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Mapping the Catechol Binding Site in Dopamine D_1 Receptors: Synthesis and Evaluation of Two Parallel Series of Bicyclic Dopamine Analogues

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A novel class of isochroman dopamine analogues, originally reported by Abbott Laboratories, have >100-fold selectivity for D_1-like over D_2-like receptors. We synthesized a parallel series of chroman compounds and showed that repositioning the oxygen atom in the heterocyclic ring decreases potency and confers D_2-like receptor selectivity to these compounds. In silico modeling supports the hypothesis that the altered pharmacology for the chroman series is due to potential intramolecular hydrogen bonding between the oxygen in the chroman ring and the *meta*-hydroxy group of the catechol moiety. This interaction realigns the catechol hydroxy groups and disrupts key interactions between these ligands and critical serine residues in TM5 of the D_1-like receptors. This hypothesis was tested by the synthesis and pharmacological evaluation of a parallel series of carbocyclic compounds. Our results suggest that if the potential for intramolecular hydrogen bonding is removed, D_1-like receptor potency and selectivity are restored.

Introduction

Dopamine is an important neurotransmitter involved in several brain neuronal pathways including reward circuitry, cognitive function, locomotion, and prolactin release. It also has several peripheral actions, including proper kidney function. Dopaminergic dysfunction can have profound effects on the human body, perhaps some of the most well recognized being Parkinson's disease and schizophrenia. Drug addiction, obesity, depression, and other mood and cognitive disorders also are directly linked to improper functioning of dopaminergic neurotransmission.[1] Elucidation of the physiological roles of the dopamine receptor subtypes is a main driving force behind the synthesis of compounds that act as selective agonists or antagonists at these sites.[2] Such selective agents could yield not only a greater understanding of dopamine neuropharmacology, but could also be used as novel therapies.

All dopamine receptors belong to the family of G-protein-coupled receptors (GPCRs) that consist of seven hydrophobic transmembrane α helices.[3] The numerous actions of dopamine are mediated by five types of receptors, divided into two main families: the D_1-like family and the D_2-like family.[4] The D_1-like family includes the D_1 and D_5 receptors; through coupling with $G\alpha_s/G\alpha_{olf}$ proteins, they increase the production of cAMP by activating adenylate cyclase. The D_2-like family, which consists of the D_2, D_3, and D_4 receptors, is coupled to $G\alpha_i/G\alpha_o$ proteins; they decrease the activity of adenylate cyclase, or are coupled with other signaling pathways.

The native ligand binding site (orthosteric site) is located in a hydrophobic region surrounded by the seven transmembrane (TM) regions. Based on deletion mutations and molecular modeling studies of the D_1 receptor active site, Asp 103$^{(3.32)}$ in TM3 is most likely responsible for binding the protonated nitrogen atom of the dopamine ethylamine side chain, whereas Ser 198$^{(5.42)}$, Ser 199$^{(5.43)}$, and Ser 202$^{(5.46)}$ (in TM5) are involved in binding to the catechol hydroxy groups.[5–7] The putative binding pocket of the D_1 receptor also contains an accessory binding region, deduced from the high affinity of compounds containing a phenyl substituent at the β side chain position (β-phenyldopamine, Figure 1).[8,9] Similarly, the D_2 receptor has an aspartate residue in TM3 (Asp 114) involved in binding the protonated amine. Two or three serines (Ser 193, 194, 197) in transmembrane helix 5 are critical for binding the catechol moiety through hydrogen bonding; however, there is no analogous accessory region to accommodate β-phenyl substituents in the D_2-like receptors. By analyzing the structures of known D_1-like selective agonist ligands and comparing them with known D_2-like selective ligands, it is apparent that a catechol moiety is crucial to conferring D_1-like potency and selectivity, whereas several non-catechol agonist molecules possess D_2-like selectivity. It can thus be presumed that the hydrogen bonding network in the D_1-like receptors is more complex and less permissive than that in the D_2-like receptors.[10]

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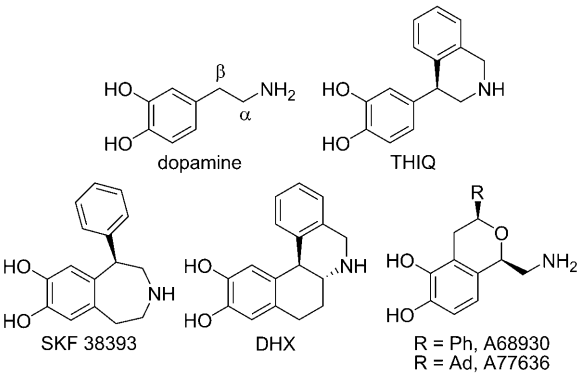


Figure 1. Dopamine and D_1-like selective agonists.

Figure 1 depicts several classes of compounds known to show selectivity toward the D_1-like receptors, including 1-phenyl-3-benzazepines (SKF 38393),[11] 4-phenyl-1,2,3,4-tetrahydroisoquinolines (THIQ),[12] benzo[*a*]phenanthridines (DHX),[13] and isochromans (A68390).[14,15] The compounds in the latter family, first synthesized by researchers at Abbott Laboratories in the early 1990s, are extremely potent and selective D_1-like dopamine agonists with high intrinsic activity. Although these compounds do not have a β-phenyl moiety, the spatial and electronic and/or hydrophobic characteristics that mimic the β-phenyl moiety are still present in the series. Interestingly, large non-aromatic substituents, such as adamantyl (A77636, **1c**), may be substituted for phenyl (A68930, **1d**) in these molecules to provide structures with high potency and D_1-like selectivity.

An attempt by our research group to develop a new D_1-like selective template based on an oxygen bioisostere of the Abbott series of molecules was surprisingly unsuccessful. As depicted in Figure 2, we constructed chroman analogues **2a**–**c**

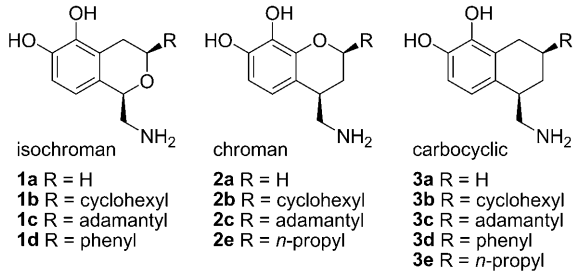


Figure 2. Bicyclic dopamine analogues evaluated in this study.

and **2e** with substituents analogous to the Abbott isochroman series **1a**–**d**. Our chroman series yielded compounds that were neither potent nor selective for the D_1-like receptors, but they did offer important new insight into the poorly understood hydrogen bonding networks of the D_1-like dopamine receptors. Importantly, the chroman series possesses a potential intramolecular hydrogen bond, as shown in Figure 3, which can force a specific orientation of the catechol hydroxy groups. We hypothesized that this orientation changes the alignment of the

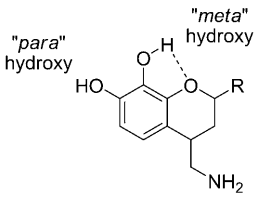


Figure 3. An intramolecular hydrogen bond is only possible with the catechol moiety in the chroman series, **2**.

molecule in the D_1-like binding pocket, decreasing its affinity and activity. There is no controversy in the literature as to whether such a bond exists, but only on the best way to measure its strength. Estácio et al.[16] calculated intramolecular hydrogen bond enthalpies for *ortho*-methoxyphenol using the *ortho–para* method and three theory levels, and obtained values in the range of 9.8–11.6 kJ mol^{-1}. Varfolomeev et al.[17] recently presented both experimental and computational evidence that such an intramolecular hydrogen bond is nearly the exclusive conformation of *ortho*-methoxyphenol in infinite dilution. In the relatively hydrophobic interior of the receptor one would therefore expect such an intramolecular hydrogen bond to be highly favorable.

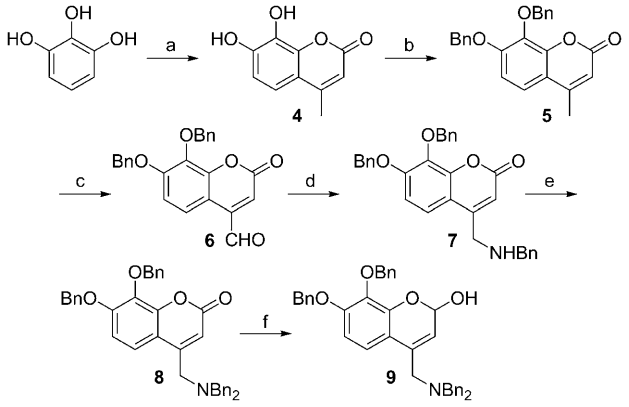
To test the hypothesis that this intramolecular hydrogen bond is responsible for the unexpected pharmacology of the chroman series, we also synthesized the carbocyclic series of compounds, **3a**–**e**, and evaluated their activity at D_1-like and D_2-like receptors. Herein we present both the synthesis and pharmacological evaluation of the chroman and carbocyclic series compared with a parallel analysis of the isochroman series. Our discussion further considers the putative hydrogen bonding network in the D_1 receptor.

Results

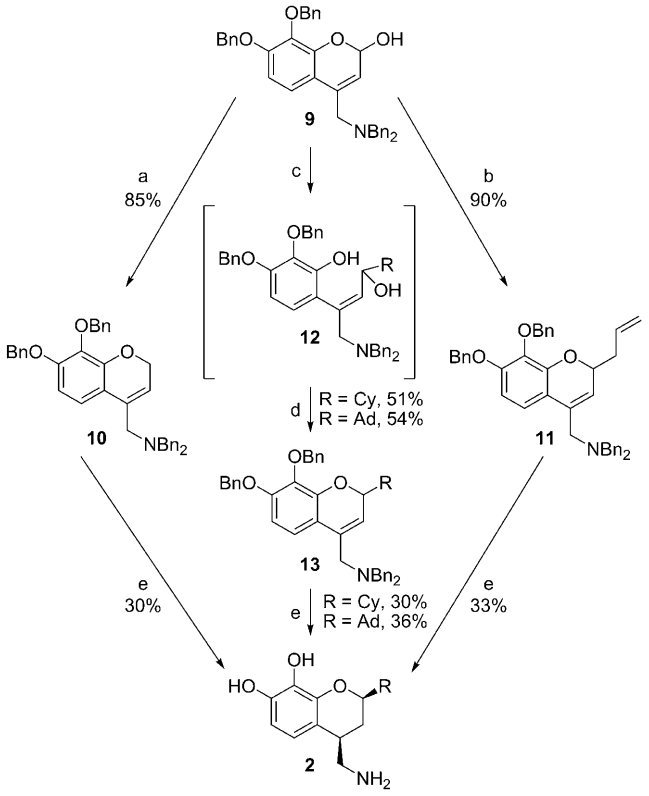
Chemistry: chroman series

The chroman compounds were synthesized from the common intermediate **9** (Scheme 1). Treating pyrogallol with ethyl acetoacetate in neat sulfuric acid with cooling yielded 7,8-dihydroxy-4-methylcoumarin (**4**). The yields were low, but both starting materials are inexpensive, and large quantities (100 g) could be produced quickly. Both catechol protection (compound **5**) and 4-methyl oxidation (compound **6**) proceeded in good yield. The choice of *O*-benzyl protection was good in that it survived the harsh selenium dioxide oxidation conditions. Reductive amination then introduced the benzylamino side chain (compound **7**) in modest yield.[18] If crude **6** was first purified by chromatography, however, yields up to 80% could be obtained. For further elaboration of the molecule, we were forced to include an additional *N*-benzyl group (compound **8**), because of the remaining relatively acidic amine proton.

At this point, we attempted to introduce aliphatic substituents at the 2-position of **8**. Treatment of the tetrabenzyl lactone **8** with cyclohexylmagnesium chloride resulted in double addition and ring opening. Similar results were obtained with



Scheme 1. Synthesis of **9**. *Reagents and conditions*: a) ethyl acetoacetate, H_2SO_4, 0 °C, 2.5 h, 25%; b) BnBr, K_2CO_3, DMF, 25 °C, 1 h, 85%; c) SeO_2, xylenes, 150 °C, 12 h, 61%; d) $BnNH_2$, $NaBH_3CN$, 25 °C, 15 h, 50–80%; e) BnBr, K_2CO_3, DMF, 100 °C, 2 h, 90%; f) DIBAH, CH_2Cl_2, −78 °C, 2 h, 72%.

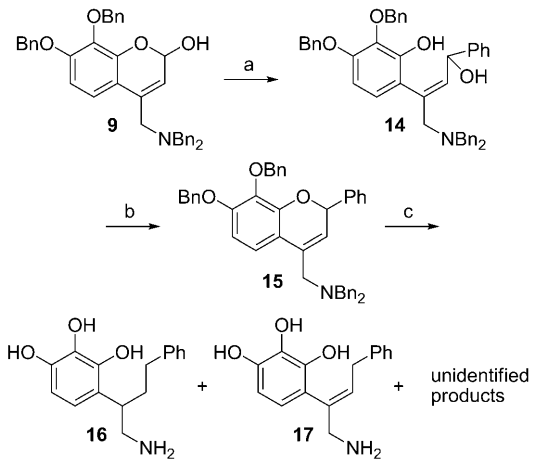


Scheme 2. Synthesis of **2a**–**c**, **e**. *Reagents and conditions*: a) $BF_3{\cdot}Et_2O$, Et_3SiH, CH_2Cl_2, 0 °C, 1 h; b) $BF_3{\cdot}Et_2O$, allylTMS, CH_2Cl_2, 25 °C, 2 h; c) CyMgCl or AdMgBr, 0 °C, 1 h; d) Mitsunobu conditions, 25 °C, 2 h; e) H_2, Pd/C, EtOH, 1 atm, 25 °C, 24 h.

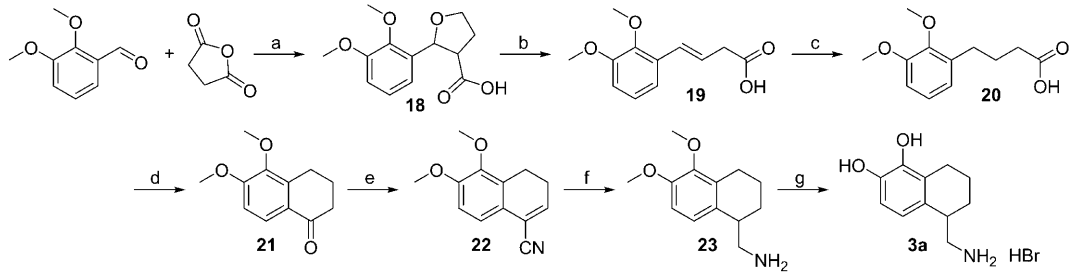
phenyllithium and phenylmagnesium bromide in either anhydrous tetrahydrofuran or diethyl ether. Treatment with the corresponding cerium–magnesium complex,[19] selective for monoaddition[20] to lactones, was unsuccessful, as was the attempted olefination with Tebbe reagent.[21] Therefore, the lactone was reduced to the lactol **9**. For this reaction, diisobutylaluminum hydride (DIBAH) in a solution of dichloromethane was the reagent of choice. The unstable lactol **9** did not require purification before further reaction. Deoxygenation of such lactol systems with boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) results in formation of oxonium ions, which in turn may be reduced with a hydride source[22] or trapped with an appropriate nucleophile.[23,24] A deep-red color was formed, indicative of the oxonium ion, but attempts to trap it with a variety of electrophilic reagents such as cyclohexylMgCl, phenylMgBr, adamantylMgCl, or adamantylZnCl at either 0 or −78 °C yielded numerous products. Triethylsilane did prove to be an effective hydride source to yield the unsubstituted **10** (Scheme 2). We were then successful in attaching an allyl group to give compound **11** in good yield by this methodology.[24,25] Catalytic hydrogenation then afforded the reduced propyl compound **2e**. Optimal yields were obtained with the use of palladium in large molar excess (4.5 equiv). Use of the hydrochloride salt of the amine gave the best results.

The synthesis was altered slightly for the introduction of other substituents to the common intermediate **9**. Adding a large excess (10 equiv) of the appropriate organomagnesium reagent to lactol **9** resulted in monoaddition and ring-opened diol **12**.[26] These compounds did not require isolation and, when subjected to Mitsunobu conditions,[27] cyclized smoothly to the desired tetrabenzylchromans **13**. The yields were ~50% for both compounds over two steps, which were deemed acceptable. The catechols (**2a**, **2b**, and **2c**) were obtained with the same hydrogenation methodology used for the propylcatechol **2e**.

Having successfully synthesized several 2-alkyl-substituted compounds, we attempted to produce the 2-phenyl compound by this same approach (Scheme 3). Addition of phenylmagnesium bromide to **9** produced the expected diol **14** in a good yield. Unfortunately, numerous attempts to cyclize this compound by the Mitsunobu reaction failed. Variations in temperature, order of addition, and type of phosphine (Bu_3P, Ph_3P) all resulted in complex mixtures that appeared to arise from deoxygenation of the activated allylic-benzylic alcohol.



Scheme 3. Attempted synthesis of phenyl-substituted chroman. *Reagents and conditions*: a) PhMgBr, 0 °C, 1 h, 85%; b) $SOCl_2$, pyridine, 0 °C, 5 min, 62%; c) H_2, catalyst, (see text).



Scheme 4. Synthesis of **3a**. *Reagents and conditions*: a) $ZnCl_2$, NEt_3, CH_2Cl_2, 80 °C, 96 h, 74%; b) 180 °C, 6 h, 65%; c) H_2, 5% Pd/C, EtOH, 25 °C, 2 h, quant.; d) PPA, 60 °C, 30 min, 98%; e) TMSCN, BF_3·Et_2O, toluene, 3 h, 84%; f) H_2, Raney Ni, NH_4OH, MeOH, 25 °C, 16 h, 49%; g) 1. BBr_3, CH_2Cl_2, 2. MeOH, 78 °C, 12 h, 99%.

This problem was successfully circumvented by replacing the problematic alcohol with a chlorine atom and performing a nucleophilic base-promoted cyclization, all in one step, to provide **15**. The most important factor for the successful generation of **15** was cooling of the reaction mixture, because hydrochloric acid generated by the reaction can catalyze cleavage of the ether linkage at slightly elevated temperatures. Unfortunately, only ring-opened products (compounds **16** and **17**) were obtained from attempts to hydrogenate this system. The benzylic ether could not be preserved, even in attempts to carry out hydrogenations with a variety of different catalysts, including Pd/C, Pt/C, Pd black, Lindlar catalyst, Wilkinson's catalyst, Pearlman's catalyst, and Adams catalyst.[28–30] Variations in pressure (1–4 atm), catalyst ratios, and solvents always produced complex mixtures of products. Various amines are sometimes also used to "poison" (deactivate) hydrogenation catalysts to alter their selectivity.[31,32] Addition of triethylamine or pyridine (varying amounts) to palladium black, palladium, or Pearlman's catalyst also produced mixtures containing unreacted starting material. Finally, transfer hydrogenation with a large excess of diimide, generated from potassium azodicarboxylate, yielded no products even at elevated temperatures.[33]

At this point, overwhelming evidence pointed to the extreme instability of the 2-phenylchroman skeleton. In hindsight, this was to be expected considering that in this particular ring system, it is highly probable that neighboring group participation of the pendant phenyl moiety favors ring opening. Therefore, further efforts to prepare this compound were abandoned.

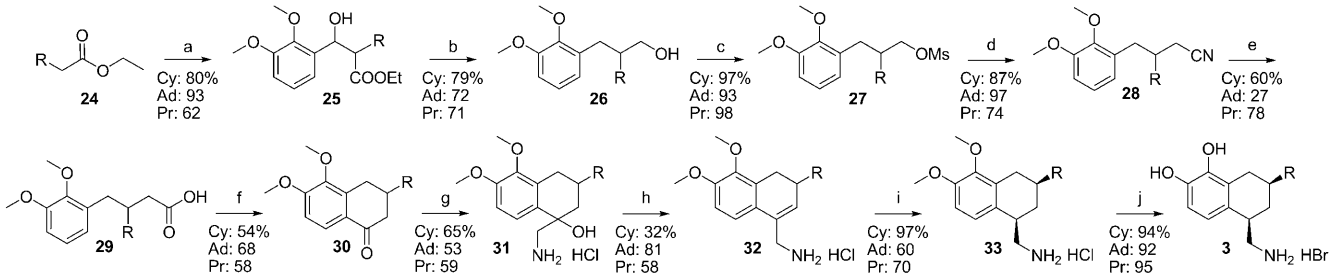
Chemistry: carbocyclic series

Unfortunately, in the carbocyclic series, there appeared to be no tractable way to incorporate the aliphatic or aromatic functionality at a late stage in the synthesis that would allow the divergent use of a common intermediate; therefore, the substituent had to be incorporated at the very beginning of each synthesis. Both the unsubstituted and phenyl-substituted carbocyclic compounds have been reported previously, although they were not pharmacologically evaluated for selectivity at dopamine receptor subtypes. The phenyl compound **3d** was made according to the procedure reported by Schoenleber and colleagues.[34] We were able to synthesize the unsubstituted compound **3a** more efficiently than previously published,[35] however, as described below.

As depicted in Scheme 4, the first step in the synthesis of **3a** was the formation of paraconic acid **18** from commercially available 2,3-dimethoxybenzaldehyde and succinic anhydride.[36] The pure, crystalline paraconic acid was then heated to effect ring opening and decarboxylation to afford **19**. The reaction typically began to yield side products before all of the starting material was consumed. The starting paraconic acid and product butenoic acid have pK_a values that differ by nearly one pH unit and thus were separated by careful titration, with the non-decarboxylated paraconic acid easily recovered. Unsaturated acid **19** was then catalytically hydrogenated, and polyphosphoric acid was used to form tetralone **21**, giving a nearly quantitative yield over two steps. Trimethylsilylcyanide and BF_3·OEt_2 were allowed to react with the tetralone to add the nitrile to the carbonyl and dehydrate the resulting protected alcohol in one step.[37,38] The unsaturated nitrile **22** was reduced with H_2 over Raney nickel to the aminomethyl tetralin **23**, which was O,O-demethylated and crystallized from methanol/ethyl acetate to afford **3a** as the hydrobromide salt.

The aliphatically substituted compounds were prepared in a fashion similar to the patented procedure for the phenyl compound, with several key differences (Scheme 5). An aldol reaction between 2,3-dimethoxybenzaldehyde and the ethyl ester of the appropriate substituted acetic acid yielded benzylic alcohols **25**, but which were completely resistant to dehydration, most likely due to an intramolecular hydrogen bond. The alcohols were thus converted into their benzylic chlorides by treatment with thionyl chloride. These chloroesters were dehalogenated and reduced to alcohols **26** in one step with lithium aluminum hydride.[39] The resulting primary alcohols were then efficiently mesylated, followed with nucleophilic substitution by cyanide ion to afford nitriles **28**. Hydrolysis of the nitriles proved nontrivial, however, and could not be achieved under a variety of stringent reaction conditions. Katsuri and colleagues have described the difficulties in hydrolyzing sterically crowded nitriles in both acidic and basic conditions.[40,41]

We therefore treated the nitriles **28** with DIBAH to provide the intermediate aldehydes.[42] Isolation of the aldehydes proved quite difficult, as they quickly decomposed. After confirming the structures by mass spectrometry and ^1H NMR spec-



Scheme 5. Synthesis of **3b**, **c**, and **e**. *Reagents and conditions*: a) 1. LDA, THF, 2. 2,3-dimethoxybenzaldehyde, 78 °C; b) 1. $SOCl_2$, benzene, 25 °C, 2 h, 2. $LiAlH_4$, Et_2O, 45 °C, 18 h; c) MsCl, NEt_3, THF, 25 °C, 2 h; d) NaCN, DMSO, 80 °C, 18 h; e) 1. DIBAH, toluene, −78–0 °C, 3 h, 2. CrO_3, $H_2SO_{4(aq)}$ (Jones' reagent), acetone, 25 °C, 10 min; f) PPA, 70 °C, 1 h; g) 1. TMSCN, ZnI_2, CH_2Cl_2, 70 °C, 20 h, 2. $LiAlH_4$, Et_2O, 3. HCl (conc.), 50 °C, 18 h; h) EtOH, reflux, 15 h; i) H_2 (4 atm), PtO_2, EtOH, 25 °C, 16 h; j) 1. BBr_3, CH_2Cl_2, 2. MeOH, −78–25 °C, 2.5 h.

troscopy, the crude materials were used directly in the next reaction without further purification. The aldehydes were oxidized to the carboxylic acids **29** with Jones' reagent[43] and then easily closed to the tetralones **30** with polyphosphoric acid. It was discovered during the synthesis of the adamantyl carboxylic acid that prolonged treatment with Jones' reagent could actually yield the tetralone directly from the aldehyde, explaining the low yield of the isolated acid.

After treatment of the tetralones **30** with trimethylsilylcyanide and zinc iodide to make the TMS-protected alcohol, the cyano functionalities were immediately reduced to the primary amines, and the alcohol moieties were simultaneously deprotected with $LiAlH_4$. The hydrochloride salts of amino alcohols **31** were dehydrated by reflux in ethanol with a trace amount of 2 N ethanolic HCl added to catalyze the reaction, and unsaturated amines **32** were then reduced catalytically to afford the desired *cis* isomers of the saturated aminomethyl compounds **33**. This material was carried forward to the final O,O-demethylation step. The catechols **3**, isolated as their hydrobromide salts, were off-white solids, and were submitted for pharmacological evaluation.

NMR evidence supports the fact that the newly synthesized series of compounds are indeed the *cis* diastereomers. 2D NOESY studies show the coupling of the diaxial protons (data not shown). In the carbocyclic series, a quartet around 1.0 ppm with a high *J* value (~12 Hz) is present, and is the signal for the axial hydrogen on C2 (identified by COSY). The two neighboring axial protons, as well as its geminal neighbor, split the signaling proton equally with the large coupling constant, typical of both diaxial and geminal splitting.

Pharmacology

The dopamine D_1-like and D_2-like receptor affinities of compounds **1a**–**d**, **2a**–**c**, **2e**, and **3a**–**e** were evaluated in competition binding assays using porcine striatal tissue homogenates. Standard antagonist ligands for D_1-like and D_2-like receptors, SCH-23390 and chlorpromazine, respectively, also were assessed for comparison with the new compounds (Table 1). All test compounds were full agonists at the cloned human D_1 receptor (data not shown).

Table 1. Binding affinities at D_1-like and D_2-like dopamine receptors.

Ligand	K_i [nM][a]		Fold D_1-like Selectivity
	D_1-like	D_2-like	
DHX[b]	10 ± 0.8	370 ± 10	37
1a	80 ± 9	1960 ± 140	24.5
1b	3.4 ± 0.6	920 ± 140	270
1c	3.9 ± 0.6	1860 ± 180	480
1d	2.6 ± 0.27	240 ± 45	92
2a	9100 ± 1300	290 ± 40	0.032
2b	770 ± 100	4600 ± 810	6.0
2c	4200 ± 760	6700 ± 460	1.6
2e	3100 ± 810	810 ± 150	0.26
3a	1100 ± 70	2000 ± 250	1.8
3b	40 ± 2.5	3500 ± 700	88
3c	220 ± 36	12200 ± 1530	55
3d	23 ± 4.3	770 ± 60	33
3e	270 ± 50	2500 ± 320	9.3
SCH-23390	0.79 ± 0.1	ND	
CPZ[c]	ND	3.2 ± 0.5	

[a] Porcine striatal binding: all values represent the mean ± SEM for at least three independent experiments; ND = not determined. [b] Dihydrexidine. [c] Chlorpromazine.

Discussion

The present work evaluated a series of closely related bioisosteres for binding affinity at D_1- and D_2-like dopamine receptors in porcine striatal homogenates. In an effort to compare the three series of compounds accurately, the Abbott isochromans **1** were assessed in parallel with the newly synthesized chromans **2** and carbocyclic series **3**. The results of the porcine striatal binding assays are summarized in Table 1. It was surprising to us that unsubstituted isochroman analogue **1a** displayed reasonable D_1/D_2 receptor subtype selectivity, being modestly D_1-like selective (24-fold) despite lacking a substituent that engages the accessory binding region. In contrast, chroman **2a**, although having low affinity, actually showed selectivity for D_2-like receptors. Also surprising was the relatively low affinity of the unsubstituted chroman and carbocyclic compounds for the D_1-like receptors ($K_i > 1$ μM) when compared with the unsubstituted isochroman **1a**. Based on previous reports for the isochromans, we hypothesized that the hy-

drophobic substitutions on each of the analogues would increase D_1 receptor affinity by engaging the receptor accessory binding region.[14,15] The results of the receptor binding studies support our hypothesis, revealing that all of the substituents increase D_1-like receptor affinity. The increases in affinity for the isochromans are most pronounced (>20-fold), whereas more modest increases in D_1-like affinity were observed for the chroman (2–10-fold) and the carbocyclic (4–25-fold) series of compounds.

The unsubstituted chroman **2a** was actually selective for D_2-like receptors, with very poor affinity for D_1-like receptors. It is our hypothesis that this poor D_1-like receptor affinity is a consequence of an intramolecular hydrogen bond that disrupts the crucial hydrogen bond network necessary within the D_1 receptor binding site. For the other chroman compounds **2b**–**e**, each of the substitutions provided an increase in D_1-like selectivity through a combination of increased D_1-like affinity and decreased D_2-like affinity. For example, the cyclohexyl-substituted **2b** shows sixfold selectivity for D_1-like receptors. Presumably, the benefit of having the cyclohexyl group in the accessory binding region of the D_1-like receptor compensates, to some extent, for the disruption of the hydrogen bonding network caused by the intramolecular hydrogen bond. When there is no possibility of this intramolecular hydrogen bond in the carbocyclic **3b**, the D_1-like selectivity is increased to 88-fold, with recovery of significant D_1-like affinity.

The same pattern is present among the adamantyl series as well (compounds **1c**, **2c**, and **3c**). Figure 4 depicts each of these three molecules docked into our in silico activated human dopamine D_1 receptor homology model. As described in the Supporting Information, an in silico activated model of the β2 adrenergic receptor was first generated. A homology model was then constructed from this receptor and, by using unbiased routines, the ligands were docked and the structures of the resulting complexes were optimized using energy minimization and molecular dynamics (MD) simulations. Figure 4A shows **1c**, a very high-affinity D_1-like ligand, participating in a likely hydrogen bonding network. The *meta*-hydroxy group of the catechol moiety is involved in a hydrogen bond with Ser198. The *para*-hydroxy hydrogen bonds with Ser202, which in turn hydrogen bonds with Thr108. These results are consistent with a study of DHX and its monohydroxy analogues in the D_1 receptor containing Ser→Ala point mutations.[44,45]

Equivalent docking and unconstrained MD simulations with **2c** in our D_1 receptor model shows the formation of a different hydrogen bond network (Figure 4B). The *meta*-hydroxy moiety is not available to interact with the protein residues because it is held tightly in an intramolecular hydrogen bond with the heterocyclic oxygen atom. This disruption alters the binding of the ligand in the receptor, as reflected in its low binding affinity at D_1-like receptors. Note that both Ser198 and Ser202 engage the *para*-hydroxy group of the ligand. In contrast, the binding of **3c** in the receptor model establishes a hydrogen bonding network identical to that of **1c** (Figure 4C). This observation directly supports our hypothesis and is validated by its nearly 20-fold higher binding affinity at D_1-like receptors relative to **2c**. Although we cannot be certain that these illustrations show the exact docked poses for the ligands we studied, they do illustrate how the intramolecular hydrogen bond in the chroman affects a potential hydrogen bonding scheme, and importantly, the proposed docking modes are consistent with our experimental receptor binding and potency results. Even though we had initially hypothesized, based entirely on chemical principles, that intramolecular hydrogen bonding in the chromans is responsible for their unexpected pharmacolo-

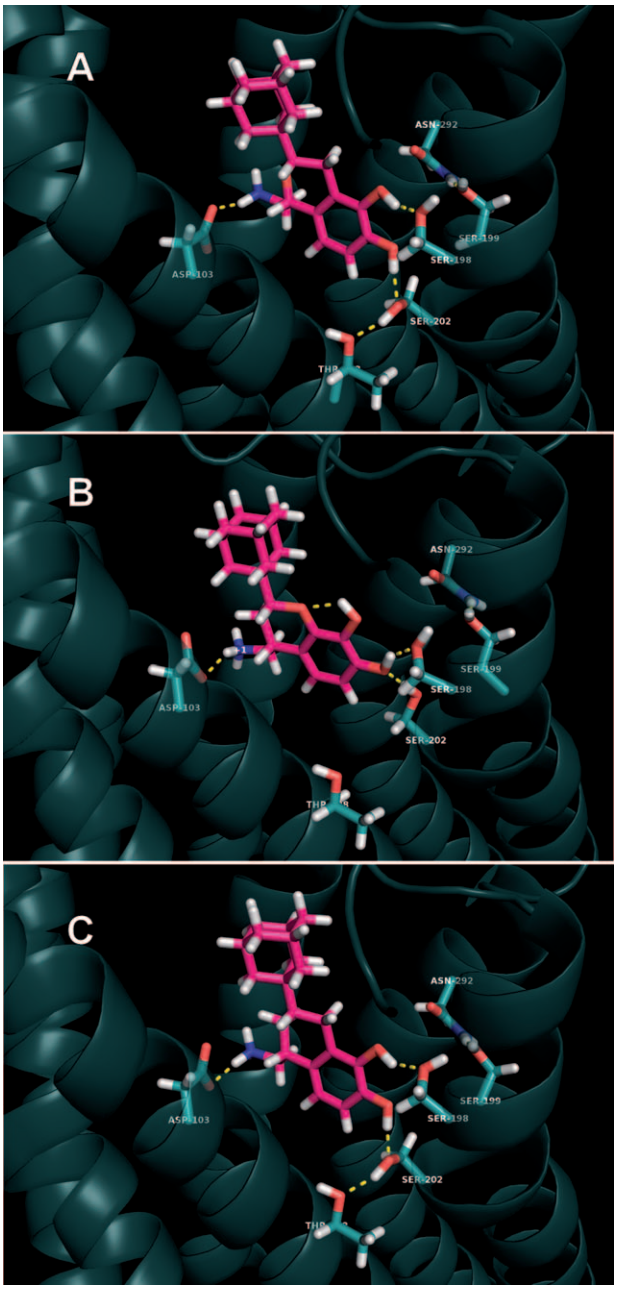


Figure 4. Simulated binding poses of A) **1c**, B) **2c**, and C) **3c**, illustrating how the heterocyclic oxygen atom in the chroman disrupts the hydrogen bonding network in the D_1 receptor. The view is within the membrane, looking from helices 3 and 5, with helix 4 hidden to allow a better view of the hydrogen bonding networks. The aspartate in TM3 is to the left of the molecule, with the three TM5 serine residues at the bottom right in each panel. Thr108 is at the very bottom, and Asn292 (6.55 in TM6) is at the top right.

gy, it was gratifying to observe the altered hydrogen bonding pattern in the unbiased docking results.

We do acknowledge that the carbocyclic series does not fully recover D_1 affinity or selectivity and that the heterocyclic oxygen atom in the isochroman series may play a role in D_1 receptor binding, in addition to the catechol moiety. One potential explanation is that the heterocyclic oxygen atom in the isochromans interacts with a polar residue in the D_1-like orthosteric binding site. Without a heterocyclic oxygen, the carbocyclic compound lacks this additional interaction. This hypothesis was explored through site-directed mutagenesis of the human D_1 receptor with no evidence that any of the mutated residues interact with the heterocyclic oxygen atom (data not shown).

Another, perhaps more plausible, explanation is that intramolecular hydrogen bonding occurs between the heterocyclic oxygen atom and the hydrogen atoms on the amine nitrogen. Such an interaction would decrease the degrees of rotational freedom and energetically favor an orientation of the aminomethyl side chain that is more complementary to the binding site. There is no possibility for this hydrogen bond in the carbocyclic molecules, and thus their flexible aminomethyl side chains can adopt various conformations, many of which are presumably not favorable for interaction with Asp 103 in the binding site. An intramolecular hydrogen bond between the isochroman oxygen and the side chain amino group of the ligand could stabilize the active binding orientation, decreasing entropy and would also likely offset the energy required to desolvate the ligand upon entry into the receptor binding site.

Such an intramolecularly hydrogen bonded side chain of **1d** would have a conformation that is essentially superimposable on an octahydrobenz[*h*]isoquinoline ring system. We recently synthesized and evaluated such a benz[*h*]isoquinoline compound[46] and discovered that, relative to **3d**, it possesses a nearly fourfold increase in D_1-like affinity, a D_1-like selectivity increase from 33- to 73-fold, and a nearly threefold increase in potency. The significant increases of affinity, selectivity, and potency over **3d** are consistent with the hypothesis of an intramolecular hydrogen bond.

Conclusions

We analyzed three analogous series of bicyclic dopamine agonists for their differential ability to bind D_1-like and D_2-like receptors. It is well known that D_1-like selective agonists require a catechol moiety to bind and fully activate the D_1-like receptors.[47] We synthesized a series of catechol-containing chroman compounds that do not bind well to the D_1-like receptors due to a hypothesized intramolecular hydrogen bond that we speculate interferes with the interaction between the catechol moiety and residues in the receptor responsible for binding. In essence, this intramolecular hydrogen bond destroys the functional characteristics of the ligand catechol moiety, so that for the purposes of ligand–receptor interactions, the ligand effectively possesses only one OH group. Unbiased docking studies with our homology model of the activated D_1 receptor are consistent with the pharmacological data, illustrating disruption of the catechol–serine hydrogen bonding network that is observed for potent compounds in the isochroman series. When a carbocyclic analogue was synthesized that lacks the ability to form an intramolecular hydrogen bond, both the D_1-like selectivity and the model's hydrogen bond network were largely restored, supporting our hypothesis and lending new insight into the complex hydrogen bonding network of the D_1-like receptors. With this information, it may be possible to design non-catechol compounds with similar hydrogen bonding abilities that would be more bioavailable and metabolically stable. Such molecules would be much improved drug candidates for the treatment of disorders in which dopamine D_1 receptor activation would be therapeutic.

Experimental Section

Chemistry

General: All reagents were commercially available (Aldrich, Alfa Aesar) and were used without further purification unless otherwise indicated. Dry THF was distilled immediately before use from benzophenone–sodium under argon. Column chromatography was carried out using SiliCycle SiliaFlash P60 silica gel (230–400 mesh). J.T. Baker flexible thin-layer chromatography sheets (silica gel IB2-F) were used to monitor reaction progress. Melting points were determined with a Mel-Temp apparatus and are reported as uncorrected values. ^{1}H NMR spectra were recorded with a 300 MHz Bruker ARX300 instrument or a 500 MHz Bruker DRX500 instrument, as indicated. Chemical shift values (δ) are reported in ppm relative to an internal reference [$(CH_3)_4Si$ in $CDCl_3$ (0.03% *v/v*)] except where noted. Abbreviations used to report NMR peaks are as follows: bs = broad singlet, d = doublet, dd = doublet of doublets, m = multiplet, q = quartet, s = singlet, t = triplet. Electrospray ionization MS analyses were carried out on a FinniganMAT LCQ Classic system (ThermoElectron, San Jose, CA, USA). Low-resolution electron impact (EI) and chemical ionization (CI) studies were carried out with a Hewlett–Packard Engine mass spectrometer (Wilmington, DE, USA). Elemental analyses were performed by the Purdue University Microanalysis Laboratory, and all compounds reported possess $\geq$95% purity. All reactions were carried out under an argon atmosphere, unless noted otherwise.

7,8-Dihydroxy-4-methylchromen-2-one, 4. Pyrogallol, (50.0 g, 0.39 mol) and ethyl acetoacetate (50 mL, 0.39 mol) were combined in a 500 mL three-neck round-bottom flask equipped with mechanical stirring. The flask was immersed in an ice bath and concentrated H_2SO_4 (80 mL) was added dropwise over 30 min. The reaction mixture was stirred an additional 2 h and poured onto ice. The resulting solid was collected, filtered, and dried for 30 min under a stream of argon gas. Recrystallization twice from hot MeOH yielded the desired product (18.7 g, 25%); mp > 240 °C (lit.[48] mp = 232 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.07 (d, 1H, J = 8.7 Hz), 6.80 (d, 1H, J = 8.7 Hz), 6.06 (s, 1H), 4.90 (bs, 2H), 2.38 ppm (s, 3H); MS (ESI): $[M+H]^+ = 193$.

7,8-Dibenzyloxy-4-methylchromen-2-one, 5. A solution of **4** (10.1 g, 52.59 mmol) in DMF (120 mL) was filtered through a fritted glass funnel to remove a small amount of insoluble material. BnBr (13.75 mL, 115.6 mmol) was added, followed by K_2CO_3 (73 g, 325 mesh), and the mixture was magnetically stirred for 1 h at room temperature. CH_2Cl_2 (500 mL) was added and the reaction mixture was filtered through a pad of Celite. The filtrate was washed with H_2O (3 × 500 mL), dried over $MgSO_4$, filtered, and concentrated to dryness. The resulting oil was dissolved in CH_2Cl_2 (10 mL) and Et_2O

was slowly added, just to turbidity. Stirring was continued until a white precipitate was produced and then more Et_2O (400 mL) was added. The white solid was collected by filtration, dried under argon, and placed on a vacuum pump for 2 h. The product weighed 16.63 g (85%); mp = 149–153 °C (lit.[49] mp = 157 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41 (m, 8H), 7.25 (m, 3H), 7.16 (d, 1H, J = 8.7 Hz), 6.18 (s, 1H), 5.25 (s, 2H), 5.13 (s, 2H), 2.43 ppm (s, 3H); MS (ESI): $[M+H]^+$ = 373; Anal. calcd (%) for $C_{24}H_{20}O_4$: C 77.40, H 5.41, found: C 77.48, H 5.53.

7,8-Dibenzyloxy-2-oxo-2*H*-chromene-4-carboxaldehyde, 6. A 500 mL round-bottom flask was charged with **5** (8.9 g, 23.9 mmol), SeO_2 (3.9 g, 35.14 mmol), and xylenes (mixed, 151 mL), and the mixture was stirred and heated at 150 °C for 12 h. The reaction mixture was allowed to cool to room temperature and was filtered through a pad of Celite, which was further washed with Et_2O. Hexane was added to the filtrate and a yellow precipitate formed, which was collected by filtration. The filtrate was concentrated by rotary evaporation and additional product was precipitated with hexane. The combined yellow solid was recrystallized from cold CH_2Cl_2/Et_2O to yield aldehyde (5.63 g, 61%) that was sufficiently pure for the next step. A small sample was dissolved in CH_2Cl_2 and passed through a short silica column (1:1 hexane/CH_2Cl_2). The pure fractions were combined and concentrated to yield an analytically pure sample; mp = 117–118 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.05 (s, 1H), 8.25 (d, 1H, J = 9.0 Hz), 7.37 (m, 10H), 6.97 (d, 1H, J = 9.0 Hz), 6.72 (s, 1H), 6.22 (s, 2H), 5.18 ppm (s, 2H); MS (ESI): $[M+H]^+$ = 387; Anal. calcd (%) for $C_{24}H_{18}O_5$: C 74.60, H 4.70; found C 74.27, H 4.80.

4-(*N*-Benzylaminomethyl)-7,8-dibenzyloxychromen-2-one, 7. A solution of **6** (24.3 g, 62.9 mmol) in $CHCl_3$ (280 mL) was filtered through a fritted glass funnel to remove a small amount of insoluble material. Benzylamine (8.73 mL, 79.59 mmol) and Na_2CO_3 (2.1 g) were added to the dark solution, which was stirred for 14 h at room temperature. The mixture was then filtered through a pad of Celite into a 500 mL round-bottom flask, and the filtrate was cooled on an ice bath. Dry MeOH (50 mL) was added, followed by portionwise addition of $NaBH_3CN$ (4.27 g, 67.95 mmol) over 30 min. The pH was monitored with moist litmus paper while the reaction mixture was kept slightly acidic using concentrated HCl. After stirring for 2 h at room temperature, the reaction was concentrated to dryness. The resulting solid was partitioned between 300 mL CH_2Cl_2 and a solution of saturated $NaHCO_3$ (200 mL). The aqueous layer was further extracted with CH_2Cl_2 (2×100 mL), and the combined organic extracts were washed with H_2O (200 mL), brine (100 mL), dried over $MgSO_4$, filtered, and concentrated to dryness. The resulting oil was placed under an aspirator vacuum, which induced solidification. The solid was recrystallized from a minimal amount of CH_2Cl_2 and excess hot MeOH to yield 17.5 g (58%) of product as colorless needles; mp = 129–130 °C. Yields of up to 80% were obtained if chromatographically pure **6** was used. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.41 (m, 16H), 7.24 (d, 1H, J = 9.0 Hz), 7.17 (d, 1H, J = 9.0 Hz), 6.41 (s, 1H), 5.27 (s, 2H), 5.08 (s, 2H), 3.87 (s, 2H), 3.78 ppm (s, 2H); MS (ESI): $[M+H]^+$ = 648; Anal. calcd for $C_{31}H_{27}NO_4$: C 77.97, H 5.70, N 2.93, found: C 77.66, H 5.59, N 2.63.

7,8-Dibenzyloxy-4-*N*,*N*-dibenzylaminomethylchromen-2-one, 8. In a 1 L round-bottom flask, 16.69 g (34.98 mmol) of **7**, 200 mL DMF, and BnBr (8.65 mL, 72.72 mmol) were heated together on an oil bath for a few minutes until the starting material had dissolved. K_2CO_3 (325 mesh, 55 g) was then added, and the mixture was heated at 110 °C with stirring until TLC indicated complete disappearance of starting material. CH_2Cl_2 (500 mL) was added to the reaction mixture, which was then filtered through a pad of Celite. The solution was washed with H_2O (3×500 mL) and the combined H_2O washes were back extracted with CH_2Cl_2 (2×100 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to afford the desired product containing a small amount of DMF. Addition of Et_2O (500 mL) produced a white precipitate that was filtered and washed with additional Et_2O (300 mL). A total of 17.88 g (90%) of product sufficiently pure for the next step was obtained. A small amount of material was recrystallized by vapor diffusion (MeOH, CH_2Cl_2/Et_2O); mp = 159–161 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48 (m, 2H), 7.33 (m, 19H), 6.82 (d, 1H, J = 9.0 Hz), 6.63 (s, 1H), 5.17 (s, 2H), 5.16 (s, 2H), 3.63 (s, 2H), 3.63 ppm (s, 4H); MS (ESI): $[M+H]^+$ = 568; Anal. calcd (%) for $C_{38}H_{33}NO_4$ (0.5 equiv MeOH): C 79.22, H 6.04, N 2.40, found: C 79.57, H 5.88, N 2.08.

7,8-Dibenzyloxy-4-*N*,*N*-dibenzylaminomethyl-2*H*-chromen-2-ol, 9. A solution of **8** (14.1 g, 24.85 mmol) in CH_2Cl_2 (700 mL) in a 1 L flask was flushed with argon for 10 min. The flask was then cooled to −78 °C and DIBAH (37.27 mL, 1 M in hexane, 37.27 mmol) was added over 10 min. After 2 h the starting material was consumed and EtOAc (200 mL) was added to quench the reaction. The solution was removed from the dry ice/acetone bath and poured into a 2 L flask containing 300 mL of saturated Rochelle's salt solution. The emulsion was stirred vigorously until the layers separated (~1 h). The organic layer was separated and washed with brine (2×200 mL), dried over $MgSO_4$, filtered, and concentrated to dryness. Chromatography (9:1 hexane/EtOAc) afforded a yellow oil that solidified under a high vacuum (10.19 g, 72%). A small amount was recrystallized from MeOH/Et_2O/hexane to afford a white solid; mp = 90–94 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31 (m, 20H), 7.04 (d, 1H, J = 8.7 Hz), 6.53 (d, 1H, J = 8.7 Hz), 5.93 (m, 2H), 5.12 (s, 2H), 5.08 (s, 2H), 3.61 (d, 2H, J = 13.5 Hz), 3.53 (d, 2H, J = 13.5 Hz), 3.40 (d, 1H, J = 14.0 Hz), 3.36 (d, 1H, J = 14.0 Hz), 2.48 ppm (d, J = 7.4 Hz); MS (ESI): $[M+H]^+$ = 570; Anal. calcd (%) for $C_{38}H_{35}NO_4$ (0.5 equiv MeOH): C 78.95, H 6.37, N 2.39; found C 78.66, H 6.26, N 2.37.

***N*,*N*-Dibenzyl-*N*-(7,8-dibenzyloxy-2*H*-chromen-4-ylmethyl)amine hydrochloride, 10**. A solution of **9** (3.88 g, 6.81 mmol) in CH_2Cl_2 (70 mL) in a 250 mL round-bottom flask was placed on an ice bath. Et_3SiH (2.14 mL, 13.40 mmol) was added, followed by dropwise addition of $BF_3{\cdot}OEt_2$ (1.7 mL, 13.42 mmol), during which the solution turned dark. The ice bath was removed, and the reaction mixture was stirred for 1 h, after which it was again placed on an ice bath. A saturated solution of NH_4Cl was added (100 mL) and the crude mixture was extracted with CH_2Cl_2 (3×150 mL). The organic layers were combined and washed with brine (200 mL), dried over $MgSO_4$, filtered, and concentrated to dryness. Column chromatography (15:3:2 hexane/CH_2Cl_2/acetone) afforded the desired product as a colorless oil (3.21 g, 85%). The HCl salt was prepared by dissolving the product in a minimal amount of CH_2Cl_2, neutralizing with 1 M HCl in dry EtOH, and precipitating with Et_2O; mp = 160–163 °C; ^{1}H NMR (500 MHz, $CDCl_3$ (free base): δ = 7.33 (m, 20H), 6.90 (d, 1H, J = 8.7 Hz), 6.44 (d, 1H, J = 8.7 Hz), 5.81 (bs, 1H), 5.09 (s, 2H), 5.02 (s, 2H), 4.71 (d, 2H, J = 6.0 Hz), 3.55 (s, 4H), 3.29 ppm (s, 2H); MS (ESI): $[M+H]^+$ = 554; Anal. calcd (%) for $C_{38}H_{36}ClNO_3$: C 77.34, H 6.15, N 2.37, found: C 76.98, H 6.29, N, 2.41.

7,8-Dihydroxy-4-aminomethylchroman hydrochloride, 2a. Absolute EtOH (220 mL) and **10** (2.8 g, 4.74 mmol) were stirred vigorously for 5 min and the solution was then filtered through a fritted glass funnel into a 500 mL round-bottom flask equipped with a stirring bar. The flask was briefly flushed with argon and 1.9 g 10% Pd/C (dry) was added. The flask was capped with a rubber septum and H_2 gas was passed through it for 20 min. A balloon

filled with H_2 was then attached and the contents of the flask were stirred at room temperature for 24 h under an atmosphere of H_2. The crude suspension was filtered through a pad of Celite that had been previously washed with absolute EtOH. After filtration the pad was washed with an additional 500 mL of EtOH. The dark filtrate was concentrated to dryness and placed under a high vacuum overnight. The resulting black solid was dissolved in MeOH (20 mL) followed by slow addition of Et_2O. Vigorous stirring and scratching with a spatula induced formation of a black gummy precipitate. The tan solution was decanted away from the black precipitate into another flask. This process was continued three times until an off-white precipitate began to form upon addition of Et_2O. Excess Et_2O was added to ensure complete precipitation of the product. Throughout the whole process a gentle stream of argon was passed through the flask to prevent oxidation. The precipitate was filtered, dried under a stream of argon, and placed under a high vacuum for 12 h. Recrystallization by vapor diffusion (MeOH/Et_2O) three times yielded an analytically pure sample (329 mg, 30%); mp = 235–238 °C (dec.); ^{1}H NMR (500 MHz, CD_3OD): δ = 6.53 (d, 1H, J = 8.5 Hz), 6.42 (d, 1H, J = 8.5 Hz), 4.22 (m, 2H), 3.26 (bs, 1H), 3.09 (m, 2H), 2.12 (m, 1H), 1.93 (m, 1H); MS (ESI): $[M+H]^+$ = 196, $[M-NH_3]$ = 179; Anal. calcd (%) for $C_{10}H_{14}ClNO_3$: C 51.84, H 6.09, N 6.05, found: C 51.48, H 5.95, N 5.70.

***N*,*N*-Dibenzyl-*N*-(2-allyl-7,8-dibenzyloxy-2*H*-chromen-4-ylmethyl)-amine hydrochloride, 11**. A solution of **9** (2.43 g, 4.32 mmol) and allyltrimethylsilane (1.38 mL, 8.64 mmol) in CH_2Cl_2 (60 mL) was placed on an ice bath, and $BF_3{\cdot}OEt_2$ (1.09 mL, 8.64 mmol) was added through a syringe. The deep-red solution was stirred at room temperature for 2 h and then quenched with 100 mL of saturated $NaHCO_3$. The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (3×80 mL). The organic fractions were combined, dried over $MgSO_4$, filtered, and concentrated to dryness. The crude product was chromatographically purified using 10% EtOAc in hexane to afford a clear oil (2.31 g, 90%). The HCl salt was prepared by dissolving the product in a minimal amount of 1:1 CH_2Cl_2/EtOH solution, neutralizing with 1 M HCl in dry EtOH, and precipitating with Et_2O; mp = 127–130 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (m, 20H), 6.58 (d, 2H, J = 8.7 Hz), 6.46 (d, 1H, J = 8.7 Hz), 5.94 (m, 1H), 5.17 (m, 2H), 5.14 (s, 2H), 5.09 (s, 2H), 4.97 (m, 1H), 4.20 (bs, 4H), 3.88 (bs, 2H), 2.61 ppm (bs, 2H); MS (ESI): $[M+H]^+$ = 594; Anal. calcd (%) for $C_{41}H_{40}ClNO_3$: C 78.14, H 6.40, N 2.22, found: C 77.83, H 6.76, N 1.88.

4-Aminomethyl-2-propylchroman-7,8-diol hydrochloride, 2e. In a method analogous to the procedure for the synthesis of **2a**, **11** (760 mg, 1.21 mmol) was converted into the title compound. An analytically pure sample was obtained by vapor diffusion recrystallization (MeOH/Et_2O) three times to yield a total of 110 mg (33%) of the catechol hydrochloride; mp = 245–255 °C; ^{1}H NMR (500 MHz, CD_3OD): δ = 6.57 (d, 1H, J = 8.5 Hz), 6.42 (d, 1H, J = 8.5 Hz), 3.98 (q, 1H, J = 6.0), 3.48 (dd, 1H, J = 3.5, 13.0 Hz), 3.27 (bs, 1H), 3.01 (dd, 1H, J = 9, 13.0 Hz), 2.19 (dd, 1H, J = 6.0, 13.0 Hz), 1.86 (m, 1H), 1.66 (m, 2H), 1.53 (m, 2H), 1.03 ppm (t, 3H, J = 7.0 Hz); MS (ESI): $[M+H]^+$ = 238; Anal. calcd (%) for $C_{13}H_{20}ClNO_3$: C 57.04, H 7.36, N 5.12, found: C 56.65, H 7.50, N 5.09.

***N*,*N*-Dibenzyl-*N*-(7,8-dibenzyloxy-2-cyclohexyl-2*H*-chromen-4-yl-methyl)amine, 13b**. A solution of **9** (3.08 g, 6.67 mmol) in 30 mL of dry THF in a 250 mL round-bottom flask was placed on an ice bath and CyMgCl (2 M, 34 mL, 68 mmol) was added slowly. The reaction mixture was stirred at room temperature for 1 h, placed on the ice bath once more and carefully quenched with ice (100 g). The crude material was partitioned between CH_2Cl_2 (300 mL) and saturated NH_4Cl (200 mL). The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (3×120 mL). The organic fractions were combined, dried over $MgSO_4$, filtered, and concentrated to dryness. The crude material was dried under a high vacuum for 3 h, and was then dissolved in 20 mL of dry THF. The solution was added by syringe to a 0 °C THF solution (40 mL) containing DEAD (1.2 mL, 7.67 mmol) and tributylphosphine (1.89 mL, 7.67 mmol) under an argon atmosphere. The orange solution was stirred at room temperature for 2 h, quenched with H_2O (100 mL), and then extracted with Et_2O (3×150 mL) and CH_2Cl_2 (100 mL). The organic fractions were combined, dried over $MgSO_4$, filtered, and concentrated to dryness. Warm benzene (50 mL) was added to the resulting solid and the mixture was stirred for 10 min. The slurry was then filtered through a fritted funnel and the filtrate concentrated once more. Column chromatography (15:3:2 hexane/CH_2Cl_2/acetone) afforded the desired product as a clear oil (2.12 g, 51%). The HCl salt was prepared by dissolving the product in a minimal amount of CH_2Cl_2/EtOH (1:1), neutralizing with 1 M HCl in dry EtOH, and precipitating with Et_2O; mp = 132–134 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34 (m, 20H), 6.89 (d, 1H, J = 8.5 Hz), 6.4 (d, 1H, J = 8.5 Hz), 5.74 (d, 1H, J = 3.0 Hz), 5.02 (m, 4H), 4.59 (bs, 1H), 3.55 (s, 4H), 3.29 (s, 2H), 1.90 (d, 1H, J = 10.5 Hz), 1.63 (m, 5H), 1.18 ppm (m, 5H); MS (ESI): $[M+H]^+$ = 636; Anal. calcd (%) for $C_{44}H_{46}ClNO_3$: C 78.61, H 6.90, N 2.08, found: C 78.66, H 6.94, N 2.02.

4-Aminomethyl-2-cyclohexylchroman-7,8-diol hydrochloride, 2b. In a method analogous to the synthesis of **2a** above, **12b** (3.65 g, 5.43 mmol) was converted into the title compound. A total of 1.26 g (70%) of the catechol hydrochloride was obtained. An analytically pure sample was obtained after four vapor diffusion recrystallizations (MeOH/Et_2O). Yields for the analytically pure samples were usually 20–30%; mp = 180 °C (solvent release) and 240 °C (dec.); ^{1}H NMR (500 MHz, CD_3OD): δ = 6.57 (d, 1H, J = 8.5 Hz), 6.41 (d, 1H, J = 8.5 Hz), 3.76 (q, 1H, J = 5.5 Hz), 3.49 (dd, 1H, J = 3.5, 13.0 Hz), 3.24 (bs, 1H), 3.13 (dd, 1H, J = 9.0, 13.0 Hz), 2.18 (dd, 1H, J = 6.0, 13.0 Hz), 2.05 (d, 1H, J = 12.0 Hz), 1.8 (m, 5H), 1.54 (q, 1H, J = 12.0 Hz), 1.31 ppm (m, 5H); MS (EI): $[M+H]^+$ = 278, 261 $[M-NH_3]$; Anal. calcd (%) for $C_{16}H_{24}ClNO_3$ (0.11 equiv MeOH): C 60.97, H 7.76, N 4.41, found: C 60.74, H 7.38, N 4.44.

***N*,*N*-Dibenzyl-*N*-(2-adamant-2-yl-7,8-dibenzyloxy-2*H*-chromen-4-ylmethyl)amine hydrochloride, 13c**. Magnesium (16 g, 658 mmol) and 1-bromoadamantane were placed in a three-neck round-bottom flask flushed with argon. Et_2O (70 mL) was added and the slurry was stirred vigorously with a magnetic stirrer. The reaction was initiated by addition of 70 μL of MeMgBr and a small crystal of iodine along with brief heating at reflux. The organomagnesium solution was stirred at room temperature for 30 min and diluted with 200 mL of dry Et_2O, after which it was placed on a dry ice/CH_3CN bath. A solution of **9** (4.7 g, 8.25 mmol) in 25 mL of dry THF was added dropwise to the grey slurry. The flask was stirred at room temperature for 1 h, placed in an ice bath, and then quenched with ice (100 g). The crude material was partitioned between EtOAc (300 mL) and saturated NH_4Cl (250 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3×120 mL). The organic fractions were combined, dried over $MgSO_4$, filtered, and concentrated to dryness. The resulting solid was dissolved in 300 mL of CH_2Cl_2, the solution was filtered, and the filtrate kept on ice. The product solution was then dried over $MgSO_4$, filtered, concentrated to dryness, and placed under high vacuum for 3 h. The residue was dissolved in 15 mL of dry THF and then added by syringe to a 0 °C THF solution (80 mL) containing 3.8 mL of DEAD (24.2 mmol) and triphenylphosphine (6.8 g, 25.93 mmol) under argon at 0 °C. The solution was stirred at

room temperature until TLC indicated complete consumption of starting material (1 h). Ice H_2O (200 mL) was added slowly and the crude mixture was extracted into Et_2O (2×200 mL) and CH_2Cl_2 (200 mL). The organic fractions were combined, dried over $MgSO_4$, filtered, and concentrated to dryness. Purification by column chromatography (20:1 hexane/EtOAc) yielded a clear oil (3.06 g, 54%). The HCl salt was obtained by dissolving the oil in a minimal amount of 1:1 CH_2Cl_2/EtOH and neutralizing with 1 M HCl in anhydrous EtOH. The product was then precipitated with Et_2O, filtered, and dried under high vacuum; mp = 155–158 °C; ^{1}H NMR (500 MHz, CD_3OD): δ = 7.32 (m, 21H), 6.43 (d, 1H, J = 8.5 Hz), 6.20 (bs, 2H), 5.03 (m, 4H), 4.29 (m, 5H), 4.18 (bs, 2H), 3.21 (s, 3H), 1.74 ppm (m, 12H); MS (EI): $[M+H]^+$ = 691; Anal. calcd (%) for $C_{48}H_{52}ClNO_3$ (1 equiv MeOH): C 77.60, H 7.44, N 1.85, found: C 77.85, H 7.18, N 1.91.

2-Adamant-1-yl-4-aminomethylchroman-7,8-diol hydrochloride, 2c. In a method analogous to the synthesis of **2a** above, **12c** (2.85 g, 3.92 mmol) was converted into the title compound. A total of 1.33 g (92%) of the crude catechol hydrochloride was obtained. The pink solid was dissolved in MeOH and treated with decolorizing carbon and filtered through a pad of Celite. Slow addition of Et_2O with vigorous stirring induced formation of a tan precipitate that was collected by filtration under argon. An analytically pure sample was obtained after four vapor diffusion recrystallizations (MeOH/Et_2O); (512 mg, 36%); mp = 210–220 °C; ^{1}H NMR (500 MHz, CD_3OD): δ = 6.57 (d, 1H, J = 8.5 Hz), 6.41 (d, 1H, J = 8.5 Hz), 3.48 (m, 2H), 3.30 (bs, 2H), 3.00 (dd, 1H, J = 9.0, 13.0 Hz), 2.23 (dd, 1H, J = 6.0, 13.0 Hz), 2.02 (bs, 3H), 1.89 (d, 3H, J = 12.0 Hz), 1.77 (m, 9H), 1.89 ppm (q, 1H, J = 12.0 Hz); MS (ESI): $[M+H]^+$ = 330; Anal. calcd (%) for $C_{20}H_{28}ClNO_3$: C 65.65, H 7.71, N 3.83,, found: C 65.28, H 8.02, N 3.92.

2,3-Dibenzyloxy-6-{1-[(*N*,*N*-dibenzylamino)methyl]-3-phenylpropenyl}phenol, 14. PhMgBr (1 M in THF, 60 mL, 60 mmol) was added dropwise to a solution of **9** (4.85 g, 8.51 mmol) in dry THF (40 mL) at 0 °C. The solution was removed from the ice bath, stirred for 1 h, and quenched with ice (50 mL). The crude reaction was partitioned between EtOAc (150 mL) and saturated NH_4Cl (100 mL). The aqueous layer was extracted with EtOAc (2×150 mL), the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to dryness. The crude product was chromatographically purified (15:3:2 hexane/CH_2Cl_2/acetone) to yield the product as a white solid (4.6 g, 83%); mp = 146–149 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31 (m, 30H), 6.60 (d, 1H, J = 8.5 Hz), 6.47 (d, 1H, J = 8.5 Hz), 5.91 (d, 1H, J = 9.6 Hz), 5.12 (m, 5H), 3.69 (d, 2H, J = 13.5 Hz), 3.52 (d, 2H, J = 13.5 Hz), 3.32 (d, 1H, J = 13.5 Hz), 3.19 (d, 1H, J = 13.2 Hz), 2.19 ppm (bs; 1H); MS (ESI): $[M+H]^+$ = 648; Anal. calcd for $C_{44}H_{41}NO_4$: C 81.58, H 6.38, N 2.16, found: C 81.54, H 6.26, N 2.30.

***N*,*N*-Dibenzyl-*N*-(7,8-dibenzyloxy-2-phenyl-2*H*-chromen-4-ylmethyl)amine hydrochloride, 15**. A stirring solution of **14** (5.13 g, 7.92 mmol) in pyridine (42 mL) in a 250 mL round-bottom flask was cooled to 0 °C. Thionyl chloride (3.5 mL, 18.12 mmol) was slowly added dropwise, during which the solution turned deep red. After 5 min, TLC indicated complete reaction, and CH_2Cl_2 (300 mL) was added. The red solution was poured into 600 mL of a cold solution of 1 M HCl and the aqueous layer was extracted with CH_2Cl_2 (2×300 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to dryness. Column chromatography (hexane→15:3:2 hexane/CH_2Cl_2/acetone) yielded the desired product as a yellow oil (3.09 g, 62%). The HCl salt was obtained by dissolving the oil in a minimal amount of 1:1 CH_2Cl_2/EtOH solution and neutralizing with 1 M ethanolic HCl solution. The product was then precipitated with Et_2O, filtered, and dried under high vacuum; mp = 162–165 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31 (m, 30H), 6.93 (d, 1H, J = 8.7 Hz), 6.42 (d, 1H, J = 8.7 Hz), 5.91 (d, 1H, J = 3.6 Hz), 5.85 (d, 1H, J = 3.6 Hz), 5.06 (d, 2H, J = 3.0 Hz), 4.85 (d, 2H, J = 9.0 Hz), 3.58 (s, 4H), 3.37 ppm (s, 2H); MS (ESI): $[M+H]^+$ = 630; Anal. calcd (%) for $C_{44}H_{40}ClNO_3$: C 79.32, H 6.05, N 2.10, found: C 79.25, H 6.07, N 2.08.

2-(2,3-Dimethoxyphenyl)-5-oxo-tetrahydrofuran-3-carboxylic acid, 18. To a flame-dried three-neck flask fitted with a condenser and dried addition funnel was added anhydrous, powdered $ZnCl_2$ (25.0 g, 0.184 mol). To this solid was added 100 mL CH_2Cl_2, followed by 2,3-dimethoxybenzaldehyde (15.3 g, 0.092 mol) and succinic anhydride (13.8 g, 0.138 mol). Triethylamine (25.6 mL, 0.184 mol) was added dropwise to the flask with rapid stirring and the mixture was heated at reflux for four days. The reaction was cooled to room temperature and poured over ice-cold 6 N HCl. The organic component was extracted with EtOAc (3×250 mL), which was then washed with 2 N HCl (1×250 mL), and brine (1×250 mL). The product was extracted into saturated $NaHCO_3$ (4×200 mL) until TLC indicated no product remaining in the organic layer. The aqueous layer was washed with CH_2Cl_2 (1×200 mL) and acidified with concentrated HCl. The white, milky solution was extracted with CH_2Cl_2 (3×250 mL), dried over Na_2SO_4, and evaporated under vacuum to afford a pale-yellow solid (18.0 g, 73.6%) that was recrystallized from EtOAc/hexanes; mp = 129–130 °C (lit.[50] mp = 132 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.01 (t, 1H, J = 7.5 Hz), 6.89 (dd, 1H, J = 2.5, 8.1 Hz), 6.82 (dd, 1H, J = 2.5, 8.1 Hz), 5.73 (d, 1H, J = 6.6 Hz), 3.81 (s, 3H), 3.80 (s, 3H), 3.44 (dt, 1H, J = 6.6, 8.5 Hz), 2.90 ppm (d, 2H, J = 8.5 Hz); MS (EI): $[M+H]^+$ = 266.

4-(2,3-Dimethoxyphenyl)but-3-enoic acid, 19. Recrystallized **18** (8.6 g, 0.032 mol) was placed into a single-neck round-bottom flask and the flask was heated for 6 h on a 180 °C oil bath. CO_2 was observed bubbling out of the dark-brown liquid. After 6 h, the reaction was cooled to room temperature and dissolved in CH_2Cl_2. The product and any unreacted starting material were extracted into 2 N NaOH (3×100 mL). The pK_a of the butenoic acid is ~4.2, whereas the pK_a of paraconic acid **18** is ~3.6, so the two compounds are separable by titration. The aqueous extract was therefore carefully acidified with 2 N HCl, with monitoring by a calibrated pH meter. At pH 4.0 the solution became very cloudy and was extracted with CH_2Cl_2. The titration was repeated until there was no turbidity at pH 4.0. Unreacted starting material could be recovered by acidifying to pH 3.0 and extracting with CH_2Cl_2. The initial organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure to yield pure **19** that solidified under reduced pressure to provide a yellow solid (4.7 g, 65.2%) that was used without further purification; mp = 84–86 °C (no lit.[51] mp reported); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.08 (dd, 1H, J = 1.2, 8.0 Hz), 6.99 (t, 1H, J = 8.0 Hz), 6.80 (m, 2H), 6.29 (dt, 1H, J = 7.2, 15.9 Hz), 3.84 (s, 3H), 3.78 (s, 3H), 3.32 ppm (dd, 2H, J = 1.2, 7.2 Hz); MS (ESI): $[M+Na]^+$ = 245.

4-(2,3-Dimethoxyphenyl)butanoic acid, 20. A 500 mL Parr hydrogenation flask containing 0.6 g of 10% Pd/C and **19** (3.7 g, 0.017 mol) dissolved in absolute EtOH was pressurized with H_2 and shaken at 2 atm H_2 for 2 h. The contents were filtered through Celite, the filtrate was evaporated, and the resulting oil was dried under high vacuum to yield a grey solid (3.7 g, quant. yield). The solid was recrystallized from EtOAc/hexanes to afford fine white needles (2.2 g, 59.5%); mp = 58–59 °C (lit.[52] mp = 58.5–60 °C) ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.97 (t, 1H, J = 8.0 Hz), 6.76 (d, 1H, J = 8.0 Hz), 6.75 (d, 1H, J = 8.0 Hz), 3.84 (s, 3H), 3.80 (s, 3H), 2.67 (t,

2H, $J=7.0$ Hz), 2.37 (t, 2H, $J=7.0$ Hz), 1.92 ppm (p, 2H, $J=7.0$ Hz); MS (ESI): $[M+Na]^+=247$.

5,6-Dimethoxy-3,4-dihydronaphthalen-1(2*H*)-one, 21. A dry, mechanically stirred flask charged with 15 g polyphosphoric acid was heated on a 60 °C oil bath for 20 min. Finely powdered **20** (1.0 g, 4.46 mmol) was added in small portions into the center of the stirring vortex. After 30 min the reaction was a rust color and no starting material remained (TLC). The reaction was quenched by pouring over ice with vigorous stirring, whereupon the desired product crystallized. The crystals were filtered and washed with H_2O to yield pearly off-white plates (900 mg, 97.9%); mp = 103–104 °C (lit.[52] mp = 104–105 °C) ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.79$ (d, 1H, $J=8.7$ Hz), 6.81 (d, 1H, $J=8.7$ Hz), 3.86 (s, 3H), 3.75 (s, 3H), 2.89 (t, 2H, $J=6.3$ Hz), 2.53 (t, 2H, $J=6.3$ Hz), 2.05 ppm (p, 2H, $J=6.3$ Hz); MS (EI): $[M]^+=206$.

5,6-Dimethoxy-3,4-dihydronaphthalene-1-carbonitrile, 22. TMSCN (1.42 mL, 10.7 mmol) was added dropwise to a slurry of **21** (1.7 g, 8.25 mmol) in freshly distilled toluene (25 mL). After stirring for 10 min, $BF_3{\cdot}OEt_2$ (1.57 mL, 12.38 mmol) was added all at once, producing an immediate color change from yellow to brown. The reaction was stirred at room temperature for 3 h, until no starting material remained (TLC). The reaction was quenched by pouring over ice H_2O (30 mL) with vigorous stirring. Et_2O (20 mL) was added to this mixture, the layers were separated, and the aqueous layer was extracted twice more with Et_2O and once with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under reduced pressure to yield a tan solid (1.7 g, 96%) that could be recrystallized from MeOH to yield fine, colorless needles in 84% over three crops; mp = 138–140 °C (lit.[35] mp = 137–139 °C); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.18$ (d, 1H, $J=8.0$ Hz), 6.80 (d, 1H, $J=8.0$ Hz), 6.75 (t, 1H, $J=4.6$ Hz), 3.88 (s, 3H), 3.76 (s, 3H), 2.87 (t, 2H, $J=8.0$ Hz), 2.44 (m, 2H); MS (EI): $[M]^+=215$.

(5,6-Dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methanamine, 23. A solution of **22** (1.25 g, 5.81 mmol) in MeOH (30 mL) was added to a Parr hydrogenation flask containing 0.5 g Raney-nickel catalyst in 10 mL MeOH. To this suspension was added 5 mL NH_4OH before pressurizing the vessel with 4 atm H_2 and shaking for 16 h. The reaction was carefully filtered through Celite and the filtrate evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 and extracted three times with 2 N HCl. The combined aqueous layers were basified with 2 N NaOH and extracted with Et_2O. The ether layers were acidified with 2 N ethanolic HCl and filtered to yield the HCl salt of the amine as a white powder (730 mg, 49%); mp = 225–227 °C (dec.) (lit.[35] mp = 249–251 °C); ^{1}H NMR (300 MHz, D_2O): $\delta=6.98$ (d, 1H, $J=8.0$ Hz), 6.87 (d, 1H, $J=8.0$ Hz), 3.76 (s, 3H), 3.66 (s, 3H), 3.02–2.90 (m, 3H), 2.69–2.56 (m, 2H), 1.78–1.61 ppm (m, 4H); MS (ESI): $[M+H]^+=222$; $[M+H]^+-NH_3=205$.

5-(Aminomethyl)-5,6,7,8-tetrahydronaphthalene-1,2-diol hydrobromide, 3a. A solution of 180 mg of **23** (0.814 mmol) dissolved in CH_2Cl_2 was placed into a flame-dried flask with magnetic stirring and cooled to −78 °C. A 1.0 M solution of BBr_3 in CH_2Cl_2 (2.5 mL) was then slowly added dropwise to the flask as the solution gradually became cloudy. The reaction was stirred at −78 °C for 1 h and allowed to warm to room temperature overnight. MeOH (25 mL) was added to quench the reaction, followed by evaporation under reduced pressure. The brown solid residue was washed with MeOH and evaporated three additional times to remove any HBr. The residue was dried under high vacuum to yield the HBr salt as a brown solid (0.222 g, 99%) that could be recrystallized from MeOH/EtOAc; mp = 203–205 °C (dec.) (lit.[35] mp = 211–213 °C); ^{1}H NMR (300 MHz, D_2O): $\delta=6.62$ (d, 1H, $J=8.0$ Hz), 6.57 (d, 1H, $J=8.0$ Hz), 3.11–2.95 (m, 3H), 2.59–2.40 (m, 2H), 1.70–1.53 ppm (m, 4H); MS (ESI): $[M+H]^+=194$; $[M+H]^+-NH_3=177$.

Ethyl 2-cyclohexyl-3-(2,3-dimethoxyphenyl)-3-hydroxypropanoate, 25b. A flame-dried single-neck round-bottom flask in a dry ice-acetone bath was charged with 50 mL of freshly distilled dry THF, followed by addition of 33.1 mL of a 2.0 M solution of lithium diisopropyl amide. A solution of **24b**[53] (10.24 g, 0.0602 mol) dissolved in distilled THF (30 mL) was added dropwise over 15 min. The enolate solution was allowed to stir at −78 °C for an additional 15 min, followed by the dropwise addition of a solution of 2,3-dimethoxybenzaldehyde (10.0 g, 0.0602 mol) in THF (75 mL). The reaction turned a bright-yellow color and was allowed to warm to ambient temperature over the next 90 min. The reaction was quenched by the dropwise addition of H_2O (30 mL). Approximately 50 mL Et_2O were added, and the layers separated. The organic layer was washed vigorously with a saturated solution of $NaHSO_3$ (2×50 mL) to remove any unreacted benzaldehyde. The ether layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to afford a dark-yellow oil. After column chromatography (1:1 EtOAc/hexanes), the major product was isolated as a diastereomeric mixture of the title compound as a yellow oil (16.3 g, 80.3%). Diastereomers: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=6.99$ (t, 1H, $J=7.8$ Hz), 6.88 (bd, 1H, $J=7.8$ Hz), 6.83 (bd, 1H, $J=7.8$ Hz), 5.26 (d, 0.3H, $J=3.9$ Hz), 5.08 (d, 0.7H, $J=8.4$ Hz), 3.95 (q, 2H, $J=6.0$ Hz), 3.94 (s, 3H), 3.86 (s, 3H), 2.81 (dd, 0.7H, $J=3.9$, 8.4 Hz), 2.67 (dd, 0.3H, $J=3.9$, 9.0 Hz), 2.04–1.68 (m, 7H), 1.32–1.08 (m, 4H), 1.04 (t, 3H, $J=6.0$ Hz); MS (ESI): $[M+Na]^+=359$; Anal. calcd for $C_{19}H_{28}O_5$: C 67.83, H 8.39, found: C 67.46, H 8.48.

Ethyl 2-adamantyl-3-(2,3-dimethoxyphenyl)-3-hydroxypropanoate, 25c. In a procedure analogous to the synthesis of **25b** above, **24c**[54] (12.0 g, 0.0540 mol) was converted into the title compound. Column chromatography (1:2 EtOAc/hexanes) produced the title compound as an off-white inseparable mixture of solid diastereomers (19.5 g, 92.9%). An analytical sample was crystallized from EtOH; mp = 90–91 °C. Diastereomers: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.03$–6.74 (m, 3H), 5.39 (d, 0.4H, $J=9.6$ Hz), 5.09 (t, 0.4H, $J=9.6$ Hz), 4.55 (d, 0.6H, $J=10.2$ Hz), 4.00 (s, 1.2H), 3.99–3.71 (m, 2H), 3.84 (bs, 4.8H), 2.98 (d, 0.4H, $J=9.6$ Hz), 2.69–2.65 (d, 0.6H, $J=10.2$ Hz), 2.47 (bs, 0.6H), 2.12–1.61 (m, 15H), 1.05 (t, 1.8H, $J=7.2$ Hz), 0.94 ppm (t, 1.2H, $J=7.2$ Hz); MS (ESI): $[M+Na]^+=411$; Anal. calcd (%) for $C_{23}H_{32}O_5$: C 71.11, H 8.30, found: C 70.82, H 8.34.

Ethyl 2-((2,3-dimethoxyphenyl)(hydroxy)methyl)pentanoate, 25e. In a procedure analogous to the synthesis of **25b** above, ethyl valerate (Aldrich, 4.48 mL, 0.0301 mol) was converted into the title compound. Although the resolution is unnecessary, column chromatography (1:1 EtOAc/hexanes), could resolve the title compound into its two diastereomers. Both diastereomers were recovered as amber oils (5.5 g, 62.0%). Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.02$ (t, 1H, $J=7.8$ Hz), 6.92 (dd, 1H, $J=1.8$, 7.8 Hz), 6.85 (dd, 1H, $J=1.8$, 7.8 Hz), 4.99 (t, 1H, $J=5.7$ Hz), 4.04 (q, 2H, $J=7.2$ Hz), 3.92 (s, 3H), 3.86 (s, 3H), 3.35 (d, 1H, $J=5.7$ Hz), 2.85–2.78 (m, 1H), 1.75–1.62 (m, 2H), 1.40–1.19 (m, 2H), 1.13 (t, 3H, $J=7.2$ Hz), 0.86 ppm (t, 3H, $J=7.0$ Hz); MS (EI): $[M]^+=296$; Anal. calcd (%) for $C_{16}H_{24}O_5$: C 64.84, H 8.16, found: C 65.03, H 8.04.

2-Cyclohexyl-3-(2,3-dimethoxyphenyl)propan-1-ol, 26b. Thionyl chloride (10.6 mL) was added to a solution of **25b** (16.2 g, 0.048 mol) in 100 mL benzene. The reaction was stirred at room temperature for 2 h, followed by the removal of solvents by rotary evaporation. Toluene (15 mL) was added to the flask, followed by

rotary evaporation to ensure that all of the thionyl chloride was removed. The resulting brown oil was dissolved in dry Et_2O (75 mL) and slowly added dropwise to a suspension of 5.4 g $LiAlH_4$ and 50 mL Et_2O in a flame-dried, three-neck flask, with magnetic stirring, The reaction flask was transferred to a 45 °C oil bath and the reaction was allowed to stir at reflux overnight. The reaction was cooled to room temperature and quenched by the slow, careful, dropwise addition of 5.4 mL of H_2O, followed by the dropwise addition of 5.4 mL 15% aqueous NaOH, followed by the addition of 16.2 mL more H_2O. This suspension was stirred at room temperature until solid granules formed that were removed by filtration. The filter cake was triturated with hot Et_2O and filtered again. The filtrates were combined, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Column chromatography (1:2 EtOAc/hexanes) was needed to purify the major product, which was isolated as a dark-yellow oil (10.4 g, 79.1%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.99 (t, 1H, J = 7.8 Hz), 6.79–6.73 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.53 (dd, 1H, J = 3.9, 11.7 Hz), 3.35 (dd, 1H, J = 3.9, 11.7 Hz), 2.69–2.66 (m, 2H), 1.89–1.05 ppm (m, 11H); MS (ESI): $[M+Na]^+$ = 301; Anal. calcd (%) for $C_{17}H_{26}O_3$: C 73.34, H 9.41, found: C 73.11, H 9.69.

2-Adamantyl-3-(2,3-dimethoxyphenyl)propan-1-ol, 26c. In a procedure analogous to the synthesis of **26b** above, **25c** (20.4 g, 0.0502 mol) was converted into the title compound. Column chromatography (1:2 EtOAc/hexanes) was again required to purify the product, which was isolated as a yellow oil (11.8 g, 71.5%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.00 (t, 1H, J = 7.8 Hz), 6.77 (d, 2H, J = 7.8 Hz), 3.86 (s, 3H), 3.85 (s, 3H), 3.72 (dd, 1H, J = 2.7, 12.0 Hz), 3.33 (dd, 1H, J = 3.3, 12.0 Hz), 2.73 (d, 2H, J = 7.8 Hz), 2.01 (bs, 3H), 1.81–1.62 (m, 12H), 1.15–1.10 ppm (m, 1H); MS (EI): $[M]^+$ = 330; Anal. calcd (%) for $C_{21}H_{30}O_3$: C 76.33, H 9.15, found: C 76.40, H 8.99.

2-(2,3-Dimethoxybenzyl)pentan-1-ol, 26e. In a procedure analogous to the synthesis of **26b** above, **25e** (12.1 g, 0.0384 mol) was converted into the title compound. Column chromatography (1:2 EtOAc/hexanes) was required to purify the title compound, which was isolated as a yellow oil (6.5 g, 70.9%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.00 (t, 1H, J = 8.1 Hz), 6.80–6.74 (m, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.36 (d, 2H, J = 4.2 Hz), 2.67–2.64 (m, 2H), 1.73–1.68 (m, 1H), 1.45–1.36 (m, 4H), 0.93 (t, 3H, J = 7.4 Hz); MS (EI): $[M]^+$ = 238; Anal. calcd (%) for $C_{14}H_{22}O_3$: C 70.56, H 9.30, found: C 70.29, H 8.95.

2-Cyclohexyl-3-(2,3-dimethoxyphenyl)propyl methanesulfonate, 27b. A solution of **26b** (10.0 g, 0.0360 mol) in freshly distilled dry THF (200 mL) was stirred in a flame-dried flask on an ice bath. To this solution, 10.0 mL (0.072 mol) of triethylamine were added through a syringe. Methanesulfonyl chloride (5.6 mL, 0.072 mol) was added dropwise through a flame-dried addition funnel, over 15 min. The reaction was stirred at 0 °C for 2 h. H_2O (100 mL) and Et_2O (100 mL) were added to the flask to quench the reaction, and the layers were separated. The aqueous layer was washed with Et_2O (2×50 mL) and the combined organic layers were washed with brine (2×75 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Column chromatography (1:2 EtOAc/hexanes) was used to purify the title compound, which was isolated as a brown oil (12.4 g, 96.7%) that slowly solidified upon standing and was recrystallized from EtOH; mp = 43–45 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.99 (t, 1H, J = 7.8 Hz), 6.80 (dd, 1H, J = 1.2, 8.1 Hz), 6.75 (dd, 1H, J = 1.2, 7.5 Hz), 4.16–4.08 (m, 2H), 3.86 (s, 3H), 3.81 (s, 3H), 2.91 (s, 3H), 2.83 (dd, 1H, J = 5.1, 13.5 Hz), 2.51 (dd, 1H, J = 9.6, 13.5 Hz), 1.96–1.89 (m, 1H), 1.80–1.08 ppm (m, 11H); MS (ESI): $[M+Na]^+$ = 379; Anal. calcd (%) for $C_{18}H_{28}O_5S$: C 60.65, H 7.92, found: C 60.56, H 8.14.

2-Adamantyl-3-(2,3-dimethoxyphenyl)propyl methanesulfonate, 27c. In a procedure analogous to the synthesis of **27b** above, **26c** (13.0 g, 0.0394 mol) was converted into the title compound. Column chromatography (1:2 EtOAc/hexanes) was required to purify the title compound, which was isolated as a pale-yellow powder (15.0 g, 93.3%) that could be crystallized from EtOH to yield colorless, cubic crystals; mp = 96–98 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.99 (t, 1H, J = 7.8 Hz), 6.78 (d, 2H, J = 7.8 Hz), 4.25 (dd, 1H, J = 3.0, 9.9 Hz), 4.05 (dd, 1H, J = 3.9, 9.9 Hz), 3.85 (s, 3H), 3.82 (s, 3H), 2.95 (dd, 1H, J = 2.7, 13.5 Hz), 2.82 (s, 3H), 2.47 (dd, 1H, J = 11.7, 13.5 Hz), 2.02 (bs, 3H), 1.77–1.55 ppm (m, 13H); MS (ESI): $[M+Na]^+$ = 431; Anal. calcd for $C_{22}H_{32}O_5S$: C 64.68, H 7.89, found: C 64.36, H 7.80.

2-(2,3-Dimethoxybenzyl)pentyl methanesulfonate, 27e. In a procedure analogous to the synthesis of **27b** above, **26e** (6.00 g, 0.0250 mol) was converted into the title compound. Column chromatography (1:2 EtOAc/hexanes) was used to purify the title compound, which was isolated as a pale-yellow oil (7.8 g, 97.5%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.98 (t, 1H, J = 8.1), 6.86 (dd, 1H, J = 1.5, 8.1), 6.75 (dd, 1H, J = 1.5, 8.1), 4.08 (ddd, 2H, J = 4.8, 7.2, 9.6 Hz), 3.86 (s, 3H), 3.81 (s, 3H), 2.95 (s, 3H), 2.71 (dd, 1H, J = 6.0, 13.5 Hz), 2.60 (dd, 1H, J = 8.4, 13.5 Hz), 2.11–2.06 (m, 1H), 1.48–1.35 (m, 4H), 0.91 ppm (t, 3H, J = 7.4 Hz); MS (ESI): $[M+Na]^+$ = 339; Anal. calcd (%) for $C_{15}H_{24}O_5S$: C 56.94, H 7.65, found: C 57.01, H 7.67.

3-Cyclohexyl-4-(2,3-dimethoxyphenyl)butanenitrile, 28b. NaCN (4.8 g, 0.0980 mol) was added all at once to a stirring solution of **27b** (11.0 g, 0.0327 mol) in 75 mL DMSO. The reaction was stirred at 80 °C overnight, until all starting material was consumed. EtOAc (100 mL) and H_2O (100 mL) were added to the reaction. The layers were separated, the aqueous phase was extracted with EtOAc (2× 75 mL), and the combined organic layers were washed with H_2O (2×100 mL) and brine (2×100 mL) to remove DMSO. The organic layer was concentrated to approximately 50 mL and the H_2O and brine washes were repeated. The organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness. Column chromatography (1:2 EtOAc/hexanes) was used to purify the title compound, which was isolated as a colorless oil that solidified into a colorless, amorphous material that was crystallized from EtOH (7.7 g, 86.7%); mp = 48–52 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.00 (t, 1H, J = 7.8 Hz), 6.81 (dd, 1H, J = 1.5, 7.8 Hz), 6.74 (dd, 1H, J = 1.5, 7.8 Hz) 3.86 (s, 3H), 3.82 (s, 3H), 2.92 (dd, 1H, J = 4.5, 13.5 Hz), 2.44 (dd, 1H, J = 10.2, 13.5 Hz), 2.29–2.17 (m, 2H), 1.91–1.84 (m, 1H), 1.81–1.09 ppm (m, 11H); MS (ESI): $[M+H]^+$ = 288; Anal. calcd (%) for $C_{18}H_{25}NO_2$: C 75.22, H 8.77, N 4.87, found: C 75.52, H 8.52, N 5.08.

3-Adamantyl-4-(2,3-dimethoxyphenyl)butanenitrile, 28c. Following the method for the synthesis of **29b** above, **27c** (5.88 g, 0.0144 mol) was converted into the nitrile. Column chromatography (1:2 EtOAc/hexanes) was used to purify the title compound, which was isolated as a colorless oil that crystallized as colorless radial crystals (3.47 g, 70.9%); mp = 68–69 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.99 (t, 1H, J = 7.8 Hz), 6.81 (d, 2H, J = 7.8 Hz), 3.86 (s, 3H), 3.83 (s, 3H), 3.04 (dd, 1H, J = 2.1, 13.5 Hz), 2.41 (dd, 1H, J = 11.4, 13.5 Hz), 2.31 (ddd, 1H, J = 1.2, 3.6, 17.6 Hz), 2.15 (dd, 1H, J = 6.0, 17.6 Hz), 2.04 (bs, 3H), 1.85–1.60 ppm (m, 13H); MS (ESI): $[M+H]^+$ = 340; Anal. calcd for $C_{22}H_{29}NO_2$: C 77.84, H 8.61, N 4.13, found: C 78.15, H 8.76, N 4.41.

3-(2,3-Dimethoxybenzyl)hexanenitrile, 28e. In a procedure analogous to the synthesis of **28b** above, **27e** (7.50 g, 0.0237 mol) was converted into the nitrile. Column chromatography (1:2 EtOAc/hexanes) was used to purify the title compound, which was isolated as

a slightly yellow oil (4.3 g, 73.9%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.00 (t, 1H, J = 8.1 Hz), 6.81 (dd, 1H, J = 1.5, 8.1 Hz), 6.75 (dd, 1H, J = 1.5, 8.1 Hz), 3.86 (s, 3H), 3.82 (s, 3H), 2.81 (dd, 1H, J = 5.1, 13.2 Hz), 2.53 (dd, 1H, J = 9.3, 13.2 Hz), 2.25 (AB spin system, 2H), 2.09–2.01 (m, 1H), 1.51–1.36 (m, 4H), 0.94 ppm (t, 3H, J = 7.4 Hz); MS (ESI): $[M+H]^+$ = 248; Anal. calcd for $C_{15}H_{21}NO_2$: C 72.84, H 8.56, N 5.66, found: C 72.60, H 8.31, N 5.70.

3-Cyclohexyl-4-(2,3-dimethoxyphenyl)butanoic acid, 29b. DIBAH (32.1 mL of a 1.0 M solution) was added through a syringe to a stirring solution of **28b** (5.0 g, 0.0178 mol) in 100 mL freshly distilled toluene cooled to −78 °C. The reaction was stirred on a dry ice/acetone bath for 2 h, and then on an ice bath for an additional 1 h. After the starting material was consumed, a 5% aqueous HCl solution (60 mL) was carefully added. The solution foamed and became cloudy, and was stirred at 0 °C for 30 min. The solution was extracted with Et_2O (3×50 mL), the organic extract was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to provide crude aldehyde as a brown oil. This oil was redissolved in acetone (100 mL) and Jones' reagent (25 g CrO_3, 25 mL H_2SO_4, and 75 mL H_2O, mixed at 0 °C) was slowly added with a pipette. As the reagent was added, the solution turned dark green, indicating the presence of aldehyde. Jones' reagent was added dropwise until the green color no longer appeared and the solution was a dark-orange color (~8 mL total were added). This orange solution was stirred at room temperature for 10 min, at which time a dark solid mass had formed in the bottom of the flask. H_2O (30 mL) was added to quench the reaction and dissolve the solid. The solution returned to a bright-green color and was extracted with Et_2O (3× 50 mL). The Et_2O layer was extracted with 1 N NaOH (3×50 mL) and the aqueous extracts were acidified with concentrated H_2SO_4. The acidic solution was extracted with Et_2O (3×50 mL), dried over Na_2SO_4, filtered, and evaporated to yield the carboxylic acid as a dark-amber oil (3.86 g, 60.2%) that could be used in the next step without purification. An analytical sample, purified by column chromatography (2:1 hexanes/EtOAc), crystallized as colorless needles; mp = 80–82 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.96 (t, 1H, J = 7.8 Hz), 6.77–6.74 (m, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 2.78 (dd, 1H, J = 5.7, 13.5 Hz), 2.45 (dd, 1H, J = 8.7, 13.5 Hz), 2.33 (dd, 1H, J = 7.2, 18.3 Hz), 2.25–2.13 (m, 2H), 1.76–1.06 ppm (m, 11H); MS (EI): $[M]^+$ = 306; Anal. calcd for $C_{18}H_{26}O_4$: C 70.56, H 8.55, found: C 70.74, H 8.61.

3-Adamantyl-4-(2,3-dimethoxyphenyl)butanoic acid, 29c. In a procedure analogous to the synthesis of **29b** above, **28c** (6.30 g, 0.0187 mol) was converted into the title compound. The desired carboxylic acid was recovered as a brown oil (1.72 g, 25.8%) that solidified upon standing. The solid was recrystallized from EtOAc/hexanes to afford a light-tan powder; mp = 113–115 °C. The neutral organic layer was evaporated to yield a crude, tan solid, from which tetralone **30c** could be crystallized from EtOAc as pale-tan plates (1.69 g, 26.6% from nitrile **28c**). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.92 (t, 1H, J = 7.8 Hz), 6.76 (dd, 1H, J = 1.2, 7.8 Hz), 6.71 (dd, 1H, J = 1.2, 7.8 Hz), 3.82 (s, 6H), 2.91 (dd, 1H, J = 3.0, 13.2 Hz), 2.37 (dd, 1H, J = 6.9, 16.5 Hz), 2.26 (dd, 1H, J = 11.1, 13.2 Hz), 2.10 (dd, 1H, J = 4.2, 16.5 Hz), 1.99 (bs, 3H), 1.77–1.53 ppm (m, 13H); MS (ESI): $[M+Na]^+$ = 381; Anal. calcd (%) for $C_{22}H_{30}O_4$: (0.5 equiv H_2O) C 71.90, H 8.50, found: C 72.06, H 8.42.

3-(2,3-Dimethoxybenzyl)hexanoic acid, 29e. In a procedure analogous to the synthesis of **29b** above, **28e** (2.20 g, 8.9 mmol) was converted into the carboxylic acid. The title compound was isolated as a pale-yellow oil (1.85 g, 78.4%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.97 (t, 1H, J = 8.1 Hz), 6.78–6.74 (m, 2H), 3.85 (s, 3H), 3.78 (s, 3H), 2.75 (dd, 1H, J = 5.7, 13.5 Hz), 2.51 (dd, 1H, J = 7.5, 13.5 Hz), 2.30–2.18 (m, 3H), 1.46–1.31 (m, 4H), 0.90 ppm (t, 3H, J = 7.4 Hz); MS (EI): $[M]^+$ = 266; Anal. calcd for $C_{15}H_{22}O_4$: C 67.64, H 8.33, found: C 67.71, H 7.96.

3-Cyclohexyl-5,6-dimethoxy-3,4-dihydronaphthalen-1(2*H*)-one, 30b. To a mechanically stirring flask of polyphosphoric acid (50 g) heated at 85 °C, carboxylic acid **29b** (8.1 g, 0.026 mol) dissolved in minimal benzene (5 mL) was added. The resulting mixture was stirred and heated for 1 h during which time it turned from tan to dark red. With vigorous manual stirring, the dark-red reaction mixture was poured over a mixture of 400 g of ice and 200 mL of H_2O. The precipitate that formed was filtered, washed with H_2O (3× 75 mL), air dried, and then dissolved in EtOAc (200 mL). The organic solution was washed with H_2O (50 mL), 0.5 N NaOH (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to provide the title compound (6.1 g, 80.3%) as a fluffy solid that was recrystallized from EtOH to yield pale-tan needles (4.1 g, 53.9%); mp = 109–111 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, 1H, J = 9.0 Hz), 6.87 (d, 1H, J = 9.0 Hz), 3.93 (s, 3H), 3.82 (s, 3H), 3.20 (dq, 1H, J = 1.9, 16.8 Hz), 2.69 (dq, 1H, J = 1.9, 16.5 Hz), 2.53 (dd, 1H, J = 11.1, 16.8 Hz), 2.32 (dd, 1H, J = 12.9, 16.5 Hz), 1.98–1.85 (m, 1H), 1.84–1.06 ppm (m, 11H); MS (ESI): $[M+H]^+$ = 289; Anal. calcd (%) for $C_{18}H_{24}O_3$ (0.5 equiv EtOH): C 73.28, H 8.74, found: C 73.36, H 8.36.

3-Adamantyl-5,6-dimethoxy-3,4-dihydronaphthalen-1(2*H*)-one, 30c. Following a procedure similar to that for **30b**, **29c** (1.5 g, 4.2 mmol) was converted into the title product as a crude solid (1.4 g, 95.8%) that was difficult to crystallize. Column chromatography (1:2 EtOAc/hexanes) afforded **30c** as a white powdery solid (0.98 g, 67.8%); mp = 189–190 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (d, 1H, J = 8.7 Hz), 6.87 (d, 1H, J = 8.7 Hz), 3.92 (s, 3H), 3.83 (s, 3H), 3.27 (dt, 1H, J = 3.0, 16.8 Hz), 2.74 (dt, 1H, J = 2.7, 16.2 Hz), 2.42 (dd, 1H, J = 12.0, 16.8 Hz), 2.26 (dd, 1H, J = 13.8, 16.2 Hz), 2.03 (bs, 3H), 1.78–1.58 ppm (m, 13H); MS (ESI): $[M+H]^+$ = 341; Anal. calcd for $C_{22}H_{28}O_3$: C 77.71, H 8.29, found: C 77.28, H 8.44.

5,6-Dimethoxy-3-propyl-3,4-dihydronaphthalen-1(2*H*)-one, 30e. Following a procedure similar to that for the synthesis of **30b**, 29e (2.8 g, 0.011 mol) provided the title compound (2.6 g, 99.9%) as a fluffy solid that was recrystallized from EtOH to yield fine, tan needles (1.5 g, 57.5%); mp = 88–91 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, 1H, J = 8.7 Hz), 6.87 (d, 1H, J = 8.7 Hz), 3.93 (s, 3H), 3.82 (s, 3H), 3.22 (ddd, 1H, J = 2.1, 3.9, 16.8 Hz), 2.70 (ddd, 1H, J = 1.8, 3.3, 16.2 Hz), 2.45 (dd, 1H, J = 10.2, 16.8 Hz), 2.25 (dd, 1H, J = 11.7, 16.2 Hz), 2.17–2.10 (m, 1H), 1.46–1.38 (m, 4H), 0.94–0.87 (m, 3H); MS (EI): $[M]^+$ = 248; Anal. calcd (%) for $C_{15}H_{20}O_3$: C 72.55, H 8.12, found: C 72.15, H 8.50.

1-(Aminomethyl)-3-cyclohexyl-5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-ol hydrochloride, 31b. Tetralone **30b** (4.1 g, 0.0142 mol) and 231 mg (0.725 mmol) of anhydrous ZnI_2 were dissolved in 75 mL of CH_2Cl_2. TMSCN (2.9 mL, 0.022 mol) was added dropwise and the solution was heated at reflux for 20 h and monitored by IR for the loss of the C=O stretch. Additional ZnI_2 could be added to speed the reaction. The mixture was cooled and concentrated, then dissolved in dry Et_2O (10 mL) and added dropwise to a slurry of 1.9 g (0.051 mol) of $LiAlH_4$ in anhydrous Et_2O (60 mL). The reaction mixture was heated at reflux for 18 h, and then cooled to room temperature. To quench the reaction, 1.9 mL of H_2O in 5 mL of THF was carefully added dropwise, followed by 1.9 mL of 15% aqueous NaOH, followed by an additional 5.7 mL of H_2O. The reaction mixture was stirred for 30 min until a granular precipitate formed. The solid was filtered, the filter cake was triturated with hot ether, and filtered again. The filtrates were combined and acidified with concentrated HCl (5 mL). A white precipi-

tate formed that was collected by filtration to afford 2.93 g (64.6%) of off-white solid that was a mixture of diastereomers; mp = 161–163 °C (dec.). Diastereomers: ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.02 (bs, 1.5H), 7.94 (bs, 1.5H), 7.26–7.20 (m, 1H), 6.98–6.90 (m, 1H), 4.01 (bs, 1H), 3.77 (s, 1.5H), 3.76 (s, 1.5H), 3.66 (s, 3H), 3.34–3.27 (m, 0.5H), 2.98–2.92 (m, 0.5H), 2.92–2.86 (m, 0.5H), 2.85–2.72 (m, 1.5H), 2.21 (dd, 0.5H, J = 11.6, 17.6 Hz), 2.09 (dd, 0.5H, J = 11.6, 16.9 Hz), 2.01 (bd, 0.5H, J = 12.9 Hz), 1.96 (bd, 0.5H, J = 12.9 Hz), 1.80–1.55 (m, 6H), 1.45–1.33 (m, 1H), 1.35–0.98 ppm (m, 6H); MS (ESI): $[M+Na]^+$ = 342; Anal. calcd (%) for $C_{19}H_{30}ClNO_3$: C 64.12, H 8.50, N 3.93, found: C 64.38, H 8.35, N 4.08.

1-(Aminomethyl)-3-adamantyl-5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-ol hydrochloride, 31c. Following the method used for synthesizing **31b**, **30c** (0.75 g, 2.2 mmol) was converted into the title compound (0.47 g, 52.6%) as a tan powder that was a mixture of diastereomers; mp = 128–130 °C (dec.). Diastereomers: ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.83 (bs, 3H), 7.24 (bd, 1H, J = 8.7 Hz), 6.95 (bd, 1H, J = 8.7 Hz), 5.65–5.56 (2 bs, 1H), 3.77–3.76 (2 s, 3H), 3.67–3.66 (2 s, 3H), 2.96–2.92 (m, 1H), 2.84–2.77 (m, 2H), 2.31–2.22 (m, 1H), 2.12–1.96 (m, 4H), 1.79–1.30 ppm (m, 13H); MS (ESI): $[M+H\text{-}H_2O]^+$ = 354; Anal. calcd (%) for $C_{23}H_{34}ClNO_3$: C 67.71, H 8.40, N 3.43, found: C 67.77, H 8.60, N 3.52.

1-(Aminomethyl)-5,6-dimethoxy-3-propyl-1,2,3,4-tetrahydronaphthalen-1-ol hydrochloride, 31e. In a fashion analogous to the synthesis of **31b**, 30e (1.5 g, 6.1 mmol) was converted into a diastereomeric mixture of the title compound (1.13 g, 59.2%) as a white powdery solid; mp = 150–152 °C (dec.). Diastereomers: ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.90 (bs, 3H), 7.27–7.21 (m, 1H), 6.97–6.93 (m, 1H), 5.65–5.56 (2 bs, 1H), 3.78–3.77 (2 s, 3H), 3.66 (2 s, 3H), 3.25 (d, 1H, J = 12.9 Hz), 2.98–2.91 (m, 2H), 2.80 (dd, 1H, J = 12.6, 19.5 Hz), 2.11–1.91 (m, 2H), 1.75–1.66 (m, 1H), 1.48–1.29 (m, 4H), 0.91 ppm (t, 3H, J = 7.4 Hz); MS (ESI): $[M+Na]^+$ = 302; Anal. calcd (%) for $C_{16}H_{26}ClNO_3$: C 60.85, H 8.30, N 4.43, found: C 60.72, H 8.32, N 4.52.

(3-Cyclohexyl-5,6-dimethoxy-3,4-dihydronaphthalen-1-yl)methanamine hydrochloride, 32b. EtOH (25 mL), **31b** (2.37 g, 6.67 mmol), and two drops of 2 N ethanolic HCl were placed into a single-neck round-bottom flask. The flask was fitted with a reflux condenser and the solution was heated at 80 °C and magnetically stirred for 14 h. The solvent was removed by rotary evaporation and the colorless oily residue dissolved in Et$_2$O (30 mL) and allowed to stand at room temperature, during which time the product crystallized as a pale-tan solid (1.64 g, 72.9%). The solid could be recrystallized from EtOH as tan needles; mp = 148–152 °C (dec.); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.57 (bs, 3H), 6.90 (d, 1H, J = 8.7 Hz), 6.73 (d, 1H, J = 8.7 Hz), 6.14 (d, 1H, J = 3.9 Hz), 3.94 (bd, 1H, J = 4.8 Hz), 3.84 (s, 3H), 3.77 (s, 3H) 2.85 (dd, 1H, J = 6.9, 16.0 Hz), 2.72 (dd, 1H, J = 9.3, 16.0 Hz), 2.20 (bs, 1H), 1.80–1.05 ppm (m, 11H); MS (ESI): $[M+H]^+$ = 302; Anal. calcd for $C_{19}H_{28}ClNO_2$: C 67.54, H 8.35, N 4.15, found: C 67.19, H 8.31, N 4.14.

(3-Adamantyl-5,6-dimethoxy-3,4-dihydronaphthalen-1-yl)methanamine hydrochloride, 32c. EtOH (25 mL), **31c** (300 mg, 0.74 mmol), and two drops of 2 N ethanolic HCl were placed into a single-neck round-bottom flask. The flask was fitted with a reflux condenser and the solution was heated at 80 °C and magnetically stirred overnight. The solvent was removed by rotary evaporation and the colorless oily residue was dissolved in Et$_2$O (10 mL) and extracted with 2 N HCl (3×10 mL). An insoluble oil formed at the interface of the two layers each time, and was recovered separately. The acidic aqueous layers were combined, washed with Et$_2$O, and basified with concentrated aqueous NaOH. The basified solution was extracted with Et$_2$O (3×15 mL), dried over Na$_2$SO$_4$, filtered, and evaporated to yield a colorless residue from which the title compound crystallized after the addition of minimal Et$_2$O (69 mg, 24.0%). The recovered oil layer was dissolved in EtOH and evaporated under reduced pressure to dryness. The residue could be crystallized from Et$_2$O to yield the desired product as an off-white powder (164 mg, 57.1%); mp = 174–177 °C (dec.); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.14 (bs, 3H), 6.99 (d, 1H, J = 8.1 Hz), 6.85 (d, 1H, J = 8.1 Hz), 6.05 (bs, 1H), 3.84 (s, 2H), 3.79 (s, 3H), 3.68 (s, 3H), 2.80 (dd, 1H, J = 6.9, 15.9 Hz), 2.61–2.52 (m, 1H), 1.93 (bs, 3H), 1.70–1.48 (m, 13H); MS (ESI): $[M+H]^+$ = 354; Anal. calcd (%) for $C_{23}H_{32}ClNO_2$: C 70.84, H 8.27, N 3.59, found: C 70.48, H 8.46, N 3.66.

(5,6-Dimethoxy-3-propyl-3,4-dihydronaphthalen-1-yl)methanamine hydrochloride, 32e. EtOH (25 mL), **31e** (150 mg, 0.48 mmol), and one drop of 2 N ethanolic HCl were placed into a single-neck round-bottom flask. The flask was fitted with a reflux condenser and the solution was heated at 80 °C and magnetically stirred overnight. The solvent was removed by rotary evaporation and the white solid residue was dissolved in minimal EtOH and Et$_2$O was added dropwise. A small amount of a granular white solid precipitated immediately and was removed by filtration. Additional Et$_2$O was added to the filtrate and large white crystals slowly formed and were collected by filtration to give the title compound (82 mg, 58.2%); mp = 126–128 °C (dec.); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.18 (bs, 3H), 7.02 (d, 1H, J = 8.4 Hz), 6.87 (d, 1H, J = 8.4 Hz), 5.97 (d, 1H, J = 3.6 Hz), 3.81 (bs, 2H), 3.80 (s, 3H), 3.66 (s, 3H), 2.85 (dd, 1H, J = 6.0, 15.3 Hz), 2.49–2.28 (m, 2H), 1.48–1.29 (m, 4H), 0.90 (t, 3H, J = 6.9 Hz); MS (ESI): $[M+H]^+$ = 262; Anal. calcd (%) for $C_{16}H_{24}ClNO_2$: C 64.53, H 8.12, N 4.70, found: C 64.14, H 8.14, N 4.80.

***Cis*-(3-cyclohexyl-5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methanamine hydrochloride, 33b**. The alkene hydrochloride **32b** (0.10 g, 0.30 mmol) was dissolved in EtOH (5 mL) and placed in an Ace hydrogenation bomb along with platinum(IV) oxide catalyst (0.15 g). The vessel was pressurized to 4 atm H_2 and shaken for 16 h. The solution was filtered through a pad of Celite to remove the catalyst, and evaporated under reduced pressure to produce the HCl salt of the desired *cis* saturated amine as a white solid. This solid was crystallized from EtOH/Et$_2$O to yield **33b** (0.097 g, 97.0%) as a white crystalline powder; mp = 242–244 °C (dec.); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.87 (bs, 3H), 7.02 (d, 1H, J = 9.0 Hz), 6.87 (d, 1H, J = 9.0 Hz), 3.75 (s, 3H), 3.56 (s, 3H), 3.41 (bd, 1H, J = 10.0 Hz), 3.02 (bs, 1H), 2.91–2.75 (m, 2H), 2.21–2.14 (m, 1H), 2.11–2.04 (m, 1H), 1.88–0.98 ppm (m, 13H); MS (ESI): $[M+H]^+$ = 304; Anal. calcd (%) for $C_{19}H_{30}ClNO_2$: C 67.54, H 8.35, N 4.15, found: C 67.19, H 8.31, N 4.14.

***Cis*-(3-adamantyl-5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methanamine hydrochloride, 33c**. Following the prior method for the synthesis of **33b**, **32c** (120 mg, 0.308 mmol) was converted exclusively to the *cis* reduced product as pale-tan crystals (118 mg, 97.5%); mp = 184–186 °C (dec.); ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.98 (bs, 3H), 7.02 (d, 1H, J = 8.6 Hz), 6.86 (d, 1H, J = 8.6 Hz), 3.75 (s, 3H), 3.65 (s, 3H), 3.42 (bd, 1H, J = 9.4 Hz), 3.01–2.94 (m, 1H), 2.85 (bd, 1H, J = 15.9 Hz), 2.79 (dd, 1H, J = 9.4, 12.0 Hz), 2.23–2.15 (m, 2H), 1.98 (bs, 3H), 1.71–1.50 (m, 12H), 1.14–1.06 (m, 1H), 0.96 (q, 1H, J = 12.1 Hz); MS (ESI): $[M+H]^+$ = 356; Anal. calcd for $C_{23}H_{34}ClNO_2$: C 70.48, H 8.74, N 3.57, found: C 70.13, H 8.81, N 3.57.

***Cis*-(5,6-dimethoxy-3-propyl-1,2,3,4-tetrahydronaphthalen-1-yl)-methanamine hydrochloride, 33e**. Following the prior method for the synthesis of **33b**, **32e** (205 mg, 0.688 mmol) was converted exclusively to the *cis* isomer of the title compound as a white crystal-

line powder (108 mg, 52.4%); mp = 236–237 °C (dec.); ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.04 (bs, 3H), 7.03 (d, 1H, J = 8.6 Hz), 6.87 (d, 1H, J = 8.6 Hz), 3.75 (s, 3H), 3.65 (s, 3H), 3.40 (dd, 1H, J = 4.5, 14.5 Hz), 3.10–3.02 (m, 1H), 2.87 (dd, 1H, J = 4.0, 18.0 Hz), 2.77 (dd, 1H, J = 9.5, 14.0 Hz), 2.13–2.01 (m, 2H), 1.55–1.49 (m, 1H), 1.49–1.26 (m, 4H), 1.01 (q, 1H, J = 12.0 Hz), 0.94 (t, 3H, J = 7.0 Hz); MS (ESI): $[M+H]^+$ = 264; Anal. calcd (%) for $C_{16}H_{26}ClNO_2$ (1.0 equiv H_2O): C 60.46, H 8.88, N 4.41, found: C 60.66, H 8.63, N 4.29.

***Cis*-5-(aminomethyl)-7-cyclohexyl-5,6,7,8-tetrahydronaphthalene-1,2-diol hydrobromide, 3b**. A magnetically stirring solution of **33b** (50 mg, 0.147 mmol) in CH_2Cl_2 (15 mL) in a flame-dried flask, was cooled to −78 °C. A 1.0 M solution of BBr_3 in CH_2Cl_2 (0.45 mL) was then slowly added dropwise to the flask as the solution gradually became cloudy. The reaction was stirred at −78 °C for 1 h and then at room temperature for an additional 90 min. The flask was cooled back to −78 °C and MeOH (2 mL) was added to quench the reaction, followed by evaporation under reduced pressure, keeping the H_2O bath temperature below 40 °C. The brown solid residue was washed with MeOH and evaporated three additional times to remove any residual boronate esters. The residue was dried under high vacuum to yield a tan foam solid that was easily powdered to afford the hydrobromide salt (49 mg, 94.2%); mp = 126–127 °C (dec.); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 9.05 (s, 1H), 8.16 (s, 1H), 7.69 (bs, 3H), 6.58 (AB spin system, 2H), 3.46–3.30 (m, 1H), 3.00–2.87 (m, 1H), 2.86–2.75 (m, 2H), 2.11–1.98 (m, 2H), 1.84–1.62 (m, 5H), 1.40–0.98 ppm (m, 8H); MS (ESI): $[M+H]^+$ = 276; HRMS (ESI): $[M+H]^+$ calcd for $C_{17}H_{26}NO_2$: 276.1964, found: 276.1966.

***Cis*-5-(aminomethyl)-7-adamantyl-5,6,7,8-tetrahydronaphthalene-1,2-diol hydrobromide, 3c**. In the same manner as **3b** above, **33c** (56 mg, 0.143 mmol) was transformed into **3c** (53 mg, 92.0%) as a light-brown powder; mp = 188 °C (dec.); ^{1}H NMR (300 MHz, CD_3OD): δ = 6.62 (AB spin system, 2H), 3.47–3.39 (m, 1H), 3.09–3.00 (m, 2H), 2.98–2.88 (m, 1H), 2.29–2.11 (m, 2H), 2.00 (bs, 3H), 1.81–1.59 (m, 12H), 1.28–1.16 (m, 1H), 1.09 ppm (q, 1H, J = 12.1 Hz); MS (ESI): $[M+H]^+$ = 328; HRMS (ESI): $[M+H]^+$ calcd for $C_{21}H_{30}NO_2$: 328.2277, found: 328.2275.

***Cis*-5-(aminomethyl)-7-propyl-5,6,7,8-tetrahydronaphthalene-1,2-diol hydrobromide, 3e**. In the same manner as **3b** above, **33e** (70 mg, 0.234 mmol) was deprotected to yield the title compound (71 mg, 95.3%); mp = 175 °C (dec.); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 9.06 (bs, 1H), 8.16 (bs, 1H), 7.71 (bs, 3H), 6.58 (AB spin system, 2H), 3.48–3.35 (m, 1H), 3.04–2.71 (m, 3H), 2.09–1.85 (m, 2H), 1.59–1.30 (m, 5H), 1.05–0.87 (m, 4H); MS (ESI): $[M+H]^+$ = 236; HRMS (ESI): $[M+H]^+$ calcd for $C_{14}H_{22}NO_2$: 236.1651, found: 236.1650.

Pharmacology

Materials. [^{3}H]Spiperone (95 Ci mmol^{-1}) and [^{3}H]SCH-23390 (81 Ci mmol^{-1}) were purchased from Amersham Biosciences (Piscataway, NJ, USA). Butaclamol, SCH-23390, ketanserin, and most other reagents were purchased from Sigma–Aldrich Chemical Co. (St. Louis, MO, USA).

Competition binding experiments. Fresh porcine striatal tissue was obtained from the Purdue Butcher Block and prepared as previously described.[55] In brief, the striatal tissue was homogenized using a potter-type homogenizer, suspended in homogenization buffer (20 mM HEPES, 0.32 M sucrose, pH 7.4), and centrifuged at 1000 *g* for 10 min at 4 °C. The pellet (P1) was discarded, and the supernatant was centrifuged at 30000 *g* for 10 min at 4 °C. The resulting pellet (P2) was resuspended in 50 mM Tris buffer (pH 7.4) by briefly using a Kinematica homogenizer, followed by centrifuging at 30000 *g* for 30 min at 4 °C. This pellet was resuspended again in 50 mM Tris buffer, dispensed into 1.0 mL aliquots, and centrifuged again at 13000 *g* for 10 min at 4 °C. A BCA protein assay was used to quantify the final protein concentration in each pellet. The supernatant was removed, and the pellets were frozen at −80 °C until use.

The radioligand binding assays were performed as previously described,[56] with minor modifications. The pellets were resuspended (1 mg mL^{-1}) in receptor binding buffer (50 mM HEPES, 4 mM $MgCl_2$, pH 7.4), and 75 μg of protein was used per assay tube. Receptor isotherms were performed with [^{3}H]SCH-23390 and [^{3}H]spiperone to determine B_{max} and K_d values for D_1-like and D_2-like receptor sites, respectively (760 fmol mg^{-1} and 0.44 nM for [^{3}H]SCH-23390; 250 fmol mg^{-1} and 0.075 nM for [^{3}H]spiperone). All D_2-like binding assays were performed with 50 nM ketanserin to block 5-HT_{2A} binding sites. Nonspecific binding was defined with 5 μM butaclamol. Drug dilutions for competition binding assays were made in receptor binding buffer and added to assay tubes containing 75 μg of protein and either 1 nM [^{3}H]SCH-23390 or 0.15 nM [^{3}H]spiperone. All binding experiments were incubated at 37 °C for 30 min and were terminated by harvesting with ice-cold wash buffer (10 mM Tris, 0.9% NaCl) using a 96-well Packard Filtermate cell harvester. After the samples were dried, 30 μL of Packard Microscint O was added to each well. Radioactivity was counted with a Packard Topcount scintillation counter.

Computational Chemistry

Methods. All renderings were performed in PyMOL.[57] Trajectories were viewed using VMD (Visual Molecular Dynamics).[58] The crystal structure of the β2 adrenergic receptor (AR) co-crystallized with the inverse agonist carazolol was downloaded from the RCSB Protein Data Bank (PDB code 2RH1).[59] The fused T4 lysozyme, acetamide group, 1,4-butanediol molecules, dodecaethylene glycol molecules, maltose molecules, and sulfate ions were removed, leaving only the palmitoyl group attached to C341 in the protein, cholesterol molecules, ligand (carazolol), and waters with two or more hydrogen bond contacts with the protein. The N187E mutation was reversed in silico using the mutation feature of PyMOL. Acetyl and *N*-methylamide caps, as well as non-standard residue hydrogen atoms were added in PyMOL; the rest were added using the pdb2gmx module of GROMACS (GROningen MAchine for Chemical Simulations).[60] The orientation of Asn, Gln, and His residues, as well as the protonation state of acidic and basic residues, was visually inspected and no modifications were deemed necessary. Ligand, cholesterol, and palmitoyl cysteine parameters were generated using the antechamber program, part of the AmberTools 1.4 package,[61,62] based on an ab initio HF/6-31G* optimization[63] performed on Gaussian03[64] and subsequent resp (restrained electrostatic potential) fitting.[65,66]

Membrane simulations. The prepared receptor system was merged into a pre-equilibrated 85×80 Å united-atom palmitoyl oleoyl phosphatidylcholine (POPC) bilayer system, solvated with 12 Å of SPC waters on either side and ionized with 0.5 M NaCl. All subsequent calculations were performed with GROMACS 4.0,[60] using the AMBER03 force field port[67] (from http://ffamber.cnsm.csulb.edu/) with optimized parameters for united-atom lipids (from http://www.bioinf.uni-sb.de/RB/).[68] The system was energy minimized (steepest descent algorithm), and MD simulations were performed for 10 ns (2 fs per step) at 300 K using the NPT ensemble (V-rescale thermostat;[69] Parrinello–Rahman barostat)[70] with posi-

tion restraints on the protein and ligand heavy atoms, followed by unrestrained simulations for 30 ns.[71] No major changes in the protein–ligand interaction profile or overall tertiary structure of the protein were observed during the simulation.

Receptor activation. The agonist isoproterenol was built in place from the structure of the antagonist carazolol inside the binding pocket, due to their topological similarity. The new protein–agonist system was energy minimized and MD simulations were performed with soft protein–ligand distance restraints for 5 ns. At this point, the simulations were modified to reflect experimental observations from different sources (see Supporting Information 1), including a comparison between the 3D structures of bovine rhodopsin and opsin (RCSB PDB codes 1U19 and 3CAP, respectively)[72,73] and a computational study of the activation of the CB1 receptor;[74] 368 ns were logged under various conditions (see Supporting Information 1). Finally, the protein–ligand restraints were removed (protein–protein restraints were conserved, mainly to retain the helicity of TMs 5 and 6, compensating for the absence of IL3) and, after another 10 ns of simulation, the system was energy minimized. A detailed description of the activation process, as well as the structures of the ligands used, can be found in the Supporting Information.

Homology models. Homology models of the D_1 receptor based on the resulting agonist-bound structure of the β2AR were created with Modeller 9 version 2.[75,76] Alignments were made manually, using key conserved residues as references. Protein sequences were obtained from the Protein Information Resource[77,78] (see Supporting Information for alignment); 1000 models were generated (including disulfide bridges between C96-C186 and C298-C307), and the model with the lowest internal score was inspected for helix conservation, loop conformations, and key residue alignment. Extracellular loop 3 (EL3) was refined with Modeller, taking the best out of 1000 structures ranked by internal score. Any necessary torsional modifications were carried out in order to preserve relevant motifs (important hydrogen bond, aromatic, and salt bridge interactions). The molecule was prepared in a manner similar to the β2AR, and embedded in the same membrane system as the original template.

The dopamine D_1 receptor agonist doxanthrine (DOX) was manually docked into the receptor binding pocket by achieving the best possible overlap between the catechol and amine moieties. After inspecting the system for bad contacts from the insertion of the protein into the membrane, the system was energy minimized. MD simulations were performed using position restraints on the protein and ligand for the first 10 ns, and then distance restraints between the protein and the ligand (see Supporting Information), as well as within the protein (corresponding to those used in the β2AR), for the next 10 ns of simulation. The protein–ligand restraints were removed for the following 20 ns of simulation, during which, after some initial shifts, the protein–ligand interaction profile remained largely unchanged. Energy minimization provided a receptor structure that was used for docking studies.

Docking. Docking of compounds **1c**, **2c**, and **3c** (constructed and energy minimized in vacuum using SYBYL 8.1 with the MMFF94s force field)[79] in the receptor binding site was performed using the GOLD program (Genetic Optimization for Ligand Docking) version 3.2.[80,81] Ten residues in the binding cavity were allowed to rotate during the docking process (see Supporting Information for full conditions). A distance constraint was used to preserve the known salt bridge between D103 and the ligand ammonium moiety, and a water molecule present in the vicinity of S199 and N292 was included; 100 docking orientations were calculated and the best five were inspected. If these were in good agreement with each other the docking pose with the best GOLD score was taken as the result for the docking run. The protein side chain torsions were modified according to the GOLD output as appropriate using SYBYL, and then the previous ligand was replaced by the docked structure in the system coordinate file via the text editor. The system was then energy minimized and MD simulations were performed *without any protein–ligand restraints* until convergence was achieved, typically 16–22 ns. After deeming the system converged (see Supporting Information), energy minimization was performed again and the output structures were used for evaluation.

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