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Identification of a 2-phenyl-substituted octahydrobenzo[*f*]quinoline as a dopamine D_3 receptor-selective full agonist ligand

Alia H. Clark, John D. McCorvy, Jason M. Conley, Whitney K. Williams, Markondaiah Bekkam, Val J. Watts, David E. Nichols *

Department of Medicinal Chemistry and Molecular Pharmacology, College of Pharmacy and Integrative Neuroscience Program, Purdue University, West Lafayette, IN 47907, USA

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ABSTRACT

This work describes the identification of a novel class of octahydrobenzo[*f*]quinolines as dopamine D_3-selective full agonists. We developed a facile method that utilizes Suzuki coupling for easy incorporations of various substituted pendant rings into the scaffold. A small focused library of octahydrobenzo[*f*]quinolines **5** was synthesized, and these compounds demonstrated at least 14-fold D_2-like selectivity over D_1 in native porcine striatal tissue. Furthermore, *n*-propyl analog **5f** was found to be a high affinity (K_i = 1.1 nM) D_3 dopamine full agonist with 145-fold selectivity over the D_2 receptor and about 840-fold selectivity over the D_1 receptor.

1. Introduction

Dopamine (DA) is a catecholamine neurotransmitter involved in various neurological functions, including motor control, cognitive processes, and reward and pleasure mechanisms.[1,2] Abnormality in dopaminergic systems has been linked to neurological disorders such as Parkinson's disease, schizophrenia, and addiction.[3–6] Thus, understanding the function of each dopamine receptor isoform and its involved pathway becomes a crucial step toward the development of potential dopaminergic therapeutics. One powerful approach to study particular dopaminergic systems is through the design of dopamine isoform-specific agonists.

Our research has been focused primarily on the development of dopamine D_1 subtype selective agonists. Dihydrexidine (DHX **1**, Fig. 1), for example, developed in this laboratory,[7] was the first high potency dopamine D_1 full agonist with selectivity over the D_2-like receptors. Inspired by the DHX scaffold, several high affinity D_1 selective agonists, such as doxanthrine (**2**), and dinapsoline (**3**), were subsequently discovered.[8,9] Structure–activity relationship (SAR) studies of these compounds indicated that a 'β-phenyldopamine' pharmacophore, in which an aryl group is attached to the β position of the ethylamine side chain moiety, may be responsible for selective dopamine D_1 agonist properties.[10] This β-phenyl moiety is thought to interact with an accessory binding region in the D_1 receptor binding site. Interestingly, compound **4**, a benzo[*h*]isoquinoline with a pendant phenyl ring attached at the 5-position (two atoms displaced from the β-position), also demonstrated full agonist activity at the D_1 receptor and selectivity over the D_2-like receptor, and has the highest functional potency of any dopamine D_1 agonist reported to date.[11] These results raised our interest in probing the approximate location of the accessory binding region in the D_1 receptor that accommodates the pendant phenyl ring. To explore further the D_1 accessory binding region, and assess the effect of position of the extended pendant accessory ring on receptor selectivity, we decided to transpose the appended phenyl ring of **4** to a location more distal from the catechol moiety, and prepared compound **5a**, along with several substituted congeners.

This work describes the synthesis of a small library of derivatives of **5**. In particular, we show that these compounds surprisingly have selective dopamine D_3 agonist activity, rather than the anticipated dopamine D_1 agonist activity.

2. Results and discussion

2.1. Chemistry

The syntheses of 7,8-dihydroxyoctahydrobenzo[*f*]quinoline **5a** and its analogs, were envisioned through a key Suzuki coupling reaction that would allow easy incorporation of various substituted phenyl rings into the benzo[*f*]quinoline scaffold. Scheme 1 outlines the preparation of the key bromide intermediate **11** that was used in the subsequent coupling reactions to provide the proposed library of benzo[*f*]quinoline analogs.

* Corresponding author.
E-mail address: drdave@purdue.edu (D.E. Nichols).

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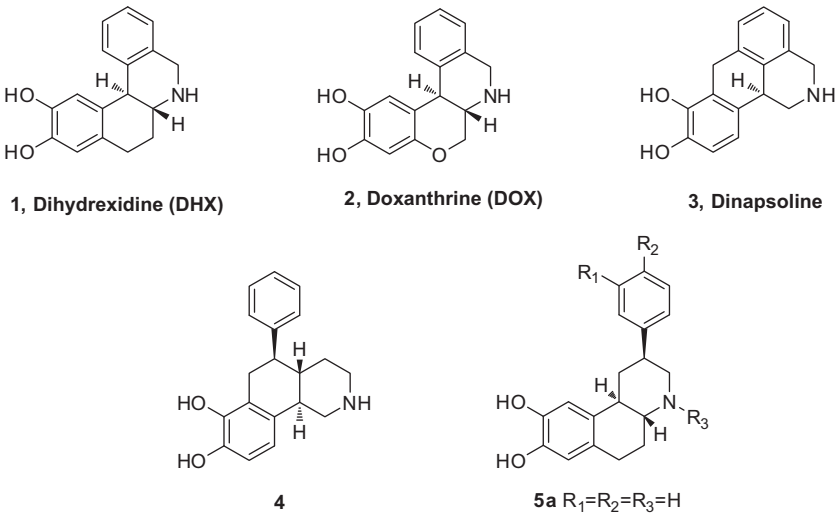
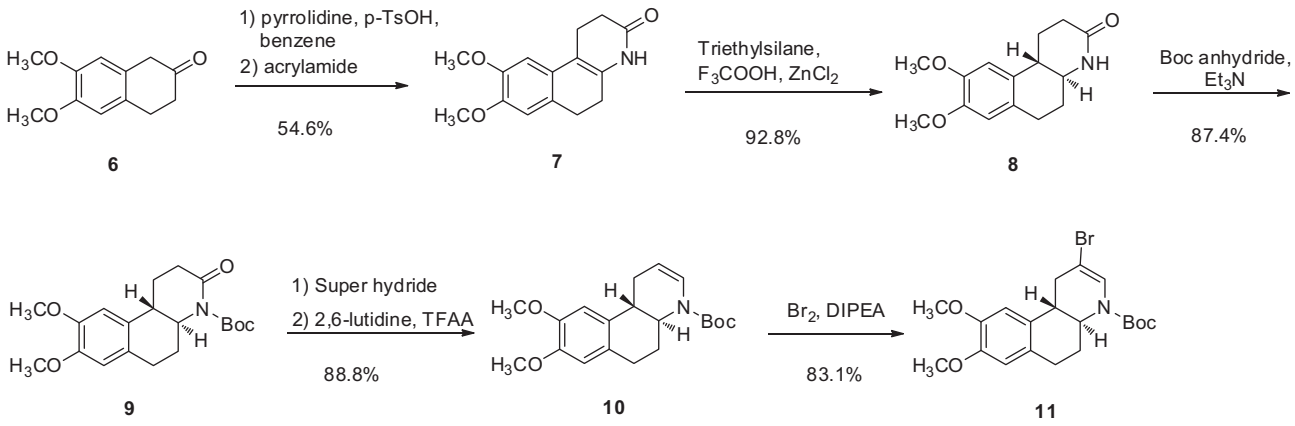


Figure 1. Structures of D_1 selective agonists (**1**–**4**) and proposed benzo[*f*]quinoline **5a**.



Scheme 1. Synthesis of the key intermediate bromide **11**.

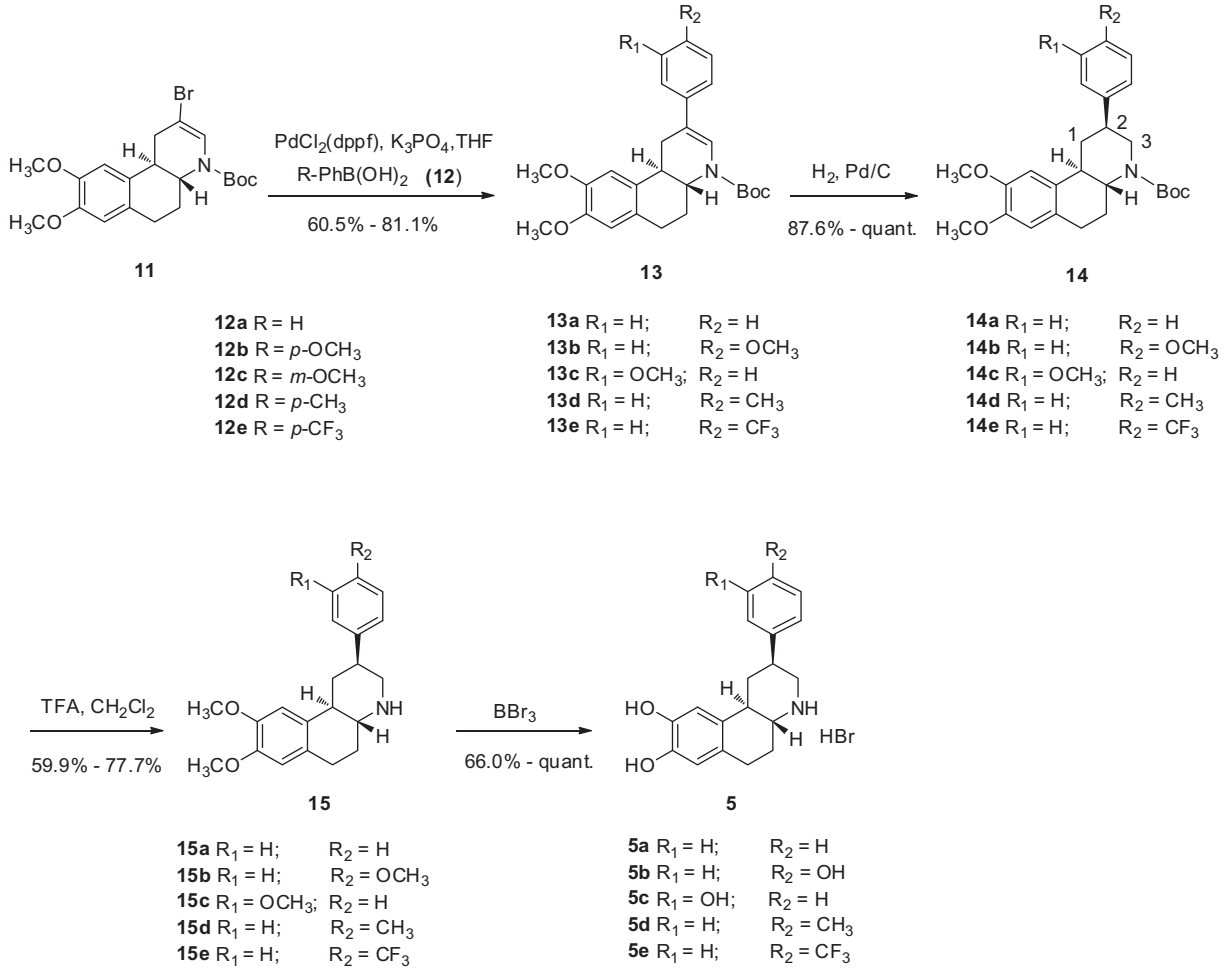
The synthesis of the piperidinone scaffold **8** began with β-tetralone **6**, which was prepared using established procedures.[12] Treatment of **6** with pyrrolidine gave the corresponding enamide, which underwent Stork–Ninomiya aza-annulation in the presence of acrylamide to give amide **7**.[13,14] Reduction of **7** with Et_3SiH/TFA to lactam **8** was successful only in the presence of $ZnCl_2$, affording exclusively the desired *trans* lactam **8** in excellent yield. After *N*-boc protection of **8**, amide **9** was first reduced with Super-Hydride, followed by dehydration in the presence of TFAA, 2,6-lutidine, and a catalytic amount of DMAP to give enamide **10**.[15] Regioselective bromination of **10** was accomplished with elemental bromine and Hunig's base to give the key bromide intermediate **11**.[16,17]

To build a small focused library of ring-substituted analogs of **5a**, a small set of substituents at the para- or meta-position of the pendant phenyl ring with varying electronic properties was proposed. The syntheses of these compounds are outlined in Scheme 2. Coupling of bromide **11** with various commercially available ring-substituted phenyl boronic acids (**12**) under Suzuki conditions in the presence of K_3PO_4 with Pd(dppf)Cl_2 as the catalyst yielded the corresponding arylated adducts **13**. Hydrogenation of **13** over Pd/C at 40 psi hydrogen for 20 h afforded only the desired equatorial isomer **14** in excellent yield. The equatorial conformation of the product was confirmed by ^{1}H NMR. The large ^{1}H–1H coupling constants ($J_{12} = J_{23} = 13$ Hz) observed for H-1/H-2 and H-2/H-3 is typical of a diaxial arrangement of these hydrogen atoms. Finally, removal of the *N*-boc group was achieved in the presence of TFA to give amines **15**. *O*,*O*-dealkylation of the aryl ethers then provided the target compounds **5**.

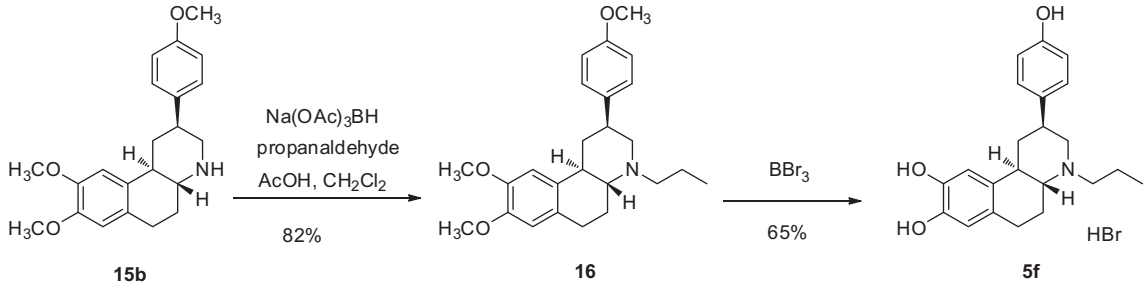
Initial pharmacological evaluation of these compounds showed an unexpected potency and selectivity at the D_2-like receptors. Moreover, previous published literature studies have shown that N-alkylation of the ethylamine moiety enhances D_2 over D_1 receptor agonist selectivity, and D_2 receptor affinity is optimized with an *n*-propyl substitution.[18–20] Thus, we selected analog **5b**, which demonstrated the highest D_2 selectivity and affinity within the library, and synthesized its *n*-propyl analog **5f** (Scheme 3) for further pharmacological evaluation.

2.2. Pharmacology

Compounds **5a–f** were compared with DHX (**2**) and **4** for affinity at D_1-like and D_2-like receptors in pig striatal homogenate (Table 1). 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]*N*-methylspiperone with added ketanserin to mask 5-HT_{2A} sites. Surprisingly, ligands **5a–f** demonstrated a higher affinity at D_2-like receptors than at D_1-like receptors. Furthermore, comparison between the substituted ring analogs showed that the para-trifluoromethyl analog **5e** demonstrated the greatest loss in D_2 affinity (fivefold) compared to **5a**. Para-methyl substitution (**5d**) also resulted in a twofold loss in



Scheme 2. Synthesis of benzo[*f*]quinolines.



Scheme 3. Synthesis of *n*-propyl analog **5f**.

affinity and selectivity. The meta-hydroxy analog **5c** showed affinity comparable to **5a**, with a slight decrease in selectivity, whereas the para-hydroxy substitution (**5b**) led to a twofold increase in affinity, and selectivity comparable to **5a**. These results seem to indicate that electron-withdrawing substituents are detrimental to binding, whereas a polar group, especially at the para-position of the phenyl ring, appears favored. Within this series, the *N*-*n*-propyl analog **5f** showed the highest affinity and 60-fold D_2-like selectivity over D_1-like receptors in porcine striatal tissue.

Compounds **4**, **5b**, and **5f** were then further evaluated in competition binding experiments at cloned human D_1, D_2, and D_3 receptor subtypes expressed in HEK cells (Table 2). In these assays **5f** exhibited low nanomolar affinity (1.1 ± 0.2) at the D_3 receptor and was 145-fold selective for D_3 over D_2 receptors, a degree of selectivity similar to 7-OH-DPAT, a known D_3 selective agonist.Because **5f** had such high affinity and selectivity at D_3 dopamine receptors, its potency and intrinsic activity at D_3 receptors was examined using the DiscoveRX PathHunter eXpress GPCR β-arrestin assay. It is known that upon GPCR activation, in addition to G protein coupling, β-arrestins translocate to the membrane and interact with an activated receptor.[21] The DiscoveRX PathHunter β-arrestin GPCR assay system is a β-galactosidase enzyme complementation assay that takes advantage of the activation-induced interaction of a ProLink-tagged receptor and EA-tagged β-arrestin.[22] The interaction between the activated ProLink-tagged receptor and EA-tagged β-arrestin reconstitutes the active β-galactosidase enzyme, ultimately allowing for a chemiluminescent readout of receptor activation.[22] U2OS cells expressing a ProLink-tagged D_3 receptor

Table 1
Affinity at porcine striatal homogenates (nM)[a]

Ligand	D_1-like K_i	D_2-like K_i	Fold D_2 over D_1-like selectivity
DHX, **1**	20 ± 2.8	200 ± 40	0.1
4	8.2 ± 0.6	180 ± 20	0.05
5a	930 ± 60	30 ± 3.5	31
5b	490 ± 3	14 ± 0.7	34
5c	580 ± 50	29 ± 2.7	20
5d	810 ± 90	56 ± 7.1	14
5e	2370 ± 280	150 ± 20	16
5f	630 ± 50	10 ± 1.0	61
SCH-23390	0.31 ± 0.02	ND	
Chlorpromazine	ND	4.1 ± 0.5	

[a] All results shown are the mean ± SEM for at least three independent experiments.

Table 2
Affinity at recombinant human D_1, D_2, and D_3 receptors in HEK cells (nM)[a]

Ligand	hD_1 K_i	hD_2 K_i	hD_3 K_i	Fold D_3 over D_2 selectivity
4	47 ± 1.3	230 ± 43	210 ± 45	1
5b	550 ± 70	490 ± 43	50 ± 6	10
5f	921 ± 120	160 ± 25	1.1 ± 0.2	145
SCH-23390	0.94 ± 0.08	ND	ND	
Chlorpromazine	ND	1.2 ± 0.1	3.8 ± 0.6	0.3
7-OH-DPAT	ND	1430 ± 260	6.9 ± 1.4	207

[a] All results shown are the mean ± SEM for at least three independent experiments.

Table 3
Stimulation of D_3 dopamine receptor activation in living cells[a]

Ligand	EC_{50} (nM)	% E_{max}
7-OH-DPAT	0.95 ± 0.01	103 ± 3.9
5f	46 ± 11	103 ± 1.7

[a] All results shown are the mean ± SEM of three experiments performed in duplicate.

and an EA-tagged β-arrestin were used to study D_3 receptor agonist activity. In addition to the pharmacological characterization of **5f** and dopamine, the D_2/D_3 receptor agonist 7-OH-DPAT was included as a control. As anticipated, 7-OH-DPAT displayed full agonist activity with low nanomolar potency. Concentration-response studies with **5f** revealed that it also was a full D_3 receptor agonist with an EC_{50} value of 46 ± 11 nM for D_3 receptor-β-arrestin coupling (E_{max} = 103 ± 1.7% of the dopamine response) (see Table 3).

2.3. Discussion

The importance of a pendant accessory ring in conferring D_1-like over D_2-like receptor selectivity has long been demonstrated. Much of our study has been focused on exploring the ligand-binding interactions involved in the D_1 accessory binding site. Although surprised by the pharmacological action of compound **5a** and its analogs, these data have provided valuable information that helps not only to define further the spatial location of the D_1 accessory binding region, but also suggests, for the first time, the possibility of a cognate binding region in the D_3 receptor.

Unlike compound **4**, which is a potent D_1-selective agonist, **5a** demonstrated high affinity at the D_2 receptor and was more than 30-fold selective at D_2 compared to D_1. Superimposition of **4** and **5a** clearly shows that the loss of D_1 affinity of **5a** is due to the placement of the pendant phenyl ring (Fig. 2). Compared to **4**, the pendant phenyl ring in **5a** is displaced about 2.9 Å horizontally toward the amine nitrogen. The ring is also displaced about 38° upward from the catechol ring plane. It is likely that the change in position of the phenyl ring prohibits it from engaging in favorable interactions with residues in the D_1 accessory binding region. In addition, protrusion of the appended ring into a sterically-restricted area of the D_1 receptor may be another consequence of shifting the phenyl ring.

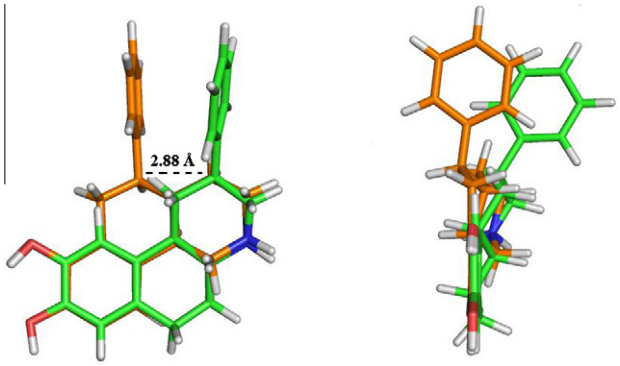


Figure 2. Molecular overlay of **4** (orange) and **5a** (green). Structures on the left are viewed from above the catechol ring plane, whereas the right panel is viewed edge-on, with the catechol towards the viewer.

Consistent with what has been called the '*N*-propyl effect'[18–20] for many D_2-like selective ligands, *n*-propyl analog **5f** demonstrated the highest affinity and selectivity at the D_2-like receptors among the library of tested compounds. Furthermore, the finding that compound **5f** is a D_3-selective full agonist leads us to propose the presence of a corresponding region in the D_3 orthosteric binding site that is similar to the D_1 accessory binding pocket. This novel class of benzo[*f*]quinolines has very different structural features compared to previously known D_3 selective agonists, which may aid in overall structure-activity relationship studies of dopamine receptor subtype selective ligands. More specifically, the synthetic method developed in this work utilizes Suzuki coupling, allowing for easy incorporation of pendant rings carrying substituents with a range of steric and electronic properties that will allow further exploration of this potential D_3 accessory binding region.

Compared to its low nanomolar affinity at the D_3 receptor, compound **5f** does not exhibit the same degree of potency at the β-arrestin assay, even though it is a full agonist in this assay. By contrast, 7-OH DPAT exhibits better potency at the β-arrestin recruitment assay in addition to its D_3 selectivity and high affinity. These findings could reflect functional selectivity, where ligands can present a bias for a particular functional pathway that can have drug development potential.[23] In fact, β-arrestin biased D_2 ligands show antipsychotic efficacy in preclinical models of schizophrenia.[24,25] Therefore, our findings may point to the development of a new class of D_3 selective ligands with a lack of β-arrestin bias having novel therapeutic value.

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 were obtained by the Purdue University Campus-wide mass Spectrometry Center. Elemental analyses were performed by the Purdue University Microanalysis Laboratory or Midwest Microlab, LLC.

3.1.2. 8,9-Dimethoxy-1,2,5,6-tetrahydrobenzo[*f*]quinolin-3(4*H*)-one (7)

Pyrrolidine (3.5 g, 48.48 mmol) was added drop-wise to a solution of β-tetralone **6** (5 g, 24.24 mmol) and *p*-toluenesulfonic acid (30 mg) in 180 mL of benzene. The reaction mixture was heated at reflux in a Dean-Stark apparatus for 5 h. The solvent was then removed under pressure. To the resulting dark residue, acrylamide (5.3 g, 72.72 mmol) was added in one portion. The mixture was heated at 80 °C for 3 h then at 130 °C for 30 min. The reaction was quenched with 60 mL of water and the mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic solvent was dried over $MgSO_4$, filtered and concentrated under vacuum to give a dark paste. Recrystallization from acetone yielded 3.43 g (54.6%) of **7**: mp darkens >200 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.63 (s, 1H, ArH); 6.60 (s, 1H, ArH); 3.81 (s, 3H, OCH_3); 3.80 (s, 3H, OCH_3); 2.773 (t, J = 13 Hz, 2H, 6-H_2); 2.64–2.58 (m, 4H, 1-H_2, 2-H_2); 2.27 (t, J = 13 Hz, 2H, 5-H_2). CIMS: m/z (relative intensity): 260 ($M+H^+$, 100) Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.41. Found: C, 69.37; H, 6.44; N, 5.37.

3.1.3. (±)-*trans*-8,9-Dimethoxy-1,4,4a,5,6,10b-hexahydrobenzo[*f*]quinolin-3(2*H*)-one (8)

To a solution of **7** (6.22 g, 23.99 mmol) in 250 mL dry CH_2Cl_2, anhydrous $ZnCl_2$ powder (6.5 g, 47.98 mmol) was added, followed by triethylsilane (11.16 g, 95.95 mmol). The reaction was stirred for 5 min then cooled to 0 °C in an ice bath, at which time trifluoroacetic acid (27.4 g, 0.24 mol) was added drop-wise. The reaction was stirred at room temperature for 20 h. An additional 1 equiv of $ZnCl_2$ (3.25 g 23.99 mmol) and triethylsilane (2.79 g, 23.99 mmol) was added and the reaction was stirred for another 20 h. The mixture was sequentially washed with aqueous saturated $NaHCO_3$ (50 mL) and H_2O (50 mL). The organic solvent was dried over $MgSO_4$, filtered, and concentrated to give the crude product, which was washed with EtOAc and filtered to provide 5.82 g (92.8%) of lactam **8**: mp >250 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.78 (s, 1H, ArH); 6.61 (s, 1H, ArH); 6.02 (s, 1H, C═ONH); 3.87 (s, 3H, OCH_3); 3.85 (s, 3H, OCH_3); 3.36 (td, J_1 = 10 Hz, J_2 = 3.0 Hz, 1H, 4a-H); 2.96–2.85 (m, 2H, 6-H_2); 2.72–2.55 (m, 4H, 10b-H, 2-H_2, 1-H_a); 2.02–1.97 (m, 1H, 5-H_a); 1.88–1.81 (m, 1H, 5-H_b); 1.76–1.68 (m, 1H, 1-H_b). CIMS: m/z (relative intensity): 262 ($M+H^+$, 100). Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 98.94; H, 7.33; N, 5.36. Found: C, 68.53; H, 7.16; N, 0.04.

3.1.4. (±)-*trans-tert*-Butyl-8,9-dimethoxy-3-oxo-1,2,3,5,6,10b-hexahydrobenzo[*f*]quinoline-4(4a*H*)-carboxylate (9)

To a solution of **8** (3.67 g, 14.04 mmol) in 150 mL dry CH_2Cl_2, Boc anhydride (7.36 g, 33.70 mmol), triethylamine (1.7 g, 16.85 mmol), and DMAP (172 mg, 1.4 mmol) were added. The reaction was heated at reflux for 24 h then quenched with 100 mL of water. The mixture was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic solvent was dried over $MgSO_4$, filtered, and concentrated to give the crude product. Repeated recrystallization from EtOH yielded 4.43 g (87.4%) of **9**: mp 153–155 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.78 (s, 1H, ArH); 6.62 (s, 1H, ArH); 3.87 (s, 3H, OCH_3); 3.86 (s, 3H, OCH_3); 3.70 (td, J_1 = 18 Hz, J_2 = 4.0 Hz, 1H, 4a-H); 2.96-2.84 (m, 3H, 10b-H, 6-H_2); 2.72–2.65 (m, 2H, 2-H_2); 2.59–2.51 (m, 1H, 5-H_a); 2.26–2.20 (m, 1H, 5-H_b); 1.82–1.68 (m, 2H, 1-H_2). EIMS: m/z (relative intensity): 362 (M^+, 11) 287 (M-C_4H_9OH, 100). Anal. Calcd. for $C_{20}H_{27}NO_5{\cdot}0.06Et_3N$: C, 66.54; H, 7.65; N, 4.04. Found: C, 66.90; H, 7.53; N, 4.04.

3.1.5. (±)-*trans-tert*-Butyl-8,9-dimethoxy-1,5,6,10b-tetrahydrobenzo[*f*]quinoline-4(4a*H*)-carboxylate (10)

N-Boc lactam **9** (990 mg, 2.74 mmol) was dissolved in 20 mL dry toluene and 5 mL of dry THF. Then 3.3 mL (3.29 mmol) of a 1 M solution of Super Hydride in THF was added drop-wise at −78 °C. The reaction was stirred for 40 min at ·78 °C, then 2,6-lutidine (1.6 g, 15.07 mmol), DMAP (10 mg, 0.082 mmol), and trifluoroacetic anhydride (748 mg, 3.56 mmol) were added. The reaction was warmed to room temperature and stirred for another 3.5 h. The mixture was quenched with 40 mL of water and extracted with 3 × 30 mL EtOAc. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated to provide a yellow oil. Silica gel flash column chromatography, eluting with 2:3 EtOAc/hexane, followed by recrystallization from EtOH afforded 840 mg (88.8%) of **10**: mp 112–115 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.79 (dd, J_1 = 8.1 Hz, J_2 = 2.6 Hz, 1H, 3-H); 6.73 (s, 1H, ArH); 6.60 (s, 1H, ArH); 5.02 (td, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H, 2-H); 3.82 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3); 3.41 (td, J_1 = 9.5 Hz, J_2 = 2.6 Hz, 1H, 4a-H); 3.06–3.02 (m, 1H, 10b-H); 2.98–2.81 (m, 4H, 1-H_2, 6-H_2); 2.68–2.62 (m, 1H, 5-H_a); 1.67–1.61 (m, 1H, 5-H_b); 1.45 (s, 9H, Boc-H_9). CIMS: m/z (relative intensity): 346 ($M+H^+$, 100). Anal. Calcd. for $C_{20}H_{27}NO_4{\cdot}0.05$ (CF_3CO) $C_{20}H_{26}NO_4$: C, 68.96; H, 7.76; N, 4.00. Found: C, 68.95; H, 7.76; N, 4.29.

3.1.6. (±)-*trans-tert*-Butyl 2-bromo-8,9-dimethoxy-1,5,6,10b-tetrahydrobenzo[*f*]quinoline-4(4a*H*)-carboxylate (11)

To a solution of enamide **10** (500 mg, 1.45 mmol) in 20 mL of dry toluene and 5 mL of dry CH_2Cl_2, bromine (249 mg, 1.59 mmol) was added drop-wise at −78 °C, followed by DIPEA (*N*,*N*-diisopropylethylamine; 196 mg, 1.52 mmol). The reaction was stirred for 10 min at −78 °C then warmed to room temperature and stirred for another 1 h. The reaction was quenched with 20 mL of 10% aqueous sodium thiosulfate and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (2 × 10 mL), dried over $MgSO_4$, filtered, and concentrated to give a yellow oil. Recrystallization from EtOH provided 510 mg (83.1%) of **11**: mp 118–120 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.15 (d, J = 2.5 Hz, 1H, 3-H); 6.69 (s, 1H, ArH); 6.62 (s, 1H, ArH); 3.87 (s, 3H, OCH_3); 3.85 (s, 3H, OCH_3); 3.38 (td, J_1 = 10.9 Hz, J_2 = 2.6 Hz, 1H, 4a-H); 3.15–3.08 (m, 2H, 10b-H, 6-H_a); 3.02–2.93 (m, 2H, 6-H_b, 1-H_a); 2.98–2.81 (m, 1H, 1-H_b); 2.51 (ddd, J_1 = 16 Hz, J_2 = 11.6 Hz, J_3 = 2.6 Hz, 1H, 5-H_a); 1.72–1.64 (m, 1H, 5-H_b); 1.51 (s, 9H, Boc-H_9). ESIMS: m/z (relative intensity): 462/464 ($M+K^+$, 100).

3.1.7. General procedure for Suzuki coupling reactions to 13a–e

Bromide **11** (1 mol equiv) was dissolved in dry THF, and powdered K_3PO_4 (3.5 mol equiv), $PdCl_2(dppf){\cdot}CH_2Cl_2$ (10 mol %), and phenyl boronic acid or the corresponding substituted phenyl boronic acid **12** (2.5 mol equiv) were added. The reaction was stirred at room temperature for 30 min then heated at 80 °C for 24 h. The reaction was quenched with water and extracted three times with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated to give a yellow oil. Silica gel flash column chromatography, eluting with 2:3 EtOAc/hexane, followed by recrystallization from EtOH provided the corresponding adducts **13a–e**.

3.1.7.1. (±)-*trans-tert*-Butyl-8,9-dimethoxy-2-phenyl-1,5,6,10b-tetrahydrobenzo[*f*]quinoline-4(4a*H*)-carboxylate (13a).

Obtained in 65.5% yield, mp 118–120 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.41 (d, J = 7.4 Hz, 1H, ArH); 7.36 (t, J = 7.4 Hz, 2H, 2ArH); 7.30 (d, J = 2.5 Hz, 1H, 3-H); 7.23 (d, J = 7.2 Hz, 1H, ArH); 6.87 (s, 1H, ArH); 6.67 (s, 1H, ArH); 3.89 (s, 3H, OCH_3); 3.87 (s, 3H, OCH_3); 3.53 (td, J_1 = 10.8 Hz, J_2 = 2.4 Hz, 1H, 4a-H); 3.08-3.01 (m, 4H, 10b-H, 6-H_2, 1-H_a); 2.93–2.88 (m, 1H, 1-H_b); 2.44 (td, J_1 = 13.3 Hz, J_2 = 2.7 Hz, 1H, 5-H_a); 1.73–1.67 (m, 1H, 5-H_b); 1.53 (s, 9H, Boc-H_9). CIMS: m/z (relative intensity): 322 ($M+H^+$-Boc 100). Anal. Calcd. for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41; N, 3.32. Found: C, 73.98; H, 7.42; N, 3.40.

3.1.7.2. (±)-*trans-tert*-Butyl-8,9-dimethoxy-2-(4-methoxyphenyl)-1,5,6,10b-tetrahydrobenzo [*f*]quinoline-4(4a*H*)-carboxylate (13b). Obtained in 68.2% yield, mp 211–214 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34 (d, J = 8.5 Hz, 2H, 2ArH); 7.20 (d, J = 2.0 Hz, 1H, 3-H); 6.96 (d, J = 8.5 Hz, 2H, 2ArH); 6.86 (s, 1H, ArH); 6.67 (s, 1H, ArH); 3.89 (s, 3H, OCH_3); 3.87 (s, 3H, OCH_3); 3.83 (s, 3H, $PhOCH_3$); 3.51 (td, J_1 = 10.5 Hz, J_2 = 2.0 Hz, 1H, 4a-H); 3.08–2.98 (m, 4H, 10b-H, 6-H_2, 1-H_a); 2.93–2.88 (m, 1H, 1-H_b); 2.40 (td, J_1 = 14.5 Hz, J_2 = 2.0 Hz, 1H, 5-H_a); 1.72–1.68 (m, 1H, 5-H_b); 1.53 (s, 9H, Boc-H_9). ESIMS: m/z (relative intensity): 452 (M+H^+ 100). Could not be purified free of traces of **11**, and was carried forward to the next step, where **14b** could be easily purified.

3.1.7.3. (±)-*trans-tert*-Butyl-8,9-dimethoxy-2-(3-methoxyphenyl)-1,5,6,10b-tetrahydrobenzo [*f*]quinoline-4(4a*H*)-carboxylate (13c). Obtained in 81.1% yield, mp 178–180 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32 (d, J = 2.5 Hz, 1H, 3-H); 7.19 (d, J = 8.0 Hz, 1H, ArH); 7.01 (d, J = 8.0 Hz, 1H, ArH); 6.95 (s, 1H, ArH); 6.86 (s, 1H, ArH); 6.78 (dd, J_1 = 8.0 Hz, J_2 = 2.5 Hz, 1H, ArH); 6.67 (s, 1H, ArH); 3.89 (s, 3H, OCH_3); 3.87 (s, 3H, OCH_3); 3.85 (s, 3H, $PhOCH_3$); 3.52 (td, J_1 = 10.0 Hz, J_2 = 2.5 Hz, 1H, 4a-H); 3.09–2.99 (m, 4H, 10b-H, 6-H_2, 1-H_a); 2.93–2.88 (m, 1H, 1-H_b); 2.42 (t, J = 13.0 Hz, 1H, 5-H_a); 1.74–1.67 (m, 1H, 5-H_b); 1.53 (s, 9H, Boc-H_9). ESIMS: m/z (relative intensity): 474 (M+Na^+ 100). Anal. Calcd. for $C_{27}H_{33}NO_5$: C, 71.82; H, 7.37; N, 3.10. Found: C, 71.80; H, 7.29; N, 3.11.

3.1.7.4. (±)-*trans-tert*-Butyl-8,9-dimethoxy-2-(p-tolyl)-1,5,6,10b-tetrahydrobenzo[*f*]quinoline-4(4a*H*)-carboxylate (13d). Obtained in 73.1% yield, mp 158–161 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.31 (d, J = 8.0 Hz, 2H, 2ArH); 7.25 (s, 1H, 3-H); 7.17 (d, J = 8.0 Hz, 2H, 2ArH); 6.86 (s, 1H, ArH); 6.66 (s, 1H, ArH); 3.89 (s, 3H, OCH_3); 3.87 (s, 3H, OCH_3); 3.52 (td, J_1 = 10.5 Hz, J_2 = 2.5 Hz, 1H, 4a-H); 3.08–2.99 (m, 4H, 10b-H, 6-H_2, 1-H_a); 2.92–2.88 (m, 1H, 1-H_b); 2.42 (td, J_1 = 12.5 Hz, J_2 = 2.5 Hz, 1H, 5-H_a); 2.36 (s, 3H, $PhCH_3$); 1.74–1.65 (m, 1H, 5-H_b); 1.53 (s, 9H, Boc-H_9). ESIMS: m/z (relative intensity): 436 (M+H^+ 100). Could not be purified free of traces of **11**, and was carried forward to the next step, where **14d** could be easily purified.

3.1.7.5. (±)-*trans-tert*-Butyl-8,9-dimethoxy-2-(4-(trifluoromethyl)phenyl)-1,5,6,10b-tetrahydrobenzo[*f*]quinoline-4(4a*H*)-carboxylate (13e). Obtained in 60.5% yield, mp 183–185 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.60 (d, J = 14.0 Hz, 2H, 2ArH); 7.49 (d, J = 14.5 Hz, 2H, 2ArH); 7.41 (d, J = 3.5 Hz, 1H, 3-H); 6.86 (s, 1H, ArH); 6.68 (s, 1H, ArH); 3.90 (s, 3H, OCH_3); 3.87 (s, 3H, OCH_3); 3.54 (td, J_1 = 17.5 Hz, J_2 = 3.5 Hz, 1H, 4a-H); 3.08-2.88 (m, 5H, 10b-H, 6-H_2, 1-H_2); 2.45 (td, J_1 = 21.0 Hz, J_2 = 4.0 Hz, 1H, 5-H_a); 1.74–1.68 (m, 1H, 5-H_b); 1.54 (s, 9H, Boc-H_9). ESIMS: m/z (relative intensity): 512 a(M+K^+ 100). Anal. Calcd. for $C_{27}H_{30}F_3NO_4$: C, 66.25; H, 6.18; N, 2.86. Found: C, 66.23; H, 6.24; N, 2.92.

3.1.8. General procedure for hydrogenation to 14a–e

The corresponding Suzuki adducts **13a–e** were suspended in EtOH and placed in an Ace hydrogenation bomb along with 10% Pd/C catalyst (10% w/w). The vessel was pressurized to 40 psi H_2, and stirred for 20 h. The mixture was filtered through a pad of Celite to remove the catalyst. The EtOH filtrate was removed under reduced pressure to give the desired products **14a–e** as white solids.

3.1.8.1. (±)-*trans-tert*-Butyl-8,9-dimethoxy-2-phenyl-1,2,3,5,6,10b-hexahydrobenzo[*f*] quinoline-4(4a*H*)-carboxylate (14a). Obtained in quantitative yield, mp 68–71 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34 (t, J = 7.4 Hz, 2H, 2ArH); 7.27–7.25 (m, 3H, 3ArH); 6.71 (s, 1H, ArH); 6.59 (s, 1H, ArH); 4.26 (dd, J_1 = 12.7 Hz, J_2 = 3.2 Hz, 1H, 3-H_a); 3.85 (s, 3H, OCH_3); 3.80 (s, 3H, OCH_3); 3.15 (td, J_1 = 13.1 Hz, J_2 = 2.6 Hz, 1H, 4a-H); 3.05–2.98 (m, 1H, 10b-H); 2.92 (dd, J_1 = 13.0 Hz, J_2 = 10.9 Hz, 2H, 2-H, 3-H_b); 2.83 (dd, J_1 = 8.4 Hz, J_2 = 3.4 Hz, 2H, 6-H_2); 2.68 (dt, J_1 = 13.0 Hz, J_2 = 2.5 Hz, 1H, 1-H_a); 2.57–2.48 (m, 1H, 5-H_a); 2.38–2.33 (m, 1H, 5-H_b); 1.68 (q, J = 13.0 Hz, 1H, 1-H_b); 1.48 (s, 9H, Boc-H_9). ESIMS: m/z (relative intensity): 446 (M+Na^+, 100). Anal. Calcd. for $C_{26}H_{33}NO_4{\cdot}0.4H_2O$: C, 72.50; H, 7.91; N, 3.25. Found: C, 72.22; H, 7.81; N, 3.29.

3.1.8.2. (±)-*trans-tert*-Butyl-8,9-dimethoxy-2-(4-methoxyphenyl)-1,2,3,5,6,10b-hexahydro benzo[*f*]quinoline-4(4a*H*)-carboxylate (14b). Obtained in 87.6% yield, mp 66–70 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.19 (d, J = 14.5 Hz, 2H, 2ArH); 6.88 (d, J = 14.5 Hz, 2H, 2ArH); 6.71 (s, 1H, ArH); 6.60 (s, 1H, ArH); 4.23 (br d, J = 16.5 Hz, 1H, 3-H_a); 3.85 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3); 3.80 (s, 3H, $PhOCH_3$); 3.14 (td, J_1 = 18.0 Hz, J_2 = 4.0 Hz, 1H, 4a-H); 3.00–2.89 (m, 3H, 2H, 10b-H, 3-H_b); 2.86–2.82 (m, 2H, 6-H_2); 2.83 (br d, J = 21.0 Hz, 1H, 1-H_a); 2.56–2.45 (m, 1H, 5-H_a); 2.37–2.32 (m, 1H, 5-H_b); 1.62 (q, J = 21.0 Hz, 1H, 1-H_b); 1.49 (s, 9H, Boc-H_9). ESIMS: m/z (relative intensity): 476 (M+Na^+, 100). Anal. Calcd. for $C_{27}H_{35}NO_5{\cdot}0.9H_2O$: C, 69.03; H, 7.90; N, 2.98. Found: C, 68.70; H, 7.74; N, 2.97.

3.1.8.3. (±)-*trans-tert*-Butyl-8,9-dimethoxy-2-(3-methoxyphenyl)-1,2,3,5,6,10b-hexahydrobenzo[*f*]quinoline-4(4a*H*)-carboxylate (14c). Obtained in 91.2% yield, mp 64–68 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26 (t, J = 5.0 Hz, 1H, ArH); 6.86 (d, J = 5.0 Hz, 1H, ArH); 6.81-6.78 (m, 2H, 2ArH); 6.71 (s, 1H, ArH); 6.59 (s, 1H, ArH); 4.25 (dd, J_1 = 15.0 Hz, J_2 = 5.0 Hz, 1H, 3-H_a); 3.85 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3, $PhOCH_3$); 3.14 (td, J_1 = 10.0 Hz, J_2 = 5.0 Hz, 1H, 4a-H); 3.01-2.96 (m, 1H, 10b-H); 2.94 (t, J_1 = 10.0 Hz, 2H, 2-H, 3-H_b); 2.84 (dd, J_1 = 8.5 Hz, J_2 = 4.0 Hz, 2H, 6-H_2); 2.68 (br d, J = 15.0 Hz, 1H, 1-H_a); 2.55–2.48 (m, 1H, 5-H_a); 2.36–2.33 (m, 1H, 5-H_b); 1.65 (q, J = 15.0 Hz, 1H, 1-H_b); 1.48 (s, 9H, Boc-H_9). ESIMS: m/z (relative intensity): 476 (M+Na^+, 100). Anal. Calcd. for $C_{27}H_{35}NO_5$: C, 71.50; H, 7.78; N, 3.09. Found: C, 71.20; H, 7.65; N, 3.19.

3.1.8.4. (±)-*trans-tert*-Butyl-8,9-dimethoxy-2-(p-tolyl)-1,2,3,5,6,10b-hexahydrobenzo[*f*]quinoline-4(4a*H*)-carboxylate (14d). Obtained in 94.0% yield, mp 63–66 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.16 (s, 4H, 4ArH); 6.71 (s, 1H, ArH); 6.59 (s, 1H, ArH); 4.24 (br d, J = 20.0 Hz, 1H, 3-H_a); 3.85 (s, 3H, OCH_3); 3.80 (s, 3H, OCH_3); 3.14 (td, J_1 = 17.5 Hz, J_2 = 4.5 Hz, 1H, 4a-H); 2.98–2.88 (m, 3H, 10b-H, 2-H, 1-H_a, 3-H_b); 2.83 (dd, J_1 = 14.0 Hz, J_2 = 5.0 Hz, 2H, 6-H_2); 2.69–2.63 (m, 1H, 5-H_a); 2.58–2.49 (m, 1H, 5-H_b); 2.34 (s, 3H, $PhCH_3$); 1.66 (q, J = 20.0 Hz, 1H, 1-H_b); 1.49 (s, 9H, Boc-H_9). ESIMS: m/z (relative intensity): 460 (M+Na^+, 100). Anal. Calcd. for $C_{27}H_{35}NO_4{\cdot}0.4H_2O$: C, 72.91; H, 8.11; N, 3.15. Found: C, 72.88; H, 7.98; N, 3.18.

3.1.8.5. (±)-*trans-tert*-Butyl-8,9-dimethoxy-2-(4-(trifluoromethyl)phenyl)-1,2,3,5,6,10b-hexahydrobenzo[*f*]quinoline-4(4a*H*)-carboxylate (14e). Obtained in 93.0% yield, mp 70–74 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.59 (d, J = 13.5 Hz, 2H, 2ArH); 7.38 (d, J = 13.5 Hz, 2H, 2ArH); 6.69 (s, 1H, ArH); 6.60 (s, 1H, ArH); 4.25 (dd, J_1 = 22.0 Hz, J_2 = 4.5 Hz, 1H, 3-H_a); 3.86 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3); 3.18 (td, J_1 = 17.5 Hz, J_2 = 4.5 Hz, 1H, 4a-H); 3.14-3.06 (m, 1H, 10b-H); 2.99–2.91(m, 2H, 1-H_a, 3-H_b); 2.84 (dd, J_1 = 14.0 Hz, J_2 = 7.0 Hz, 2H, 6-H_2); 2.68 (d, J = 20.0 Hz, 1H, 1-H_a); 2.52–2.44 (m, 1H, 5-H_a); 2.40–2.33 (m, 1H, 5-H_b); 2.34 (s, 3H, $PhCH_3$); 1.67 (q, J = 20.5 Hz, 1H, 1-H_b); 1.49 (s, 9H, Boc-H_9). ESIMS: m/z (relative intensity): 514 (M+Na^+, 100). Anal. Calcd. for $C_{27}H_{32}F_3NO_4$: C, 65.97; H, 6.56; N, 2.85. Found: C, 65.58; H, 6.49; N, 2.78.

3.1.9. General procedure for deprotecting *N*-Boc group to obtain amines 15a–e

The corresponding *N*-Boc benzoisoquinoline **14a–e** was dissolved in CH_2Cl_2, and trifluoroacetic acid (TFA, 10 mol equiv) was added. The reaction was stirred for 6 h at room temperature then quenched with saturated aqueous NH_4Cl. The mixture was extracted three times with CH_2Cl_2.The combined organic solvent was removed under reduced pressure and the resulting TFA salt was recrystallized from EtOAc/Et_2O. The salt was then dissolved in CH_2Cl_2 and the solution was washed twice with freshly made saturated $NaHCO_3$ solution. The organic solvent was dried over $MgSO_4$, filtered, and concentrated to give amines **15a–e** as white solids.

3.1.9.1. (±)-*trans*-8,9-Dimethoxy-2-phenyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (15a). Obtained in 65.0% yield, mp 175–179 °C. ^{1}H NMR (as HCl salt) ($CDCl_3$, 500 MHz): δ 7.35 (t, J = 7.4 Hz, 2H, 2ArH); 7.28–7.25 (m, 3H, 3ArH); 6.75 (s, 1H, ArH); 6.61 (s, 1H, ArH); 3.85 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3); 3.27 (dd, J_1 = 11.5 Hz, J_2 = 2.7 Hz, 1H, 3-H_a); 3.30-2.92 (m, 2H, 4a-H, 10b-H); 2.86 (dd, J_1 = 11.6 Hz, J_2 = 7.8 Hz, 2H, 2-H, 3-H_b); 2.66–2.56 (m, 3H, 1-H_a, 6-H_2); 2.0–1.93 (m, 1H, 5-H_a); 1.82–1.73 (m, 1H, 5-H_b); 1.60 (q, J = 11.5 Hz, 1H, 1-H_b). ESIMS (as HCl salt): m/z (relative intensity): 324 ($M+H^+$, 100). Anal. Calcd. for $C_{21}H_{25}NO_2{\cdot}HCl{\cdot}0.5H_2O$: C, 68.37; H, 7.38; N, 3.80. Found: C, 68.21; H, 7.33; N, 3.77.

3.1.9.2. (±)-*trans*-8,9-Dimethoxy-2-(4-methoxyphenyl)-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*] quinoline (15b). Obtained in 77.7% yield, mp 168–170 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.21 (d, J = 14.5 Hz, 2H, 2ArH); 6.89 (d, J = 14.5 Hz, 2H, 2ArH); 6.75 (s, 1H, ArH); 6.61 (s, 1H, ArH); 3.85 (s, 3H, OCH_3); 3.81 (s, 6H, OCH_3, $PhOCH_3$); 3.25 (dd, J_1 = 19.0 Hz, J_2 = 4.5 Hz, 1H, 3-H_a); 3.00–2.88 (m, 2H, 4a-H, 10b-H); 2.81 (q, J = 19.0 Hz, 2H, 2-H, 3-H_b); 2.64–2.51 (m, 3H, 1-H_a, 6-H_2); 1.99–1.93 (m, 1H, 5-H_a); 1.84–1.70 (m, 1H, 5-H_b); 1.54 (q, J = 19.5 Hz, 1H, 1-H_b). ESIMS: m/z (relative intensity): 354 ($M+H^+$, 100). Anal. Calcd. for $C_{22}H_{27}NO_3{\cdot}0.25H_2O$: C, 73.82; H, 7.74; N, 3.91. Found: C, 73.74; H, 7.74; N, 3.97.

3.1.9.3. (±)-*trans*-8,9-Dimethoxy-2-(3-methoxyphenyl)-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*] quinoline (15c). Obtained in 64.1% yield, mp 122–124 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.27 (t, J = 13.5 Hz, 1H, ArH); 6.89 (d, J = 13.0 Hz, 1H, ArH); 6.84 (br d, J = 3.5 Hz, 1H, ArH); 6.80 (dd, J_1 = 13.5 Hz, J_2 = 4.0 Hz, 2H, 2ArH); 6.75 (s, 1H, ArH); 6.61 (s, 1H, ArH); 3.86 (s, 3H, OCH_3); 3.82 (s, 6H, OCH_3, $PhOCH_3$); 3.28 (dd, J_1 = 18.5 Hz, J_2 = 3.0 Hz, 1H, 3-H_a); 3.03–2.90 (m, 2H, 4a-H, 10b-H); 2.86 (q, J = 19.0 Hz, 2H, 2-H, 3-H_b); 2.62–2.52 (m, 3H, 1-H_a, 6-H_2); 2.00–1.94 (m, 1H, 5-H_a); 1.85–1.72 (m, 1H, 5-H_b); 1.59 (q, J = 20.0 Hz, 1H, 1-H_b). ESIMS: m/z (relative intensity): 354 ($M+H^+$, 100). Anal. Calcd. for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.79; H, 7.65; N, 3.99.

3.1.9.4. (±)-*trans*-8,9-Dimethoxy-2-(p-tolyl)-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (15d). Obtained in 77.3% yield, mp 162–164 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.19, 7.16 (2d, J = 14.5 Hz, 4H, 4ArH); 6.75 (s, 1H, ArH); 6.61 (s, 1H, ArH); 3.85 (s, 3H, OCH_3); 3.80 (s, 3H, OCH_3); 3.26 (dd, J_1 = 18.0 Hz, J_2 = 3.0 Hz, 1H, 3-H_a); 2.97–2.79 (m, 2H, 4a-H, 10b-H); 2.85 (q, J = 19.0 Hz, 2-H, 3-H_b); 2.65-2.55 (m, 3H, 1-H_a, 6-H_2); 2.35 (s, 1H, $PhCH_3$); 1.99–1.93 (m, 1H, 5-H_a); 1.82–1.70 (m, 1H, 5-H_b); 1.58 (q, J = 19.5 Hz, 1H, 1-H_b). ESIMS: m/z (relative intensity): 338 ($M+H^+$, 100). Anal. Calcd. for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15. Found: C, 78.26; H, 8.03; N, 4.17.

3.1.9.5. (±)-*trans*-8,9-Dimethoxy-2-(4-(trifluoromethyl)phenyl)-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (15e). Obtained in 59.9% yield, mp 175–178 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.60 (d, J = 13 Hz, 2H, 2ArH); 7.40 (d, J = 13.0 Hz, 2H, 2ArH); 6.73 (s, 1H, ArH); 6.62 (s, 1H, ArH); 3.86 (s, 3H, OCH_3); 3.82 (s, 3H, OCH_3); 3.28 (dd, J_1 = 19.0 Hz, J_2 = 4.5 Hz, 1H, 3-H_a); 3.05–2.94 (m, 2H, 4a-H, 10b-H); 2.87 (q, J = 19 Hz, 2-H, 3-H_b); 2.70.65–2.58 (m, 3H, 1-H_a, 6-H_2); 2.01–1.93 (m, 1H, 5-H_a); 1.85–1.76 (m, 1H, 5-H_b); 1.58 (q, J = 19.0 Hz, 1H, 1-H_b). ESIMS: m/z (relative intensity): 392 ($M+H^+$, 100).

3.1.10. General procedure for *O*,*O*-demethylation to target compounds 5a–e

The corresponding amine **15a–e** was dissolved in dry CH_2Cl_2 and cooled to -78 °C. Into this flask, 3 mol equiv of a 1 M solution of BBr_3 in CH_2Cl_2 was added drop-wise. The reaction was stirred for 2 h at −78 °C and another 4 h at room temperature. The reaction was then cooled to 0 °C and 5 mL of MeOH was added drop-wise. The solvents were removed under reduced pressure, and 5 mL of MeOH was once again added and removed. The process was repeated one more time. The residue was recrystallized from EtOH/EtOAc to afford the products **5a–e** as hydrobromide salts.

3.1.10.1. (±)-*trans*-2-Phenyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline-8,9-diol Hydrobromide (5a). Obtained in 86.0% yield, mp 200–203 °C. ^{1}H NMR (CD_3OD, 500 MHz): δ 7.38–7.34 (m, 4H, 4ArH); 7.30–7.27 (m, 1H, ArH); 6.67 (s, 1H, ArH); 6.52 (s, 1H, ArH); 3.48 (d, J = 8.5 Hz, 1H, 3-H_a); 3.26–3.17 (m, 3H, 2-H, 4a-H, 3-H_a); 2.95–2.84 (m, 3H, 6-H_2, 10b-H); 2.66 (q, J = 12.1 Hz, 1H, 1-H_a); 2.21–2.18 (m, 1H, 5-H_a); 1.92–1.86 (m, 1H, 5-H_b); 1.74 (q, J = 11.8 Hz, 1H, 1-H_b). ESIMS: m/z (relative intensity): 296 ($M+H^+$, 100). Anal. Calcd. for $C_{19}H_{22}BrNO_2{\cdot}0.5H_2O$: C, 59.23; H, 6.02; N, 3.64. Found: C, 59.06; H, 5.74; N, 3.57.

3.1.10.2. (±)-*trans*-2-(4-Hydroxyphenyl)-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline-8,9-diol Hydrobromide (5b). Obtained in 82.7% yield, mp >270 °C. ^{1}H NMR (CD_3OD, 500 MHz): δ 7.17 (d, J = 14.0 Hz, 2H, 2ArH); 6.79 (d, J = 14 Hz, 2H, 2ArH); 6.69 (s, 1H, ArH); 6.53 (s, 1H, ArH); 3.44 (d, J = 13.0 Hz, 1H, 3-H_a); 3.21–3.07 (m, 3H, 2-H, 4a-H, 3-H_a); 2.94–2.85 (m, 3H, 6-H_2, 10b-H); 2.63 (d, J = 21 Hz, 1H, 1-H_a); 2.24–2.15 (m, 1H, 5-H_a); 1.96–1.82 (m, 1H, 5-H_b); 1.69 (q, J = 20.0 Hz, 1H, 1-H_b). ESIMS: m/z (relative intensity): 312 ($M+H^+$, 100). Anal. Calcd. for $C_{19}H_{22}BrNO_3{\cdot}0.4H_2O$: C, 57.12; H, 5.75; N, 3.51. Found: C, 57.13; H, 6.03; N, 3.42.

3.1.10.3. (±)-*trans*-2-(3-Hydroxyphenyl)-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline-8,9-diol Hydrobromide (5c). Obtained in 72.1% yield, mp >270 °C. ^{1}H NMR (CD_3OD, 500 MHz): δ 7.19 (d, J = 13.0 Hz, 1H, ArH); 6.81 (d, J = 13.0 Hz, 1H, ArH); 6.76 (d, J = 4.0 Hz, 1H, ArH); 6.72 (dd, J_1 = 14.0 Hz, J_2 = 3.0 Hz, 1H, ArH); 6.69 (s, 1H, ArH); 6.53 (s, 1H, ArH); 3.47 (d, J = 16.5 Hz, 1H, 3-H_a); 3.24–3.12 (m, 3H, 2-H, 4a-H, 3-H_a); 2.94–2.87 (m, 3H, 6-H_2, 10b-H); 2.66 (br d, J = 21 Hz, 1H, 1-H_a); 2.22–2.16 (m, 1H, 5-H_a); 1.93–1.86 (m, 1H, 5-H_b); 1.70 (q, J = 20.0 Hz, 1H, 1-H_b). ESIMS: m/z (relative intensity): 312 ($M+H^+$, 100). Anal. Calcd. for $C_{19}H_{22}BrNO_3$: C, 58.17; H, 5.65; N, 3.57. Found: C, 57.82; H, 5.73; N, 3.40.

3.1.10.4. (±)-*trans*-2-(*p*-Tolyl)-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline-8,9-diol Hydrobromide (5d). Obtained in quantitative yield, mp 217–220 °C. ^{1}H NMR (CD_3OD, 500 MHz): δ 7.24, 7.19 (2d, J = 14 Hz, 4H, 4ArH); 6.69 (s, 1H, ArH); 6.53 (s, 1H, ArH); 3.46 (d, J = 14.0 Hz, 1H, 3-H_a); 3.29–3.11 (m, 3H, 2-H, 4a-H, 3-H_a); 2.94–2.87 (m, 3H, 6-H_2, 10b-H); 2.64 (d, J = 20 Hz, 1H, 1-H_a); 2.32 (s, 3H, $PhCH_3$); 2.22–2.18 (m, 1H, 5-H_a); 1.93–1.86 (m, 1H, 5-H_b); 1.72 (q, J = 19.5 Hz, 1H, 1-H_b). ESIMS: m/z (relative intensity): 310 ($M+H^+$, 100). Anal. Calcd. for $C_{20}H_{24}BrNO_2$: C, 61.54; H, 6.20; N, 3.59. Found: C, 61.18; H, 6.04; N, 3.48.

3.1.10.5. (±)-*trans*-2-(4-(Trifluoromethyl)phenyl)-1,2,3,4,4a,5,6, 10b-octahydrobenzo[*f*] quinoline-8,9-diol Hydrobromide (5e).

Obtained in 66.0% yield, mp 205–209 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.82 (s, 1H, OH); 8.78 (s, 1H, OH); 7.72 (d, J = 8.5 Hz, 2H, 2ArH); 7.59 (d, J = 8.0 Hz, 2H, 2ArH); 6.60 (s, 1H, ArH); 6.44 (s, 1H, ArH); 3.46 (d, J = 9.5 Hz, 1H, 3-H_a); 3.32–3.17 (m, 2H, 4a-H, 10b-H); 3.11 (d, J = 10.5 Hz, 1H, 3-H_a); 2.84 (d, J = 10.5 Hz, 1H, 2-H); 2.73–2.71 (m, 2H, 6-H_2); 2.52 (d, J = 12.0 Hz, 1H, 1-H_a); 2.10–2.08 (m, 1H, 5-H_a); 1.80–1.74 (m, 1H, 5-H_b); 1.62 (q, J = 12.0 Hz, 1H, 1-H_b). ESIMS: m/z (relative intensity): 364 ($M+H^+$, 100). Anal. Calcd. for $C_{20}H_{22}BrNO_2 \cdot 0.9H_2O$: C, 52.16; H, 4.99; N, 3.04. Found: C, 51.87; H, 4.81; N, 3.21.

3.1.11. 1,2,3,4,4a,5,6,10b-Octahydro-8,9-dimethoxy-2-(4-methoxyphenyl)-4-propylbenzo[*f*]quinoline (16)

To a stirred solution of amine **15b** (76 mg, 0.215 mmol) in dry CH_2Cl_2 (6 mL) was added propanaldehyde (24 mg, 0.43 mmol) and AcOH (36 μL) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 1.5 h. Then sodium triacetoxyborohydride (180 mg, 0.848 mmol) was added and stirring was continued for an additional 12 h at room temperature. The reaction mixture was quenched by addition of H_2O and extracted with CH_2Cl_2. The crude reaction mixture was purified by Chromatotron to give the *n*-propyl amine **16** (70 mg, 82% yield) as an oily yellow liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.21 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 6.76 (s, 1H), 6.60 (s, 1H), 3.85 (s, 3H), 3.80 (s, 6H), 3.22–3.05 (m, 2H), 2.91-2.80 (m, 4H), 2.78–2.58 (m, 2H), 2.50–2.26 (m, 3H), 1.80–1.50 (m, 4H), 0.91 (t, J = 7.3 Hz, 3H). HRMS-ESI (m/z): Calcd for $C_{25}H_{33}NO_3$ $[M+H]^+$: 396.2539, found: 396.2537.

3.1.12. 1,2,3,4,4a,5,6,10b-Octahydro-2-(4-hydroxyphenyl)-4-propylbenzo[*f*]quinoline-8,9-diol Hydrobromide (5f)

n-Propylamine **16** (70 mg, 0.177 mmol) was dissolved in 10 mL dry CH_2Cl_2 and cooled to -78 °C. Into this flask, 3 mol equiv of a 1 M solution of BBr_3 in CH_2Cl_2 were added drop-wise. The reaction was stirred for 2 h at −78 °C and another 4 h at room temperature. The reaction was cooled to 0 °C and 5 mL of MeOH was added drop-wise. The solvents were removed under reduced pressure, 5 mL of MeOH was once again added and removed, and the process was repeated one more time. The residue was recrystallized from EtOH/EtOAc to afford the *n*-propyl compound **5f** (50 mg, 65% yield) as off-white solid (mp 195–197 °C). ^{1}H NMR (MeOD, 500 MHz): δ 7.16 (d, J = 8.5 Hz, 2H), 6.77 (d, J = 8.5 Hz, 2H), 6.69 (s, 1H), 6.52 (s, 1H), 3.43–3.41 (m, 1H), 3.39–3.33 (m, 1H), 3.25–3.11 (m, 4H), 3.03–2.96 (m, 1H), 2.90-2.84 (m, 2H), 2.64–2.56 (m, 1H), 2.56–2.47 (m, 1H), 1.87–1.67 (m, 4H), 1.02 (t, J = 7.3 Hz, 3H). ESIMS: m/z (relative intensity): 354 ($M+H^+$, 100). Anal. Calcd. for $C_{22}H_{28}BrNO_3$: C, 60.83; H, 6.50; N, 3.22. Found: C, 60.58; H, 6.60; N, 3.22.

3.2. Pharmacology

3.2.1. Materials

Radioligands used for this study were [^{3}H] SCH-23390 (80.5 Ci/mmol) and [^{3}H] *N*-methylspiperone (85.5 Ci/mmol), and were purchased from PerkinElmer Life Sciences (Massachusetts, United States). Chlorpromazine was purchased from VWR (West Chester, PA), SCH-23390 and ketanserin were purchased from Tocris Bioscience (Minneapolis, MN), and (±)-7-hydroxy-2-(di-*n*-propylamino)tetralin hydrobromide (7-OH-DPAT), and (+)-butaclamol were purchased from Sigma-Aldrich Chemical Company (St. Louis, MO, United States). Fatty acid free bovine serum albumin was purchased from MP biomedicals (Solon, OH). The DiscoveRX PathHunter eXpress GPCR β-arrestin assay for U2OS DRD3 β-arrestin cells was purchased from DiscoveRX (Fremont, CA). Opti-MEM was purchased from Invitrogen (Grand Island, NY). DHX and compound **4** were synthesized by our laboratory previously.[7,11] Striatal tissue used for competition binding experiments was dissected from porcine brain tissue obtained from Purdue Butcher Block and prepared as described previously.[8]

3.2.2. Cell culture

Human embryonic kidney 293 cells (HEK 293) were transiently transfected with pcDNA V5 His TOPO subcloned with the human dopamine D_1 receptor (hD_1), or pcDNA3.1(+) subcloned with either the human dopamine D_{2Long} receptor isoform (hD_2) or human dopamine D_3 receptor (hD_3) The hD_1 receptor expressed approximately 2840 fmol/mg protein as determined by saturation binding with [^{3}H] SCH-23390, and hD_2 and hD_3 receptors expressed approximately 2500 and 1980 fmol/mg protein, respectively, as determined by saturation binding with [^{3}H] *N*-methylspiperone. 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. Cells were grown at 37 °C in a humidified incubator with 5% CO_2.

3.2.3. Competition binding experiments

Competition binding experiments utilized 1–2 nM [^{3}H] SCH-23390 for D_1-like and HEK D_1 receptor binding, and 0.2–0.4 nM [^{3}H] *N*-methylspiperone for D_2-like and HEK D_2 and D_3 receptor binding. For D_2-like binding in porcine striatal tissue, 50 nM ketanserin was included to block native 5-HT_{2A} receptors. Experiments were performed with either porcine binding buffer (50 mM HEPES, 4 mM $MgCl_2$, pH 7.4) or receptor binding buffer (50 mM Tris, 4 mM $MgCl_2$, pH 7.4) in the case of HEK cells. Experiments used 96 well assay tubes containing several dilutions of test drug, radioligand, and either porcine striatal or HEK membrane preparations. Non-specific 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 by 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.

3.2.4. D_3 receptor functional assay

The DiscoveRX PathHunter eXpress GPCR β-arrestin assay for D_3 dopamine receptor function in U2OS-D_3 cells was performed as described in the manufacturer's protocol. Briefly, cryopreserved cells were rapidly thawed, resuspended in optimized cell culture (OCC) media, seeded into Costar 96 well half area plates (solid, white), and incubated at 37 °C and 5% CO_2 for 48 h. Cells were stimulated with test compounds in assay buffer (opti-MEM, 0.1% fatty acid free bovine serum albumin) at 37 °C and 5% CO_2 for 1.5 h. Working reagent was prepared according to the manufacturer's instructions and added to the cells. Following an incubation at room temperature for 1 h, the resulting luminescence was read using a Synergy4 (BioTek) plate reader.

3.2.5. Data analysis

Nonlinear regression for radioligand displacement and dose-response curves was performed using GraphPad Prism version 4 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com. For radioligand displacement, the bottoms of curves were set to nonspecific binding values to generate IC50 values for test compounds. K_i values were calculated by the Cheng-Prusoff equation using the radioligand concentration and previously established K_d values as determined by saturation analysis. For porcine striatal tissue, K_d values used were 0.44 nM and 0.075 nM for D_1-like and D_2-like binding, respectively. For HEK recombinant systems, K_d values used were 1.2, 0.045, and 0.57 nM

for hD_1, hD_2, and hD_3, respectively. For D_3 dopamine receptor function, nonlinear regression sigmoidal dose-response analysis (fixed slope) was used to generate EC_{50} values. All data from D_3 receptor functional assay were expressed as a percent of the basal response, and percent E_{max} ($\%E_{max}$) was calculated relative to 1 μM dopamine.

3.3. Molecular modeling

Molecules were energy minimized as the protonated species in a vacuum using Sybyl for Linux, version 8.1.1 (Tripos, St. Louis, MO.). All possible confomers of each molecule were manually constructed and geometry-optimized using MMFF94s force fields.

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