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Further delineation of hydrophobic binding sites in dopamine D_2/D_3 receptors for N-4 substituents on the piperazine ring of the hybrid template 5/7-{[2-(4-aryl-piperazin-1-yl)-ethyl]-propyl-amino}-5,6,7,8-tetrahydro-naphthalen-2-ol

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ABSTRACT

Here we report a structure–activity relationship (SAR) study of analogues of 5/7-{[2-(4-aryl-piperazin-1-yl)-ethyl]-propyl-amino}-5,6,7,8-tetrahydro-naphthalen-2-ol. Our SAR is focused on introduction of various substitutions in the piperazine ring of the hybrid template. The goal behind this study is to delineate the nature of the binding pocket for *N*-aryl substitution in the piperazine ring by observing the effect of various hydrophobic and other heteroaromatic substitutions on binding affinity (K_i), as measured with tritiated spiperone and HEK-293 cells expressing either D_2 or D_3 receptors. Functional activity of selected compounds was assessed with the GTPγS binding assay. Compound **8d** was the most selective for the D_3 receptor in the spiperone binding assay. An interesting similarity in binding affinity was observed between isoquinoline derivative D-301 and the 2-substituted pyridine derivative **8d**, suggesting the importance of relative spatial relationships between the N-atom of the ligand and the molecular determinants of the binding pocket in D_2/D_3 receptors. Functional activity assays demonstrated high potency and selectivity of (+)-**8a** and (−)-**28b** (D_2/D_3 (ratio of EC_{50}): 105 and 202, respectively) for the D_3 receptor and both compounds were more selective compared to the reference drug ropinirole (D_2/D_3 (ratio of EC_{50}): 29.5).

1. Introduction

Dopamine receptors play important roles in diverse physiological functions in the central nervous system (CNS).[1] Imbalances of dopamine level have been implicated in psychiatric disorders such as schizophrenia and depression, and movement disorders including Parkinson's disease.[2,3] Dopamine D_2 and D_3 receptors have been targeted for drug development for many years.[4] Although D_2 and D_3 receptors have similar pharmacological properties, recent studies indicate important differences between these two receptors.[5] Some of the differences are due to divergent neuroanatomical locations of D_2 and D_3 receptors, others to different signaling cascades associated with the two receptor subtypes.[5,6] Interestingly, the D_3 receptor which is found in highest density in the nucleus accumben,[7] has been implicated in upregulation in neurotrophic factors and in neurogenesis in the substantia nigra.[8,9]

Considerable efforts have been expended to develop selective agonists and antagonists for the D_3 receptor. These efforts resulted in the development of many ligands with varying selectivities for the D_3 receptor.[10] In general higher selectivity was achieved in newly developed antagonists than agonists.[11,12] This might be due to the fact that antagonist may not necessarily bind to the orthosteric binding site in the receptor as required by agonist,[13] thereby, is able to exploit structural differences in D_2 and D_3 receptors to a greater degree than agonist. We have reported some time ago about our hybrid approach of drug development for D_2/D_3 receptors.[14–16] This hybrid approach, which combined a known aminotetralin dopamine agonist with a substituted piperazine fragment via a suitable linker, produced potent preferential agonists for D_3 receptors as shown by SAR studies. Some key findings from our recent SAR studies demonstrated that the linker length between the piperazine and aminotetralin fragments is important in potency and selectivity for the D_3 receptor. In this regard, a 2-methylene linker length was found to be optimal for such hybrid derivatives, in contrast to the 4-methylene length required for optimal affinity and selectivity for D_3 antagonists derived from piperazine and benzamide fragments.[17] Replacement of the phenolic moiety in D-237 by the bioisosteric amino thiazole moiety produced one of the highest selective D_3 agonist. These hybrid derivatives were in general more potent than their parent 7-OH-DPAT or 5-OH-DPAT, thus, indicating contribution of the

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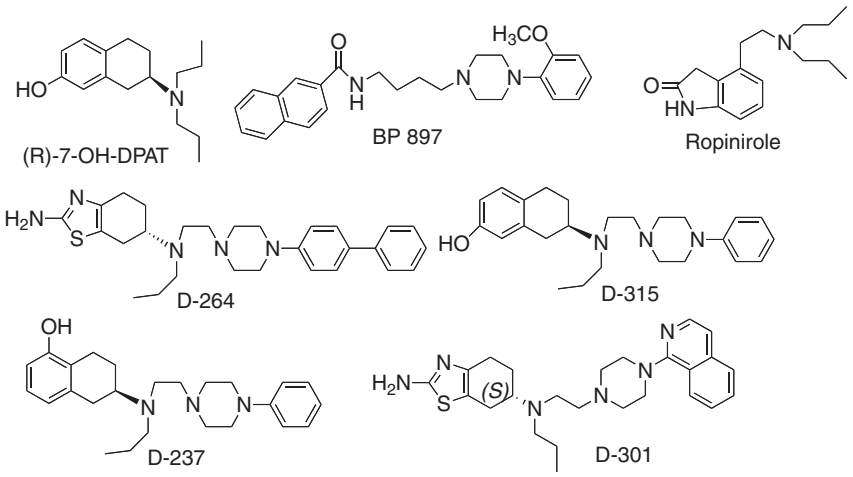


Figure 1.

piperazine moiety in additional interaction.[17] Some of our lead agonists are shown in Figure 1. Lead D_3 preferring agonist developed from our studies exhibited potent in vivo activity in Parkinson's disease animal models indicating their efficacy.[18]

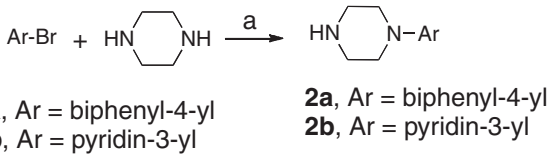
In our current SAR studies, we anticipated to further extend our exploration of the influence of *N*-piperazine substitutions on affinity and selectivity for the D_3 receptor. Compounds containing various aromatic heterocyclic rings and linearly fused biphenyl moieties were explored. The current SAR studies provide a more comprehensive picture of the nature of the binding pocket in D_2/D_3 receptors that accommodates *N*-piperazine substitutions in hybrid aminotetraline–piperazine derivatives.

2. Chemistry

Scheme 1 outlines the syntheses of two aryl piperazines **2a** and **2b** used in the synthesis of target compounds. Compounds **2a** and **2b** were synthesized by palladium(II)-catalyzed amination reaction with two corresponding aryl halides 4-bromobiphenyl and 3-bromopyridine, **1a** and **1b**, with excess piperazine.[19]

Scheme 2 describes the syntheses of five target compounds. Starting materials **2a** and **2b** and the rest commercially available starting materials **2c**–**2e** were subjected to N-alkylation reaction with 2-chloroacetonitrile in the presence of potassium carbonate in toluene to yield intermediates **3a**–**3e** which were then reduced in the presence of Raney nickel using a Parr hydrogenetor resulted in amine intermediates **4a**–**4e**. These amines were then treated with 7-methoxy-2-tetralone in standard reductive amination conditions to obtain intermediates **5a**–**5e** which were subjected to N-alkylation reaction with propionyl chloride to afford amides **6a**–**6e**. The amides were then reduced with LAH/THF followed by demethylation in the presence of boron tribromide (1 M) solution in dichloromethane at −40 °C temperature afforded final compounds **8a**–**8e**.

Scheme 3 describes the preparation of some intermediates that were used toward, the synthesis of target compounds shown in



Scheme 1. Reagents and conditions: (a) 3–5 mol % $PdCl_2[P(o\text{-tol})_3]_2$, NaO*t*-Bu, diglyme, reflux, 48 h.

Scheme 4. In this scheme either 7-methoxy or 5-methoxy-2-tetralone was subjected to reductive amination with *n*-propyl amine in standard reductive amination conditions to give aminotetraline moieties **10a** and **10b**. These amines were resolved to their *S*(−) or *R*(+) enantiomers.[16,20] N-Amidation of amines using chloroacetylchloride in the presence of triethyl amine produced the chloro-intermediates **12a**–**12c**.

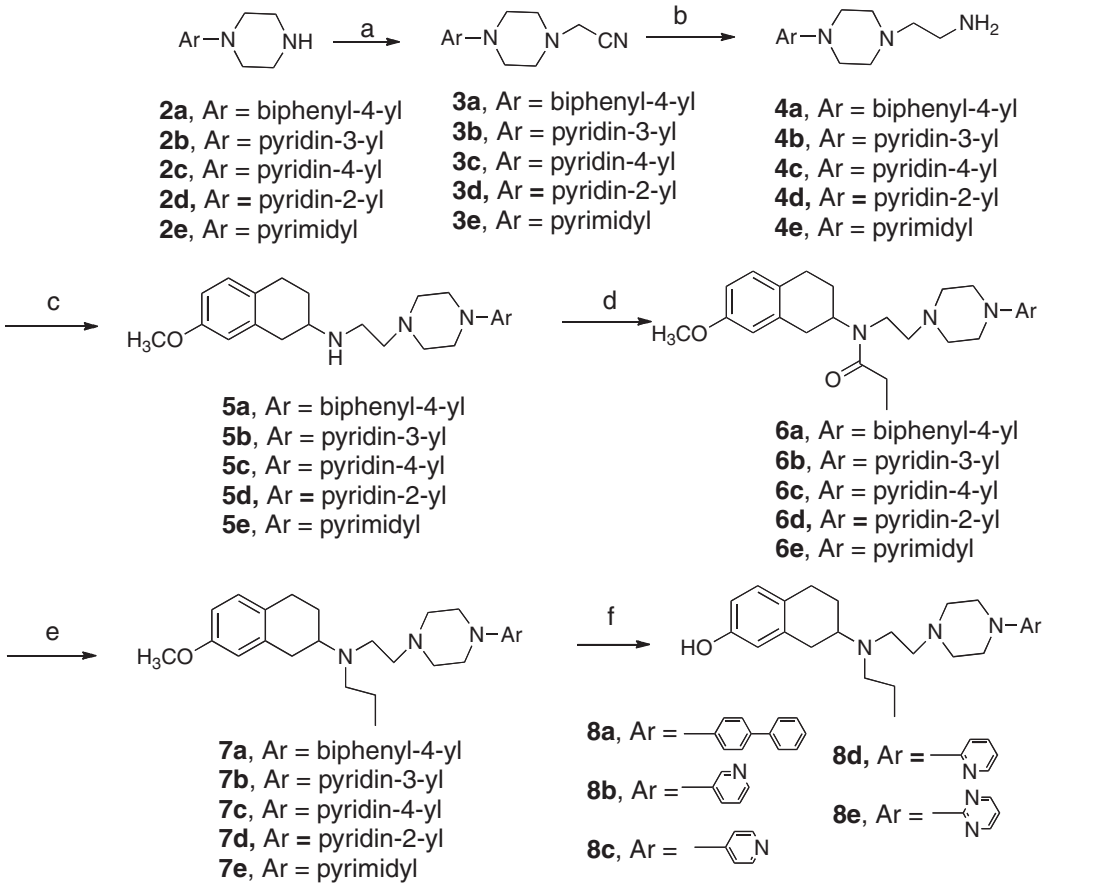
Scheme 4 depicts the syntheses of four final compounds. Commercially available 1-(4-iodophenyl)piperazine was treated with Boc-anhydride to make mono-Boc-protected intermediate which was then exposed to Suzuki coupling reaction[21,22] with 3- or 4-pyridinyl boronic acid to give **17a** and **17b**. Pyridinyl boronic acid was made from pyridinyl bromides using the reported procedure.[21] The amine protecting group, Boc was removed using trifluoroacetic acid and subjected to N-amidation reaction with chloroacetylchloride to get intermediates **19a** and **19b** which was then treated with either racemic or enantiomerically pure 7-methoxy- or 5-methoxy-2-aminotetralin in standard N-alkylation reaction condition to produce corresponding amides **20a–20d** which after LAH reduction gave the amines **21a**–**21d**. Demethylation in the presence of boron tribromide in dichloromethane at −40 °C or in aq HBr at reflux yielded the final compounds **22a**–**22d**.

Scheme 5 shows the preparation of final compound **25**. Racemic 7-methoxy-2-tetralin was treated with chloroacetylchloride to give intermediate **12c** which was then subjected to N-alkylation reaction with 1-(4-iodophenyl)piperazine to produce amide **23**. Next LAH reduction gave the amine **24** and the final compound **25** was afforded by demethylation of the amine using boron tribromide solution (1 M in dichloromethane).

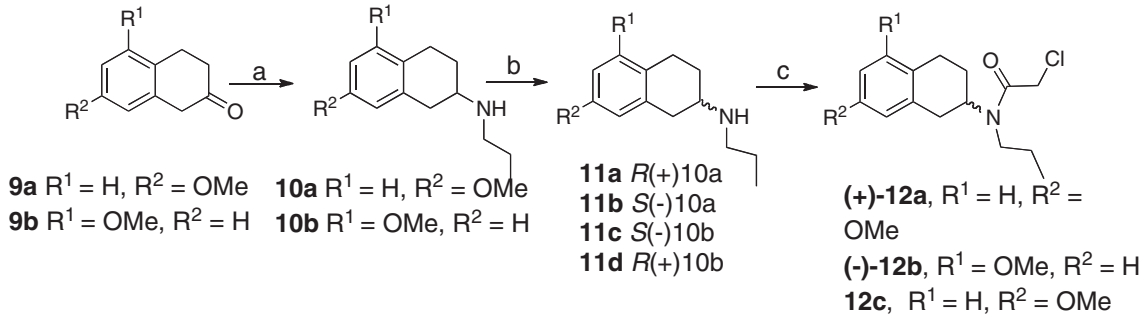
Scheme 6 represents the preparation of two enantiomerically pure compounds. One of the intermediates **2a** described in Scheme 1 was subjected to N-alkylation reaction with **12a** and **12b** to get the corresponding amides which were then reduced by LAH in THF to produce amine intermediates **27a**–**27b**. Demethylation yielded the final compounds (**+**)-**8a** and (−)-**28b**.

3. Results and discussion

As mentioned before, linearly fused *N*-biphenyl and *N*-isoquinoline moieties in the piperazine ring of D-264 and D-301 were tolerated well as these compounds exhibited potent binding affinity and high selectivity for the D_3 receptor. The results of D-264 and D-301 are consistent with the interpretation that compounds containing a thiazolidinium moiety generally exhibit high selectivity for the D_3 receptor, although N-aromatic substitutions in the



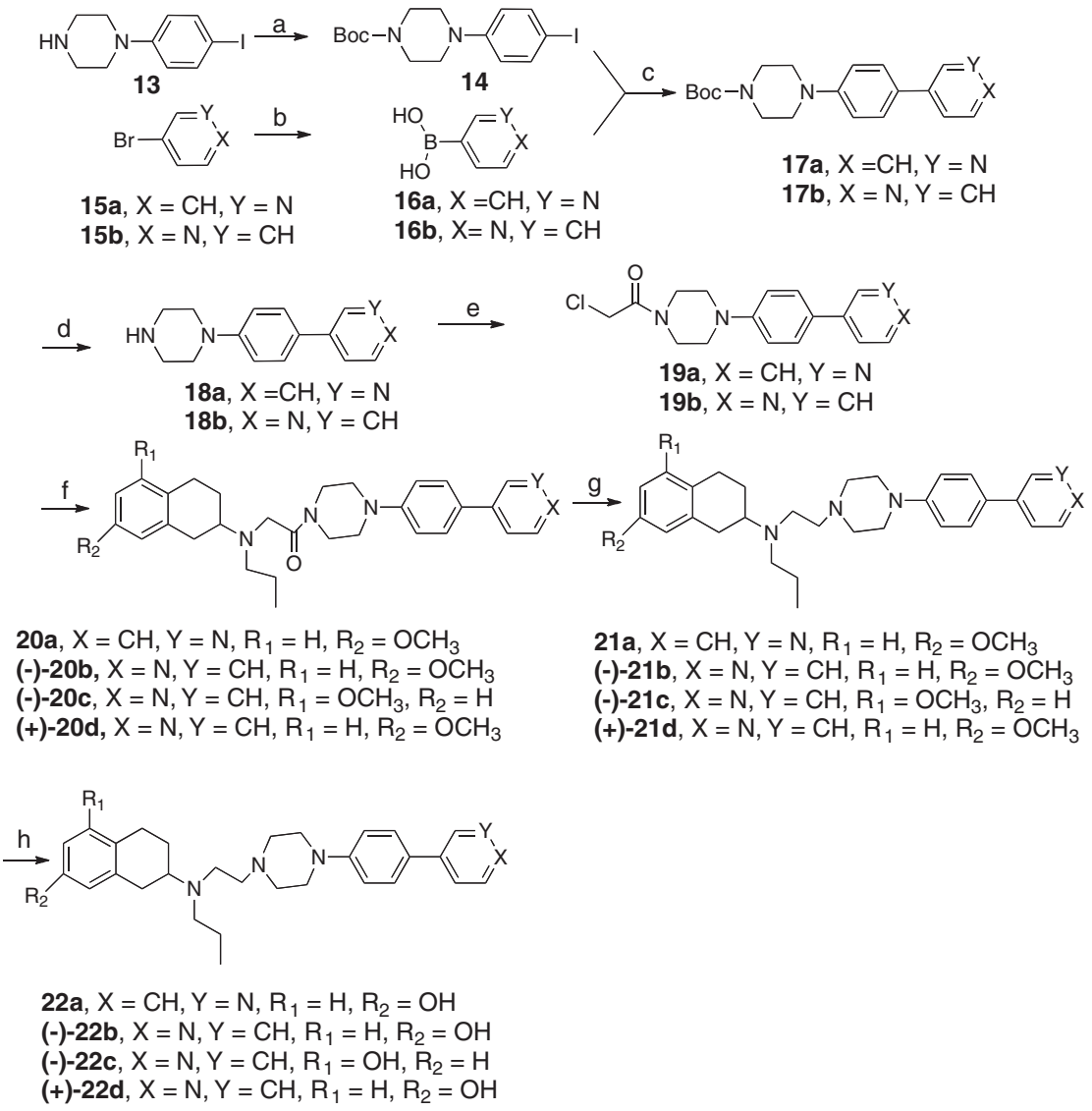
Scheme 2. Reagents and conditions (a) chloroacetonitrile, K_2CO_3, toluene, reflux, 3 h; (b) Raney nickel, H_2, 60 psi, 8 h; (c) 7-methoxy-2-tetralone, $NaCNBH_3$, AcOH, dichloroethane, rt, overnight; (d) propionyl chloride, Et_3N, CH_2Cl_2, 0 °C to rt, 4 h; (e) $LiAlH_4$, THF, reflux, 4 h; (f) BBr_3, CH_2Cl_2, −40 °C to rt, overnight.



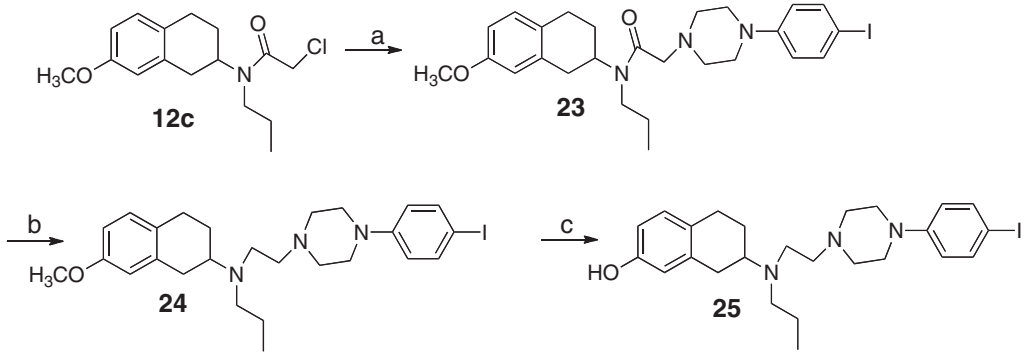
Scheme 3. Reagents and conditions: (a) *n*-propylamine, $NaCNBH_3$, CH_3COOH, dichloroethane, rt, overnight; (b) chlocyphos, EtOH; (c) chloroacetylchloride, Et_3N, dichloromethane, 0 °C, 30 min.

piperazine ring might also play a role in selectivity. Our next goal was to explore replacement of the thiazolidinium ring in D-264 by a hydroxy-phenolic moiety with an hydroxyl group located at either the 5- or 7-position, and to observe the effect of such replacement on the binding affinity compared to D-264 and D-301. Racemic 7-hydroxy derived **8a** was potent at D_3 and was moderately potent at D_2 (K_i; D_2 = 64 and D_3 = 5.22 nM), Table 1. Next, compound (+)-**8a** was selectively synthesized as the (+)-isomeric form of the 7-hydroxy derived hybrid molecules consistently exhibited higher affinity than its (−)-enantiomeric counterpart.[15,16] Compound (+)-**8a** exhibited twofold higher affinity at D_3 compared to racemic **8a** whereas the affinity at D_2 did not change appreciably (K_i; D_3 = 2.79 nM, D_2/D_3 = 20.77). However, the selectivity compared to D-264 was far less. Similarly, 5-hydroxy derived (−)-**28b** was synthesized selectively as it has been found almost in all the cases the (−)-isomer in this series is more active than the (+)-counterpart.[15,16] Compound (−)-**28b** was found to exhibit a profile similar to (+)-8a (K_i; D_3 = 2.36 nM, D_2/D_3 = 22.69), Table 1. In comparison to D-264 and D-301, both compounds (+)-**8a** and (−)-**28b** were similar in binding affinity for the D_3 receptor, but D-264 was more selective for the D_3 receptor due to its lower affinity for D_2 receptor. Effect of replacement of the phenyl ring by iodine in the biphenyl moiety as shown in **25** reduced the affinity for the D_3 receptor but maintained the affinity for D_2.

Next, we wanted to modify the biphenyl moiety in (+)-**8a** and (−)-**28b** to a phenyl-pyridine linearly fused moiety to observe the introduction of pyridine on affinity and selectivity. An N-containing pyridine ring can potentially provide additional interac-

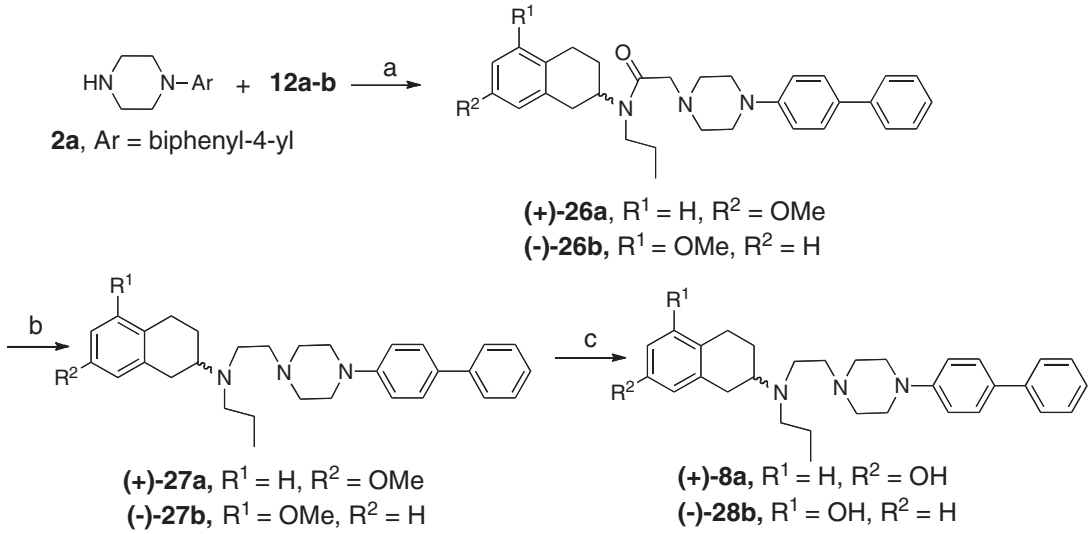


Scheme 4. Reagents and conditions: (a) $(Boc)_2O$, CH_2Cl_2, 0 °C, 2 h; (b) (i) *n*-BuLi, $(i\text{-PrO})_3B$, toluene, THF, −78 °C to rt; (ii) NaOH, 50%; (c) 1,2-dimethoxyethane, *t*-BuOK, 5 mol % $Pd(PPh_3)_4$, H_2O, 90 °C; (d) TFA/DCM (1/1), rt, overnight; (e) chloroacetylchloride, Et_3N, dichloromethane, 0 °C, 30 min; (f) **10a**/**11a**/**11b**/**11c** (tetralins) K_2CO_3, KI, acetonitrile, 60 °C, 4 h; (g) $LiAlH_4$, THF, reflux, 2 h; (h) BBr_3, −78 °C, CH_2Cl_2, overnight or 48% aq HBr, reflux, 2 h.



Scheme 5. Reagents and conditions: (a) 4-iodophenylpiperazine, K_2CO_3, KI, acetonitrile, 60 °C, 4 h; (b) $LiAlH_4$, THF, reflux, 2 h; (c) BBr_3, −78 °C, CH_2Cl_2, overnight.

tions besides predominant hydrophobic interactions from the phenyl group. Thus, compounds **22a**, (−)-**22b**, (−)-**22c** and (+)-**22d** were designed. 5-Hydroxy derived compound (−)-**22c** displayed very high affinity for both D_2 and D_3 receptors (K_i; D_2 = 13.2 nM and D_3 = 1.53 nM). Similarly, 7-hydroxy derived compound (+)-**22d** exhibited relatively higher affinity at D_3 receptor with improved selectivity for D_3 (K_i; D_3 = 0.78 nM; D_2/D_3 = 32). As expected, 7-hydroxy derived (−)-**22b** exhibited much weaker



Scheme 6. Reagents and conditions: (a) K_2CO_3, KI, acetonitrile, 60 °C, 4 h; (b) $LiAlH_4$, THF, reflux, 2 h; (c) BBr_3, −78 °C, CH_2Cl_2, overnight.

Table 1
K_i values (nM) are for inhibition of [^{3}H] spiroperidol binding to HEK-D_2/D_3 cells and are given as the mean ± SEM for 3–6 independent experiments carried out in triplicate

Compound	K_i, (nM), D_2 [^{3}H]spiperone	K_i, (nM), D_3 [^{3}H]spiperone	D_2/D_3	*C*Log *P*
(±)-7-OH-DPAT	311 ± 47	6.19 ± 1.4		4.00
(−)-5-OH-DPAT	58.8 ± 11.0	1.36 ± 0.28	43.2	4.00
Ropinirole	2674 ± 305	29.3 ± 4.2	91	2.79
D-315	40.6 ± 3.6	1.77 ± 0.42	22.9	5.46
D-237[a]	26.0 ± 7.5	0.825 ± 0.136	31.5	5.46
D-264[b]	264 ± 40	0.92 ± 0.23	253	6.10
D-301	269 ± 16	2.23 ± 0.60	121	4.44
D-214 (**8a**)	64.1 ± 14.8	5.22 ± 0.73		7.35
D-216 (**8d**)	103 ± 28	1.96 ± 0.19	52.6	4.51
D-222 (**8e**)	165 ± 21	6.84 ± 1.83	24.1	3.75
D-243 (**8b**)	21.7 ± 4.8	2.89 ± 0.52	7.51	4.51
D-288 (**8c**)	68.3 ± 8.5	14.1 ± 2.11	4.84	4.51
D-292 (**22a**)	59.1 ± 0.9	3.01 ± 0.88	19.6	5.96
D-293 (**25**)	46.4 ± 3.2	7.66 ± 1.56	6.06	6.75
(+)-D-335 (**8a**)	58.0 ± 14.7	2.79 ± 0.73	20.8	7.35
(−)-D-352 (**28b**)	53.6 ± 12.3	2.36 ± 0.87	22.7	7.35
(−)-D-304 (**22c**)	13.2 ± 1.3	1.53 ± 0.15	8.63	5.96
(−)-D-305 (**22b**)	399 ± 16	16.2 ± 1.8	24.6	5.96
(+)-D-414 (**22d**)	24.7 (4) ± 5.8	0.780 ± 0.22	32	5.96

[a,b]Refs. 15,16.

potency (K_i; D_2 = 399 nM and D_3 = 16.2 nM). Racemic **22a**, which is a 7-hydroxy derived 3-pyridine derivative, displayed high affinity for D_2/D_3 receptor (K_i; D_2 = 59 nM and D_3 = 3 nM), Table 1.

Next, we synthesized the three isomeric *N*-pyridine analogues **8d**, **8b**, **8c**, and the 2-substituted pyrimidine derivative **8e**. Among the three pyridine derivatives, 2-substituted derivative **8d** exhibited highest affinity and selectivity for the D_3 receptor (K_i; D_3 = 1.96 nM; D_2/D_3 = 53). This compound bears a structural resemblance to the isoquinoline compound D-301 where the relative position of the N-atom in the *N*-isoquinoline substitution is similar to the 2-pyridine substitution in **8d**. If isoquinoline is considered a phenyl ring with fused 2-substituted pyridine ring then for both the compounds, **8d** and D-301, the N-atoms should have similar locations in the space with respect to the target receptors. It is apparent that such a position of the heterocyclic N-atom in both the molecules leads to production of an unfavorable interaction with the dopamine D_2 receptor, thereby, increasing the selectivity for D_3. Binding data for **8b** bear a striking resemblance to **22a**. Compound **8b** resembles structurally to **22a** as they are both 3-substituted pyridine derivatives although in **22a** pyridine ring is part of a biphenyl system. Current results from three isomeric pyridine substituted compounds indicate that the location of N-atom in substituted pyridine is important for interaction when the 2-substituted pyridine ring produced highest affinity and selectivity. On the other hand, 4-substituted pyridine compound, **8c**, was least active and selective (K_i; D_3 = 14.1 nM; D_2/D_3 = 4.5), indicating generation of unfavorable interaction. Finally, we have added *C*log *P* values (calculated from CHEMDRAW program) of all the compounds in Table 1 which indicates a broad range of values depending on the structure of the target compounds.

Following binding evaluation, optically active compounds (+)-**8a** and (−)-**28b** were evaluated in the GTPγS binding functional assay for D_2 and D_3 receptors. The assays were carried out with the cloned human D_2 and D_3 receptors expressed in CHO cells and ropinirole was used as a reference compound for comparison purpose. Both compounds (+)-**8a** and (−)-**28b** exhibited high potency for the D_3 receptor whereas (−)-**28b** was more potent compared to (+)-**8a** (EC_{50}; 1.03 and 0.25 nM for **28a** and **28b**, respectively), Table 2. In regards to selectivity for D_3 receptor with respect to D_2 receptor, both compounds exhibited high selectivity for D_3 receptor while compound (−)-**28b** was more selective compared to (+)-**8a** (D_2/D_3 (ratio of EC_{50}): 105 vs 202), Table 2. Compared to reference ropinirole, both compounds (+)-**8a** and (−)-**28b** exhibited higher potency and selectivity for D_3 receptor.

Table 2
EC_{50} values (nM) for stimulating [^{35}S]GTPγS binding

Compound	CHO-D_2		CHO-D_3		D_2/D_3
	EC_{50} (nM) [^{35}S]GTPγS	$\%E_{max}$	EC_{50} (nM) [^{35}S]GTPγS	$\%E_{max}$	
Dopamine	209 ± 29	100	4.76 ± 0.87	100	43.9
Ropinirole	304 ± 11	83.9 ± 0.3	10.3 ± 1.5	66.6 ± 8.1	29.5
(+)-D-335 (**8a**)	108 ± 39	42.1 ± 7.0	1.03 ± 0.47	69.1 ± 7.4	105
(−)-D-352 (**28b**)	52.6 ± 10.9	71.8 ± 5.3	0.26 ± 0.058	74.6 ± 4.7	202

Results are means ± SEM for 3–5 experiments each performed in triplicate.

4. Conclusion

In this report we have shown that various N-aromatic and bulky substitutions on the piperazine moiety were tolerated well by both D_2 and D_3 receptors. Compound **8d** turned out to be the most selective for the D_3 receptor in the binding assay. The similarity in binding affinity observed for the isoquinoline derivative D-301 and the 2-substituted pyridine derivative **8d**, suggest the importance of relative spatial relationships between the N-atom of the ligand and the molecular determinants of the binding pocket in D_2/D_3 receptors. In the functional activity assay, compounds (+)-**8a** and (−)-**28b** were more potent and selective for the D_3 receptor compared to the reference drug ropinirole.

5. Experimental

Analytical silica gel-coated TLC plates (Silica Gel 60 F_{254}) were purchased from EM Science and were visualized with UV light or by treatment with phosphomolybdic acid (PMA). Flash chromatography was carried out on Baker Silica Gel 40 mM. ^{1}H NMR spectra were routinely obtained on GE-300 MHz and Varian 400 MHz FT NMR. The NMR solvent used was either $CDCl_3$ or CD_3OD or DMSO-d_6 as indicated. TMS was used as an internal standard. Elemental analyses were performed by Atlantic Microlab, Inc. and were within ±0.4% of the theoretical value.

5.1. Procedure A

5.1.1. Synthesis of 1-(4-biphenylyl)piperazine (2a)

Into a solution of 4-bromobiphenyl **1a** (3 g, 12.87 mmol) and piperazine (4.43 g, 51.48 mmol) in 100 mL of diglyme was added K-*t*-butoxide (4.33 g, 38.61 mmol). The reaction mixture was stirred for few minutes before the addition of palladium catalyst, dichlorobis(tri-*o*-tolylphosphine)palladium (0.386 g, 0.386 mmol) and refluxed at 170 °C for 48 h. The reaction mixture was cooled and the diglyme was evaporated under reduced pressure. The solid residue was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layer was dried (Na_2SO_4), evaporated under reduced pressure to obtain the crude product which was purified by column chromatography (ethyl acetate/MeOH 9:1) to yield 1.99 g of pure compound **2a** (65%) as a yellow color solid: ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 3.05 (t, 4H, J = 4.4 Hz), 3.20 (t, 4H, J = 5.2 Hz), 6.99–7.01 (d, 2H, J = 8.8 Hz), 7.26–7.30 (m, 1H), 7.40 (t, 2H, J = 7.6 Hz), 7.51–7.57 (m, 4H).

5.1.2. Synthesis of 1-(pyridin-3-yl)piperazine (2b)

Compound **2b** was prepared from 3-bromopyridine **1b** (3.10 mL, 31.6 mmol) and piperazine (10.9 g, 12.66 mmol) according to the procedure A to afford 3.15 g of resinous compound **2b** (61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 3.05 (t, 4H, J = 4.4 Hz), 3.20 (t, 4H, J = 5.2 Hz), 7.17–7.19 (m, 2H), 8.120–8.135 (dd, 1H, J_1 = 2 Hz, J_2 = 4 Hz), 8.31–8.31 (s, 1H).

5.2. Procedure B

5.2.1. Synthesis of 2-(4-(biphenyl-4-yl)piperazin-1-yl)acetonitrile (3a)

A suspension of 1-(biphenyl-4-yl)piperazine (**2a**) (2.5 g, 10.5 mmol), potassium carbonate (2.9 g, 21 mmol), and 2-chloroacetonitrile (1.3 mL, 21 mmol) in toluene was refluxed for 3 h. Toluene was removed under reduced pressure, and the residue was diluted with ethyl acetate, washed with water and brine, dried over sodium sulfate (Na_2SO_4), concentrated, and purified by column chromatography (ethyl acetate/hexane = 1:1) to afford the product **3a** as a thick yellow solid (2.33 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.76–2.79 (t, 4H, J = 6 Hz), 3.27–3.30 (t, 4H, J = 6 Hz), 3.58 (s, 2H), 6.98–7.00 (d, 2H, J = 8 Hz), 7.25–7.30 (m, 1H), 7.39–7.42 (t, 2H, J = 6 Hz), 7.50–7.57 (m, 4H).

5.2.2. Synthesis of 2-(4-(pyridin-3-yl)piperazin-1-yl)acetonitrile (3b)

Compound **3b** was synthesized from 1-(pyridin-3-yl)piperazine, **2b** (3.15 g, 19.28 mmol) and 2-chloroacetonitrile (3.66 mL, 57.9 mmol) according to the procedure B to afford product **3b** as a yellow mass (3.08 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.76–2.78 (t, 4H, J = 4 Hz), 3.26–3.27 (t, 4H, J = 6 Hz), 3.56 (s, 2H), 7.17–7.19 (m, 2H), 8.120–8.135 (dd, 1H, J_1 = 2 Hz, J_2 = 4 Hz), 8.31–8.31 (s, 1H).

5.2.3. Synthesis of 2-(4-(pyridin-4-yl)piperazin-1-yl)acetonitrile (3c)

Compound **3c** was synthesized from commercially available 1-(pyridin-4-yl)piperazine (**2c**) (4.00 g, 24.5 mmol) and 2-chloroacetonitrile (4.6 mL, 73.52 mmol) according to the procedure B to afford product **3c** (2.57 g, 52%) as yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.76–2.78 (t, 4H, J = 4 Hz), 3.26–3.27 (t, 4H, J = 6 Hz), 3.56 (s, 2H), 6.99–7.03 (m, 2H), 8.20–8.22 (d, 2H, J = 8 Hz).

5.2.4. Synthesis of 2-(4-(pyridin-2-yl)piperazin-1-yl)acetonitrile (3d)

Compound **3d** was also synthesized from commercially available 1-(pyridin-2-yl)piperazine (**2d**) (2.24 mL, 15.32 mmol) and 2-chloroacetonitrile (2.9 mL, 45.95 mmol) according to the procedure B to afford product **3d** (3.02 g, 97.5%) as yellow thick oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.63–2.66 (t, 4H, J = 6 Hz), 3.52 (s, 2H), 3.54–3.57 (t, 4H, J = 6 Hz), 6.58–6.62 (m, 2H), 7.42–7.46 (t, 1H, J = 8 Hz), 8.14–8.15 (d, 1H, J = 4 Hz).

5.2.5. Synthesis of 2-(4-(pyrimidin-2-yl)piperazin-1-yl)acetonitrile (3e)

Compound **3e** was synthesized from commercially available 2-(piperazin-1-yl)pyrimidine (**2e**) (2.16 mL, 15.22 mmol) and 2-chloroacetonitrile (2.89 mL, 45.67 mmol) according to the procedure B to afford product **3e** as viscous oil (2.4 g, 77.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.63–2.66 (t, 4H, J = 6 Hz), 3.58 (s, 2H), 3.88–3.91 (t, 4H, J = 6 Hz), 6.50–6.53 (t, 1H, J = 6 Hz), 8.31–8.32 (d, 2H, J = 4 Hz).

5.3. Procedure C

5.3.1. Synthesis of 2-(4-(biphenyl-4-yl)piperazin-1-yl)ethanamine (4a)

A solution of compound **3a** in methanol (2.33 g, 8.41 mmol) was hydrogenated in a Parr hydrogenator apparatus in the presence of Raney nickel catalyst at a pressure of 60 psi for 12 h. The reaction mixture was passed through Celite, dried over Na_2SO_4, evaporated, and purified over a silica gel column using the solvent system ethyl acetate/methanol/triethylamine (80:15:5) to afford compound **4a** as thick oil (2.73 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.47–2.50 (t, 2H, J = 6 Hz), 2.68–2.70 (t, 4H, J = 4 Hz), 2.87–2.90 (t, 2H, J = 6 Hz), 3.13–3.15 (t, 4H, J = 4 Hz), 6.97–6.99 (d, 2H, J = 8 Hz), 7.26–7.30 (m, 1H), 7.38–7.41 (t, 2H, J = 6 Hz), 7.49–7.55 (m, 4H).

5.3.2. Synthesis of 2-(4-(pyridin-3-yl)piperazin-1-yl)ethanamine (4b)

Compound **4b** was synthesized from 2-(4-(pyridin-3-yl)piperazin-1-yl)acetonitrile, **3b** (3.08 g, 15.13 mmol) according to the procedure C to afford product **4b** as thick oil (3.01 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.47–2.50 (t, 2H, J = 6 Hz), 2.68–2.70 (t, 4H, J = 4 Hz), 2.87–2.90 (t, 2H, J = 6 Hz), 3.13–3.15 (t, 4H, J = 4 Hz), 7.17–7.19 (m, 2H), 8.120–8.135 (dd, 1H, J_1 = 2 Hz, J_2 = 4 Hz), 8.31–8.31 (s, 1H).

5.3.3. Synthesis of 2-(4-(pyridin-4-yl)piperazin-1-yl)ethanamine (4c)

Compound **4c** was synthesized from 2-(4-(pyridin-4-yl)piperazin-1-yl)acetonitrile, **3c** (2.57 g, 12.7 mmol) according to the procedure C to afford product **4c** as thick oil (2.43 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.46–2.49 (t, 2H, J = 6 Hz), 2.67–2.71 (t, 4H, J = 8 Hz), 2.86–2.89 (t, 2H, J = 6 Hz), 3.14–3.16 (t, 4H, J = 4 Hz), 6.96–7.04 (m, 2H), 8.18–8.20 (d, 2H, J = 8 Hz).

5.3.4. Synthesis of 2-(4-(pyridin-2-yl)piperazin-1-yl)ethanamine (4d)

Compound **4d** was synthesized from 2-(4-(pyridin-2-yl)piperazin-1-yl)acetonitrile, **3d** (3.02 g, 14.9 mmol) according to the procedure C to afford product **4d** as thick oil (2.91 g, 94.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.33–2.36 (t, 2H, J = 6 Hz), 2.63–2.66 (t, 4H, J = 6 Hz), 2.71–2.86 (m, 2H), 3.64–3.67 (t, 4H, J = 6 Hz), 6.58–6.62 (m, 2H), 7.42–7.46 (t, 1H, J = 8 Hz), 8.14–8.15 (d, 1H, J = 4 Hz).

5.3.5. Synthesis of 2-(4-(pyrimidin-2-yl)piperazin-1-yl)ethanamine (4e)

Compound **4e** was synthesized from 2-(4-(pyrimidin-2-yl)piperazin-1-yl)acetonitrile, **3e** (2.4 g, 11.81 mmol) according to the procedure C to afford product **4e** as thick oil (2.35 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.33–2.36 (t, 2H, J = 6 Hz), 2.63–2.66 (t, 4H, J = 6 Hz), 3.58 (m, 2H), 3.88–3.91 (t, 4H, J = 6 Hz), 6.50–6.53 (t, 1H, J = 6 Hz), 8.31–8.32 (d, 2H, J = 4 Hz).

5.4. Procedure D

5.4.1. Synthesis of *N*-(2-(4-(biphenyl-4-yl)piperazin-1-yl)ethyl)-7-methoxy-1,2,3,4-tetrahydronaphthalen-2-amine (5a)

A mixture of compound **4a** (1.2 g, 4.3 mmol), 7-methoxy-2-tetralone (0.82 g, 4.7 mmol), and glacial acetic acid (HOAc) (0.25 mL) in 1,2-dichloroethane (50 mL) was stirred at room temperature under N_2 atmosphere for 20 min. Sodium cyanoborohydride ($NaCNBH_3$) (1.08 g, 17.2 mmol) dissolved in a minimum volume of methanol was added to the reaction mixture. The reaction mixture was stirred at room temperature under nitrogen atmosphere for 12 h. The solvent was evaporated, and saturated $NaHCO_3/H_2O$ (50 mL) was added to the mixture, which was then extracted with ethyl acetate (3 × 100 mL). The combined organic phase was dried over Na_2SO_4 and evaporated to afford the crude product, which was purified by flash chromatography (EtOAc/MeOH/Et_3N = 95:4:1) to give the product **5a** as brown solid (0.55 g, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.66–1.69 (m, 2H), 2.09 (br s, 1H), 2.59–2.72 (m, 6H), 2.81–3.02 (m, 6H), 3.23–3.25 (t, 4H, J = 4 Hz), 3.77 (s, 3H), 6.62 (s, 1H), 6.67–6.70 (d, 1H, J = 12 Hz), 6.98–7.01 (m, 3H), 7.26–7.30 (t, 1H J = 8 Hz), 7.38–7.42 (t, 2H, J = 8 Hz), 7.50–7.57 (m, 4H).

5.4.2. Synthesis of 7-methoxy-*N*-(2-(4-(pyridin-3-yl)piperazin-1-yl)ethyl)-1,2,3,4-tetrahydronaphthalen-2-amine (5b)

Compound **4b** (0.96 g, 4.5 mmol) was reacted with 7-methoxy-2-tetralone (1.16 g, 6.6 mmol), $NaCNBH_3$ (1.17 g, 18.75 mmol), and HOAc (0.28 mL) in 1,2-dichloroethane (50 mL) to yield **5b** as brown mass (1.11 g, 65%) (procedure D). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.73–1.82 (m, 1H), 1.99–2.03 (m, 1H), 2.15 (s, 1H), 2.28 (br s, 1H), 2.53–2.92 (m, 6H), 3.11–3.26 (m, 3H), 3.65–3.77 (m, 9H), 6.58 (s, 1H), 6.65–6.68 (m, 2H), 6.94–6.98 (t, 2H, J = 8 Hz), 7.11–7.16 (m, 1H), 8.01–8.22 (m, 1H).

5.4.3. Synthesis of 7-methoxy-*N*-(2-(4-(pyridin-4-yl)piperazin-1-yl)ethyl)-1,2,3,4-tetrahydronaphthalen-2-amine (5c)

Compound **4c** (1.2 g, 5.82 mmol) was reacted with 7-methoxy-2-tetralone (1.53 g, 8.73 mmol), $NaCNBH_3$ (1.09 g, 17.45 mmol), and HOAc (0.7 mL) in 1,2-dichloroethane (50 mL) to yield **5c** as brown color solid (1.3 g, 61%) (procedure D). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.69–1.78 (m, 1H), 1.96–2.01 (m, 1H), 2.13 (s, 1H), 2.31 (br s, 1H), 2.51–2.91 (m, 6H), 3.09–3.21 (m, 3H), 3.65–3.77 (m, 9H), 6.63–6.65 (m, 2H), 6.81–6.82 (d, 2H, J = 4 Hz), 6.98–7.00 (d, 1H, J = 8 Hz), 8.27–8.29 (d, 2H, J = 8 Hz).

5.4.4. Synthesis of 7-methoxy-*N*-(2-(4-(pyridin-2-yl)piperazin-1-yl)ethyl)-1,2,3,4-tetrahydronaphthalen-2-amine (5d)

Compound **4d** (1.3 g, 6.3 mmol) was reacted with 7-methoxy-2-tetralone (1.33 g, 7.56 mmol), $NaCNBH_3$ (1.58 g, 25.21 mmol), and HOAc (0.4 mL) in 1,2-dichloroethane (50 mL) to yield **5d** (1.23 g, 69.2%) (procedure D). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.94–1.99 (m, 2H), 2.37–2.46 (m, 2H), 2.56–2.85 (m, 8H), 3.42–3.59 (m, 6H), 3.73, 3.76 (t, 4H, J = 6 Hz), 6.58–6.73 (m, 4H), 6.96–7.02 (dd, 1H, J_1 = 8.4 Hz, J_2 = 14.8 Hz), 7.43–7.45 (t, 1H, J = 4 Hz), 8.16–8.17 (d, 1H, J = 4 Hz).

5.4.5. Synthesis of 7-methoxy-*N*-(2-(4-(pyrimidin-2-yl)piperazin-1-yl)ethyl)-1,2,3,4-tetrahydronaphthalen-2-amine (5e)

Compound **4e** (1.59 g, 7.7 mmol) was reacted with 7-methoxy-2-tetralone (1.62 g, 9.2 mmol), $NaCNBH_3$ (1.93 g, 30.68 mmol), and HOAc (0.45 mL) in 1,2-dichloroethane (50 mL) to yield **5e** as semisolid (1.42 g, 50%) (procedure D). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.55–1.59 (m, 1H), 1.79 (br s, 1H), 1.98–2.02 (m, 2H), 2.44–2.52 (m, 7H), 2.71–2.92 (m, 5H), 3.7 (s, 3H), 3.76–3.78 (t, 4H, J = 4 Hz), 6.39 (t, 1H, J = 4 Hz), 6.57 (s, 1H), 6.62–6.64 (d, 1H, J = 8 Hz), 6.92–6.95 (d, 1H, J = 12 Hz), 8.23–8.24 (d, 2H, J = 4 Hz).

5.5. Procedure E

5.5.1. Synthesis of *N*-(2-(4-(biphenyl-4-yl)piperazin-1-yl)ethyl)-*N*-(7-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)propionamide (6a)

Propionyl chloride (0.33 mL, 3.75 mmol) was added into a solution of compound **5a** (0.55 g, 1.25 mmol) and Et_3N (1.0 mL) in anhydrous methylene chloride at 0 °C under N_2 atmosphere and then stirred at room temperature for 4 h. The reaction was diluted with CH_2Cl_2 and washed with water and brine, and the organic layer was dried over Na_2SO_4, evaporated, and purified by flash chromatography (EtOAc/MeOH/Et3 N = 95:4:1) to yield **6a** as solid (0.78 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.12–1.14 (m, 3H), 1.66–1.69 (m, 2H), 2.09 (br s, 1H), 2.59–2.72 (m, 6H), 2.81–3.02 (m,

6H), 3.19–3.22 (br s, 2H), 3.23–3.25 (t, 4H, *J* = 4 Hz), 3.77 (s, 3H), 6.62 (s, 1H), 6.67–6.70 (d, 1H, *J* = 12 Hz), 6.98–7.01 (m, 3H), 7.26–7.30 (t, 1H *J* = 8 Hz), 7.38–7.42 (t, 2H, *J* = 8 Hz), 7.50–7.57 (m, 4H).

5.5.2. Synthesis of *N*-(7-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-(2-(4-(pyridin-3-yl)piperazin-1-yl)ethyl)propionamide (6b)

Compound **5b** (0.80 g, 2.2 mmol) was reacted with propionyl chloride (0.57 mL, 6.55 mmol) and Et_3N (2.0 mL) in CH_2Cl_2 (20 mL) (procedure E). The crude product was purified by flash chromatography using solvent system EtOAc/MeOH = 90:10 to yield pure compound **6b** as semisolid (0.48 g, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.05–1.08 (m, 3H), 1.72–1.82 (m, 1H), 1.98–2.03 (m, 1H), 2.14 (s, 1H), 2.28–2.30 (br s, 1H), 2.54–2.94 (m, 6H), 3.21–3.26 (m, 3H), 3.67–3.74 (m, 11H), 6.56 (s, 1H), 6.64–6.67 (m, 2H), 6.93–6.98 (t, 2H, *J* = 8 Hz), 7.12–7.15 (m, 1H), 8.11–8.22 (m, 1H).

5.5.3. Synthesis of *N*-(7-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-(2-(4-(pyridin-4-yl)piperazin-1-yl)ethyl)propionamide (6c)

Compound **5c** (1.3 g, 3.55 mmol) was reacted with propionyl chloride (0.93 mL, 10.64 mmol) and Et3 N (3.0 mL) in CH_2Cl_2 (20 mL) (procedure E). The crude product was purified by flash chromatography using solvent system EtOAc/MeOH = 90:10 to yield pure compound **6c** as solid (0.70 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.05–1.08 (m, 3H), 1.71–1.82 (m, 1H), 1.91–2.03 (m, 1H), 2.13 (s, 1H), 2.32 (br s, 1H), 2.74–2.91 (m, 6H), 3.19–3.26 (m, 3H), 3.67–3.74 (m, 11H), 6.63–6.65 (m, 2H), 6.81–6.82 (d, 2H, *J* = 4 Hz), 6.98–7.00 (d, 1H, *J* = 8 Hz), 8.27–8.29 (d, 2H, *J* = 8 Hz).

5.5.4. Synthesis of *N*-(7-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-(2-(4-(pyridin-2-yl)piperazin-1-yl)ethyl)propionamide (6d)

Compound **5d** (2.74 g, 7.5 mmol) was reacted with propionyl chloride (0.98 mL, 11.2 mmol) and Et3 N (3.0 mL) in CH_2Cl_2 (20 mL) (procedure E). The crude product was purified by flash chromatography using solvent system EtOAc/MeOH = 90:10 to yield pure compound **6d** as solid (1.81 g, 57.2%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.12–1.16 (t, 3H, *J* = 8 Hz), 1.94–1.99 (m, 2H), 2.37–2.46 (m, 2H), 2.56–2.85 (m, 10H), 3.42–3.59 (m, 6H), 3.73, 3.76 (t, 4H, *J* = 6 Hz), 6.58–6.73 (m, 4H), 6.96–7.02 (dd, 1H, J_1 = 8.4 Hz, J_2 = 14.8 Hz), 7.43–7.45 (t, 1H, *J* = 4 Hz), 8.16–8.17 (d, 1H, *J* = 4 Hz).

5.5.5. Synthesis of *N*-(7-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-(2-(4-(pyrimidin-2-yl)piperazin-1-yl)ethyl)propionamide (6e)

Compound **5e** (1.4 g, 3.81 mmol) was reacted with propionyl chloride (0.99 mL, 11.43 mmol) and Et3 N (3.0 mL) in CH_2Cl_2 (20 mL) (procedure E). The crude product was purified by flash chromatography using solvent system EtOAc/MeOH = 90:10 to yield pure compound **6e** as solid (1.08 g, 67.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.99–1.02 (t, 3H, *J* = 6 Hz), 1.55–1.59 (m, 1H), 1.79 (br s, 1H), 1.98–2.02 (m, 2H), 2.44–2.52 (m, 7H), 2.71–2.92 (m, 7H), 3.7 (s, 3H), 3.76–3.78 (t, 4H, *J* = 4 Hz), 6.39 (t, 1H, *J* = 4 Hz), 6.57 (s, 1H), 6.62–6.64 (d, 1H, *J* = 8 Hz), 6.92–6.95 (d, 1H, *J* = 12 Hz), 8.23–8.24 (d, 2H, *J* = 4 Hz).

5.6. Procedure F

5.6.1. Synthesis of *N*-(2-(4-(biphenyl-4-yl)piperazin-1-yl)ethyl)-7-methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (7a)

Compound **6a** (0.78 g, 1.6 mmol) in anhydrous THF (30 mL) was added dropwise into a suspension of lithium aluminum hydride ($LiAlH_4$) (0.36 g, 9.44 mmol) in anhydrous THF (15 mL) at 0 °C under N_2 atmosphere. The reaction mixture was refluxed for 8 h, cooled to room temperature, and then cooled further to 0 °C. Saturated $NaOH/H_2O$ (3 mL) was added dropwise to quench excess $LiAlH_4$. The mixture was filtered, and the reaction mixture was dried over Na_2SO_4. The solvent was removed under vacuum to afford compound **7a** as transparent viscous liquid (0.52 g, 68.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.90–0.93 (t, 3H, *J* = 6 Hz), 1.26 (s, 1H), 1.48–1.53 (m, 2H), 2.02–2.2.05 (br s, 1H), 2.18 (s, 1H), 2.53–2.99 (m, 14H), 3.255–3.279 (t, 4H, *J* = 4.8 Hz), 3.78 (s, 3H), 6.64 (s, 1H), 6.68–6.71 (d, 1H, *J* = 12 Hz), 6.99–7.01 (m, 3H), 7.27–7.30 (t, 1H *J* = 6 Hz), 7.39–7.43 (t, 2H, *J* = 8 Hz), 7.51–7.57 (m, 4H).

5.6.2. Synthesis of 7-methoxy-*N*-propyl-*N*-(2-(4-(pyridin-3-yl)piperazin-1-yl)ethyl)-1,2,3,4-tetrahydronaphthalen-2-amine (7b)

Compound **6b** (0.48 g, 1.14 mmol) was reacted with LiAlH4 (0.25 g, 6.8 mmol) in THF (20 mL) by following the procedure F. The crude product was purified by flash chromatography using solvent system EtOAc/MeOH/Et3 N = 95:4:1 to yield compound **7b** as an oil (0.46 g, 90.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.98–1.02 (t, 3H, *J* = 8 Hz), 1.72–1.79 (m, 1H), 1.98–2.03 (m, 1H), 2.14 (s, 1H), 2.30–2.35 (br s, 1H), 2.62–2.92 (m, 8H), 3.12–3.25 (m, 3H), 3.63–3.72 (m, 11H), 6.57 (s, 1H), 6.64–6.67 (m, 2H), 6.93–6.97 (t, 2H, *J* = 8 Hz), 7.12–7.15 (m, 1H), 8.11–8.16 (m, 1H).

5.6.3. Synthesis of 7-methoxy-*N*-propyl-*N*-(2-(4-(pyridin-4-yl)piperazin-1-yl)ethyl)-1,2,3,4-tetrahydronaphthalen-2-amine (7c)

Compound **6c** (0.50 g, 1.18 mmol) was reacted with LiAlH4 (0.26 g, 7.09 mmol) in THF (20 mL) by following the procedure F. The crude product was purified by flash chromatography using solvent system EtOAc/MeOH/Et3 N = 95:4:1 to yield compound **7c** as thick liquid (0.37 g, 77.8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.88–0.90 (t, 3H, *J* = 4 Hz), 1.48 (br s, 2H), 1.59–1.62 (m, 1H), 1.996–2.034 (d, 1H, *J* = 15.2 Hz), 2.51–2.97 (m, 15H), 3.32–3.35 (t, 4H, *J* = 6 Hz), 3.77 (s, 3H), 6.63–6.65 (m, 4H), 6.98 (br s, 1H), 8.266 (br s, 2H).

5.6.4. Synthesis of 7-methoxy-*N*-propyl-*N*-(2-(4-(pyridin-2-yl)piperazin-1-yl)ethyl)-1,2,3,4-tetrahydronaphthalen-2-amine (7d)

Compound **6d** (0.67 g, 1.58 mmol) was reacted with LiAlH4 (0.36 g, 9.5 mmol) in THF (20 mL) by following the procedure F. The crude product was purified by flash chromatography using solvent system EtOAc/MeOH/Et3 N = 95:4:1 to yield compound **7d** as thick liquid (0.64 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.85–0.87 (t, 3H, *J* = 4 Hz), 1.18–1.22 (m, 1H), 1.41–1.49 (m, 2H), 1.99–2.00 (t, 2H, *J* = *2* Hz), 2.45–2.97 (m, 14H), 3.49–3.51 (t, 4H, *J* = 4 Hz), 3.7 (s, 3H).

5.6.5. Synthesis of 7-methoxy-*N*-propyl-*N*-(2-(4-(pyrimidin-2-yl)piperazin-1-yl)ethyl)-1,2,3,4-tetrahydronaphthalen-2-amine (7e)

Compound **6e** (1.00 g, 2.57 mmol) was reacted with LiAlH4 (0.58 g, 15.4 mmol) in THF (20 mL) by following the procedure F. The crude product was purified by flash chromatography using solvent system EtOAc/MeOH/Et3 N = 95:4:1 to yield compound **7e** as thick oil (0.55 g, 53.2%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.87–0.91 (t, 3H, *J* = 8 Hz), 1.57–1.66 (m, 1H), 1.99–2.03 (br s, 1H), 2.48–2.65 (m, 9H), 2.71–2.99 (m, 8H), 3.77 (s, 3H), 3.81–3.84 (t, 4H, *J* = 6 Hz), 6.46–6.48 (t, 1H, *J* = 4 Hz), 6.62 (s, 1H), 6.660–6.688 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.4 Hz), 6.97–6.99 (d, 1H, *J* = 8 Hz), 8.29–8.30 (d, 2H, *J* = 4 Hz).

5.7. Procedure G

5.7.1. Synthesis of 7-((2-(4-(biphenyl-4-yl)piperazin-1-yl)ethyl)(propyl)amino)-5,6,7,8-tetrahydronaphthalen-2-ol (8a)

Boron tribromide (1 M solution in dichloromethane) (3.22 mL, 3.22 mmol) was added into a solution of **7a** (0.52 g, 1.07 mmol) in anhydrous methylene chloride (CH_2Cl_2) (30 mL) at −40 °C under N_2 atmosphere. The reaction mixture was stirred at −40 °C for 2 h and was continued overnight at room temperature. The reaction was quenched by the addition of saturated $NaHCO_3$ solution, and the mixture was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and evaporated under vacuum, and the crude product was purified by flash chromatography (EtOAc/MeOH = 95:5) to afford compound **8a** as white solid (0.27 g, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.90–0.93 (t, 3H, J = 6 Hz), 1.26 (s, 1H), 1.48–1.53 (m, 2H), 2.02–2.2.05 (br s, 1H), 2.18 (s, 1H), 2.53–2.99 (m, 14H), 3.25–3.27 (t, 4H, J = 4.8 Hz), 6.57 (s, 1H), 6.61–6.64 (d, 1H, J = 12 Hz), 6.94–6.96 (d, 1H, J = 8 Hz), 6.99–7.01 (d, 2H, J = 8 Hz), 7.31–7.32 (d, 1H, J = 4 Hz), 7.39–7.43 (t, 2H, J = 8 Hz), 7.51–7.57 (m, 4H).

The product was converted into the corresponding trihydrochloride salt as white solid; mp: 180–182 °C. Anal. Calcd for ($C_{31}H_{42}N_3Cl_3O$, $0.7H_2O$) C, H, N.

5.7.2. Synthesis of 7-(propyl(2-(4-(pyridin-3-yl)piperazin-1-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-2-ol (8b)

Compound **7b** (0.42 g, 1.3 mmol) was reacted with 1 M BBr_3/CH_2Cl_2 (3.08 mL, 3.08 mmol) in CH_2Cl_2 (15 mL) by following the procedure G to furnish **8b** as white semisolid (0.245 g, 49.2%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.90–0.95 (t, 3H, J = 10 Hz), 1.69 (br s, 3H), 2.165 (br s, 1H), 2.71–2.95 (m, 15H), 3.22–3.24 (t, 4H, J = 4 Hz), 6.95 (s, 1H), 6.44–6.67 (d, 2H, J = 12 Hz), 6.87–6.89 (d, 1H, J = 8 Hz), 7.19 (s, 1H), 8.08–8.09 (t, 1H, J = 2 Hz), 8.26 (s, 1H).

The product was converted into the corresponding tetrahydrochloride salt as white solid; mp: 184–186 °C. Anal. Calcd for ($C_{24}H_{38}N_4Cl_4O$, $0.5H_2O$) C, H, N.

5.7.3. Synthesis of 7-(propyl(2-(4-(pyridin-4-yl)piperazin-1-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-2-ol (8c)

Compound **7c** (0.18 g, 0.44 mmol) was reacted with 1 M BBr_3/CH_2Cl_2 (1.76 mL, 1.76 mmol) in CH_2Cl_2 (15 mL) by following the procedure G to furnish **8c** as white semisolid (0.10 g, 57.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.06–1.09 (t, 3H, J = 6 Hz), 1.88–1.96 (m, 1H), 2.39 (br s, 1H), 2.90–2.94 (m, 2H), 3.10–3.31 (m, 11H), 3.46–3.54 (m, 4H), 3.73–3.84 (m, 4H), 6.60–6.62 (m, 2H), 6.93–6.96 (d, 1H, J = 12 Hz), 7.30–7.32 (d, 2H, J = 8 Hz), 8.255–8.274 (d, 2H, J = 7.6 Hz).

The product was converted into the corresponding oxalate salt as yellow solid, mp: 149–152 °C. Anal. Calcd for ($C_{30}H_{40}N_4O_{13}$, $1.3H_2O$) C, H, N.

5.7.4. Synthesis of 7-(propyl(2-(4-(pyridin-2-yl)piperazin-1-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-2-ol (8d)

Compound **7d** (0.63 g, 1.54 mmol) was reacted with 1 M BBr_3/CH_2Cl_2 (4.63 mL, 4.63 mmol) in CH_2Cl_2 (25 mL) by following the procedure G to furnish **8d** as white semisolid (0.298 g, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.86–0.88 (t, 3H, J = 4 Hz), 1.41–1.55 (m, 3H), 1.92–1.99 (br s, 1H), 2.49–2.72 (m, 14H), 2.91 (br s, 1H), 3.57–3.59 (t, 4H, J = 4 Hz), 6.47 (s, 1H), 6.55–6.57 (d, 1H, J = 8 Hz), 6.62–6.65 (m, 2H), 7.455–7.499 (t, 1H, 8.8 Hz), 8.17–8.18 (d, 1H, J = 4 Hz).

The product was converted into the corresponding trihydrochloride salt yellowish solid; mp: 190–192 °C. Anal. Calcd for ($C_{24}H_{37}N_4Cl_3O$, $1.4H_2O$) C, H, N.

5.7.5. Synthesis of 7-(propyl(2-(4-(pyrimidin-2-yl)piperazin-1-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-2-ol (8e)

Compound **7e** (0.55 g, 1.37 mmol) was reacted with 1 M BBr_3/CH_2Cl_2 (4.9 mL, 4.9 mmol) in CH_2Cl_2 (25 mL) by following the procedure G to furnish **8e** as semisolid (0.38 g, 71.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.86–0.88 (t, 3H, J = 4 Hz), 1.41–1.54 (m, 1H), 1.92–1.98 (br s, 1H), 2.472.89 (m, 17H), 3.86–3.87 (t, 4H, J = 2 Hz), 6.48–6.58 (m, 3H), 6.86–6.88 (d, 1H, J = 8 Hz), 8.29–8.31 (d, 2H, J = 8 Hz).

The product was converted into the corresponding oxalate salt yellow solid; mp: 90–92 °C. Anal. Calcd for ($C_{27}H_{37}N_5O_9$) C, H, N.

5.8. Procedure H

5.8.1. Synthesis of (7-methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-propyl-amine (10a)

7-Methoxy-2-tetralone (10 g, 56.75 mmol) and acetic acid (13.5 mL, 226.9 mmol) were dissolved in dichloroethane (150 mL) and cooled to 0 °C. *n*-Propylamine (11.7 mL, 141.87 mmol) was added and the mixture stirred under a N_2 atmosphere for 30 min. $NaCNBH_3$ (8.91 g, 141.87 mmol) in anhydrous MeOH (15 mL) was then added to the mixture and allowed to stir overnight at ambient temperature. The volatiles were then evaporated and saturated $NaHCO_3$ solution was added. It was then extracted with dichloromethane dried over Na_2SO_4, filtered, and concentrated. The crude residue was then taken up in EtOAc, at which time ethereal HCl was added, and the crude salt was filtered and dried over vacuum oven. The crude salt was then recrystallized in ethanol to yield 9.5 g as white solid (yield 65%) and used in the subsequent transformations. ^{1}H NMR (free base) (400 MHz, $CDCl_3$) 0.91–0.95 (t, 3H, J = 7.6 Hz), 1.38 (br s, 1H), 1.48–1.60 (m, 3H), 2.04–2.09 (m, 1H), 2.54–2.62 (m, 2H), 2.67–2.71 (t, 3H, J = 7.6 Hz), 2.88–2.92 (m, 2H), 2.97–3.04 (m, 1H), 3.81 (s, 3H), 6.60–6.61 (dd, 1H, J = 1.6 Hz), 6.65–6.78 (m, 1H), 6.95–6.98 (d, 1H, J = 8.8 Hz).

5.8.2. Synthesis of (5-methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-propyl-amine(10b)

Compound **10b** was prepared following procedure H from 5-methoxy 2-tetralone (64%). ^{1}H NMR (free base) (400 MHz, $CDCl_3$) 0.92–0.96 (t, 3H, J = 7.6 Hz), 1.39 (br s, 1H), 1.49–1.61 (m, 3H), 2.05–2.10 (m, 1H), 2.53–2.62 (m, 2H), 2.66–2.70 (t, 3H, J = 7.6 Hz), 2.87–2.94 (m, 2H), 2.98–3.03 (m, 1H), 3.81 (s, 3H), 6.65–6.67 (d, 1H, J = 8 Hz), 6.96–6.71 (d, 1H, J = 8 Hz), 7.07–7.11 (t, 1H, J = 7.2 Hz).

5.9. Procedure I

5.9.1. Resolution of 5-methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine for preparation of 11c and 11d

Racemic (**±**)**-10b** was resolved into its (+) and (−) isomers by using the both (−) and the (+) isomers of the synthetic resolving agent 4-(2-chlorophenyl)-5,5-dimethyl-2-hydroxy-1,3,2-dioxaphosphorinane 2-oxide. This optically active resolving agents were prepared according to the published procedure.[20] **10b** (free base 14.77 g, 67.36 mmol) and (+)-4-(2-chlorophenyl)-5,5-dimethyl-2-hydroxy-1,3,2-dioxaphosphorinane 2-oxide (20.5 g, 74.1 mmol) were dissolved by warming in 100 mL of ethanol. The solution was cooled to room temperature and then at 0°C. The precipitated crystals were filtered off, washed with cold ether to yield 17.4 g of the salt ($[\alpha]_D$ = (−)1.2, c = 1 in methanol). Further recrystallization two times from hot ethanol yielded the salt (12.9 g, $[\alpha]_D$ = (−)14.1, c = 1 in methanol). Further crystallization of the salt from hot ethanol did not change the optical rotation to a significant extent. The salt was then hydrolyzed in the presence of 20% NaOH solution in water under stirred condition for 2 h at room temperature. The aqueous layer

was extracted with dichloromethane (3 × 100 mL), dried over Na_2SO_4 and evaporated to dryness to yield **11c** (5.8 g, $[\alpha]_D$ of the white solid HCl salt of **11c** = (−)71.5, (*c* = 1 in methanol) yield: 78.5%.

Compound (±)-**10b** (18.5 g, 84.35 mmol) was similarly treated using (−)-4-(2-chlorophenyl)-5,5-dimethyl-2-hydroxy-1,3,2-dioxaphosphorinane 2-oxide (24.5 g, 88.57 mmol). Recrystallization from hot ethanol yielded the salt (16.2 g, $[\alpha]_D$ = (+)-13.0, *c* = 1 in methanol). Yield is 78%. Further crystallization of the salt from hot ethanol did not change the optical rotation to a significant extent. Hydrolysis of the chlocyphos salt following above mentioned procedure yielded **11d** white solid hydrochloride salt, $[\alpha]_D$ of the HCl salt is (+)-69.8, *c* = 1 in methanol).

5.9.2. Resolution of 7-methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine for preparation of 11a and 11b

This resolution was done by using the above procedure I. Compound (**±**)-**10a** (5.99 g, 27.31 mmol) was similarly treated using (−)-4-(2-chlorophenyl)-5,5-dimethyl-2-hydroxy-1,3,2-dioxaphosphorinane 2-oxide (7.93 g, 28.68 mmol). Recrystallization from hot ethanol yielded the salt (5.4 g, $[\alpha]_D$ = (+)-12.9, *c* = 1 in methanol). Yield is 80%. Further crystallization of the salt from hot ethanol did not change the optical rotation to a significant extent. Hydrolysis of the chlocyphos salt following above mentioned procedure yielded **11a** as white solid hydrochloride salt, $[\alpha]_D$ of the HCl salt is (+)-71.1 (*c* = 1 in methanol).

Compound (**±**)-**10a** was similarly treated using (+)-4-(2-chlorophenyl)-5,5-dimethyl-2-hydroxy-1,3,2-dioxaphosphorinane 2-oxide to afford **11b** as white solid hydrochloride salt, $[\alpha]_D$ of the HCl salt is (−)-69.8, *c* = 1 in methanol).

5.10. Procedure J

5.10.1. Synthesis of (+)-2-chloro-*N*-(7-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylacetamide (12a)

Compound **11a** (1.1 g, 5.01 mmol) and Et_3N (3.5 mL, 25.05 mmol) was stirred at 0 °C in CH_2Cl_2 (25 mL) for 15 min. Chloroacetylchloride (1.0 mL, 12.54 mmol) was added dropwise and the resulting solution was stirred at room temperature for 20 min. The reaction mixture was poured into a 1 M solution of NaOH (25 mL) and the product was extracted with dichloromethane, dried (Na_2SO_4), filtered, and concentrated. The crude material was purified by column chromatography (hexane/EtOAc, 3:1) to give **12a** as thick transparent liquid (1.26 g, 93.4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90–0.98 (m, 3H), 1.64–1.72 (m, 2H), 1.83–2.12 (m, 2H), 2.58–2.70 (m, 1H), 2.84–2.89 (dd, 1H, J_1 = 16.0 Hz, J_2 = 4.8 Hz), 3.00–3.10 (m, 2H), 3.15- 3.26 (m, 2H), 3.82 (s, 3H), 3.95–4.03 (m, 1H), 4.08–4.12 (m, 2H), 6.61–6.62 (dd, 1H, J_1 = 1.6 Hz, J_2 = 4.8 Hz), 6.64–6.77 (m, 1H), 6.96–6.99 (d, 1H, *J* = 8.8 Hz).

5.10.2. Synthesis of (−)-2-chloro-*N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylacetamide (12b)

Compound **12b** was prepared by following similar conditions as reported in the procedure J. Compound **11c** (HCl salt, 6.0 g, 23.46 mmol) was treated with chloroacetylchloride (5.6 mL, 70.37 mmol) at 0 °C in CH_2Cl_2 (100 mL) for 15 min to afford the optically pure **12b** as a viscous oil (6.52 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.92–0.96 (t, 3H, *J* = 8 Hz), 1.64–1.72 (m, 2H), 1.83–2.12 (m, 2H), 2.58–2.70 (m, 1H), 2.84–2.89 (dd, 1H, J_1 = 16.0 Hz, J_2 = 4.8 Hz), 3.00–3.10 (m, 2H), 3.19–3.27 (m, 2H), 3.86 (s, 3H), 3.95–4.03 (m, 1H), 4.08–4.12 (m, 2H), 6.61–6.68 (m, 2H), 7.07–7.11 (t, 1H, *J* = 8 Hz).

5.10.3. Synthesis of 2-chloro-*N*-(7-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylacetamide (12c)

Compound **12c** was prepared by following the similar conditions as reported in Procedure J. Compound **10a** (HCl salt, 3.11 g, 12.18 mmol) was treated with chloroacetylchloride (1.94 mL, 24.37 mmol) at 0 °C in CH_2Cl_2 (100 mL) for 15 min to afford the racemic **12c** as a viscous oil (3.42 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.90–0.98 (m, 3H), 1.64–1.72 (m, 2H), 3.19–3.27 (m, 2H), 4.00 (s, 3H), 6.61–6.62 (dd, 1H, *J* = 1.6 Hz), 6.64–6.77 (m, 1H), 6.96–6.99 (d, 1H, *J* = 8.8 Hz).

5.10.4. Synthesis of *tert*-butyl 4-(4-iodophenyl)piperazine-1-carboxylate (14)

To a stirring solution of 1-(4-iodophenyl)piperazine, **13** (3.0 g, 9.24 mmol) in dichloromethane (25 mL), di-*tert*-butyl dicarbonate (2.42 g, 11.09 mmol) and triethylamine (3.84 mL, 27.73 mmol) were added at 0 °C and stirring was continued for another 4 h. The brine was added to the reaction mixture and extracted with dichloromethane and concentrated under vacuum which was then purified by column chromatography using ethyl acetate/methanol: Et_3N (80:15:5) to get pure compound **14** as yellow solid (2.44 g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.38 (s, 9H), 3.33–3.35 (t, 8H, *J* = 4 Hz), 6.53 (d, 2H, *J* = 6 Hz), 7.48 (m, 2H).

5.11. Procedure K

5.11.1. Synthesis of pyridin-3-ylboronic acid (16a)

A 100 mL three-necked flask was charged with toluene (17 mL) and cooled below −60 °C, and a solution of *n*-BuLi (2.85 M in hexanes, 6.1 mL, 17.4 mmol) was added dropwise over 10 min. After the internal temperature reached −60 °C, a solution of 3-bromopyridine (1.6 mL, 15.8 mmol) in toluene (8 mL) was added dropwise to keep the internal temperature below −50 °C. A brownish black solid precipitated, and the resultant slurry was stirred for 20 min. THF (10 mL) was added dropwise to keep the internal temperature below −50 °C, and the resultant slurry was stirred for 15 min. To the slurry was added triisopropyl borate (4.37 mL, 19 mmol) in one portion via syringe. The solution was warmed to −15 °C, the reaction was quenched with HCl (aq) (2.7 N, 14 mL), and the solution was transferred to a separatory funnel. The aqueous layer was collected, the organic layer was washed with water (10 mL), and the combined aqueous layers were neutralized to pH 7 with NaOH (aq) (10 N) and extracted with THF (30 mL × 3). The combined organic layers were concentrated in vacuo, and the residue was dissolved in THF/CH_3OH (1:1, 30 mL), filtered, and diluted to 30 mL with CH_3CN. The solvent was switched to CH_3CN by distillation and concentrated to 20 mL. The solids were collected by filtration to afford the title compound **16a** as a solid (0.98 g, 50% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.71–7.74 (t, 1H, *J* = 6 Hz), 8.43–8.45 (d, 1H, *J* = 8 Hz), 8.51–8.53 (d, 1H, *J* = 8 Hz), 8.58 (s, 1H).

5.11.2. Synthesis of pyridin-4-ylboronic acid (16b)

This compound was prepared by following the procedure K using *n*-BuLi (2.85 M in hexanes, 13.5 mL, 38.57 mmol), a slurry of hydrochloride salt of 4-bromopyridine (3.0 g, 15.4 mmol) in toluene (24.64 mL) and triisopropyl borate (5.3 mL, 23.14 mmol) to afford compound **16b** as a solid (1.13 g, 60% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.78–7.80 (d, 2H, *J* = 8 Hz), 8.32–8.34 (d, 2H, *J* = 8 Hz).

5.12. Procedure L

5.12.1. Synthesis of *tert*-butyl 4-(4-(pyridin-3-yl)phenyl)piperazine-1-carboxylate (17a)

Into a glass vial containing a magnetic stir bar is added the *tert*-butyl 4-(4-iodophenyl)piperazine-1-carboxylate (1.65 g, 4.26 mmol), and the vial is purged with argon. Into the vial was added a solution of tetrakis(triphenylphosphine) palladium(0) (0.32 g, 0.27 mmol) in dimethoxyethane (6.6 mL) and sodium carbonate (aq) (2 M,

5.53 mL, 11.06 mmol), and the vial was once again purged with argon. The resultant solution was stirred at room temperature for 5 min when the slurry of pyridin-3-ylboronic acid, **16a** (0.68 g, 5.53 mmol) in ethanol (6.6 mL) was added, the vial was purged with argon and capped, and the mixture was heated to 90 °C and stirred for 1 h. The solution was cooled to room temperature and filtered through a pad of Celite (washed with dichloromethane) into a flask containing anhydrous magnesium sulfate. The solution was dried and filtered through filter paper and the solvent was removed in vacuo to afford the crude product, which was chromatographed on silica gel using ethyl acetate/hexane (15:85) solvent system to afford pure compound **17a** (0.85 g, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.48 (s, 9H), 3.23–3.25 (t, 4H, J = 4 Hz), 3.56–3.60 (t, 4H, J = 8 Hz), 7.08–7.10 (d, 2H, J = 8 Hz), 7.45–7.48 (dd, 1H, J_1 = 5.2 Hz, J_2 = 8 Hz), 7.56–7.58 (m, 2H), 8.02–8.05 (d, 1H, J = 12 Hz), 8.41–8.44 (d, 1H, J = 12 Hz), 8.75 (s, 1H).

5.12.2. Synthesis of *tert*-butyl 4-(4-(pyridin-4-yl)phenyl)piperazine-1-carboxylate (17b)

Compound **17b** was prepared according to the procedure L using *tert*-butyl 4-(4-iodophenyl)piperazine-1-carboxylate (0.22 g, 0.57 mmol), a solution of tetrakis(triphenylphosphine) palladium(0) (0.047 g, 0.041 mmol) in dimethoxyethane (1.0 mL) and sodium carbonate(aq) (2 M, 0.8 mL, 1.63 mmol), and the slurry of pyridin-4yl boronic acid, **16b** (0.22 g, 5.53 mmol) in ethanol (1.0 mL) to afford pure compound **17b** (0.10 g, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.48 (s, 9H), 3.22–3.23 (t, 4H, J = 2 Hz), 3.58–3.60 (t, 4H, J = 4 Hz), 6.98–6.99 (d, 2H, J = 4 Hz), 7.45–7.46 (d, 2H, J = 4 Hz), 7.57–7.58 (d, 2H, J = 4 Hz), 8.58–8.59 (d, 2H, J = 4 Hz).

5.13. Procedure M

5.13.1. Synthesis of 1-(4-(pyridin-3-yl)phenyl)piperazine (18a)

Into the solution of *tert*-butyl 4-(4-(pyridin-3-yl)phenyl)piperazine-1-carboxylate (0.85 g, 2.5 mmol) in 10 mL of dry CH_2Cl_2 was added trifluoroacetic acid (10 mL) dropwise at room temperature. Reaction mixture was stirred at room temperature for 6 h. The reaction mixture was concentrated under reduced pressure. The trifluoroacetate salt was recrystallized from ethanol and the pure compound was made free base using sodium bicarbonate to afford sufficiently pure compound **18a** as semisolid (0.55 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.02–3.04 (t, 4H, J = 4 Hz), 3.23–3.26 (t, 4H, J = 6 Hz), 7.08–7.10 (d, 2H, J = 8 Hz), 7.45–7.48 (dd, 1H, J_1 = 5.2 Hz, J_2 = 8 Hz), 7.56–7.58 (m, 2H), 8.02–8.05 (d, 1H, J = 12 Hz), 8.41–8.44 (d, 1H, J = 12 Hz), 8.75 (s, 1H).

5.13.2. Synthesis of 1-(4-(pyridin-4-yl)phenyl)piperazine (18b)

Compound **17b** (0.86 g, 2.5 mmol) was deprotected by trifluoroacetic acid in dichloromethane (1:1) to yield compound **18b** (procedure M) as semisolid (0.55 g, 91%).^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.29–3.32 (m, 8H), 7.08–7.10 (d, 2H, J = 8 Hz), 7.65–7.71 (m, 4H), 8.48–8.49 (d, 2H, J = 4 Hz).

5.13.3. Synthesis of 2-chloro-1-(4-(4-(pyridin-3-yl)phenyl)piperazin-1-yl)ethanone (19a)

Compound **19a** was prepared under similar conditions as reported in procedure J. Compound **18a** (0.60 g, 2.5 mmol) was treated with chloroacetylchloride (0.4 mL, 5.0 mmol) at 0 °C in CH_2Cl_2 (25 mL) for 15 min to afford the **19a** as thick yellow liquid (0.72 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.23–3.25 (t, 4H, J = 4 Hz), 3.56–3.60 (t, 4H, J = 8 Hz), 4.08–4.12 (m, 2H), 7.08–7.10 (d, 2H, J = 8 Hz), 7.45–7.48 (dd, 1H, J_1 = 5.2 Hz, J_2 = 8 Hz), 7.56–7.58 (m, 2H), 8.02–8.05 (d, 1H, J = 12 Hz), 8.41–8.44 (d, 1H, J = 12 Hz), 8.75 (s, 1H).

5.13.4. Synthesis of 2-chloro-1-(4-(4-(pyridin-4-yl)phenyl)piperazin-1-yl)ethanone (19b)

Compound **19b** was prepared under similar conditions as reported in procedure J. Compound **18b** (0.48 g, 2.03 mmol) was treated with chloroacetylchloride (0.2 mL, 2.44 mmol) at 0 °C in CH_2Cl_2 (10 mL) for 15 min to afford the **19b** as thick yellow liquid (0.22 g, 44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.29–3.32 (m, 8H), 3.61–3.66 (m, 2H), 7.08–7.10 (d, 2H, J = 8 Hz), 7.65–7.71 (m, 4H), 8.48–8.49 (d, 2H, J = 4 Hz).

5.14. Procedure N

5.14.1. Synthesis of 2-((7-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)-1-(4-(4-(pyridin-3-yl)phenyl)piperazin-1-yl)ethanone 20a

This was made following the general procedure for N-alkylation where compound **19a** (0.72 g, 2.28 mmol) was refluxed with **10a** (0.58 g, 2.28 mmol) in CH_3CN (50 mL) in the presence of K_2CO_3 (0.947 g, 6.85 mmol) for 1 h to furnish **20a** as semisolid (0.61 g, 53.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.80–0.84 (t, 3H, J = 8 Hz), 1.38–1.48 (m, 1H), 1.90–1.98 (m, 1H), 2.46–2.49 (t, 2H, J = 6 Hz), 2.62–2.76 (m, 4H), 2.82–2.88 (m, 2H), 2.94–2.99 (br s, 1H), 3.16–3.18 (t, 4H, J = 4 Hz), 3.41 (s, 2H), 3.63–3.83 (m, 4H), 3.91 (s, 3H), 6.61 (s, 1H), 6.65–6.67 (d, 1H, J = 8 Hz), 6.82–6.85 (d, 1H, J = 12 Hz), 6.93–6.95 (m, 2H), 7.26–7.29 (dd, 1H, J_1 = 5.2 Hz, J_2 = 8.4 Hz), 7.44–7.46 (d, 2H, J = 8 Hz), 7.77–7.80 (m, 1H), 8.45–8.46 (d, 1H, J = 4 Hz), 8.75 (s, 1H).

5.14.2. Synthesis of (−)-2-((7-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)-1-(4-(4-(pyridin-4-yl)phenyl)piperazin-1-yl)ethanone (−)-20b

This was made by following the procedure N when compound **19b** (0.25 g, 0.79 mmol) was reacted with **11b** (0.17 g, 0.79 mmol) in CH_3CN (25 mL) to furnish **20b** as semisolid (0.12 g, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.88–0.91 (t, 3H, J = 6 Hz), 1.48–1.54 (m, 3H), 2.0 (br s, 1H), 2.55–2.59 (t, 2H, J = 8 Hz), 2.79–2.83 (m, 4H), 2.99–3.01 (m, 1H), 3.21–3.31 (m, 6H), 3.50 (s, 2H), 3.7 (s, 3H), 3.78–3.81 (t, 2H, J = 6 Hz), 6.61–6.64 (m, 2H), 6.91–6.93 (d, 1H, J = 8 Hz), 7.04–7.06 (d, 2H, J = 8 Hz), 7.62–7.68 (m, 4H), 8.46–8.47 (d, 2H, J = 1 Hz).

5.14.3. Synthesis of (−)-2-((5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)-1-(4-(4-(pyridin-4-yl)phenyl)-piperazin-1-yl)ethanone (−)-20c

This was made by following the procedure N when compound **19b** (0.22 g, 0.71 mmol) was reacted with **11c** (0.133 g, 0.61 mmol) in CH_3CN (15 mL) to furnish **20c** as semisolid (0.12 g, 41.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.91–0.93 (t, 3H, J = 4 Hz), 1.42–1.56 (m, 3H), 2.18 (br s, 1H), 2.46–3.12 (m, 13H), 3.32–3.34 (t, 4H, J = 4 Hz), 3.86 (s, 3H), 6.61–6.67 (m, 3H), 7.01–7.06 (m, 2H), 7.62–7.67 (m, 4H), 8.51–8.53 (d, 2H, J = 8 Hz).

5.14.4. Synthesis of (+)-2-((7-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)-1-(4-(4-(pyridin-4-yl)phenyl)piperazin-1-yl)ethanone (+)-20d

This was made by following the procedure N when compound **19b** (0.25 g, 0.78 mmol) was reacted with **11a** (0.17 g, 0.78 mmol) in CH_3CN (20 mL) to furnish **20d** as semisolid (0.13 g, 33.7%). ^{1}H NMR (400 MHz, MeOH-d_4) δ ppm 0.89–0.93 (t, 3H, J = 7.2 Hz), 1.46–1.68 (m, 3H), 2.0 (br s, 1H), 2.57–2.61 (t, 2H, J = 7.6 Hz), 2.72–2.84 (m, 4H), 2.99–3.01 (m, 1H), 3.22–3.31 (m, 6H), 3.53 (s, 2H), 3.72 (s, 3H), 3.78–3.82 (m, 2H), 6.61–6.65 (m, 2H), 6.93–6.95 (d, 1H, J = 8 Hz), 7.07–7.09 (d, 2H, J = 8.8 Hz), 7.62–7.70 (m, 4H), 8.48–8.50 (d, 2H, J = 5.6 Hz).

5.14.5. Synthesis of 7-methoxy-*N*-propyl-*N*-(2-(4-(4-(pyridin-3-yl)phenyl)piperazin-1-yl)ethyl)-1,2,3,4-tetrahydronaphthalen-2-amine (21a)

Compound **20a** (0.61 g, 1.22 mmol) was reacted with $LiAlH_4$ (0.23 g, 6.1 mmol) in THF (20 mL) by following the procedure F to furnish **21a** as oil (0.302 g, 51%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.80–0.84 (t, 3H, J = 8 Hz), 1.38–1.48 (m, 1H), 1.90–1.98 (m, 1H), 2.46–2.49 (t, 2H, J = 6 Hz), 2.62–2.76 (m, 4H), 2.82–2.88 (m, 2H), 2.94–2.99 (br s, 1H), 3.16–3.18 (t, 4H, J = 4 Hz), 3.41 (s, 2H), 3.63–3.83 (m, 6H), 3.91 (s, 3H), 6.61 (s, 1H), 6.65–6.67 (d, 1H, J = 8 Hz), 6.82–6.85 (d, 1H, J = 12 Hz), 6.93–6.95 (m, 2H), 7.266–7.299 (dd, 1H, J_1 = 5.2 Hz, J_2 = 8.4 Hz), 7.44–7.46 (d, 2H, J = 8 Hz), 7.77–7.80 (m, 1H), 8.45–8.46 (d, 1H, J = 4 Hz), 8.75 (s, 1H).

5.14.6. Synthesis of (−)-7-methoxy-*N*-propyl-*N*-(2-(4-(4-(pyridin-4-yl)phenyl)piperazin-1-yl)ethyl)-1,2,3,4-tetrahydronaphthalen-2-amine (−)-21b

Compound **20b** (0.07 g, 0.15 mmol) was reacted with $LiAlH_4$ (0.06 g, 1.5 mmol) in THF (20 mL) by following the procedure F to furnish **21b** as oil (0.041 g, 56.2%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.94–0.96 (t, 3H, J = 4 Hz), 1.58–1.63 (m, 2H), 2.15–2.18 (m, 1H), 2.61–2.94 (m, 12H), 3.12 (br s, 1H), 3.28–3.31 (t, 4H, J = 6 Hz), 3.86 (s, 3H), 6.61 (s, 1H), 6.65–6.67 (d, 1H, J = 8 Hz), 6.84–6.86 (d, 2H, J = 8 Hz), 6.96–6.98 (d, 1H, J = 8 Hz), 7.63–7.68 (m, 4H), 8.50–8.52 (d, 2H, J = 8 Hz).

5.14.7. Synthesis of (−)-5-methoxy-*N*-propyl-*N*-(2-(4-(4-(pyridin-4-yl)phenyl)piperazin-1-yl)ethyl)-1,2,3,4-tetrahydronaphthalen-2-amine (−)-21c

Compound **20c** (0.125 g, 0.25 mmol) was reacted with $LiAlH_4$ (0.095 g, 2.5 mmol) in THF (15 mL) by following the procedure F to furnish **21c** as oil (0.70 g, 72%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.91–0.93 (t, 3H, J = 4 Hz), 1.42–1.56 (m, 3H), 2.18 (br s, 1H), 2.46–3.12 (m, 15H), 3.32–3.34 (t, 4H, J = 4 Hz), 3.86 (s, 3H), 6.61–6.67 (m, 3H), 7.01–7.06 (m, 2H), 7.62–7.67 (m, 4H), 8.51–8.53 (d, 2H, J = 8 Hz).

5.14.8. Synthesis of (+)-7-methoxy-*N*-propyl-*N*-(2-(4-(4-(pyridin-4-yl)phenyl)piperazin-1-yl)ethyl)-1,2,3,4-tetrahydronaphthalen-2-amine (+)-21d

Compound **20d** (0.12 g, 0.24 mmol) was reacted with $LiAlH_4$ (0.09 g, 2.4 mmol) in THF (15 mL) by following the procedure F to furnish **21d** as oil (0.072 g, 62.1%). ^1H NMR (400 MHz, MeOH-d_4) δ ppm 0.93–0.96 (t, 3H, J = 7.2 Hz), 1.55–1.67 (m, 3H), 2.01–2.15 (m, 1H), 2.57–2.91 (m, 16H), 3.00–3.07 (m, 2H), 3.57 (m, 1H), 3.73 (s, 3H), 6.64–6-67 (m, 2H), 6.94–6.96 (d, 1H, J = 8 Hz), 7.04–7.06 (d, 2H, J = 8.8 Hz), 7.63–7.68 (m, 4H), 8.46–8.48 (d, 2H, J = 6 Hz).

5.14.9. Synthesis of 7-(propyl(2-(4-(4-(pyridin-3-yl)phenyl)-piperazin-1-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-2-ol (22a)

Compound **21a** (0.302 g, 0.62 mmol) was reacted with 1 M BBr_3/CH_2Cl_2 (2.5 mL, 2.5 mmol) in CH_2Cl_2 (20 mL) by following the procedure G to furnish **22a** (0.181 g, 62%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.87–0.91 (t, 3H, J = 8 Hz), 1.46–1.58 (m, 2H), 1.97–2.00 (br s, 1H), 2.53–2.79 (m, 15H), 2.97 (br s, 1H), 3.27–3.30 (t, 4H, J = 6 Hz); 6.52 (s, 1H), 6.59–6.61 (d, 1H, J = 8 Hz), 6.88–6.90 (d, 1H, J = 8 Hz), 6.98–7.00 (d, 2H, J = 8 Hz), 7.316–7.349 (dd, 1H, J_1 = 5.6 Hz, J_2 = 8.88 Hz), 7.48–7.50 (d, 2H, J = 8 Hz), 7.83–7.86 (m, 1H), 8.50–8.515 (d, 1H, J = 6 Hz), 8.81 (s, 1H).

The product was converted into the corresponding oxalate salt as white solid; mp is 161–163 °C. Anal. Calcd for ($C_{36}H_{44}N_4O_{13}$, $0.5H_2O$) C, H, N.

5.14.10. Synthesis of (−)-7-(propyl(2-(4-(4-(pyridin-4-yl)-phenyl)piperazin-1-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-2-ol (−)-22b

Compound **21b** (0.04 g, 0.083 mmol) was reacted with 1 M BBr_3/CH_2Cl_2 (0.41 mL, 0.41 mmol) in CH_2Cl_2 (10 mL) by following the procedure G to furnish **22b** (0.02 g, 59%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.94–0.96 (t, 3H, J = 4 Hz), 1.58–1.63 (m, 2H), 2.15–2.18 (m, 1H), 2.61–2.94 (m, 12H), 3.12 (br s, 1H), 3.28–3.31 (t, 4H, J = 6 Hz), 6.60 (s, 1H), 6.66–6.68 (d, 1H, J = 8 Hz), 6.84–6.86 (d, 2H, J = 8 Hz), 6.98–7.00 (d, 1H, J = 8 Hz), 7.63–7.68 (m, 4H), 8.50–8.52 (d, 2H, J = 8 Hz). $[\alpha]_D^{25} = -22.4$, c = 0.5 in MeOH. The product was converted into the corresponding tetrahydrochloride salt as white solid; mp is 227–230 °C. Anal. Calcd for ($C_{30}H_{42}N_4Cl_4O$, $2H_2O$) C, H, N.

5.14.11. Synthesis of (−)-6-(propyl(2-(4-(4-(pyridin-4-yl)-phenyl)piperazin-1-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol (−)-22c

Compound **21c** (0.07 g, 0.14 mmol) was reacted with 1 M BBr_3/CH_2Cl_2 (0.72 mL, 0.72 mmol) in CH_2Cl_2 (15 mL) by following the procedure G to furnish **22c** (0.05 g, 81%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.91–0.94 (t, 3H, J = 6 Hz), 1.48–1.65 (m, 3H), 2.08–2.13 (br s, 1H), 2.46–3.03 (m, 15H), 3.26–3.30 (t, 4H, J = 8 Hz), 6.53–6.57 (m, 2H), 6.87–6.90 (t, 1H, J = 6 Hz), 7.03–7.05 (d, 2H, J = 8 Hz), 7.62–7.67 (m, 4H), 7.45–8.47 (d, 2H, J = 8 Hz). $[\alpha]_D^{25} = -37.5$, c = 1 in MeOH. The product was converted into the corresponding oxalate salt as white solid; mp: 162–165 °C. Anal. Calcd for ($C_{36}H_{44}N_4O_{13}$, $0.5C_4H_{10}O$) C, H, N.

5.14.12. Synthesis of (+)-7-(propyl(2-(4-(4-(pyridin-4-yl)-phenyl)piperazin-1-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-2-ol (+)-22d

A solution of compound **21d** (0.06 g, 0.12 mmol) in 48% aq. HBr (3 mL) was refluxed for 2 h. The reaction mixture was cooled to room temperature and evaporated to give a solid. The resulting solid was neutralized by addition of saturated $NaHCO_3$ solution at 0 °C and extracted with dichloromethane, and concentrated under reduced pressure. The crude material was purified by column chromatography (DCM/MeOH, 9:1) to give compound **22d** (0.035 g, 60%). ^1H NMR (400 MHz, MeOH-d_4) δ ppm 0.96–1.00 (t, 3H, J = 7.2 Hz), 1.62–1.76 (m, 3H), 2.12–2.15 (m, 1H), 2.66–2.97 (m, 14H), 3.06 (m, 2H), 3.28–3.34 (m, 3H), 6.55–6.58 (m, 2H), 6.88–6.90 (d, 1H, J = 8 Hz), 7.04–7.06 (d, 2H, J = 8.8 Hz), 7.63–7.68 (m, 4H), 8.46–8.47 (d, 2H, J = 5.6 Hz). ^{13}C NMR (400 MHz, MeOH-d_4) δ ppm 10.65; 20.21; 25.39; 28.09; 30.92; 53.16; 53.54; 55.60; 59.34; 113.63; 115.19; 115.70; 120.79; 126.44; 127.53; 127.59; 129.28; 135.43; 149.08; 149.14; 152.31; 155.34. $[\alpha]_D^{25} = +27.2$, c = 0.5 in MeOH. The product was converted into the corresponding tetrahydrochloride salt; mp is 132–134 °C. Anal. Calcd for ($C_{30}H_{42}N_4Cl_4O$, $2.3H_2O$) C, H, N.

5.14.13. Synthesis of 2-(4-(4-iodophenyl)piperazin-1-yl)-*N*-(7-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylacetamide (23)

This compound was prepared by following the N-alkylation procedure N. Compound **13** (HCl salt, 0.50 g, 1.39 mmol) was reacted with **12c** (0.61 g, 2.08 mmol) in CH_3CN (50 mL) to furnish **23** as semisolid (0.51 g, 67.4%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.87–0.89 (t, 3H, J = 4 Hz), 1.60–1.66 (m, 3H), 1.98–2.04 (br s, 1H), 2.48–2.52 (t, 2H, J = 8 Hz), 2.69–2.81 (m, 4H), 2.96–3.01 (m, 1H), 3.10–3.14 (t, 4H, J = 8 Hz), 3.44–3.45 (d, 2H, J = 4 Hz), 3.65–3.86 (m, 4H), 3.91 (s, 3H), 6.61 (s, 1H), 6.65–6.66 (d, 1H, J = 4 Hz), 6.67–6.69 (d, 2H, J = 8 Hz), 6.96–6.98 (d, 1H, J = 8 Hz), 7.52–7.54 (d, 2H, J = 8 Hz).

5.14.14. Synthesis of *N*-(2-(4-(4-iodophenyl)piperazin-1-yl)-ethyl)-7-methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (24)

Compound **23** (0.51 g, 0.93 mmol) was reacted with $LiAlH_4$ (0.17 g, 4.68 mmol) in THF (20 mL) by following the procedure F to furnish **24** as white semisolid (0.34 g, 68.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.87–0.89 (t, 3H, J = 4 Hz), 1.60–1.66 (m, 3H), 1.98–2.04 (br s, 1H), 2.48–2.52 (t, 2H, J = 8 Hz), 2.69–2.81 (m, 4H), 2.96–3.01 (m, 3H), 3.10–3.14 (t, 4H, J = 8 Hz), 3.44–3.45 (d, 2H, J = 4 Hz), 3.65–3.86 (m, 4H), 3.91 (s, 3H),), 6.61 (s, 1H), 6.65–6.66 (d, 1H, J = 4 Hz); 6.67–6.69 (d, 2H, J = 8 Hz), 6.96–6.98 (d, 1H, J = 8 Hz), 7.52–7.54 (d, 2H, J = 8 Hz).

5.14.15. Synthesis of 7-((2-(4-(4-iodophenyl)piperazin-1-yl)-ethyl)(propyl)amino)-5,6,7,8-tetrahydronaphthalen-2-ol (25)

Compound **24** (0.30 g, 0.56 mmol) was reacted with 1 M BBr_3/CH_2Cl_2 (2.25 mL, 2.25 mmol) in CH_2Cl_2 (20 mL) by following the procedure G to furnish **25** (0.15 g, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.87–0.90 (t, 3H, J = 6 Hz), 1.12–1.13 (t, 2H, J = 2 Hz), 1.48–1.54 (m, 3H), 1.95 (br s, 1H), 2.47–2.77 (m, 12H), 2.94 (br s, 1H), 3.17–3.19 (t, 4H, J = 4 Hz), 6.49 (s, 1H), 6.55–6.58 (d, 1H, J = 12 Hz), 6.64–6.68 (m, 2H), 6.89–6.90 (d, 1H, J = 4 Hz), 7.48–7.50 (d, 2H, J = 8 Hz).

The product was converted into the corresponding oxalate salt as yellowish solid; mp is 177–179 °C. Anal. Calcd for ($C_{29}H_{38}N_3O_9I$, $0.1C_4H_{10}O$) C, H, N.

5.14.16. Synthesis of (+)-2-(4-(biphenyl-4-yl)piperazin-1-yl)-*N*-(7-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylacetamide (26a)

Following the procedure N compound **12a** (0.75 g, 2.5 mmol) and **2a** (0.73 g, 3.04 mmol), K_2CO_3 (1.75 g, 12.68 mmol) were refluxed in CH_3CN (25 mL) for 1 h to get 0.77 g (61%) of compound **26a** as semisolid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.895–0.934 (t, 3H, J = 7.8 Hz), 1.64–1.71(m, 2H), 1.88–2.04 (m, 2H), 2.166–2.172 (d, 2H), 2.69–3.39 (m, 15H), 3.76 (s, 3H), 6.59 (s, 1H), 6.68–6.73 (t, 1H, J = 10 Hz), 6.97–7.03 (m, 3H), 7.26–7.30 (t, 1H, J = 8 Hz), 7.38–7.42 (m, 2H), 7.50–7.56 (m, 4H).

5.14.17. Synthesis of (−)-2-(4-(biphenyl-4-yl)piperazin-1-yl)-*N*-(5-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylacetamide (26b)

Compound **12b** (0.25 g, 0.85 mmol) was reacted with **2a** (0.24 g, 1.01 mmol) in CH_3CN (25 mL) by following the procedure N to furnish **26b** as semisolid (0.24 g, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.89–0.93 (t, 3H, J = 8 Hz), 1.67–1.70 (m, 2H), 2.07–2.08 (br s, 1H), 2.54–2.60 (m, 3H), 2.66–2.69 (t, 4H, J = 6 Hz), 2.75–3.03 (m, 6H), 3.24–3.27 (t, 4H, J = 6 Hz), 3.68–3.71 (t, 1H, J = 6 Hz), 3.81 (s, 3H), 6.64–6.66 (d, 1H, J = 8 Hz), 6.71–6.73 (d, 1H, J = 8 Hz), 6.98–7.01 (d, 2H, J = 12 Hz), 7.07–7.11 (t, 1H, J = 8 Hz), 7.26–7.29 (t, 1H, J = 6 Hz), 7.38–7.42 (t, 2H, J = 8 Hz), 7.50–7.56 (m, 4H).

5.14.18. Synthesis of (+)-*N*-(2-(4-(biphenyl-4-yl)piperazin-1-yl)ethyl)-7-methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (27a)

Compound **27a** was prepared by using the procedure F where compound **26a** (0.77 g, 1.55 mmol) in anhydrous THF (20 mL) was added dropwise into a suspension of lithium aluminum hydride ($LiAlH_4$) (0.15 g, 4.07 mmol) in anhydrous THF (15 mL) at 0 °C under N_2 atmosphere to afford compound **27a** as semisolid (0.62 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.89–0.93 (t, 3H, J = 8 Hz), 1.49–1.69 (m, 2H), 2.03–2.05 (br s, 1H), 2.54–2.88 (m, 15H), 3.01 (br s, 1H), 3.25–3.27 (t, 4H, J = 4 Hz), 3.77 (3, 3H), 6.64 (s, 1H), 6.67–6.69 (d, 1H, J = 8 Hz), 6.98–7.00 (d, 3H, J = 8 Hz), 7.26–7.29 (t, 1H, J = 6 Hz), 7.38–7.42 (t, 2H, J = 8 Hz), 7.50–7.56 (m, 4H).

5.14.19. Synthesis of (−)-*N*-(2-(4-(biphenyl-4-yl)piperazin-1-yl)ethyl)-5-methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (27b)

Compound **26b** (0.24 g, 0.45 mmol) was reacted with $LiAlH_4$ (0.14 g, 3.9 mmol) in THF (20 mL) by following the procedure F to furnish **27b** as semisolid (0.18 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.89–0.93 (t, 3H, J = 8 Hz), 1.67–1.70 (m, 2H), 2.07–2.08 (br s, 1H), 2.54–2.60 (m, 3H), 2.66–2.69 (t, 4H, J = 6 Hz), 2.75–3.03 (m, 8H), 3.24–3.27 (t, 4H, J = 6 Hz), 3.68–3.71 (t, 1H, J = 6 Hz), 3.81 (s, 3H), 6.64–6.66 (d, 1H, J = 8 Hz), 6.71–6.73 (d, 1H, J = 8 Hz), 6.98–7.01 (d, 2H, J = 12 Hz), 7.07–7.11 (t, 1H, J = 8 Hz), 7.26–7.29 (t, 1H, J = 6 Hz), 7.38–7.42 (t, 2H, J = 8 Hz), 7.50–7.56 (m, 4H).

5.14.20. Synthesis of (+)-7-((2-(4-(biphenyl-4-yl)piperazin-1-yl)ethyl)(propyl)amino)-5,6,7,8-tetrahydronaphthalen-2-ol (+)-8a

Compound **27a** (0.62 g, 1.28 mmol) was reacted with 1 M BBr_3/CH_2Cl_2 (5.13 mL, 5.13 mmol) in CH_2Cl_2 (20 mL) by following the procedure G to furnish (**+**)-**8a** (0.46 g, 77.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.88–0.92 (t, 3H, J = 8 Hz), 1.47–1.54 (m, 2H), 1.95–1.98 (br s, 1H), 2.55–2.73 (m, 15H), 2.95 (br s, 1H), 3.29 (m, 4H), 6.48 (s, 1H), 6.56–6.59 (d, 1H, J = 12 Hz), 6.88–6.90 (d, 1H, J = 8 Hz), 6.97–6.99 (d, 2H, J = 8 Hz), 7.26–7.30 (t, 1H, J = 8 Hz), 7.38–7.42 (t, 2H, J = 8 Hz), 7.50–7.56 (m, 4H). $[\alpha]_D^{25} = +33.4$, c = 1 in MeOH. The product was converted into the corresponding trihydrochloride salt, white solid, mp is 190–192 °C. Anal. Calcd for ($C_{31}H_{42}N_3Cl_3O$, $1.2H_2O$) C, H, N.

5.14.21. Synthesis of (−)-6-((2-(4-(biphenyl-4-yl)piperazin-1-yl)ethyl)(propyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol (−)-28b

Compound **27b** (0.18 g, 0.372 mmol) was reacted with 1 M BBr_3/CH_2Cl_2 (1.9 mL, 1.9 mmol) in CH_2Cl_2 (20 mL) by following the procedure G to furnish **28b** (0.13 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.88–0.92 (t, 3H, J = 8 Hz), 1.50 (m, 3H), 2.05 (br s, 1H), 2.46–2.73 (m, 13H), 2.91–2.95 (m, 2H), 3.29–3.30 (t, 4H, J = 2 Hz), 6.545–6.599 (dd, 2H, J_1 = 8 Hz, J_2 = 14.4 Hz), 6.94–7.00 (m, 3H), 7.26–7.30 (t, 1H, J = 8 Hz), 7.38–7.42 (t, 2H, J = 8 Hz), 7.50–7.56 (m, 4H). $[\alpha]_D^{25} = -35.6$, c = 1 in MeOH. The product was converted into the corresponding trihydrochloride salt, white solid, mp is 200–203 °C. Anal. Calcd for ($C_{31}H_{42}N_3Cl_3O$, H_2O) C, H, N.

5.15. Biological experiments: potencies at dopamine D_2 and D_3 receptors

Compounds were tested for inhibition of radioligand binding to dopamine receptors as described in our previous studies.[12,21] Briefly, membranes from human embryonic kidney (HEK) 293 cells expressing rat D_2 and D_3 receptors were incubated with each test compound and [^{3}H]spiperone (1.6 nM, 15 Ci/mmol, Perkin–Elmer) for 1 h at 30 °C in 50 mM Tris–HCl (pH 7.4), 0.9% NaCl, and 0.025% ascorbic acid. The final volume of the assay was 0.2 mL under conditions corresponding to our 'high [radioligand] protocol' as described recently.[21] (+)-Butaclamol (2 μM) was used to define nonspecific binding. Assays were terminated by filtration in the MACH 3-96 Tomtec harvester (Wallac, Gaithersburg, MD). Observed IC_{50} values were converted to inhibition constants (K_i) by the Cheng–Prusoff equation.[20] In this conversion, the K_d values for [^{3}H]spiperone binding were 0.057 nM for D_2 receptors and 0.125 nM for D_3 receptors.

Functional activity of test compounds in activating dopamine hD_2 and hD_3 receptors expressed in CHO cells was measured by

stimulation of binding of [^{35}S]GTPγS (1250 Ci/mmol, Perkin–Elmer) in comparison to stimulation by the full agonist dopamine as described by us previously.[12]

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2010.06.025.

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