Bioorganic & Medicinal Chemistry 18 (2010) 6763–6770

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Facile synthesis of octahydrobenzo[*h*]isoquinolines: Novel and highly potent D_1 dopamine agonists

Lisa A. Bonner [†], Benjamin R. Chemel, Val J. Watts, David E. Nichols [*]

Department of Medicinal Chemistry and Molecular Pharmacology, School of Pharmacy and Pharmaceutical Sciences, Purdue University, 575 Stadium Mall Drive, West Lafayette, IN 47907, United States

ARTICLE INFO

Article history:
Received 12 May 2010
Revised 16 July 2010
Accepted 22 July 2010
Available online 27 July 2010

Keywords:
Dopamine agonist
Tetrahydroisoquinoline
Conjugate addition
Oxazoline

ABSTRACT

The octahydrobenzo[*h*]isoquinoline scaffold is of interest as a conformationally-restricted phenethylamine that may be useful for constructing biologically active products. Surprisingly, however, no tractable synthesis of this ring system has been reported. We now describe a facile method for obtaining this framework, and illustrate that our approach is easily amenable to substitutions at the 5-position. Importantly, we demonstrate that the 7,8-dihydroxy-5-phenyl-substituted ligand is an extremely potent, high-affinity, full D_1 dopamine receptor-selective agonist.

1. Introduction

Dopamine (DA) is a monoamine neurotransmitter that is important in locomotor control, reward circuitry, cognitive and endocrine function, and plays a role in a variety of other key physiological processes. Dopaminergic dysfunctions have been implicated in Parkinson's disease, schizophrenia, addiction, attention deficit hyperactivity disorder (ADHD), and certain sexual disorders.[1] Useful dopaminergic therapeutics result, however, only when a thorough understanding is gained of the particular system and dopamine receptor isoforms that are involved. One approach that we have found most useful to aid in identifying the critical receptor types involves the design and use of conformationally-restricted analogues.[2–8] Conformationally-restricted analogues can be especially powerful when combined with computationally-derived receptor models and conformational analysis,[9–11] as well as site-directed mutagenesis.[12,13]

Nearly three decades ago, Joseph Cannon and his colleagues investigated the pharmacological activities of different rotamers of DA using rigid analogues designed around an octahydrobenzoquinoline or an octahydrobenzoisoquinoline framework. One of his conclusions was that the amine nitrogen needed to be coplanar with, and anti with respect to the catechol ring[14] (Fig. 1). He also showed that *trans* ring fusions, which confer a rigid and relatively planar structure, were more active than the corresponding *cis* ring fusions, which cannot simultaneously adopt both an anti and planar conformation.[3] His conclusions[15] were extremely important in the early SAR work on DA pharmacology and many have been consistently validated over the years, but his studies were carried out in an era prior to more modern insight into the existence of different DA receptor subtypes (although Cannon does suggest that multiple receptor types would explain some of his observations.[15])

About the same time as Cannon's work, Kebabian and Calne discovered that there were two classes of DA receptor, which they named D_1 and D_2.[16] In order to study the different receptor classes, highly selective agonists and antagonists were needed. Because of their potential for treating Parkinson's disease[17] and improving cognition,[18] selective D_1 dopamine receptor agonists (Fig. 2) should be prime therapeutic candidates for the pharmaceutical industry and have been a major focus of our research for more than three decades. The first high-affinity D_1-selective agonist discovered

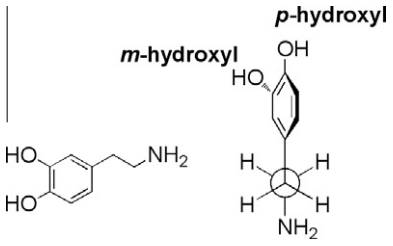

Figure 1. *trans*-β-Dopamine.

* Corresponding author. Tel.: +1 765 494 1461; fax: +1 765 494 1414.
E-mail addresses: DRDAVE@PURDUE.EDU, drdave@pharmacy.purdue.edu (D.E. Nichols).
† Present address: Department of Chemistry, Saint Anselm College, 100 Saint Anselm Drive #1709, Manchester, NH 03102, United States.

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doi:10.1016/j.bmc.2010.07.052

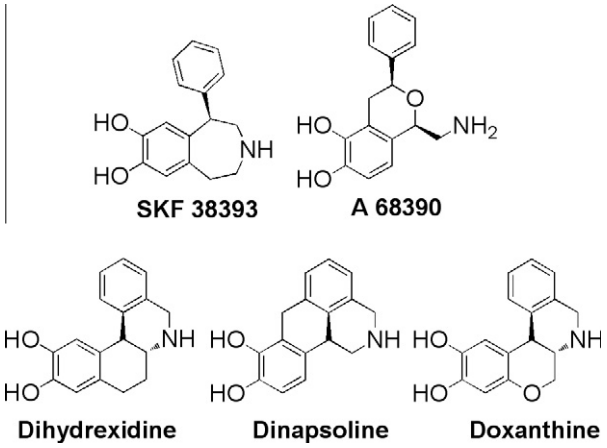


Figure 2. Known D_1-like dopamine agonists.

was SKF38393,[19,20] but it proved to be only a partial agonist at DA D_1 receptors. Abbott Laboratories subsequently developed a series of potent isochroman compounds, many of which showed significant D_1 selectivity.[21,22] Our laboratory discovered the first D_1-selective full agonist, dihydrexidine,[2,23] followed by dinapsoline,[24,25] dinoxyline,[26] and more recently the highly D_1-selective full agonist, doxanthrine.[27]

Much effort has been invested by our laboratory, and others, to determine the requirements for D_1 receptor subtype selectivity. Mottola et al.[10] used the Active Analogue Approach to map out the spatial requirements of the D_1 pharmacophore. It was proposed to include a catechol ring with the meta hydroxyl 7 Å away from the amine nitrogen, with the ethylamine side chain in the *trans*-β-rotameric conformation, as first defined by Cannon.[15] Interestingly, Cannon asserted that this was the ''wrong' conformation of dopamine'[16] for the assays he was using, which one may now conclude to have been D_2-like mediated biological responses. The D_1 pharmacophore model also calls for an accessory ring, typically a phenyl ring, attached at the side chain β carbon, and in near coplanarity with the catechol ring.

Taking all of these points into consideration, as well as prior SAR studies, we proposed the synthesis of 7,8-dihydroxyoctahydrobenzo[*h*]isoquinoline compounds (Fig. 3), all of which possess the *trans*-β-rotameric conformation of dopamine, and are the subject of this report. We predicted that the *cis* compound **1** would have low affinity at both DA receptor subtypes, but that the *trans* phenyl compound **3** would be a D_1-selective agonist due to the presence of the phenyl ring, which we anticipated was positioned to engage the postulated accessory binding region in the receptor. Although the appended phenyl ring is not directly connected to the β carbon of the embedded dopamine moiety, we still predicted that **3** would possess D_1 selectivity because the overall distance from the centroid of the appended phenyl ring to the meta hydroxyl group is not significantly different from our working model. Furthermore, potent and D_1-selective isochroman compounds prepared at Abbott laboratories[21,22] possessed accessory groups in the comparable position.

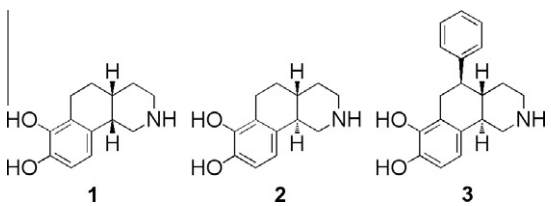


Figure 3. Target compounds: octahydrobenzo[*h*]isoquinolines **1**, **2**, and **3**.

Oppolzer originally published a method for the synthesis of benzo[*h*]isoquinolines,[28] which was subsequently adapted by Cannon et al.[6] for the preparation of an 8,9-dioxygenated compound. Oppolzer's method, however, relies on intramolecular thermal rearrangements to build the tricyclic ring system, and difficultly-accessible benzocyclobutene intermediates are required. The *cis* ring junctions were often the major products and the cyclic rearrangements were highly sensitive to heteroatom substitutions. Cannon's adaptation worked specifically for an 8,9-dioxygenation substitution pattern, but overall this approach was not a general one, and in particular did not allow for 5-substituted compounds. Subsequently, Napier and Griffith,[29] patented a series of 6-substituted octahydrobenzo[*h*]isoquinolines as antidepressant agents. Their general synthetic approach, however, was more broadly applicable than that of Oppolzer and was modified for the preparation of target compounds **1**–**3**.

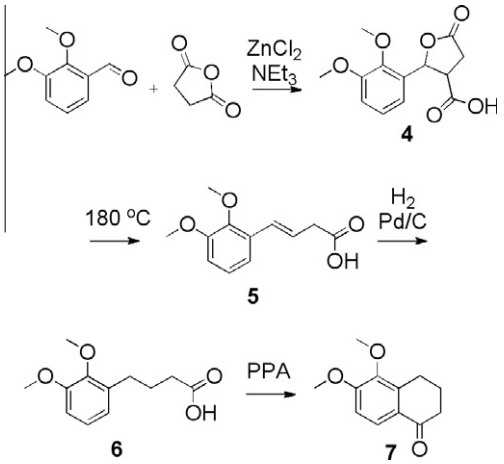
2. Results

2.1. Chemistry

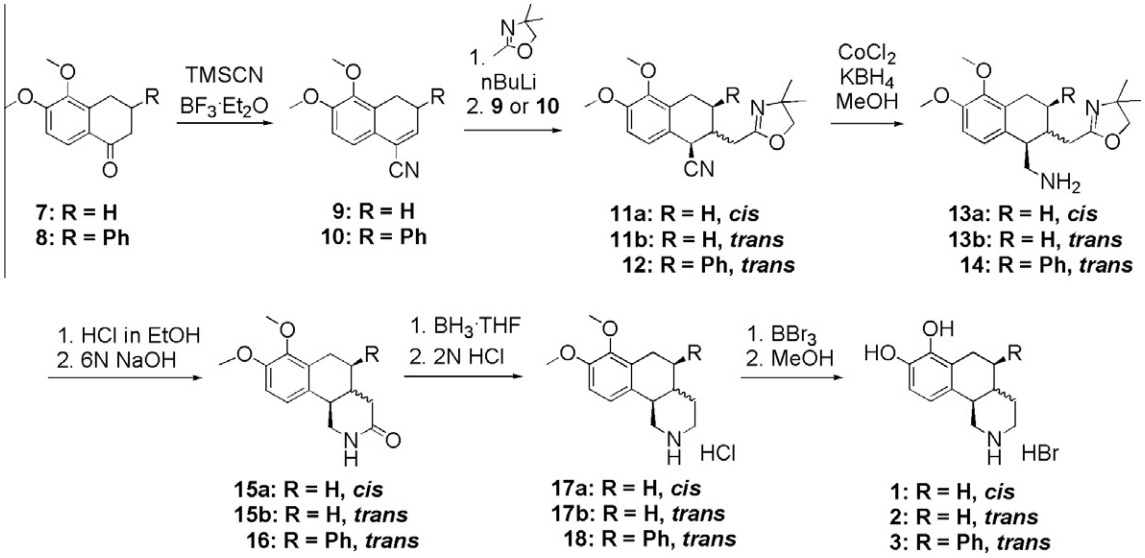
An initial goal of this project was to develop an improved and high-yielding synthesis of tetralone **7** (Scheme 1).[30,31] We envisioned that this ketone could then be functionalized to allow annulation of the desired heterocyclic ring. The first step of our synthesis of **7** was the formation of paraconic acid **4** from commercially available 2,3-dimethoxybenzaldehyde and succinic anhydride.[32] Pure, crystalline **4** was heated at 180 °C to effect both ring opening and decarboxylation. The unsaturated acid **5** was then catalytically hydrogenated and the reduced acid was treated with polyphosphoric acid to form **7** in nearly quantitative yield over two steps.

We envisioned that the phenyl tetralone **8** could be made in a parallel manner using phenyl succinic anhydride and 2,3-dimethoxybenzaldehyde. The paraconic acid formed as expected; however, all of our decarboxylation attempts yielded decomposed material, with no evidence of gas evolution. We were able to synthesize large quantities of **8**, however, using a procedure similar to one reported by Abbott Laboratories.[33]

Scheme 2 illustrates construction of the tricyclic ring system from the alpha tetralone. Our approach was inspired by Simonelli et al.,[34] who used lithiated 2,4,4-trimethyl-2-oxazoline to prepare γ amino acids. Realizing that unsaturated nitriles can serve as Michael acceptors for carbon nucleophiles,[35,34] we envisioned that this method could be modified to prepare desired lactam **15**. That is, tetralone **7** was converted into unsaturated nitrile **9** by treat-



Scheme 1. Synthesis of intermediate **7** by paraconic acid decarboxylation.



Scheme 2. Synthesis of target compounds **1**, **2**, and **3** by conjugate addition to unsaturated nitriles.

ment with trimethylsilylcyanide and boron trifluoride etherate (Scheme 2).[36] Lithiation of 2,4,4-trimethyl-2-oxazoline, followed by addition of the resulting carbanion to **9**, afforded nearly equal amounts of the diastereomers from both the *cis* and the *trans* addition. This reaction also was attempted with an organocuprate reagent, anticipating that it might favor the desired *trans* addition, but it also yielded a nearly equal mixture of diastereomers, albeit in much lower yield. Fortunately, the *cis* and the *trans* addition products could be cleanly separated by column chromatography and each was carried forward in parallel syntheses. The stereochemistry of the addition products was confirmed by the ^{1}H NMR signal corresponding to the methine proton alpha to the cyano group. The *cis* addition product appeared as a doublet with a *J* value of 4.5 Hz, whereas the stereoisomer identified as *trans* had an equivalent signal with a *J* value of 9.3 Hz.

We were able to reduce the nitriles **9** to the amines **11** in high yield using cobalt boride[37] without the epimerization that occurred when lithium aluminum hydride or Raney nickel were employed. Highest yields were achieved using potassium borohydride, rather than sodium borohydride, possibly due to its higher stability in methanol. The lactams **15** were then formed in one step by hydrolysis of the oxazoline moiety in acidic ethanol, followed by quenching in aqueous sodium hydroxide. Reduction to the isoquinolines **17**, followed by demethylation yielded the catechols **1** and **2** as hydrobromide salts.

The synthesis of the phenyl substituted isoquinoline followed the same steps as the unsubstituted compounds. The only notable difference was that the separation of the *cis* and *trans* oxazoline-addition products was readily accomplished by fractional crystallization. The *trans* isomer was the only one carried forward through the rest of the synthesis because the prior literature had shown that *cis*-fused polycyclic dopamine analogues invariably lacked biological activity. The hydrobromide salt of catechol **3** was prepared, and all three compounds were submitted for pharmacological assessment.

2.2. Pharmacology

The receptor binding properties of these new compounds at dopamine receptors are presented in Table 1. As anticipated, *cis* compound **1** had poor affinity at both classes of receptors, whereas **2** had slightly higher affinity at D_2-like receptors than at D_1-like receptors. When the phenyl substituent was incorporated into the ligand, **3**, the affinity at D_1-like receptors increased significantly, with a K_i of 6 nM, threefold better than doxanthrine (DOX).[27]

Because **3** had such high affinity at D_1-like receptors, its potency and intrinsic activity at cloned human D_1 receptors also was evaluated in comparison with DHX and DOX (Table 2). These results indicate that not only is **3** a full agonist at D_1 receptors, but it also is 6–7-fold more potent at these receptors than either DHX or DOX. The compound was then submitted to the NIMH-sponsored PDSP program for screening against a panel of other brain receptors http://PDSP.MED.UNC.EDU/. It had low affinities (>1 μM) for all but a small subset of targets, which included the following (K_i value, nM): 5-HT_3 (870), 5-HT_7 (220), α_{1A} (340), α_{2A} (3.5), α_{2B} (6.4), α_{2C} (1.1), and KOR (820). Affinities reported from the PDSP screens for dopamine receptors were: D_1 (18), D_2 (750), D_3 (130), D_4

Table 1
Binding affinity at porcine striatal homogenates[a]

Ligand	D_1-like (K_i, nM)	D_2-like (K_i, nM)	Fold D_1-like selectivity
DOX	18 ± 0.6	4400 ± 620	240
1	6800 ± 490	2800 ± 210	0.4
2	850 ± 65	670 ± 36	0.8
3	6 ± 0.2	440 ± 72	73
SCH[b]	0.79 ± 0.1	ND	
CPZ[c]	ND	3.2 ± 0.5	

[a] All results shown are the mean ± SEM for at least three independent experiments.
[b] SCH-23390.
[c] Chlorpromazine.

Table 2
Potency[a] at cloned hD_1 receptors

Ligand	EC_{50} (nM)	I.A. (%)
Dopamine	20 ± 1	100 ± 0
DHX	3.9 ± 0.5	107 ± 3
DOX	4.3 ± 0.6	98 ± 3
3	0.64 ± 0.1	103 ± 7

[a] All results shown are the mean ± SEM for at least four independent experiments. I.A. is intrinsic activity, the maximum stimulation observed relative to the response of dopamine, which is defined as 100% I.A.

(2650), and D_5 (2.8). Thus, based on affinities, the D_1-like affinity that we measured in porcine striatal homogenate likely reflects a large high-affinity component contributed by the D_5 receptor. We might note that to date no one has yet succeeded in discovering a D_1- or D_5-selective agonist molecule, and all known 'D_1 agonists' are nonselective D_1/D_5 agonists, most often with a small preference for D_5 receptors. The affinities at the α_2 subtypes are similar to what we have found with other D_1 agonists, and may reflect some structural similarities between the D_1 and α_2 receptors. For example, doxanthrine has affinities at the α_{2B} and α_{2C} receptors of 10 and 2 nM, respectively.[27] Surprisingly, resolution of the enantiomers of that compound revealed that the affinity for the D_1 receptor resides primarily in the (+) enantiomer, whereas the affinity for the α_{2C} receptor was in the (−) enantiomer.[38] Thus, studies are now underway to resolve **3** into its enantiomers to determine whether a similar reversed stereoselectivity occurs.

3. Discussion

Our concepts of the binding requirements in the orthosteric binding site of D_2-like versus D_1-like receptors have been further validated by the results of the present study, which are consistent with our initial predictions. That is, that *cis* compound **1** would have the lowest affinity at either class of receptors, and that the phenyl substituent on **3** would interact favorably with the accessory binding region of the D_1 receptor binding pocket to afford a ligand with increased affinity at D_1-like receptors. Not only does **3** possess higher affinity at the D_1-like receptors than other ligands such as DOX, it is 73-fold selective for D_1-like receptors over D_2-like receptors, and is 6–7-fold more potent than any previous full D_1 dopamine agonist discovered. We can say with confidence that our new ring system constricts the ethylamine side chain of the imbedded dopamine moiety into the conformation required to activate the D_1-like receptors, further refining our model of the D_1-like receptor binding pocket.

4. Conclusion

We have developed a tractable method for synthesizing the previously unreported 7,8-dihydroxyoctahydrobenzo[*h*]isoquinolines. This method is amenable to preparing analogues bearing substituents at the 5-position, as illustrated by the synthesis of **3**. This latter molecule is a novel, rigid dopaminergic full agonist ligand with high-affinity and very high potency at D_1-like receptors and significant selectivity over D_2-like receptors. In addition, screening indicated that **3** also has high-affinity at α_2 adrenergic receptors. The practical consequences of this finding are unclear but it is known that stimulation of α_2 adrenergic receptors in prefrontal cortex has a beneficial effect on spatial working memory performance (Ref. 39 and citations contained therein). Thus, this framework will serve as the lead scaffold for further structure–activity relationship studies of ligands for the various dopamine receptor isoforms.

5. Experimental

5.1. Chemistry

5.1.1. 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 using a Mel-Temp apparatus and are reported as uncorrected values. ^{1}H NMR spectra were recorded using a 300 MHz Bruker ARX300 NMR spectrometer or 500 MHz Bruker DRX500 NMR spectrometer, as noted. Chemical shifts are reported in δ values (ppm) relative to an internal reference (0.03%, v/v) of tetramethylsilane (TMS) in $CDCl_3$, except where noted. Abbreviations used to report NMR peaks are as follows: br s = broad singlet, d = doublet, dd = doublet of doublets, m = multiplet, q = quartet, s = singlet, t = triplet. Chemical ionization mass spectra (CIMS) using isobutane as a carrier gas were obtained with a Finnigan 4000 spectrometer. Elemental analyses were performed by the Purdue University Microanalysis Laboratory or Midwest Microlabs. All reactions were carried out under an argon atmosphere, unless noted otherwise.

5.1.1.1. 2-(2,3-Dimethoxyphenyl)-5-oxo-tetrahydrofuran-3-carboxylic acid, 4. To a flame-dried three-neck flask fitted with a condenser and dried addition funnel were added 25.0 g (0.184 mol) of anhydrous, powdered zinc chloride. To this solid were added 100 mL CH_2Cl_2, followed by 15.3 g (0.092 mol) of 2,3-dimethoxybenzaldehyde and 13.8 g (0.138 mol) succinic anhydride. Triethylamine (25.6 mL, 0.184 mol) was added dropwise to the flask with rapid stirring. The reaction was heated at reflux for 4 days, then cooled to room temperature and poured over ice-cold 6 N HCl. The organic component was extracted with EtOAc (3 × 250 mL), then washed with 2 N HCl (1 × 250 mL), and brine (1 × 250 mL). The product was extracted with saturated $NaHCO_3$ (4 × 200 mL) until TLC indicated no product remained in the organic layer. The aqueous layer was washed with CH_2Cl_2 (1 × 200 mL) and acidified with concd 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 18.0 g (0.068 mol, 74%) of pale yellow solid that was recrystallized from EtOAc–hexanes; mp 129–130 °C (lit.[40] mp 132 °C). ^{1}H NMR: (300 MHz, $CDCl_3$): δ 7.01 (t, 1H, *J* = 7.5 Hz, Ar*H*); 6.89 (dd, 1H, *J* = 2.5, 8.1 Hz, Ar*H*); 6.82 (dd, 1H, *J* = 2.5, 8.1 Hz, Ar*H*); 5.73 (d, 1H, *J* = 6.6 Hz, ArC*H*); 3.81 (s, 3H, ArOCH_3); 3.80 (s, 3H, ArOCH_3); 3.44 (dt, 1H, *J* = 6.6, 8.5 Hz, C*H*CO_2H); 2.90 (d, 2H, *J* = 8.5 Hz, COCH_2). EIMS: (M^+) = 266.

5.1.1.2. 4-(2,3-Dimethoxyphenyl)but-3-enoic acid, 5. To a one-neck round bottom flask were added 8.6 g (0.032 mol) of recrystallized **4** and the solid was heated on a 180 °C oil bath for 6 h. Carbon dioxide 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 approximately 4.2, whereas the pK_a of the paraconic acid is approximately 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 and extraction were repeated until there was no turbidity at pH 4.0. Unreacted starting material was then recovered by acidifying to pH 3.0 and extracting with CH_2Cl_2. The organic extracts containing product were dried over Na_2SO_4, and evaporated under reduced pressure to yield pure **11**, which solidified under reduced pressure to provide a yellow solid (4.7 g, 0.021 mol, 65%) that was used without further purification; mp 84–86 °C (no lit.[41] mp reported). ^{1}H NMR: (300 MHz, $CDCl_3$): δ 7.08 (dd, 1H, *J* = 1.2, 8.0 Hz, Ar*H*); 6.99 (t, 1H, *J* = 8.0 Hz, Ar*H*); 6.80 (m, 2H, Ar*H* and ArC*H*=CH); 6.29 (dt, 1H, *J* = 7.2, 15.9 Hz, ArCHC*H*); 3.84 (s, 3H, ArOCH_3); 3.78 (s, 3H, ArOCH_3); 3.32 (dd, 2H, *J* = 1.2, 7.2 Hz, CH_2COOH). ESIMS: ($M+Na^+$) = 245.

5.1.1.3. 4-(2,3-Dimethoxyphenyl)butanoic acid, 6. A 500 mL Parr hydrogenation flask containing 0.6 g of 10% Pd/C and **5** (3.7 g, 0.017 mol) dissolved in 100 mL absolute EtOH was pressurized with H_2 gas and shaken at 25 psi H_2 for 2 h. The contents were filtered through Celite, the solvents were evaporated, and the resulting oil was dried under high vacuum to yield a gray solid (3.7 g, 0.017 mol, quant. yield). The solid was recrystallized from EtOAc–hexanes to produce fine white needles (2.2 g, 59.5%); mp 58–59 °C (lit.[30] mp. 58.5–60 °C). ^{1}H NMR: (300 MHz, $CDCl_3$): δ 6.97 (t, 1H, J = 8.1 Hz, Ar*H*); 6.76 (d, 1H, J = 8.1 Hz, Ar*H*); 6.75 (d, 1H, J = 8.1 Hz, Ar*H*); 3.84 (s, 3H, ArOCH_3); 3.80 (s, 3H, ArOCH_3); 2.67 (t, 2H, J = 7.2 Hz, $CH_2CH_2CO_2H$); 2.37 (t, 2H, J = 7.2 Hz, ArCH_2); 1.92 (p, 2H, J = 7.2 Hz, C$H_2CH_2CO_2H$). ESIMS: (M+Na$^+$) = 247.

5.1.1.4. 5,6-Dimethoxy-3,4-dihydronaphthalen-1(2*H*)-one, 7. A mechanically stirred flask charged with 15 g polyphosphoric acid was heated on a 60 °C oil bath for 20 min. Powdered **6** (1.0 g, 4.46 mmol) was added in small portions to 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 collected by filtration and washed with water to yield pearly off-white plates (900 mg, 4.37 mmol, 98%); mp 103–104 °C (lit.[30] mp 104–105 °C) ^{1}H NMR: (300 MHz, $CDCl_3$): δ 7.79 (d, 1H, J = 8.7, Ar*H*); 6.81 (d, 1H, J = 8.7, Ar*H*); 3.86 (s, 3H, ArOCH_3); 3.75 (s, 3H, ArOCH_3); 2.89 (t, 2H, J = 6.3 Hz, ArCH_2); 2.53 (t, 2H, J = 6.3 Hz, C(O)CH_2); 2.05 (p, 2H, J = 6.3 Hz, $CH_2CH_2CH_2$). EIMS: (M^+) = 206.

5.1.1.5. 5,6-Dimethoxy-3,4-dihydronaphthalene-1-carbonitrile, 9. TMSCN (1.42 mL, 10.7 mmol) was added dropwise to a slurry of **7** (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, and was then quenched by pouring over 30 mL ice water with vigorous stirring. To this aqueous mixture were added 20 mL of Et_2O. 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, 7.9 mmol, 96%) that could be recrystallized from MeOH to yield fine, colorless needles in 84% yield over three crops; mp 138–140 °C (lit.[42] mp 137–139 °C). ^{1}H NMR: (300 MHz, $CDCl_3$): δ 7.18 (d, 1H, J = 8.1 Hz, Ar*H*); 6.80 (d, 1H, J = 8.1 Hz, Ar*H*); 6.75 (t, 1H, J = 4.6 Hz, ArCH$_2$CH$_2$C*H*); 3.88 (s, 3H, ArOCH_3); 3.76 (s, 3H, ArOCH_3); 2.87 (t, 2H, J = 8.1 Hz, ArCH_2); 2.44 (m, 2H, ArCH$_2$CH_2). EIMS: (M^+) = 215.

5.1.1.6. 5,6-Dimethoxy-3-phenyl-3,4-dihydronaphthalene-1-carbonitrile, 10. TMSCN (1.20 mL, 9.22 mmol) was added to a solution of phenyl tetralone **8** (2.00 g, 7.09 mmol) in dry toluene (100 mL). $BF_3{\cdot}OEt_2$ (1.34 mL, 10.6 mmol) was then added slowly through a syringe and the reaction was stirred at ambient temperature overnight. The mixture was poured into 100 mL cold H_2O and extracted with EtOAc (3 × 50 mL). Column chromatography (2:1 EtOAc/hexanes) was used to purify the product and also to recover 0.674 g (2.39 mmol) of unreacted starting tetralone. The unsaturated nitrile (1.31 g, 4.50 mmol, 63.6%; 96% BRSM) was obtained as a white powder; mp 106–107 °C. ^{1}H NMR: (300 MHz, $CDCl_3$): δ 7.36–7.21 (m, 6H, Ph*H*, Ar*H*); 6.84 (d, 1H, J = 8.7 Hz, Ar*H*); 6.78 (d, 1H, J = 3.9 Hz, C=C*H*); 3.90 (s, 3H, ArOCH_3); 3.81 (ddd, 1H, J = 3.9, 7.2, 11.4 Hz, ArCH$_2$C*H*); 3.71 (s, 3H, ArOCH_3); 3.35 (dd, 1H, J = 7.2, 16.5 Hz, ArCH_2); 2.92 (dd, 1H, J = 11.4, 16.5 Hz, ArCH_2). EIMS: (M^+) = 291. Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.21; H, 5.91; N, 4.89.

5.1.1.7. *cis*- and *trans* -2-((4,4-Dimethyl-2-oxazolin-2-yl)methyl)-5,6-dimethoxy-1,2,3,4-tetrahydro-naphthalene-1-carbonitrile, 11a, 11b. A solution of 2,4,4-trimethyloxazoline (Aldrich) (1.80 mL, 14.2 mmol) in 50 mL distilled THF was placed in a flask on a dry ice/acetone bath. A 2.0 M solution of *n*-BuLi in cyclohexane (7.55 mL, 15.1 mmol) was then added dropwise with a syringe. The solution slowly turned bright yellow and was stirred at −78 °C for 1 h. Nitrile **9** (2.03 g, 9.44 mmol) dissolved in distilled THF (50 mL) was added dropwise to the solution of lithiated oxazoline. The yellow color faded and the mixture was stirred at −78 °C for 2 h, followed by 1 h at ambient temperature. The reaction was then quenched by the addition of 50 mL of 10% NH_4OH in saturated aqueous NH_4Cl. The solution was extracted with Et_2O (3 × 25 mL), and the organic layers were combined and extracted with 2 N HCl (4 × 25 mL). The aqueous layer was basified with $NaHCO_3$, extracted with Et_2O, and the organic extract was dried over Na_2SO_4, filtered, and evaporated. This residue was separated by column chromatography (7:1 EtOAc/hexanes) to give the *cis* (R_f = 0.35, 0.990 g, 3.02 mmol, 32%) and *trans* (R_f = 0.28, 1.10 g, 3.35 mmol, 35.5%) addition products. The *cis* addition product was a colorless oil, but the *trans* product formed colorless needlelike crystals upon standing; mp 92–94 °C. *cis* **11a**: ^{1}H NMR: (300 MHz, $CDCl_3$): δ 6.96 (d, 1H, J = 8.7 Hz, Ar*H*); 6.77 (d, 1H, J = 8.7 Hz, Ar*H*); 4.18 (d, 1H, J = 4.5 Hz (*cis*), ArC*H*CN); 3.93 (s, 2H, OCH_2C(CH$_3$)$_2$); 3.83 (s, 3H, ArOCH_3); 3.77 (s, 3H, ArOCH_3); 3.00 (ddd, 1H, J = 2.4, 5.7, 18.0 Hz, ArCH_2); 2.72–2.60 (m, 1 H, ArCH_2); 2.56 (dd, 1H, J = 8.4, 15.9 Hz, CH_2C(N)O); 2.47 (dd, 1H, J = 6.3, 15.9 Hz, CH_2C(N)O); 2.46–2.32 (m, 1H, ArCH$_2$CH_2); 1.99–1.90 (m, 1H, ArCH(CN)C*H*); 1.83–1.68 (m, 1H, ArCH$_2$CH_2); 1.28 (s, 3H, C(CH_3)$_2$); 1.26 (s, 3H, C(CH_3)$_2$). EIMS: (M^+) = 328. Anal. Calcd for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.37; N, 8.53. Found: C, 69.41; H, 7.34; N, 8.36. *trans* **11b**: ^{1}H NMR: (300 MHz, $CDCl_3$): δ 7.11 (d, 1H, J = 8.4 Hz, Ar*H*); 6.80 (d, 1H, J = 8.4 Hz, Ar*H*); 3.93 (s, 2H, OCH_2C(CH$_3$)$_2$); 3.85 (d, 1H, J = 9.3 Hz (*trans*), ArC*H*CN); 3.83 (s, 3H, ArOCH_3); 3.77 (s, 3H, ArOCH_3); 2.90 (dt, 1H, J = 5.1, 17.7 Hz, ArCH_2); 2.75–2.63 (m, 1H, ArCH_2); 2.59 (dd, 1H, J = 4.8, 13.5 Hz, CH_2C(N)O); 2.50–2.33 (m, 2H, ArCH$_2$CH_2, CH_2C(N)O); 2.16–2.07 (m, 1H, ArCH(CN)C*H*); 1.59–1.45 (m, 1H, ArCH$_2$CH_2); 1.27 (s, 3H, C(CH_3)$_2$); 1.26 (s, 3H, C(CH_3)$_2$). EIMS: (M^+) = 328. Anal. Calcd for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.37; N, 8.53. Found: C, 69.21; H, 7.49; N, 8.39.

5.1.1.8. *trans* -2-((4,4-Dimethyl-2-oxazolin-2-yl)methyl)-5,6-dimethoxy-3-phenyl-1,2,3,4-tetrahydronaph-thalene-1-carbonitrile, 12. In a method analogous to the synthesis of **11** above, nitrile **10** (0.770 g, 2.65 mmol) was converted to the title compound. The *trans* isomer was crystallized from the crude mixture using 1:1 EtOAc/hexanes to yield 0.262 g (0.649 mmol, 25%) of a white powder. The mother liquor was further purified by column chromatography (1:1 EtOAc/hexanes) to isolate 0.378 g (0.936 mmol) of a mixture of the cis and trans isomers of the desired product, from which an additional 0.029 g (0.0718 mmol, 2.7%) of the *trans* isomer was crystallized; mp 131–133 °C. ^{1}H NMR: (300 MHz, $CDCl_3$): δ 7.39–7.19 (m, 6H, Ph*H*, Ar*H*); 6.88 (d, 1H, J = 8.7 Hz, Ar*H*); 4.57 (d, 1H, J = 10.5 Hz (*trans*), ArC*H*CN); 3.87 (s, 3H, ArOCH_3); 3.88–3.75 (m, 2H, OCH_2C(CH$_3$)$_2$); 3.74 (s, 3H, ArOCH_3); 3.22 (dd, 1H, J = 4.5, 16.8 Hz, ArCH_2); 3.03 (dt, 1H, J = 4.5, 11.4 Hz, ArCH$_2$C*H*); 2.81 (dd, 1H, J = 11.4, 16.8 Hz, ArCH_2); 2.72–2.61 (m, 1H, ArCH(CN)C*H*); 2.55 (dd, 1H, J = 3.9, 16.2 Hz, CH_2C(N)O); 2.55 (dd, 1H, J = 6.3, 16.2 Hz, CH_2C(N)O); 1.27 (s, 3H, C(CH_3)$_2$); 1.22 (s, 3H, C(CH_3)$_2$). EIMS: (M^+) = 404. Anal. Calcd for $C_{25}H_{28}N_2O_3$: C, 74.23; H, 6.98; N, 6.93. Found: C, 73.90; H, 7.01; N, 6.71.

5.1.1.9. *cis*-(2-((4,4-Dimethyl-2-oxazolin-2-yl)methyl)-5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-methanamine, 13a. A solution of *cis* nitrile **11a** (0.880 g, 2.68 mmol) in MeOH (30 mL) was placed in a flask and stirred on an ice bath. Solid $CoCl_2{\cdot}6H_2O$

(1.28 g, 5.36 mmol) was added and the mixture was stirred until all solids dissolved. KBH_4 (1.45 g, 0.0268 mol) was then added carefully in three portions over 10 min. The black solution was removed from the ice bath and stirred at ambient temperature for 1 h. The reaction was then quenched by the addition of 10 mL of concd HCl, and the bright blue solution was evaporated to near dryness. The residue was re-dissolved in H_2O (50 mL) and washed once with Et_2O (10 mL). The aqueous layer was basified with NH_4OH and extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and evaporated to yield the desired product (0.813 g, 2.45 mmol, 91%) as a white solid; mp 208 °C (decomp.). ^{1}H NMR: (300 MHz, $CDCl_3$): δ 6.82 (d, 1H, J = 8.4 Hz, Ar*H*); 6.76 (d, 1H, J = 8.4 Hz, Ar*H*); 3.84 (s, 3H, ArOCH_3); 3.79 (s, 3H, ArOCH_3); 3.59 (dd, 1H, J = 6.0, 15.6 Hz, CH_2NH$_2$); 3.50 (s, 2H, OCH_2C(CH$_3$)$_2$); 3.22 (dd, 1H, J = 10.8, 15.6 Hz, CH_2NH$_2$); 3.04–2.95 (m, 1H, ArCH_2); 2.88–2.79 (m, 1H, ArC*H*); 2.72–2.55 (m, 2H, CH_2C(N)O); 2.22–2.13 (m, 1H, ArCH$_2$CH$_2$C*H*); 2.11–2.01 (m, 1H, ArCH_2); 1.77–1.65 (m, 2H, ArCH$_2$CH_2); 1.28 (s, 3H, C(CH_3)$_2$); 1.26 (s, 3H, C(CH_3)$_2$). EIMS: (M^+) = 332. Anal. Calcd for $C_{19}H_{28}N_2O_3$ (0.5 equiv MeOH): C, 67.21; H, 8.68; N, 8.04. Found: C, 66.86; H, 8.35; N, 8.07.

5.1.1.10. *trans* -(2-((4,4-Dimethyl-2-oxazolin-2-yl)methyl)-5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methanamine, 13b. A procedure identical to that above was used to convert 0.500 g of *trans* nitrile **11b** (1.52 mmol) into the desired amine (0.480 g, 1.45 mmol, 94%), recovered as a white solid; mp 181 °C (decomp.). ^{1}H NMR: (300 MHz, $CDCl_3$): δ 6.93 (d, 1H, J = 8.4 Hz, Ar*H*); 6.78 (d, 1H, J = 8.4 Hz, Ar*H*); 4.18 (dd, 1H, J = 5.1, 15.3 Hz, CH_2NH$_2$); 3.84 (s, 3H, ArOCH_3); 3.80 (s, 3H, ArOCH_3); 3.53 (d, 1H, J = 17.4 Hz, OCH_2C(CH$_3$)$_2$); 3.49 (d, 1H, J = 17.4 Hz, OCH_2C(CH$_3$)$_2$); 3.17 (dd, 1H, J = 11.1, 15.3 Hz, CH_2NH$_2$); 3.03 (dd, 1H, J = 3.9, 17.4 Hz, ArCH_2); 2.70–2.56 (m, 1H, ArCH_2); 2.49 (dt, 1H, J = 5.1, 11.1 Hz, ArC*H*); 2.30 (dd, 1H, J = 4.2, 15.9, CH_2C(N)O); 2.04 (dd, 1H, J = 12.0, 15.9, CH_2C(N)O); 1.94–1.87 (m, 1H, ArCH$_2$CH_2); 1.77–1.62 (m, 1H, ArCH$_2$CH$_2$C*H*); 1.38 (dq, 1H, J = 3.0, 12.6 Hz, ArCH$_2$CH_2); 1.27 (s, 3H, C(CH_3)$_2$); 1.25 (s, 3H, C(CH_3)$_2$). EIMS: (M^+) = 332. Anal. Calcd for $C_{19}H_{28}N_2O_3$ (+0.33 equiv MeOH): C, 67.68; H, 8.62; N, 8.16. Found: C, 67.81; H, 8.43; N, 7.96.

5.1.1.11. *trans* -(2-((4,4-Dimethyl-2-oxazolin-2-yl)methyl)-5,6-dimethoxy-3-phenyl-1,2,3,4-tetrahydro-naphthalen-1-yl)methanamine, 14. Using the method employed for **13**, nitrile **12** (0.157 g, 0.389 mmol) was converted to the title compound (0.149 g, 0.365 mmol, 94%) as a white solid; mp 213 °C (decomp.). ^{1}H NMR: (300 MHz, $CDCl_3$): δ 7.40–7.22 (m, 5H, Ph*H*); 7.01 (d, 1H, J = 8.7 Hz, Ar*H*); 6.83 (d, 1H, J = 8.7 Hz, Ar*H*); 4.25 (dd, 1H, J = 5.4, 15.0 Hz, ArCHCH_2NH$_2$); 3.86 (s, 3H, ArOCH_3); 3.77 (s, 3H, ArOCH_3); 3.73 (br s, 2H, NH_2); 3.51–3.42 (m, 2H, OCH_2C(CH$_3$)$_2$); 3.30–3.21 (m, 2H, ArCH_2, ArCHCH_2NH$_2$); 2.85–2.46 (m, 3H, ArC*H*CH$_2$NH$_2$, ArCH_2C*H*); 2.01 (dq, 1H, J = 5.4, 11.1 Hz, ArCH$_2$CH(Ph)C*H*); 1.89–1.74 (m, 2H, CH_2C(N)O); 1.20 (s, 3H, C(CH_3)$_2$); 1.16 (s, 3H, C(CH_3)$_2$). ESIMS: (M+H^+) = 409. Anal. Calcd for $C_{25}H_{32}N_2O_3$ (0.66 equiv H_2O): C, 71.40; H, 7.99; N, 6.66. Found: C, 71.58; H, 7.70; N, 6.40.

5.1.1.12. *cis*-7,8-Dimethoxy-1,2,4,4a,5,6-hexahydrobenzo[*h*]isoquinolin-3(10b*H*)-one, 15a. *cis* Amine **13a** (0.530 g, 1.60 mmol) was dissolved in 30 mL of a 10% solution of H_2SO_4 in absolute EtOH and the solution was heated at 85 °C for 48 h. The reaction was cooled to room temperature, 30 mL H_2O were added and, with stirring, 6 N NaOH was added until a white solid formed and the reaction pH >12. The basic mixture was stirred for 15 min and the solid was collected by filtration to afford the desired lactam as an off-white solid (0.234 g, 0.870 mmol, 55%). The filtrate was extracted with EtOAc to recover an additional 0.100 g (0.372 mmol, 23%, total 78%) of product; mp 185–187 °C. ^{1}H NMR: (300 MHz, $CDCl_3$): δ 6.83 (d, 1H, J = 8.4 Hz, Ar*H*); 6.75 (d, 1H, J = 8.4 Hz, Ar*H*); 5.91 (br s, 1H, N*H*); 3.84 (s, 3H, ArOCH_3); 3.80 (s, 3H, ArOCH_3); 3.42–3.37 (m, 2H, CH_2NH); 3.19–2.99 (m, 2H, ArC*H*, ArCH_2); 2.80–2.63 (m, 2H, ArCH_2, C(O)CH_2); 2.33 (d, 1H, J = 17.1 Hz, C(O)CH_2); 2.32–2.21 (m, 1H, ArCH$_2$CH$_2$C*H*); 1.90–1.59 (m, 2H, ArCH$_2$CH_2). ESIMS: (M+H^+) = 262. HR ESIMS: calcd mass = 262.1443, actual mass = 262.1445.

5.1.1.13. *trans*-7,8-Dimethoxy-1,2,4,4a,5,6-hexahydrobenzo[*h*]isoquinolin-3(10b*H*)-one, 15b. In an identical fashion, 1.24 g (3.73 mmol) of the *trans* amine **13b** was converted into 0.656 g (2.51 mmol, 67%) of the *trans* lactam as a white solid; mp 240 °C (decomp.). ^{1}H NMR: (300 MHz, $CDCl_3$): δ 6.86 (d, 1H, J = 8.4 Hz, Ar*H*); 6.78 (d, 1H, J = 8.4 Hz, Ar*H*); 6.09 (br s, 1H, N*H*); 3.94 (dt, 1H, J = 4.1, 11.4 Hz, CH_2NH); 3.85 (s, 3H, ArOCH_3); 3.81 (s, 3H, ArOCH_3); 3.18 (t, 1H, J = 11.4, CH_2NH); 3.09 (dd, 1H, J = 3.9, 17.7 Hz, ArCH_2); 2.78 (dt, 1H, J = 5.4, 11.4, ArC*H*); 2.71–2.59 (m, 1H, ArCH_2); 2.60 (dd, 1H, J = 4.8, 17.4, COCH_2); 2.19 (dd, 1H, J = 12.3, 17.4, C(O)CH_2); 2.03–1.93 (m, 1H, ArCH$_2$CH_2); 1.90–1.74 (m, 1H, ArCH$_2$CH$_2$C*H*); 1.42 (dq, 1H, J = 5.4, 12.4 Hz, ArCH$_2$CH_2). ESIMS: (M+H^+) = 262. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.60; H, 7.01; N, 5.38.

5.1.1.14. *trans*-7,8-Dimethoxy-5-phenyl-1,2,4,4a,5,6-hexahydrobenzo[*h*]isoquinolin-3(10b*H*)-one, 16. Following the method for the synthesis of **15** above, amine **14** (0.200 g, 0.490 mmol) was converted into the desired lactam as a white solid (0.110 g, 0.326 mmol, 67%). The filtrate was extracted with EtOAc to recover an additional 0.032 g (0.095 mmol, 19%) of the product; mp >250 °C. ^{1}H NMR: (300 MHz, $CDCl_3$): δ 7.38–7.19 (m, 5H, Ph*H*); 6.93 (d, 1H, J = 8.7 Hz, Ar*H*); 6.82 (d, 1H, J = 8.7 Hz, Ar*H*); 5.98 (br s, 1H, N*H*); 4.00 (dt, 1H, J = 4.6, 11.4 Hz, CH_2NH); 3.86 (s, 3H, ArOCH_3); 3.78 (s, 3H, ArOCH_3); 3.37–3.21 (m, 2H, CH_2NHCOCH_2); 3.20 (dt, 1H, J = 5.1, 10.5 Hz, ArC*H*CH$_2$); 2.83 (dd, 1H, J = 12.3, 17.4 Hz, NHCOCH_2); 2.66 (dt, 1H, J = 4.2, 10.5 Hz, ArCH$_2$CH(Ph)C*H*); 2.23 (dd, 1H, J = 4.2, 17.1 Hz, ArCH_2); 2.17–2.04 (m, 1H, ArCH$_2$C*H*); 1.94 (dd, 1H, J = 12.6, 17.1 Hz, ArCH_2). ESIMS: (M+H^+) = 338. HR ESIMS: calcd mass = 338.1756, actual mass = 338.1753.

5.1.1.15. *cis*-7,8-Dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*h*]isoquinoline hydrochloride, 17a. A flame-dried single-neck flask was charged with 50 mL of distilled THF, and 0.130 g (0.498 mmol) of the *cis* lactam **15a** were added. A 1.0 M solution of BH_3 in THF (2.49 mL, 2.49 mmol) was added dropwise to the flask and the reaction was heated at reflux overnight. The reaction was then cooled to room temperature, quenched carefully with H_2O, and evaporated to about one-third the volume. Following the addition of 10 mL 2 N HCl, the solution was stirred at ambient temperature for 4 h. The aqueous solution was washed once with Et_2O, basified with NH_4OH, and extracted with CH_2Cl_2 (3 × 25 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and evaporated to yield a colorless residue, which was dissolved in Et_2O and acidified with 6 N HCl in EtOH. The solid that formed was collected by filtration to yield 0.084 g (0.297 mmol, 60%) of isoquinoline HCl **17a** as a white powder and crystallized from MeOH; mp 186 °C (decomp.). ^{1}H NMR: (500 MHz, DMSO-d_6): δ 8.80 (br s, 2H, NH_2); 6.87 (m, 2H, Ar*H*); 3.75 (s, 3H, ArOCH_3); 3.66 (s, 3H, ArOCH_3); 3.16 (dd, 1H, J = 4.2, 12.4 Hz, ArCHCH_2NH$_2$); 3.12–3.05 (m, 2H, CH_2NH$_2$CH_2); 2.99–2.82 (m, 3H, ArC*H*CH$_2$NH$_2$CH_2, ArCH_2); 2.59–2.48 (m, 1H, ArCH_2); 2.10–1.89 (m, 3H, ArCH$_2$CH_2C*H*CH$_2$); 1.72 (br d, 1H, J = 11.8 Hz, NH$_2$CH$_2$CH_2); 1.62–1.54 (m, 1H, ArCH$_2$CH_2). ESIMS: (M+H^+) = 248. Anal. Calcd for $C_{15}H_{22}ClNO_2$: C, 63.48; H, 7.81; N, 4.94. Found: C, 63.37; H, 7.79; N, 5.00.

5.1.1.16. *trans*-7,8-Dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*h*]isoquinoline hydrochloride, 17b. An identical procedure was used to convert 0.500 g (1.92 mmol) of *trans* lactam **15b** into 0.325 g (1.15 mmol, 60.0%) of the *trans* isoquinoline HCl **17b**, obtained as a white powder that was crystallized from MeOH; mp 228 °C (decomp.). ^{1}H NMR: (300 MHz, DMSO-d_6): δ 8.91 (br s, 2H, NH_2); 6.95 (d, 1H, J = 8.7 Hz, ArH); 6.86 (d, 1H, J = 8.7 Hz, ArH); 3.96 (d, 1H, J = 8.4 Hz, ArCHCH_2NH$_2$); 3.76 (s, 3H, ArOCH_3); 3.66 (s, 3H, ArOCH_3); 3.30 (d, 1H, J = 8.4 Hz, ArCHCH$_2$NH$_2$CH_2); 2.94–2.81 (m, 2H, ArCHCH$_2$NH$_2$CH_2CH_2); 2.74–2.55 (m, 3H, ArCH_2, ArCHCH$_2$); 1.90–1.79 (m, 2H, ArCH_2CH$_2$CHCH_2); 1.56–1.30 (m, 3H, ArCH$_2$CH_2CH). ESIMS: (M+H$^+$) = 248. Anal. Calcd for $C_{15}H_{22}ClNO_2$ (0.33 equiv MeOH): C, 62.54; H, 7.99; N, 4.76. Found: C, 62.78; H, 7.70; N, 4.78.

5.1.1.17. *trans*-7,8-Dimethoxy-5-phenyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*h*]isoquinoline hydrochloride, 18. Analogous to the procedure for **17**, lactam **16** (0.190 g, 0.564 mmol) was converted into the title compound (0.169 g, 0.471 mmol, 84%) as a white powder; mp >250 °C. ^{1}H NMR: (500 MHz, DMSO-d_6): δ 9.15 (br s, 1H, NH_2); 8.88 (br s, 1H, NH_2); 7.39–7.20 (m, 5H, PhH); 7.04 (d, 1H, J = 9.0 Hz, ArH); 6.92 (d, 1H, J = 9.0 Hz, ArH); 4.04 (br d, 1H, J = 11.0 Hz, CHCH_2NH); 3.78 (s, 3H, ArOCH_3); 3.64 (s, 3H, ArOCH_3); 3.21 (br d, 1H, J = 11.5 Hz, CH$_2$CH_2NH); 3.03 (d, 1H, J = 12.5 Hz, ArCH_2); 2.90 (br t, 1H, J = 11.0 Hz, ArCH); 2.85–2.68 (m, 4H, ArCH_2CH, CH_2NH$_2$CH_2); 1.91–1.83 (m, 1H, ArCH$_2$CH(Ph)CH); 1.39–1.31 (m, 1H, CH$_2$NH$_2$CH$_2$CH_2); 1.29–1.19 (m, 1H, CH$_2$NH$_2$CH$_2$CH_2). ESIMS: (M+H$^+$) = 324. Anal. Calcd for $C_{21}H_{26}ClNO_2$: C, 70.08; H, 7.28; N, 3.89. Found: C, 69.71; H, 7.22; N, 3.73.

5.1.1.18. *cis*-1,2,3,4,4a,5,6,10b-Octahydrobenzo[*h*]isoquinoline-7,8-diol hydrobromide, 1. A solution of **17a** (0.050 g, 0.177 mmol) in dry CH_2Cl_2 (15 mL) in a flame-dried single-neck flask was cooled to −78 °C, and 0.55 mL of a 1.0 M solution of BBr_3 in CH_2Cl_2 (0.55 mmol) were added dropwise to the flask. The reaction was stirred at −78 °C for 2 h and then at room temperature for 2 h. The solution was returned to the dry ice/acetone bath and carefully quenched by the addition of 3 mL anhydrous MeOH. The quenched reaction was evaporated to dryness, keeping the water bath below 40 °C. The solid residue was re-dissolved in MeOH, and evaporated again, repeating this process a total of four times. The resulting tan solid was dried under high vacuum overnight and then crystallized from MeOH–Et_2O to yield a fine, white powder (0.043 g, 0.144 mmol, 81%); mp >250 °C. ^{1}H NMR: (500 MHz, DMSO-d_6): δ 9.08 (s, 1H, ArOH); 8.47 (m, 1H, NH_2); 8.34 (m, 1H, NH_2); 8.19 (s, 1H, ArOH); 6.60 (d, 1H, J = 8.0 Hz, ArH); 6.43 (d, 1H, J = 8.0 Hz, ArH); 3.18–3.06 (m, 2H, ArCHCH_2NH$_2$CH_2); 2.99–2.88 (m, 3H, ArCHCH$_2$NH$_2$CH_2); 2.79 (dd, 1H, J = 3.5, 17.5 Hz, ArCH_2); 2.45–2.33 (m, 1H, ArCH_2); 2.04–1.87 (m, 3H, ArCH$_2$CH_2CHCH_2); 1.71 (br d, 1H, J = 16.0 Hz, ArCH$_2$CH$_2$CHCH_2); 1.58–1.52 (m, 1H, ArCH$_2$CH_2). ESIMS: (M+H$^+$) = 220. Anal. Calcd for $C_{13}H_{18}BrNO_2$ (+0.66 equiv MeOH): C, 51.05; H, 6.48; N, 4.36. Found: C, 51.02; H, 6.24; N, 4.32.

5.1.1.19. *trans*-1,2,3,4,4a,5,6,10b-Octahydrobenzo[*h*]isoquinoline-7,8-diol hydrobromide, 2. The same procedure as above was used to convert 0.076 g (0.269 mmol) of *trans* isoquinoline **17b** into 0.056 g (0.187 mmol, 70.0%) of the *trans* catechol HBr salt **2**, crystallized from MeOH–Et_2O as a fine, off-white powder; mp >250 °C. ^{1}H NMR: (300 MHz, DMSO-d_6): δ 9.10 (br s, 1H, ArOH); 8.81 (br d, 1H, J = 10.5 Hz, NH_2); 8.46 (br d, 1H, J = 10.5 Hz, NH_2); 8.19 (br s, 1H, ArOH); 6.59 (d, 1H, J = 8.3 Hz, ArH); 6.49 (d, 1H, J = 8.3 Hz, ArH); 3.90 (d, 1H, J = 10.5 Hz, ArCHCH_2NH$_2$); 3.31 (d, 1H, J = 10.5 Hz, ArCHCH$_2$NH$_2$CH_2); 3.00–2.81 (m, 1H, ArCHCH$_2$NH$_2$CH_2); 2.76 (dd, 1H, J = 5.5, 17.5 Hz, ArCHCH_2NH$_2$); 2.65 (q, 1H, J = 11.0 Hz, ArCH$_2$CH$_2$CHCH_2); 2.59–2.48 (m, 2H, ArCH_2, ArCH); 1.88–1.77 (m, 2H, ArCH_2CH$_2$CHCH_2); 1.51–1.40 (m, 2H, ArCH$_2$CH_2CH); 1.39–1.29 (m, 1H, ArCH$_2$CH_2). ESIMS: (M+H$^+$) = 220. Anal. Calcd for $C_{13}H_{18}BrNO_2$ (0.33 equiv MeOH): C, 51.51; H, 6.27; N, 4.51. Found: C, 51.17; H, 5.89; N, 4.45.

5.1.1.20. *trans*-5-Phenyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*h*]isoquinoline-7,8-diol hydrobromide, 3. In a procedure analogous to that for **2**, isoquinoline **18** (0.070 g, 0.195 mmol) was converted into the title compound, recrystallized from MeOH–Et_2O and isolated as a fine, white powder (0.044 g, 0.117 mmol, 60%); mp >250 °C. ^{1}H NMR: (300 MHz, DMSO-d_6): δ 9.14 (s, 1H, ArOH); 8.81–8.72 (m, 1H, NH_2); 8.50–8.35 (m, 1H, NH_2); 8.26 (s, 1H, ArOH); 7.38–7.20 (m, 5H, PhH); 6.64 (d, 1H, J = 8.4 Hz, ArH); 6.58 (d, 1H, J = 8.4 Hz, ArH); 3.97 (br d, 1H, J = 9.6 Hz, CHCH_2NH); 3.22 (br d, 1H, J = 10.8 Hz, CH$_2$CH_2NH); 2.95 (d, 1H, J = 11.7 Hz, ArCH_2); 2.89–2.55 (m, 5H, ArCH_2CH, ArCHCH$_2$NH$_2$CH_2); 1.91–1.80 (m, 1H, ArCH$_2$CH(Ph)CH); 1.40–1.32 (br d, 1H, J = 12.6 Hz, CH$_2$NH$_2$ CH$_2$CH_2); 1.28–1.12 (m, 1H, CH$_2$NH$_2$CH$_2$CH_2). ESIMS: (M+H$^+$) = 296. Anal. Calcd for $C_{19}H_{22}BrNO_2$ (1 equiv MeOH): C, 58.83; H, 6.42; N, 3.43. Found: C, 58.55; H, 6.77; N, 3.24.

5.2. Pharmacology

5.2.1. Materials

Affinity and functional data for all compounds were obtained using well-established methodology.[43–46] [^{3}H]Spiperone (95 Ci/mmol) and [^{3}H]SCH-23390 (81 Ci/mmol) were purchased from Amersham Biosciences (Piscataway, NJ). Butaclamol, SCH-23390, ketanserin, and most other reagents were purchased from Sigma–Aldrich Chemical Co. (St. Louis, MO).

5.2.1.1. Competition binding experiments. Fresh porcine striatal tissue was obtained from the Purdue Butcher Block and prepared as previously described.[43] 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 spun at 30,000*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 30,000*g* for 30 min at 4 °C. This pellet was resuspended again in 50 mM Tris buffer, dispensed into 1 mL aliquots, and spun again at 13,000*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,[44] with minor modifications. The pellets were resuspended (1 mg/mL) 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 for D_1-like and D_2-like receptor sites, respectively (760 fmol/mg and 0.44 nM for [^{3}H]SCH-23390; 250 fmol/mg and 0.075 nM for [^{3}H]spiperone). All D_2-like binding assays were performed with 50 nM ketanserin to mask 5-HT_{2A} binding sites. Nonspecific binding was defined with 5 μM butaclamol. Drug dilutions for competitive 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.

5.2.1.2. Cyclic AMP accumulation assay. Assays were performed on confluent monolayers of cells in 48-well plates. All drugs were diluted in Earle's balanced salt solution (EBSS) assay buffer (EBSS containing 2% bovine calf serum, 0.025% ascorbic acid, and 15 mM HEPES, pH 7.4) and added in duplicate on ice. cAMP stimulation assays were incubated for 15 min at 37 °C in the presence of 500 μM isobutylmethylxanthine (IBMX) and terminated with 3% trichloroacetic acid. cAMP levels in cell lysates were quantified using a previously published method.[46] Aliquots (15 μL) of cellular lysate was added in duplicate to cAMP binding buffer (100 mM Tris–HCl, pH 7.4, 100 mM NaCl, 5 mM EDTA) in 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). These were incubated on ice at 4 °C for 2–3 h and terminated by harvesting with ice-cold wash buffer (100 mM Tris, 0.9% NaCl) using a 96-well Packard Filtermate cell harvester. After the filter plates were dried overnight, 30 μL of Packard Microscint O was added to each well. Radioactivity was counted using a Packard Topcount Scintillation counter. Standard curves ranging from 0.01 to 300 pmol of cAMP were used to determine the concentration of cAMP in each sample.

5.2.1.3. Data analysis. Graphpad Prism was used to generate dose–response, receptor saturation, and competition binding curves, and to perform statistical analyses (GraphPad Software, San Diego, CA). Data from D_1 cAMP stimulation assays were normalized to 10 μM dopamine. K_i values were calculated from competition binding experiments using the Cheng–Prusoff equation.

Acknowledgments

This work was funded by NIH Grants MH42705 (DEN), MH60397 (VJW), and an endowed AFPE fellowship (LAB). The authors would like to thank Dr. Juan Pablo Cueva for his helpful comments on oxazoline chemistry.

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