

Design and Synthesis of Substituted Furobenzopyrans as New Serotonergic Molecular Probes

Jennifer A. Prescher

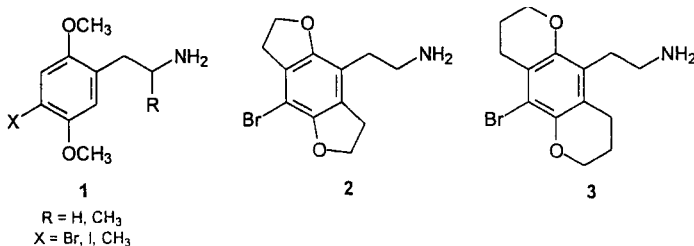
Faculty Sponsor: Aaron Monte, Department of Chemistry

ABSTRACT

Two chemical probes (**4**, **5**) for the agonist binding sites of serotonin 5-HT_{2A} and 5-HT_{2C} receptors were designed as rigid analogs of the methoxylated hallucinogenic phenylalkylamines. These drugs, hybrids of previously constructed heterocycles, include 5- and 6-membered oxygen-containing rings that restrict the conformational freedom of the alkoxy ring substituents. In an effort to construct the target molecules, two alternate phenol alkylations and a selective demethylation reaction were used to prepare an intermediate tricyclic compound (**6**). This key intermediate was then formylated to yield two regioisomeric aldehydes with similar physical properties. The aldehydes were separated using flash column chromatography and were subsequently condensed with nitromethane, reduced, and brominated to yield the desired target molecules, **4** and **5**. Pharmacological testing of **4** and **5** will provide more detailed information about the three-dimensional structure and topography of the agonist binding sites in serotonin 5-HT₂ receptors.

INTRODUCTION

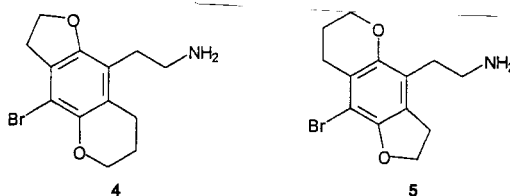
Previous investigations into the topography of the agonist binding sites of the 5-HT_{2A} and 5-HT_{2C} serotonin receptor subtypes have used molecular probes of general structure **1**.^{1,2} These hallucinogenic phenylalkylamines contain the essential structural features required for high-affinity binding to 5-HT_{2A} and 5-HT_{2C} agonist sites.^{1,2} However, the directionality of the oxygen lone-pair electrons involved in putative hydrogen-bonding interactions at the receptor sites could not be confirmed due to free rotation about the arene-oxygen bonds in these compounds. Structure-activity relationship (SAR) studies of a series of heterocyclic, conformationally-restricted analogs of **1** ultimately revealed that molecular probe **2** possessed the optimal orientation of the arene oxygen lone-pair electrons.³ In that work, rat behavioral and *in vitro* radioligand binding assays clearly showed that **2** is among the most potent and selective phenylalkylamine 5-HT_{2A} and 5-HT_{2C} receptor agonists designed, suggesting that these agonist binding sites conform well to the shape of this rigid molecule.³



Most recently, the substituted benzodipyrans, **3**, was prepared as a bulkier analog of **2**.⁴ Preliminary data indicate that the affinity of **3** for the 5-HT₂ receptor sites was found to be slightly lower than that of **2**, but roughly equipotent to the prototype, 2C-B (**1**, R = H, X = Br).⁴ The attenuated potency of **3** must be attributed to the greater steric bulk of one, or both, of the pyranyl groups that flank the arene ring.

The present study sought to address the hypothesis that there may be different-sized binding pockets in the two regions of the receptor that correspond to the alkoxy moieties on either side of the arene ring. In search for the answer to this puzzle, the homologous dihydrofuranochromans, **4** and **5**, were designed as new probes for the serotonin 5-HT_{2A} and 5-HT_{2C} receptor subtypes. These agonists can be viewed as hybrids of molecules **2** and **3**, as each contains one 5- and one 6-membered O-heterocycle, but their respective locations are on alternate sides of the central arene ring.

If one of the proposed dihydrofuranochromans exhibits greater affinity for the serotonin receptors over the other, valuable insight into the relative sizes of the regions involved in binding interactions with agonists will be gained. Additionally, molecules **4** and **5** may have the potential to be the first drugs ever synthesized to discriminate between the very similar serotonin 5-HT_{2A} and 5-HT_{2C} receptor subtypes.



CHEMISTRY

In planning the synthesis of **4** and **5**, it was obvious that a divergent synthesis could be devised in which both of the target compounds could be prepared from the unsubstituted tricyclic intermediate, 2,3-dihydrofuran[2,3-*g*]chroman (**6**) (Figure 1). However, the synthesis of this tricyclic intermediate was not as straightforward as the synthesis of the symmetrical tricyclic intermediates *en route* to analogs **2** and **3** because the asymmetric ring system of **6** warrants independent construction of the two different heterocycles. Several reaction schemes beginning with oxygen-containing starting materials were explored in an attempt to construct **6**, but the tricyclic intermediate was ultimately prepared using the approach outlined in Scheme 1

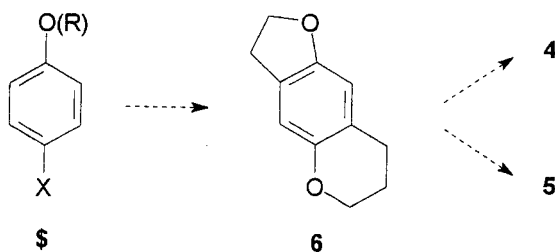
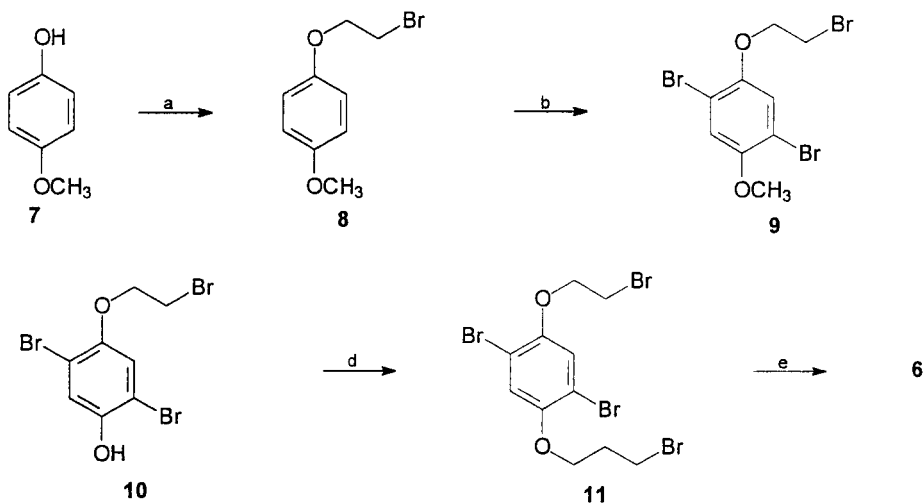


Figure 1. Overall synthetic route to **4** and **5**

In this synthetic scheme, 4-methoxyphenol (**7**) was first alkylated with 1,2-dibromoethane and potassium carbonate in acetone. A 10% CH_2Cl_2 -90% hexanes solution was found to precipitate most of the dimeric byproduct while solubilizing the desired monomer. Following removal of the dimer by filtration, sheet-like crystals of the alkylated product **8** were obtained upon recrystallization from ethyl acetate-hexanes. The diether **8** was subsequently brominated with the addition of 2 equivalents of bromine to a solution of **8** dissolved in CH_2Cl_2 , and needle-like crystals of the desired product **9** were isolated in 92% yield, following recrystallization.

To convert **9** to the desired phenol **10**, an ether-cleavage reaction was devised using *B*-bromo-9-BBN.^{5,6} This mild demethylating agent was preferred to more rigorous reagents, such as BBr_3 and BCl_3 , that were found to cleave both alkyl chains of the diether. We also discovered that 2 equivalents of *B*-bromo-9-BBN and strong heating were necessary to facilitate the selective demethylation of **9**. Ethanamine was used to precipitate the excess *B*-bromo-9-BBN from the reaction mixture,⁵ and the desired phenol **10** was isolated following basic extraction and flash-column chromatography.⁷

Scheme 1^a

^a(a) $\text{BrCH}_2\text{CH}_2\text{Br}$, K_2CO_3 ; (b) Br_2 , Fe ; (c) *B*-bromo-9-BBN, Δ ; (d) $\text{Br}(\text{CH}_2)_3\text{Br}$, K_2CO_3 ; (e) *n*-BuLi, THF

Alkylation of the phenol **10** in a dilute mixture of 1,3-dibromopropane, potassium carbonate, and acetone at reflux produced needle-like crystals of **11** (50%), and cyclization of the alkylated product **11** with *n*-butyllithium gave the desired tricyclic intermediate **6** upon recrystallization from ethyl acetate-hexanes. The relative locations of the observed peaks in the $^1\text{H-NMR}$ spectrum of **6** were consistent with those reported for molecules **2** and **3**. Three peaks assigned to the pyranyl protons of **6** were observed at δ 1.97 ppm, 2.72 ppm, and 4.10 ppm, while resonances due to the protons of the furanyl ring appeared at δ 3.12 ppm and 4.48 ppm.

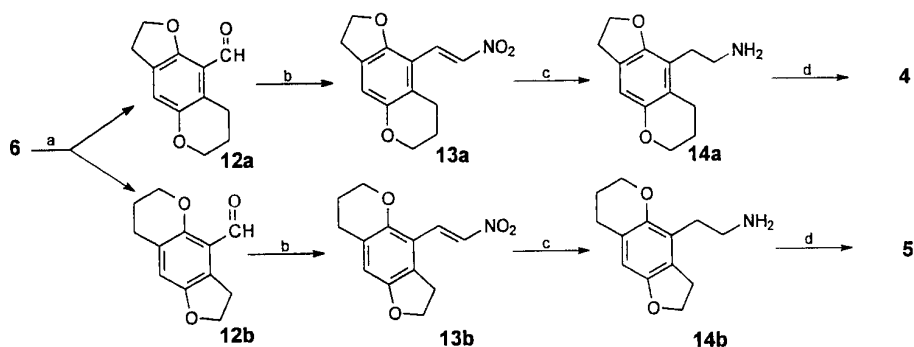
With the construction of intermediate **6**, the remaining route to molecular probes **4** and **5** could follow a well-established literature precedent (Scheme 2).^{3,4} Thus, the tricyclic intermediate **6** was first stirred with SnCl_4 and $\text{Cl}_2\text{CHOCH}_3$ at 0°C to add the formyl group to the central arene ring. Because acylation could occur at both free arene positions of **6**, the reaction yielded two regioisomeric aldehydes. The $^1\text{H-NMR}$ spectrum of the isolated crude product revealed two resonances just beyond δ 10.0, confirming the presence of these two aldehydes in the crude reaction product. The separation of these two isomers was originally thought to present a significant challenge as the aldehydes were expected to possess very similar physical and chromatographic properties. Fortunately, the regioisomers were easily separated using flash column chromatography.⁷ Thus, the two-component aldehydic mixture obtained from the formylation reaction was introduced to a silica gel column, whereupon isomer **12b** was discovered to elute from the column before isomer **12a** using a 95% CH_2Cl_2 -5% hexanes solution. While an effective separation of the two aldehydes was achieved, **12a** was isolated in substantially greater yield than **12b** (5:1 ratio of **12a**:**12b**).

Following their chromatographic separation, aldehydes **12a** and **12b** were carried through identical reaction pathways to produce the desired targets **4** and **5**, respectively (Scheme 2). First, the aldehydes were heated with nitromethane and ammonium acetate (in separate reaction vessels) to afford the orange-colored nitrostyrene compounds, **13a** and **13b**. Each nitrostyrene was reduced with lithium aluminum hydride to produce the aminoethanes **14a** and **14b**, which were isolated as their respective hydrochloride salts in 34% and 36% yields, respectively. These amine salts were then brominated using a solution of elemental bromine in acetic acid to give the desired targets, **4** and **5**. $^1\text{H-NMR}$ spectra obtained for both **4** and **5** revealed the absence of aromatic protons in the two products, consistent with the expected fully substituted aromatic rings in the target molecules.

CONCLUSIONS/FUTURE WORK

With the synthesis of **4** and **5** complete, rat behavioral assay and radioligand competition studies of these drug molecules will be performed to determine their affinity for 5-HT_{2A} and 5-HT_{2C} serotonin receptors. If one of the probes exhibits greater affinity at the receptor sites relative to the other, more detailed information will be gained regarding the three-dimension-

Scheme 2^a



^a(a) $\text{Cl}_2\text{CHOCH}_3$, SnCl_4 , CH_2Cl_2 ; (b) CH_3NO_2 , NH_4OAc , Δ ; (c) LiAlH_4 , THF, reflux; (d) Br_2 , HOAc

al topography of these sites. Specifically, the precise locations of binding pockets more tolerant of the bulkier pyran ring may be determined, providing insight into the relative size of receptor regions involved in binding interactions with the alkoxy substituents in this class of compounds.

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. $^1\text{H-NMR}$ spectra were obtained using a 300 MHz Bruker AC 300 NMR spectrometer with TMS as the internal standard. Abbreviations used in NMR analyses are as follows: b = broad, s = singlet, d = doublet, t = triplet, p = pentet, m = multiplet, Ar = aromatic. Infrared spectra were recorded on a Midac Prospect FT-IR spectrometer. Elemental analyses were performed by Quantitative Technologies, Inc. and are within $\pm 0.4\%$ of the calculated values. Thin-layer chromatography (TLC) was performed using Baker-flex silica gel plastic-backed plates with fluorescent indicator, developing with CH_2Cl_2 , and visualizing with UV light. All solvents (acetone, diethyl ether, CH_2Cl_2 , THF, ethyl acetate, hexanes, acetic acid) were obtained from Fisher Scientific and used as received. Most inorganic reagents, along with 4-nitrophenol, 4-methoxyphenol, 1,3-dibromopropane, 1,2-dibromoethane, 1.0 M *B*-bromo-9-BBN in CH_2Cl_2 , and α,α -dichloromethyl methyl ether were used as received from Aldrich.

1-Bromo-2-(4-methoxyphenoxy)ethane (8).⁸ A solution of 10.05 g (0.089 mol) of 4-methoxyphenol dissolved in 100 mL of acetone was added over a 12 h period to a mixture of 35 mL (0.406 mol) of 1,2-dibromoethane, 35 g (0.253 mol) of finely powdered anhydrous potassium carbonate, and 300 mL of acetone at reflux. The reaction mixture was held at reflux for an additional 125 h, and the potassium carbonate was removed by filtration through Celite. After the acetone was removed in vacuo, the remaining residue was dissolved in CH_2Cl_2 , washed with 2.5 M NaOH (3 x 25 mL), 1 M HCl (3 x 25 mL), and 50 mL of saturated NaCl, and dried over anhydrous MgSO_4 . The drying agent was removed by filtration through Celite, and evaporation of the volatiles yielded an orange-colored solid. The solid was treated with 100 mL of a 10% CH_2Cl_2 -90% hexanes solution to precipitate dimeric material present. Following filtration through a bed of Celite, the solvent was evaporated in vacuo until crystallization occurred. Recrystallization from ethyl acetate-hexanes yielded 8.42 g (45%) of translucent sheet-like crystals (mp 50-51 °C) with a $^1\text{H-NMR}$ spectrum identical to that reported by Pomillo and Tettamanzi.⁸

1-Bromo-2-(2,5-dibromo-4-methoxyphenoxy)ethane (9). A solution of bromine (0.0272 mol, 2.1 eq) in 50 mL of CH_2Cl_2 was dripped into a stirred mixture of the diether **8**, 100 mL of CH_2Cl_2 , and a few iron filings over a 2 h period. The red-colored mixture was stirred overnight, and subsequent washing with 2.5 M NaOH (4 x 25 mL) removed the red color of the solution. The organic phase was further washed with 3 x 25 mL of 1 M HCl and saturated NaCl (1 x 40 mL), and dried over anhydrous MgSO_4 . Following filtration through Celite, the filtrate was placed on the rotatory evaporator to remove the volatiles. The remaining solid was recrystallized from ethyl acetate-hexanes to yield 4.64 g (92%) of colorless crystals: mp 65-66 °C, $^1\text{H-NMR}$ (CDCl_3) δ 3.61 (t, 2, $\text{ArOCH}_2\text{Cl}_2\text{Br}$), 3.82 (s, 3, ArOCH_3), 4.23 (t, 2, $\text{ArOCH}_2\text{CH}_2\text{Br}$), 7.04 (s, 1, ArH), 7.08 (s, 1, ArH). Anal. ($\text{C}_9\text{H}_9\text{Br}_3\text{O}_2$) C, H.

2,5-Dibromo-4-(2-bromoethoxy)phenol (10). The brominated diether **9** (13.0 g, 0.0334 mol) was dissolved in CH_2Cl_2 (75 mL) and placed under a N_2 atmosphere. A solution of 1.0 M *B*-bromo-9-BBN in CH_2Cl_2 (100.0 mL, 0.10 mol) was slowly added to the stirred solution,

and the resulting mixture was heated at reflux for 110 h. After removal of the solvent on the rotatory evaporator, the gold-colored residue was combined with ether and chilled over ice. Dropwise addition of 6.2 mL (0.10 mol) of 2-aminoethanol precipitated a white *B*-bromo-9-BBN adduct which was removed by filtration through Celite. The remaining yellow filtrate was washed with 6 M HCl (3 x 30 mL) and extracted with 3 x 25 mL of 2.5 M NaOH. The basic layers were combined, acidified with 6 M HCl, and extracted with diethyl ether (3 x 25 mL). The organic extracts were combined and washed with saturated NaCl, dried (MgSO₄), and filtered through Celite. Following solvent removal in vacuo, purification of the yellow-colored residue was carried out using flash column chromatography with a silica gel stationary phase and eluting with CH₂Cl₂. The colorless fractions containing the desired product (as revealed by TLC) were combined, and CH₂Cl₂ removal gave 11.4 g (91%) of the demethylated phenol as a white solid: mp 108–109 °C, ¹H-NMR (CDCl₃) (3.64 (t, 2, ArOCH₂CH₂Br), 4.24 (t, 2, ArOCH₂CH₂Br), 5.25 (s, 1, ArOH), 7.02 (s, 1, ArH), 7.26 (s, 1, ArH), Anal. (C₈H₇Br₃O₂) C, H.

1-Bromo-3-(2,5-dibromo-4-(2-bromoethoxy)phenoxy)propane (11). The demethylated phenol **10** (9.62 g, 0.0257 mol) was dissolved in acetone (175 mL) and slowly added (over an 18 h period) to a dilute mixture of acetone (500 mL), finely ground anhydrous potassium carbonate (11.3 g, 0.0815 mol), and 16 mL of 1,3-dibromopropane held at reflux. The mixture was held at reflux for an additional 4 h before being cooled to room temperature, and the potassium carbonate was removed by filtration through Celite. Acetone removal was carried out on the rotatory evaporator, and the remaining yellow residue was taken up in CH₂Cl₂ and washed with 3 x 25 mL of 2.5 M NaOH, 3 M HCl (3 x 25 mL), and saturated NaCl (1 x 50 mL). The organics were dried (MgSO₄), filtered through Celite to remove the drying agent, and placed under vacuum for solvent removal. The residual 1,3-dibromopropane in the crude product was recovered using Kügelrohr distillation, and the remaining organic residue was recrystallized using ethyl acetate-hexanes to yield 6.38 g (50%) of **18** as a fluffy white solid: mp 68–69 °C, ¹H-NMR (CDCl₃) δ 2.33 (p, 2, ArOCH₂CH₂CH₂Br), 3.65 (pair of superimposed triplets, 4, ArOCH₂CH₂Br, ArOCH₂CH₂CH₂Br), 4.10 (t, 2, ArOCH₂CH₂CH₂Br), 4.27 (t, 2, ArOCH₂CH₂Br), 7.12 (s, 1, ArH), 7.13 (s, 1, ArH), Anal. (C₁₁H₁₂Br₄O₂) C, H.

2,3-Dihydrofurano[2,3-g]chroman (6). A solution of 20.32 g (0.0410 mol) of **11** in 75 mL of anhydrous THF was placed in a N₂ atmosphere and cooled to -78 °C. A solution of 10.0 M *n*-butyllithium in hexanes (8.2 mL, 0.082 mol) was added slowly via syringe to the stirred solution. The yellow reaction mixture was stirred for an additional 4 h before being quenched with 10 mL of distilled water. After the solvent was removed in vacuo, the organic residue was partitioned between Et₂O and water. The organic phase was washed with distilled H₂O (2 x 25 mL), saturated NaCl (50 mL), dried (MgSO₄), and filtered. The volatiles were evaporated in vacuo until crystallization occurred. The solid was recrystallized from ethyl acetate-hexanes to yield 2.08 g (49%) of **6** as a white solid: mp: 77–78 °C, ¹H-NMR (CDCl₃) δ 1.97 (p, 2, ArOCH₂CH₂CH₂), 2.72 (t, 2, ArOCH₂CH₂CH₂), 3.12 (t, 2, ArOCH₂CH₂), 4.10 (t, 2, ArOCH₂CH₂CH₂), 4.48 (t, 2, ArOCH₂CH₂), 6.45 (s, 1, ArH), 6.64 (s, 1, ArH), Anal. (C₁₁H₁₂O₂) C, H.

Formylated isomers (12a and 12b). A solution of 3.617 g (0.205 mol) of the tricyclic intermediate **6** in CH₂Cl₂ was stirred under N₂ and cooled to 0 °C in an ice bath. Tin (IV) chloride (2.6 mL, 0.022 mol) was added to the solution via a syringe, and the resulting gold-

colored solution was stirred for 10 min. Dichloromethyl methyl ether (2.03 mL, 0.022 mol) was added to the reaction mixture dropwise over a 2 min period. The resulting purple solution was stirred for an additional hour before the reaction was quenched with 25 mL of cold water. The two-layer mixture was separated, and the aqueous phase was extracted with 3 x 25 mL of CH_2Cl_2 . The combined organic extracts were washed with 1 M HCl (3 x 25 mL), 50 mL of saturated NaCl, and dried over anhydrous MgSO_4 . After filtration through Celite, the solvent was removed on the rotatory evaporator. The remaining oil (4.304 g), comprised of a mixture of **12a** and **12b**, was re-dissolved in a minimal amount of CH_2Cl_2 and introduced onto a flash column containing silica gel. The column was eluted with 95% CH_2Cl_2 -5% hexanes and N_2 pressure, and the separation was monitored by TLC. The fractions containing **12a** (the aldehyde to elute second from the column, as determined from $^1\text{H-NMR}$ studies) were combined and placed under reduced pressure for solvent removal, yielding 1.13 g of a bright yellow solid: mp 71-72 °C, $^1\text{H-NMR}$ (CDCl_3) δ 1.95 (p, 2, $\text{ArOCH}_2\text{CH}_2\text{CH}_2$), 3.12 (pair of superimposed triplets, 4, $\text{ArOCH}_2\text{CH}_2\text{CH}_2$, $\text{ArOCH}_2\text{CH}_2$), 4.11 (t, 2, $\text{ArOCH}_2\text{CH}_2\text{CH}_2$), 4.61 (t, 2, $\text{ArOCH}_2\text{CH}_2$), 6.90 (s, 1, ArH), 10.37 (s, 1, ArCHO).

Similarly, the fractions containing **12b** (the aldehyde to elute first, as determined from $^1\text{H-NMR}$ studies) were combined and placed under reduced pressure for solvent removal, affording 0.067 g of a dark yellow solid: mp 72-73 °C, $^1\text{H-NMR}$ (CDCl_3) δ 2.00 (p, 2, $\text{ArOCH}_2\text{CH}_2\text{CH}_2$), 2.76 (t, 2, $\text{ArOCH}_2\text{CH}_2\text{CH}_2$), 3.45 (t, 2, $\text{ArOCH}_2\text{CH}_2$), 4.21 (t, 2, $\text{ArOCH}_2\text{CH}_2\text{CH}_2$), 4.53 (t, 2, $\text{ArOCH}_2\text{CH}_2$), 6.69 (s, 1, ArH), 10.45 (s, 1, ArCHO).

The fractions that contained a mixture of both **12a** and **12b** were pooled and placed under reduced pressure for solvent removal. The remaining solid (2.403 g) was redissolved in a small amount of warm CH_2Cl_2 introduced to another silica gel column, and eluted with 95% CH_2Cl_2 -5% hexanes and N_2 pressure to give an additional 0.924 g (2.06 g total) of **12a** and 0.336 g (0.403 g total) of **12b**. Thus, the two isomers were isolated in a 5:1 ratio (**12a:12b**), with an overall yield of 86%.

Nitroethene-substituted dihydrofuranochroman (13a). The aldehyde **12a** (0.656 g, 3.21 mmol) was dissolved in an excess of nitromethane (13 mL, 0.24 mol). Ammonium acetate (0.256 g, 3.32 mmol) was added to the yellow solution, and the resulting mixture was stirred under N_2 at 85-90 °C for 4 h. After cooling, the residual nitromethane was removed in vacuo, and the remaining orange-colored solid was taken up in CH_2Cl_2 and washed with distilled H_2O , (1 x 25 mL), 3 M HCl (3 x 25 mL), and brine (1 x 50 mL). The organic phase was dried over anhydrous MgSO_4 and filtered through Celite. The filtrate was placed under reduced pressure for solvent removal. The remaining solid was recrystallized from methanol to yield 0.650 g (82%) of **13a** as pumpkin-orange crystals: mp 129-130°C, $^1\text{H-NMR}$ (CDCl_3) δ 2.04 (p, 2, $\text{ArOCH}_2\text{CH}_2\text{CH}_2$), 2.87 (t, 2, $\text{ArOCH}_2\text{CH}_2\text{CH}_2$), 3.18 (t, 2, $\text{ArOCH}_2\text{CH}_2$), 4.09 (t, 2, $\text{ArOCH}_2\text{CH}_2\text{CH}_2$), 4.67 (t, 2, $\text{ArOCH}_2\text{CH}_2$), 6.81 (s, 1, ArH), 8.11 (s, 2, $\text{ArCH}=\text{CH}$).

Nitroethene-substituted dihydrofuranochroman (13b). The aldehyde **12b** (0.337 g, 1.65 mmol) was combined with 0.127 g (1.65 mmol) of ammonium acetate and an excess of nitromethane (10 mL, 0.185 mol). The resulting mixture was stirred under N_2 at 85-88 °C for 2 h before the residual nitromethane was removed under reduced pressure. The remaining orange-colored solid was taken up in CH_2Cl_2 and washed with 3 M HCl (3 x 25 mL), distilled H_2O (1 x 25 mL), and brine (1 x 35 mL), dried (MgSO_4), and filtered. Following solvent removal under vacuum, the resulting orange solid was recrystallized from methanol to yield 0.301 g (74%) of **12b** as blaze-orange needles: mp 139-140 °C, $^1\text{H-NMR}$ (CDCl_3) δ 2.01 (p,

2, ArOCH₂CH₂CH₂), 2.77 (t, 2, ArOCH₂CH₂CH₂), 3.31 (t, 2, ArOCH₂CH₂), 4.26 (t, 2, ArOCH₂CH₂CH₂), 4.58 (t, 2, ArOCH₂CH₂), 6.81 (s, 1, ArH), 7.96 (d, 1, ArCH=CH), 8.01 (d, 1, ArCH=CH).

Ethylamine-substituted dihydrofuranochroman hydrochloride (14a•HCl). A solution of 5.50 mL of 1 M LiAlH₄ (Et₂O) in 20 mL of dry THF was stirred under N₂ and placed in an ice bath. After 10 min, a solution of 0.501 g (2.03 mmol) of the nitrostyrene **13a** in 8 mL of anhydrous THF was added dropwise to the stirred LiAlH₄ solution. The reaction mixture was heated at reflux for 4.5 h before being cooled over an ice bath. The reaction was quenched with the cautious addition of 5 mL of 5 M NaOH, followed by a small portion of Celite. The resulting mixture was filtered through Celite, and the filter cake was washed thoroughly with CH₂Cl₂. The yellow-colored filtrate was placed under vacuum for solvent removal, and the free amine was taken up in CH₂Cl₂ and washed with 3 M HCl (4 x 20 mL). The aqueous extracts were combined and basified with 5 M NaOH, and the free amine was extracted into CH₂Cl₂ (4 x 20 mL). The organic extracts were pooled together and washed with brine (1 x 30 mL), dried (MgSO₄), and filtered. The solvents were removed under reduced pressure, and the hydrochloride salt of the amine was precipitated with the addition of 1.1 eq of 1 M HCl in anhydrous ethanol. The salt was collected and recrystallized using ethanol-ether to yield 0.174 g (34%) of **14a•HCl** as a white crystalline solid: ¹H-NMR (free base in CDCl₃) δ 1.11 (bs, 2, NH₂) 1.96 (p, 2, ArOCH₂CH₂CH₂), 2.69 (pair of nearly superimposed triplets, 4, ArOCH₂CH₂CH₂, ArCH₂CH₂CH₂), 2.85 (t, 2, ArCH₂CH₂NH₂) 3.12 (t, 2, ArOCH₂CH₂), 4.06 (t, 2, ArOCH₂CH₂CH₂), 4.45 (t, 2, ArOCH₂CH₂), 6.56 (s, 1, ArH).

Ethylamine-substituted dihydrofuranochroman hydrochloride (14b•HCl). A solution of 2.76 mL of 1 M LiAlH₄ (Et₂O) in 20 mL of dry THF was stirred under N₂ and placed in an ice bath. After 10 min, a solution of 0.273 g (1.10 mmol) of the nitrostyrene **13a** in 6 mL of anhydrous THF was added dropwise to the stirred LiAlH₄ solution. The resulting mixture was then heated at reflux for 4 h, then cooled over an ice bath. The reaction was quenched with the careful addition of 5 mL of 5 M NaOH. A white solid appeared suspended within the reaction mixture, and Celite was added to the mixture to facilitate the precipitate, s removal. The mixture was filtered through a bed of Celite, and the filtrate was placed on the rotatory evaporator for solvent removal. The resulting amine residue was taken up in CH₂Cl₂ and washed with 3 M HCl (3 x 25 mL). The aqueous extracts were combined and basified with 5 M NaOH, and the free amine was extracted into CH₂Cl₂ (4 x 25 mL). The CH₂Cl₂ extracts were combined and washed with brine (1 x 25 mL), dried over MgSO₄, and filtered. After removing the solvents under reduced pressure, the hydrochloride salt of the amine was precipitated with the addition of 1 eq of 1 M HCl in ethanol. The salt was collected and recrystallized from ethanol and diethyl ether to yield 60 mg of **14b•HCl** as a white crystalline solid: ¹H-NMR (free base in CDCl₃) (1.27 (bs, 2, NH₂) 1.93 (p, 2, ArOCH₂CH₂CH₂), 2.70 (pair of nearly superimposed triplets, 4, ArOCH₂CH₂CH₂, ArCH₂CH₂NH₂), 2.87 (t, 2, ArCH₂CH₂NH₂) 3.11 (t, 2, ArOCH₂CH₂), 4.10 (t, 2, ArOCH₂CH₂CH₂), 4.49 (t, 2, ArOCH₂CH₂), 6.34 (s, 1, ArH).

Substituted dihydrofuranochroman hydrochloride (4•HCl). The hydrochloride salt **14a•HCl** (0.133 g, 0.520 mol) was combined with 10 mL of glacial acetic acid and stirred under N₂. To the mixture was added 0.75 mL of 0.776 M Br₂ in HOAc, dropwise, over 1 min.

The salt dissolved in the acidic solution after 7 min to give a dark-orange solution. After 30 min, a white solid precipitated from the solution, and the mixture was stirred for an additional 3 h. The volatiles were removed under reduced pressure, and the remaining white solid was taken up in 3 M HCl. The aqueous phase was made strongly basic with the addition of 5 M NaOH and extracted with 4 x 30 mL of CH_2Cl_2 . The organic extracts were combined, washed with brine (1 x 35 mL), dried (MgSO_4), and filtered through Celite. After removing the solvent *in vacuo*, the free amine (0.144 g, 93%) was isolated as a pale yellow oil. The hydrochloride salt was formed by dissolving the oily residue in ether and adding 1.1 eq of 1.0 M HCl in anhydrous EtOH to the solution. Following solvent removal, the white solid was recrystallized from ethanol-ether to yield **4•HCl** as a white crystalline solid: $^1\text{H-NMR}$ (free base in CDCl_3) δ 1.09 (bs, 2, NH_2) 1.98 (p, 2, $\text{ArOCH}_2\text{CH}_2\text{CH}_3$), 2.63 (t, 2, $\text{ArCH}_2\text{CH}_2\text{NH}_2$), 2.72 (t, 2, $\text{ArOCH}_2\text{CH}_2\text{CH}_3$) 2.83 (p, 2, $\text{ArCH}_2\text{CH}_2\text{NH}_2$) 3.18 (t, 2, $\text{ArOCH}_2\text{CH}_2\text{CH}_3$), 4.17 (t, 2, $\text{ArOCH}_2\text{CH}_2\text{CH}_3$), 4.51 (t, 2, $\text{ArOCH}_2\text{CH}_2\text{CH}_3$).

Substituted dihydrofuranochroman hydrochloride (5•HCl). The hydrochloride salt **14b•HCl** (0.051 g, 0.199 mmol) was combined with 8 mL of glacial acetic acid and stirred under N_2 . A solution of 0.388 M Br_2 in HOAc (0.51 mL) was added dropwise to the mixture. After 10 min, the salt dissolved in the acidic solution to give a dark-orange solution. A white solid precipitated from the solution after 40 min, and the mixture was stirred for an additional 4 h. The volatiles were removed under reduced pressure, and the remaining white solid was taken up in 3 M HCl. The aqueous phase was made strongly basic with the addition of 5 M NaOH and extracted with 4 x 30 mL of ether. The organic extracts were combined, washed with brine (1 x 35 mL), dried (MgSO_4), and filtered through Celite. After removing the solvent *in vacuo*, the free amine was isolated as a pale yellow oil. The hydrochloride salt was formed by dissolving the oily residue in ether and adding 1.1 eq of 1.0 M HCl in anhydrous EtOH to the solution. Following solvent removal, the white solid was recrystallized from ethanol-ether to yield **5•HCl** as a white crystalline solid: $^1\text{H-NMR}$ (free base in CDCl_3) δ 1.24 (bs, 2, NH_2) 1.98 (p, 2, $\text{ArOCH}_2\text{CH}_2\text{CH}_3$), 2.65 (t, 2, $\text{ArOCH}_2\text{CH}_2\text{NH}_2$), 2.71 (t, 2, $\text{ArCH}_2\text{CH}_2\text{CH}_3$), 2.86 (t, 2, $\text{ArCH}_2\text{CH}_2\text{NH}_2$), 3.24 (t, 2, $\text{ArOCH}_2\text{CH}_3$), 4.06 (t, 2, $\text{ArOCH}_2\text{CH}_2\text{CH}_3$), 4.60 (t, 2, $\text{ArOCH}_2\text{CH}_3$).

REFERENCES

- Glennon, R. A.; Young, R.; Benington, F.; Morin, R. D. "Behavioral and Serotonin Receptor Properties of 4-Substituted Derivatives of the Hallucinogen 1-(2,5-Dimethoxyphenyl)-2-aminopropane." *J. Med. Chem.*, **1982**, 25, 1163-1168.
- Glennon, R. A.; Raghupathi, R.; Bartyzel, P.; Teitler, M.; Leonhardt, S. "Binding of Phenylalkylamine Derivatives at the 5-HT_{1C} and 5-HT₂ Serotonin Receptors: Evidence for a Lack of Selectivity." *J. Med. Chem.*, **1992**, 35, 734-740.
- Monte, A. P.; Marona-Lewicka, D.; Parker, M. A.; Wainscott, D. B.; Nelson, D. L.; Nichols, D. E. "Dihydrobenzofuran Analogues of Hallucinogens." *J. Med. Chem.* **1996**, 39, 2953-2961.
- Whiteside, M. S.; Kurrasch, D.; Nichols, D. E.; Monte, A. P. "Substituted Hexahydrobenzodipyrans as Conformationally Restricted Serotonin 5-HT_{2A} and 5-HT_{2C} Receptor Probes." In preparation.
- Bhatt, M. V. "B-bromo-9-Borabicyclo[3.3.1]nonane: A Convenient and Selective Reagent for Ether Cleavage." *J. Organometallic Chem.*, **1978**, 156, 221-226.

Brown, H. C.; Krishnamurthy, S.; Yoon, N. M. "9-Bora-bicyclo[3.3.1]nonane in Tetrahydrofuran as a New Selective Reducing Agent in Organic Synthesis." *J. Org. Chem.*, **1976**, *41*(10), 1778-1791.

Pomilio, A. B.; Tettamanzi, M. C. "NMR Study of Substituted 1-Bromo-2-aryloxyethanes and Monosubstituted Xanthenes." *Magn. Reson. Chem.*, **1996**, *34*(2), 165-171.

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