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Modification of agonist binding moiety in hybrid derivative 5/7-{[2-(4-aryl-piperazin-1-yl)-ethyl]-propyl-amino}-5,6,7,8-tetrahydro-naphthalen-1-ol/-2-amino versions: Impact on functional activity and selectivity for dopamine D2/D3 receptors

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ABSTRACT

The goal of the present study was to explore, in our previously developed hybrid template, the effect of introduction of additional heterocyclic rings (mimicking catechol hydroxyl groups as bioisosteric replacement) on selectivity and affinity for the D_3 versus D_2 receptor. In addition, we wanted to explore the effect of derivatization of functional groups of the agonist binding moiety in compounds developed by us earlier from the hybrid template. Binding affinity (K_i) of the new compounds was measured with tritiated spiperone as the radioligand and HEK-293 cells expressing either D_2 or D_3 receptors. Functional activity of selected compounds was assessed in the GTPγS binding assay. In the imidazole series, compound **10a** exhibited the highest D_3 affinity whereas the indole derivative **13** exhibited similar high D_3 affinity. Functionalization of the amino group in agonist (+)-**9d** with different sulfonamides derivatives improved the D_3 affinity significantly with (+)-**14f** exhibiting the highest affinity. However, functionalization of the hydroxyl and amino groups of **15** and (+)-**9d**, known agonist and partial agonist, to sulfonate ester and amide in general modulated the affinity. In both cases loss of agonist potency resulted from such derivatization.

1. Introduction

The dopamine (DA) receptor system has been targeted for drug development for a number of central nervous system (CNS) disorders, including drug abuse, schizophrenia, and Parkinson's disease (PD).[1,2] DA receptors are found throughout the CNS and periphery. So far five subtypes of DA receptors have been identified and are classified as being either D_1-like or D_2-like.[3] These classifications are based on receptor pharmacology and function.[4–7] The D_1-like receptors, which include the D_1 and D_5 subtypes, activate adenylate cyclase activity upon receptor activation. The D_2-like receptors, which include the D_2, D_3, and D_4 subtypes, inhibit adenylate cyclase activity. The D_3 receptor was found to have a distribution in the brain that is different from that of the D_2 receptor.[8,9] Recent study on the brain distribution of D_3 receptors indicated highest density in the nucleus accumbens. In addition D_3 receptors are also expressed at a higher level compared to D_2 receptors in the extrastriatal regions and also in the thalamus.[9] The D_2 and D_3 receptor subtypes posses 50% overall structural homology, and 75–80% in the agonist binding domains.[10,11] It is important to mention that D_3 receptor bound to an antagonist was recently crystallized to provide a detail molecular structure.[12]

Many compounds with various selectivities for the D_3 versus D_2 receptor have been developed.[13,14] Due to high homology, development of selective agonists for D_3 receptor is rather difficult as both receptors share nearly identical active binding sites for agonist interaction.[15–17] Some of the well known D_3 selective agonists include ropinirole and pramipexole, and these agonists were shown to exhibit a 4- to 10-fold higher affinity for the D_3 than D_2 receptor.[18] In comparison, the field has faced fewer obstacles in developing highly selective D_3 antagonists. In the majority of these compounds there is a piperazine ring connected to a suitable benzamide-type moiety via a variable-size linker, such as in BP 897 (Fig. 1).[13,14,19]

Based on our previously developed hybrid molecular template, we have recently generated highly selective D_3 agonists such as D-264, D-301 and D-440 (see Fig. 1).[20–24] Our subsequent structure-

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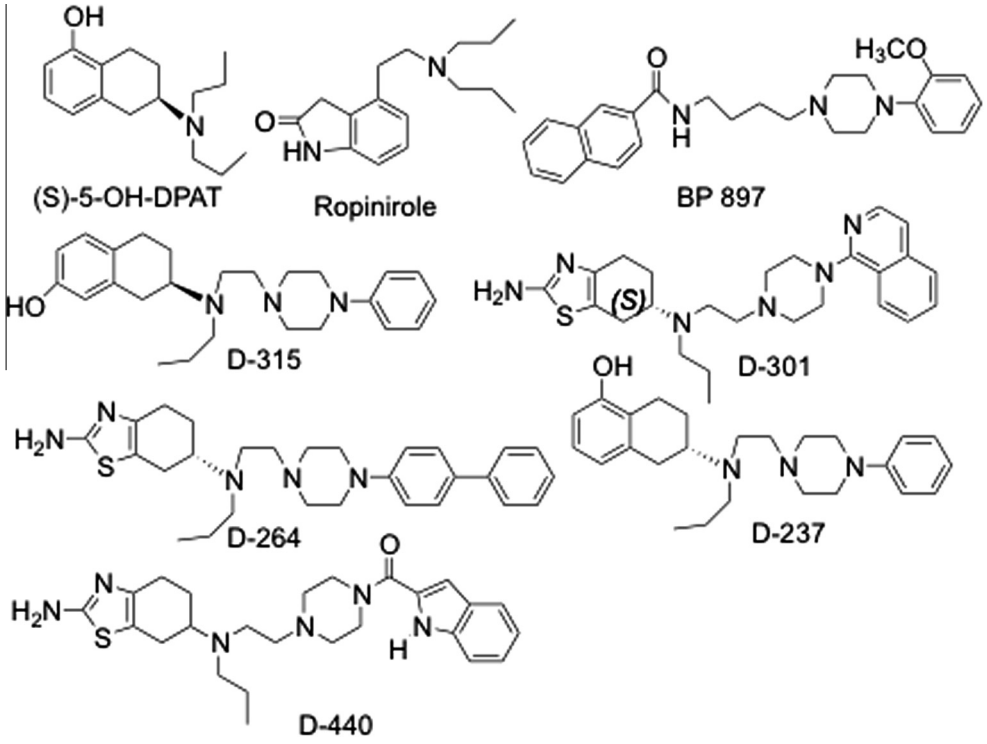


Figure 1.

activity relationship (SAR) studies explored the effect of replacement of the catechol moiety by different heterocyclic rings and also the impact of various molecular modifications at the distal aromatic site connected to the piperazine ring.[21–26] In our current SAR studies, we wanted to explore the effect of introduction of additional heterocyclic rings mimicking catechol hydroxyl groups as bioisosteric replacement, on selectivity and affinity for the D_3 receptor. In addition, we wanted to explore the effect of substitutions in functional groups of the agonist binding moiety in our hybrid template.

2. Chemistry

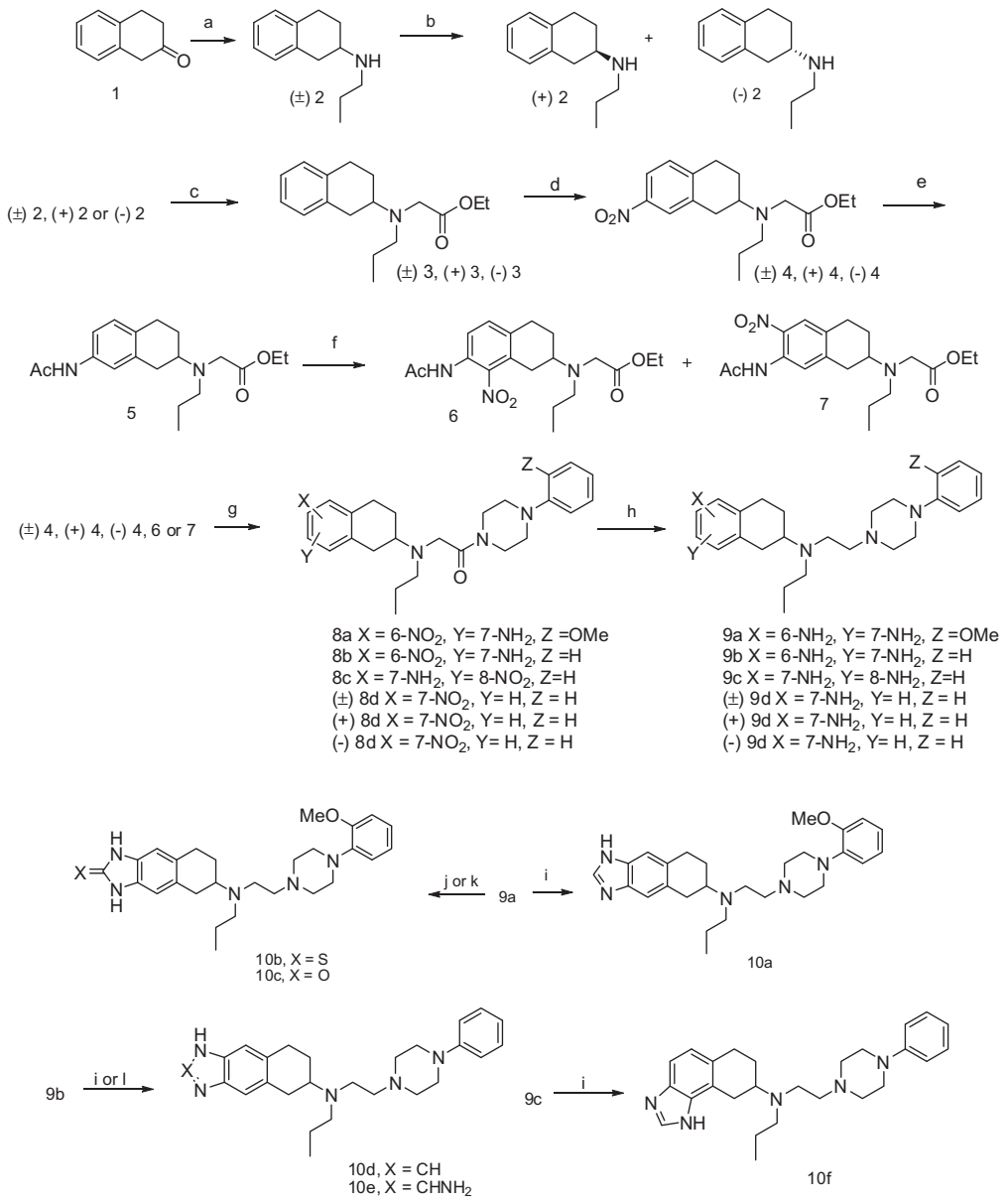
Scheme 1 describes the synthesis of final targets **10a**–**f**. Tetralone **1** was reacted with *N*-propylamine under reductive amination reaction conditions to give **2**, which was resolved by chiral 4-(2-chlorophenyl)-2-hydroxy-5,5-dimethyl-1,3,2-dioxaphosphorinane 2-oxide, prepared according to the literature.[22] Then, N-alkylation of (±)-**2**, (+)-**2**, and (−)-**2** with ethylbromoacetate in acetonitrile in the presence of K_2CO_3 was achieved to produce compounds (±)-**3**, (+)-**3**, and (−)-**3** in quantitative yield. Nitration of these compounds was achieved by using fuming HNO_3 to yield 7-nitro derivative (±)-**4**, (+)-**4**, (−)-**4** exclusively. Subsequent reduction of (±)-**4** and acetylation of the resulting aniline yielded **5** quantitatively. Further nitration of **5** with fuming HNO_3 resulted in isomeric mixture of 6- and 8-nitro derivatives **7** and **6**, respectively and which were separated from one another by column chromatography. The acetate esters (±)-**4**, (+)-**4**, (−)-**4**, **6**, and **7** were subjected to acid hydrolysis followed by coupling with (un)substituted piperazines, thus producing piperazine amides **8a**–**d**, (+)-**8d**, and (−)-**8d**. Catalytic reduction of the nitro group followed by amide reduction using borane/THF complex gave intermediates **9a**–**d**, (+)-**9d**, and (−)-**9d** which were used as the starting materials for preparation of the final compounds **10a**–**f**. Phenylenediamine **9a** was treated[27] with formic acid to form imidazole **10a** and under similar conditions compounds **9b** and **9c** gave isomeric imidazoles **10d** and **10f**, respectively.[28] Compound **10e** was obtained by reaction of compound **9b** with CNBr.[29] In another synthesis, compound **9a** on reaction[30] with CS_2 and KOH gave imidazol-2-thione **10b**, whereas reaction of **9a** with 1,1′-carbonyldiimidazole resulted[31] in imidazol-2-one **10c**.

Scheme 2 outlines the synthesis of compounds **13** and **14a**–**f**. In order to synthesize indole **13**, compound **9d** was reacted with bromoacetaldehyde diethyl acetal to give **11**. N-Acetylation with subsequent hydrolysis and cyclization to indole intermediate of **11** was carried out using a mixture of trifluoroacetic acid and trifluoroacetic anhydride to yield **12** in moderate yield. Removal of *N*-trifluoroacetyl group was performed in refluxing MeOH leading to the final compound **13**.[32] In order to make sulfonamides and amides (**14a**–**f**), compound **9d** and (+)-**9d** were reacted with corresponding sulfonyl chlorides and benzoyl/acetyl chlorides in the presence of pyridine to yield sulfonamides **14a**–**f** and (**+**)-**14f**.[33]

Scheme 3 depicts the synthesis of compounds **16a**, **16b**, and **18**. Compound **15**[22] was treated with 4-methyl benzenesulfonyl chloride and 4-methoxy benzenesulfonyl chloride in the presence of triethylamine in dichloromethane to afford compounds **16a** and **16b**, respectively. Finally, compound **18** was achieved by reaction of known compound **17**[20] with 4-methoxy benzenesulfonyl chloride.

3. Results and discussion

In our goal to explore the effect of addition of an heterocyclic moiety mimicking catechol hydroxyl groups bioisosterically on a phenyl ring, compounds **10a**–**f** and **13** were designed and synthesized. In this set, compound **10a** exhibited relatively higher affinity for the D_3 receptor with good selectivity (K_i, D_3 = 19.7 nM, D_2/D_3 = 22.5). Compounds **10f** and **10d** were moderately potent at the D_3 receptor. These three compounds are imidazole derivatives, and in the past such derivatives have shown high affinity for the D_2 receptor.[34] Similar to imidazole containing compounds, indole derivative **13** displayed similar modest affinity at D_3 and weaker

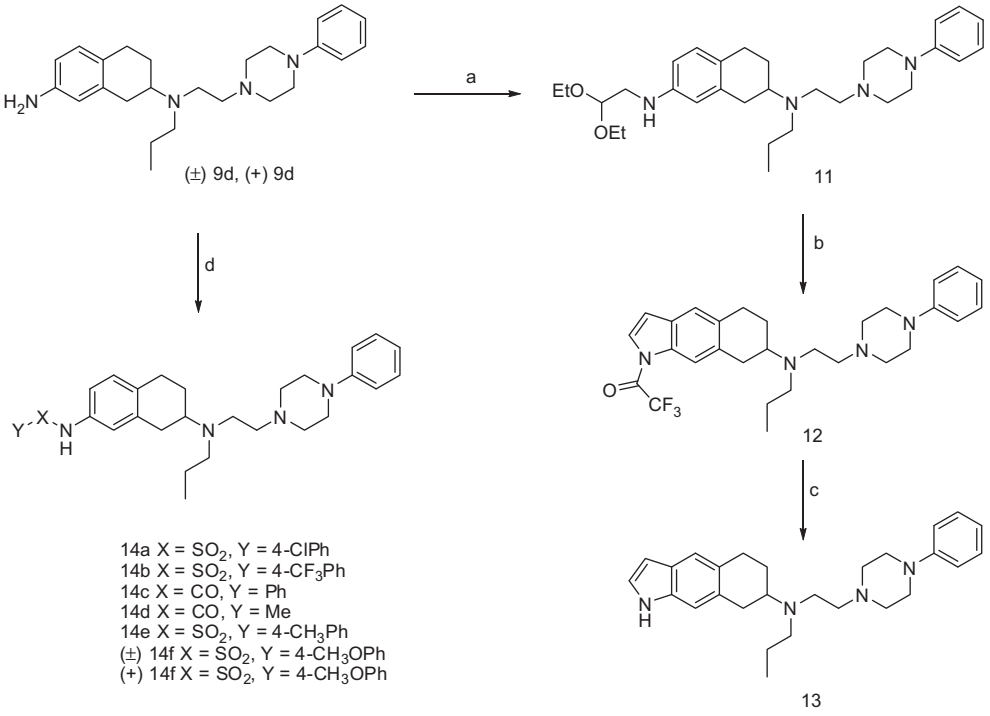


Scheme 1. Reagents and conditions: (a) *n*-Propylamine, $NaCNBH_3$, AcOH, 1,2-dichloroethane; (b) (+) or (−) chlocyphos, ethanol, recrystallized from isopropanol; (c) $BrCH_2$ CO_2 Et, K_2 CO_3, AcCN; (d) fuming HNO_3; (e) (i) 10% Pd/C, H_2, EtOH, (ii) AcCl, Et_3N, CH_2 Cl_2; (f) fuming HNO_3; (g) (i) conc, HCl, (ii) EDCI, HtOH, 1-(2-substituted phenyl)piperazine, CH_2Cl_2; (h) (i) 10% Pd/C, H_2, CH_3 OH, (ii) BH_3, THF; (i) HCOOH; (j) CS_2, KOH, EtOH; (k) 1,1′-carbonyldiimidazole, AcCN; (I)CNBr, H_2O.

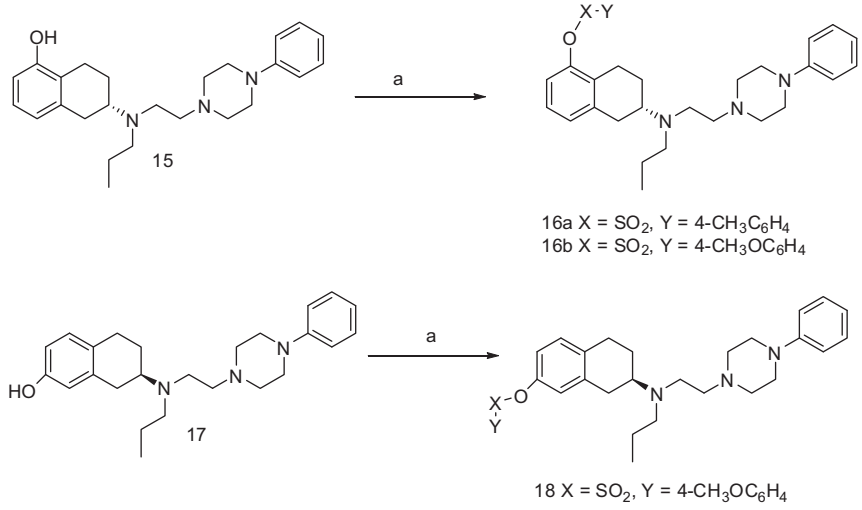
affinity at D_2 receptors (K_i; D_2 = 127 nM and D_3 = 10.7 nM, Table 1). Benz[*e*]indole derivatives have been shown in the past to exhibit potent agonist activity for the dopamine D_2 receptor.[35] The remaining compounds in the series were weak to inactive. Collectively, the current results show that introduction of a heterocyclic moiety in our hybrid molecules are well to modestly tolerated.

We next wanted to evaluate the effect of various substitutions on the amino and hydroxyl functional groups of **9d**, **15** and **17**. We previously characterized these molecules as potent and selective agonists for D_3 receptors.[22,25] Compounds **14a**–**f** were designed to explore the effect of different electron withdrawing and donating groups on affinity and selectivity for the D_3 receptor. In this effort, compound **9d** was converted into **14a**–**f** by derivatization of the amino group to various sulfonamides and amides. The sulfonamides **14e** and **14f** containing electron donating groups exhibited the highest affinity for D_3 receptor (K_i, D_3 = 3.69 and 2.22 nM for **14e** and **14f**, respectively, Table 1) in this series. In this regard, **14f** was relatively more selective for D_3 receptors compared to p-toluene sulfonamide derivative **14e** (D_2/D_3, 29.2 vs 10.6 for **14f** and **14e**, respectively). Enantiomerically pure (+)-**14f** exhibited higher selectivity (D_2/D_3 = 43.5). Similarly, sulfonamides **14a**–**b** showed an interesting trend of activity. Thus, **14a** and **14b** containing electronegative 4-Cl and 4-CF_3 substitutions exhibited high affinity (K_i; D_3 = 4.13 and 8.64 nM for **14a** and **14b**, respectively) although they were less potent compared to **14e** and **14f**. Interestingly, benzamide and acetamide compounds **14c**–**d** were much weaker at D_3 (K_i; D_3 = 109 and 174 nM for **14c** and **14d**, respectively, Table 1).

Next in our effort to evaluate the effect on modification of functional OH group in D_3 preferring potent agonists **15**[22] and D_3 preferring compound **17**, compounds **16a**–**b** and **18** were designed. Previously, compound **15** was shown to exhibit potent agonist activity in vitro and in vivo experiments.[22] Conversion of the hydroxyl group in this compound to sulfonate ester provided **16a**,



Scheme 2. Reagent and conditions: (a) Bromoacetaldehyde diethyl acetal, Na_2CO_3, EtOH, reflux; (b) $(CF_3CO)_2/CF_3$ COOH, reflux; (c) MeOH, reflux; (d) YXCl, pyridine (for **14a**, 4-$ClC_6H_4SO_2Cl$; for **14b**, 4-$CF_3C_6H_4SO_2Cl$); for **14c**, PhCOCl; for **14d**, AcCl; for **14e**, 4-$CH_3C_6h_4SO_2Cl$; for (±)**14f** and (+)**14f**, 4-$CH_3OC_6h_4SO_2Cl$).



Scheme 3. Reagents and conditions: (a) YXCl, Et_3N, DCM, over night (For **16a**, 4-$CH_3C_6H_4SO_2Cl$; for **16b** and **18**, 4-$CH_3OC_6H_4SO_2Cl$).

16b and **18**. Compound **16b**, containing the 4-methoxy substituent, exhibited comparable activity to 4-methyl substituted **16a** (K_i, D_3 = 17.6 vs 32.0 nM for **16b** and **16a**, respectively). Overall, sulfonamide derivatives produced from **9d** showed higher affinity for D_2/D_3 compared to sulfone ester derived from (−)-**15** and (+)-**17** (see Table 1).

Our recent work points to hydroxyl group functionality playing a critical role in agonist activity of hybrid compounds.[36] Thus, compound **15** (D-237), a potent agonist for D_2/D_3 receptors, was shown to exhibit much lower affinity for the D_3 receptor mutant S192A, indicating a critical role of the hydroxyl group in interacting with serine-192 in the agonist binding cavity of the receptor.[36] In this regard, it has been demonstrated that serine-192 plays a critical role via H-bond formation in agonist activity at the D_3 receptor. Thus, we wanted to evaluate whether functionalization of this hydroxyl group in **15** will lead to any changes in agonist activity. Indeed, compound (−)-**16b** which is derived from agonist (−)-**15** (**D-237**), failed to show any agonist activity in the GTPγS binding assay (Table 2). Similarly, (+)-**14f**, derived from partial agonist (+)-**9d**, displays high affinity and selectivity for D_3 selective molecule but was inactive in the functional assay (Table 2). These results reinforce the critical requirement of the hydroxyl and amino groups for interaction with the agonist binding domains e.g. S192A, in the D_3 binding pocket, in order for the receptor to become activated. Finally, recently a crystal structure of human D_3 receptor complexed with D_2/D_3 antagonist eticlopride was identified.[12] Further docking of another D_3 antagonist in D_3 molecular structure identified a second binding pocket unique to D_3 receptor,

Table 1
Affinity for cloned rat D_{2L} and D_3 receptors expressed in HEK293 cells measured by inhibition of [^{3}H]spiperone binding

Compound	K_i (nM), rD2L [^{3}H]spiperone	K_i (nM), rD3 [^{3}H]spiperone	D2L/D3
(−)-5-OH-DPAT	58.8 ± 11.0	1.36 ± 0.28	43.2
Ropinirole	2,674 ± 305	29.3 ± 4.2	91.3
(+)-**17** D-315[c]	40.6 ± 3.6	1.77 ± 0.42	22.9
(−)-**15** D-237[a]	26.0 ± 7.5	0.825 ± 0.136	31.5
D-264[b]	264 ± 40	0.92 ± 0.23	253
D-301	269 ± 16	2.23 ± 0.60	121
D-440	1,073 ± 92	1.84 ± 0.51	583
9d	638 ± 40	22.2 ± 3.8	28.7
(+)-**9d** (D-515)	601 ± 98	20.2 ± 2.1	29.8
(−)-**9d** (D-516)	2,707 ± 178	45.5 ± 8.8	59.6
10a (D-261)	443 ± 57	19.7 ± 1.3	22.5
10b (D-262)	230 ± 25	112 ± 41	2.05
10c (D-263)	417 ± 93	195 ± 62	2.14
10f (D-311)	520 ± 22	54.1 ± 12.8	9.61
10d (D-312)	1,280 ± 218	60.0 ± 12.9	21.3
10e (D-314)	15,922 ± 3,820	1,790 ± 215	8.89
13 (D-355)	127 ± 2	10.7 ± 2.32	11.9
14a (D-357)	72.4 ± 7.3	4.13 ± 0.90	17.5
14b (D-358)	91.2 ± 6.1	8.64 ± 2.10	10.6
14c (D-359)	624 ± 54	109 ± 37	5.72
14d (D-360)	1,296 ± 322	174 ± 28	7.44
14e (D-397)	39.2 ± 6.1	3.69 ± 0.61	10.6
14f (D-401)	64.9 ± 12.0	2.22 ± 0.22	29.2
(+)-**14f** (D-532)	101 ± 10	2.32 ± 0.35	43.5
(−)-**16b** (D-399)	497 ± 214	17.6 ± 3.1	28.2
16a (D-400)	632 ± 264	32.0 ± 12.6	19.8
18 (D-398)	1,076 ± 375	26.9 ± 4.77	40.0

Results are the mean ± SEM for three to eight experiments, each performed in triplicate.
[a] From our previous work (Ref. 22).
[b] From our previous work (Ref. 21).
[c] From our previous work (Ref. 25).

Table 2
Stimulation of [^{35}S]GTPγS binding to cloned human D2 and D3 receptors expressed in CHO cells

D-compound	hCHO-D2		hCHO-D3		
	EC_{50} (nM)	E_{max} (%)	EC_{50} (nM)	E_{max} (%)	D_2/D_3
Dopamine	227 ± 11[a]	100	7.64 ± 0.56	100	26.6
D-301[a]	116 ± 16	88.4 ± 3.9	0.82 ± 0.20	102 ± 2	141
D-440[c]	114 ± 12	101 ± 5	0.26 ± 0.07	103 ± 10	438
(−)-**15** D-237[b]	2.22 ± 0.27	63.4 ± 3.5			
(−)-**16b** D-399	Not active		Not active		
(+)-**9d** D-515	179 ± 47	36.8 ± 8.7	30.3 ± 6.4	58.6 ± 4.8	
(+)-**14f** D-532	Not active		Not active		

EC_{50}, the concentration producing half-maximal stimulation, is shown as the mean ± SEM for three to four experiments, each performed in triplicate.
[a] From our previous work.[23]
[b] From our previous work.[22]
[c] From our previous work.[24]

indicating the reason for selectivity for D_3.[12] This information should be useful for development of selective antagonist. In the current context of our work, which focuses on development of agonist, it would be interesting to see whether the D_3 molecular structure could potentially be used to develop selective D_3 agonist even though the agonist binding domains for both D_2 and D_3 receptors are very similar. Although, identification of involvement of any accessory binding sites for agonists unique to D_3 receptor should provide selectivity for D_3 preferring agonists.

4. Conclusion

The results from our current SAR studies have provided additional insight on molecular structural requirements for introduction of an heterocyclic ring onto the phenyl ring of the hybrid template. Appropriate location of *N*-atoms in these heterocyclic ring can potentially provide H-bonding thereby acting as a bioisosteric replacement of hydroxyl group. Imidazole derivative **10a** and the indole derivative **13** produced comparable affinity for D_3 receptor, however, **13** exhibited higher affinity for D_2 compared to **10a**. Interestingly, the effect of substitutions on amino functionality in compound **9d** was different compared to the effect of substitutions on the hydroxyl group of **15** and **17**. Sulfonamide derivative (+)-**14f** derived from (+)-**9d** produced significant gain in affinity for both D_2 and D_3 receptors compared to the parent molecule but lost functional agonist activity.

5. Experimental section

Reagents and solvents were purchased from commercial suppliers and used as received unless otherwise noted. Dry solvents were obtained following the standard procedure. All reactions were performed under N_2 atmosphere unless otherwise indicated. Analytical silica gel 60 F_{254}-coated TLC plates were purchased from EMD Chemicals, Inc. and were visualized with UV light or by treatment with phosphomolybdic acid (PMA), Dragendorff's reagent or ninhydrin. Whatman Purasil® 60A silica gel 230–400 mesh was used for flash column chromatographic purifications. The proton nuclear magnetic resonance (^{1}H NMR) spectra were measured on Varian 400 MHz FT NMR spectrometer using tetramethylsilane (TMS) as an internal standard. The NMR solvent used was $CDCl_3$ unless otherwise indicated. Mass spectra were recorded on Micromass QuattroLC triple quadrupole mass spectrometer. Melting points were recorded using MEL-TEMP II (Laboratory Devices Inc., USA) capillary melting point apparatus and were uncorrected. Elemental analyses were performed by Atlantic Microlab, Inc. and were within ±0.4% of the theoretical value.

5.1. *N*-Propyl-1,2,3,4-tetrahydronaphthalen-2-amine ((±)-2)

A mixture 2-tetralone **1** (5 g, 35.7 mmol), *n*-propylamine (4.22 g, 71.3 mmol) and glacial acetic acid (3 mL) in 1,2-dichloro-

ethane (100 mL) was stirred at room temperature for 20 min. $NaCNBH_3$ (6.72 g, 107 mmol) dissolved in methanol (15 mL) was added to the above reaction mixture. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and saturated $NaHCO_3$ solution (30 mL) was added to the mixture, which was then extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated in vacuo to afford the crude product, which was further purified by column chromatography (EtOAc/MeOH/Et_3N 95:4:1) to give the product (±)-**2** (6.14 g, 91%) as a brown viscous liquid. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.94 (t, J = 7.6 Hz, 3H), 1.28 (br s, 1H), 1.49–1.64 (m, 3H), 2.02–2.08 (m, 1H), 2.56–2.62 (m, 1H), 2.68 (t, J = 7.2 Hz, 2H), 2.81–2.87 (m, 2H), 2.89–2.92 (m, 1H), 3.02 (dd, J = 15.2, 4.8 Hz, 1H), 7.05–7.11 (m, 4H).

5.2. Resolution of *N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine ((±)-2)

Racemic (±)-**2** was resolved into its (+)- and (−)-isomers by using both (−)- and (+)-isomers of the synthetic resolving agent 4-(2-chlorophenyl)-2-hydroxy-5,5-dimethyl-1,3,2-dioxaphosphorinane 2-oxide. This optically active resolving agent was prepared according to the published procedure. Compound (±)-**2** (7.5 g, 39.62 mmol) and (+)-4-(2-chlorophenyl)-2-hydroxy-5,5-dimethyl-1,3,2-dioxaphosphorinane 2-oxide (10.85 g, 39.22 mmol) were dissolved by warming in 40 mL of ethanol. The solution was cooled to room temperature and then to 0 °C. The precipitated crystals were filtered off, washed with cold ether to yield 7.5 g of the salt ($[\alpha]_D^{25}$ = −4.6° (*c* 1, MeOH). Further recrystallization (two times) from hot isopropanol yielded the salt, 6.8 g ($[\alpha]_D^{25}$ = −11.7° (*c* 1, MeOH). Further crystallization of the salt from hot isopropanol did not change the optical rotation any further. The salt was then hydrolyzed in the presence of 20% NaOH solution in water under stirring conditions for 2 h at room temperature. The aqueous layer was extracted with dichloromethane (3 × 150 mL), dried over Na_2SO_4, and evaporated to dryness to yield (−)-**2** (2.6 g, 35%). ($[\alpha]_D^{25}$ = −84.6° (*c* 1, MeOH).

(±)-**2** (4.4 g, 23.24 mmol) was similarly treated by using (−)-4-(2-chlorophenyl)-2-hydroxy-5,5-dimethyl-1,3,2-dioxaphosphorinane 2-oxide (6.36 g, 23.01 mmol). Recrystallization from hot isopropanol yielded the salt, 3.8 g ($[\alpha]_D^{25}$ = +11.6° (*c* 1, MeOH). Further crystallization of the salt from hot isopropanol did not change the optical rotation to a significant extent. Hydrolysis of the salt following the above-mentioned procedure yielded (+)-**2** (1.4 g, 32%). ($[\alpha]_D^{25}$ = +82. 8° (*c* 1, MeOH).

5.3. Procedure A: ethyl 2-(propyl(1,2,3,4-tetrahydronaphthalen-2-yl)amino)acetate ((±)-3)

Into the stirred suspension of compound (±)-**2** (9.0 g, 47.54 mmol), anhydrous K_2CO_3 (19.71 g, 143 mmol) in acetonitrile (200 mL) was added ethyl 2-bromoacetate (9.53 g, 57.05 mmol). The reaction mixture was refluxed overnight, cooled to room temperature and filtered. The residue was washed with ethyl acetate and the combined filtrate was evaporated to obtain the crude product, which was purified by column chromatography (hexanes/EtOAc 1:4) to afford (±)-**3** (12.3 g, 94%) as a brown viscous liquid. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.86 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 1.47–1.65 (m, 3H), 2.04–2.11 (m, 1H), 2.64–2.69 (m, 2H), 2.69–2.97 (m, 4H), 3.06–3.13 (m, 1H), 3.40 (s, 2H), 4.17 (q, J = 7.2 Hz, 2H), 7.05–7.11 (m, 4H).

5.4. (*R*)-Ethyl 2-(propyl(1,2,3,4-tetrahydronaphthalen-2-yl)amino)acetate ((+)-3)

This compound was prepared following procedure A in which compound (+)-**2** (1.2 g, 6.34 mmol), ethyl 2-bromoacetate (0.84 mL, 7.61 mmol), and anhydrous K_2CO_3 (2.63 g, 19.02 mmol) were used to afford compound (+)-**3** (1.58 g, 90%) as a brown viscous liquid. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.86 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 1.47–1.65 (m, 3H), 2.04–2.11 (m, 1H), 2.64–2.69 (m, 2H), 2.69–2.97 (m, 4H), 3.06–3.13 (m, 1H), 3.40 (s, 2H), 4.17 (q, J = 7.2 Hz, 2H), 7.05–7.11 (m, 4H).

5.5. (*S*)-Ethyl 2-(propyl(1,2,3,4-tetrahydronaphthalen-2-yl) amino)acetate ((−)-3)

This compound was prepared following procedure A in which compound (−)-**2** (0.6 g, 3.17 mmol), ethyl 2-bromoacetate (0.42 mL, 3.80 mmol), and anhydrous K_2CO_3 (1.31 g, 9.51 mmol) were used to afford compound (−)-**3** (0.72 g, 88%) as a brown viscous liquid. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.86 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 1.47–1.65 (m, 3H), 2.04–2.11 (m, 1H), 2.64–2.69 (m, 2H), 2.69–2.97 (m, 4H), 3.06–3.13 (m, 1H), 3.40 (s, 2H), 4.17 (q, J = 7.2 Hz, 2H), 7.05–7.11 (m, 4H).

5.6. Procedure B: Ethyl 2-((7-nitro-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)acetate ((±)-4)

Fuming HNO_3 (90%, 90 mL) was transferred through cannula into a 250-mL round bottom flask cooled to −50 °C containing compound (±)-**3** (11.0 g, 39.97 mmol). The mixture was stirred at −20 °C for 30 min and poured onto ice. It was neutralized by 20% NaOH solution at 0 °C and extracted by ethyl acetate (3 × 150 mL). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated to obtain the crude product, which was purified by column chromatography (hexanes/EtOAc 1:4) to afford (±)-**4** (11.0 g, 86%) as a brown viscous liquid. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.90 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 1.45–1.54 (m, 2H), 1.58–1.72 (m, 1H), 2.11–2.15 (m, 1H), 2.66 (t, J = 7.6 Hz, 2H), 2.76–2.92 (m, 2H), 2.98–3.07 (m, 2H), 3.12–3.20 (m, 1H), 3.42 (s, 2H), 4.17 (q, J = 6.8 Hz, 2H), 7.19–7.23 (m, 1H), 7.92–7.96 (m, 2H).

5.7. (*R*)-Ethyl 2-((7-nitro-1,2,3,4-tetrahydronaphthalen-2-yl) (propyl)amino)acetate ((+)-4)

This compound was prepared following procedure B in which compound (+)-**3** (0.6 g, 2.18 mmol) and Fuming HNO_3 (90%, 6 mL) were used to afford compound (+)-**4** (0.61 g, 87%) as a brown viscous liquid. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.90 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 1.45–1.54 (m, 2H), 1.58–1.72 (m, 1H), 2.11–2.15 (m, 1H), 2.66 (t, J = 7.6 Hz, 2H), 2.76–2.92 (m, 2H), 2.98–3.07 (m, 2H), 3.12–3.20 (m, 1H), 3.42 (s, 2H), 4.17 (q, J = 6.8 Hz, 2H), 7.19–7.23 (m, 1H), 7.92–7.96 (m, 2H).

5.8. (*S*)-Ethyl 2-((7-nitro-1,2,3,4-tetrahydronaphthalen-2-yl) (propyl)amino)acetate ((−)-4)

This compound was prepared following procedure B in which compound (−)-**3** (0.2 g, 0.73 mmol) and Fuming HNO_3 (90%, 2 mL) were used to afford compound (−)-**4** (0.2 g, 87%) as a brown viscous liquid. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.90 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 1.45–1.54 (m, 2H), 1.58–1.72 (m, 1H), 2.11–2.15 (m, 1H), 2.66 (t, J = 7.6 Hz, 2H), 2.76–2.92 (m, 2H), 2.98–3.07 (m, 2H), 3.12–3.20 (m, 1H), 3.42 (s, 2H), 4.17 (q, J = 6.8 Hz, 2H), 7.19–7.23 (m, 1H), 7.92–7.96 (m, 2H).

5.9. Ethyl 2-((7-acetamido-1,2,3,4-tetrahydronaphthalen-2-yl) (propyl)amino)acetate (5)

To the stirred solution of (±)-**4** (11.0 g, 34.36 mmol) in dry EtOH (100 mL) was added 10% Pd/C (1.10 g). The reaction was continued

under 50 psi H_2 for 3 h and the reaction mixture was filtered through celite. Solvent was evaporated to afford crude compound (9.8 g, 98%). Acetyl chloride (2.94 mL, 41.32 mmol) was added into a solution of the crude compound (9.8 g, 33.75 mmol) and Et_3N (14.4 mL) in anhydrous CH_2Cl_2 at 0 °C and then stirred at room temperature for 4 h. The reaction mixture was diluted with CH_2Cl_2, washed with brine and the organic layer was dried (Na_2SO_4), evaporated in vacuo and the residue was purified by column chromatography (EtOAc/hexanes 1:1) to afford compound **5** (11.0 g, 98%) as a brown viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.89 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 1.44–1.52 (m, 2H), 1.54–1.60 (m, 1H), 2.04–2.10 (m, 1H), 2.15 (s, 3H), 2.64 (t, J = 7.2 Hz, 2H), 2.72–2.92 (m, 4H), 3.05–3.09 (m, 1H), 3.39 (s, 2H), 4.17 (q, J = 7.2 Hz, 2H), 6.99–7.01 (m, 1H), 7.16–7.08 (m, 1H), 7.26–7.27 (m, 1H).

5.10. Ethyl 2-((7-acetamido-8-nitro-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)acetate (6) and ethyl 2-((7-acetamido-6-nitro-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)acetate (7)

Compound **5** (6.5 g, 19.55 mmol) was placed in 250-mL flask and cooled down to −50 °C, 70 mL of 90% HNO_3 was transferred dropwise through cannula into the flask. The mixture was stirred at −20 °C for 30 min and poured onto ice. The mixture was neutralized by 20% NaOH solution at 0 °C and extracted by EtOAc (3 × 100 mL). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated to obtain the crude product which was purified by column chromatography (hexanes/EtOAc 1:1).The first eluent afforded **7** (4.0 g, 54%) as a brown viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.90 (t, J = 7.2 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H), 1.45–1.57 (m, 2H), 1.59–1.69 (m, 1H), 2.10–2.12 (m, 1H), 2.27 (s, 3H), 2.68 (t, J = 7.2 Hz, 2H), 2.72–2.87 (m, 2H), 2.89–3.16 (m, 2H), 3.10–3.06 (m, 1H), 3.41 (s, 2H), 4.18 (q, J = 7.2 Hz, 2H), 7.90 (d, J = 6.0 Hz,1H), 8.45 (d, J = 5.2 Hz,1H), 10.21 (s, 1H). MS (ESI): 378.40 ($C_{19}H_{28}N_3O_5$, $[M+H]^+$). The second eluent provided **6** (2.4 g, 33%) as a brown viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.91 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 1.42–1.55 (m, 2H), 1.57–1.67 (m, 1H), 2.06–2.10 (m, 1H), 2.16 (s, 3H), 2.62 (t, J = 7.2 Hz, 2H), 2.72–2.86 (m, 3H), 2.86–3.00 (m, 1H), 3.02–3.12 (m, 1H), 3.41 (s, 2H), 4.16 (q, J = 7.2 Hz, 2H), 7.19–7.22 (m, 1H), 7.79–7.83 (m, 1H), 8.23–8.25 (m, 1H). MS (ESI): 378.30 ($C_{19}H_{28}N_3O_5$, $[M+H]^+$).

5.11. Procedure C: 2-((7-amino-6-nitro-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)-1-(4-(2-methoxyphenyl)-piperazin-1-yl)ethanone (8a)

Compound **7** (280 mg, 0.742 mmol) was refluxed in 12 N HCl overnight. The mixture was evaporated to dryness followed by overnight drying under vacuum at 70 °C. The yellow solid was dissolved in CH_2Cl_2 (40 mL). EDCI (242 mg, 1.26 mmol), HOBT (150 mg, 1.11 mmol) and Et_3N (1.48 mL, 14.84 mmol) were added and stirred at room temperature for 1 h. Then, 1-(2-methoxylphenyl)-piperazine (339 mg, 1.48 mmol) was added into the reaction mixture and stirred for 24 h. The reaction mixture was diluted with CH_2Cl_2, washed with water, brine, the organic layer was dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography (hexanes/EtOAc/MeOH/Et_3N 40:52:4:4) to afford **8a** (300 mg, 84%) as a brown viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.90 (t, J = 7.2 Hz, 3H), 1.46–1.55 (m, 2H), 1.57–1.68 (m, 1H), 2.01–2.04 (m, 1H), 2.52–2.57(m, 2H), 2.65–2.76 (m, 2H), 2.83–2.87 (m, 2H), 2.95–3.05 (m, 5H), 3.47 (s, 2H), 3.70–3.84 (m, 4H), 3.88 (s, 3H), 6.09 (br s, 2H), 6.52–6.54 (m, 1H), 6.88–6.95 (m, 3H), 7.01–7.05 (m, 1H), 7.77–8.00 (m,1H).

5.12. 2-((7-Amino-6-nitro-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)-1-(4-phenylpiperazin-1-yl)ethanone (8b)

This compound was prepared following procedure C in which compound **7** (1.5 g, 3.97 mmol) and 1-phenylpiperazine (1.32 g, 7.95 mmol) were used to afford compound **8b** (0.92 g, 55%) as a brown viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.90 (t, J = 7.2 Hz, 3H), 1.45–1.55 (m, 2H), 1.59–1.66 (m, 1H), 2.01 (br s, 1H), 2.51–2.55 (m, 2H), 2.69–2.75 (m, 2H), 2.78–2.87 (m, 2H), 3.00–3.04 (m, 1H), 3.13–3.19 (m, 4H), 3.45–3.46 (m, 2H), 3.69–3.83 (m, 4H), 5.83 (br s, 2H), 6.51–6.52 (m,1H), 6.90–6.95 (m, 3H), 7.29–7.31 (m, 2H), 7.84–7.86 (m,1H).

5.13. 2-((7-Amino-8-nitro-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)-1-(4-phenylpiperazin-1-yl)ethanone (8c)

This compound was prepared following procedure C in which compound **6** (2.35 g, 6.23 mmol) and 1-phenylpiperazine (2.07 g, 12.45 mmol) were used to afford compound **8c** (1.50 g, 53%) as a brown viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.89 (t, J = 7.2 Hz, 3H), 1.46–1.56 (m, 2H), 1.59–1.64 (m, 1H), 2.01–2.05 (m, 1H), 2.53–2.58 (m, 2H), 2.69–3.04 (m, 4H), 3.13–3.18 (m, 4H), 3.39–3.52 (m, 2H), 3.70–3.83 (m, 4H), 4.84–4.87 (m, 2H), 6.59–6.61 (m,1H), 6.88–7.00 (m, 4H), 7.27–7.31 (m, 2H).

5.14. 2-((7-Nitro-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)-1-(4-phenylpiperazin-1-yl)ethanone ((±)8d)

This compound was prepared following procedure C in which compound (±)**-4** (8.56 g, 26.73 mmol) and 1-phenylpiperazine (8.89 g, 53.47 mmol) were used to afford compound (±)**-8d** (8.17 g, 70%) as a brown viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.91 (t, J = 7.2 Hz, 3H), 1.47–1.56 (m, 2H), 1.65–1.75 (m, 1H), 2.09–2.13 (m, 1H), 2.55–2.59 (m, 2H), 2.83–2.90 (m, 2H,), 2.97–3.02 (m, 2H), 3.10–3.18 (m, 5H), 3.49 (s, 2H), 3.70–3.82 (m, 4H), 6.88–6.94 (m, 3H), 7.17–7.33 (m, 3H), 7.90–7.95 (m, 2H).

5.15. (*R*)-2-((7-Nitro-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)-1-(4-phenylpiperazin-1-yl)ethanone ((+)-8d)

This compound was prepared following procedure C in which compound (**+**)**-4** (0.61 g, 1.90 mmol) and 1-phenylpiperazine (0.58 mL, 3.80 mmol) were used to afford compound (**+**)**-8d** (0.6 g, 72%) as a brown viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.91 (t, J = 7.2 Hz, 3H), 1.47–1.56 (m, 2H), 1.65–1.75 (m, 1H), 2.09–2.13 (m, 1H), 2.55–2.59 (m, 2H), 2.83–2.90 (m, 2H,), 2.97–3.02 (m, 2H), 3.10–3.18 (m, 5H), 3.49 (s, 2H), 3.70–3.82 (m, 4H), 6.88–6.94 (m, 3H), 7.17–7.33 (m, 3H), 7.90–7.95 (m, 2H).

5.16. (*S*)-2-((7-Nitro-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)-1-(4-phenylpiperazin-1-yl)ethanone ((−)-8d)

This compound was prepared following procedure C in which compound (−)**-4** (0.35 g, 1.09 mmol) and 1-phenylpiperazine (0.33 mL, 2.18 mmol) were used to afford compound (−)**-8d** (0.31 g, 65%) as a brown viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.91 (t, J = 7.2 Hz, 3H), 1.47–1.56 (m, 2H), 1.65–1.75 (m, 1H), 2.09–2.13 (m, 1H), 2.55–2.59 (m, 2H), 2.83–2.90 (m, 2H,), 2.97–3.02 (m, 2H), 3.10–3.18 (m, 5H), 3.49 (s, 2H), 3.70–3.82 (m, 4H), 6.88–6.94 (m, 3H), 7.17–7.33 (m, 3H), 7.90–7.95 (m, 2H).

5.17. Procedure D: N^6-(2-(4-(2-methoxyphenyl)piperazin-1-yl) ethyl)-N^6-propyl-5,6,7,8-tetrahydronaphthalene-2,3,6-triamine (9a)

To a solution of **8a** (290 mg, 0.603 mmol) in dry MeOH (20 mL) was added 10% Pd/C (58 mg). The reaction was continued under 70 psi H_2 for 36 h and the reaction mixture filtered through celite. Solvent was evaporated to afford crude compound 250 mg (92%). Into the solution of this crude product (220 mg, 0.487 mmol) in dry THF was added 2.4 mL solution of BH_3–THF complex (1 M). The reaction mixture was refluxed overnight, cooled to room temperature and then quenched with MeOH at 0 °C. The solvent was evaporated and the solid complex was suspended in 6 N HCl in methanol. After refluxing for 5 h, MeOH was evaporated in vacuo. Reaction mixture was made alkaline using saturated K_2CO_3 solution. The aqueous layer was extracted with EtOAc (3 × 20 mL), the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography (Hex/EtOAc/MeOH/Et_3N 40:52:4:4) to yield pure compound **9a** (138 mg, 65%) as a brown viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.91 (t, J = 7.2 Hz, 3H), 1.49–1.57 (m, 2H), 1.64–1.74 (m, 1H), 2.07–2.11 (m, 1H), 2.56–2.64 (m, 6H), 2.73–2.83 (m, 6H), 2.87–3.0 (m, 7H), 3.83 (s, 3H), 6.84–6.86 (m, 1H), 6.89–6.96 (m, 2H), 6.97–7.02 (m, 1H), 7.21 (br s, 2H).

5.18. N^6-(2-(4-Phenylpiperazin-1-yl)ethyl)-N^6-propyl-5,6,7,8-tetrahydronaphthalene-2,3,6-triamine (9b)

This compound was prepared from compound **8b** (0.9 g, 1.99 mmol) following procedure D to give compound **9b** (0.73 g, 84%) as a brown viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.92 (t, J = 7.2 Hz, 3H), 1.46–1.56 (m, 2H), 1.57–1.65 (m, 1H), 1.99–2.01 (m, 1H), 2.52–2.56 (m, 2H), 2.59–2.77 (m, 8H), 2.91–2.99 (m, 1H), 3.21–3.24 (m, 4H), 3.32 (br s, 1H), 6.43 (s, 1H), 6.44 (s, 1H), 6.87 (t, J = 7.2 Hz, 1H), 6.94–6.96 (m, 2H), 7.26–7.30 (m, 2H).

5.19. N^7-[2-(4-Phenylpiperazin-1-yl)-ethyl]-N^7-propyl-5,6,7,8-tetrahydro-naphthalene-1,2,7-triamine (9c)

This compound was prepared from compound **8c** (0.9 g, 1.99 mmol) following procedure D to give compound **9c** (0.73 g, 84%) as a brown viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.90 (t, J = 7.2 Hz, 3H), 1.47–1.59 (m, 2H), 1.65–1.68 (m, 1H), 1.99 (br s, 1H), 2.52–2.59 (m, 5H), 2.66 (br s, 4H), 2.71–2.80 (m, 5H), 3.20–3.22 (m, 4H), 3.65–3.68 (m, 1H), 6.47–6.49 (m, 1H), 6.56–6.60 (m, 1H), 6.86 (t, J = 7.2 Hz, 1H), 6.2–6.94 (m, 2H), 7.25–7.29 (m, 2H).

5.20. N^2-[2-(4-Phenylpiperazin-1-yl)-ethyl]-N^2-propyl-1,2,3,4-tetrahydronaphthalene-2,7-diamine ((±)-9d)

This compound was prepared from compound (±)-**8d** (7.2 g, 17.04 mmol) following procedure D to give compound (±)-**9d** (6.27 g, 97%) as a brown viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.90 (t, J = 7.2 Hz, 3H), 1.46–1.54 (m, 2H), 1.55–1.64 (m, 1H), 1.99 (br s, 1H), 2.50–2.59 (m, 4H), 2.64–2.67 (m, 4H), 2.70–2.81 (m, 4H), 3.19–3.22 (m, 4H), 3.51–3.60 (m, 3H), 6.44–6.57 (m, 2H), 6.83–6.98 (m, 4H), 7.21–7.28 (m, 2H).

5.21. (*R*)-N^2-(2-(4-Phenylpiperazin-1-yl)ethyl)-N^2-propyl-1,2,3,4-tetrahydronaphthalene-2,7-diamine ((+)-9d)

This compound was prepared from compound (+)-**8d** (0.55 g, 1.26 mmol) following procedure D to give compound (+)-**9d** (0.32 g, 65%) as a brown viscous liquid. $[\alpha]_D^{25}$ = +38.4 (c 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.90 (t, J = 7.2 Hz, 3H), 1.46–1.54 (m, 2H), 1.55–1.64 (m, 1H), 1.99 (br s, 1H), 2.50–2.59 (m, 4H), 2.64–2.67 (m, 4H), 2.70–2.81 (m, 4H), 3.19–3.22 (m, 4H), 3.51–3.60 (m, 3H), 6.44–6.57 (m, 2H), 6.83–6.98 (m, 4H), 7.21–7.28 (m, 2H). The free base was converted into HCl salt, mp: 202–204 °C Anal. [$C_{25}H_{36}N_4$·4HCl·H_2O] C, H, N.

5.22. (*S*)-N^2-(2-(4-Phenylpiperazin-1-yl)ethyl)-N^2-propyl-1,2,3,4-tetrahydronaphthalene-2,7-diamine ((−)-9d)

This compound was prepared from compound (−)-**8d** (0.3 g, 0.69 mmol) following procedure D to give compound (−)-**9d** (0.17 g, 63%) as a brown viscous liquid. $[\alpha]_D^{25}$ = −39.6 (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.90 (t, J = 7.2 Hz, 3H), 1.46–1.54 (m, 2H), 1.55–1.64 (m, 1H), 1.99 (br s, 1H), 2.50–2.59 (m, 4H), 2.64–2.67 (m, 4H), 2.70–2.81 (m, 4H), 3.19–3.22 (m, 4H), 3.51–3.60 (m, 3H), 6.44–6.57 (m, 2H), 6.83–6.98 (m, 4H), 7.21–7.28 (m, 2H). The free base was converted into HCl salt, mp: 200–202 °C Anal. [$C_{25}H_{36}N_4$·4HCl] C, H, N.

5.23. Procedure E: *N*-(2-(4-(2-methoxyphenyl)piperazin-1-yl) ethyl)-*N*-propyl-5,6,7,8-tetrahydro-1*H*-naphtho[2,3-*d*]imidazol-6-amine (10a)

Diamine **9a** (65 mg, 0.149 mmol) and 98% HCOOH (22 μL, 0.357 mmol) were heated under N_2 at 140 °C for 5 h. After cooling to room temperature, 5 mL of saturated $NaHCO_3$ were added and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), concentrated in vacuo and purified by column chromatography (Hex/EtOAc/MeOH/Et_3N 40:52:4:4) to yield **10a** (45 mg, 67%) as a brown viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.92 (t, J = 7.2 Hz, 3H), 1.53–1.62 (m, 2H), 1.66–1.76 (m, 1H), 2.09–2.12 (m, 1H), 2.63–2.69 (m, 4H), 2.6 (br s, 4H), 2.85–3.17 (m, 11H), 3.84 (s, 3H), 6.84–6.86 (m, 1H), 6.88–6.92 (m, 2H), 6.97–7.02 (m, 1H), 7.34 (s, 2H), 7.99 (s, 2H). MS (ESI): 448.50 ($C_{27}H_{38}N_5O$, $[M+H]^+$). The free base was converted into HCl salt, mp: 90–93 °C. Anal. [$C_{27}H_{37}N_5O$·4HCl ·1.5H_2O·0.4CH_3CH_2OH] C, H, N.

5.24. 6-((2-(4-(2-Methoxyphenyl)piperazin-1-yl)ethyl) (propyl)amino)-5,6,7,8-tetrahydro-1*H*-naphtho-[2,3-d]imidazole-2(3*H*)-thione (10b)

A mixture of diamine **9a** (100 mg, 0.228 mmol), CS_2 (51 mg, 0.663 mmol), KOH (32 mg, 0.570 mmol), H_2O (0.1 mL) and EtOH (2 mL) was refluxed for 3 h. The reaction mixture was evaporated to dryness and purified by column chromatography (Hex/EtOAc/MeOH/Et_3N 40:52:4:4) offered **10b** (92 mg, 84%) as a brown viscous liquid. ^{1}H NMR (400 MHz, DMSO) δ ppm 0.86 (t, J = 7.2 Hz, 3H), 1.37–1.46 (m, 2H), 1.54–1.58 (m, 1H), 1.91–1.97 (m, 1H), 2.41–2.64 (m, 10H), 2.74–2.93 (m, 9H), 3.76 (s, 3H), 6.82–6.85 (m, 6H), 12.30 (s, 2H). MS (ESI): 480.50 ($C_{27}H_{38}N_5OS$, $[M+H]^+$). The free base was converted into HCl salt, mp: 162–166 °C. Anal. [$C_{27}H_{37}N_5OS$·3HCl·0.7H_2O·0.3CH_3CH_2OH] C, H, N.

5.25. 6-((2-(4-(2-Methoxyphenyl)piperazin-1-yl)ethyl) (propyl)amino)-5,6,7,8-tetrahydro-1*H*-naphtho-[2,3-*d*] imidazol-2(3*H*)-one (10c)

Diamine **9a** (160 mg, 0.366 mmol) was added to 1,1′-carbonyldiimidazole (118 mg, 1.574 mmol) in AcCN (5 mL), the mixture was stirred at room temperature for 2 h and then refluxed overnight. The solvent was removed and the residue was purified by column chromatography (Hex/EtOAc/MeOH/Et_3N 40:52:4:4) offered **10c** (140 mg, 83%) as a brown viscous liquid. ^{1}H NMR (400 MHz, DMSO) δ ppm 0.89 (t, J = 7.2 Hz, 3H), 1.43–1.51 (m, 2H), 1.52–1.61 (m, 1H), 1.97–1.99 (m, 1H), 2.48–2.66 (m, 4H),

2.69–2.76 (m, 10H), 2.89–3.12 (m, 5H), 3.83 (s, 3H), 6.69–6.71 (m, 2H), 6.84–6.89 (m, 1H), 6.91–6.94 (m, 2H), 6.95–7.01 (m, 1H), 7.34 (s, 2H), 7.68 (s, 2H), 9.20 (s, 1H), 9.27 (s, 1H). MS (ESI): 464.50 ($C_{27}H_{38}N_5O_2$, $[M+H]^+$). The free base was converted into HCl salt, mp: 112–116 °C. Anal. [$C_{27}H_{37}N_5O_2{\cdot}3HCl{\cdot}1.4H_2O{\cdot}0.3CH_3CH_2OH$] C, H, N.

5.26. *N*-(2-(4-Phenylpiperazin-1-yl)ethyl)-*N*-propyl-5,6,7,8-tetrahydro-1*H*-naphtho[2,3-*d*]imidazol-6-amine (10d)

This compound was prepared from compound **9b** (0.13 mg, 0.33 mmol) following procedure E to give compound **10d** (110 mg, 81%) as a brown viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.92 (t, J = 7.2 Hz, 3H), 1.58–1.62 (m, 2H), 1.63–1.80 (m, 1H), 2.27 (br s, 1H), 2.66–2.69 (m, 7H), 2.85–3.13 (m, 8H), 3.18–3.20 (m, 4H), 6.83–6.92 (m, 3H), 7.23–7.27 (m, 4H), 7.35 (s, 2H), 7.97 (s, 1H). The free base was converted into oxalate salt, mp: 101–103 °C. Anal. [$C_{26}H_{35}N_5{\cdot}3(COOH)_2{\cdot}H_2O$] C, H, N.

5.27. N^6-(2-(4-Phenylpiperazin-1-yl)ethyl)-N^6-propyl-5,6,7,8-tetrahydro-1*H*-naphtho[2,3-*d*]imidazole-2,6-diamine (10e)

CNBr (68 mg, 0.638 mmol) was added to a solution of **9b** (260 mg, 0.638 mmol) in H_2O/EtOH (30 mL, 2:1). The mixture was stirred overnight and neutralized by ammonia. After extraction by CH_2Cl_2 (3 × 30 mL), the organic layer was evaporated and the residue was purified by column chromatography (Hex/EtOAc/MeOH/Et_3N 40:52:4:4) offered **10e** (130 mg, 47%) as a brown viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.91 (t, J = 7.2 Hz, 3H), 1.54–1.60 (m, 2H), 1.60–1.69 (m, 1H), 1.96 (br s, 1H), 2.60–2.74 (m, 7H), 3.16–3.29 (m, 8H), 3.36–3.38 (m, 2H), 3.66–3.70 (m, 2H), 5.58 (br s, 2H), 5.80 (br s, 2H), 6.86–6.94 (m, 3H), 7.24–7.28 (m, 2H). The free base was converted into oxalate salt, mp: 105–108 °C. Anal. [$C_{28}H_{36}N_4O_2{\cdot}3(COOH)_2{\cdot}3H_2O$] C, H, N.

5.28. *N*-(2-(4-Phenylpiperazin-1-yl)ethyl)-*N*-propyl-6,7,8,9-tetrahydro-1*H*-naphtho[1,2-*d*]imidazol-8-amine (10f)

This compound was prepared from compound **9c** (0.43 mg, 1.05 mmol) following procedure E to give compound **10f** (300 mg, 68%) as a brown viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.91 (t, J = 7.2 Hz, 3H), 1.49–1.55 (m, 2H), 1.72–1.77 (m, 1H), 2.10–2.17 (m, 1H), 2.58–2.66 (m, 8H), 2.2.77–2.81 (m, 2H), 2.87–3.01 (m, 4H), 3.19–3.20 (m, 5H), 6.83–6.87 (m, 2H), 6.84–6.89 (m, 1H), 6.91–6.93 (m, 2H), 7.02–7.04 (m, 1H), 7.24–7.28 (m, 3H), 7.99–8.0 (m, 1H). The free base was converted into oxalate salt, mp: 98–100 °C. Anal. [$C_{26}H_{35}N_5{\cdot}3(COOH)_2{\cdot}H_2O$] C, H, N.

5.29. N^7-(2,2-Diethoxyethyl)-N^2-(2-(4-phenylpiperazin-1-yl)ethyl)-N^2-propyl-1,2,3,4-tetrahydronaphthalene-2,7-diamine (11)

A solution of **9d** (0.3 g, 0.764 mmol), Na_2CO_3 (81 mg, 0.764 mmol), and bromoacetaldehyde diethyl acetal (0.166 g, 0.84 mmol) in EtOH (3 mL), was heated at reflux for 1.5 days. The solvent was removed in vacuo and the residue was purified by column chromatography (CH_2Cl_2/MeOH 5:0.25) to yield pure compound **11** (0.23 g, 60%) as a brown viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.92 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.2 Hz, 6H), 1.52–1.64 (m, 3H), 2.03 (m, 1H), 2.58 (m, 5H), 2.65–2.68 (m, 5H), 2.77 (m, 5H), 3.04 (br s, 1H), 3.19–3.22 (m, 6H), 3.53–3.60 (m, 2H), 3.68–3.76 (m, 2H), 4.67 (t, J = 6.8 Hz, 1H), 6.38 (m, 1H), 6.43–6.47 (m, 1H), 6.83–6.94 (m, 4H), 7.25 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H).

5.30. 2,2,2-Trifluoro-1-(7-((2-(4-phenylpiperazin-1-yl)ethyl)(propyl)amino)-5,6,7,8-tetrahydro-1*H*-benzo[*f*]indol-1-yl)ethanone (12)

A cooled mixture of trifluoroacetic anhydride in trifluoroacetic acid (1:1) was added to compound **11** (0.135 g, 0.27 mmol) at 0 °C. After stirring for 30 min, the cold mixture was diluted with trifluoroacetic acid (3 mL) and heated at reflux for 2.5 days. After removal of the solvent under reduced pressure, the residue was taken into CH_2Cl_2 (15 mL) and washed with saturated $NaHCO_3$, dried (Na_2SO_4) and the solvent evaporated to get crude **12** which was purified by column chromatography (CH_2Cl_2/MeOH 5:0.25) to afford pure **12** (50 mg, 37%) as a brown viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.04 (t, J = 6.4 Hz, 3H), 1.90 (m, 3H), 2.44 (m, 1H), 3.03–3.26 (m, 6H), 3.43–3.48 (m, 8H), 3.80 (m, 5H), 6.67–6.70 (m, 1H), 6.95–6.96 (d, J = 7.2 Hz, 2H), 7.02 (t, J = 7.2 Hz, 1H), 7.29–7.33 (m, 3H), 7.43 (br s, 1H), 8.21–8.22 (br s, 1H).

5.31. *N*-(2-(4-Phenylpiperazin-1-yl)ethyl)-*N*-propyl-5,6,7,8-tetrahydro-1*H*-benzo[*f*]indol-7-amine (13)

A solution of compound **12** (25 mg, 0.05 mmol) in dry MeOH (5 mL) was heated at reflux for 24 h. Solvent was evaporated in vacuo and the residue was purified by column chromatography (CH_2Cl_2/MeOH 9:1) to yield pure compound **13** (10 mg, 50%) as a light brown viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.98 (t, J = 7.2 Hz, 3H), 1.90 (m, 3H), 2.37 (m, 1H), 2.71–2.73 (m, 4H), 2.83–3.36 (m, 14H), 3.78 (br s, 1H), 6.43 (br s, 1H), 6.85–6.91 (m, 3H), 7.15–7.19 (m, 2H), 7.24–7.27 (m, 2H), 7.34 (s, 1H). MS (ESI): 417.1 ($C_{27}H_{37}N_4$, $[M+H]^+$). The free base was converted into HCl salt, mp: 158–160 °C.

Anal. [$C_{27}H_{36}N_4{\cdot}3HCl{\cdot}0.6H_2O{\cdot}0.1C_2H_5OC_2H_5$)] C, H, N.

5.32. Procedure F for the syntheses of compounds 14a–f

4-Substituted benzenesulfonyl chloride/benzoyl chloride/acetyl chloride (1 equiv) was added to cooled solution (0 °C) of **9d** (1 equiv) in pyridine (5 mL). The mixture was stirred at RT overnight. The solvent was removed in reduced pressure and the residue was purified by column chromatography (CH_2Cl_2/MeOH 9:1) to yield pure **14a–f**.

5.33. 4-Chloro-*N*-(7-((2-(4-phenylpiperazin-1-yl)ethyl)(propyl)amino)-5,6,7,8-tetrahydronaphthalen-2-yl)benzenesulfonamide (14a)

This compound was prepared following procedure F in which compound (±)-**9d** (37 mg, 0.09 mmol) and 4-chloro benzenesulfonyl chloride (20 mg, 0.09 mmol) were used to afford compound **14a** (42 mg, 80%) as a light brown viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.96 (t, J = 7.2 Hz, 3H), 1.76 (m, 3H), 2.36 (m, 1H), 2.67–2.99 (13H, m), 3.24 (br s, 4H), 6.87–6.92 (m, 6H), 7.27 (t, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.8 Hz, 2H). The free base was converted into HCl salt, mp: 164–166 °C. Anal. [$C_{31}H_{39}ClN_4O_2S{\cdot}2HCl{\cdot}H_2O$] C, H, N.

5.34. *N*-(7-((2-(4-Phenylpiperazin-1-yl)ethyl)(propyl)amino)-5,6,7,8-tetrahydronaphthalen-2-yl)-4-(trifluoromethyl)benzenesulfonamide (14b)

This compound was prepared following procedure F in which compound (±)-**9d** (54 mg, 0.14 mmol) and 4-(trifluoromethyl) benzenesulfonyl chloride (34 mg, 0.14 mmol) were used to afford compound **14b** (58 mg, 71%) as a light brown viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.95 (t, J = 7.2 Hz, 3H), 1.72 (m, 3H), 2.18 (m, 1H), 2.65–2.97 (13H, m), 3.23 (br s, 4H), 6.85–6.92

(m, 6H), 7.27 (t, J = 8.0 Hz, 2H), 7.63 (d, J = 7.6 Hz, 2H), 7.93 (d, J = 8.0 Hz, 2H). The free base was converted into HCl salt, mp: 172–174 °C. Anal. [$C_{32}H_{39}F_3N_4O_2S$·3HCl] C, H, N.

5.35. *N*-(7-((2-(4-Phenylpiperazin-1-yl)ethyl)(propyl)amino)-5,6,7,8-tetrahydronaphthalen-2-yl)benzamide (14c)

This compound was prepared following procedure F in which compound (±)-**9d** (34 mg, 0.09 mmol) and benzoyl chloride (10 μL, 0.09 mmol) were used to afford compound **14c** (33 mg, 78%) as a light brown viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.96 (t, J = 7.6 Hz, 3H), 1.82–1.84 (m, 3H), 2.36 (m, 1H), 2.73–3.19 (m, 18H), 3.51 (br s, 1H), 6.87–6.91 (m, 3H), 6.97–7.03 (m, 1H), 7.24–7.29 (m, 2H), 7.41–7.58 (m, 5H), 7.97 (d, J = 7.2 Hz, 2H), 8.50 (br s, 1H). The free base was converted into HCl salt, mp: 162–164 °C. Anal. [$C_{32}H_{40}N_4O$·3HCl] C, H, N.

5.36. *N*-(7-((2-(4-Phenylpiperazin-1-yl)ethyl)(propyl)amino)-5,6,7,8-tetrahydronaphthalen-2-yl)-acetamide (14d)

This compound was prepared following procedure F in which compound (±)-**9d** (50 mg, 0.13 mmol) and acetyl chloride (9 μL, 0.13 mmol) were used to afford compound **14d** (30 mg, 55%) as a light brown viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.99 (t, J = 7.2 Hz, 3H), 1.86 (m, 3H), 2.18 (s, 3H), 2.34 (m, 1H), 2.77–3.22 (m, 18H), 3.59 (br s, 1H), 6.87–6.93 (m, 3H), 7.00 (d, J = 8.4 Hz, 1H), 7.21–7.29 (m, 3H), 7.39 (s, 1H), 7.67 (br s, 1H). MS (ESI): 435.1 ($C_{27}H_{39}N_4O$, $[M+H]^+$). The free base was converted into HCl salt, mp: 172–174 °C. Anal. [$C_{27}H_{38}N_4O$·3HCl·0.3$C_2H_5OC_2H_5$] C, H, N.

5.37. 4-Methyl-*N*-(7-((2-(4-phenylpiperazin-1-yl)ethyl)(propyl)amino)-5,6,7,8-tetrahydronaphthalen-2-yl)benzenesulfonamide (14e)

This compound was prepared following procedure F in which compound (±)-**9d** (50 mg, 0.13 mmol) and 4-methyl benzenesulfonyl chloride (25 mg, 0.13 mmol) were used to afford compound **14e** (45 mg, 65%) as a light brown viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.93 (t, J = 6.4 Hz, 3H), 1.52–1.82 (m, 3H), 2.37 (s, 3H), 2.39 (m, 1H), 2.50–3.18 (m, 16H), 3.22 (br s, 4H), 6.80–6.96 (m, 6H), 7.22 (t, J = 8.0 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 11.88, 21.80, 25.31, 28.84, 29.94, 47.88, 49.04, 53.44, 53.68, 58.78, 116.38, 119.66, 119.95, 120.20, 121.66, 122.68, 127.50, 129.39, 129.83, 130.27, 134.96, 136.69, 143.74, 151.19. The free base was converted into HCl salt, mp: 225–227 °C. Anal. [$C_{32}H_{42}N_4O_2S$·2HCl·2H_2O] C, H, N.

5.38. 4-Methoxy-*N*-(7-((2-(4-phenylpiperazin-1-yl)ethyl)(propyl)amino)-5,6,7,8-tetrahydronaphthalen-2-yl)benzenesulfonamide ((±)-14f)

This compound was prepared following procedure F in which compound (±)-**9d** (50 mg, 0.13 mmol) and 4-methoxy benzenesulfonyl chloride (26 mg, 0.13 mmol) were used to afford compound (±)-**14f** (45 mg, 63%) as a light brown viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.91 (t, J = 7.2 Hz, 3H), 1.52–1.70 (m, 3H), 2.08 (m, 1H), 2.58–2.92 (m, 16H), 3.21 (br s, 4H), 3.81 (s, 3H), 6.80–6.96 (m, 8H), 7.26 (t, J = 7.6 Hz, 2H), 7.72 (d, J = 6.8 Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 11.98, 21.80, 25.41, 29.16, 29.93, 48.10, 49.14, 53.53, 53.84, 57.77, 58.08, 114.36, 116.31, 119.71, 119.86, 120.07, 121.95, 122.80, 129.37, 129.51, 129.65, 130.33, 131.18, 134.64, 151.33, 163.17. The free base was converted into HCl salt, mp: 230–232 °C. Anal. [$C_{32}H_{42}N_4O_3S$·2HCl·2H_2O] C, H, N.

5.39. (*R*)-4-Methoxy-*N*-(7-((2-(4-phenylpiperazin-1-yl)ethyl)(propyl)amino)-5,6,7,8-tetrahydronaphthalen-2-yl)benzenesulfonamide ((+)-14f)

This compound was prepared following procedure F in which compound (+)-**9d** (35 mg, 0.09 mmol) and 4-methoxy benzenesulfonyl chloride (19 mg, 0.09 mmol) were used to afford compound (+)-**14f** (35 mg, 70%) as a light brown viscous liquid. $[\alpha]_D^{25}$ = +106.4 (c 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.91 (t, J = 7.2 Hz, 3H), 1.52–1.70 (m, 3H), 2.08 (m, 1H), 2.58–2.92 (m, 16H), 3.21 (br s, 4H), 3.81 (s, 3H), 6.80–6.96 (m, 8H), 7.26 (t, J = 7.6 Hz, 2H), 7.72 (d, J = 6.8 Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 11.98, 21.80, 25.41, 29.16, 29.93, 48.10, 49.14, 53.53, 53.84, 57.77, 58.08, 114.36, 116.31, 119.71, 119.86, 120.07, 121.95, 122.80, 129.37, 129.51, 129.65, 130.33, 131.18, 134.64, 151.33, 163.17. The free base was converted into HCl salt, mp: 232–234 °C. Anal. [$C_{32}H_{42}N_4O_3S$·2HCl·2H_2O] C, H, N.

5.40. Procedure G for the syntheses of 16a, 16b, and 18

To cooled solution (0 °C) of **15** or **17** (1 equiv) in DCM (5 mL), were added Et_3N (3 equiv) and 4-Substituted benzenesulfonyl chloride (1.5 equiv). The mixture was stirred at room temperature overnight. The reaction mixture was extracted with DCM and H_2O. Solvent was removed in reduced pressure and the residue was purified by column chromatography (CH_2Cl_2/MeOH 9:1) to yield pure products.

5.41. (*S*)-6-((2-(4-Phenylpiperazin-1-yl)ethyl)(propyl)amino)-5,6,7,8-tetrahydronaphthalen-1-yl 4-methylbenzenesulfonate (16a)

This compound was prepared following procedure G in which compound **15** (50 mg, 0.13 mmol), triethyl amine (53 μL, 0.38 mmol), and 4-methyl benzenesulfonyl chloride (36 mg, 0.19 mmol) were used to afford compound **16a** (52 mg, 74%) as a light brown viscous liquid. $[\alpha]_D^{25}$ = −34.4 (c 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.90 (t, J = 7.2 Hz, 3H), 1.50 (m, 3H), 2.00 (m, 1H), 2.47 (s, 3H), 2.48–3.00 (m, 15H), 3.21 (m, 4H), 6.74 (d, J = 7.2 Hz, 1H), 6.86 (t, J = 7.2 Hz, 1H), 6.93 (d, J = 8.4 Hz, 2H), 6.98–7.40 (m, 2H), 7.27 (t, J = 7.2 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.77 (d, J = 7.6 Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 12.07, 21.99, 24.49, 25.15, 32.31, 48.27, 49.25, 53.52, 53.97, 57.20, 58.34, 116.28, 119.47, 119.97, 126.56, 128.42, 128.59, 129.35, 130.05, 130.57, 133.58, 139.33, 145.53, 148.16, 151.47. The free base was converted into HCl salt, mp: 220–222 °C. Anal. [$C_{32}H_{41}N_3O_3S$·2HCl·2H_2O] C, H, N.

5.42. (*S*)-6-((2-(4-Phenylpiperazin-1-yl)ethyl)(propyl)amino)-5,6,7,8-tetrahydronaphthalen-1-yl 4-methoxybenzenesulfonate (16b)

This compound was prepared following procedure G in which compound **15** (45 mg, 0.11 mmol), triethyl amine (48 μL, 0.34 mmol), and 4-methoxy benzenesulfonyl chloride (35 mg, 0.17 mmol) were used to afford compound **16b** (47 mg, 73%) as a light brown viscous liquid. $[\alpha]_D^{25}$ = −39.2 (c 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.91 (t, J = 7.2 Hz, 3H), 1.53 (m, 3H), 2.04 (m, 1H), 2.42–3.04 (m, 15H), 3.21 (m, 4H), 3.90 (s, 3H), 6.74 (d, J = 7.6 Hz, 1H), 6.86 (t, J = 7.6 Hz, 1H), 6.93 (d, J = 8.0 Hz, 2H), 6.96–7.04 (m, 4H), 7.26 (t, J = 7.6 Hz, 2H), 7.81 (d, J = 8.8 Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 12.02, 21.80, 24.42, 25.05, 32.18, 48.20, 49.22, 53.50, 53.92, 55.99, 57.33, 57.93, 114.60, 116.29, 119.58, 119.99, 126.58, 127.86, 128.36, 129.35, 130.51, 130.82, 139.08, 148.16, 151.43, 164.32. The free base was con-

verted into HCl salt, mp: 225–227 °C. Anal. [$C_{32}H_{41}N_3O_4S{\cdot}2HCl{\cdot}2H_2O$] C, H, N.

5.43. (*R*)-7-((2-(4-Phenylpiperazin-1-yl)ethyl)(propyl)amino)-5,6,7,8-tetrahydronaphthalen-2-yl 4-methoxybenzenesulfonate (18)

This compound was prepared following procedure G in which compound **17** (35 mg, 0.09 mmol), triethyl amine (37 μL, 0.27 mmol), and 4-methoxy benzenesulfonyl chloride (28 mg, 0.13 mmol) were used to afford compound **18** (37 mg, 74%) as a light brown viscous liquid. $[\alpha]_D^{25}$ = +26.2 (c 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.92 (t, J = 7.2 Hz, 3H), 1.50–1.72 (m, 3H), 2.15 (m, 1H), 2.60–2.88 (m, 14H), 3.20 (m, 5H), 3.88 (s, 3H), 6.64 (d, J = 8.0 Hz, 1H), 6.74–7.02 (m, 7H), 7.26 (t, J = 8.0 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 11.97, 21.35, 25.43, 29.20, 31.73, 48.06, 49.13, 53.45, 53.82, 55.98, 57.84, 114.55, 116.34, 120.05, 120.12, 123.16, 127.11, 129.37, 129.79, 130.92, 135.17, 147.79, 151.30, 164.28. The free base was converted into HCl salt, mp: 195–197 °C. Anal. [$C_{32}H_{41}N_3O_4S{\cdot}2HCl{\cdot}2H_2O$] C, H, N.

5.44. Assessment of affinity for and activation of dopamine D2 and D3 receptors

Binding potency was monitored by inhibition of [^{3}H]spiroperidol (16.2 Ci/mmole, Perkin-Elmer) binding to dopamine rD2 and rD3 receptors expressed in HEK293 cells, in a buffer containing 0.9% NaCl under conditions corresponding to our 'high [radioligand] protocol' as described by us previously.[23,37] Observed IC_{50} values were converted to inhibition constants (K_i) by the Cheng–Prusoff equation.[23] Functional activity of test compounds in activating dopamine hD2 and hD3 receptors expressed in CHO cells was measured by stimulation of [^{35}S]GTPγS (1250 Ci/mmole, Perkin–Elmer) binding in comparison to stimulation by the full agonist dopamine as described by us previously.[23]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2013.03.059.

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