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Assessment of dopamine D_1 receptor affinity and efficacy of three tetracyclic conformationally-restricted analogs of SKF38393

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ABSTRACT

To assess the effect of conformational mobility on receptor activity, the β-phenyl substituent of dopamine D_1 agonist ligands of the phenylbenzazepine class, (±)-6,6a,7,8,9,13b-hexahydro-5*H*-benzo[*d*]naphtho[2,1-*b*]azepine-11,12-diol (**8**), and its oxygen and sulfur bioisosteres **9** and **10**, respectively, were synthesized as conformationally-restricted analogs of SKF38393, a dopamine D_1-selective partial agonist. Compounds *trans*-**8b**, **9**, and **10** showed binding affinity comparable to that of SKF38393, but functionally, they displayed only very weak agonist activity. These results suggest that the conformationally-restricted structure of the analogs cannot adopt a binding orientation that is necessary for agonist activity.

1. Introduction

Dopamine (DA, **1**) is a catecholamine neurotransmitter involved in the regulation of a range of physiological functions, including motor control, cognition, and the ability to experience pleasure.[1,2] Abnormalities in the dopaminergic system have been linked to disorders such as Parkinson's disease, schizophrenia, and addiction.[3–6] Dopamine exerts its actions primarily through DA receptors, which belong to the superfamily of class A (rhodopsin-like) G-protein coupled receptors (GPCR). The D_1-like receptors (D_1/D_5) activate Gs proteins and are linked to adenylate cyclase stimulation and cAMP synthesis, whereas the D_2-like receptors (D_2/D_3/D_4) are coupled to Gi/o proteins that inhibit adenylate cyclase activity, among other effects.[6,7] In a continuing effort to develop ligands selective for specific dopamine receptor-isoforms, we have focused our research on the design of D_1-like receptor agonists.

Studies of D_1-selective dopamine receptor full agonists have shown they can produce a dramatic reversal of motor deficits in MPTP-treated monkeys with Parkinson-like symptoms, validating this receptor as a potential target for treatment of Parkinson's disease.[8] The D_1 dopamine receptor also has been implicated in working memory processes, suggesting the potential use of D_1-selective agonists for the treatment of cognitive deficits in conditions such as schizophrenia and age-related cognitive decline.[9,10] Another area of great interest is the role of dopamine in reward phenomena. Studies of the effect of dopamine D_1 agonists in cocaine-seeking animal models have demonstrated the potential utility of D_1 agonists in the treatment of drug abuse, particularly of psychostimulants.[1,4]

The first pharmacological tool available to study D_1 receptor function was SKF38393 (**2**), which contains a benzazepine ring that constrains the ethylamine side chain in a *cis*-like conformation, and possesses a β-phenyl substituent (Fig. 1). Discovery of this prototypical D_1 receptor-selective partial agonist led to the development of a large number of related molecules, many of which demonstrated selectivity and agonist activity at the dopamine D_1 receptor subtype.[1,7] Structure–activity relationship (SAR) studies of these compounds indicated that a 'β-phenyldopamine' pharmacophore, in which an aryl group is attached to the position β to the amine moiety, may confer selective dopamine D_1-like agonist properties (e.g., **3** and **4**).[11,12] This β-phenyl moiety is thought to interact with an accessory binding region in the D_1 receptor orthosteric binding site, and its orientation within this region also may influence receptor activation.[11–13] Despite the cyclic nature of the benzazepines, they still possess a degree of conformational flexibility. In the case of

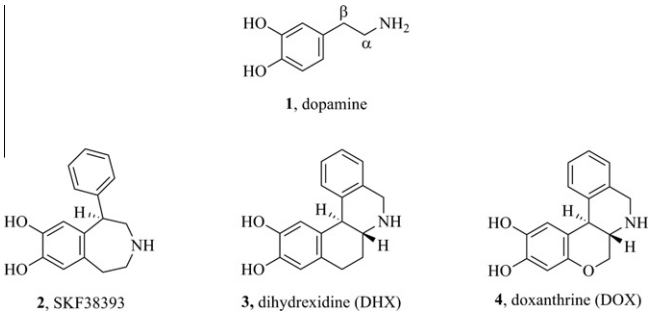

Figure 1. Structures of dopamine and D_1 selective agonists.

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SKF38393 (**2**), molecular modeling studies indicated that it possesses two minimum-energy conformations having only a slight energetic difference (<1 kcal/mol), in which the pendant phenyl ring is either pseudo-axial or pseudo-equatorial.[14] Although several energetically favorable conformations for the β-phenyl ring are available to the free ligand, when bound to the receptor, the phenyl ring is likely to adopt an orientation that optimizes ligand–receptor interaction. Thus, a number of researchers have put effort into elucidating the bioactive conformation of the β-phenyl substituent.

To study the effect of the orientation of the β-phenyl ring, Berger et al.[14] prepared conformationally-restricted analogs of SCH23390 (**5**), a D_1 dopamine receptor *antagonist* belonging to the phenylbenzazepine series, as a probe for the active conformation (Fig. 2). Pharmacological evaluation of these analogs indicated that highest receptor affinity was associated with the *trans* configuration. The 6a*S*,13b*R* isomer of **6b**, in particular, showed greatest D_1 affinity and receptor selectivity. The lack of activity for the *cis* isomer suggested that the axial orientation of the phenyl ring might be unfavorable for receptor binding. The authors reported that ring D is locked equatorially in the *trans* isomer (**6b**), which they reported as the preferred low-energy conformation.[14] In fact, however, like **2**, the azepine ring can exist in two distinct conformations, one of which places the phenyl into a pseudo-equatorial position, and the other in which it is in an axial orientation. These two conformations differ by only 1.7 kcal/mol (H-F, 6-31G*), and in either conformation, the amino group is about 2.5 Å out of the ring A plane.

The presence of the 7-halogen atom in benzazepine-like ligands confers antagonist properties, and it has been observed that, in general, alkylation of the amine nitrogen decreases D_1-like agonist activity.[7,15] What caught our attention was the finding that the dihydroxy analog **7** was reported to have high affinity at D_1 receptors, but D_1 agonist activity 'could not be demonstrated'.[14] We hypothesized that the presence of the *N*-methyl group on the basic nitrogen might be responsible for the lack of functional activity, and thus, we had interest in examining the properties of the secondary amine **8b** as a potential dopamine D_1 receptor agonist.

Although benzazepine type agonists demonstrate high affinity and selectivity at the dopamine D_1 receptor, they generally do not possess full intrinsic activity. In endeavors to develop novel dopamine D_1 selective agonists, dihydrexidine (DHX) **3** was synthesized by Nichols et al. as the first potent D_1-selective full agonist.[16] It is noteworthy that in **3**, the ethylamine fragment is in an extended *trans* conformation. Molecular modeling of SKF38393 (**2**) and DHX (**3**) also revealed that although they are both high affinity D_1-selective ligands, the positioning of the β-phenyl relative to the catechol ring is significantly different between the two molecules.[13] For DHX (**3**), the β-phenyl ring is nearly coplanar with the catechol ring, whereas the low energy conformation of SKF38393 (**2**) displays an orientation of the β-phenyl moiety that resides in a plane approximately perpendicular to the catechol ring plane. This observation led to the hypothesis that the conformation of the β-phenyl ring relative to the catechol plane is crucial for agonist activity.

In addition, previous work in our laboratory led to the synthesis of the oxygen and sulfur 'bioisosteres' of DHX (**3**), of which the oxygen analog (doxanthrine, DOX, **4**) showed high affinity, selectivity, and full intrinsic activity at D_1 dopamine receptors.[17] Encouraged by these results, and with the use of the facile conjugate chemistry developed for the synthesis of doxanthrine **4**, we have now prepared **8**, **9**, and **10** as structurally constrained analogs of SKF38393 (**2**) (Fig. 2).

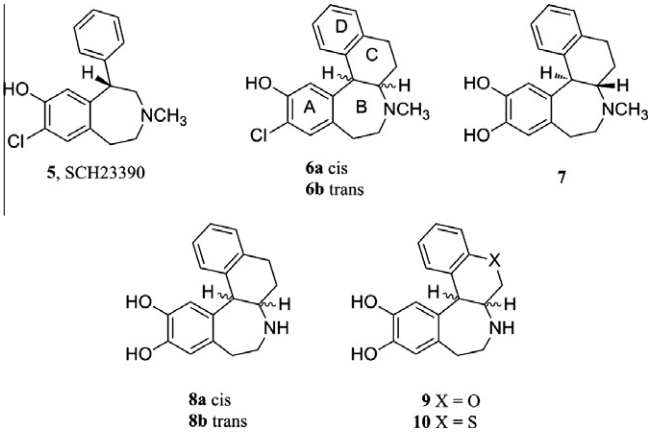


Figure 2. Structures of D_1 selective ligands.

2. Results and discussion

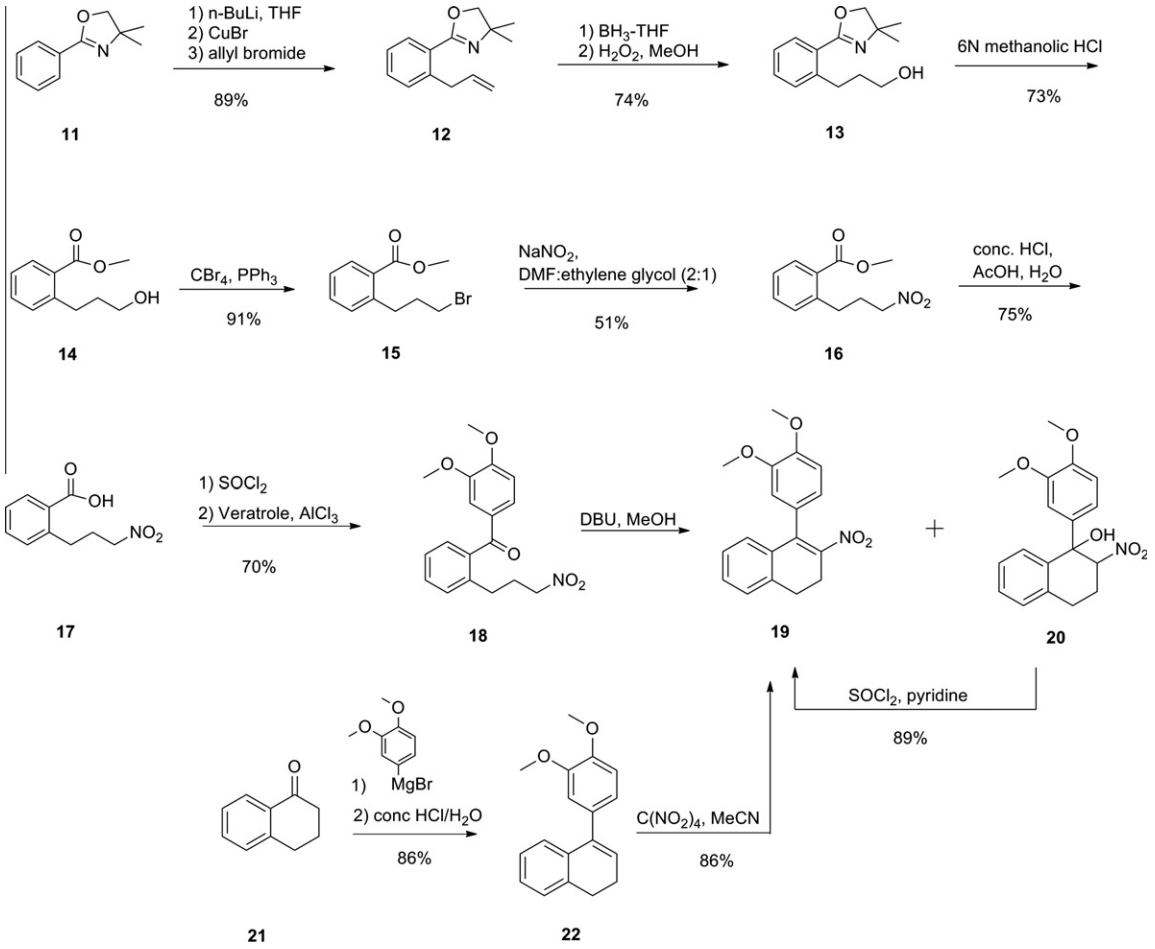
2.1. Chemistry

We first envisioned the construction of **8**, **9**, and **10** through a key diastereoselective conjugate addition of metallated 4-bromoveratrole to the corresponding nitroalkene. Although this method was efficient for the synthesis of the oxygen and sulfur analogs (**9** and **10**), it unfortunately failed for the synthesis of **8**, likely due to the acidity of the benzylic protons that were not present in the oxygen and sulfur analogs. Consequently, an alternative method was developed for the preparation of **19** as the key intermediate in the synthesis of **8** (Scheme 1).

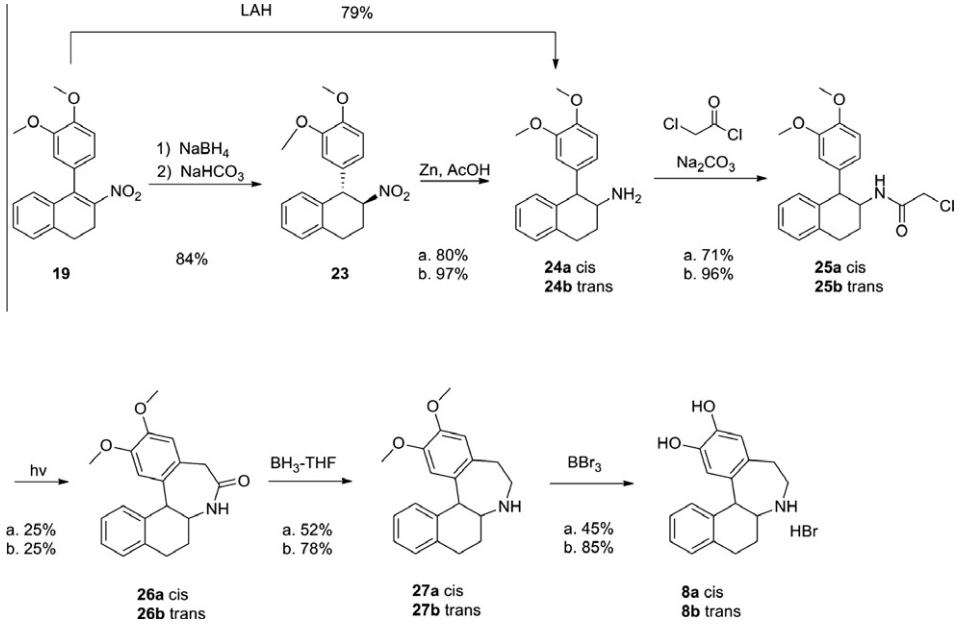
Allyl bromide was treated with the organocuprate derivative of phenyl oxazoline **11** to provide alkene **12**, which was easily purified by vacuum distillation.[18] Hydroboration–oxidation of **12**, followed by methanolysis of the oxazoline moiety afforded ester **14**, which was brominated to provide intermediate **15**. Conversion of bromide **15** to the corresponding nitro intermediate **16** with sodium nitrite was best carried out in a 2:1 mixture of DMF and ethylene glycol. Hydrolysis of **16** under acidic conditions afforded acid **17**, which was converted to the corresponding acyl chloride with $SOCl_2$. Friedel–Crafts acylation of veratrole with this acyl chloride afforded nitro ketone **18**. Henry cyclization with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base afforded nitroalkene **19**. Nitroalcohol **20** was the major side product, but was readily converted back into **19** with thionyl chloride and pyridine (Scheme 1).

Although nitroalkene **19** could be prepared by this method, this multistep synthetic approach was very tedious. Thus, a new method was developed that greatly reduced the synthetic effort required to prepare this intermediate. Treatment of α-tetralone **21** with the Grignard reagent prepared from 4-bromoveratrole, followed by acid-catalyzed dehydration of the alcohol readily afforded olefin **22**. Nitration of **22** using tetranitromethane then provided the desired nitroalkene **19** (Scheme 1).

To obtain both the *cis* and *trans* isomers of **8**, two different reduction methods for **19** were employed. Treatment with lithium aluminum hydride (LAH) gave exclusively the *cis* amine **24a**. Acylation of this amine with chloroacetyl chloride under basic conditions then afforded chloroacetamide **25a**, which underwent photocyclization to give lactam **26a**. Reduction of this lactam with borane, followed by *O,O*-demethylation of the aryl ethers, afforded target compound **8a** (Scheme 2). To prepare the *trans* isomer, **19** was first treated with sodium borohydride in a 2:3 solution of THF/EtOH, which yielded a 2:1 mixture of *cis* and *trans* **23**, as indicated by NMR. Treatment of this product mixture with ethanolic $NaHCO_3$ solution resulted in exclusively the *trans* product **23**. Reduction of **23** with zinc powder and glacial acetic acid afforded



Scheme 1. Synthesis of 4-(3,4-dimethoxyphenyl)-3-nitro-1,2-dihydronaphthalene **19**.



Scheme 2. Synthesis of (±)-6,6a,7,8,9,13b-hexahydro-5*H*-benzo[*d*]naphtho[2,1-*b*]azepine-11,12-diol **8**.

amine **24b**. The *trans* analog **8b** was prepared from amine **24b** using the same methods as for the *cis* analog **8a**.

The synthetic approach for the oxygen and sulfur analogs **9** and **10** was devised based on methodology similar to that employed in

the synthesis of doxanthrine **4**.[17] The nitrochromene intermediate **29** was obtained from the reaction of salicylaldehyde **28** with nitroethene (generated in situ from nitroethanol) in basic solution. To avoid undesired polymerization, a low concentration of nitroethene was ensured by using a steady and slow addition of nitroethanol through a syringe pump. A 1,4-addition of the Grignard reagent prepared from 4-bromoveratrole to **29** gave exclusively *trans* **30**, as indicated by proton NMR. Reduction of the nitro moiety of **30** with zinc powder and glacial acetic acid afforded amine **31** in quantitative yield. Chloroacetamide **32**, prepared from amine **31** and chloroacetyl chloride, then underwent photocyclization to give lactam **33**. Reduction of the lactam with borane, followed by *O*,*O*-dealkylation of the aryl ethers then afforded the target compound **9** (Scheme 3).

Analogously, the preparation of thio-derivative **10** (Scheme 4) paralleled the synthetic route developed for the oxygen derivative. Aldehyde **36** was prepared by *ortho*-formylation of thiophenol **35** with DMF.[19] Due to its instability, this aldehyde was used immediately in subsequent reactions. Intermediates **37**, **38**, **39**, and **40** were synthesized uneventfully following reaction conditions established for the oxygen analog. Surprisingly, however, photocyclization of **40** proved quite unsatisfactory, producing only a 5–7% yield of lactam **41**, compared to the 31% yield obtained for the oxygen analog. Significant decomposition under the photoirradiation conditions was observed, and modification of the reaction conditions either with respect to solvent systems or reaction time did not significantly improve the yield. Sulfur compounds can undergo various photochemical oxidations, resulting in cleavage and rearrangement of the sulfide bond, which could account for the low yield of the desired product. Nonetheless, despite the unsatisfactory yield for production of lactam **41**, an amount of target compound **10** sufficient for pharmacological testing was ultimately obtained.

2.2. Pharmacology

The conformationally restricted analogs **8a**, **8b**, **9**, and **10** were compared with SKF38393 (**2**), DHX (**3**), and SCH39166 for affinity at D_1- and D_2-like receptors in pig striatal homogenate. The D_1-like receptor affinities were determined using [^{3}H]SCH23390 displacement, and D_2-like receptor affinities were obtained using displacement of [^{3}H]spiperone, with added ketanserin to mask 5-HT_{2A} sites.

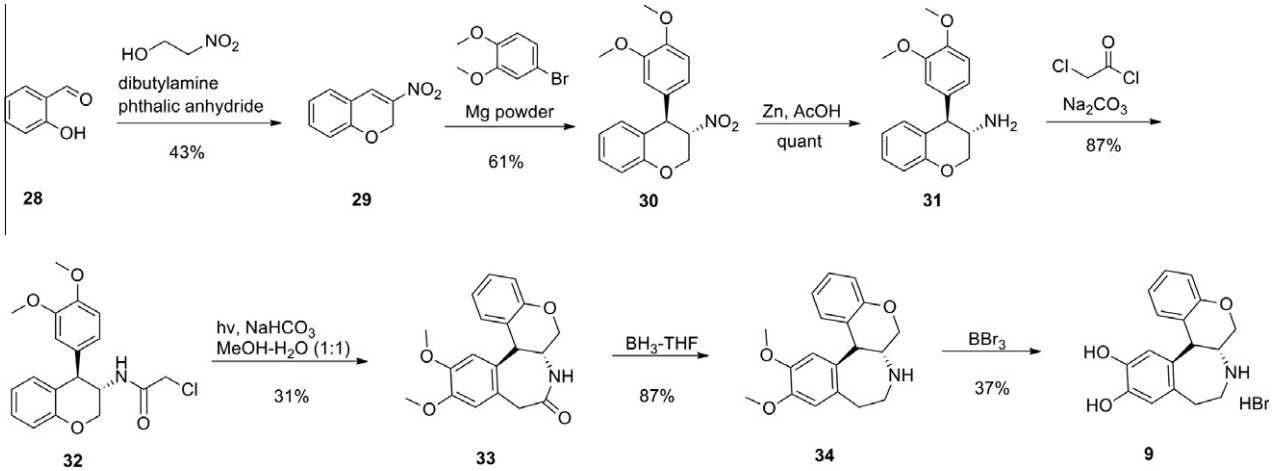
To establish the functional effects of compounds **8b**, **9**, and **10**, standard cAMP quantification assays were employed using stably transfected cell lines expressing cloned human D_1 receptors.[20] Full intrinsic activity was defined as the maximal activation induced by 10 μM of the endogenous neurotransmitter dopamine.

Consistent with the results obtained by Berger et al.[14] comparison of the *cis* and *trans* isomers **8a** and **8b** (Table 1) clearly shows that higher receptor affinity is associated with the *trans* isomer. Furthermore, the competition binding experiments also demonstrate that compounds **8b**, **9**, and **10** have D_1 binding affinities that are similar to that of SKF38393 (**2**), with **8b** being least potent, showing a 1.7-fold decrease in affinity compared to SKF38393 (**2**), and sulfur analog **10** being the most active, with 1.6-fold improvement in affinity over **2** (Table 1). Within this series, the increase in binding affinity from **8b** to its oxygen and sulfur analogs **9** and **10** might be explained by the slight difference in the conformation of the β-phenyl ring due to the oxygen or sulfur replacement at the three-position. Although the size of an oxygen atom is not much different from a CH_2 group, a sulfur atom is closer to the size of an ethylene group. Thus, substitution of the CH_2 group with a sulfur atom would result in a greater change in the orientation of the β-phenyl ring compared to the carbocyclic or oxacyclic analogs.

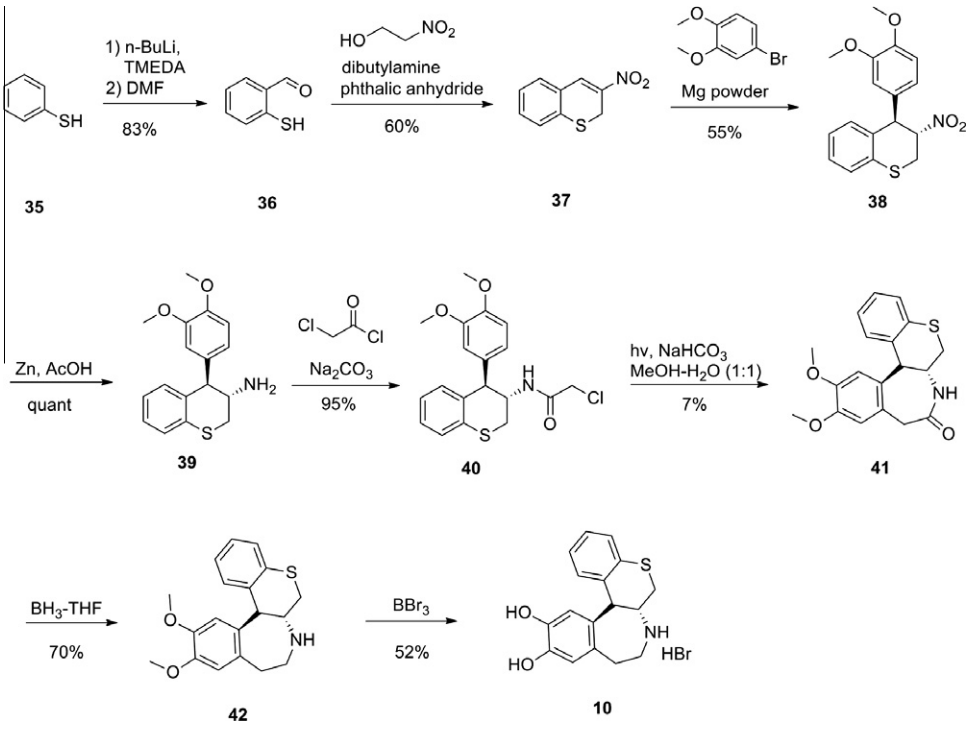
Functionally, **8b**, **9**, and **10** show a greater than eightfold decrease in potency compared to SKF38393 (**2**), and demonstrate partial intrinsic activity of less than 60% relative to dopamine (Table 2). In our assays the receptors are overexpressed, with the consequence that partial agonists can show full or nearly full agonist activity. For example, SKF38393 is known to be a weak partial agonist, but in our assays it displays almost full agonist activity (93% compared to dopamine). Thus, compounds **8b**, **9**, and **10** in a native expression system would be expected to have even lower intrinsic activity than was observed in our experiments.

2.3. Conformational analyses

Although disappointed by the lack of functional activity for **8b**, **9**, and **10**, we believe these results provide further insight into the nature of the requirements for dopamine D_1 agonist activity. In the full agonist **3**, the amino nitrogen resides essentially in the plane of the catechol ring (Fig. 3A, right column). Based on what is known from modern molecular modeling studies about the orthosteric binding site in the receptor, this placement of the nitrogen is likely crucial for high agonist activity. The azepine ring of SKF38393 can achieve a twist conformation that places the nitrogen approximately in the catechol ring plane, but in doing so the pendant phenyl ring is forced to twist to avoid a nonbonded interaction between H(9), at the top of the catechol ring, and the *ortho*-hydrogen atoms of the appended phenyl ring. This twist conformation will be of significantly higher energy than the calculated low energy minima.



Scheme 3. Synthesis of (±)-*trans*-6,6a,7,8,9,13b-hexahydrobenzo[*d*]chromeno[3,4-*b*]azepine-11,12-diol **9**.



Scheme 4. Synthesis of (±)-*trans*-6,6a,7,8,9,13b-hexahydrobenzo[*d*]thiochromeno[3,4-*b*]azepine-11,12-diol **10**.

Table 1
Affinity at porcine striatal homogenates (nM)

Ligand	D_1-like K_i	D_2-like K_i
2	151 ± 18	2364 ± 146
3	22 ± 1.3	320 ± 42
5	0.64 ± 0.06	ND
6b	1.30 ± 0.21	2011 ± 331
8a	22000 ± 4000	88000 ± 8000
8b	257 ± 42	8479 ± 891
9	186 ± 32	44840 ± 7900
10	92 ± 8.5	27980 ± 146
Chlorpromazine	ND	2.67 ± 0.42

Table 2
cAMP assay at HEK human D_1 receptor

Ligand	EC_{50} (nM)	Intrinsic activity (%)
DA	37 ± 1.1	100 ± 3
2	56 ± 5.2	93 ± 7
3	7.2 ± 0.6	103 ± 2
8b	438 ± 42	28 ± 2
9	570 ± 41	60 ± 2
10	584 ± 63	21 ± 1

By contrast, for the tetracyclic congeners to adopt an azepine ring conformation that would place the nitrogen atom approximately in the catechol ring plane requires the appended phenyl ring to lie nearly coplanar with the catechol ring. This phenyl ring is no longer free to twist, and therefore in that conformation a nonbonded interaction between the analogous hydrogen atom of the catechol and the hydrogen on the phenyl cannot be avoided (Fig. 3C and D). Thus, the more rigid tetracyclic analogs cannot adopt a low energy conformation that places the nitrogen atom approximately in the plane of the catechol ring. In addition, for any of the azepine type molecules, even if the nitrogen atom resides in the catechol ring plane, it is displaced from the position of that in the full agonist **3** by virtue of its cisoid conformation, whereas full agonists such as **3** have their ethylamine fragment in an extended *trans* configuration.

These same conformational arguments would apply to the antagonist molecule SCH39166 (**6b**). Yet, **6b** has very high affinity for the receptor. Clearly, the structural requirements for antagonists must vary significantly from those of agonists. First of all, replacing one of the catechol hydroxys with a halogen is key to obtaining antagonist activity. Second, the *N*-methyl is tolerated for antagonists, but not for agonists, suggesting a fundamental realignment of the ligand so as to present its nitrogen atom to the aspartate residue in helix **3** of the receptor in a complementary way. Finally, it is probably not necessary for the amine nitrogen to lie approximately in the plane of the substituted aromatic ring for antagonists, whereas that may be a crucial structural requirement for agonist activity.

In summary, compounds **8b**, **9**, and **10** show binding affinity comparable to SKF38393, with the sulfur analog **10** possessing the most favorable binding of all. By contrast, the new analogs are only very weak partial agonists, suggesting that conformational and other structural features prevent them from adopting shapes that are complementary to the receptor activation process.

3. Experimental

3.1. Chemistry

3.1.1. Chemistry general

All reagents were commercially available and used without further purification unless stated otherwise. Flash column chromatography was carried out using silica gel having a particle size of 40–65 μm. Melting points were determined in open capillaries with a Meltemp apparatus. ^{1}H NMR spectra were obtained using a 300 MHz Bruker ARX-300 spectrometer or a 500 MHz Bruker DRX-500 spectrometer. Mass spectra data were obtained by the Purdue University Campus-wide Mass Spectrometry Center.

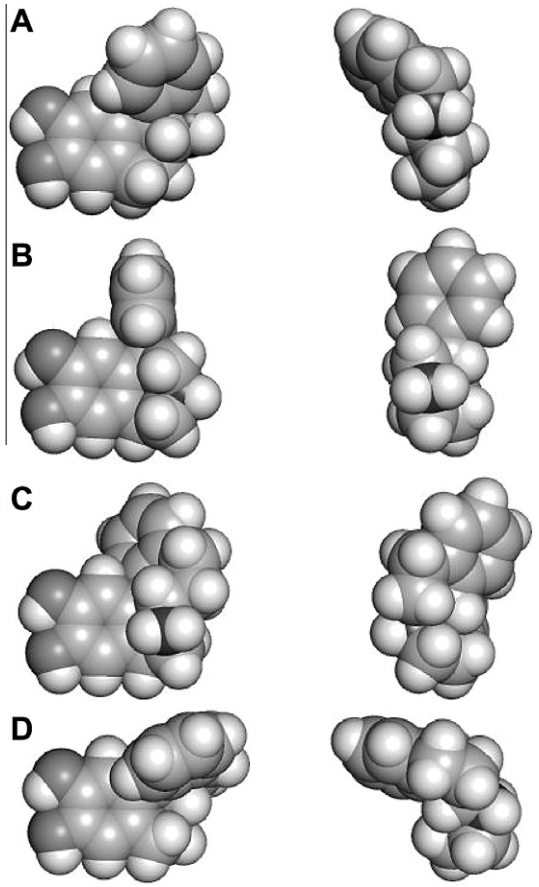


Figure 3. Space filling energy-minimized representations of: (A) the full agonist DHX (**3**, top row), (B) the partial agonist SKF38393 **2**, (C) **8b** with the pendant phenyl ring in a pseudo-equatorial position, and (D) **8b** with the pendant phenyl ring in an axial position. Structures on the left are viewed from the top, whereas the right column is viewed edge-on, with the amine towards the viewer.

3.1.2. 3-(2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)phenyl)propan-1-ol (13)

Alkene **12** (2.0 g, 9.3 mmol) was dissolved in 20 mL of dry THF and 28 mL (14 mmol) of a 0.5 M solution of 9-BBN in THF was added drop-wise at 0 °C. After stirring at room temperature for 4 h, 5 mL of water were added, followed by 15 mL of H_2O_2 (30 wt % in H_2O) in 2 N NaOH (20 mL).The reaction was heated at 60 °C for 2.5 h. The reaction was cooled to room temperature, extracted with EtOAc (3 × 60 mL). The organic solvent was washed with brine, dried over $MgSO_4$, filtered, and the solvents removed under reduced pressure. Silica gel flash column chromatography, eluting with 1:4 hexanes/EtOAc, provided 1.9 g (87.7%) of alcohol **13** as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.74 (dd, J_1 = 9.0 Hz, J_2 = 1.5 Hz, 1H, ArH); 7.51 (dt, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1H, ArH); 7.29–7.22 (m, 2H, 2ArH); 5.90 (br s, 1H, OH); 4.10 (s, 2H, Oxazolinyl-CH_2); 3.43 (t, J = 4.8 Hz, 2H, CH_2OH); 3.16 (t, J = 6.3 Hz, 2H, $ArCH_2$); 1.98–1.92 (m, 2H, 2-H_2); 1.41 (s, 6H, $2CH_3$). CIMS: m/z (relative intensity): 234 ($M+H^+$, 100). Anal. Calcd For $C_{14}H_{19}NO_2 \cdot 0.11C_4H_8O_2$: C, 71.37; H, 8.25; N, 5.76. Found: C, 71.38; H, 8.06; N, 5.62.

3.1.3. Methyl 2-(3-hydroxypropyl)benzoate (14)

Alcohol **13** (0.9 g, 3.86 mmol) was dissolved in 50 mL of 6 M methanolic HCl and heated at reflux for 30 h. The solvent was removed under reduced pressure, and the residue was partitioned between water and CH_2Cl_2. The aqueous solution was extracted twice more with CH_2Cl_2. The combined organic solvent was washed with brine, dried over $MgSO_4$, filtered, and the solvents removed under reduced pressure. Silica gel flash column chromatography, eluting with 2:3 hexanes/EtOAc, provided 408 mg (54.5%) of ester **14** as a light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.88 (dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1H, ArH); 7.42 (dt, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H, ArH); 7.30–7.23 (m, 2H, 2ArH); 3.90 (s, 3H, OCH_3); 3.62 (t, J = 6.0 Hz, 2H, CH_2OH); 3.06 (t, J = 7.2 Hz, 2H, $ArCH_2$); 1.96–1.87 (m, 2H, 2-H_2). CIMS: m/z (relative intensity): 195 ($M+H^+$, 44), 177 ($M+H-H_2O$, 38), 163 ($M+H-CH_3OH$, 100). Anal. Calcd For $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.84; H, 7.20.

3.1.4. Methyl 2-(3-bromopropyl)benzoate (15)

Triphenylphosphine (8.4 g, 32.13 mmol) was added in small portions at 0 °C to a flask containing ester **14** (4.16 g, 21.42 mmol) and carbon tetrabromide (8.5 g, 25.7 mmol) in 100 mL of CH_2Cl_2. The reaction was stirred for 1 h, and the solvent was removed under reduced pressure. The residue was washed with ether, and the white precipitates were removed by filtration. The filtrate was concentrated and purified by silica gel flash column chromatography, eluting with 1:1 hexanes/EtOAc, to give 5.18 g (94%) of bromide **15** as a yellow oil. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.91 (d, J = 7.5 Hz, 1H, ArH); 7.44 (dt, J_1 = 8.7 Hz, J_2 = 1.5 Hz, 1H, ArH); 7.31–7.26 (m, 2H, 2ArH); 3.90 (s, 3H, OCH_3); 3.45 (t, J = 6.6 Hz, 2H, CH_2Br); 3.11 (t, J = 7.5 Hz, 2H, $ArCH_2$); 2.18 (q, J = 7.0 Hz, 2H, 2-H_2). CIMS: m/z (relative intensity): 257/259 ($M+H^+$, 47), 177 (M+H–HBr, 100).

3.1.5. Methyl 2-(3-nitropropyl)benzoate (16)

Bromide **15** (3.0 g, 12.34 mmol) was dissolved in 45 mL of a mixture of 2:1 DMF/ethylene glycol. Sodium nitrite (3.4 g, 49.36 mmol) was then added to the mixture. After stirring at room temperature for 4 h, the reaction was poured into ice-water and extracted with CH_2Cl_2 (3 × 50 mL). The organic solvent was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give a yellow oil. Silica gel flash column chromatography, eluting with 3:2 hexanes/EtOAc, provided 1.62 g of unreacted bromide **15** and 0.65 g (51%) of nitrobenzoate **16**: mp 105–106 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.94 (d, J = 8.0 Hz, 1H, ArH); 7.47 (dt, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1H, ArH); 7.32 (d, J = 7.5 Hz, 1H, ArH); 7.28–7.24 (m, 1H, 1ArH); 4.44 (t, J = 6.9 Hz, 2H, CH_2NO_2); 3.89 (s, 3H, OCH_3); 3.05 (t, J = 7.2 Hz, 2H, $ArCH_2$); 2.34 (q, J = 7.0 Hz, 2H, 2-H_2). CIMS: m/z (relative intensity): 224 ($M+H^+$, 100).

3.1.6. 2-(3-Nitropropyl)benzoic acid (17)

Nitrobenzoate **16** (6.5 g, 29.12 mmol) was dissolved in a mixture of 100 mL of AcOH and 40 mL of 6 M HCl. The reaction was heated at reflux for 14 h, then cooled to room temperature and extracted with CH_2Cl_2 (3 × 80 mL). The extract was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give a yellow oil. The crude product was dissolved in EtOAc and extracted with saturated $NaHCO_3$ solution (3 × 100 mL). The combined aqueous solution was acidified with 1 M HCl and extracted with CH_2Cl_2 (3 × 80 mL). The organic extract was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to yield 4.5 g (73.9%) of acid **17**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.11 (dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1H, ArH); 7.53 (dt, J_1 = 7.5 Hz, J_2 = 1.0 Hz, 1H, ArH); 7.38–7.30 (m, 2H, 2ArH); 4.51 (t, J = 7.0 Hz, 2H, CH_2NO_2); 3.13 (t, J = 7.5 Hz, 2H, $ArCH_2$); 2.34 (q, J = 7.3 Hz, 2H, 2-H_2). CIMS: m/z (relative intensity): 208 (M–H, 100).

3.1.7. (3,4-Dimethoxyphenyl)(2-(3-nitropropyl)phenyl)methanone (18)

Thionyl chloride (1.87 mL, 25.6 mmol) was added to a flask containing acid **17** (1.34 g, 6.41 mmol) in 30 mL of benzene. The reaction was heated at reflux for 2.5 h. Excess thionyl chloride was then azeotropically removed from the reaction with toluene. The resulting acyl chloride was dried under vacuum and used

without further purification. To the flask containing the acyl chloride in CH_2Cl_2, $AlCl_3$ (1.28 g, 9.61 mmol) was added, followed by drop-wise addition of veratrole (1.2 mL, 9.61 mmol) at 0 °C. The reaction was stirred overnight at room temperature, and then was quenched with water and extracted with CH_2Cl_2 (3 × 60 mL). The organic solution was washed with brine, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. Silica gel flash column chromatography, eluting with 1:1 hexanes/EtOAc, provided 1.68 g of ketone **18**: mp 70–72 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.55 (d, J = 2.7 Hz, 1H, ArH); 7.49–7.42 (m, 1H, ArH); 7.35–7.29 (m, 2H, 2ArH); 7.21 (dd, J_1 = 8.4 Hz, J_2 = 2.1 Hz, 1H, ArH); 6.91 (d, J = 3.0 Hz, 1H, ArH); 6.84 (d, J = 8.4 Hz, 1H, ArH); 4.36 (t, J = 6.9 Hz, 2H, CH_2NO_2); 3.95 (s, 3H, OCH_3); 3.89 (s, 3H, OCH_3); 2.75 (t, J = 6.9 Hz, 2H, $ArCH_2$); 2.32 (p, J = 7.2 Hz, 2H, 2-H_2). CIMS: m/z (relative intensity): 330 ($M+H^+$, 100). Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.55; H, 5.69; N, 4.14.

3.1.8. 4-(3,4-Dimethoxyphenyl)-3-nitro-1,2-dihydronaphthalene (19)

3.1.8.1. Method 1. Ketone **18** (720 mg, 2.19 mmol) was dissolved in 60 mL of a mixture of 1:1 MeOH/THF. DBU (1 mL, 6.56 mmol) was then added to this solution, and the reaction was heated at reflux for 24 h. The solvent was then removed under reduced pressured and the residue was partitioned between 1 M HCl and CH_2Cl_2. The aqueous layer was extracted twice more with CH_2Cl_2. The combined organic extract was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. Silica gel flash column chromatography, eluting with 3:2 hexanes/EtOAc, provided 230 mg (33.8%) of nitronaphthalene **19** and 216 mg (30%) of alcohol **20** as the major side product, the latter being easily dehydrated to give desired nitronaphthalene **19**.

3.1.8.2. Method 2. Alkene **22** (8.5 g, 31.9 mmol) and pyridine (2.5 g, 31.9 mmol) were dissolved in 300 mL of dry MeCN. Into this stirring solution, tetranitromethane (3.8 mL, 31.9 mmol) was added drop-wise at 0 °C. The reaction was stirred for 3.5 h at room temperature, and quenched by pouring into ice-cold water. The mixture was concentrated under reduced pressure. The residue was partitioned between water and CH_2Cl_2. The aqueous solution was extracted twice more with CH_2Cl_2 (100 mL). The organic extract was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. Recrystallization from MeOH yielded 7.65 g (83.5%) of nitronaphthalene **19** as a yellow powder: mp 150–158 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.33–7.23 (m, 2H, 2ArH); 7.15 (dt, J_1 = 8.2 Hz, J_2 = 2.5 Hz, 1H, ArH); 6.92 (d, J = 8.4 Hz, 1H, ArH); 6.87 (d, J = 7.5 Hz, 1H, ArH); 6.75 (dd, J_1 = 8.1 Hz, J_2 = 2.1 Hz, 1H, ArH); 6.69 (d, J = 1.8 Hz, 1H, ArH); 3.93 (s, 3H, OCH_3); 3.84 (s, 3H, OCH_3); 3.10–3.00 (m, 4H, $ArCH_2$, CH_2CNO_2). EIMS: m/z (relative intensity): 311 (M^+, 100). Anal. Calcd for $C_{18}H_{17}NO_4$ $0.18C_2H_6O$: C, 68.99; H, 5.70; N, 4.38. Found: C, 68.87; H, 5.50; N, 4.38.

Alcohol **20**: mp 150–158 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33–7.19 (m, 4H, 4ArH); 6.77 (d, J = 2.0 Hz, 1H, ArH); 6.72 (d, J = 8.5 Hz, 1H, ArH); 6.49 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H, ArH); 5.04 (dd, J_1 = 11.0 Hz, J_2 = 4.0 Hz, 1H, NO_2CH); 3.83 (s, 3H, OCH_3); 3.79 (s, 3H, OCH_3); 3.16 (td, J_1 = 17.5 Hz, J_2 = 3.5 Hz, 1H, $ArCH_a$); 3.10–3.02 (m, 1H, $ArCH_b$); 2.38–2.34 (m, 2H, CH_2CNO_2). EIMS: m/z (relative intensity): 311 (M^+, 100). Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.59; H, 5.80; N, 4.32.

3.1.9. 1-(3,4-Dimethoxyphenyl)-3,4-dihydronaphthalene (22)

To a stirred solution of 4-bromoveratrole (11.1 g, 0.051 mol) in 100 mL of dry THF was added magnesium powder-50 mesh (1.7 g, 0.068 mol), and the mixture was heated at reflux for 2 h to form the Grignard reagent. α-Tetralone (5 g, 0.034 mol) was added drop-wise to the refluxing mixture, which was heated for another 2.5 h. After cooling to room temperature, the reaction was quenched with 40 mL of ice cold 6 M HCl, and stirred for another 1 h. The mixture was extracted with EtOAc (3 × 50 mL), the extract was dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Recrystallization from EtOH/hexane yielded 5.3 g (58%) of alkene **22**: mp 66–68 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.19–7.03 (m, 4H, 4ArH); 6.90–6.87 (m, 3H, 3ArH); 6.07 (t, J = 9.3 Hz, 1H, 3-H); 3.92 (s, 3H, OCH_3); 3.86 (s, 3H, OCH_3); 2.85 (t, J = = 7.7 Hz, 2H, 1-H_2); 2.43–2.38 (m, 2H, 2-H_2). CIMS: m/z (relative intensity): 267 ($M+H^+$, 100). Anal. Calcd For $C_{18}H_{18}O_2$: C, 81.17; H, 6.8. Found: C, 80.86; H, 6.73.

3.1.10. (±)-*Trans*-1-(3,4-dimethoxyphenyl)-2-nitro-1,2,3,4-tetrahydronaphthalene (23)

Nitronaph-thalene **19** (1.5 g, 4.82 mmol) was dissolved in 250 mL of a mixture of 2:3 THF/EtOH. Sodium borohydride (729 mg, 19.27 mmol) was then added to the solution. The reaction was stirred at room temperature for 16 h, at which time two more molar equivalents of sodium borohydride were added. After stirring for another 7 h, the reaction was quenched with diluted aqueous urea/AcOH solution. The solvent was removed under reduced pressure, and the residue was partitioned between water and CH_2Cl_2. The aqueous solution was extracted twice more with CH_2Cl_2 (2 × 50 mL). The combined organic extract was dried over $MgSO_4$, filtered, and the solvents removed under reduced pressure to afford a mixture of a 2:1 ratio of *cis* and *trans* **23**, as determined from the ^{1}H NMR spectrum of the product. Epimerization of *cis* **23** was achieved by dissolving the *cis*/*trans* mixture of **23** in 100 mL of $NaHCO_3$-saturated 95% EtOH. The mixture was heated at reflux for 6 h. The solvent was then removed under reduced pressure, and the residue partitioned between water and CH_2Cl_2. The aqueous solution was extracted twice more with CH_2Cl_2 (2 × 50 mL). The combined organic extract was dried over $MgSO_4$, filtered, and the solvents removed under reduced pressure. Recrystallization from EtOH yielded 1.28 g (84.4%) of *trans* **23**: mp 129–131 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.19–7.15 (m, 2H, 2ArH); 7.09 (dt, J_1 = 7.7 Hz, J_2 = 1.9 Hz, 1H, ArH); 6.84 (d, J = 7.7 Hz, 1H, ArH); 6.80 (d, J = 7.9 Hz, 1H, ArH); 6.67 (dd, J_1 = 8.7 Hz, J_2 = 1.9 Hz, 1H, ArH); 6.61 (d, J = 1.9 Hz, 1H, ArH); 4.93 (ddd, J_1 = 14.7 Hz, J_2 = 8.8 Hz,, J_3 = 1.9 Hz, 1H, $CHNO_2$); 4.86 (d, J = 8.8 Hz, 1H, 1-H); 3.86 (s, 3H, OCH_3); 3.80 (s, 3H, OCH_3); 3.10–3.03 (m, 2H, 4-H_2); 2.49–2.47 (m, 2H, 3-H_2). EIMS: m/z (relative intensity): 313 (M^+, 100). Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.01; H, 6.03; N, 4.48.

3.1.11. (±)-*Cis*-1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydronaphthalen-2-amine (24a)

Nitronaphthalene **19** (1.0 g, 3.21 mmol) in 30 mL dry THF was added drop-wise to a flask containing LAH (488 mg, 12.85 mmol) in 40 mL of dry THF. The reaction was heated at reflux for 3 h, cooled to room temperature, and quenched with 2 M HCl. After stirring for another 10 min, 2 M NaOH was added to the reaction. The mixture was extracted with CH_2Cl_2 (3 × 50 mL), the extract was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to afford a dark oil. The crude product was dissolved in EtOAc and extracted with aqueous 2 N HCl solution (3 × 60 mL). The combined aqueous layer was basified with 2 N NaOH solution and extracted with CH_2Cl_2 (3 × 40 mL). The organic solution was then dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to yield 720 mg (79%) of amine **24a**: mp (HCl salt) 272–275 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.06–6.96 (m, 3H, 3ArH); 6.89 (d, J = 7.5 Hz, 1H, ArH); 6.70 (d, J = 8.1 Hz, 1H, ArH); 6.57 (d, J = 8.0 Hz, 1H, ArH); 6.48 (d, J = 7.9 Hz, 1H, ArH); 4.12 (d, J = 4.5 Hz, 1H, 1-H); 3.80–3.75 (m, 1H, $CHNH_2$); 3.77 (s, 3H, OCH_3); 3.72 (s, 3H, OCH_3); 3.05–2.80 (m, 2H, 4-H_2); 1.75–1.72 (m, 2H, 3-H_2). ESIMS: m/z (relative inten-

sity): 284 ($M+H^+$, 100). Anal. Calcd for $C_{18}H_{21}NO_2{\cdot}HCl$: C, 67.60; H, 6.93; N, 4.38. Found: C, 67.31; H, 6.78; N, 4.39.

3.1.12. (±)-*Trans*-1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydronaphthalen-2-amine (24b)

Naph-thalene **23** (500 mg, 1.60 mmol) was dissolved in 40 mL of AcOH and 1.05 g (16.0 mmol) of powdered zinc were added. The mixture was stirred vigorously at room temperature for 16 h, at which time the reaction was filtered through Celite, and the filtered solids were rinsed on the filter with AcOH. The filtrate was concentrated to about 1/3 volume and water (80 mL) was added. The aqueous solution was then basified with conc ammonium hydroxide and extracted with CH_2Cl_2 (3 × 40 mL). The organic solvent was then washed twice with brine, dried over $MgSO_4$, filtered, and the solvents removed under reduced pressure to give a yellow oil. Acid/base purification of crude product (same method as in **24a**) yielded 440 mg (97.4%) of amine **24b**: mp (HCl salt) 248–250 °C. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.20–7.13 (m, 2H, 2ArH); 7.05 (dt, J_1 = 8.1 Hz, J_2 = 1.9 Hz, 1H, ArH); 6.98 (d, J = 9.0 Hz, 1H, ArH); 6.78 (d, J = 1.9 Hz, 1H, ArH); 6.75–6.71 (m, 2H, 2ArH); 4.06 (d, J = 9.1 Hz, 1H, 1-H); 3.84 (s, 3H, OCH_3); 3.77 (s, 3H, OCH_3); 4.93 (dt, J_1 = 10.5 Hz, J_2 = 3.3 Hz,, 1H, $CHNH_2$); 3.16–3.11 (m, 1H, 4-H_a); 3.06–2.99 (m, 1H, 4-H_b); 2.32–2.28 (m, 1H, 3-H_a); 2.03–1.95 (m, 1H, 3-H_b). CIMS: *m*/*z* (relative intensity): 284 ($M+H^+$, 100). Anal. Calcd for $C_{18}H_{21}NO_2{\cdot}HCl$: C, 67.60; H, 6.93; N, 4.38. Found: C, 65.14; H, 6.90; N, 4.25.

3.1.13. (±)-*Cis*-2-chloro-*N*-(1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide (25a)

Amine **24a** (750 mg, 2.65 mmol) was dissolved in 100 mL of Et_2O, and Et_3N (402 mg, 3.97 mmol) was added. The reaction was cooled to 0 °C, and chloroacetyl chloride (330 mg, 2.92 mmol) was added drop-wise to the reaction mixture. After stirring for 16 h at room temperature, water was added to quench the reaction. The mixture was extracted with CH_2Cl_2 (3 × 30 mL), the organic extract was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product, which was recrystallization from EtOH to afford 670 mg (71.1%) acetamide **25a**: mp 127–130 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.02–7.01 (m, 2H, 2ArH); 7.00–6.99 (m, 1H, ArH); 6.88 (d, J = 7.8 Hz, 1H, ArH); 6.72 (d, J = 8.4 Hz, 1H, ArH); 6.50 (d, J = 1.8 Hz, 1H, ArH); 6.40 (dd, J_1 = 8.4 Hz, J_2 = 2.1 Hz, 1H, ArH); 4.45–4.37 (m, 1H, CHN); 4.25 (d, J = 5.7 Hz, 1H, 1-H); 3.96 (s, 2H, CH_2Cl); 3.77 (s, 3H, OCH_3); 3.73 (s, 3H, OCH_3); 3.00–2.95 (m, 2H, 4-H_2); 1.84–1.75 (m, 2H, 3-H_2). CIMS: *m*/*z* (relative intensity): 360/362 ($M+H^+$, 100). Anal. Calcd for $C_{20}H_{22}ClNO_3$: C, 66.75; H, 6.16; N, 3.89. Found: C, 66.49; H, 6.01; N, 3.91.

3.1.14. (±)-*Trans*-2-chloro-N-(1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide (25b)

Amine **24b** (5.6 g, 19.76 mmol) was dissolved in 250 mL of CH_2Cl_2, and Na_2CO_3 (8.4 g, 15.32 mmol) was added. The reaction was cooled to 0 °C, and chloroacetyl chloride (6.7 g, 59.29 mmol) was added drop-wise to the reaction mixture. After stirring for 16 h at room temperature, water was added to quench the reaction. The mixture was extracted with CH_2Cl_2 (3 × 30 mL), the organic solvent was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product, which was recrystallized from EtOH to yield 6.82 g (95.9%) of acetamide **25b**: mp 171–174 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.18 (d, J = 4.0 Hz, 1H, ArH); 7.10–7.07 (m, 1H, ArH); 6.86 (d, J = 8.0 Hz, 1H, ArH); 6.78 (d, J = 8.5 Hz, 1H, ArH); 6.67–6.57 (m, 3H, 3ArH); 4.32 (qd, J_1 = 8.0 Hz, J_2 = 2.5 Hz, 1H, CHN); 4.00 (d, J = 7.5 Hz, 1H, 1-H); 3.99, 3.90 (ABq, J_{AB} = 20.0 Hz, 2H, CH_2Cl); 3.85 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3); 3.10–3.07 (m, 1H, 4-H_a); 2.96–2.91 (m, 1H, 4-H_b); 2.23–2.21 (m, 1H, 3-H_a); 1.84–1.57 (m, 1H, 3-H_b). CIMS: *m*/*z* (relative intensity): 360 ($M+H^+$, 100). Anal. Calcd for $C_{20}H_{22}ClNO_3$: C, 66.75; H, 6.16; N, 3.89. Found: C, 66.45; H, 6.07; N, 3.89.

3.1.15. (±)-*Cis*-11,12-dimethoxy-6a,7,9,13b-tetrahydro-5*H*-benzo[*d*]naphtho[2,1-*b*]azepin-8(6*H*)-one (26a)

A solution of chloroacetamide **25a** (800 mg, 2.22 mmol) and $NaHCO_3$ (560 mg, 6.67 mmol) in 500 mL of a mixture of 3:1 MeOH/H_2O was irradiated for 55 min at room temperature with a medium pressure mercury lamp, with cooling. The resulting solution was reduced in volume under pressure, and partitioned between water and CH_2Cl_2. The aqueous solution was extracted twice more with CH_2Cl_2. The pooled organic solution was dried over $MgSO_4$, filtered, and the solvents removed under reduced pressure. Silica gel flash column chromatography, eluting with EtOAc, provided 180 mg (25.1%) of lactam **26a**: mp 220–222 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.19–7.16 (m, 1H, ArH); 7.15–7.11 (m, 1H, ArH); 7.00 (d, J = 7.2 Hz, 1H, ArH); 6.83 (d, J = 8.4 Hz, 1H, ArH); 6.61 (d, J = 2.1 Hz, 1H, ArH); 6.51 (dd, J_1 = 8.4 Hz, J_2 = 2.1 Hz, 1H, ArH); 5.43 (br s, 1H, NH); 4.60–4.53 (m, 1H, 6a-H); 4.37 (d, J = 5.7 Hz, 1H, 13b-H); 4.08 (s, 2H, 9-H_2); 3.90 (s, 3H, OCH_3); 3.86 (s, 3H, OCH_3); 3.13–3.10 (m, 2H, 5-H_2); 1.97–1.88 (m, 2H, 6-H_2). CIMS: *m*/*z* (relative intensity): 324 ($M+H^+$, 100). Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.04; H, 6.56; N, 4.32.

3.1.16. (±)-*Trans*-11,12-dimethoxy-6a,7,9,13b-tetrahydro-5*H*-benzo[*d*]naphtho[2,1-*b*]azepin-8(6*H*)-one (26b)

A solution of chloroacetamide **25b** (700 mg, 1.95 mmol) and $NaHCO_3$ (1.31 g, 15.56 mmol) in 500 mL of a mixture of 3:1 MeOH/H_2O was irradiated for 55 min at room temperature with a medium pressure mercury lamp, with cooling. The resulting solution was reduced in volume under reduced pressure, and partitioned between water and CH_2Cl_2. The aqueous solution was extracted twice more with CH_2Cl_2. The pooled organic solvent was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. Silica gel flash column chromatography, eluting with EtOAc, provided 154 mg (24.5%) of lactam **26b**: mp 232–234 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.23–7.15 (m, 3H, 3ArH); 7.08 (d, J = 7.3 Hz, 1H, ArH); 6.76 (s, 1H, ArH); 6.42 (s, 1H, ArH); 5.59 (s, 1H, NH); 4.62 (d, J = 10.8 Hz, 1H, 13b-H); 4.13, 3.65 (ABq, J_{AB} = 15.9 Hz, 2H, 9-H_2); 3.89 (s, 3H, OCH_3); 3.65 (s, 3H, OCH_3); 3.54 (dt, J_1 = 11.0 Hz, J_2 = 3.9 Hz,, 1H, 6a-H); 2.96–2.91 (m, 2H, 5-H_2); 2.05–1.99 (m, 1H, 6-H_a); 1.97–1.89 (m, 1H, 6-H_b). ESIMS: *m*/*z* (relative intensity): 324 ($M+H^+$, 100). Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.10; H, 6.45; N, 4.34.

3.1.17. (±)-*Cis*-11,12-dimethoxy-6,6a,7,8,9,13b-hexahydro-5*H*-benzo[*d*]naphtho[2,1-*b*]azepine hydrochloride (27a)

Lactam **26a** (100 mg, 0.31 mmol) was suspended in 60 mL of dry THF, and 1.86 mL (1.86 mmol) of a 1 M solution of BH_3 in THF was added. This solution was stirred at reflux for 24 h, then cooled and quenched with excess MeOH. The solvent was removed under reduced pressure and the residue was stirred for 4 h with 30 mL of 6 M ethanolic HCl solution at reflux. The solvent was removed, and MeOH was added and removed under vacuum three times. The residue was partitioned between 2 M aqueous NaOH and CH_2Cl_2. The aqueous solution was extracted twice more with CH_2Cl_2 (2 × 40 mL). The combined organic extract was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude amine was dissolved in a small amount CH_2Cl_2, and 2 M HCl in ether was added to the solution. The solvent was removed under reduced pressure, and the hydrochloride salt was recrystallized from EtOH to give 50 mg (52.6%) of amine hydrochloride **27a**: mp >175 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.21–7.18 (m, 2H, 2ArH);

7.13–7.10 (m, 1H, ArH); 7.01 (s, 1H, ArH); 6.96–6.93 (m, 1H, ArH); 6.81 (s, 1H, ArH); 4.45 (m, 1H, 13b-H); 3.70 (m, 1H, 6a-H); 3.88 (s, 3H, OCH_3); 3.85 (s, 3H, OCH_3); 3.24–3.19 (m, 3H, 8-H_2, 9-H_a); 3.05–2.91 (m, 2 H, 5-H_2); 2.63 (m, 1H, 9-CH_b); 1.86–1.65 (m, 2H, 6-H_2). CIMS: *m*/*z* (relative intensity): 310 ($M+H^+$, 100). Anal. Calcd for $C_{20}H_{24}ClNO_2$: C, 69.45; H, 6.99; N, 4.05. Found: C, 69.22; H, 6.85; N, 4.02.

3.1.18. (±)-*Trans*-11,12-dimethoxy-6,6a,7,8,9,13b-hexahydro-5*H*-benzo[*d*]naphtho[2,1-*b*]azepine hydrochloride (27b)

Lactam **26b** (300 mg, 0.93 mmol) was suspended in 60 mL of dry THF, and 7.42 mL (7.42 mmol) of a 1 M solution of BH_3 in THF was added. This solution was stirred at reflux for 24 h, then cooled and quenched with excess MeOH. The solvent was removed under reduced pressure. The residue was then stirred for 4 h at reflux with 50 mL of 6 M ethanolic HCl solution. The solvent was removed and MeOH was added and removed under vacuum three times. The residue was partitioned between 2 M aqueous NaOH and CH_2Cl_2. The aqueous solution was extracted twice more with CH_2Cl_2 (2 × 40 mL). The combined organic extract was dried over $MgSO_4$, filtered, and the solvents removed under reduced pressure. The crude amine was dissolved in a small amount of CH_2Cl_2, and 2 M HCl in ether was added to the solution. The solvent was removed under reduced pressure, and the hydrochloride salt was recrystallized from EtOH to provide 250 mg (77.9%) of amine hydrochloride **27b**: mp 279–282 °C. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.23–7.22 (m, 3H, 3ArH); 7.06 (d, J = 5.1 Hz, 1H, ArH); 6.92 (s, 1H, ArH); 6.07 (s, 1H, ArH); 4.75 (d, J = 8.4 Hz, 1H, 13b-H); 3.82 (s, 3H, OCH_3); 3.68 (dd, J_1 = 14.2 Hz, J_2 = 5.1 Hz, 1H, 6a-H); 3.56–3.45 (m, 2H, 8-H_2); 3.45 (s, 3H, OCH_3); 3.09–3.01 (m, 2H, 5-H_2); 2.91–2.88 (m, 2H, 9-CH_2); 2.27–2.21 (m, 1H, 6-H_a); 1.83–1.77 (m, 1H, 6-H_b). ESIMS: *m*/*z* (relative intensity): 310 ($M+H^+$, 100). Anal. Calcd for $C_{20}H_{24}ClNO_2$: C, 69.45; H, 6.99; N, 4.05. Found: C, 69.19; H, 6.82; N, 4.10.

3.1.19. (±)-*Cis*-6,6a,7,8,9,13b-hexahydro-5*H*-benzo[*d*]naphtho[2,1-*b*]azepine-11,12-diol hydrobromide (8a)

Amine **27a** (40 mg, 0.129 mmol) was dissolved in 15 mL of CH_2Cl_2 and cooled to −78 °C. Into this flask, 0.39 mL (0.39 mmol) of a 1 M BBr_3 solution in CH_2Cl_2 was added drop-wise. The reaction was stirred at −78 °C for 2 h and another 4 h at room temperature. The reaction mixture was then cooled to 0 °C and 5 mL of MeOH were added drop-wise. The solvents were then removed under reduced pressure, and 5 mL of MeOH were once again added and removed. The process was repeated one more time. The residue was then recrystallized from EtOH to afford 20 mg (42.8%) of the hydrobromide salt of **8a**: mp >300 °C. ^{1}H NMR (D_6MSO, 500 MHz): δ 8.87 (s, 1H, OH); 8.76 (s, 1H, OH); 7.21–7.18 (m, 3H, 3ArH); 6.83 (br s, 1H, ArH); 6.62 (s, 1H, ArH); 5.91 (br s, 1H, ArH); 4.52 (s, 1H, 13b-H); 3.64 (s, 1H, 6a-H); 3.16–3.15 (m, 3H, 8-H_2, 9-CH_a); 2.92–2.89 (m, 2 H, 5-H_2); 2.67 (br s, 1H, 9-CH_b); 1.86–1.85 (m, 1H, 6-H_a); 1.66–1.62 (m, 1H, 6-H_b). High res. ESIMS for $C_{18}C_{19}NO_2$ (M^+): calcd 282.1494, found 282.1493.

3.1.20. (±)-*Trans*-6,6a,7,8,9,13b-hexahydro-5*H*-benzo[*d*]naphtho[2,1-*b*]azepine-11,12-diol hydrobromide (8b)

Amine **27b** (300 mg, 0.97 mmol) was dissolved in 50 mL of CH_2Cl_2 and cooled to −78 °C. Into this flask, 3.4 mL (3.4 mmol) of a 1 M BBr_3 solution in CH_2Cl_2 was added drop-wise. The reaction was stirred at −78 °C for 2 h and another 4 h at room temperature. The reaction mixture was then cooled to 0 °C and 5 mL of MeOH were added drop-wise. The solvents were then removed under reduced pressure, and 5 mL of MeOH were once again added and removed. The process was repeated one more time. The residue was then recrystallized from EtOH to afford 300 mg (85.5%) of the hydrobromide salt of **8b**: mp >310 °C dec ^{1}H NMR (CD_3OD, 300 MHz): δ 7.22–7.19 (m, 3H, 3ArH); 7.08–7.06 (m, 1H, ArH); 6.70 (s, 1H, ArH); 6.97 (s, 1H, ArH); 4.67 (d, J = 8.2 Hz, 1H, 13b-H); 3.65 (ddd, J_1 = 13.2 Hz, J_2 = 5.1 Hz, J_3 = 1.5 Hz, 1H, 6a-H); 3.44 (t, J = 114.7 Hz, 1H, 8-CH_a); 3.31–3.24 (m, 1 H, 5-H_a); 3.02 (t, J = 12.9 Hz, 1H, 8-H_b); 2.92–2.85 (m, 3H, 9-H_2, 5-H_b); 2.27–2.21 (m, 1H, 6-H_a); 1.80–1.74 (m, 1H, 6-H_b). ESIMS: *m*/*z* 282 ($M+H^+$, 100). Anal. Calcd for $C_{18}H_{20}BrNO_2$: C, 59.68; H, 5.56; N, 3.87. Found: C, 59.44; H, 5.65; N, 3.94.

3.1.21. 3-Nitro-2*H*-chromene (29)

In a three-necked flask equipped with a Dean Start trap, condenser and mechanical stirring, salicylaldehyde (17.4 g, 0.142 mol) was dissolved in 400 mL of toluene containing di-*n*-butyl amine (9.2 g, 0.071 mol) and phthalic anhydride (42.14 g, 0.285 mol). The mixture was heated at reflux with vigorous stirring as 2-nitroethanol (27.1 mL, 0.384 mol) was added very slowly into the reaction flask using a syringe pump set at a rate of approximately 0.5 mL/h. After the addition of 2-nitroethanol was completed (ca. 55 h), the reaction was stirred at reflux for another 12 h. The mixture was cooled to room temperature and was filtered through Celite. The filtrate was washed with 2 N NaOH (3 × 250 mL), brine (100 mL), and dried over $MgSO_4$. The organic solvent was then filtered, and removed by rotary evaporation to yield a dark oil. Silica gel flash column chromatography, eluting with 4:1 hexanes/EtOAc, provided 11.08 g (43.9%) of **29** as an oil that crystallized upon standing, and which could be easily recrystallized from EtOH: mp 65–69 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.78 (s, 1H, $CHNO_2$); 7.33–7.23 (m, 2H, 2ArH); 6.99–6.85 (m, 2H, 2ArH); 5.24 (s, 2H, OCH_2). EIMS: *m*/*z* (relative intensity): 130 (M−OH, –NO, 100), 160 (M−OH, 94), 177 (M^+, 81). Anal. Calcd For $C_9H_7NO_3$: C, 61.02; H, 3.98; N, 7.91. Found: C, 60.88; H, 4.11; N, 7.90.

3.1.22. (±)-*Trans*-4-(3,4-dimethoxyphenyl)-3-nitrochroman (30)

To a solution of 4-bromoveratrole (25.73 g, 0.117 mol) in 150 mL of dry THF was added magnesium powder-50 mesh (3.09 g, 0.125 mol), and the mixture was heated at reflux for 2 h to form the Grignard reagent. The reaction mixture was then cooled to −78 °C, and a solution of nitrochromene **29** (7.4 g, 0.042 mol) in 50 mL of dry THF was added drop-wise through an addition funnel. After stirring for another 30 min, 100 mL of aqueous NH_4Cl solution was added to quench the reaction. The mixture was extracted with CH_2Cl_2 (3 × 60 mL), the extract was washed with brine, dried over MgSO4, filtered, and concentrated under vacuum to provide a dark oil. Silica gel flash column chromatography, eluting with 4:1 hexanes/EtOAc, afforded a yellow oil, which was crystallized from MeOH gave 8.01 g (60.9%) of **30**: mp 123–126 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.21–7.15 (m, 1H, ArH); 6.93–6.90 (m, 2H, 2ArH); 7.38 (d, J = 9 Hz, 1H, ArH); 6.64–6.60 (m, 2H, 2ArH); 4.91–4.83 (m, 2H, OCH_2); 4.59 (ddd, J_1 = 10.8 Hz, J_2 = 6.0 Hz, J_3 = 1.5 Hz, 1H, $CHNO_2$); 4.42 (dd, J_1 = 10.8 Hz, J_2 = 3.0 Hz, 1H, ArCH); 3.84 (s, 3H, OCH_3); 3.80 (s, 3H, OCH_3). CIMS: *m*/*z* (relative intensity): 269 (M+H–NO_2, 100), 316 ($M+H^+$, 32). Anal. Calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.62; H, 5.54; N, 4.47.

3.1.23. (±)-*Trans*-4-(3,4-dimethoxyphenyl)chroman-3-amine (31)

Nitrochroman **30** (2.9 g, 9.2 mmol) was dissolved in 100 mL of AcOH and 3.6 g (55.2 mmol) of powdered zinc were added. The mixture was stirred vigorously at room temperature for 16 h, at which time the reaction was filtered through Celite, and the filtered solids were rinsed on the filter with AcOH. The filtrate was concentrated to 1/3 of its volume and water (300 mL) was added. The aqueous solution was then basified with conc ammo-

nium hydroxide and extracted with CH_2Cl_2 (3 × 40 mL). The organic solution was then washed twice with brine, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to provide 2.6 g (quant yield) of amine **31**: mp 84–88 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.17–7.11 (m, 1H, ArH); 6.91–6.81 (m, 4H, 4ArH); 6.72–6.65 (m, 2H, 2ArH); 4.23 (dd, J_1 = 13.6 Hz, J_2 4.1 Hz, 1H, ArCH); 3.93–3.78 (m, 2H, OCH_2); 3.88 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3); 3.37–3.31 (m, 1H, $CHNH_2$). CIMS: *m*/*z* (relative intensity): 286 ($M+H^+$, 100), 369 ($M-NH_3$, 60). Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.61; H, 6.82; N, 4.94.

3.1.24. (±)-*Trans*-2-chloro-*N*-(4-(3,4-dimethoxyphenyl)chroman-3-yl)acetamide (32)

Amine **31** (500 mg, 1.75 mmol) was dissolved in 80 mL of CH_2Cl_2, and powd Na_2CO_3 (0.74 g, 7.0 mmol) was added. The reaction was cooled to 0 °C, and chloroacetyl chloride (0.6 g, 5.26 mmol) was added drop-wise to the reaction mixture. After stirring for 16 h at room temperature, water was added to quench the reaction. The mixture was extracted with CH_2Cl_2 (3 × 30 mL), the organic solvent was dried over MgSO4 and removed under pressure to give the crude product, which upon recrystallization with EtOH yielded 550 mg (87%) acetamide **32**: mp 105–109 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25–7.20 (m, 1H, ArH); 7.00–6.91 (m, 4H, 4ArH); 6.83 (d, J = 1.8 Hz, 1H, ArH); 6.78 (d, J = 8.4 Hz, 1H, ArH); 6.56 (dd, J_1 = 8.4 Hz, J_2 = 2.1 Hz, 1H, ArH); 4.33–4.30 (m, 1H, ArCH); 4.16 (dd, J_1 = 11.4 Hz, J_2 = 1.5 Hz, 2H, OCH_2); 4.08–4.06 (m, 1H, CHNH); 4.04 (d, J = 1.2 Hz, 2H, CH_2Cl); 3.85 (s, 6H, $2OCH_3$). CIMS: *m*/*z* (relative intensity): 362/364 ($M+H^+$, 100). Anal. Calcd for $C_{19}H_{20}ClNO_4$: C, 63.07; H, 5.57; N, 3.87. Found: C, 63.04; H, 5.62; N, 3.88.

3.1.25. (±)-*Trans*-11,12-dimethoxy-6a,7,9,13b-tetrahydrobenzo[*d*]chromeno[3,4-*b*]azepin-8(6*H*)-one (33)

A solution of chloroacetamide **32** (800 mg, 2.21 mmol) and $NaHCO_3$ (1.5 g, 17.86 mmol) in 500 mL of a mixture of 1:1 MeOH/H_2O was irradiated for 55 min at room temperature with a medium pressure mercury lamp, with cooling. The resulting solution was reduced in volume under vacuum, and partitioned between water and CH_2Cl_2. The aqueous solution was extracted twice more with CH_2Cl_2. The pooled organic solvent was dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The resulting crude product was recrystallized from EtOH to give 220 mg (30.6%) of lactam **33**: mp 220–224 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.21–7.18 (m, 2H, 2ArH); 6.99 (dt, J_1 = 9.0 Hz, J_2 = 1.2 Hz, 2H, 2ArH); 6.78 (s, 1H, ArH); 6.52 (d, 1H, ArH); 6.18 (br s, 1H, NH); 4.78 (d, J = 10.8 Hz, 1H, 13b-H); 4.3–4.30, 3.58 (ABq, J_{AB} = 16.2 Hz, 2H, 9-H_2); 4.17 (dd, J_1 = 10.2 Hz, J_2 = 3.9 Hz, 1H, 6-H_a); 3.91 (t, J = 10.8 Hz, 1H, 6a-H); 3.89 (s, 3H, OCH_3); 3.70 (dd, J_1 = 11.1 Hz, J_2 = 4.3 Hz, 1H, 6-H_b); 3.67 (s, 3H, OCH_3). EIMS: *m*/*z* 325 (M^+, 100). Anal. Calcd for $C_{19}H_{19}NO_4 \cdot 0.11H_2O$: C, 69.71; H, 5.92; N, 4.28. Found: C, 69.69; H, 6.22; N, 4.18.

3.1.26. (±)-*Trans*-11,12-dimethoxy-6,6a,7,8,9,13b-hexahydrobenzo[*d*]chromeno[3,4-*b*]azepine (34)

Lactam **33** (400 mg, 1.23 mmol) was suspended in 100 mL of dry THF and 7.83 mL (7.38 mmol) of a 1 M solution of BH_3 in THF was added. This solution was stirred at reflux for 24 h, cooled and quenched with excess MeOH, and the solvent was removed under reduced pressure. The residue was then stirred for 4 h at reflux with 50 mL of 6 N ethanolic HCl solution. The solvent was removed and MeOH was added and removed under vacuum 3 times. The crude product was dissolved and EtOAc and extracted with aqueous 2 N HCl solution (3 × 60 mL). The combined aqueous layer was basified with 2 N NaOH solution and extracted with CH_2Cl_2 (3 × 40 mL). The organic solution was then dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to yield 336 mg (87.7%) of amine **34**: mp 106–109 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.19 (dt, J_1 = 7.5 Hz, J_2 = 1.9 Hz, 1H, ArH); 7.13–7.08 (m, 1H, ArH); 6.99–6.93 (m, 2H, 2ArH); 6.70 (s, 1H, ArH); 6.22 (s, 1H, ArH); 4.44 (d, J = 7.8 Hz, 1H, 13b-H); 4.15 (dd, J_1 = 10.3 Hz, J_2 = 4.0 Hz, 1H,6-H_a); 3.88 (s, 3H, OCH_3); 3.61 (t, J = 10.3 Hz, 1H,6-H_b); 3.56 (s, 3H, OCH_3); 3.40–3.31 (m, 1H, 6a-H); 3.30–3.24 (m, 1H, 8-H_a); 3.05–2.97 (m, 1H, 8-H_b); 2.86–2.73 (m, 2H, 9-H_2). CIMS: *m*/*z* 312 ($M+H^+$, 100). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 72.94; H, 6.79; N, 4.42.

3.1.27. (±)-*Trans*-6,6a,7,8,9,13b-hexahydrobenzo[*d*]chromeno[3,4-*b*]azepine-11,12-diol hydrobromide (9)

Amine **34** (336 mg, 1.08 mmol) was dissolved in 40 mL of CH_2Cl_2 and cooled to −78 °C. A 1 M BBr_3 solution in CH_2Cl_2 (4.32 mL, 4.32 mmol) was then added drop-wise. This solution was then warmed to room temperature and stirred overnight. The reaction mixture was then cooled to 0 °C and 5 mL of MeOH were added drop-wise. The solvents were removed under reduced pressure, and 5 mL of MeOH were again added and removed. The process was repeated one more time. The residue was then recrystallized from MeOH/EtOAc and dried under vacuum to afford 147 mg (37.4%) of the hydrobromide salt of **9**: mp >300 °C dec ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.11 (br s, 2 H, NH_2^+); 8.82 (s, 1H, OH); 8.77 (s, 1H, OH); 7.26 (dt, J_1 = 8.4 Hz, J_2 = 2.1 Hz, 1H, ArH); 7.12–6.98 (m, 3H, 3ArH); 6.66 (s, 1H, ArH); 5.93 (s, 1H, ArH); 4.72 (d, J = 8.7 Hz, 1H, 13b-H); 4.34 (dd, J_1 = 10.2 Hz, J_2 = 4.5 Hz, 1H, 6-H_a); 3.72 (t, J_1 = 10.8 Hz, 1H, 6-H_b); 3.63–3.55 (m, 1H, 6a-H); 3.44–3.27 (m, 2H, 8-H_2); 2.98–2.84 (m, 1H, 9-H_a); 2.48 (dd, J_1 = 15.6 Hz, J_2 = 5.1 Hz, 1H, 9-H_b). ESIMS: *m*/*z* 284 ($M+H^+$, 100). Anal. Calcd for $C_{17}H_{18}BrNO_3$: C, 56.06; H, 4.98; N, 3.85. Found: C, 55.70; H, 4.95; N, 3.68.

3.1.28. 3-Nitro-2*H*-thiochromene (37)

A solution of thiosalicylaldehyde **36** (24.3 g, 0.176 mol) in 300 mL of toluene containing di-*n*-butyl amine (8.1 mL, 0.044 mol) and phthalic anhydride (14.3 g, 0.097 mol) was placed into a three-necked flask equipped with a Dean-Stark trap, condenser, and mechanical stirring. The mixture was heated at reflux with vigorous stirring and then 2-nitroethanol (6.2 mL, 0.088 mol) was added very slowly into the reaction flask using a syringe pump set at a rate of approximately 0.5 mL/h (about 12 h). After addition of 2-nitroethanol was completed, the reaction was stirred at reflux for another 12 h. The reaction mixture was cooled to room temperature and filtered through Celite. The filtrate was washed with 2 N NaOH (3 × 200 mL), brine (60 mL), and dried over $MgSO_4$. The organic solvent was then filtered and concentrated under reduced pressure to yield a dark oil. Silica gel flash column chromatography, eluting with 4:1 hexanes/EtOAc, provided a red oil, which was crystallized from EtOAc/Hexane to give 10.2 g (60%) of **37**: mp 37–41 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.91 (s, 1H, $CHNO_2$); 7.46–7.18 (m, 4H, 4ArH); 4.10 (s, 2H, SCH_2). CIMS: *m*/*z* (relative intensity): 194 ($M+H^+$, 100), 147 ($M-NO_2$, 26). Anal. Calcd For $C_9H_7NO_2S$: C, 55.94; H, 3.65; N, 7.25. Found: C, 56.02; H, 3.70; N, 7.20.

3.1.29. (±)-*Trans*-4-(3,4-dimethoxyphenyl)-3-nitrothiochroman (38)

To a solution of 4-bromoveratrole (13.5 g, 0.062 mol) in 80 mL of dry THF was added magnesium powder (mesh?) (2.0 g, 0.082 mol), and the mixture was heated at reflux for 2 h to form the Grignard reagent. The reaction mixture was then cooled to −78 °C, and a solution of thionitrochromene **37** (4.0 g, 0.021 mol) in 30 mL of dry THF was added drop-wise through an addition funnel. After stirring for another 30 min, 100 mL of aqueous NH_4Cl

solution was added to quench the reaction. The mixture was extracted with CH_2Cl_2 (3 × 60 mL), the extract was washed with brine, dried over $MgSO_4$, filtered, and the solvent removed to give a dark oil. Silica gel flash column chromatography, eluting with 4:1 hexanes/EtOAc, provided an yellow oil, which crystallized from MeOH gave 3.0 g (43.7%) of **38**: mp 137–140 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20–7.11 (m, 2H, 2ArH); 7.05 (dt, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H, ArH); 6.90 (d, J = 8.0 Hz, 1H, ArH); 6.82 (d, J_1 = 8.0 Hz, 1H, ArH); 6.67 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H, ArH); 6.62 (d, J = 2.0 Hz, 1H, ArH); 5.17 (dt, J_1 = 9.0 Hz, J_2 = 3.0 Hz, 1H, $CHNO_2$); 4.79 (d, J = 9.0 Hz, 1H, ArCH); 3.87 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3); 3.61 (dd, J_1 = 12.9 Hz, J_2 = 8.6 Hz, 1H, SCH_a); 3.61 (dd, J_1 = 12.9 Hz, J_2 = 3.4 Hz, 1H, SCH_b). EIMS: *m*/*z* (relative intensity): 313 (M^+, 100). Anal. Calcd For $C_{17}H_{17}NO_4S$: C, 61.61; H, 5.17; N, 4.23. Found: C, 61.36; H, 5.35; N, 4.19.

3.1.30. (±)-*Trans*-4-(3,4-dimethoxyphenyl)thiochroman-3-amine (39)

Thionitrochroman **38** (3.69 g, 11.13 mmol) was dissolved in 150 mL of AcOH and 4.4 g (66.8 mmol) of powdered zinc were added. The mixture was stirred vigorously at room temperature for 16 h, at which time the reaction was filtered through Celite, and the filtered solids were rinsed on the filter with AcOH. The filtrate was concentrated to 1/3 of its volume and water (300 mL) was added. The aqueous solution was then basified with conc ammonium hydroxide and extracted with CH_2Cl_2 (3 × 40 mL). The organic extract was then washed twice with brine, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give 3.35 g (quant yield) of amine **39**: mp (HCl salt) 228–230 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.21–7.10 (m, 2H, 2ArH); 7.00–7.90 (m, 2H, 2ArH); 6.79 (d, J = 8.1 Hz, 1H, ArH); 6.63 (d, J = 1.5 Hz, 1H, ArH); 6.56 (dd, J_1 = 8.4 Hz, J_2 = 1.4 Hz, 1H, ArH); 3.97–3.88 (m, 1H, ArCH); 3.85 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3); 3.60–3.51 (m, 1H, $CHNH_2$); 3.11 (dd, J_1 = 12.6 Hz, J_2 = 2.4 Hz, 1H, SCH_a); 2.76 (dd, J_1 = 12.6 Hz, J_2 = 6.0 Hz, 1H, SCH_b). CIMS: *m*/*z* (relative intensity): 302 (M+H$^+$, 100). Anal. Calcd For $C_{17}H_{20}NO_2S$·HCl: C, 60.43; H, 5.97; N, 4.15. Found: C, 60.21; H, 5.95; N, 4.22.

3.1.31. (±)-*Trans*-2-chloro-*N*-(4-(3,4-dimethoxyphenyl)thiochroman-3-yl)acetamide (40)

Amine **39** (6.78 g, 22.5 mmol) was dissolved in 300 mL of CH_2Cl_2, and powd Na_2CO_3 (9.5 g, 90.0 mmol) was added. The reaction was cooled to 0 °C with stirring, and chloroacetyl chloride (7.6 g, 67.5 mmol) was added drop-wise to the reaction mixture. After stirring for 16 h at room temperature, water was added to quench the reaction. The mixture was extracted with CH_2Cl_2 (3 × 30 mL), the organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a dark oil, which upon crystallization from MeOH yielded 8.06 mg (94.8%) of acetamide **40**: mp 94–97 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.23–7.16 (m, 2H, 2ArH); 7.08–7.98 (m, 2H, 2ArH); 6.76 (d, J = 8.1 Hz, 1H, ArH); 6.72 (d, J = 2.1 Hz, 1H, ArH); 6.48 (dd, J_1 = 8.7 Hz, J_2 = 2.4 Hz, 1H, ArH); 4.65–4.58 (m, 1H, ArCH); 4.31–4.29 (m, 1H, CHNH); 4.03 (d, J = 1.8 Hz, 1H, CH_2Cl); 3.84 (s, 3H, OCH_3); 3.83 (s, 3H, OCH_3); 3.11 (dd, J_1 = 6.7 Hz, J_2 = 2.4 Hz, 1H, SCH_a); 2.76 (dd, J_1 = 6.7 Hz, J_2 = 1.1 Hz, 1H, SCH_b). CIMS: *m*/*z* (relative intensity): 378 (M+H$^+$, 35) 285 (M^+-NH_2COCH_2Cl, 25), 240 (M^+-2(OCH_3)Ph, 100). Anal. Calcd For $C_{19}H_{20}ClNO_3S$·0.38H_2O: C, 59.32; H, 5.44; N, 3.64. Found: C, 59.32; H, 5.40; N, 3.63.

3.1.32. (±)-*Trans*-11,12-dimethoxy-6a,7,9,13b-tetrahydrobenzo[*d*]thiochromeno[3,4-*b*]azepin-8(6*H*)-one (41)

A solution of chloroacetamide **40** (700 mg, 1.85 mmol) and $NaHCO_3$ (1.5 g, 17.9 mmol) in 500 mL of a mixture of 1:1 MeOH: H_2O was irradiated for 55 min at room temperature with a medium pressure mercury lamp, with cooling. The resulting solution was concentrated under reduced pressure, and the residue partitioned between water and CH_2Cl_2. The aqueous solution was extracted twice more with CH_2Cl_2. The pooled organic extract was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Silica gel flash column chromatography, eluting with 1:9 hexanes:EtOAc, provided a yellow oil that crystallized from EtOH to afford 43 mg (6.8%) of lactam **41**: mp >240 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.70 (d, J = 3.0 Hz, 1H, ArH); 7.30 (dd, J_1 = 6.6 Hz, J_2 = 0.9 Hz, 1H, ArH); 7.16 (dt, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1H, ArH); 7.16 (dt, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1H, ArH); 6.92 (s, 1H, ArH); 6.63 (s, 1H, ArH); 4.28–4.19 (m, 1H, 13b-H); 3.87–3.82 (m, 2H, 6a-H, 9-H_a); 3.80 (s, 3H, OCH_3); 3.63 (s, 3H, OCH_3); 3.23 (dd, J_1 = 11.1 Hz, J_2 = 5.7 Hz, 2H, 6-H_a, 9-H_b); 3.12 (t, J = 11.1 Hz, 1H, 6-H_b). CIMS: *m*/*z* (relative intensity): 342 (M+H$^+$, 100). Anal. Calcd For $C_{19}H_{19}NO_3S$·0.45H_2O: C, 65.29; H, 5.74; N, 4.01. Found: C, 65.29; H, 5.68; N, 3.97.

3.1.33. (±)-*Trans*-11,12-dimethoxy-6,6a,7,8,9,13b-hexahydrobenzo[*d*]thiochromeno[3,4-*b*]azepine (42)

Lactam **41** (120 mg, 0.35 mmol) was suspended in 50 mL of dry THF and 3.51 mL (3.51 mmol) of a 1 M solution of BH_3 in THF was added. This solution was stirred at reflux for 24 h, then cooled and quenched with excess MeOH. The solvent was removed under reduced pressure and the residue was then stirred for 4 h at reflux with 30 mL of 6 N ethanolic HCl solution. The solvent was removed and MeOH was added and removed under vacuum 3 times. The crude product was dissolved and EtOAc and extracted with aqueous 2 N HCl solution (3 × 30 mL). The combined aqueous layer was basified with 2 N NaOH solution and extracted with CH_2Cl_2 (3 × 20 mL). The organic solution was then dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to yield 80 mg (70%) of amine **42**: mp (HCl salt) 170–190 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.31–7.03 (m, 4H, 4ArH); 6.76 (s, 1H, ArH); 6.25 (s, 1H, ArH); 5.06 (d, J = 8.4 Hz, 1H, 13b-H); 4.90 (dd, J_1 = 8.6 Hz, J_2 = 4.3 Hz, 1H, 6a-H); 4.22 (t, J = 10.8 Hz, 1H, 6-H_a); 3.93 (s, 3H, OCH_3); 3.87–3.83 (m, 2H, 6-H_b, 8-H_a); 3.60 (s, 3H, OCH_3); 3.55–3.45 (m, 1H, 8-H_b); 3.05–2.98 (m, 2H, 9-H_2). ESIMS: *m*/*z* (relative intensity): 328 (M+H$^+$, 100). Anal. Calcd For $C_{19}H_{22}ClNO_2S$·1.26H_2O: C, 59.03; H, 6.39; N, 3.62. Found: C, 59.01; H, 6.61; N, 3.62.

3.1.34. (±)-*Trans*-6,6a,7,8,9,13b-hexahydrobenzo[*d*]thiochromeno[3,4-*b*]azepine-11,12-diol hydrobromide (10)

Amine **42** (50 mg, 0.153 mmol) was dissolved in 20 mL of CH_2Cl_2 and cooled to −78 °C. Into this flask, 0.54 mL (0.54 mmol) of a 1 M BBr_3 solution in CH_2Cl_2 was added drop-wise. This solution was then warmed to room temperature and stirred overnight. The reaction mixture was then cooled to 0 °C and 5 mL of MeOH were added drop-wise. The solvents were removed under reduced pressure, and 5 mL of MeOH were once again added and removed. The process was repeated one more time. The residue was then recrystallized from MeOH/EtOAc and dried under vacuum to afford 30 mg (51.7%) of the hydrobromide salt of **10**: mp >300 °C dec ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.96 (br s, 2H, NH_2^+); 8.75 (s, 1H, OH); 8.67 (s, 1H, OH); 7.31 (d, J = 7.3 Hz, 1H, ArH); 7.20 (t, J = 4.5 Hz, 1H, ArH); 7.15 (d, J = 4.5 Hz, 1H, ArH); 7.05 (d, J = 4.5 Hz, 1H, ArH); 6.61 (s, 1H, ArH); 5.56 (s, 1H, ArH); 4.71–4.69 (m, 1H, 13b-H); 3.51 (dd, J_1 = 11.9 Hz, J_2 = 1.2 Hz, 1H, 6a-H); 3.45–3.35 (m, 2H, 6-H_2); 3.05 (d, J = 11.5 Hz, 1H, 9-H_a); 2.91 (t, J = 12.5 Hz, 1H, 8-H_a); 2.81 (t, J = 12.5 Hz, 1H, 8-H_a); 2.73 (dd,, J_1 = 15.5 Hz, J_2 = 4.5 Hz, 1H, 9-H_b). ESIMS: *m*/*z* 300 (M+H$^+$, 100).

3.2. Pharmacology

3.2.1. Materials

Radioligands used for this study were [^{3}H]SCH23390 (73.1 Ci/mmol), [^{3}H]-*N*-methylspiperone (75 Ci/mmol), and [^{3}H] cyclic

AMP (30 Ci/mmol) and were purchased from PerkinElmer Life Sciences (Massachusetts, United States). Test ligands used were chlorpromazine, SKF38393, SCH23390, (+)-butaclamol, dopamine hydrochloride and all were purchased from Sigma–Aldrich Chemical Company (St. Louis, MO, United States). SCH 39166 and ketanserin were purchased from Tocris Bioscience (Ellisville, MO, United States). DHX was previously synthesized in our laboratory.[16] Striatal tissue used for competition binding experiments was dissected from porcine brain tissue obtained from Purdue Butcher Block and prepared as described previously.[17]

3.2.2. Competition binding experiments

Competition binding experiments were done with porcine striatal tissue and utilized 1.5 nM [^{3}H]SCH23390 for D_1-like binding and 0.2 nM [^{3}H]-*N*-methylspiperone for D2-like binding. For D2-like binding, 50 nM ketanserin was included to block native 5-HT_{2A} receptors. All experiments were performed with receptor binding buffer (50 mM HEPES, 4 mM $MgCl_2$, pH 7.4) and used 96 well assay tubes with drug dilutions, radioligand, and 75 μg porcine striatal membrane protein per tube. Nonspecific binding was defined in the presence of 5 μM (+)-butaclamol. All experiments were incubated at 37 °C for 30 min and terminated by rapid filtration with a 96-well Packard Filtermate cell harvester with ice cold wash buffer (10 mM Tris, 0.9% NaCl). Filter plates were dried and 40 μL of Packard Microscint-O was added to each filter well. Radioactivity was counted as counts per minute (CPM) using a Packard Topcount scintillation counter.

3.2.3. Cell line and culture methods

Human embryonic kidney cells (HEK 293) stably transfected with pcDNA V5 His TOPO subcloned with the human dopamine D_1 receptor (hD1) were used to assess cAMP accumulation. The hD1 receptor expressed at approximately 1800 fmol/mg protein, as determined by saturation binding with [^{3}H]SCH23390. Cells were grown in DMEM supplemented with 5% fetal clone serum, 5% bovine calf serum, 100 U/mL Penicillin, 100 μg/mL streptomycin, 0.25 μg/mL amphotericin B, and maintained in 100 μg/mL G418 for selection of hD1. Cells were grown at 37 °C in a humidified incubator with 5% CO_2.

3.2.4. Cyclic AMP accumulation assay

Cells were seeded into 96 wells and allowed to grow to 90–95% confluency until the day of the assay. All drug dilutions were made in EBSS assay buffer (Earle's balanced salt solution containing 2% bovine calf serum, 0.025% ascorbic acid, and 15 nM HEPES pH 7.4). First, all media was decanted and 500 μM isobutylmethylxanthine (IBMX) in EBSS buffer was added to all wells. Next, drug dilutions were added in duplicate, and allowed to incubate for 15 min in a 37 °C water bath. Cyclic AMP accumulation assays were terminated by decanting the media followed by addition of 3% trichloroacetic acid. Plates were stored at 4 °C for at least 24 h until quantification of cyclic AMP using the cyclic AMP binding assay.

3.2.5. Cyclic AMP binding assay

Cyclic AMP accumulation assays were quantified using a previously described protocol.[20] Cellular lysate was added to 96 well assay tubes containing [^{3}H]cAMP (1 nM final concentration) and bovine adrenal gland cAMP binding protein (100–150 μg in 500 μL of buffer) diluted in cAMP binding buffer (100 mM Tris–HCl, pH 7.4, 100 mM NaCl, 5 mM EDTA). Assay tubes were allowed to incubate on ice at 4 °C for 2 h, and terminated by harvesting with ice-cold wash buffer (10 mM Tris, 0.9% NaCl) using a 96-well Packard Filtermate cell harvester. Filter plates were dried, 40 μL of Packard Microscint-O was added to each well, and radioactivity was counted using a Packard Topcount scintillation counter. Standard curves ranging from 0.01 to 300 pmol of cAMP were used to estimate the concentration of cAMP in each cell lysate sample.

3.2.6. Data analysis

Nonlinear regression for radioligand displacement and dose–response curves was performed using GraphPad Prism, version 4.00 for Windows (GraphPad Software, San Diego California USA, www.graphpad.com.) For radioligand displacement, Hill slopes were fixed and the bottoms of curves were set to nonspecific binding values to generate IC_{50} values for test compounds. K_i values were calculated by the Cheng-Prusoff equation using the radioligand concentration and previously established porcine striatal K_d values of 0.44 and 0.075 nM for D_1- and D_2-like binding, respectively. For cAMP dose–response curves, nonlinear regression sigmoidal dose–response analysis (variable slope) was used to generate EC_{50} values. Intrinsic activity (IA) was calculated as percent maximum response of cAMP accumulation compared to 10 μM dopamine.

3.3. Molecular modeling

Molecules were minimized as the protonated species in a vacuum using Spartan '10 for Windows, version 1.0.1 (Wavefunction Inc., Irvine, CA). All possible conformers of each molecule were manually constructed and geometry optimized using the semi-empirical AM-1 potentials in Spartan. The lowest energy structure obtained for each molecule was then selected and geometry optimized using Hatree-Fock, with 6-31G* force fields.

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