Further Structure–Activity Relationships Study of Hybrid 7-{[2-(4-Phenylpiperazin-1-yl)ethyl]propylamino}-5,6,7,8-tetrahydronaphthalen-2-ol Analogues: Identification of a High-Affinity D3-Preferring Agonist with Potent in Vivo Activity with Long Duration of Action

Swati Biswas,[†] Suhong Zhang,[†] Fernando Fernandez,[†] Balaram Ghosh,[†] Juan Zhen,[§] Eldo Kuzhikandathil,[#] Maarten E. A. Reith,[§] and Aloke K. Dutta*[,†]

Department of Pharmaceutical Sciences, Wayne State University, Detroit, Michigan 48202, Millhauser Laboratories, Department of Psychiatry, New York University School of Medicine, New York, New York 10016, and Department of Pharmacology and Physiology, UMDNJ—New Jersey Medical School, Newark, New Jersey 07103

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This paper describes an extended structure–activity relationships study of aminotetralin—piperazine-based hybrid molecules developed earlier for dopamine D2/D3 receptors. Various analogues as positional isomers have been developed where location of the phenolic hydroxyl group has been varied on the aromatic ring. Between two catechol derivatives, compound **6e** with a two methylene linker length exhibited higher affinity and selectivity for D3 over D2 receptors over compound **6f** with four methylene linkers (D2/D3 = 50.6 vs 7.51 for **6e** and **6f**, respectively). In general, the (−)-isomer was more potent than the (+)-isomeric counterpart. Binding results indicated highest selectivity for D3 receptors in compound (−)-**10** (K_i = 0.35 nM; D2/D3 = 71). In the 5-hydroxy series, highest selectivity for D3 receptors was exhibited by compound (−)-**25** (K_i = 0.82 nM; D2/D3 = 31.5). Most potent compounds exhibited binding and functional affinities at the subnanomolar level for the D3 receptor. Binding assays were carried out with HEK-293 cells expressing either D2 or D3 receptors by using tritiated spiperone as radioligand for competition studies to evaluate inhibition constants (K_i). A functional assay of selected compounds for stimulating GTPγS binding was carried out with CHO cells expressing human D2 receptors and AtT-20 cells expressing human D3 receptors. The functional assay results indicated partial to full agonist characteristics of test compounds. Compound (−)-**25** was selected further for in vivo study to evaluate its potency in producing contralateral rotations in rats with unilateral lesion in the nigrostriatal region induced by neurotoxin 6-OHDA, a Parkinsonian animal model. Compound (−)-**25** at 5 μmol/kg exhibited rotational activity that lasted beyond 12 h, whereas at a 1 μmol/kg dose the rotations lasted beyond 8 h.

Introduction

The dopamine (DA)[a] receptor system has been targeted for drug development for treatment of psychiatric illness, neurodegeneration, drug abuse, and other therapeutic areas.[1–3] The DA receptor system, a G-protein-coupled receptor (GPCR), in the central nervous system (CNS) was initially classified into two main classes, D1 and D2.[4] So far, five subtypes of DA receptor have been discovered, and they are grouped into two main classes as D1-type and D2-type. D2-type receptors include D2, D3, and D4 receptors, whereas D1-type receptors include D1 and D5.[5–9] Interestingly, it was discovered that the DA D3 receptor had a different distribution in the brain compared to the D2 receptor.[5,6] The DA D3 receptor was found to be located predominantly in the limbic region, which has been implicated in a number of psychiatric disorders.[10] In the human brain, the highest expression of D3 receptor was found in the area of the ventral striatum and associated striatum.[10,11] The D3 receptor has been suggested as an interesting target for the development of potential atypical antipsychotic agents, antiparkinsonian drugs, and pharmacotherapeutics for treatment of drugs of abuse.[12–14] Cloning of D2 and D3 receptors revealed a molecular structural sequence containing 50% homology between these two receptor subtypes. A higher homology of 75–80% was found in the helical transmembrane spanning regions between these two receptor subtypes, where agonist binding sites are believed to be located.[3,15]

DA receptor agonists have been used frequently in the therapy of Parkinson's disease (PD), which is a progressive, chronic neurodegeneration disorder and is characterized by a gradual loss of dopaminergic neurons in the par compacta of the substantia nigra.[16] It is estimated that PD affects approximately 1% of people older than 65 years of age. As mentioned above, dopaminergic agents have been used more extensively in the therapy for PD than any other class of drug molecules.[17,18] Development of DA agonists started with the goal to address the shortcomings of L-dopa therapy, specifically, the problems associated with development of dyskinesia and its implication in toxicity to dopaminergic cells.[19] DA agonists are known to provide neuroprotection.[13,20] Neuroprotection by DA agonists might be derived from the following effects: (a) Stimulation of DA autoreceptors results in decreased DA synthesis, release, and turnover. This leads to production of less DA-related

* Address correspondence to this author at the Department of Pharmaceutical Sciences, Room 3128, Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, MI 48202 [telephone (313) 577-1064; fax (313) 577-2033; e-mail adutta@wayne.edu].

[†] Wayne State University.

[§] New York University School of Medicine.

[#] UMDNJ—New Jersey Medical School.

[a] Abbreviations: DA, dopamine; CNS, central nervous system; GPCR, G-protein-coupled receptor; PD, Parkinson's disease; ROS, reactive oxygen species; SAR, structure—activity relationship; GTPγS, guanosine 5′-[γ-thio]triphosphate; 7-OH-DPAT, 7-hydroxy-2-(dipropylamino)tetralin; 6-OHDA, 6-hydroxydopamine; CHO, Chinese hamster ovary; HEK, human embryonic kidney; PMA, phosphomolybdic acid.

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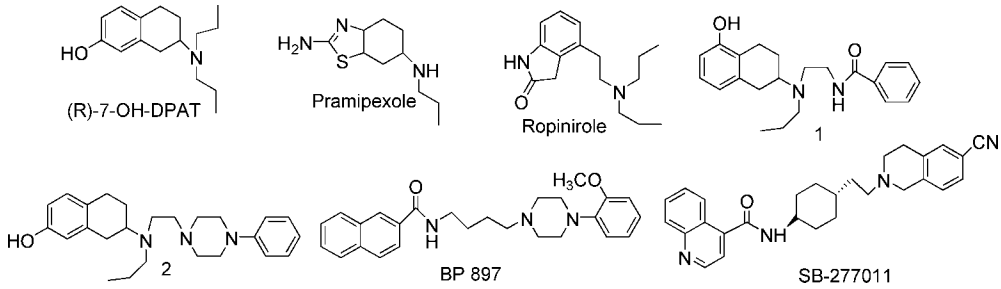


Figure 1. Molecular structures of selective D3 receptor agonists and antagonists.

neurotoxicity by reducing production of reactive oxygen species (ROS).[20] (b) DA agonists will reduce the need for L-dopa and, thus, will reduce the production of ROS.[21] (c) DA agonist therapy causes a lower incidence of motor complications when compared to L-dopa therapy.[22,23] (d) DA agonists have longer plasma half-lives than L-dopa. (e) DA D3 receptor preferring agonists were shown to provide additional neuroprotective effects relative to DA D2 receptor agonists, possibly via production of neurotrophic factors.[24–26] Furthermore, it has been demonstrated in a primate model that L-dopa-induced dyskinesia can be reduced by treatment with a D3 partial agonist.[27–29] This may indicate a superior property of D3 selective agonist or partial agonist in adjunct therapy with levodopa.

An enormous amount of work has already been performed in developing selective agonists and antagonists for the D3 receptor.[12,30,31] Aminotetralin derivatives were among the earliest classes of molecules that were investigated for D3 activity.[32] 7-OH-DPAT (Figure 1), an aminotetralin derivative, was analyzed in various binding assays to evaluate its binding activity for D2/D3 receptors. From these studies, 7-OH-DPAT was shown to exhibit preferential affinity for the D3 receptor even though the selectivity ratio varied among different laboratories, largely due to different assay conditions, radioligands, and transfected cell lines applied.[33] Recently, a bioisosteric analogue of 7-OH-DPAT, pramipexole, was developed by replacing the phenolic group by a more metabolically stable thiazolidinium moiety (Figure 1). Pramipexole represents one of the highest D3 selective agonists reported to date.[34] Numerous other aminotetralins have been developed including structurally constrained version analogues, which exhibited a wide array of activity. In another recent study, the aminotetralin moiety was combined with substituted benzamides, which led to the development of a series of molecules as both agonists and antagonists exhibiting high affinity for D2, D3, and 5HT1a receptors.[35] Compound **1** (Figure 1) represents the prototypical structure derived from this class of molecules. Besides aminotetralin derivatives, other structural classes of D2/D3 agonists have also been developed. Ropinirole is one such example, which is also a D3 preferring agonist and is used in the therapy for PD.[36] Similar to the development of agonists, numerous antagonists, for example, SB-277011, selective for the D3 receptor have been developed over the years.[37] The majority of the highly selective D3 antagonists thus far developed contain a piperazine moiety.[12,38–40] Interestingly, compound BP 897, which was initially identified as a partial agonist but later displayed antagonist property in other experiments, could reduce cocaine-seeking behavior in rats.[41,42]

In our previous effort to develop selective molecules for the D3 receptor, we adopted a hybrid approach by which the aminotetralin moiety and the piperazine fragment were fused together to develop the target molecules. It was perceived that the aminotetralin moiety will interact with the agonist binding sites in the DA receptor and that the piperazine fragment will interact with the accessory binding sites in the D3 receptor to provide selectivity. Our initial work in this area led to the development of selective ligands for the D3 receptor compared to the D2 receptor.[43,44] Measurement of thymidine incorporation by mitogenesis, a functional activity assay, indicated agonist activity in these hybrid molecules. One of the lead compounds, compound **2** (D-74) in Figure 1, exhibited high D3 selectivity and produced potent in vivo contralateral rotational activity in unilaterally lesioned 6-OHDA-treated rats, indicating good blood−brain barrier crossing ability of the drug.[44]

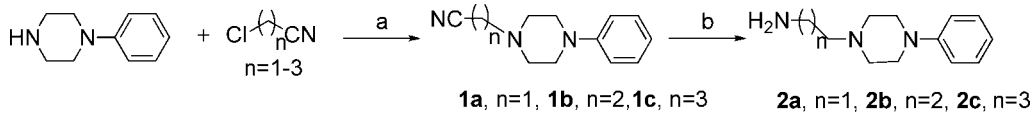
In our current study, we have explored the hybrid structure template in greater detail to delineate molecular determinants that can be attributed toward selectivity of these compounds for the D3 receptor. Specifically, we wanted to explore the positional effect of the hydroxyl functionality in the aromatic ring in binding interaction with the receptors. We also wanted to observe the effect of replacement of the phenolic aromatic moiety by a bioisosteric indol-2-one derivative on affinity for the DA receptors. We have also introduced different linker lengths between aminotetralin and piperazine moieties to further establish the role of linker size in affinity and selectivity for the D3 receptor. In addition, for the most active racemic compounds, their enantiomers were synthesized in enantiomeric purity. Finally, a selective compound was evaluated in 6-OHDA unilaterally lesioned rats to observe its ability to produce contralateral rotations.

Chemistry

Syntheses of the target compounds are described in Schemes 1−5. Synthesis of intermediate amines **2a**−**c** was accomplished by first treating phenylpiperazine with appropriate chloroacetonitrile in the presence of a base followed by reduction of the acetonitrile group with Raney nickel to provide intermediates **2a**−**c**.

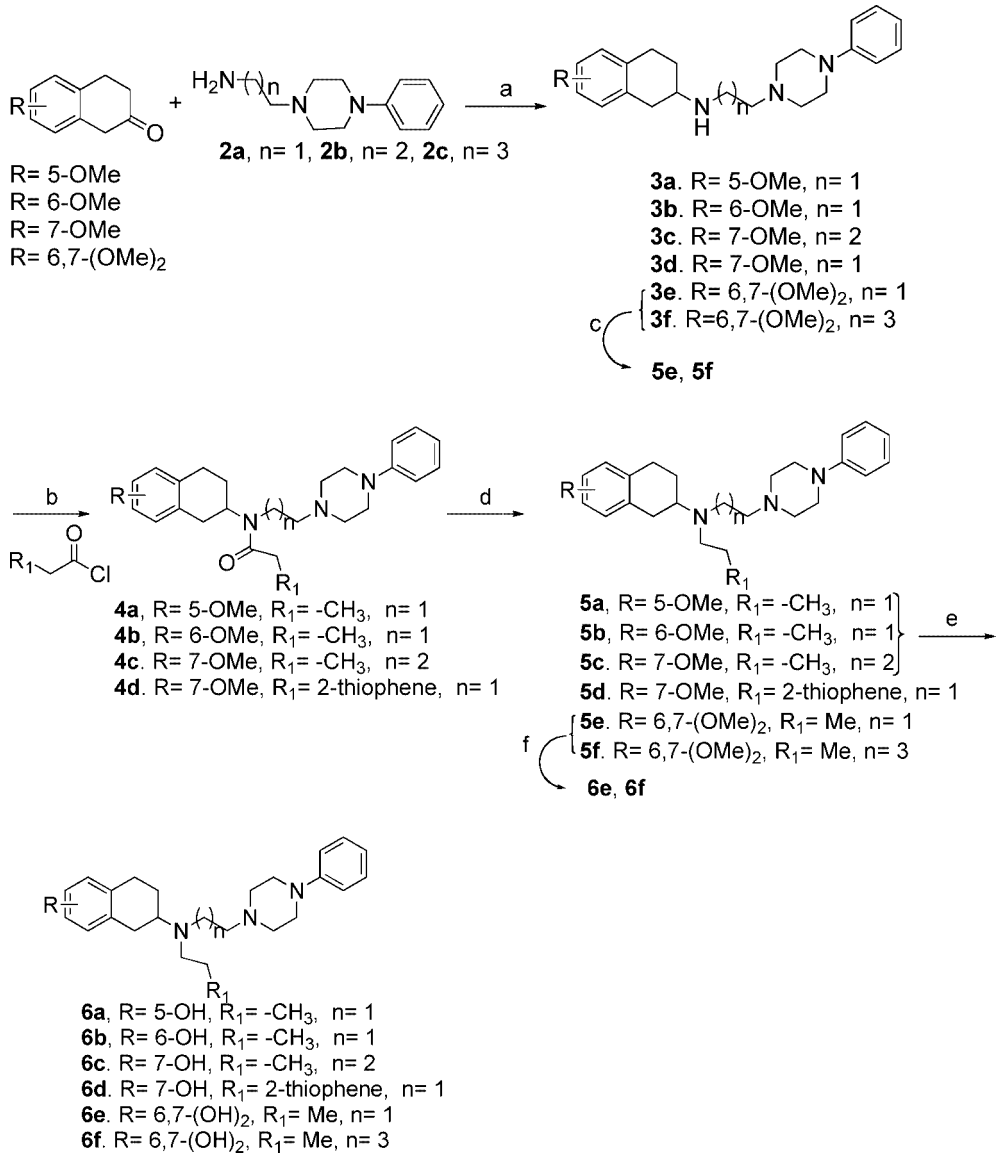
Scheme 2 describes the synthesis of the final targets **6a**−**f**. Appropriate 2-tetralone reacted with amines under reductive

Scheme 1[a]



[a] a, K_2CO_3, toluene, reflux, 3 h; b, Raney nickel, H_2, 60 psi, 8 h.

Scheme 2[a]



[a] a, $NaCNBH_3$, AcOH, dichloroethane, RT, overnight; b, Et_3N, CH_2Cl_2, 0 °C to RT, 4 h; c, 1-bromopropane, K_2CO_3, DMF, reflux, 3 h; d, $LiAlH_4$, THF, reflux, 4 h; e, BBr_3, CH_2Cl_2, −40 °C to RT, overnight; f, 48% aq HBr, 4 h.

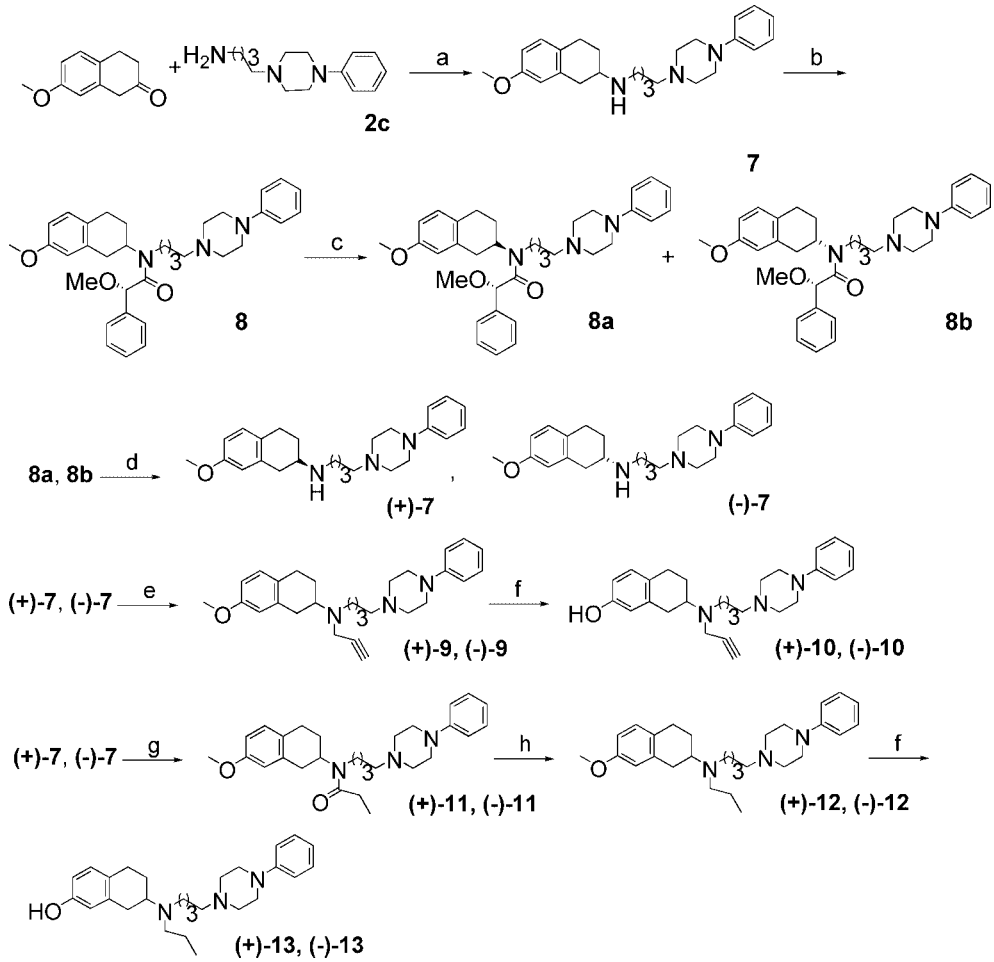
amination reaction condition to yield compounds **3a**−**f** in good yields. Amines were next acylated with appropriate acyl chloride to yield **4a**−**d**, which were then reduced by LAH to produce **5a**−**d**. Compounds **3e** and **3f** were directly converted to **5e** and **5f** by N-alkylation. Final targets **6a**−**f** were produced by demethylation of the methoxy group either by boron tribromide or by 48% HBr.

Next, in Scheme 3 the enantiomeric compounds (+)-**10**, (−)-**10**, (+)-**13**, and (−)-**13** were synthesized by following our published procedure to yield the respective target molecules.[44]

In Scheme 4, we describe the synthesis of amino and 1,3-dihydro-2*H*-indol-2-one derivatives. 2-Tetralone was mononitrated in the presence of nitric acid to produce nitro derivative **14**. Compound **14** was next reacted with piperazine amine **2a** under reductive amination condition to yield **15**. Acylation of the free amine followed by reduction of the nitro and acyl groups produced intermediate **18**. This compound was next treated with chloral hydrate and hydroxyl amine to produce an intermediate that was cyclized under acidic condition to generate benzo[*e*]indole-1,2(3*H*)-dione derivative **19**.[45] Reduction with hydrazine produced the second target molecule, **20**.[46]

Scheme 5 describes the synthesis of both the optically active 5-hydroxy derivatives and the corresponding racemic versions. 5-Methoxy-2-tetralone under reductive amination condition produced compound **21**. Treatment of intermediate **21** with a chiral 4-(2-chlorophenyl)-5,5-dimethyl-2-hydroxy-1,3,2-dioxaphosphorinane 2-oxide agent, prepared by following the literature procedure,[47] followed by hydrolysis provided two pure enantiomers of **21** in good yield. To synthesize the final target 2-methoxy derivative **24a** and its enantiomers, compounds (±)-**21**, (+)-**21**, and (−)-**21** were first reacted with boron tribromide to yield (±)-**21a**, (+)-**21a**, and (−)-**21a**, which were treated with chloroacetyl chloride to produce (±)-**22a** and its enantiomers. Reaction of these intermediates with appropriate aryl-piperazine derivatives yielded racemic (±)-**23a** and its enantiomers, respectively, in good yields. The final targets (±)-**24a**, (+)-**24a**, and (−)-**24a** were produced by reducing the amide intermediate with LAH. The other target molecules were synthesized by treating the enantiomers and the racemic mixtures of compound **21** with chloroacetyl chloride follwed by N-alkylation and reduction in the similar way as described for compound **24a**. In the final step, the methyl group was removed

Scheme 3[a]



[a] a, $NaCNBH_3$, dichloroethane, AcOH, RT, overnight; b, (*R*)-(−)-α-methoxyphenylacetic acid, EDCI, HOBT, ET_3N, CH_2Cl_2; c, preparative HPLC; d, (i) t-BUOK, THF, overnight, (ii) MeLi, THF, 30 min; e, propargyl bromide, NaH, THF, DMF, 50 °C, 6 h; f, BBr_3, CH_2Cl_2, −40 °C to RT, overnight; g, propionyl chloride, Et_3N, CH_2Cl_2, 0 °C to RT, 2 h; h, $LiAlH_4$, THF, reflux, 4 h.

by standard methods to produce the targets (+)-**25**, (−)-**25**, and (±)-**25b** in good yield.

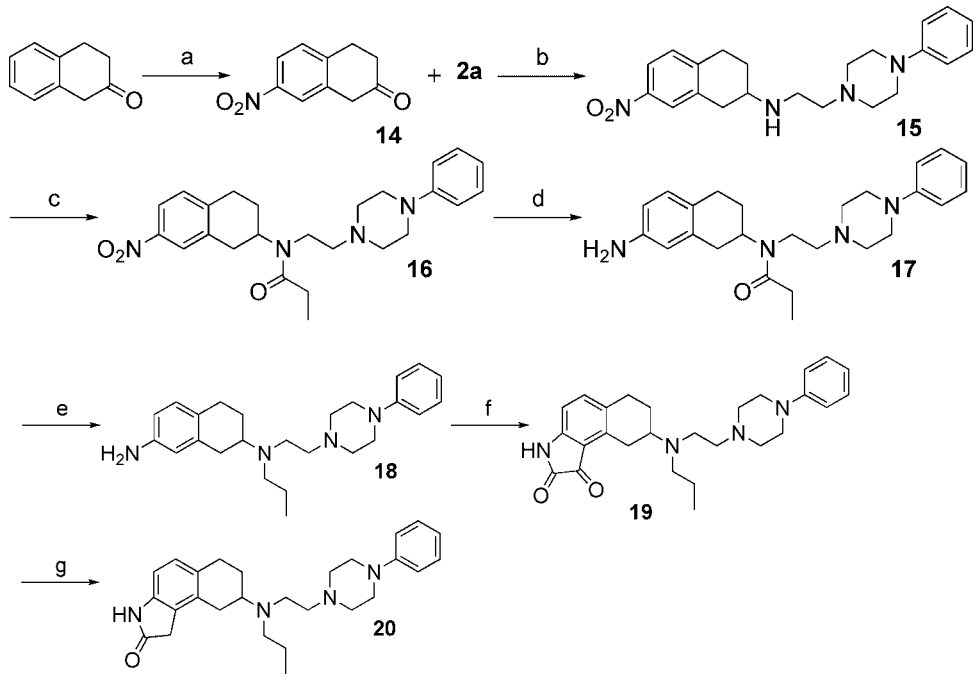
Results and Discussion

Our earlier paper on a hybrid drug development approach for D2/D3 receptors described the development of aminotetralin–piperazine-based hybrid derivatives exhibiting D3 preferential activity both in binding and in functional assays. One of the enantiomerically pure lead molecules, **2** (Figure 1), indicated good blood−brain barrier penetrability as it produced potent contralateral rotations in rats with 6-OHDA-induced unilateral lesions in the nigrostriatal DA system.[44] The results from the in vivo study thus indicated site-specific agonist activity of **2** in the CNS.

In our current structure−activity relationship (SAR) work we wanted to evaluate the binding activity of enantiomers of the racemates **13** and **10**, which were evaluated earlier in both binding and functional assays.[44] Both racemates exhibited high-affinity binding for the D3 receptor with moderate selectivity for the D3 over D2 receptor. In the functional assay these racemic compounds were agonists with preferential affinity for the D3 receptor.[44] The enantiomers derived from these two racemates in the current study displayed differential potencies for DA receptors. In the case of compound **13**, the (+)- and (−)-isomers were almost equipotent at D2/D3 receptors, with (+)-**13** exhibiting slightly higher potency for the D3 receptor over (−)-**13** (K_i = 0.748 vs 1.22 nM). Similar to **13**, both enantiomers of compound **10** exhibited sub-nanomolar affinity for the D3 receptor. However, like enantiomers of **13**, both (−)-**10** and (+)-**10** exhibited comparable potencies at the D3 receptor (K_i = 0.35 and 0.76 nM).

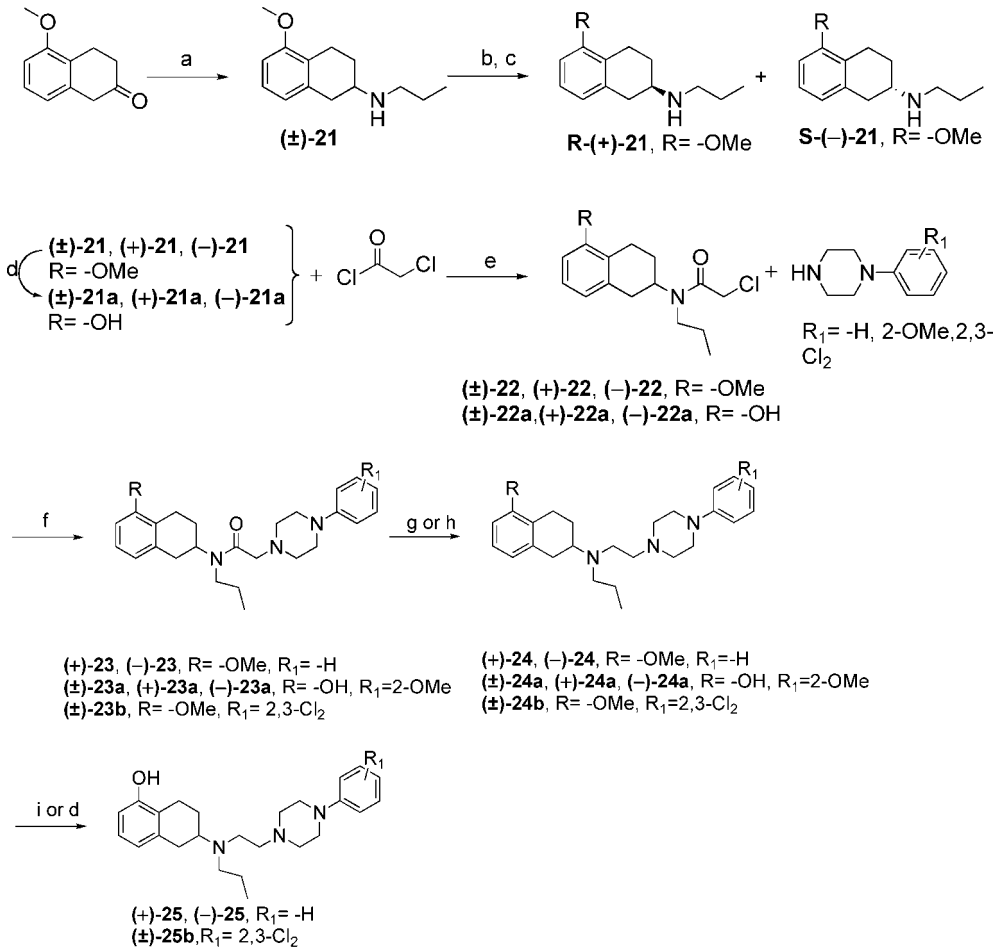
Next, the positional effect of the hydroxyl functionality on the aromatic moiety of our lead derivative was explored in binding interaction. This modification was also accompanied with other molecular alterations involving changes in methylene linker length, introduction of a thiophene moiety on the *N*-alkyl side chain, and addition of one more hydroxyl group in the tetrahydrophenol moiety. Thus, compounds **6a**−**f** were designed and synthesized. In this regard, for the sake of consistency with the literature references and to avoid any confusion, we are referring to compound **6a** and the corresponding analogues as 5-hydroxy-, **6b** as 6-hydroxy-, and **6c** as 7-hydroxy-substituted derivatives throughout this paper. It is evident from Table 1 that when the hydroxyl group was moved to the 5-position as in compound **6a**, an enhancement of potency took place compared to our original lead **2** (0.82 vs 1.56 nM). However, it was less selective for the D3 receptor compared to **2**. The change of the hydroxyl group to position 6 yielded compound **6b**, which was less potent and selective at the D3 compared to **2** and **6a** (K_i = 11.2 nM, D2/D3 = 57.9 for **6b**). To evaluate the effect of a three-methylene linker size, compound **6c** was designed and synthesized. This compound exhibited similar

Scheme 4[a]



[a] a, HNO_3, −30 °C, 8 min; b, $NaCNBH_3$, dichloroethane, AcOH, RT, overnight; c, propionyl chloride, Et_3N, CH_2Cl_2, 0 °C to RT, 2 h; d, H_2 1 atm, 10% Pd/C, MeOH, RT, 4 h; e, $LiAlH_4$, THF, reflux, 4 h; f, (i) chloral hydrate, Na_2SO_4, $NH_2OH \cdot H_2O \cdot HCl$, 60−80 °C, (ii) H_2SO_4, 80 °C, 20 min; g, NH_2NH_2, reflux, 30 min, (ii) EtOH, EtONa, 80 °C, 30 min.

Scheme 5[a]



[a] a, *n*-Propylamine, $NaCNBH_3$, AcOH, dichloroethane, RT, overnight; b, (+)- or (−)-chlocyphos, ethanol, recrystallized from isopropanol; c, 20% NaOH, RT, 2 h; d, BBr_3, CH_2Cl_2, −40 °C, overnight; e, Et_3N, CH_2Cl_2, 0 °C to RT, 2 h; f, K_2CO_3, CH_3CN, 60 °C, 4 h; g, $LiAlH_4$, reflux, 4 h; h, BH_3, THF, reflux, 6 h; i, 48% aq HBr, reflux, 3 h.

Table 1. Affinity for Cloned D2L and D3 Receptors Expressed in Human Embryonic Kidney Cells Measured by Inhibition of [^{3}H]Spiperone Binding[a]

compd	K_i (nM), D2L [^{3}H]spiperone	K_i (nM), D3 [^{3}H]spiperone	D2L/D3
(D-74) **2**	142 ± 23	1.56 ± 0.36	91
7-OH-DPAT	202 ± 34	2.35 ± 0.29	86
6a	58.6 ± 7.1	0.80 ± 0.27	72.9
6b	649 ± 96	11.2 ± 2.0	57.9
6c	167 ± 40	10.3 ± 1.5	16.2
6d	24.6 ± 4.0	23.9 ± 6.1	1.03
6e	70.3 ± 16.8	1.39 ± 0.14	50.6
6f	21.7 ± 4.8	2.89 ± 0.52	7.51
(−)-**10**	25.2 ± 7.3	0.35 ± 0.03	71.0
(+)-**10**	32.9 ± 8.6	0.76 ± 0.079	43.2
(−)-**13**	19.4 ± 1.3	1.22 ± 0.37	15.9
(+)-**13**	19.3 ± 1.5	0.74 ±0.069	25.8
18	638 ± 40	22.2 ± 3.8	28.7
20	90.6 ± 21.0	10.9 ± 2.5	8.27
(+)-**24a**	88.7 ± 3.1	18.8 ± 4.2	4.72
(±)-**24a**	35.8 ± 6.3	2.80 ± 0.71	12.8
(−)-**24a**	9.56 ± 2.29	0.46 ± 0.12	20.9
(±)-**25b**	14.6 ± 1.7	0.45 ± 0.16	32.2
(+)-**25**	238 ± 14	18.4 ± 1.0	12.9
(−)-**25**	26.0 ± 7.5	0.82 ± 0.13	31.5

[a] Results are means ± SEM for three to seven experiments, each performed in triplicate.

affinity and selectivity to **6b** and was less potent compared to **2** and **6a**. Thus, it further demonstrates that the optimal methylene linker size is 2 in a similarly substituted series of this hybrid template, unlike reported with other classes of D3 selective molecules.[48] In a further structural modification, the propyl group was replaced by a 2-thiophene ethyl fragment, which resulted in the development of **6d**. Compound **6d** interestingly exhibited good potency for both D2 and D3 receptors (K_i = 24.6 and 23.9 nM for D2 and D3, respectively), even though it lacked a propyl group. In the next two compounds, **6e** and **6f**, 6,7-dihydroxy functionalities were introduced in our lead structure with the variation of the methylene linker length. In agreement with our earlier results, compound **6e** with the two methylene linker size was more potent and selective for the D3 receptor although both compounds were very potent at D3 (K_i = 1.39 and 2.89 nM and D2/D3; 50.6 and 7.5 for **6e** and **6f**, respectively). Thus, compound **6e** represents addition of one extra hydroxyl functionality into the structure of **2**, which resulted in retention of almost identical affinity at D3 with slightly higher affinity for D2, resulting in lower selectivity of **6e** for D3 compared to **2**.

To evaluate the effect of bioisosteric replacement of the hydroxyl moiety in **2** on affinity and selectivity, compounds **18** and **20** were designed and synthesized. In **18**, the hydroxyl functionality was replaced by an amino group, whereas in compound **20**, the amino group has been converted into the benzo[*e*]indole-1,2(3*H*)-dione derivative. It is expected that in both cases H-bonding interaction of parent hydroxyl group should be maintained with much retention of affinity and selectivity. Replacement of the hydroxyl group by amino in compound **18** produced considerably less potency at D3 compared to **2** (K_i = 22.2 vs 1.56 nM for **18** and **2**, respectively) with lowering of affinity for D2 as well. However, conversion of **18** into its 2-oxoindole derivative resulted in regaining of some of its potency. The gain of potency was 2-fold at the D3 receptor, and in case of D2 the increase of potency was 7-fold (K_i = 10.9 vs 22.2 nM for D3 and 638 vs 90 nM for D2).

Finally, the 5-hydroxy derivative **6a** was further explored as it exhibited high selectivity and potency for the D3 receptor in the current series. In this regard, we have developed an efficient method of separation of enantiomers for these compounds as the initial binding results from the lead **6a** looked promising for in vivo study. Thus, in Scheme 5 the amine intermediate (±)-**21** was selected for chiral separation. The three racemic derivatives belonging to the 5-hydroxy series displayed high potency for the D3 receptor with low to sub-nanomolar potency (K_i = 0.80, 2.80, and 0.45 nM for (±)-**6a**, (±)-**24a**, and (±)-**25b**, respectively). All three compounds also exhibited appreciable affinity for the D2 receptor. Among the three racemic compounds, **6a** exhibited maximum selectivity for the D3. The two enantiomers of **6a** exhibited differential activity for the dopamine receptors with (−)-**25** more potent and selective for the D3 (K_i = 0.82 nM; D2/D3 = 31.5). Similarly, enantiomers of the 2-methoxy derivative (±)-**24a** also exhibited differential activity, with (−)-**24a** being the most potent and selective for the D3 receptor (K_i = 0.45 nM; D2/D3 = 20.9). It is evident that in the 5-hydroxy series the (−)-enantiomer exhibited the higher potency. The racemic dichloro derivative (±)-**25b** was the most potent among the three analogues.

On the basis of the binding results, compounds (−)-**25**, (−)-**24a**, and **2** were selected for the GTPγS binding functional assay for D2 and D3 receptors. In this assay, stimulation of the binding of nonhydrolyzable [^{35}S]GTPγS by agonist was measured and compared with the full agonist DA. The results indicated, as shown in Table 2, that compounds (−)-**24a** and (−)-**25** are highly potent partial to full agonists at the D2 and D3 receptors and that both of them exhibited similar selectivities for the D3 receptor (D2/D3 = 19.4 and 18.3, respectively). The half-maximal stimulation (EC_{50}) for theD3 receptor of these compounds was in the sub-nanomolar range [EC_{50} = 0.08 and 0.12 nM for (−)-**24a** and (−)-**25**, respectively]. On the other hand, compound **2** turned out to be a potent partial agonist with high receptor maximum stimulation potency for the D3 receptor. The functional selectivity of compound **2** for the D3 receptor was comparable with to those of (−)-**24a** and (−)-**25** as shown above (D2/D3 = 17.6 for **2**). The compounds were considerably more potent in stimulating [^{35}S]GTPγS binding than in inhibiting [3*H*]spiperone binding.

In Vivo Rat Rotational Study. Next compound (−)-**25** was evaluated in vivo in the 6-OHDA-lesioned rat rotational model. In this animal model, the DA neurons of one side of the nigrostriatal DA system are selectively and completely degenerated by intracebral injection of the neurotoxin 6-OH-DA. This will induce a postsynaptic supersensitivity to develop on the lesioned side. DA agonist when administered systemically will produce contralateral rotations in the rat, that is, toward the nonlesioned side.[49] As the unilaterally lesioned 6-OH-DA rat represents a well-accepted rodent model for PD, the results from this experiment will indicate a potential future applicability of these drugs in PD and an implication of the relative role of D3 receptors in inducing antiparkinsonian effect.[36] Furthermore, the results from this experiment will indicate in vivo agonist potency of test compounds and, thus, may serve as a further screening device for developing PD treatment compounds. In addition, results from this experiment will also indicate whether a drug is able to cross the blood− brain barrier efficiently or not.

Compound (−)-**25** was selected for evaluation in this rat rotational model to determine its potency in producing contralateral rotations. Two different doses of (−)-**25** were tested. At 5 μmol/kg (2.87 mg/kg), compound (−)-**25** produced potent rotations that lasted beyond 12 h and produced more than 4319 total number of rotations. At a lower dose of 1 μmol/kg (0.53 mg/kg), (−)-**25** exhibited rotational activity lasting for 9 h with a total number of rotations of 3609. It is evident that the higher

Table 2. Stimulation of [^{35}S]GTPγS Binding to the Cloned hD2 Receptor Expressed in CHO Cells and Cloned hD3 Receptor Expressed in AtT-20 Cells

	CHO-D2L		AtT-20-D3		
compound	EC_{50} (nM) [^{35}S]GTPγS	% E_{max}	EC_{50} (nM) [^{35}S]GTPγS	% E_{max}	D2/D3
dopamine	209 ± 29	100	8.53 ± 0.62	100	24.5
2	12.2 ± 0.9	32.1 ± 2.8	0.69 ± 0.39	40.5 ± 7.5	17.6
(−)-**25**	2.22 ± 0.27	63.4 ± 3.5	0.12 ± 0.002	78.5 ± 9.5	18.3
(−)-**24a**	1.56 ± 0.72	61.8 ± 1.0	0.080 ± 0.041	78.0 ± 3.4	19.4

[a] EC_{50} is the concentration producing half-maximal stimulation; for each compound, maximal stimulation (E_{max}) is expressed as percent of the E_{max} observed with 1 mM (D2) or 100 μM (D3) of the full agonist DA (% E_{max}). Results are means ± SEM for three or four experiments, each performed in triplicate.

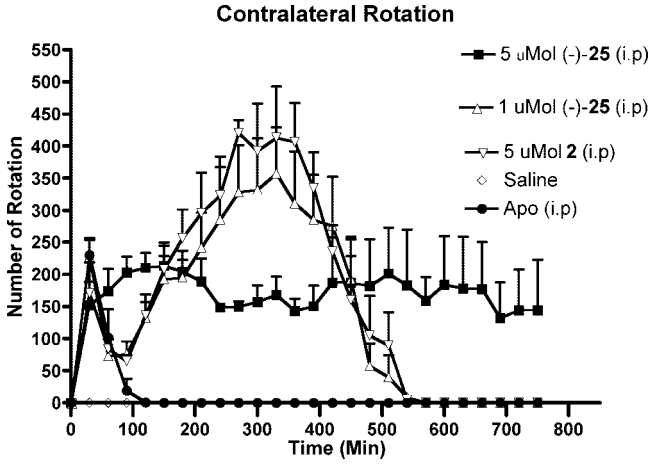


Figure 2. Effect on turning behavior of (−)-**25a**, **2**, apomorphine (0.05 mg/kg or 0.16 μmol/kg), and vehicle in unilaterally 6-OH-DA-lesioned rats studied over 12 h. Each point is the mean ± SEM of four to five rats. All drugs were administered ip. One-way ANOVA analysis demonstrates significant effect among treatments: $F(5,95) = 19.14$ ($P < 0.0001$). Dunnett's analysis showed that the effect of (−)-**25** on rotations at two doses (5 and 1 μmol/kg) was statistically significant different compared to vehicle ($P < 0.01$). The effect of **2** (5 μmol/kg) on rotation was statistically significantly different from that of vehicle ($P < 0.01$).

dose was more potent in producing contralateral rotations. For comparison with the 7-hydroxy compound, **2** was also tested at 5 μmol/kg (2.51 mg/kg), which produced a rotational profile similar to that produced by 1 μmol/kg of (−)-**25**. The control vehicle under the same experimental condition produced no rotation. It is evident from the results that at a similar dose, (−)-**25** is more potent in producing contralateral rotations compared to **2**. Interestingly, (−)-**25** at a lower dose of 1 μmol/kg and **2** at a dose of 5 μmol/kg, produced initial increases of rotational motor activity followed by a brief decrease of activity before a steady increase of rotational activity took place. At present, the reason for such initial biphasic activity is unknown. The standard reference compound used for comparison purposes was apomorphine (Figure 2), which exhibited a much shorter duration of action. Compound (−)-**25** thus exhibited potent in vivo activity with a long duration of action, and in this regard, it is one of the most potent DA agonists known to date. A higher dose of (−)-**25** produced an activation profile that stayed on a plateau for the entire duration of the study (>12 h).

Additionally, it is interesting to observe different rotational activity profiles for **2** and (−)-**25**, with the latter compound exhibiting higher potency and longer duration of action. Aminotetralins have been known to produce poor oral activity and bioavailability due to their inactivation by glucuronidation in the metabolism process.[50] In that context, it is interesting to see that hybrid tetralin derivative (−)-**25** exhibited such a long duration of activity at a low dose, which indicates either its high in vivo stability or formation of an active metabolite. This will be investigated in more detail in a future study.

Conclusion. In this paper we describe a SAR study on an aminotetralin and piperazine hybrid template, which yielded some highly potent agonists for D2 and D3 receptors. 5-Hydroxy derivatives proved to be the most potent agonists for DA D2/D3 receptors in the current series of compounds. Conversion of the phenolic hydroxyl group in the 2-oxoindole derivative retained most of its potency. For the most potent compounds, potency was at the sub-nanomolar level. In the GTPγS stimulation binding functional assay, selected compounds exhibited partial agonist to full agonist characteristics with preferential affinity for the D3 receptor. Interestingly, even though the 7-hydroxy compound **2** exhibited a potent EC_{50} value, it was much less active in producing maximum stimulation and in this respect was less intrinsically active than the 5-hydroxy derivative (−)-**25**. Thus, compound **2** displays a partial agonist character. Compound (−)-**25** exhibited potent and extended *I* rotational activity in rats with unilateral 6-OHDA lesions in the striatum. Future pharmacokinetic analysis will increase our understanding of its mechanism of in vivo action.

Experimental Section

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 equipment. The NMR solvent used was either $CDCl_3$ or CD_3OD 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. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. [^{3}H]Spiperone (15.0 Ci/mmol) and [^{35}S]GTPS (1250 Ci/mmol) were from Perkin-Elmer (Boston, MA). 7-OHDPAT, quinpirole, and (+)-butaclamol were from Sigma-Aldrich (St. Louis, MO).

Procedure A. Synthesis of 1-(4-Phenylpiperazin-1-yl)acetonitrile (1a). A suspension of 1-phenylpiperazine (10 g, 61.64 mmol), potassium carbonate (4.26 g, 30.82 mmol), and chloroacetonitrile (4.50 mL, 70.88 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 **1a** as a thick yellow solid (11.24 g, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.77 (t, 4H, J = 4.8 Hz), 3.24 (t, 4H, J = 4.8 Hz, Ph-N(CH_2)$_2$), 3.58 (s, 2H), 6.87 (t, 1H, J = 7.4 Hz, Ar-H), 6.94 (d, 2H, J = 8.8 Hz, Ar-H), 7.26–7.30 (m, 2H, Ar-H).

Synthesis of 3-(4-Phenylpiperazin-1-yl)-propanenitrile (1b). Compound **1b** was synthesized from 1-phenylpiperazine (12 g, 73.96 mmol) and 3-chloropropionitrile (17.4 mL, 221.88 mmol) according to procedure A to afford product **1b** (12.42 g, 78%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44–2.48 (t, 2H, J = 7.2, N-CH_2CH$_2$CN), 2.49–2.53 (t, 2H, J = 7.2 Hz, CH$_2$CH_2CN), 2.61(t, 4H, J = 4.8 Hz, CH$_2$N(CH_2)$_2$), 3.20 (t, 4H, J = 4.8 Hz,

Ar-N(CH_2)$_2$), 6.85–6.88 (t, 1H, J = 7.6 Hz, Ar-H), 6.92–6.94 (d, J = 7.6 Hz, Ar-H), 7.25–7.29 (m, 2H, Ar-H).

Synthesis of 4-(4-Phenylpiperazin-1-yl)butanenitrile (1c). 1-Phenylpiperazine (12 g, 73.96 mmol) was treated with chlorobutyronitrile (21.28 mL, 221.89 mmol) (procedure A) to afford **1c** (12.8 g, 75.6%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83–1.89 (q, 2H, J = 6.8 Hz, $CH_2CH_2CH_2CN$), 2.43–2.47 (t, 2H, J = 7.2, N-CH_2CH$_2$-CH$_2$CN), 2.49–2.53 (t, 2H, J = 7.2 Hz, $CH_2CH_2CH_2CN$), 2.59–2.61 (t, 4H, J = 4.8 Hz, CH_2N(CH_2)$_2$), 3.19 (t, 4H, J = 4.8 Hz, Ar-N(CH_2)$_2$), 6.85–6.88 (t, 1H, J = 7.6 Hz, Ar-H), 6.92–6.94 (d, J = 7.6 Hz, Ar-H), 7.25–7.29 (m, 2H, Ar-H).

Procedure B. Synthesis of 2-(4-Phenylpiperazin-1-yl)ethylamine (2a). A solution of compound **1a** in methanol (12.5 g, 62.1 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 **2a** (8.9 g, 70%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (t, 2H, J = 6.4 HZ), 2.69 (t, 4H, J = 4.8 Hz), 2.89 (t, 2H, J = 6.4 Hz), 3.14 (t, 4H, J = 4.8 Hz, Ph-NCH$_2$), 6.82 (t, 1H, J = 8.0 Hz, Ar-H), 6.89 (d, 2H, J = 8.0 Hz, Ar-H), 7.21–7.27 (m, 2H, Ar-H).

Synthesis of 3-(4-Phenylpiperazin-1-yl)propan-1-amine (2b). Compound **2b** was synthesized from compound **1b** (12 g, 55.74 mmol) according to procedure B to afford **2b** (9.0 g, 74%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76–1.83 (q, 2H, J = 6.4 Hz), 2.56 (t, 2H, J = 6.4 Hz), 2.65 (t, 2H, J = 5.2 Hz), 2.96 (t, J = 6.0 Hz), 3.19 (t, 4H, J = 5.2 Hz, Ph-NCH$_2$), 6.86 (t, 1H, J = 7.2 Hz, Ar-H), 6.90–6.92 (d, 2H, J = 8.4 Hz, Ar-H), 7.24–7.27 (m, 2H, Ar-H).

Synthesis of 4-(4-Phenylpiperazin-1-yl)butan-1-amine (2c). Compound **2c** was synthesized from compound **1c** (12 g, 52.33 mmol) according to procedure B to afford **2c** (9.2 g, 75%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45–1.61 (m, 4H), 2.39–2.42 (t, 2H, J = 7.2 Hz, NCH$_2$), 2.59–2.62 (t, 4H, J = 4.5 Hz, CH_2N(CH$_2$)$_2$), 2.70–2.74 (t, 2H, CH_2NH$_2$), 3.19–3.22 (t, 4H, J = 4.6 Hz, Ar-N(CH$_2$)$_2$), 6.83–6.87 (t, 1H, J = 7.2 Hz, Ar-H), 6.92–6.94 (d, J = 7.6 Hz, Ar-H), 7.24–7.28 (m, 2H, Ar-H).

Procedure C. Synthesis of 5-Methoxy-*N*-[2-(4-phenylpiperazin-1-yl)ethyl]-1,2,3,4-tetrahydronaphthalen-2-amine (3a). A mixture of compound **2a** (0.4 g, 1.95 mmol), 5-methoxy-2-tetralone (0.38 g, 2.14 mmol), and glacial acetic acid (HOAc) (0.14 mL) in 1,2-dichloroethane (20 mL) was stirred at room temperature under N_2 atmosphere for 20 min. Sodium cyanoborohydride ($NaCNBH_3$) (0.49 g, 7.79 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 (20 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 **3a** (0.65 g, 91.3%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73–1.83 (m, 1H), 2.02–2.09 (m, 1H), 2.23 (m, 1H), 2.6–2.78 (m, 5H), 2.87–3.22 (m, 7H), 3.31–3.33 (m, 1H), 3.76 (s, 2H), 3.8 (s, 3H, −OCH$_3$), 4.05–4.15 (m, 1H, −NH-C*H*), 6.65–6.71 (m, 3H), 6.84–6.90 (m, 2H), 7.08–7.13 (td, 1H, J_1 = 7.8 Hz, J_2 = 2.8 Hz), 7.26 (t, 2H, J = 7.2 Hz).

Synthesis of 6-Methoxy-*N*-[2-(4-phenylpiperazin-1-yl)ethyl]-1,2,3,4-tetrahydronaphthalen-2-amine (3b). Compound **2a** (0.28 g, 1.37mmol) was reacted with 6-methoxy-2-tetralone (0.27 g, 1.50 mmol), $NaCNBH_3$ (0.34 g, 5.47mmol), and HOAc (0.09 mL) in 1,2-dichloroethane (20 mL) to yield **3b** (0.45 g, 90%) (procedure C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72–1.84 (m, 1H), 2.02–2.08 (m, 1H), 2.23 (m, 1H), 2.6–2.78 (m, 5H), 2.87–3.25 (m, 7H), 3.31–3.33 (m, 1H), 3.76 (s, 2H), 3.8 (s, 3H, −OCH$_3$), 4.05–4.15 (m, 1H, −NH-C*H*), 6.63–6.74 (m, 2H), 6.85–7.01 (m, 3H), 7.25–7.29 (m, 3H).

Synthesis of 7-Methoxy-*N*-[3-(4-phenylpiperazin-1-yl)propyl]-1,2,3,4-tetrahydronaphthalen-2-amine (3c). Compound **2b** (0.50 g, 2.28 mmol) was reacted with 7-methoxy-2-tetralone (0.44 g, 2.51 mmol), $NaCNBH_3$ (0.57 g, 9.12 mmol), and HOAc (0.14 mL) in 1,2-dichloroethane (20 mL) to yield compound **3c** (1.42 g, 55%) (procedure C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60–1.75 (m, 1H), 1.76–1.86 (m, 2H), 2.03–2.06 (m, 2H), 2.46–2.51 (m, 2H), 2.56–2.70 (m, 5H), 2.74–2.84 (m, 4H), 2.94–3.02 (m, 1H), 3.10–3.21 (m, 4H), 3.73–3.74 (m, 3H, −OCH$_3$), 6.58−6.68 (m, 2H), 6.86–7.0 (m, 4H), 7.25–7.29 (m, 2H).

Synthesis of 7-Methoxy-*N*-[2-(4-phenylpiperazin-1-yl)ethyl]-1,2,3,4-tetrahydronaphthalen-2-amine (3d). Compound **2a** (0.81 g, 3.95 mmol) was reacted with 7-methoxy-2-tetralone (0.73 g, 4.14 mmol), $NaCNBH_3$ (0.99 g, 15.78 mmol), and HOAc (0.26 mL) in 1,2-dichloroethane (30 mL) to yield **3d** (1.0 g, 69.44%) (procedure C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60–1.68 (m, 2H), 2.60–2.63 (m, 6H, CH_2N(CH$_2$)$_2$), 2.76–3.04 (m, 7H), 3.16–3.20 (t, J = 4.8 Hz, N(CH$_2$)$_2$), 3.77 (s, 3H, OCH$_3$), 6.62–6.71 (m, 2H, Ar-H), 6.64–7.02 (m, 4H, Ar-H), 7.24–7.30 (m, 2H, Ar-H).

Synthesis of 6,7-Dimethoxy-*N*-[2-(4-phenylpiperazin-1-yl)ethyl]-1,2,3,4-tetrahydronaphthalen-2-amine (3e). 6,7-Dimethoxy-2-tetralone was prepared from 2-(3,4-dimethoxyphenyl) acetic acid by following a previously described procedure.[51] Compound **2a** (0.358 g, 1.75 mmol) was reacted with 6,7-dimethoxy-2-tetralone (0.3 g, 1.46 mmol), sodium triacetoxyborohydride (Na(OAc)$_3$BH) (0.925 g, 4.37 mmol), and HOAc (0.5 mL) in 1,2-dichloroethane (30 mL) (procedure C). The crude product was purified by flash chromatography (EtOAc/MeOH/Et_3N = 80:15:5) to yield compound **3e** (0.53 g, 92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58–1.68 (m, 2H), 2.58–2.65 (m, 6H), 2.74–2.98 (m, 7H), 3.16–3.18 (t, J = 4.8 Hz, 4H, N(CH$_2$)$_2$), 3.81 (s, 3H, OCH$_3$), 3.82 (s, 3H, OCH$_3$), 6.56–6.57 (m, 2H, Ar-H), 6.82–6.87 (m, 1H, Ar-H), 6.90–6.92 (m, 2H, Ar-H), 7.23–7.27 (m, 2H, Ar-H).

Synthesis of 6,7-Dimethoxy-*N*-[4-(4-phenylpiperazin-1-yl)butyl]-1,2,3,4-tetrahydronaphthalen-2-amine (3f). Compound **2c** (0.340 g, 1.46 mmol) was reacted with 6,7-dimethoxy-2-tetralone (0. 250 g, 1.21 mmol), Na(OAc)$_3$BH (0.771 g, 3.64 mmol), and HOAc (0.5 mL) in 1,2-dichloroethane (20 mL) (procedure C) to furnish **3f** (0.467 g, 91%): ^{1}H NMR (400 MHz, $CDCl_3$) 1.65 (br s, 6H), 2.44–2.48 (m, 2H), 2.63–2.65 (m, 4H), 2.76–2.81 (m, 4H), 2.99–3.01 (m, 2H), 3.19–3.22 (t, J = 4.8 Hz, 4H, N(CH$_2$)$_2$), 3.82 (s, 3H, OCH$_3$), 3.83 (s, 3H, OCH$_3$), 6.55–6.57 (m, 2H, Ar-H), 6.84–6.87 (m, 1H, Ar-H), 6.91–6.93 (m, 2H, Ar-H), 7.24–7.28 (m, 2H, Ar-H).

Procedure D. Synthesis of *N*-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-[2-(4-phenylpiperazin-1-yl)ethyl]propionamide (4a). Propionyl chloride (0.49 mL, 5.75 mmol) was added into a solution of compound **3a** (0.70 g, 1.92 mmol) and Et_3N (2.0 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/Et3N = 95:4:1) to yield **4a** (0.4 g, 59.5%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13–1.17 (t, 3H, J = 7.2 Hz, −NCOCH$_2$CH_3), 1.85–2.04 (m, 2H), 2.36–2.46(m, 2H), 2.59–2.68 (m, 7H), 2.78–2.88 (td, 1H, J_1 = 16.6 Hz, J_2 = 4.0 Hz), 2.97–3.06 (m, 2H), 3.20 (t, 4H, J = 4.8 Hz, Ar-N(CH_2)$_2$), 3.41–3.55 (m, 2H), 3.81–3.82 (d, 3H, J = 5.6 Hz, −OCH$_3$), 3.98–4.03 (m, 1H, −NC*H*), 6.65–6.71 (m, 2H), 6.82–6.93 (m, 3H), 7.07–7.15 (m, 1H), 7.23–7.28 (m, 2H).

Synthesis of *N*-(6-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-[2-(4-phenylpiperazin-1-yl)ethyl]propionamide (4b). Compound **3b** (0.29 g, 0.79 mmol) was reacted with propionyl chloride (0.21 mL, 2.38 mmol) and Et_3N (1.0 mL) in CH_2Cl_2 (10 mL) (procedure D). The crude product was purified by flash chromatography using solvent system EtOAc/MeOH = 90:10 to yield pure compound **4b** (0.4 g, 90.64%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14–1.18 (t, 3H, J = 7.6 Hz, −NCOCH$_2$CH_3), 1.93–2.00 (m, 2H), 2.39–2.45 (m, 2H), 2.56–2.99 (m, 10H), 3.19–3.26 (m, 4H, Ar-N(CH_2)$_2$), 3.40–3.54 (m, 2H), 3.77–3.28 (d, 3H, J = 4.8 Hz, −OCH$_3$), 4.01–4.05 (m, 1H, −NC*H*), 6.63–6.74 (m, 2H, Ar-H), 6.85–7.01 (m, 3H, Ar-H), 7.25–7.29 (m, 3H, Ar-H).

Synthesis of *N*-(7-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-[3-(4-phenylpiperazin-1-yl)propyl]propionamide (4c). Com-

pound **3c** (0.78 g, 2.06 mmol) was reacted with propionyl chloride (0.54 mL, 6.18 mmol) and Et_3N (2.0 mL) in CH_2Cl_2 (15 mL) (procedure D). The crude product was purified by flash chromatography using solvent system EtOAc/MeOH = 90:10 to yield pure compound **4c** (0.8 g, 89.2%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14–1.18 (t, 3H, J = 7.6 Hz, $-NCOCH_2CH_3$), 1.93–2.00 (m, 3H), 2.39–2.45 (m, 2H), 2.56–2.99 (m, 12H), 3.19–3.26 (m, 4H, Ar-$N(CH_2)_2$), 3.42–3.54 (m, 2H), 3.77–3.28 (d, 3H, J = 4.8 Hz, $-OCH_3$), 4.01–4.05 (m, 1H, $-NCH$), 6.63–6.74 (m, 2H), 6.85–7.01 (m, 3H), 7.25–7.29 (m, 3H).

Synthesis of *N*-(7-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-[2-(4-phenylpiperazin-1-yl)ethyl]-2-(thiophen-2-yl)acetamide (4d). Compound **3d** (1.4 g, 3.83 mmol) was reacted with 2-thiophene acetyl chloride (0.47 mL, 3.83 mmol) and Et_3N (2.0 mL) in CH_2Cl_2 (20 mL) (procedure D). The crude product was purified by flash chromatography using solvent system EtOAc/MeOH = 90:10 to yield pure compound **4d** (0.6 g, 32%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84–2.0 (m, 2H), 2.6–2.90 (m, 9H), 2.96–3.02 (m, 1H), 3.18–3.22 (m, 4H), 3.41–3.56 (m, 2H), 3.76–3.77 (d, 3H, J = 6.0 Hz, $-OCH_3$), 3.94–4.01 (m, 2H), 4.09–4.17 (m, 1H), 6.56–6.58 (m, 1H, Ar-H), 6.68–6.74 (m, 1H, Ar-H), 6.83–7.01 (m, 6H, Ar-H), 7.19–7.29 (m, 3H, Ar-H).

Procedure E. Synthesis of 5-Methoxy-*N*-[2-(4-phenylpiperazin-1-yl)ethyl)]-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (5a). Compound **4a** (0.48 g, 1.14 mmol) in anhydrous THF (20 mL) was added dropwise into a suspension of lithium aluminum hydride ($LiAlH_4$) (0.35 g, 9.11 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 **5a** (0.4 g, 87%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.6 Hz, $CH_2CH_2CH_3$), 1.44–1.60 (m, 3H), 2.07–2.09(m, 1H), 2.50–2.55 (m, 5H), 2.65 (t, 4H, J = 5.2 Hz, $CH_2N(CH_2)_2$), 2.72–3.02 (m, 6H), 3.2 (t, 4H, J = 4.8 Hz, Ar-$N(CH_2)_2$), 3.81 (s, 3H, $-OCH_3$), 6.65 (d, 1H, J = 7.6 Hz), 6.71 (d, 1H, J = 7.6 Hz), 6.85 (t, 1H, J = 8.0 Hz), 6.93 (d, 2H, J = 8.0 Hz), 7.09 (t, 1H, J = 7.6 Hz), 7.24–7.28 (m, 2H, J = 7.2 Hz).

Synthesis of 6-Methoxy-*N*-[2-(4-phenylpiperazin-1-yl)ethyl]-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (5b). Compound **4b** (0.303 g, 0.72 mmol) was reacted with $LiAlH_4$ (0.27 g, 7.19 mmol) in THF (20 mL) by following procedure E. The crude product was purified by flash chromatography using solvent system EtOAc/MeOH/Et_3N = 95:4:1 to yield compound **5b** (0.26 g, 87.4%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.6 Hz, $CH_2CH_2CH_3$), 1.46–1.70 (m, 3H), 2.01–2.05 (m, 1H), 2.52–2.57 (m, 4H), 2.65–2.86 (m, 10H), 2.97–2.99 (m, 1H), 3.2 (t, 4H, J = 4.8 Hz, Ar-$N(CH_2)_2$), 3.77 (s, 3H, $-OCH_3$), 6.62 (d, 1H, J=2.8 Hz), 6.68–6.70 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.4 Hz), 6.85 (t, 1H, J = 7.2 Hz), 6.93 (d, 2H, J = 8.0 Hz), 7.00 (d, 1H, J = 8.0 Hz), 7.26 (t, 2H, J = 7.2 Hz).

Synthesis of 7-Methoxy-*N*-[3-(4-phenylpiperazin-1-yl)propyl]-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (5c). Compound **4c** (0.90 g, 2.06 mmol) was reacted with $LiAlH_4$ (0.47 g, 12.3 mmol) in THF (30 mL) by following procedure E. The crude product was purified by flash chromatography using solvent system EtOAc/MeOH/Et_3N = 95:4:1 to yield compound **5c** (0.54 g, 63%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.8 Hz, $CH_2CH_2CH_3$), 1.43–1.75 (m, 5H), 1.98–2.02 (m, 1H), 2.41–2.51 (m, 4H), 2.55–2.62 (m, 6H), 2.74–2.85 (m, 4H), 2.93–3.0 (m, 1H), 3.2 (t, 4H, J = 4.8 Hz, Ar-$N(CH_2)_2$), 3.77 (s, 3H, $-OCH_3$), 6.62–6.63 (d, 1H, J = 2.8 Hz), 6.66–6.69 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.4 Hz), 6.85 (t, 1H, J = 7.2 Hz), 6.93 (d, 2H, J = 8.0 Hz), 6.98 (d, 1H, J = 8.0 Hz), 7.26 (t, 2H, J = 8.0 Hz).

Synthesis of 7-Methoxy-*N*-[2-(4-phenylpiperazin-1-yl)ethyl]-*N*-[2-(thiophen-2-yl)ethyl]-1,2,3,4-tetrahydronaphthalen-2-amine (5d). Compound **4d** (0.46 g, 0.94 mmol) was reacted with $LiAlH_4$ (0.29 g, 7.52 mmol) in THF (30 mL) by following procedure E. The crude product was purified by flash chromatography using solvent system EtOAc/MeOH/Et_3N = 95:4:1 to give compound **5d** (0.39 g, 87%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58–1.70 (m, 2H), 1.99–2.01 (m, 1H), 2.58–2.69 (m, 6H), 2.71–3.05 (m, 9H), 3.18–3.23 (m, 4H), 3.26–3.31 (m, 1H), 3.78 (s, 3H, $-OCH_3$), 6.62 (br s, 1H, Ar-H), 6.67–6.69 (m, 1H, Ar-H), 6.82–7.01 (m, 6H, Ar-H), 7.23–7.28 (m, 3H, Ar-H).

Procedure F. Synthesis of 6,7-Dimethoxy-*N*-[2-(4-phenylpiperazin-1-yl)ethyl]-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (5e). A mixture of amine **3e** (510 mg, 1.29 mmol), 1-bromopropane (634 mg, 5.16 mmol), and K_2CO_3 (534 mg, 3.87 mmol) in dry DMF (10 mL) was stirred at 80 °C for 20 h. The reaction mixture was poured into water (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic phase was washed with brine and dried over Na_2SO_4. The solvent was removed by evaporation, and the residue was purified by flash chromatography (EtOAc/MeOH/ Et_3N = 80:8:4) to yield **5e** (0.50 g, 89%): ^{1}H NMR (400 MHz, $CDCl_3$) 0.87–0.91 (t, J = 7.2 Hz, 3H, $CH_3CH_2CH_2N$), 1.50–1.61 (m, 4H), 1.96–2.04 (m, 2H), 2.52–2.54 (br s, 2H, CH_2N), 2.66–2.80 (br s, 4H, $N(CH_2)_2$), 2.88–2.96 (m, 7H), 3.20 (br s, 4H, $N(CH_2)_2$), 3.78 (br s, 6H, CH_3O), 6.58 (br s, 2H, Ar-H), 6.85 (brs, 1H, Ar-H), 6.92 (br s, 2H, Ar-H), 7.26–7.28 (m, 2H, Ar-H).

Synthesis of 6,7-Dimethoxy-*N*-[4-(4-phenylpiperazin-1-yl)butyl]-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (5f). Amine **3f** (380 mg, 0.90 mmol) was reacted with 1-bromopropane (441 mg, 3.59 mmol) and K_2CO_3 (429 mg, 3.10 mmol) in DMF (10 mL) by following procedure F to obtain **5f** (0.24 g, 57%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90–0.94 (t, J = 7.2 Hz, 3H, $CH_3CH_2CH_2N$), 1.48–1.56 (m, 8H), 2.39–2.41 (m, 2H), 2.61–2.62 (m, 6H), 2.80 (br s, 4H), 2.99–3.01 (m, 2H), 3.20–3.22 (t, J = 4.8 Hz, 4H, $N(CH_2)_2$), 3.82 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.56–6.57 (m, 2H, Ar-H), 6.83–6.87 (m, 1H, Ar-H), 6.92–6.94 (m, 2H, Ar-H), 7.24–7.28 (m, 2H, Ar-H).

Procedure G. Synthesis of 6-[(2-(4-Phenylpiperazin-1-yl)ethyl)(propyl)amino]-5,6,7,8-tetrahydronaphthalen-1-ol (6a). Boron tribromide (1 M solution in dichloromethane) (3.24 mL, 3.24 mmol) was added into a solution of **5a** (0.44 g, 1.08 mmol) in anhydrous methylene chloride (CH_2Cl_2) (20 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 **6a** (0.2 g, 47%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 7.2 Hz, $CH_2CH_2CH_3$), 1.36–1.51 (m, 3H), 1.93–1.97 (m, 1H), 2.40–2.54 (m, 6H), 2.64–2.68 (m, 3H), 2.73 (t, 4H, J = 4.8 Hz, $CH_2N(CH_2)_2$), 2.82–2.94 (m, 2H), 3.26 (t, 4H, J = 5.6 Hz, Ar-$N(CH_2)_2$), 6.46–6.48 (d, 1H, J = 8.0 Hz), 6.55–6.57 (d, 1H, J = 7.6 Hz), 6.86 (t, 1H, J = 7.2 Hz), 6.91–6.95 (m, 3H), 7.24–7.28 (m, 2H).

The product was converted into the corresponding dioxalate salt, mp 130–132 °C. Anal. Calcd for $C_{25}H_{35}N_3O\cdot 2C_2H_2O_4$: C, H, N.

Synthesis of 6-[(2-(4-Phenylpiperazin-1-yl)ethyl)(propyl)amino]-5,6,7,8-tetrahydronaphthalen-2-ol (6b). Compound **5b** (0.26 g, 0.63 mmol) was reacted with 1 M BBr_3/CH_2Cl_2 (1.88 mL, 1.88 mmol) in CH_2Cl_2 (20 mL) by following procedure G to furnish **6b** (0.074 g, 30%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 7.2 Hz, $CH_2CH_2CH_3$), 1.30–1.50 (m, 3H), 1.81–1.84 (bd, 1H, J = 10.8 Hz), 2.41–2.80 (m, 15H), 3.26 (t, 4H, J = 4.8 Hz, Ar-$N(CH_2)_2$), 6.43 (bs, 1H), 6.51–6.54 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.4 Hz), 6.82–6.88 (m, 2H), 6.91–6.93 (d, 2H, J = 7.6 Hz), 7.24–7.28 (m, 2H).

The product was converted into the corresponding trihydrochloride salt, mp 155–158 °C. Anal. Calcd for $C_{25}H_{35}N_3O\cdot 3HCl$: C, H, N.

Synthesis of 7-[(3-(4-Phenylpiperazin-1-yl)propyl)(propyl)amino]-5,6,7,8-tetrahydronaphthalen-2-ol (6c). Compound **5c** (0.54 g, 1.28 mmol) was reacted with 1 M BBr_3/CH_2Cl_2 (3.85 mL, 3.85 mmol) in CH_2Cl_2 (20 mL) by following procedure G to yield **6c** (0.32 g, 61.1%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.2 Hz, $CH_2CH_2CH_3$), 1.45–1.65 (m, 4H), 1.70–1.88 (m, 4H), 2.45–2.82 (m, 14H), 3.24 (t, 4H, J = 4.8 Hz, Ar-$N(CH_2)_2$), 6.52

(d, 1H, $J = 2.4$ Hz), 6.58–6.60 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.4$ Hz), 6.84–6.87 (t, 2H, $J = 7.2$ Hz), 6.89–6.94 (m, 2H), 7.26(t, 2H, $J = 7.2$ Hz).

The product was converted into the corresponding trihydrochloride salt, mp 122–125 °C. Anal. Calcd for $C_{26}H_{37}N_3O \cdot 3HCl$: C, H, N.

Synthesis of 7-[(2-(4-Phenylpiperazin-1-yl)ethyl)(2-(thiophen-2-yl)ethyl)amino]-5,6,7,8-tetrahydronaphthalen-2-ol (6d). Compound **5d** (0.41 g, 0.86 mmol) was reacted with 1 M BBr_3/CH_2Cl_2 (2.58 mL, 2.58 mmol) in CH_2Cl_2 (20 mL) following procedure G to yield **6d** (0.15 g, 38%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45–1.49 (m, 1H), 1.91–1.93 (m, 1H), 2.54–2.98 (m, 17H), 3.24 (t, 4H, $J = 4.4$ Hz, Ar-N(CH_2)$_2$), 6.43–6.55 (m, 2H, Ar-H), 6.80–6.94 (m, 6H, Ar-H), 7.11–7.12 (d, 1H, $J = 5.2$ Hz, Ar-H), 7.23–7.27 (m, 2H, Ar-H).

The product was converted into the corresponding trioxalate salt, mp 147–151 °C. Anal. Calcd for $C_{28}H_{35}N_3OS \cdot 2C_2H_2O_4$: C, H, N.

Procedure H. Synthesis of 6-[(2-(4-Phenylpiperazin-1-yl)ethyl)(propyl)amino]-5,6,7,8-tetrahydronaphthalene-2,3-diol (6e). A mixture of 580 mg (1.33 mmol) of **3** and 10 mL of 48% HBr was refluxed under N_2 for 3 h. The reaction mixture was then evaporated to dryness. The resulting solid was then crystallized with acetone/methanol to get a white solid of **6e** in HBr salt form (0.691 mg, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88–0.93 (t, $J = 7.2$ Hz, 3H, $CH_3CH_2CH_2N$), 1.35–150 (m, 4H), 1.71–1.85 (m, 2H), 2.41–2.60 (br s, 2H, CH_2N), 2.65 (br s, 4H, N(CH_2)$_2$), 2.70–2.73 (m, 7H), 3.25 (br s, 4H, N(CH_2)$_2$), 6.45–6.48 (m, 2H, Ar-H), 6.84–6.87 (m, 1H, Ar-H), 6.89–6.92 (m, 2H, Ar-H), 7.23–7.27 (m, 2H, Ar-H).

The product was converted into the corresponding trihydrobromide salt, mp 185–188 °C. Anal. Calcd for $C_{25}H_{35}N_3O_2 \cdot 3HBr \cdot H_2O$: C, H, N.

Synthesis of 6-[(4-(4-Phenylpiperazin-1-yl)butyl)(propyl)amino]-5,6,7,8-tetrahydronaphthalene-2,3-diol (6f) (Procedure H). Compound **5f** (240 mg, 0.52 mmol) and 10 mL of 48% HBr was refluxed by following procedure H to provide **6f** in HBr salt form (0.265 g, 75%): ^{1}H NMR (400 MHz, CD_3OD) δ 1.04–1.08 (t, $J = 7.2$ Hz, 3H, $CH_3CH_2CH_2N$), 1.81–1.94 (m, 8H), 2.83–2.85 (m, 2H), 2.99–3.05 (m, 6H), 3.09–3.21 (m, 4H), 3.40 (br s, 2H), 3.73–3.8 (t, $J = 4.8$ Hz, 4H, N(CH_2)$_2$), 6.52–6.5 (m, 2H, Ar-H), 6.95–6.98 (m, 1H, Ar-H), 7.06–7.08 (m, 2H, Ar-H), 7.28–7.32 (m, 2H, Ar-H).

The product was converted into the corresponding trihydrobromide salt, mp 180–183 °C. Anal. Calcd for $C_{27}H_{39}N_3O_2 \cdot 3HBr \cdot 1.5H_2O$: C, H, N.

Synthesis of 7-Methoxy-*N*-[4-(4-phenylpiperazin-1-yl)butyl]-1,2,3,4-tetrahydronaphthalen-2-amine (7). Compound **2c** (2.56 g, 10.97 mmol) was reacted with 7-methoxy-2-tetralone (2.32 g, 13.16 mmol) and $Na(OAc)_3BH$ (6.98 g, 32.91 mmol) and HOAc (0.4 mL) in 1,2-dichloroethane (30 mL) by following procedure C. The crude product was purified by flash chromatography (ethyl acetate/methanol/triethylamine = 85:10:5) to afford the product **7** (2.72 g, 60%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48–1.56 (m, 4H), 1.95–1.97 (m,2H), 2.33–2.36 (t, 2H, $J = 6.8$ Hz), 2.52–2.55 (m, 5H), 2.64–2.79 (m, 4H), 2.82–2.94 (m, 2H), 3.12–3.15 ((t, 4H, $J = 4.8$ Hz, Ar-N(CH_2)$_2$), 3.68 (s, OCH_3), 6.54–6.63 (m, 2H, Ar-H), 6.76–6.93 (m, 4H, Ar-H), 7.17–7.21 (m, 2H, Ar-H).

Synthesis of 2-Methoxy-*N*-(7-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-2-phenyl-*N*-[4-(4-phenylpiperazin-1-yl)butyl]acetamide (8). A mixture of (*R*)-(−)-α-methoxyphenylacetic acid (1.013 g, 6.09 mmol), 1,3-(dimethylamino)propyl]-3-ethylcarbodiimide-hydrochloride (EDCI) (1.17 g, 6.09 mmol), 1-hydroxybenzotriazole (HOBT) (0.87 g, 6.40 mmol), and Et_3N (0.85 mL, 6.09 mmol) in anhydrous methylene chloride (50 mL) was stirred at room temperature under nitrogen atmosphere for 1 h. A solution of compound **7** (1.20 g, 3.05 mmol) in anhydrous methylene chloride was added into the reaction mixture under nitrogen at room temperature and stirred for 20 h. The mixture was diluted with CH_2Cl_2 and washed with 5% HCl acid solution, sodium bicarbonate, and brine. The solvent was removed under vacuum, dried over Na_2SO_4, and purified by column chromatography over silica gel using the solvent system ethyl acetate/methanol/triethylamine (95:4:1) to afford 1.22 g of compound **8** (1.22 g, 74%), which is a mixture of two diastereomers.

Separation of Diastereomers of Compounds 8a and 8b. The diastereomeric mixture of compound **8** (1.22 g) was separated into the corresponding pure diasteriomers **8a** and **8b** by semipreparative HPLC using a normal phase column (Nova-Pak silica 6 μm). The mobile phase used was 6.5% isopropanol in hexane with a flow rate of 16 mL/min. Two fractions were eluted with a retention times of 11.5 min for (+,−)-**8a** and 14.5 min for (−,−)-**8b**. Final purity of the separated diasterieomers was checked by an analytical normal phase column (Nova-Pak silica 60 Å, 4 μm) using the same mobile phase with a flow rate of 1 mL/min. Pure diasteriomers **8a** and **8b** were eluted from the analytical column at 9.5 and 12.0 min, respectively. Compound **8a** was isolated in 0.57 g (34.54%), and compound **8b** was isolated in 0.46 g (28%).

8a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.80 (m, 6H), 2.26–2.38 (m,1H), 2.39–2.48 (t, 2H, $J = 6.4$ Hz), 2.49–2.64 (m, 6H), 2.75–2.94 (m, 2H), 3.10–3.34 (m, 6H), 3.53 (s, 3H), 3.74 (s, 3H), 5.09 (s, 1H), 6.52 (d, 1H, $J = 2.4$ Hz), 6.68 (d, 1H, $J = 8.4$ Hz), 6.85 (t, 1H, $J = 7.2$ Hz), 6.91 (d, 2H, $J = 7.6$ Hz), 6.96 (m, 1H), 7.20–7.50 (m, 7H).

8b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35–1.79 (m, 6H), 2.26–2.38 (m,1H), 2.39–2.49 (t, 2H, $J = 6.4$ Hz), 2.51–2.64 (m, 6H), 2.75–2.94 (m, 2H), 3.11–3.34 (m, 6H), 3.46 (s, 3H), 3.74 (s, 3H), 5.03 (s, 1H), 6.45 (d, 1H, $J = 2.4$ Hz), 6.67 (d, 1H, $J = 8.4$ Hz), 6.85 (t, 1H, $J = 7.2$ Hz), 6.90 (d, 2H, $J = 7.6$ Hz), 6.96 (m, 1H), 7.20–7.50 (m, 7H).

Synthesis of (+)-7-Methoxy-*N*-[4-(4-phenylpiperazin-1-yl)butyl]-1,2,3,4-tetrahydronaphthalen-2-amine ((+)-7). Potassium *tert*-butoxide (0.57 g, 5.09 mmol) was added into a solution of **8a** (0.46 g, 0.85 mmol) in THF at room temperature under nitrogen atmosphere and stirred overnight. TLC revealed complete consumption of the starting material. The solvent was removed, and the residue was suspended in EtOAc and washed with water, NH_4Cl solution, and brine. The solution was dried and concentrated under vacuum. Into the solution of this mixture in dry THF was added a solution of MeLi (0.074 g, 3.39 mmol) at room temperature under nitrogen atmosphere and stirred for 0.5 h when TLC revealed completion of the reaction. The mixture was quenched with water, the solvent was evaporated, and the residue was suspended in EtOAc. The organic layer was washed with water and brine and dried over Na_2SO_4. The solution was concentrated under vacuum, and the product was purified by column chromatography using the solvent system EtOAc/MeOH/Et_3N (90:10:1) to afford the optically pure amine (+)-**7** (0.29 g, 86.94%). Optical rotation of (+)-**7** was $[\alpha]_D = +10.95$ (*c* 1 in MeOH): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40–1.80 (m, 6H), 2.00–2.10 (m, 1H), 2.42 (t, 2H, $J = 6.8$ Hz), 2.52–2.66 (m, 5H), 2.68–2.87 (m, 4H), 2.88–3.05 (m, 2H), 3.21 (t, 4H, $J = 4.8$ Hz), 3.77 (s, 3H), 6.61 (d, 1H, $J = 2.4$ Hz), 6.69 (dd, 1H, $J = 2.4$ Hz, $J = 8.0$ Hz), 6.85 (t, 1H, $J = 7.2$ Hz), 6.93 (d, 2H, $J = 7.6$ Hz), 7.00 (d, 1H, $J = 8.4$ Hz), 7.26 (t, 2H, $J = 8.0$ Hz).

Synthesis of (−)-7-Methoxy-*N*-[4-(4-phenylpiperazin-1-yl)butyl]-1,2,3,4-tetrahydronaphthalen-2-amine ((−)-7). Compound **8b** (0.45 g, 0.85 mmol) was hydrolyzed under similar conditions as described above to afford the optically pure amine (−)-**7** (0.28 g, 85%). Optical rotation of (–)-**7** was $[\alpha]_D = -10.3$ (*c* 1 in MeOH): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48–1.56 (m, 4H), 1.95–1.97 (m, 2H), 2.33–2.36 (t, 2H, $J = 6.8$ Hz), 2.52–2.55 (m, 5H), 2.64–2.79 (m, 4H), 2.82–2.94 (m, 2H), 3.12–3.15 ((t, 4H, $J = 4.8$ Hz, Ar-N(CH_2)$_2$), 3.68 (s, OCH_3), 6.54–6.63 (m, 2H, Ar-H), 6.76–6.93 (m, 4H, Ar-H), 7.17–7.21 (m, 2H, Ar-H).

Synthesis of (+)-7-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl-[4-(4-phenylpiperazin-1-yl)butyl]prop-2-ynylamine ((+)-9). A solution of (+)-**7** (0.17 g, 0.43 mmol) in a mixture of THF and DMF (5:1) at 24 °C under nitrogen was treated with NaH (0.072 g, 3 mmol). The reaction mixture was stirred for 30 min before propargyl bromide (0.31 g, 2.58 mmol) was added. The reaction mixture was stirred for 6 h at 50 °C and then was poured onto water (15 mL). THF was removed under vacuum, and the reaction

mixture was extracted with ether (3 × 100 mL); the combined organic layer was washed thoroughly with brine, dried over Na_2SO_4, and evaporated under vacuum. The crude mass was purified by column chromatography on a silica gel column using the solvent system ethyl acetate/methanol/triethylamine = 95:4:1 to yield pure compound (+)-**9** (0.11 g, 52%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55–1.67 (m, 5H), 2.11–2.18 (m, 2H), 2.41 (t, 2H, J = 6.4 Hz), 2.58–2.66 (m, 5H), 2.68–2.86 (m, 4H), 2.96–2.98 (m, 2H), 3.18–3.21 (t, 4H, J = 5.2 Hz), 3.51–3.52 (m, 2H, $-NCH_2CCH$), 3.75 (s, 3H, $-OCH_3$), 6.62–6.69 (m, 2H, Ar-H), 6.82–6.97 (m, 4H), 7.32–7.27 (t, 2H, J = 8.4 Hz, Ar-H).

Synthesis of (−)-7-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl-[4-(4-phenylpiperazin-1-yl)butyl]prop-2-ynylamine ((−)-9). Compound (−)-**7**(0.15 g, 0.38 mmol) was reacted under similar conditions as described above to afford the optically pure amine (−)-**9** (0.12 g, 55%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55–1.66 (m, 5H), 2.11–2.20 (m, 2H), 2.42 (t, 2H, J = 6.4 Hz), 2.58–2.70 (m, 5H), 2.68–2.85 (m, 4H), 2.96–2.98 (m, 2H), 3.18–3.21 (t, 4H, J = 5.2 Hz), 3.51–3.53 (m, 2H, $-NCH_2CCH$), 3.75 (s, 3H, $-OCH_3$), 6.62–6.71 (m, 2H, Ar-H), 6.82–6.96 (m, 4H), 7.33–7.27 (t, 2H, J = 8.4 Hz, Ar-H).

Synthesis of (+)-7-{[4-(4-Phenylpiperazin-1-yl)butyl]prop-2-ynylamino}-5,6,7,8-tetrahydronaphthalen-2-ol ((+)-10). Boron tribromide (1 M solution in dichloromethane) (0.83 mL, 0.834 mmol) was added into a solution of (+)-**9** (0.12 g, 0.28 mmol) in anhydrous CH_2Cl_2 (20 mL) at −40 °C for 2 h and then at overnight at room temperature to give product (+)-**10** (0.08 g, 67%) (procedure G): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51–1.64 (m, 5H), 2.05–2.11 (m, 2H), 2.42–2.46 (t, 2H, J = 8.0), 2.64–2.97 (m, 11H), 3.21–3.23 (t, 4H, Ph-N$(CH_2)_2$, J = 6.0 Hz), 3.45–3.49 (m, 2H, $-NCH_2CCH$), 6.48–6.66 (m, 2H, Ar-H), 6.84–6.93 (m, 4H, Ar-H), 7.23–7.27 (m, 2H, Ar-H).

The product was converted into the corresponding trihydrobromide salt. Anal. Calcd for $C_{27}H_{35}N_3O\cdot 3HBr\cdot 2H_2O$: C, H, N. Compound was highly hygroscopic.

Synthesis of (−)-7-{[4-(4-Phenylpiperazin-1-yl)butyl]prop-2-ynylamino}-5,6,7,8-tetrahydronaphthalen-2-ol ((−)-10). Compound (−)-**9** (0.15 g, 0.35 mmol) was reacted under similar conditions as described in procedure G to afford the optically pure amine (−)-**10** (0.083 g, 70%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51–1.68 (m, 5H), 2.05–2.10 (m, 2H), 2.42–2.48 (t, 2H, J = 8.0), 2.64–2.97 (m, 11H), 3.21–3.23 (t, 4H, Ph-N$(CH_2)_2$, J = 6.0 Hz), 3.45–3.50 (m, 2H, $-NCH_2CCH$), 6.48–6.67 (m, 2H, Ar-H), 6.84–6.95 (m, 4H, Ar-H), 7.23–7.30 (m, 2H, Ar-H).

The product was converted into the corresponding trihydrobromide salt. Anal. Calcd for $C_{27}H_{35}N_3O\cdot 3HBr\cdot 2.2\ H_2O$: C, H, N. Compound was highly hygroscopic.

Synthesis of (+)-*N*-(7-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-[4-(4-phenylpiperazin-1-yl)butyl]propionamide ((+)-11). Compound (+)-**7** (0.17 g, 0.44 mmol) was reacted with propionyl chloride (0.1 mL, 1.15 mmol) and Et_3N (1.0 mL) in dry CH_2Cl_2 (10 mL) by following procedure D. The crude product was purified by flash chromatography using the solvent system EtOAc/MeOH = 95:5 to afford (+)-**11** (0.16 g, 85%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10–1.22 (m, 3H), 1.48–1.74 (m, 4H), 1.86–2.04 (m, 2H), 2.32–2.48 (m, 4H), 2.52–2.68 (m, 4H), 2.74–3.06 (m, 4H), 3.12–3.36 (m, 6H), 3.74–3.76 (s, 3H), 6.58–6.60 (d, 1H, J = 2.4 Hz), 6.69–6.73 (dd, 1H, J = 2.4 Hz, J = 8.0 Hz), 6.81–6.90 (m, 1H), 6.92 (d, 2H, J = 8.4 Hz), 6.96–7.06 (m, 1H), 7.20–7.32 (m, 1H).

Synthesis of (−)-*N*-(7-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-[4-(4-phenylpiperazin-1-yl)butyl]propionamide ((−)-11). Compound (−)-**7** (0.20 g, 0.52 mmol) was reacted under similar conditions as described above to afford the optically pure amine (−)-**11** (0.18 g, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10–1.22 (m, 3H), 1.46–2.04 (m, 6H), 2.33–2.52 (m, 4H), 2.54–2.70 (m, 4H), 2.76–3.06 (m, 4H), 3.10–3.36 (m, 6H), 3.75–3.77 (s, 3H), 6.56–6.64 (d, 1H, J = 8.0 Hz), 6.66–6.76 (m, 1H), 6.82–6.90 (m, 1H), 6.92 (d, 2H, J = 8.0 Hz), 6.96–7.05 (m, 1H), 7.20–7.30 (m, 1H).

Synthesis of (+)-7-Methoxy-*N*-[4-(4-phenylpiperazin-1-yl)butyl]-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine ((+)-12). Compound (+)-**11** (0.13 g, 0.29 mmol) was reacted with $LiAlH_4$ (0.06 g, 1.58 mmol) in dry THF (15 mL) by following procedure E. The crude product was purified by flash chromatography using the solvent system EtOAc/MeOH = 90:10 to afford compound (+)-**12** (0.12 g, 94%): $[\alpha]_D$ = +0.77 (*c* 19.5 mg/mL in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, 3H, J = 7.2 Hz), 0.93–1.00 (m, 1H), 1.40–1.70 (m, 8H), 1.95–2.05 (m, 1H), 2.41 (t, 2H, J = 6.8 Hz), 2.48 (t, 2H, J = 6.8 Hz), 2.54 (t, 2H, J = 6.8 Hz), 2.61 (t, 4H, J = 5.2 Hz), 2.68–2.90 (m, 4H), 3.21 (t, 4H, J = 5.2 Hz), 3.76 (s, 3H), 6.62 (d, 1H, J = 3.0 Hz), 6.68 (dd, 1H, J = 2.8 Hz, J = 8.4 Hz), 6.85 (t, 1H, J = 7.2 Hz), 6.93 (d, 2H, J = 7.6 Hz), 6.98 (d, 1H, J = 8.0 Hz), 7.26 (t, 1H, J = 7.6 Hz).

Synthesis of (−)-7-Methoxy-*N*-[4-(4-phenylpiperazin-1-yl)butyl]-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine ((−)-12). Compound (−)-**11** (0.13 g, 0.29 mmol) was reacted under similar condition as reported in procedure E to afford the optically pure (−)-**12** (0.10 g, 78%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, 3H, J = 7.2 Hz), 0.92–1.00 (m, 1H), 1.40–1.80 (m, 8H), 1.94–2.10 (m, 1H), 2.41 (t, 2H, J = 7.2 Hz), 2.48 (t, 2H, J = 6.8 Hz), 2.54 (t, 2H, J = 6.8 Hz), 2.61 (t, 4H, J = 4.8 Hz), 2.66–2.88 (m, 4H), 3.21 (t, 4H, J = 4.8 Hz), 3.77 (s, 3H), 6.62 (d, 1H, J = 2.8 Hz), 6.67 (dd, 1H, J = 2.8 Hz, J = 8.4 Hz), 6.85 (t, 1H, J = 7.2 Hz), 6.93 (d, 2H, J = 8.0 Hz), 6.98 (d, 1H, J = 8.0 Hz), 7.26 (t, 1H, J = 7.6 Hz).

Synthesis of (+)-7-[(4-(4-Phenylpiperazin-1-yl)butyl)(propyl)amino]-5,6,7,8-tetrahydronaphthalen-2-ol ((+)-13). Compound (+)-**12** (0.1 g, 0.23 mmol) was reacted with boron tribromide (1 M solution in dichloromethane, 0.70 mL, 0.70 mmol) in dry CH_2Cl_2 (10 mL) at −40 °C by following procedure G. The crude product was purified by flash chromatography using the solvent system EtOAc/MeOH/Et_3N = 95:4:1 to afford compound (+)-**13** (0.07 g, 73%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 7.6 Hz), 1.40–1.64 (m, 7H), 1.94–2.03 (m, 1H), 2.38–2.58 (m, 6H), 2.64 (t, 4H, J = 4.4 Hz), 2.66–2.84 (m, 4H), 2.88–3.00 (m, 1H), 3.22 (t, 4H, J = 4.8 Hz), 6.49 (d, 1H, J=2.0 Hz), 6.55 (dd, 1H, J = 2.4 Hz, J = 8.0 Hz), 6.82–6.96 (m, 4H), 7.25 (t, 2H, J = 8.4 Hz).

Free base was converted into its HCl salt, mp 110–113 °C. Anal. Calcd for $(C_{27}H_{39}N_3O\cdot 3HCl\cdot 0.8H_2O$: C, H, N.

Synthesis of (−)-7-[(4-(4-Phenylpiperazin-1-yl)butyl)(propyl)amino]-5,6,7,8-tetrahydronaphthalen-2-ol ((−)-13). Compound (−)-**12** (0.14 g, 0.32 mmol) was reacted with 1 M BBr_3/CH_2Cl_2 (1.0 mL, 1.0 mmol) (procedure G) to give (−)-**13** (0.95 g, 70%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 7.6 Hz), 1.40–1.66 (m, 7H), 1.94–2.06 (m, 1H), 2.38–2.58 (m, 6H), 2.64 (t, 4H, J = 4.4 Hz), 2.66–2.84 (m, 4H), 2.88–3.06 (m, 1H), 3.22 (t, 4H, J = 4.8 Hz), 6.53 (d, 1H, J = 2.0 Hz), 6.58 (dd, 1H, J = 2.4 Hz, J = 8.0 Hz), 6.80–6.98 (m, 4H), 7.26 (t, 2H, J = 8.4 Hz).

Free base was converted into its HCl salt, mp 112–115 °C. Anal. Calcd for $C_{27}H_{39}N_3O\cdot 3HCl\cdot 0.6H_2O$: C, H, N.

Synthesis of 7-Nitro-2-tetralone (14). Into cold (−30 °C) concentrated nitric acid (8 mL, 90%) was added 2-tetralone dropwise (0.66 mL, 5.0 mmol) with vigorous stirring under N_2. The reaction mixture was stirred for 8 min and poured into a beaker containing a solution of 4.0 M NaOH (40 mL) and ice. The solution was decanted, and the yellow precipitate was dissolved in EtOAC (50 mL), washed with water (2 × 50 mL), and dried over $MgSO_4$. The crude product was purified by flash chromatography over a silica gel column using hexane/ethyl acetate (4:1) to afford the title compound **14** (0.102 g, 11%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.60 (t, J = 6.4 Hz, 2H), 3.18 (t, J = 6.4 Hz, 2H), 3.69 (s, 2H), 7.42 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 2.4 Hz, 1H), 8.10 (dd, J = 2.4 Hz, J = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 28.64, 37.43, 44.98, 95.00, 122.38, 123.51, 128.85.

Synthesis of 7-Nitro-*N*-[2-(4-phenylpiperazin-1-yl)ethyl)]-1,2,3,4-tetrahydronaphthalen-2-amine (15). Into a solution of 7-nitro-2-tetralone (0.29 g, 1.52 mmol) and acetic acid (0.3 mL) in 1,2-dichloroethane (40 mL) was added a solution of 2-(4-phenylpiperazin-1-yl)ethanamine **2a** (0.37 mg, 1.80 mmol) in 1,2-dichloroethane (10 mL). The reaction mixture was stirred for 1 h at room temperature under N_2, followed by the addition of a solution of $NaBH_3CN$ (0.30 g, 4.77 mmol) in MeOH (3 mL). The reaction

mixture was stirred overnight and then neutralized with a solution of $NaHCO_3$. The organic phase was separated and dried over $MgSO_4$. The crude product was purified by flash chromatography over a silica gel column using ethyl acetate/methanol (19:1) to afford the title compound **15** (0.37 g, 65%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.62–1.76 (m, 1H), 2.04–2.16 (m, 1H), 2.56–2.76 (m, 8H), 2.82–2.93 (m, 3H), 2.95–3.06 (m, 2H), 3.07–3.16 (m,1H), 3.16–3.25 (t, J = 4.8 Hz, 4H), 6.86 (t, J = 7.2 Hz, 1H), 6.92 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 1H), 7.26 (t, J = 8.0 Hz, 2H), 7.93 (d, J = 2.0 Hz, 1H), 7.95 (s, 1H).

Synthesis of *N*-(7-Nitro-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-[2-(4-phenylpiperazin-1-yl)ethyl]propionamide (16). Into a solution of 7-nitro-*N*-[2-(4-phenylpiperazin-1-yl)ethyl]-1,2,3,4-tetrahydronaphthalen-2-amine (**15**) (0.31 g, 0.82 mmol) and Et_3N (0.85 mL) in dry CH_2Cl_2 (40 mL) under N_2 at 0 °C was added propionyl chloride (0.16 mL, 1.83 mmol) dropwise. The solution was stirred for 4 h followed by the addition of a saturated solution of NaCl. The organic phase was separated and dried over $MgSO_4$. The crude product was purified by flash chromatography over a silica gel column using ethyl acetate to afford the title compound **16** (0.27 g, 77%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.12 (m, 3H), 1.94–2.16 (m, 2H), 2.36–2.50 (m, 2H), 2.54–2.80 (m, 6H), 2.90–3.16 (m, 5H), 3.20 (t, J = 4.8 Hz, 4H), 3.40–3.60 (m, 2H), 6.80–6.90 (dd, J = 7.2 Hz, 2H), 6.92 (d, J = 8.0 Hz, 1H), 7.18–7.32 (m, 3H), 7.90–8.02 (m, 2H).

Synthesis of *N*-(7-Amino-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-[2-(4-phenylpiperazin-1-yl)ethyl]propionamide (17). Into a solution of *N*-(7-nitro-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-[2-(4-phenylpiperazin-1-yl)ethyl]propionamide (**16**) (0.07 g, 0.15 mmol) in dry methanol (10 mL) was added 10% Pd/C (0.02 g). The reaction mixture was stirred under hydrogen for 4 h and filtered through Celite. Solvent was evaporated to afford compound **17** (0.06 g, 93%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.10–1.22 (t, J = 7.2 Hz, 3H), 1.86–2.08 (m, 2H), 2.34–2.50 (m, 2H), 2.56–3.10 (m, 11H), 3.16–3.26 (t, J = 4.8 Hz, 1H), 3.26–3.50 (m, 4H), 3.56–3.78 (m, 2H), 3.94–4.08 (m, 1H), 6.41 (s, 1H), 6.46–6.56 (dd, J = 2.0 Hz, J = 8.0 Hz, 1H), 6.80–7.00 (m, 4H), 7.27 (t, J = 8.0 Hz, 2H).

Synthesis of N^2-[2-(4-Phenylpiperazin-1-yl)ethyl]-N^2-propyl-1,2,3,4-tetrahydronaphthalene-2,7-diamine (18). Into a suspension of $LiAlH_4$ (0.03 g, 0.74 mmol) in dry THF (20 mL) at 0 °C under N_2 was added *N*-(7-amino-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-(2-(4-phenylpiperazin-1-yl)ethyl)propionamide (**17**) (0.06 g, 0.15 mmol) in dry THF (10 mL) to afford compound **18** (0.05 g, 86%) (procedure E): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, J = 7.2 Hz, 3H), 1.40–1.52 (q, J = 7.2 Hz, J = 14.0 Hz, 2H), 1.94–2.04 (m, 1H), 2.46–2.56 (t, J = 8.0 Hz, 4H), 2.60–2.84 (m, 11H), 2.88–3.00 (m 1H), 3.20 (t, J = 4.8 Hz, 4H), 3.50 (br s, 2H), 6.44 (d, J = 2.0 Hz, 1H), 6.46–6.50 (dd, J = 2.4 Hz, J = 8.0 Hz, 1H), 6.82–6.90 (m, 2H), 6.93 (d, J = 8.0 Hz, 2H), 7.26 (t, J = 8.0 Hz, 2H).

Free base was converted into the tetrahydrochloride salt, mp 117–120 °C. Anal. Calcd for $C_{25}H_{36}N_4 \cdot 4HCl \cdot 0.4H_2O$: C, H, N.

Synthesis of 8-[(2-(4-Phenylpiperazin-1-yl)ethyl)(propyl)amino]-6,7,8,9-tetrahydro-1*H*-benzo[*e*]indole-1,2(3*H*)-dione (19). Chloral hydrate (0.063 g, 0.38 mmol) and sodium sulfate (0.44 g, 3.08 mmol) were dissolved in 4 mL of water and warmed in an oil bath at 60 °C. Then N^2-[2-(4-phenylpiperazin-1-yl)ethyl]-N^2-propyl-1,2,3,4-tetrahydronaphthalene-2,7-diamine (**18**) (0.136 g, 0.35 mmol) in 1 N HCl (5 mL) and $NH_2OH \cdot HCl$ (0.077 g, 1.10 mmol) in water (2 mL) were successively added. After the addition was completed, the reaction mixture was heated at 80 °C for 20 min and allowed to cool to room temperature. Ethyl acetate was added as well as diluted ammonium hydroxide solution (until pH 8). The organic phase was separated and dried over $MgSO_4$. The solution was filtered and solvent evaporated to afford an off-white solid. This product was added portion-wise to a rapidly stirred concentrated sulfuric acid (5 mL) at 80 °C. After 20 min, the reaction mixture was allowed to cool at room temperature, poured onto crushed ice, and basified with diluted ammonium hydroxide. Ethyl acetate was added, and the organic phase was separated and dried over $MgSO_4$. The crude product was purified by flash chromatography over a silica gel column using ethyl acetate/methanol (19:1) to afford the title compound **19** (0.03 g, 20%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, J = 7.2 Hz, 3H), 1.16–1.34 (br s, 1H), 1.42–1.54 (q, J = 8.0 Hz, J = 14.4 Hz, 2H), 1.55–1.70 (m, 1H), 1.96–2.08 (m, 1H), 2.46–2.60 (m, 4H), 2.61–2.90 (m, 9H), 2.92–3.04 (m, 1H), 3.20 (t, J = 4.8 Hz, 4H), 6.62 (d, J = 8.0 Hz, 1H), 6.85 (t, J = 7.2 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.0 Hz, 1H), 7.26 (t, J = 8.0 Hz, 2H).

Synthesis of 8-[(2-(4-Phenylpiperazin-1-yl)ethyl)(propyl)amino]-6,7,8,9-tetrahydro-1*H*-benzo[*e*]indol-2(3*H*)-one (20). A solution of 8-[(2-(4-phenylpiperazin-1-yl)ethyl)(propyl)amino]-6,7,8,9-tetrahydro-1*H*-benzo[*e*]indole-1,2(3*H*)-dione (**19**) (0.03 g, 0.06 mmol) in hydrazine (98%) was refluxed for 30 min in an oil bath. The reaction mixture was poured onto an ice–water bath, and ethyl acetate was added (20 mL). The organic phase was separated and dried over $MgSO_4$. Evaporation of the solvent and purification by column chromatography afforded the corresponding hydrazone, which was dissolved in a previously prepared solution of sodium metal (0.2 g) in absolute ethanol (5 mL). The reaction mixture was stirred at 80 °C under N_2 for 30 min, allowed to cool at room temperature, and poured onto an ice–water bath. Ethyl acetate (2 × 30 mL) was added, and the organic phase was separated and dried over $MgSO_4$. The crude product was purified by flash chromatography over a silica gel column using ethyl acetate/methanol (19:1) to afford the target compound **20** (0.013 g, 45%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.84–0.96 (m, 3H), 1.20–1.30 (br s, 1H), 1.44–1.68 (m, 3H), 1.98–2.10 (m, 1H), 2.44–2.60 (m, 4H), 2.62–2.92 (m, 9H), 2.94–3.08 (m, 1H), 3.21 (t, J = 4.8 Hz, 4H), 3.31 (s, 2H), 6.65 (d, J = 8.0 Hz, 1H), 6.85 (t, J = 8.0 Hz, 1H), 6.88–7.00 (m, 3H), 7.26 (t, J = 8.0 Hz, 2H), 8.47 (br s, 1H).

Free base was converted into the trihydrochloric salt, mp 133–136 °C. Anal. Calcd for $C_{27}H_{36}N_4O \cdot 3HCl \cdot 1.8H_2O$.

Synthesis of 5-Methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine ((±)-21). *n*-Propylamine (9.33 mL, 1.75 mmol) was reacted with 5-methoxy-2-tetralone (10 g, 56.75 mmol), $NaCNBH_3$ (10.69 g, 170.24 mmol), and HOAc (8.4 mL) in 1,2-dichloroethane (100 mL) by following procedure C. The crude product was dissolved in ethanol and was converted into hydrochloride salt by treatment with HCl in ether solution. The pure precipitated HCl salt (±)-**21** (12.73 g, 88%) was filtered off and washed with ether and dried under vacuum. This racemic salt was converted to free base by using saturated $NaHCO_3$ solution. Free base was extracted with ethyl acetate and was subjected to resolution in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, 3H, J = 7.2 Hz, CH_2CH_3), 1.65–1.77 (m, 3H), 2.18–2.23 (m, 1H), 2.53−2.62 (m, 1H), 2.76–2.85 (m, 3H), 2.88−2.98 (dq, 1H, J_1 = 18 Hz, J_2 = 3.2 Hz), 3.06–3.15 (m, 2H), 3.8 (s, 3H, $-OCH_3$), 5.07 (br s, 1H, −NH), 6.68 (t, 2H, J = 8.8 Hz, −CHC*H*CH), 7.10 (t, 1H, J = 2.4 Hz, J = 8.0 Hz).

Resolution of 5-Methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine ((±)-20). Racemic (±)-**21** was resolved into its (+)- and (−)-isomers by using both (−)- and (+)-isomers of the synthetic resolving agent 4-(2-chlorophenyl)-5,5-dimethyl-2-hydroxy-1,3,2-dioxaphosphorinane 2-oxide. This optically active resolving agent was prepared according to the published procedure.[47] Compound (±)-**21** (5.22 g, 23.80 mmol) and (+)-4-(2-chlorophenyl)-5,5-dimethyl-2-hydroxy-1,3,2-dioxaphosphorinane 2-oxide (6.52 g, 23.56 mmol) were dissolved by warming in 25 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 5.07 g of the salt ($[\alpha]_D = -5.6°$, *c* 1 in methanol). Further recrystallization (two times) from hot isopropanol yielded the salt, 4.5 g ($[\alpha]_D = -13.4°$, *c* 1 in methanol) (yield = 76.27%). 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 × 100 mL), dried over Na_2SO_4, and evaporated to dryness to yield (−)-**21**, 1.99 g (76.25%), $[\alpha]_D$ of the HCl salt of (−)-**21** = −70.6°, *c* 1 in methanol).

(±)-**21** (3.12 g, 14.23 mmol) was similarly treated by using (−)-4-(2-chlorophenyl)-5,5-dimethyl-2-hydroxy-1,3,2-dioxaphosphorinane 2-oxide (3.94 g, 14.23 mmol). Recrystallization from hot isopropanol yielded the salt, 3.94 g (56%), $[\alpha]_D = +13.2$, *c* 1 in methanol). 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 (+)-**21**, 1.74 g, (56%), $[\alpha]_D$ of the HCl salt of (+)-**21** = +69.4°, *c* 1 in methanol).

Synthesis of 6-(Propylamino)-5,6,7,8-tetrahydronaphthalen-1-ol ((±)-21a). Compound (±)-**21** (0.77 g, 3.51 mmol) was reacted with boron tribromide (1 M solution in dichloromethane, 7.8 mL, 7.81 mmol) in dry CH_2Cl_2 (10 mL) at −40 °C by following procedure G. The crude product was purified by flash chromatography using the solvent system hexane/EtOAc = 60:40 to afford compound (±)-**21a** (0.70 g, 97%): ^{1}H NMR (400 MHz, CD_3OD) δ 1.05–1.08 (t, 3H, J = 7.6 Hz, CH_2CH_3), 1.74–1.85 (m, 3H), 2.32–2.37 (m, 1H), 2.61−2.70 (m, 1H), 2.82–2.90 (m, 1H), 2.96 −3.03 (dq, 1H, J_1 = 17.6 Hz, J_2 = 3.6 Hz), 3.08–3.12 (m, 2H), 3.19–3.24 (m, 1H), 3.44–3.52 (m, 1H), 6.61–6.63 (d, 2H, J = 8.0 Hz, −CHC*H*CH), 6.98 (t, 1H, J = 2.4 Hz, J = 8.0 Hz).

Synthesis of (+)-6-(Propylamino)-5,6,7,8-tetrahydronaphthalen-1-ol ((+)-21a). Compound (+)-**21** (0.6 g, 2.74 mmol) was reacted under similar conditions as reported above (procedure G) to afford the optically pure (+)-**21a** (0.55 g, 98%): ^{1}H NMR (400 MHz, CD_3OD) δ 1.05–1.07 (t, 3H, J = 7.6 Hz, CH_2CH_3), 1.74–1.85 (m, 3H), 2.32–2.39 (m, 1H), 2.61−2.69 (m, 1H), 2.82–2.92 (m, 1H), 2.96 −3.00 (dq, 1H, J_1 = 17.6 Hz, J_2 = 3.6 Hz), 3.09–3.14 (m, 2H), 3.19–3.25 (m, 1H), 3.44–3.50 (m, 1H), 6.61–6.63 (d, 2H, J = 8.0 Hz, −CHC*H*CH), 6.98 (t, 1H, J = 2.4 Hz, J = 8.0 Hz).

Synthesis of (−)-6-(Propylamino)-5,6,7,8-tetrahydronaphthalen-1-ol ((−)-21a). Compound (−)-**21** (0.80 g, 3.65 mmol) was reacted under similar conditions as reported above (procedure G) to afford the optically pure (−)-**21a** (0.72 g, 96%): ^{1}H NMR (400 MHz, CD_3OD) δ 1.05–1.08 (t, 3H, J = 7.6 Hz, CH_2CH_3), 1.74–1.85 (m, 3H), 2.32–2.38 (m, 1H), 2.61 −2.69 (m, 1H), 2.82–2.92 (m, 1H), 2.96−3.05 (dq, 1H, J_1 = 17.6 Hz, J_2 = 3.6 Hz), 3.10–3.12 (m, 2H), 3.19–3.24 (m, 1H), 3.44–3.53 (m, 1H), 6.61–6.63 (d, 2H, J = 8.0 Hz, −CHC*H*CH), 6.98 (t, 1H, J = 2.4 Hz, J = 8.0 Hz).

Synthesis of 2-Chloro-*N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylacetamide ((±)-22). Compound (±)-**21** (1.58 g, 7.20 mmol) was reacted with chloroacetyl chloride (1.2 mL, 1.44 mmol) and Et_3N (2.0 mL) in CH_2Cl_2 (20 mL) by following procedure D. The crude product was purified by flash chromatography using the solvent system hexane/EtOAc = 90:10 to yield pure compound (±)-**22** (2.03 g, 95%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90–0.97 (m, 3H, CH_2CH_3), 1.62–1.73 (m, 2H), 1.85–2.14 (m, 2H), 2.60−2.71 (m, 1H), 2.84–2.91 (dd, 1H, J_1 = 16.0 Hz, J_2 = 4.8 Hz), 3.00–3.12 (m, 2H), 3.15–3.29 (m, 2H), 3.80–3.82 (d, 3H, $-OCH_3$), 3.95–4.01 (m, 1H), 4.08–4.10 (m, 2H), 6.65–6.70 (m, 2H), 7.07–7.16 (m, 1H).

Synthesis of (+)-2-Chloro-*N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylacetamide ((+)-22). Compound (+)-**21** (1.75 g, 7.98 mmol) was reacted under similar conditions as reported above (procedure D) to afford the optically pure (+)-**22** (2.30 g, 97%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90–0.97 (m, 3H, CH_2CH_3), 1.61–1.72 (m, 2H), 1.83–2.10 (m, 2H), 2.58−2.71 (m, 1H), 2.84–2.90 (dd, 1H, J_1 = 16.0 Hz, J_2 = 4.8 Hz), 3.00–3.10 (m, 2H), 3.15–3.29 (m, 2H), 3.80–3.82 (d, 3H, $-OCH_3$), 3.95–4.02 (m, 1H), 4.08–4.10 (m, 2H), 6.65–6.70 (m, 2H), 7.07–7.14 (m, 1H).

Synthesis of (−)-2-Chloro-*N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylacetamide ((−)-22). Compound (−)-**21**(1.20 g, 5.47 mmol) was reacted under similar conditions as reported above (procedure D) to afford the optically pure (−)-**22** (1.58 g, 97%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90–0.97 (m, 3H, CH_2CH_3), 1.61–1.73 (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), 3.80–3.82 (d, 3H, $-OCH_3$), 3.95–4.03 (m, 1H), 4.08–4.12 (m, 2H), 6.65–6.71 (m, 2H), 7.07–7.15 (m, 1H).

Synthesis of 2-Chloro-*N*-(5-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylacetamide ((±)-22a). Compound (±)-**21a** (1.64 g, 7.99 mmol) was reacted with chloroacetyl chloride (1.3 mL, 16.0 mmol) and Et_3N (2.0 mL) in CH_2Cl_2 (20 mL) to yield (±)-**22a** (0.96 g, 43%) by following procedure D: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90–0.98 (m, 3H, CH_2CH_3), 1.64–1.72 (m, 2H), 1.90–2.12 (m, 2H), 2.61−2.74 (m, 1H), 2.83–3.09 (m, 3H), 3.19–3.27 (m, 2H), 4.00–4.15 (m, 3H), 6.61–6.68 (m, 2H), 6.96–7.04 (m, 1H).

Synthesis of (+)-2-Chloro-*N*-(5-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylacetamide ((+)-22a). Compound (+)-**21a** (2.0 g, 9.74 mmol) was reacted under similar conditions as reported above (procedure D) to afford the optically pure (+)-**22a** (1.38 g, 50.2%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90–0.98 (m, 3H, CH_2CH_3), 1.62–1.72 (m, 2H), 1.91–2.03 (m, 2H), 2.64−2.75 (m, 1H), 2.86–3.10 (m, 3H), 3.21–3.29 (m, 2H), 4.00–4.17 (m, 3H), 6.60–6.70 (m, 2H), 6.97–7.07 (m, 1H).

Synthesis of (−)-2-Chloro-*N*-(5-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylacetamide ((−)-22a). Compound (−)-**21a** (1.5 g, 7.31 mmol) was reacted under similar conditions as reported above (procedure D) to afford the optically pure (−)-**22a** (0.82 g, 39.8%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90–0.98 (m, 3H, CH_2CH_3), 1.63–1.73 (m, 2H), 1.91–2.04 (m, 2H), 2.65−2.75 (m, 1H), 2.85–3.10 (m, 3H), 3.20–3.29 (m, 2H), 4.01–4.15 (m, 3H), 6.60–6.70 (m, 2H), 6.97–7.06 (m, 1H).

Procedure I. Synthesis of (+)-*N*-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-2-(4-phenylpiperazin-1-yl)-*N*-propylacetamide ((+)-23). Into a suspension of compound (+)-**22** (0.76 g, 2.60 mmol), potassium carbonate (0.71 g, 5.14 mmol), and a catalytic amount of potassium iodide (40 mg) in acetonitrile (30 mL) was added 1-phenylpiperazine (0.60 g, 3.85 mmol) under nitrogen atmosphere with stirring. The reaction mixture was refluxed for 3 h and cooled to room temperature, and the reaction solution was filtered. Inorganic residue was washed with ethyl acetate. The combined solvent was evaporated to obtain the crude product, which was purified by flash chromatography using the solvent system hexane/ethyl acetate (70:30) to afford (+)-**23** (0.92 g, 85%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89–0.95 (m, 3H, CH_2CH_3), 1.61–1.71 (m, 2H), 1.83–1.89 (m, 1H), 1.98–2.03 (m, 1H), 2.63–2.66 (t, 4H, J = 5.2 Hz), 2.73–2.74 (m, 1H), 2.82–2.88 (dd, 1H, J_1 = 15.8 Hz, J_2 = 4.4 Hz)), 2.97–3.36 (m, 10H), 3.81 (d, 3H, $-OCH_3$), 4.26–4.32 (m, 1H), 6.65–6.71 (m, 2H), 6.84–6.87 (t, 1H, J = 7.2 Hz), 6.90–6.95 (t, 2H, J = 8.0 Hz), 7.06–7.14 (m, 1H), 7.24–7.28 (m, 2H).

Synthesis of (−)-*N*-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-2-(4-phenylpiperazin-1-yl)-*N*-propylacetamide ((−)-23). Compound (−)-**22** (0.8 g, 2.70 mmol) was reacted under similar conditions as reported above (procedure I) to afford the optically pure (−)-**23** (0.98 g, 86%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89–0.95 (m, 3H, CH_2CH_3), 1.61–1.71 (m, 2H), 1.83–1.89 (m, 1H), 1.98–2.03 (m, 1H), 2.63–2.66 (t, 4H, J = 5.2 Hz), 2.73–2.74 (m, 1H), 2.82–2.88 (dd, 1H, J_1=15.8 Hz, J_2 = 4.4 Hz)), 2.97–3.36 (m, 10H), 3.81 (d, 3H, $-OCH_3$), 4.26–4.32 (m, 1H), 6.65–6.71 (m, 2H), 6.84–6.87 (t, 1H, J = 7.2 Hz), 6.90–6.95 (t, 2H, J = 8.0 Hz), 7.06–7.14 (m, 1H), 7.24–7.28 (m, 2H).

Synthesis of *N*-(5-Hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-2-[4-(2-methoxyphenyl)piperazin-1-yl]-*N*-propylacetamide ((±)-23a). Compound (±)-**22a** (0.96 g, 3.41 mmol) with potassium carbonate (0.57 g, 10.22 mmol) was reacted with 1-(2-methoxy)phenylpiperazine HCl (1.013 g, 4.43 mmol) in the presence of a catalytic amount of potassium iodide by following procedure I. The crude product was purified by flash chromatography using the solvent system hexane/ethyl acetate = 40:60 to afford (±)-**23a** (1.09 g, 73.12%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88–0.95 (m, 3H, CH_2CH_3), 1.64–1.72 (m, 2H), 1.83–2.05 (m, 2H), 2.63–3.52 (m, 16H), 3.83–3.85 (d, 3H, $-OCH_3$), 4.28–4.34 (m, 1H), 6.61–6.63 (d, 1H, J = 8.0 Hz), 6.69–6.71 (d, 1H, J = 8.0 Hz), 6.83–6.86 (t, 1H, J = 7.6 Hz), 6.90–7.02 (m, 4H).

Synthesis of (+)-*N*-(5-Hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-2-[4-(2-methoxyphenyl)piperazin-1-yl]-*N*-propylaceta-

mide ((+)-23a). Compound (+)-**22a** (0.42 g, 1.49 mmol) was reacted under similar conditions as reported above (procedure I) to afford the optically pure (+)-**23a** (0.48 g, 73.6%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88–0.97 (m, 3H, CH_2CH_3), 1.64–1.70 (m, 2H), 1.80–2.06 (m, 2H), 2.65–3.57 (m, 16H), 3.83–3.88 (d, 3H, $-OCH_3$), 4.28–4.34 (m, 1H), 6.61–6.65 (d, 1H, J = 8.0 Hz), 6.69–6.72 (d, 1H, J = 8.0 Hz), 6.83–6.84 (t, 1H, J = 7.6 Hz), 6.90–7.03 (m, 4H).

Synthesis of (−)-*N*-(5-Hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-2-[4-(2-methoxyphenyl)piperazin-1-yl]-*N*-propylacetamide ((−)-23a). Compound (−)-**22a** (0.72 g, 2.55 mmol) was reacted under similar conditions as reported above (procedure I) to afford the optically pure (−)-**23a** (0.85 g, 76%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89–0.98 (m, 3H, CH_2CH_3), 1.61–1.72 (m, 2H), 1.82–2.10 (m, 2H), 2.58–3.38 (m, 16H), 3.78–3.88 (m, 3H, $-OCH_3$), 4.28–4.34 (m, 1H), 6.61–6.70 (m, 2H), 6.83–6.87 (t, 1H, J = 7.6 Hz), 6.90–7.02 (m, 4H).

***N*-[2-(4-(2,3-Dichlorophenyl)piperazin-1-yl)ethyl]-*N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)propionamide (±)-23b.** A mixture of compound (±)-**22** (0.4 g, 1.35 mmol) with potassium carbonate (0.93 g, 6.76 mmol) was reacted with 1-(2,3-dichloro)phenylpiperazine HCl (0.72 g, 2.70 mmol) in the presence of a catalytic amount of potassium iodide by following procedure I. The crude product was purified by flash chromatography using the solvent system hexane/ethyl acetate = 40:60 to afford (±)-**23b** (0.55 g, 83%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88–0.95 (m, 3H, CH_2CH_3), 1.64–1.74 (m, 2H), 1.80–2.05 (m, 2H), 2.67–3.52 (m, 16H), 3.81 (s, 3H, $-OCH_3$), 4.30–4.34 (m, 1H), 6.64–6.66 (d, 1H, J = 8.0 Hz), 6.69–6.71 (d, 1H, J = 8.0 Hz), 6.90–6.93 (dd, 1H, J_1 = 7.6 Hz, J_2 = 2.0 Hz), 7.06–7.10 (t, 1H, J = 8.0 Hz), 7.14–7.21 (m, 2H).

Synthesis of (+)-5-Methoxy-*N*-[2-(4-phenylpiperazin-1-yl)ethyl]-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine ((+)-24). Compound (+)-**23** (0.92 g, 2.18 mmol) was reacted with $LiAlH_4$ (0.66 g, 17.46 mmol) in dry THF (40 mL) under refluxing conditions for 4 h by following procedure E. The crude product was purified by flash chromatography using the solvent system hexane/EtOAc (1:1) to afford compound (+)-**24** (0.67 g, 56%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88–0.92 (t, 3H, J = 7.2 Hz, CH_2CH_3), 1.41–1.60 (m, 3H), 2.04–2.05 (m, 1H), 2.50–2.60 (m, 5H), 2.64–2.68 (t, 4H, J = 4.8 Hz), 2.74–2.80 (m, 3H), 2.83–3.05 (m, 3H), 3.19–3.20 (t, 4H, J = 5.4 Hz), 3.80 (s, 3H, $-OCH_3$), 6.64–6.69 (d, 1H, J = 8.6 Hz), 6.71–6.73 (d, 1H, J = 7.6 Hz), 6.83–6.86 (t, 1H, J = 7.2 Hz), 6.91–6.94 (d, 2H, J = 8.0 Hz), 7.07–7.10 (t, 1H, J = 8.0 Hz), 7.24–7.32 (m, 2H).

Synthesis of (−)-5-Methoxy-*N*-[2-(4-phenylpiperazin-1-yl)ethyl]-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine ((−)-24). Compound (−)-**23** (0.98 g, 2.32 mmol) was reacted under similar conditions as reported above (procedure E) to afford the optically pure (−)-**24** (0.53 g, 56%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88–0.91 (t, 3H, J = 7.2 Hz, CH_2CH_3), 1.43–1.62 (m, 3H), 2.04–2.09 (m, 1H), 2.50–2.56 (m, 5H), 2.64–2.67 (t, 4H, J = 4.8 Hz), 2.72–2.79 (m, 3H), 2.83–3.02 (m, 3H), 3.19–3.21 (t, 4H, J = 5.2 Hz), 3.80 (s, 3H, $-OCH_3$), 6.64–6.66 (d, 1H, J = 8.4 Hz), 6.70–6.72 (d, 1H, J = 7.6 Hz), 6.83–6.86 (t, 1H, J = 7.2 Hz), 6.91–6.93 (d, 2H, J = 8.0 Hz), 7.07–7.10 (t, 1H, J = 8.0 Hz), 7.24–7.28 (m, 2H).

Synthesis of 6-[(2-(4-(2-Methoxyphenyl)piperazin-1-yl)ethyl)(propyl)amino]-5,6,7,8-tetrahydronaphthalen-1-ol ((±)-24a). Compound (±)-**23a** (1.09 g, 2.49 mmol) was reacted with $LiAlH_4$ (0.76 g, 19.9 mmol) in dry THF (40 mL) under refluxing conditions for 4 h by following procedure E. The crude product was purified by flash chromatography using solvent EtOAc to afford (±)-**24a** (0.60 g, 57%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86–0.90 (t, 3H, J = 7.6 Hz, CH_2CH_3), 1.31–1.48 (m, 3H), 1.92–1.95 (m, 1H), 2.22–2.29 (m, 1H), 2.43–2.96 (m, 14H), 3.16 (br s, 4H), 3.86 (s, 3H, $-OCH_3$), 6.46–6.48 (d, 1H, J = 8.0 Hz), 6.54–6.56 (d, 1H, J = 7.2 Hz), 6.85–7.02 (m, 5H), 7.85–8.2 (bs, 1H, −OH).

The product was converted into the corresponding dioxalate salt, mp 122–125 °C. Anal. Calcd for $C_{26}H_{37}N_3O_2 \cdot 2C_2H_2O_4 \cdot 0.5H_2O$: C, H, N.

Synthesis of (+)-6-[(2-(4-(2-Methoxyphenyl)piperazin-1-yl)ethyl)(propyl)amino]-5,6,7,8-tetrahydronaphthalen-1-ol ((+)-24a). Compound (+)-**23a** (0.48 g, 1.10 mmol) was reacted under similar conditions as reported above (procedure E) to afford the optically pure (+)-**24a** (0.14 g, 30.43%): $[\alpha]_D$ = (+) −31.6°, c 1 in methanol; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86–0.90 (t, 3H, J = 7.6 Hz, CH_2CH_3), 1.40–1.49 (m, 3H), 1.92–2.00 (m, 1H), 2.27–2.36 (m, 1H), 2.44–2.96 (m, 14H), 3.15 (br s, 4H), 3.87 (s, 3H, $-OCH_3$), 6.49–6.51 (d, 1H, J = 8.0 Hz), 6.55–6.60 (d, 1H, J = 7.2 Hz), 6.85–7.02 (m, 5H).

The product was converted into the corresponding dioxalate salt, mp 130–132 °C. Anal. Calcd for $C_{26}H_{37}N_3O_2 \cdot 2C_2H_2O_4 \cdot 0.5H_2O$: C, H, N.

Synthesis of (−)-6-[(2-(4-(2-Methoxyphenyl)piperazin-1-yl)ethyl)(propyl)amino]-5,6,7,8-tetrahydronaphthalen-1-ol ((−)-24a). Compound (−)-**23a** (0.85 g, 1.94 mmol) was reacted under similar conditions as reported above (procedure E) to afford the optically pure (−)-**24a** (0.53 g, 64.4%): $[\alpha]_D$ = −33.4°, c 0.5 in methanol; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86–0.90 (t, 3H, J = 7.6 Hz, CH_2CH_3), 1.35–1.50 (m, 3H), 1.95–1.99 (m, 1H), 2.22–2.29 (m, 1H), 2.43–2.96 (m, 14H), 3.16 (br s, 4H), 3.87 (s, 3H, $-OCH_3$), 6.47–6.49 (d, 1H, J = 8.0 Hz), 6.53–6.55 (d, 1H, J = 7.2 Hz), 6.85–7.02 (m, 5H).

The product was converted into the corresponding dioxalate salt, mp 132–134 °C. Anal. Calcd for $C_{26}H_{37}N_3O_2 \cdot 2C_2H_2O_4 \cdot 0.8\ H_2O$: C, H, N.

Synthesis of *N*-[2-(4-(2,3-Dichlorophenyl)piperazin-1-yl)ethyl]-5-methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine ((±)-24b). Into a solution of (±)-**23b** (1.05 g, 2.14 mmol) in dry THF was added 21.4 mL of a solution of borane−THF complex (1 M solution) with stirring under nitrogen atmosphere. The reaction mixture was refluxed for 6 h, cooled to room temprature, and quenched with methanol. The solvent was evaporated. The white solid complex was suspended in 6 N HCl in methanol and stirred for 2 h at 50 °C. Methanol was evaporated under vacuum. The reaction mixture was made alkaline using saturated Na_2CO_3/$NaHCO_3$ solution. The aqueous layer was extracted with ethyl acetate (3 × 100 mL), dried over Na_2SO_4, concentrated under vacuum, and purified by flash chromatography using the solvent system ethyl acetate/methanol (90:10) to afford (±)-**24b** (0.8 g, 78%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88–0.92 (t, 3H, J = 7.2 Hz, CH_2CH_3), 1.43–1.63 (m, 3H), 2.04–2.09 (m, 1H), 2.51–2.57 (q, 5H), 2.69–3.07 (m, 14H), 3.81 (s, 3H, $-OCH_3$), 6.64–6.66 (d, 1H, J = 8.4 Hz), 6.70–6.72 (d, 1H, J = 7.6 Hz), 6.94–6.97 (dd, 1H, J_1 = 6.8 Hz, J_2 = 3.2 Hz), 7.07–7.16 (m, 3H).

Synthesis of (+)-6-[(2-(4-Phenylpiperazin-1-yl)ethyl)(propyl)amino]-5,6,7,8-tetrahydronaphthalen-1-ol ((+)-25). Compound (+)-**24** (0.67 g, 1.64 mmol) was refluxed in 20 mL of 48% aqueous HBr solution for 3 h. The reaction mixture was evaporated under vacuum. The crude HBr salt was converted to free base by using a saturated Na_2CO_3 solution. The aqueous layer was extracted with ethyl acetate (3 × 100 mL), dried (Na_2SO_4), concentrated under vacuum, and purified by flash chromatography using the solvent system ethyl acetate/methanol (90:10) to afford (+)-**25** (0.39 g, 60%): $[\alpha]_D$ = +34.8°, c 1 in methanol; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06–1.10 (t, 3H, J = 7.2 Hz, CH_2CH_3), 1.91–2.02 (m, 3H), 2.46–2.50 (m, 1H), 2.67–2.76 (m, 1H), 3.10–3.95 (m, 18H), 6.61–6.69 (m, 2H), 6.96–7.04 (m, 2H), 7.13–7.14 (m, 2H), 7.32–7.35 (t, 2H, J = 7.2 Hz).

The product was converted into the corresponding dioxalate salt, mp 120–123 °C. Anal. Calcd for $C_{25}H_{35}N_3O \cdot 2C_2H_2O_4$: C, H, N.

Synthesis of (−)-6-[(2-(4-Phenylpiperazin-1-yl)ethyl)(propyl)amino]-5,6,7,8-tetrahydronaphthalen-1-ol ((−)-25). Compound (−)-**24** (0.53 g, 1.3 mmol) was reacted under similar conditions as reported above (procedure H) to afford the optically pure (−)-**25** (0.32 g, 63%): $[\alpha]_D$ = −35.6°, c 1 in methanol; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87–0.91 (t, 3H, J = 7.2 Hz, CH_2CH_3), 1.40–1.52 (m, 3H), 1.96–2.03 (m, 1H), 2.32–2.75 (m, 13H), 2.86–2.95 (m, 2H), 3.25–3.27 (t, 4H, J = 4.8 Hz), 6.49–6.51 (d, 1H, J = 7.6 Hz), 6.53–6.55 (d, 1H, J = 7.6 Hz), 6.84–6.88 (t, 1H, J = 7.6 Hz), 6.92–6.96 (m, 3H), 7.24–7.28 (m, 2H).

The product was converted into the corresponding dioxalate salt, mp 122–124 °C. Anal. Calcd for $C_{25}H_{35}N_3O \cdot 2C_2H_2O_4$: C, H, N.

Synthesis of 6-[(2-(4-(2,3-Dichlorophenyl)piperazin-1-yl)ethyl)(propyl)amino]-5,6,7,8-tetrahydronaphthalen-1-ol ((±)-25b). Compound (±)-**24b** (1.1 g, 2.31 mmol) was stirred with boron tribromide (1 M solution in dichloromethane, 7.0 mL, 7.0 mmol) in dry CH_2Cl_2 (20 mL) at −40 °C following procedure G. The crude product was purified by flash chromatography using the solvent system hexane/EtOAc = 60:40 to afford compound (±)-**25b** (0.60 g, 56%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88–0.92 (t, 3H, J = 7.6 Hz, CH_2CH_3), 1.45–1.55 (m, 3H), 1.98–2.00 (m, 1H), 2.42–2.64 (m, 6H), 2.72–2.96 (m, 9H), 3.12 (br s, 4H), 6.54–6.56 (m, 2H), 6.92–6.96 (m, 2H), 7.12–7.17 (m, 2H), 7.6–7.84 (bs, 1H, −OH).

The product was converted into corresponding dihydrochloride salt, mp 180–183 °C. Anal. Calcd for $C_{25}H_{33}Cl_2N_3O \cdot 2HCl \cdot H_2O$: C, H, N.

Measurement of Binding Potencies at DA D2 and D3 Receptors: [^{3}H]Spiperone Binding. Binding affinities were assessed according to the general procedure described in our previous study.[44] Briefly, membranes were prepared from human embryonic kidney (HEK) 293 cells expressing human D2L and D3 receptors. Approximately 20 (for D2L) or 50 (for D3) μg of protein was incubated with each test compound and [^{3}H]spiperone (0.4 nM) for 1 h at 30 °C in 50 mM Tris-HCl (pH 7.4), with 0.9% NaCl and 0.025% ascorbic acid in the absence of GTP, in a total volume of 0.8 mL. (+)-Butaclamol (2 μM) was used to define nonspecific binding. Assays were terminated by the addition of ice-cold buffer and filtration through glass fiber filtermats with cold saline as wash buffer in the MACH 3-96 Tomtec harvester (Wallac, Gaithersburg, MD). IC_{50} values were estimated by nonlinear regression analysis with the logistic model in the least-squares fitting program ORIGIN and converted to inhibition constants (K_i) by the Cheng−Prusoff equation.[52] In this conversion, the K_d values for [^{3}H]spiperone binding were 0.057 nM for D2 receptors and 0.125 nM for D3 receptors.

Measurement of Stimulation of DA D2 and D3 Receptors: [^{35}S]GTPγS Binding. Chinese hamster ovary (CHO) cells expressing human D2 receptors were grown in Dulbecco's modified Eagle's medium enriched with 5% bovine calf serum, 1% L-glutamine, 0.5% penicillin/streptomycin, and 2 μg/mL puromycin. ATt-20 cells expressing human D3 receptors were grown in Gibco F10 medium with 10% horse serum, 5% fetal bovine serum, 1% L-glutamine, 50 μg/mL gentamicin, and 500 μg/mL G418. The general procedures used for measuring [^{35}S]GTPγS binding are modified from protocols described for DA receptors[53] and other G protein-coupled receptors.[54,55] To make membranes, cells were washed with phosphate-buffered saline (PBS) and then centrifuged in PBS at 1000*g* for 5 min at 4 °C. The supernatant was removed, and cells were resuspended in 50 mM Tris-HCl, 1 mM EDTA (pH 7.4) (resuspension buffer), by polytron, and then centrifuged at 35000*g* for 15 min at 4 °C. This was done once more, at which point cells were resuspended with assay buffer (D2, 20 mM HEPES, 3 mM $MgCl_2$, 150 mM NaCl, 0.2 mM EGTA, 0.001% bovine serum albumin (BSA); D3, 20 mM HEPES, 3 mM $MgCl_2$, 100 mM NaCl, 0.2 mM EGTA, 0.001% BSA). The [^{35}S]GTPγS binding assays were performed in triplicates. The final 1 mL volume was composed of 100 μL of 10% (v/v) dimethyl sulfoxide (DMSO) as vehicle, drug dilution (in 10% DMSO), or DA (1 mM for D2 cells and 100 μM for D3 cells) as an indicator of binding plateau; 400 μL of [^{35}S]GTPγS dilution (4.3 pmol in 10 mL of assay buffer per 24 well filter mat); and 500 μL of cell suspension (cells suspended, per 24 well filter, in 12.5 mL of assay buffer and 7.5 μL of GDP, for a final concentration of 3 μM in assay). This solution was incubated at room temperature in a shaking water bath for 60 min. Cells were harvested using Brandel GF/B filter mats and a 24 pin Brandel harvester (Biomedical Research and Development Laboratories, Inc., Gaithersburg, MD) with cold resuspension buffer as the washing fluid. A Beckman LS 6500 scintillation counter was used to determine ^{35}S radioactivity at 70% efficiency. Nonspecific binding of [^{35}S]GTPγS measured in the presence of 10 μM GTPγS was a very small fraction (5% or less) of basal binding in the absence of drug (vehicle) and did not affect the EC_{50} (concentration producing half-maximal stimulation) of the test drug estimated by nonlinear logarithmic fitting (logistics model) with OriginPro 7.0. The plateau binding (maximal binding stimulation) with test drug was expressed as percent of maximal binding observed with the full agonist DA (% E_{max}); each filter mat used for harvesting and scintillation counting contained varying concentrations of test drug (for EC_{50} determination) and a fixed [DA] (see above, for maximally achievable binding with full agonist under the conditions of a given experiment).

In Vivo Rotational Experiment with 6-OH-DA-Lesioned Rats. The lesioned rats were purchased from Taconic Biotechnology (Rensselaer, NY), and their unilateral lesion was checked twice by apomorphine challenge following the surgery.The first 14 days postlesion challenge with apomorphine was done to observe a complete rotation session postadministration. In the second challenge with apomorphine (0.05 mg/kg) 21 days postlesion, contralateral rotations were recorded for 30 min; apomorphine produced rotations in all four rats (average rotation > 250), indicating successful unilateral lesion. In these rats, lesion was performed on the left side with the rotations produced upon agonist challenge occurring clockwise. In our current study, apomorphine was also used as a reference compound. The test drugs were dissolved in sterile water and were administered as water solution. The number of rotations was measured over 12 h. For control, vehicle was administered alone. Rotations were measured in the Rotomax Rotometry System (AccuScan Instruments, Inc., Columbus, OH) equipped with a Rotomax Analyzer, high-resolution sensor, and animal chambers with harnesses. Data were analyzed with the Rotomax Window software program. Test drugs (−)-**25** (1 and 5 μmol/kg) and **2** (5 μmol/kg) were dissolved in sterile water and were administered ip. Apomorphine (0.05 mg/kg) was also administered, in the same manner, as a reference compound. The rotations were measured in a rotational chamber immediately after administration of drugs. The data were collected every 30 min. Data were analyzed by Graph Pad (version 4, San Diego, CA) program. Compounds (–)-**25** and **2** produced contralateral rotations in all lesioned rats, which lasted over 8–12 h. The reference drug apomorphine (0.16 μmol/kg) exhibited a fast onset of action with the peak effect occurring within the first 30 min. It exhibited a short duration of action.

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Supporting Information Available: Elemental analysis results. This material is available free of charge via the Internet at http://pubs.acs.org.

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