved (with heating) in AcOH (15 mL) and dioxane (5 mL). The solution was cooled to 15 °C and covered with foil before the dropwise addition of a bromine-dioxane solution (8.10 mL:0.10 mL bromine in 8.00 mL of dioxane) over a 10 min period. The reaction continued at 25 °C for 6 h before being quenched with  $\text{H}_2\text{O}$  and a saturated sodium bisulfite solution. The mixture was extracted with  $\text{CH}_2\text{Cl}_2$ , and the organic fractions were combined and washed once with brine, dried over  $\text{MgSO}_4$ , and the volatiles were removed in vacuo. The off-white solid that remained in the flask was recrystallized from EtOAc/hexanes to yield 0.425 g (63.9%) of **20** as white crystals:



mp 156 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.31 (d, 3,  $\text{ArCH}_2\text{CHCH}_3$ ,  $J = 6.6$  Hz), 2.02 (p, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ), 2.68 (m, 2,  $\text{ArCH}_2\text{CHCH}_3$ ), superimposed upon 2.72 (m, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ), 3.22 (t, 2,  $\text{ArOCH}_2\text{CH}_2$ ,  $J = 8.7$  Hz), 4.17 (m, 1,  $\text{ArCH}_2\text{CHCH}_3$ ), superimposed upon 4.21 (m, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ), 4.55 (t, 2,  $\text{ArOCH}_2\text{CH}_2$ ,  $J = 8.4$  Hz), 7.41 (br s, 1, NH). Low-resolution CIMS,  $m/z$  408/410 ( $\text{M}+\text{H}$ ), 329 ( $(\text{M}+\text{H})-\text{Br}$ ). Anal. Calcd for  $\text{C}_{16}\text{H}_{17}\text{BrF}_3\text{NO}_3$ : C, 47.08; H, 4.20; N, 3.43. Found: C, 47.36; H, 4.14; N, 3.40.

#### 4.5.3. *N*-[2-(4-Bromo-7,8-dihydro-6*H*-furo[2,3-*g*]chromen-9-yl)-1-methylethyl]-2,2,2-trifluoroacetamide (**21**).

To a round bottom flask, **20** (0.408 g, 0.999 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.590 g, 2.60 mmol) were added and dissolved in toluene (50 mL). The reaction refluxed for 3.5 h and was cooled to room temperature. The volatiles were removed in vacuo to afford a brown oil that was purified by silica gel flash chromatography (eluting with  $\text{CH}_2\text{Cl}_2$ ) to afford a light yellow solid that was recrystallized from EtOAc/hexanes to afford 0.152 g (37.4%) of **21** as white crystals.  $^1\text{H}$  NMR (free base in  $\text{CDCl}_3$ )  $\delta$  1.31 (d, 3,  $\text{ArCH}_2\text{CHCH}_3$ ,  $J = 6.6$  Hz), 2.08 (p, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ), 2.92 (qd, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ), 3.07 (qd, 2,  $\text{ArCH}_2\text{CHCH}_3$ ), 4.27 (m, 1,  $\text{ArCH}_2\text{CHCH}_3$ ), superimposed upon 4.28 (m, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ), 6.57 (br s, 1, NH), 6.75 (d, 1,  $\text{ArOCH}=\text{CH}$ ,  $J = 2.1$  Hz), 7.56 (d, 1,  $\text{ArOCH}=\text{CH}$ ,  $J = 2.1$  Hz). Low-resolution EIMS,  $m/z$  404/406 ( $\text{M}-\text{H}$ ), 69  $\text{CF}_3^+$ . High-resolution MALDI-TOF  $m/z$  calculated for  $\text{C}_{16}\text{H}_{15}\text{BrF}_3\text{NO}_3$  ( $\text{M}+\text{H}$ ) 406.0263. Found 406.0260.

**4.5.4. 1-(4-Bromo-7,8-dihydro-6*H*-furo[2,3-*g*]chromen-9-yl)propan-2-amine (**6**).** To a solution of **21** (0.146 g, 0.359 mmol) dissolved in MeOH (20 mL) and cooled to 0 °C, 5 M KOH (10 mL) was added, and the reaction mixture was allowed to warm to room temperature over a 5 h period. The mixture was diluted with Et<sub>2</sub>O and extracted with 3 M HCl. The aqueous fractions were combined, cooled to 0 °C, and made basic with the addition of 5 M KOH. The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$ , and the organic fractions were combined, washed with brine, and dried over  $\text{MgSO}_4$ . The solvent was removed under reduced pressure to afford 0.109 g (98.2%) of **6** as yellow oil. The hydrochloride salt was formed by adding 1.1 equivalents of 1 M HCl in anhydrous EtOH to the free amine dissolved in Et<sub>2</sub>O.  $^1\text{H}$  NMR (free base in  $\text{CDCl}_3$ )  $\delta$  1.23 (d, 3,  $\text{ArCH}_2\text{CHCH}_3$ ), 2.06 (p, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ), superimposed upon 2.07 (m, 2,  $\text{ArCH}_2\text{CHCH}_3$ ), 2.49 (br s, 2,  $\text{NH}_2$ ), 2.92 (m, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ), 3.02 (d, 2,  $\text{ArCH}_2\text{CHCH}_3$ ), 4.27 (t, 2,  $\text{ArOCH}_2\text{CH}_2\text{CH}_2$ ), 6.78 (d, 1,  $\text{ArOCH}=\text{CH}$ ,  $J = 2.1$  Hz), 7.58 (d, 1,  $\text{ArOCH}=\text{CH}$ ,  $J = 2.1$  Hz). Low-resolution ESIMS,  $m/z$  (rel intensity) 310/312 ( $\text{M}+\text{H}$ , 72/79), 293/295 ( $(\text{M}+\text{H})-\text{NH}_3$ , 92/100). High-resolution MALDI-TOF  $m/z$  calculated for  $\text{C}_{14}\text{H}_{18}\text{BrNO}_2$  ( $\text{M}+\text{H}$ ) 310.0428. Found 310.0437.

## 4.6. Pharmacology

**4.6.1. Materials.** [ $^3\text{H}$ ]Ketanserin was obtained from Perkin-Elmer Life and Analytical Sciences (Boston, MA).

Serotonin (5-HT) was obtained from Sigma–Aldrich (St. Louis, MO).

**4.6.2. Cell culture methods.** NIH-3T3 cells stably expressing the rat 5-HT<sub>2A</sub> receptor (GF-6; 5500 fmol/mg) were the kind gift from Dr. David Julius (University of California, San Francisco, CA). Cells were maintained as described previously by Braden et al.<sup>23</sup> All DMEM media contained 300  $\mu\text{g}/\text{mL}$  G-418 (Sigma–Aldrich).

**4.6.3. Radioligand binding assays.** Membrane preparations and competition binding assays were performed as previously described.<sup>7,24</sup> Competition binding assays were carried out using 0.5 nM [ $^3\text{H}$ ]ketanserin in the presence of increasing concentrations of test compound (ca. 10 pM–10  $\mu\text{M}$ ).  $K_d$  values and competition curves were calculated using Prism (Graphpad Software, San Diego, CA).

**4.6.4. Inositol phosphate accumulation assays.** The ability of test compounds to stimulate radiolabeled inositol phosphate accumulation in NIH-3T3 cells stably expressing the rat 5-HT<sub>2A</sub> receptor was performed as previously described.<sup>13</sup> Each assay plate was normalized to wells stimulated with water (0%) and 10  $\mu\text{M}$  serotonin (100%).

## 4.6.5. Behavioral pharmacology methods.

**4.6.5.1. Animals.** Four male Sprague–Dawley rats (Harlan Laboratories, Indianapolis, IN) weighing 200–220 g at the beginning of the drug discrimination study were trained to discriminate LSD (186 nmol/kg; 0.08 mg/kg) from saline. The animal protocols used in the present experiments were consistent with current NIH principles of good laboratory animal care and were approved by the Purdue University Animal Care and Use Committee.

**4.6.5.2. Discrimination training and testing.** A fixed ratio (FR) 50 schedule of food reinforcement in a two-lever paradigm was used. This method is described in detail elsewhere.<sup>25</sup> Briefly, training sessions lasted 15 min and were conducted at the same time each day. Training continued until an accuracy of at least 85% was attained for eight of 10 consecutive sessions. Once criterion performance was attained, test sessions were interspersed between training sessions, either one or two times per week. At least one drug and one saline session separated each test session. Rats were required to maintain the 85% correct responding criterion on training days in order to be tested. In addition, test data were discarded when the accuracy criterion of 85% was not achieved on the two training sessions following a test session. Test drugs were administered ip 30 min prior to sessions; test sessions were run under conditions of extinction, with rats removed from the operant chamber when 50 presses were emitted on one lever. If 50 presses on one lever were not completed within 5 min, the session was ended and scored as a disruption. In combination tests, antagonists were administered 30 min before the training drug. The percentage of rats selecting the drug lever (% SDL) for each dose of test compound was determined. Treatments were randomized at the beginning of the study.

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