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Bioorganic & Medicinal Chemistry 12 (2004) 4361–4373
Bioorganic & Medicinal Chemistry

# Synthesis and biological characterization of novel hybrid 7-{[2-(4-phenyl-piperazin-1-yl)-ethyl]-propyl-amino}-5,6,7,8-tetrahydro-naphthalen-2-ol and their heterocyclic bioisosteric analogues for dopamine D2 and D3 receptors

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Received 21 April 2004; accepted 11 June 2004
Available online 7 July 2004

**Abstract**—In a recent preliminary communication we described the development of a series of hybrid molecules for the dopamine D2 and D3 receptor subtypes. The design of these compounds was based on combining pharmacophoric elements of aminotetralin and piperazine molecular fragments derived from known dopamine receptor agonist and antagonist molecules. Molecules developed from this approach exhibited high affinity and selectivity for the D3 receptor as judged from preliminary [$^3$H]spiperone binding data. In this report, we have expanded our previous finding by developing additional novel molecules and additionally evaluated functional activities of these novel molecules in the [$^3$H]thymidine incorporation mitogenesis assay. The binding results indicated highest selectivity in the bioisosteric benzothiazole derivative *N*6-[2-(4-phenyl-piperazin-1-yl)-ethyl]-*N*6-propyl-4,5,6,7-tetrahydro-benzothiazole-2,6-diamine (**14**) for the D3 receptor whereas the racemic compound 7-({2-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-ethyl}-propyl-amino)-5,6,7,8-tetrahydro-naphthalen-2-ol (**10c**) showed the strongest potency. Mitogenesis studies to evaluate functional activity demonstrated potent agonist properties in these novel derivatives for both D2 and D3 receptors. In this regard, compound 7-{[4-(4-phenyl-piperazin-1-yl)-butyl]-prop-2-ynyl-amino}-5,6,7,8-tetrahydro-naphthalen-2-ol (**7b**) exhibited the most potent agonist activity at the D3 receptor, 10 times more potent than quinpirole and was also the most selective compound for the D3 receptor in this series. Racemic compound **10a** was resolved; however, little separation of activity was found between the two enantiomers of **10a**. The marginally more active enantiomer (−)-**10a** was examined in vivo using the 6-OH-DA induced unilaterally lesioned rat model to evaluate its activity in producing contralateral rotations. The results demonstrated that in comparison to the reference compound apomorphine, (−)-**10a** was quite potent in inducing contralateral rotations and exhibited longer duration of action.


## 1. Introduction

The major neurotransmitter dopamine (DA) exhibits a variety of pharmacological actions in the central nervous system (CNS) and also in the periphery. The dopamine receptor system has been traditionally targeted for drug development for treatment of psychiatric illness, neurodegeneration, and recently, for drugs of abuse.[1–3] The receptors for DA in the CNS were initially classified into two main classes D1 and D2.[4] This classification was based on distinct physiological and pharmacological properties of these two receptors as stimulation of the D1 receptor leads to activation of adenylate cyclase, which promotes synthesis of cAMP, whereas D2 receptor activation leads to inhibition of adenylate cyclase activity.[4] However, recent advances in molecular biological techniques have led to the identification of additional DA receptor subtypes. So far, five subtypes of the 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 includes D1 and D5.[5–9] In

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doi:10.1016/j.bmc.2004.06.019

the CNS, D1-type receptors are located post-synaptically, whereas D2-type receptors are located both pre- and post-synaptically and have a high affinity for DA.[1,10]

The DA D3 receptor was discovered a decade ago and was found to have different distribution in the brain compared to the D2 receptor.[5,6] The distribution of the D3 receptor is particularly interesting given that its location in the brain is mostly limited to the limbic regions that have been implicated in a number of psychiatric disorders.[11] In the human brain, the highest expression of the D3 receptor was found in the area of the ventral striatum and associated striatum.[11,12] The neuroanatomical distribution of D3 receptors is consonant with their function as both presynaptic autoreceptors and postsynaptic receptors.[13] It has also recently been proposed that the D3 receptor-mediated motor inhibition, unlike the D2-mediated inhibition, is postsynaptically located.[14] However, another study with quinpirole suggested presynaptic locations of D3 autoreceptors in the striatum.[15] The D3 receptor has been suggested as an interesting target for development of potential atypical antipsychotic agents, antiparkinsonian drugs, and pharmacotherapeutics for treatment of drug abuse.[16,17] Cloning of D2 and D3 receptors revealed a molecular structural sequence containing 50% homology between these two receptors. A higher homology of 75–80% was found in helical transmembrane spanning regions between these two receptor subtypes where agonists binding sites are believed to be located.[18] As a result, development of drugs selective for either one of these two receptors is a challenging task.

An enormous amount of work has already been performed in developing selective agonists for the D3 receptor.[19,20] Aminotetralin derivatives were among the earliest molecules that were investigated for D3 activity.[21] 7-OH-DPAT (Fig. 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.[22] However, high selectivity of 7-OH-DPAT for the D3 receptor, found in the antagonist radioligand binding assay, presumably G protein uncoupled low-affinity sites, was decreased substantially when the binding activity was measured in the radiolabeled agonists binding assay, a high-affinity G protein coupled functional state.[22,23] Similarly, in vitro functional assay of D2/D3 agonists indicated a good correlation of intrinsic activity of different agonists with their high affinity binding values.[24] Numerous other aminotetralin derived ligands have been synthesized and characterized.[25] Recently, a bioisosteric analog of 7-OH-DPAT, pramipexole, was developed by replacing the phenolic group by a more metabolically stable thiazolidinium moiety. Pramipexole represents one of the highest D3 selective compounds and is currently being used for Parkinson's disease (PD) therapy.[26] 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 the D2, D3, and 5HT1a receptors, for example, compound **1a** (Fig. 1).[27,28]

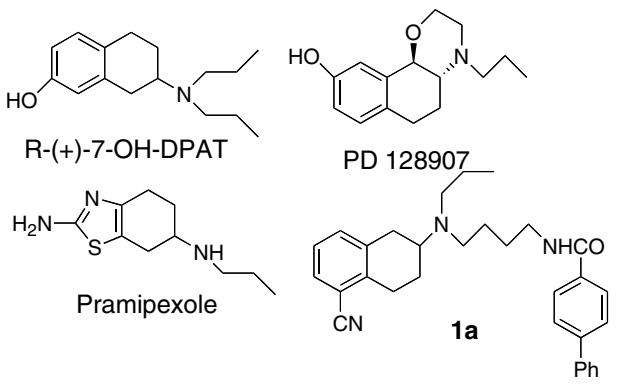


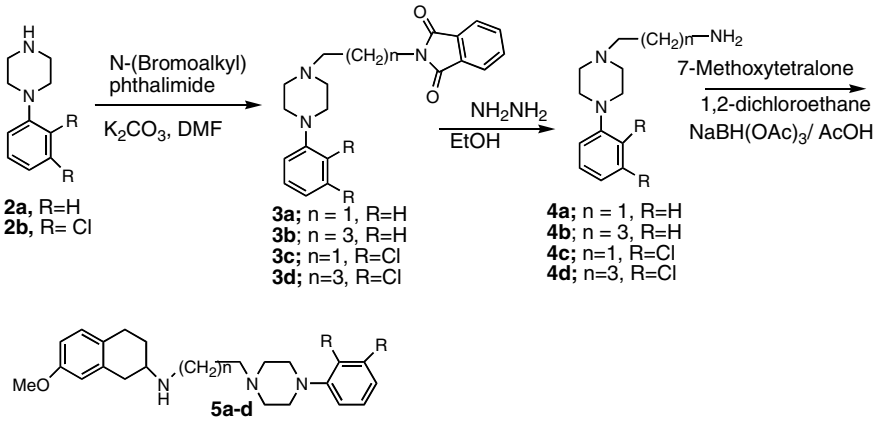

**Figure 1.** Molecular structures of D3 preferring agonists.

In our effort to design and develop selective and novel ligands for D2/D3 receptors, we have adopted a hybrid structure approach by incorporating a disubstituted piperazine fragment into the aminotetralin pharmacophoric moiety.[29] Interaction of the aminotetralin moiety with the dopamine receptors was expected to produce agonist activity and the piperazine fragment was thought to impart selectivity for the D3 receptor subtype by accessing the accessory binding sites in the receptor molecule. In this regard, disubstituted piperazine derivatives have already been demonstrated to exhibit high selectivity for the D3 receptor.[30] In our preliminary communication of this work, we demonstrated successful application of this strategy in the development of potent compounds exhibiting preferential affinity for the D3 receptor. We have now expanded our studies by incorporating additional compounds and also have evaluated functional activity of selected potent compounds. Furthermore, we have incorporated bioisosteric replacement of the phenolic moiety in one of our potent molecules by more metabolically stable heterocyclic moieties.

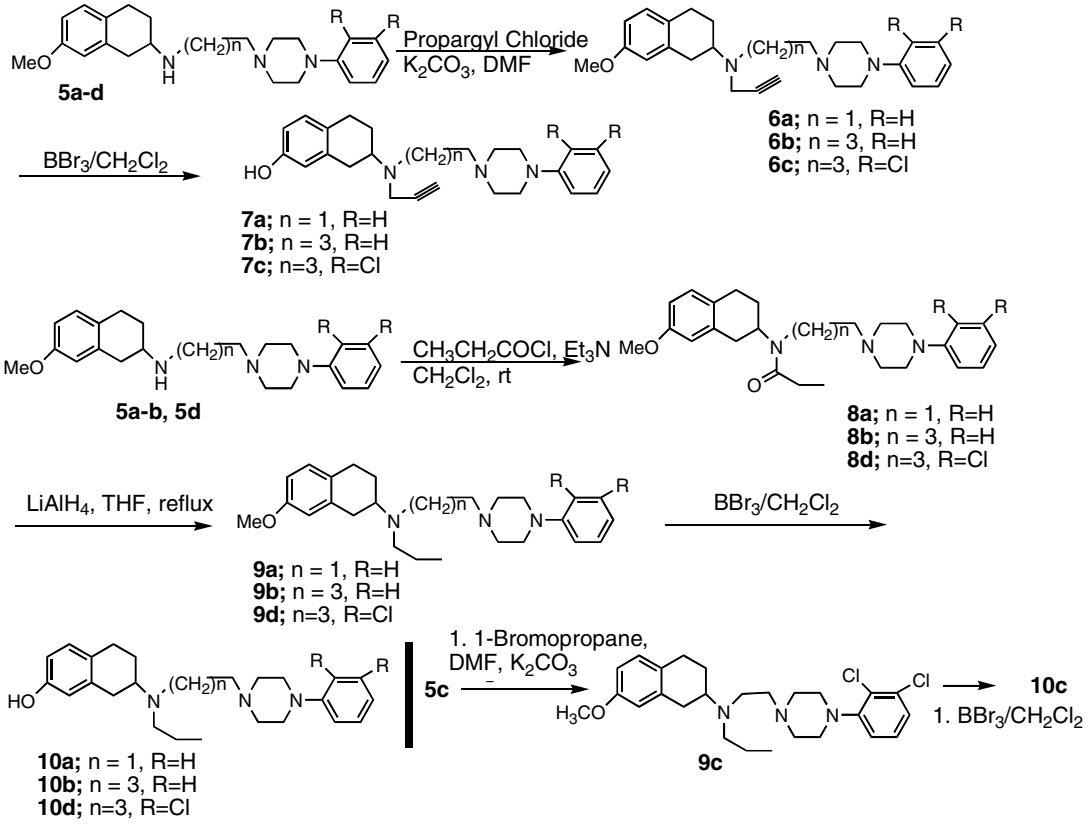
Additionally, we have carried out an experiment with one of the enantiomers of an active lead derivative to observe its in vivo activity to produce contralateral rotations in 6-OH-DA-induced unilaterally lesioned rats. In this model, the DA neurons of one side of the nigrostriatal DA system are selectively and completely lesioned by intracerebral injection of the neurotoxin 6-OH-DA, which induces a postsynaptic supersensitivity at the lesioned side. DA agonists, when administered systemically, will produce contralateral rotations in rats, that is, toward the nonlesioned side.[31] The results from this experiment will indicate potency of an agonist test compound in vivo including its blood brain barrier crossing ability and thus, may serve as a further screening device for developing novel D3-selective compounds.

## 2. Chemistry

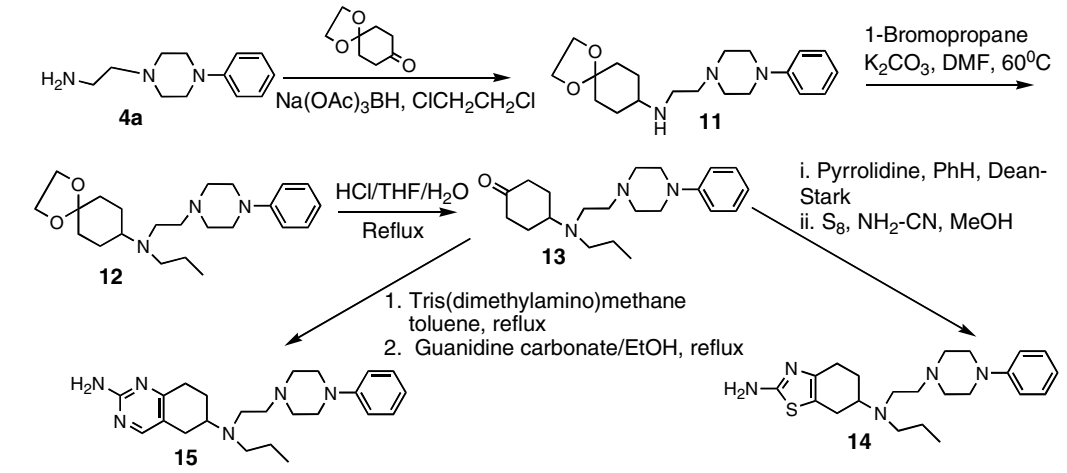
Synthesis of the target molecules, shown in Schemes 1–4, was carried out mainly in two stages which involved first synthesis of the starting amines **4a**–**d** from phenyl piperazine **2a**–**b** via *N*-alkylation with the appropriate phthalimide-protected alkyl bromide followed by reaction with hydrazine. Thus, the phthalimide derivatives **3a**–**d** on reaction with hydrazine liberated free amines **4a**–**d**. Reductive amination of the free amines with 7-methoxytetralone produced aminotetralin derivatives **5a**–**d** in good yield. Next, *N*-alkylation of the amines **5a**–**d** was carried out in two different ways as shown in Scheme 2. Reaction with propargyl chloride under basic conditions produced targets **6a**–**c**, which after demethylation of the methoxy group produced **7a**–**c** in an overall good yield. On the other hand, targets **10a**–**d** were produced by a series of reactions, which involved first acylation with propionyl chloride followed by reduction of the intermediate amides and subsequent demethylation to produce the final targets in an overall good yield. Compound **10c** was prepared by



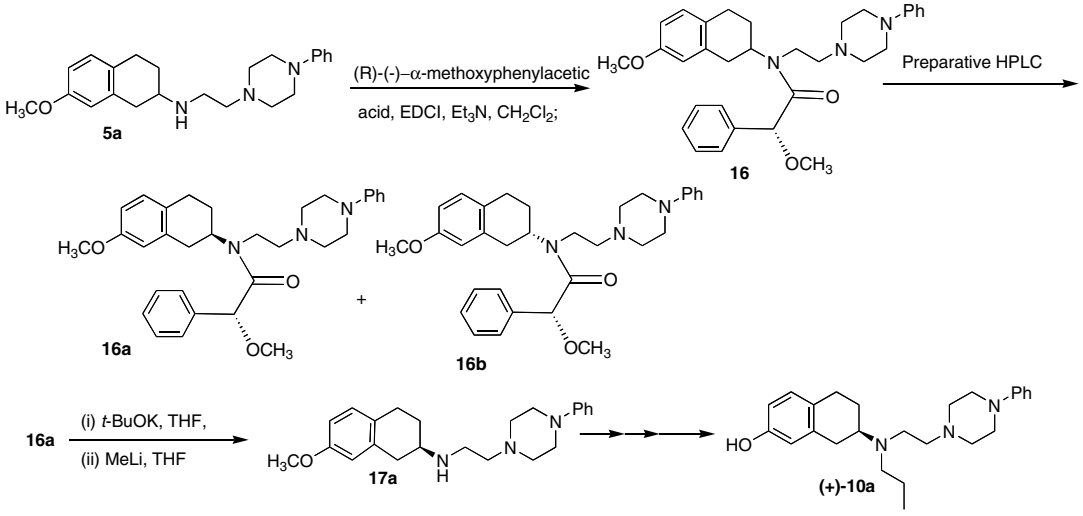

**Scheme 1.**




**Scheme 2.**




Scheme 3.




Scheme 4.

*N*-alkylation of **5c** with bromopropane followed by demethylation of methoxy group.

Bioisosteric analogues **14** and **15** were prepared by following a different synthetic route as shown in Scheme 4. Reductive amination of commercially available cyclohexanedione monoethylene ketal with amine **4a** yielded **11** in good yield. *N*-Propylation of **11** with 1-bromopropane produced **12**, which on acidic hydrolysis liberated keto compound **13**. Thiazolidinium derivative **14** was synthesized from the keto derivative **13** by following a two steps synthetic procedure in a reasonably good yield.[32] On the other hand, reaction of keto compound **13** with tris(dimethylamino)methane followed by treatment with guanidine carbonate under refluxing condition in ethanol provided **15** in reasonably good yield.[33]

Resolution of the racemic compound **10a** was achieved by synthesizing diastereomers from the reaction of the intermediate amine **5a** with *R*-(−)-α-methoxyphenylacetic acid in the presence of the coupling agent 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide, Scheme 4. The two diastereomers, **16a** and **16b**, were separated by preparative HPLC. Each individual diastereomer was first hydrolyzed in the presence of potassium-*t*-butoxide followed by treatment with methyl lithium to generate optically active amine **17a** which, after a series of reactions as described in Scheme 2, produced the optically pure enantiomers (+)-**10a** and (−)-**10a**. We have not yet determined the absolute configuration of (+)-**10a** and (−)-**10a**.

## 3. Results and discussion

In our previous short communication, we have demonstrated that our adopted hybrid approach of combining aminotetralin and piperazine fragments could produce novel compounds exhibiting high affinity and selectivity for the D3 receptor.[29] Our earlier study revealed that the length of the linker connecting the aminotetralin moiety with the piperazine fragment plays an important role in

exhibiting selectivity for the D3 receptor. Selectivity for the D3 receptor was more pronounced in compounds with a shorter methylene chain link connecting the aminotetralin moiety with the piperazine fragment although compound **7b** with a longer linker size was also quite selective. In addition, most of these compounds exhibited high potency for the D3 receptor.

One of the more selective compounds in binding D3, racemic **10a**, was subjected to enantiomeric resolution to isolate pure enantiomers through a diastereoisomeric separation approach as described earlier. Both enantiomers were characterized for their binding to cloned D2 and D3 receptors. Results indicated a somewhat higher D3 binding potency and selectivity in the (−)-**10a** isomer compared to the (+)-**10a** isomer (Table 1). The functional assay for the two enantiomers indicated that no appreciable separation of activity exists between these two enantiomers (Table 2). On the contrary, the aminotetralin derivative 7-OH-DPAT and other related aminotetralin-derived DA agonists displayed appreciable differential binding activity in their corresponding enantiomers.[34] It seems logical to conclude that the lack of differential activity between the two enantiomers of **10a** might be due to the presence of the piperazine fragment in this hybrid molecule.

In our effort to replace the phenolic moiety by a more metabolically stable bioisosteric heterocyclic moiety, compounds **14** and **15** were designed and synthesized. In compound **14**, the phenolic moiety was replaced by a thiazolidinium moiety, which is a known bioisostere of a phenolic group. Thiazolidinium moiety containing DA agonists like pramipexole displayed interesting biological activity in the past by showing preferential activity for the D3 receptor and also exhibited potent antioxidant activity.[35,36] As was mentioned earlier, pramipexole is currently being used in the clinic for the therapy of PD.[26] Binding results indicate that compound **14** exhibited high potency for the D3 receptor and was the most selective compound in the current series for the D3 receptor (D2/D3; 502). In comparison to the reference (+)-7-OH-DPAT, compound **14** was five-fold more selective (D2/D3; 502 vs 108) for D3 while their D3 potencies were comparable (Table 1). On the other hand, amino pyrimidine derivative **15** was less potent and less selective for the D3 receptor compared to **14**.

We next evaluated functional activity of the selected potent compounds in [$^3$H]thymidine incorporation mitogenesis assay in CHOp-cell lines transfected with human D2 and D3 receptors. Agonist activity of a test compound was measured by assessing the capability to induce cell division by incorporation of [$^3$H]thymidine. Intrinsic activity of our compounds was compared against the reference quinpirol, which is considered a full agonist at both receptors. Intrinsic activity was expressed as the ratio of the EC50 value of drug over that of the reference standard compound quinpirole. Maximum stimulation of receptor was also evaluated. It is apparent from the results that these novel analogs are agonists as all the compounds exhibited potent intrinsic activity. The highest selectivity in intrinsic activity for the D3 receptor was exhibited by **7b** (Table 2), even though **14** exhibited the highest selectivity in the binding assay (Table 1).

**Table 1.** Inhibition constants for displacing [3H]spiperone binding to the cloned D2L and D3 receptors expressed in HEK cells

| Compound | $K_i$ (nM), D2 [$^3$H]spiperone | $K_i$ (nM), D3 [$^3$H]spiperone | D2/D3 |
|---|---|---|---|
| 7-OH-DPAT | 538 ± 108 | 5.00 ± 1.18 | 108 |
| (±)-**7a**[a] | 245 ± 26 | 14.2 ± 1.7 | 17 |
| (±)-**7b**[a] | 68.4 ± 7.6 | 1.40 ± 0.14 | 49 |
| (±)-**10a** | 213 ± 26 | 1.75 ± 0.34 | 122 |
| (−)-**10a** | 241 ± 7 | 1.88 ± 0.42 | 128 |
| (+)-**10a** | 229 ± 17 | 2.36 ± 0.41 | 97 |
| (±)-**10b**[a] | 114 ± 8 | 3.79 ± 0.40 | 30 |
| (±)-**10d**[a] | 8.78 ± 0.81 | 2.26 ± 0.50 | 4 |
| (±)-**7c**[a] | 7.37 ± 0.27 | 3.59 ± 0.58 | 2 |
| (±)-**10c**[a] | 27.4 ± 1.0 | 1.13 ± 0.04 | 24 |
| (±)-**14** | 2080 ± 162 | 4.14 ± 0.55 | 502 |
| (±)-**15** | 1120 ± 144 | 22.3 ± 2.3 | 50 |

Results are means ± SEM for three experiments each performed in triplicate.

[a] Value taken from Ref. 29.

**Table 2.** Evaluation of agonist potency in [$^3$H]thymidine incorporation mitogenesis assay

| Compound | D2 ($EC_{50}$ drug/$EC_{50}$ quinpirole) | Maximum stimulation relative to quinpirole | D3 ($EC_{50}$ drug/$EC_{50}$ quinpirole) | Maximum stimulation relative to quinpirole | D2/D3 ratio of drug $EC_{50}$ |
|---|---|---|---|---|---|
| 7-OH-DPAT[a] | 0.42 ± 0.22 | | 0.30 ± 0.2 | | 4.6 |
| **7a**[a] | 0.7 ± 0.00 | 0.87 ± 0.02 | 0.41 ± 0.1 | 0.94 ± 0.06 | 4.9 |
| **7b**[a] | 0.3 ± 0.1 | 0.85 ± 0.06 | 0.10 ± 0.03 | 0.72 ± 0.10 | 14.2 |
| **10a** | 0.465 ± 0.015 | 0.84 ± 0.01 | 0.57 ± 0.17 | 0.83 ± 0.03 | 2.73 |
| (+)-**10a** | 0.285 ± 0.005 | 0.78 ± 0.02 | 0.24 ± 0.03 | 0.76 ± 0.03 | 3.78 |
| (−)-**10a** | 0.245 ± 0.015 | 0.86 ± 0.36 | 0.21 ± 0.03 | 0.73 ± 0.03 | 3.60 |
| **10b**[a] | 0.415 ± 0.08 | 1.20 ± 0.26 | 0.41 ± 0.19 | 0.75 ± 0.09 | 3.5 |
| **10d**[a] | 0.785 ± 0.10 | 0.80 ± 0.08 | 1.85 ± 0.45 | 0.86 ± 0.01 | 1.28 |
| **7c**[a] | 1.125 ± 0.235 | 0.86 ± 0.09 | 0.92 ± 0.26 | 0.90 ± 0.15 | 3.83 |
| **14** | 0.315 ± 0.025 | 0.90 ± 0.04 | 0.2 ± 0.02 | 0.86 ± 0.03 | 5.07 |

[a] Quinpirole had an EC50 of 9.98 ± 0.68 nM at D2 and 2.91 ± 0.25 nM at D3. These values were used to normalize the D2/D3 ratios of drug EC50 for compounds without asterisk (see Section 6). Maximum stimulation is observed stimulation relative to that produced by the full agonist quinpirole (defined as 1.00).

## 4. Contralateral turning by (−)10a in 6-OH-DA lesioned rats

After resolving racemic mixture of **10a**, the slightly more potent enantiomer (−)-**10a** was evaluated for in vivo activity. Agonist property of (−)-**10a** was evaluated in rats with a unilaterally lesioned nigrostriatal dopamine system induced by 6-OH-DA. As expected from functional studies, compound (−)-**10a** turned out to be a potent agonist at DA receptors as it produced rapid contralateral rotations, which lasted over 6 h. In contrast, the reference compound apomorphine had a faster onset of action but much shorter duration of action compared to (−)-**10a** (Fig. 2). The total number of rotations produced by (−)-**10a** was much greater than that produced by apomorphine (1608 vs 345). This result also demonstrated that the compound (−)-**10a** penetrated the blood brain–barrier effectively with long duration of action at the concentration tested and its action in the CNS was specific. It is not known whether this long duration of action is due to the activity of the drug alone or a combination of the drug and an active metabolite. Interestingly, long duration of activity emanating from compounds containing a phenolic hydroxyl group has been reported in the past.[37]

## 5. Conclusion

In this report, we have been able to demonstrate the development of novel potent agonists for DA D2 and D3 receptors. In vitro [$^3$H]spiperone binding studies indicated preferential affinity of most of these molecules for the D3 receptor with compound (±)-**14** exhibiting the highest selectivity. In this current series compounds with the shorter methylene linker generally exhibited higher selectivity for the D3 receptor. In the functional assay, all of these derivatives exhibited higher intrinsic activity at the D3 receptor compared to the D2 receptor, thus, correlating well with their binding data. The pure enantiomer, (−)-**10a**, was tested in vivo in 6-OH-DA induced unilaterally lesioned rats and found to display high activity for producing contralateral rotations with long duration of action. This result confirmed potent agonist action of (−)-**10a** and its rapid blood brain barrier crossing ability. Further structural exploration is ongoing to produce compounds with higher selectivity for the D3 receptor.

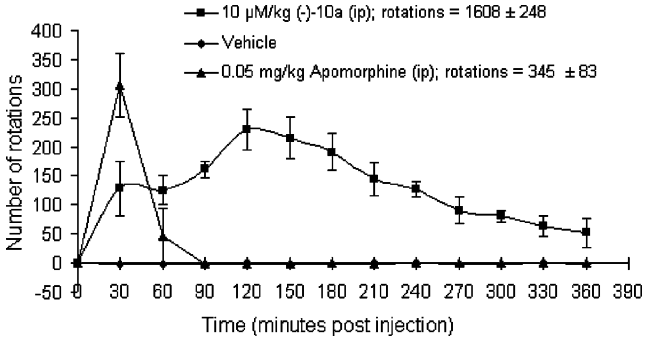



**Figure 2.** Effect on turning behavior of (−)-**10a**, apomorphine, and vehicle in unilaterally 6-OH-DA lesioned rats studied over 6 h. Each point is the mean ± SEM of four rats. The analysis of variance (ANOVA) performed with repeated measures indicated significant effects for treatments ($F[3,6] = 26.48$, $p < 0.05$) and intervals ($F[11,22] = 10.03$, $p < 0.05$).

## 6. Experimental

Analytical silica gel-coated TLC plates (Silica Gel 60 $F_{254}$) were purchased from EM Science and were visualized with UV light or by treatment with phosphomolybdic acid (PMA). Flash chromatography was carried out on Baker Silica Gel 40 mM. 1H NMR spectra were routinely obtained on GE-300 MHz and Varian 400 MHz FT NMR. The NMR solvent used was either $CDCl_3$ or $CD_3OD$ 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 (16.5 Ci/mmol) was from NEN Life Sciences Products, Boston, MA, and (+)-butaclamol from Research Biochemical Corp. (Natick, MA).

*Materials for the mitogenesis assay (D2 and D3)*: Cell lines: human D2- and D3-receptor containing CHOp cells. Growth medium: α-MEM complete contains: alfa minimum essential medium from Gibco (Invitrogen Corp); FBS = fetal bovine serum from Atlas Biologicals, Fort Collins, CO; penicillin–streptomycin from Gibco (Invitrogen Corp.); Geneticin (G418 sulfate) from Gibco. Assay medium: alpha MEM incomplete (same as above, but without the FBS). Subculturing: Trypsin–EDTA solution (10X) from Sigma. [$^3$H]Thymidine from NEN (NET-355), aqueous solution, specific activity 18.00 Ci/mmol. Quinpirole from Sigma/RBI. Buffer items: NaCl, KCl, $KH_2PO_4$, $NaHCO_3$, HEPES, glucose, and NaOH are either from Mallinckrodt or Sigma.

## 7. Procedure A

### 7.1. 2-[2-(4-Phenyl-piperazin-1-yl)-ethyl]-isoindole-1,3-dione (3a)

A mixture of 1-phenylpiperazine **2** (2.59 g, 15.98 mmol), N-(2-bromoethyl)phthalimide (8.12 g, 31.96 mmol), $Et_3N$ (2.0 mL) and $K_2CO_3$ (8.0 g) in DMF (40 mL) was stirred at 70 °C overnight under a nitrogen atmosphere. The reaction mixture was cooled, water (100 mL) was added and the mixture extracted with diethyl ether. The organic phase was combined dried over $Na_2SO_4$ and evaporated under vacuo to give the crude product, which was purified by flash chromatography (hexane/EtOAC = 1:1) to furnish **3a**, 3.81 g (71% yield). $^1$H NMR ($CDCl_3$) 2.68–2.72 (m, 6H, $N(CH_2)_3$, 3.12–3.15 (t, $J = 4.8$ Hz, 4H, $N(CH_2)_2$), 3.84–3.89 (t, $J = 6.3$ Hz, 2H $CONCH_2$), 6.80–6.82 (t, $J = 8.1$ Hz, 1H, Ar-H), 6.88–6.91 (d, $J = 8.1$ Hz, 2H, Ar-H), 7.21–7.26 (t, $J = 8.1$ Hz, 2H, Ar-H), 7.69–7.86 (m, 4H, Ar-H).

### 7.2. 2-[4-(4-Phenyl-piperazin-1-yl)-butyl]-isoindole-1,3-dione (3b)

1-Phenylpiperazine **2** (2.21 g, 7.81 mmol) was reacted with N-(4-bromobutyl)-phthalimide (1.26 g, 7.81 mmol), $K_2CO_3$ (8.0 g), $Et_3N$ (1.0 mL), and DMF (20 mL) as described in Procedure A to afford a yellow solid **3a**, 2.70 (55% yield). $^1$H NMR ($CDCl_3$) 1.55–1.82 (m, 4H, $CH_2CH_2$), 2.40–2.45 (t, $J = 7.5$ Hz, 2H, $NCH_2$), 2.57–2.61 (t, $J = 4.8$ Hz, 4H, $N(CH_2)_2$), 3.17–3.20 (t, $J = 4.8$ Hz, 4H, $N(CH_2)_2$), 3.71–3.75 (t, $J = 6.7$ Hz, 2H, $CONCH_2$), 6.82–6.94 (3H, Ar-H), 7.23–7.28 (m, 2H, Ar-H), 7.70–7.74 (m, 2H, Ar-H), 7.83–7.86 (m, 2H, Ar-H).

## 8. Procedure B

### 8.1. 2-(4-Phenyl-piperazin-1-yl)-ethylamine (4a)

Hydrazine (1.0 g, 31.2 mmol) was added to a solution of **3a** (1.97 g, 5.88 mmol) in EtOH (25 mL) under a $N_2$ atmosphere and the reaction mixture was stirred at room temperature for 24 h. The solvent was removed under vacuo and EtOAc was added to the residue. The solids were filtered off and the solution collected was dried over $Na_2SO_4$ and evaporated under vacuo to give a white solid **4a**, 1.18 g (98% yield) $^1$H NMR ($CDCl_3$) 2.46–2.51 (t, $J = 6.3$ Hz, 2H, $CH_2NH_2$), 2.68–2.71 (t, $J = 4.8$ Hz, 4H, $N(CH_2)_2$), 2.86–2.92 (t, $J = 6.3$ Hz, 2H, $NCH_2$), 3.12–3.16 (t, $J = 4.8$ Hz, 4H, $N(CH_2)_2$), 6.81–6.83 (t, $J = 8.1$ Hz, 1H, Ar-H), 6.88–6.91 (d, $J = 8.1$ Hz, 2H, Ar-H), 7.21–7.26 (t, $J = 8.1$ Hz, 2H, Ar-H).

### 8.2. 4-(4-Phenyl-piperazin-1-yl)-butylamine (4b)

Compound **3b** (7.70 g, 21.21 mmol) was reacted with $NH_2NH_2$ (3.0 g, 93.75 mmol) as detailed in Procedure B to give **4b**, 4.60 g (93% yield). $^1$H NMR ($CDCl_3$) 1.48–1.61 (m, 4H), 2.40–2.43 (t, $J = 7.2$ Hz, 2H, $NCH_2$), 2.61–2.63 (t, $J = 4.5$ Hz, 4H, $N(CH_2)_2$), 2.72–2.76 (t, $J = 6.4$ Hz, 2H, $CH_2NH_2$), 3.19–3.22 (t, $J = 4.6$ Hz, 4H, $N(CH_2)_2$), 6.33–6.94 (m, 3H, Ar-H), 7.23–7.28 (m, 2H, Ar-H).

## 9. Procedure C

### 9.1. (7-Methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-[2-(4-phenyl-piperazin-1-yl)-ethyl]-amine (5a)

A mixture of compound **4a** (1.18 g, 5.75 mmol), 7-methoxy-2-tetralone (1.22 g, 6.93 mmol), and $Na(OAc)_3BH$ (3.60 g, 17.26 mmol) and HOAc (1.0 mL) in 1,2-dichloroethane (20 mL) was stirred at room temperature under a $N_2$ atmosphere overnight. The solvent was evaporated and saturated $NaHCO_3/H_2O$ (10 mL) was added to the mixture, which was then extracted with EtOAc. The combined organic phase was dried over $Na_2SO_4$ and evaporated to give the crude product which was purified by flash chromatography (EtOAc/MeOH/$Et_3N$ = 50:5:1) to give the product **(5a)**, 1.95 g (93%). $^1$H NMR($CDCl_3$) 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).

### 9.2. (7-Methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-[4-(4-phenyl-piperazin-1-yl)-butyl]-amine (5b)

4-(4-Aminobutyl)-1-phenylpiperazine **4b** (4.30 g, 18.30 mmol) was reacted with 7-methoxy-2-tetralone (3.21 g, 18.24 mmol) and $Na(OAc)_3BH$ (11.40 g, 54.03 mmol) and HOAc (1.0 mL) in 1,2-dichloroethane (50 mL) to give **5b** 5.80 g (81% yield) (Procedure C). $^1$H NMR ($CDCl_3$) 1.58–1.60 (m, 4H), 2.03–2.07 (m, 2H), 2.40–2.47 (t, $J = 6.7$ Hz, 2H), 2.59–2.60 (t, $J = 4.8$ Hz, m, 4H, $N(CH_2)_2$), 2.68–2.85 (m, 5H), 2.91–3.03 (m, 2H), 3.19–3.22 (t, $J = 4.8$ Hz, 4H, $N(CH_2)_2$), 3.76 (s, 3H, $CH_3O$), 6.61–6.67 (m, 2H, Ar-H), 6.82–6.97 (m, 4H, Ar-H), 7.23–7.29 (m, 2H, Ar-H).

### 9.3. {2-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-ethyl}-(7-methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-amine (5c)

Compound **5c** was synthesized from **2b** by following procedures A, B, and C (73%, 3 steps). $^1$H NMR (300 MHz, $CD_3Cl$) 1.61–1.67 (m, 2H), 2.60–2.64 (m, 6H, $CH_2N(CH_2)_2$), 2.76–3.05 (m, 7H), 3.16–3.20 (t, $J = 4.8$ Hz, $N(CH_2)_2$), 3.78 (s, 3H, $CH_3O$), 6.72–6.82 (m, 2H, Ar-H), 6.90–6.90 (m, 2H, Ar-H), 7.10–7.28 (m, 2H, Ar-H).

### 9.4. {4-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-butyl}-(7-methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-amine (5d)

Compound **5d** was synthesized from **2b** by following the procedures A, B, and C (70%, 3 steps). $^1$H NMR ($CDCl_3$) 1.58–1.64 (m, 4H), 2.04–2.10 (m, 2H), 2.43–2.47 (t, $J = 6.6$ Hz, 2H), 2.60–2.65 (m, 4H, $(N(CH_2)_2)$, 2.76–2.82 (m, 5H), 2.93–2.98 (m, 2H), 3.02–3.08 (m, 4H, $N(CH_2)_2$), 3.77 (s, 3H, $CH_3O$), 6.62–6.71 (m, 2H, Ar-H), 6.94–7.01 (m, 2H, Ar-H), 7.14–7.16 (m, 2H, Ar-H).

## 10. Procedure D

### 10.1. (7-Methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-[2-(4-phenyl-piperazin-1-yl)-ethyl]-prop-2-ynyl-amine (6a)

Compound **5a** (1.18 g, 3.04 mmol) was reacted with propargyl chloride (1.20 g, 16.11 mmol) in the presence of $K_2CO_3$ (4.0 g) and DMF (25 mL) at 60 °C for 5 h. The mixture was cooled and was diluted with water, extracted with diethyl ether, and washed with brine. The combined ether fraction was dried over $Na_2SO_4$, evaporated, and purified by flash chromatography to furnish **6a**, 0.35 g (29% yield). $^1$H NMR ($CDCl_3$) 1.59–1.71 (m, 2H), 2.13–2.18 (m, 2H), 2.20–2.34 (t, $J = 2.1$ Hz, 1H, C≡CH), 2.56–2.60 (t, $J = 6.9$ Hz, 2H, $NCH_2$), 2.65–2.68 (t, $J = 4.8$ Hz, 4H, $N(CH_2)_2$), 2.75–2.81 (m, 2H), 2.84–2.89 (t, $J = 7.2$ Hz, 2H). 2.98–3.02 (m, 3H), 3.20–3.23 (t,

$J = 4.8$ Hz, 4H, $N(CH_2)_2$), 3.60 (s, 2H, $NCH_2C{\equiv}CH$), 3.77 (s, 3H, $CH_3O$), 6.60–6.83 (m, 2H, Ar-H), 6.85–6.98 (m, 4H, Ar-H), 7.23–7.29 (m, 2H, Ar-H).

### 10.2. (7-Methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-[4-(4-phenyl-piperazin-1-yl)-butyl]-prop-2-ynyl-amine (6b)

A mixture of **5b** (0.65 g, 1.65 mmol), propargyl chloride (0.30 mL, 4.63 mmol), $K_2CO_3$ (1.0 g), and $Et_3N$ (1.0 mL) was stirred in DMF (20 mL) as shown in Procedure D to give a thick oil **6b**, 0.33 g (46%). $^1$H NMR ($CDCl_3$) 1.51–1.56 (m, 4H), 2.11–2.15 (m, 2H), 2.17–2.19 (t, $J = 2.2$ Hz, 1H, C≡CH), 2.40–2.44 (t, $J = 7.2$ Hz, 2H), 2.59–2.63 (t, $J = 4.8$ Hz, 4H, $N(CH_2)_2$), 2.67–2.83 (m, 5H), 2.93–3.01 (m, 2H), 3.19–3.23 (t, $J = 4.5$ Hz, 4H, $N(CH_2)_2$), 3.52–3.53 (d, $J = 2.1$ Hz, 2H, $CH_2C{\equiv}CH$), 3.77 (s, 3H, $CH_3O$), 6.62–6.70 (m, 2H, Ar-H), 6.83–7.00 (m, 4H, Ar-H), 7.24–7.29 (m, 2H, Ar-H).

### 10.3. {4-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-butyl}-(7-methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-prop-2-ynyl-amine (6c)

Compound **5d** was reacted with propargyl chloride (1.50 g, 20.13 mmol) and $K_2CO_3$ (4.50 g) in DMF (20 mL) (Procedure D) to give **6c**, 0.48 g (24%). $^1$H NMR ($CDCl_3$) 1.55–1.68 (m, 4H), 2.11–2.15 (m, 2H), 2.17–2.18 (t, $J = 1.8$ Hz, 1H, C≡CH), 2.43–2.47 (t, $J = 6.6$ Hz, 2H), 2.49–2.66 (br s, 4H, $N(CH_2)_2$), 2.68–2.88 (m, 8H), 2.98–3.00 (m, 1H), 3.06–3.10 (br s, 4H, $N(CH_2)_2$), 3.52–3.53 (d, $J = 1.8$ Hz, 2H, $CH_2C{\equiv}CH$), 3.77 (s, 3H, $CH_3O$), 6.30–6.72 (m, 2H, Ar-H), 6.94–7.00 (m, 2H, Ar-H), 6.97–7.16 (m, 2H, Ar-H).

## 11. Procedure E

### 11.1. 7-{[2-(4-Phenyl-piperazin-1-yl)-ethyl]-prop-2-ynyl-amino}-5,6,7,8-tetrahydro-naphthalen-2-ol (7a)

Borontribromide (1 M solution in dichloromethane), (1.5 mL, 1.5 mmol) was added to a solution of **6a** (0.28 g, 0.70 mmol) in anhydrous $CH_2Cl_2$ (10 mL) at −40 °C under $N_2$ atmosphere. The reaction mixture was stirred at −40 °C for 2 h and then at 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 $Na_2SO_4$, evaporated under vacuo, and the crude product was purified by flash chromatography (EtOAc/$Et_3N$ = 50:1) to afford compound **7a**, 0.23 g (85%). $^1$H NMR($CDCl_3$) 1.56–1.68 (m, 2H), 2.11–2.15 (m, 2H), 2.20–2.22 (t, $J = 2.1$ Hz, 1H, C≡CH), 2.57–2.61 (t, $J = 6.6$ Hz, 2H, $NCH_2$), 2.65–2.69 (t, $J = 4.8$ Hz, 4H, $N(CH_2)_2$), 2.75–2.81 (m, 2H), 2.84–2.86 (m, 5H), 2.86–2.91(t, $J = 4.8$ Hz, 2H, $N(CH_2)_2$) 3.58 (s, 2H, $CH_2C{\equiv}CH$), 6.55–6.61 (m, 2H, Ar-H), 6.83–6.94 (m, 4H, Ar-H). 7.23–7.27 (m, 2H, Ar-H). Free base was converted into its HCl salt. Mp = 164–166 °C. Anal. Calcd for ($C_{27}H_{31}N_3O{\cdot}3HCl{\cdot}0.8H_2O$) C, H, N.

### 11.2. 7-{[4-(4-Phenyl-piperazin-1-yl)-butyl]-prop-2-ynyl-amino}-5,6,7,8-tetrahydro-naphthalen-2-ol (7b)

Compound **6b** (0.195 g, 0.742 mmol) was reacted with 1 M $BBr_3/CH_2Cl_2$ (0.80 mL, 0.80 mmol) (Procedure E) to give compound **7b**, 0.13 g (72%). $^1$H NMR ($CDCl_3$) 1.54–1.68 (m, 4H), 2.09–2.14 (m, 2H), 2.17–2.18 (t, $J = 2.1$ Hz, 1H), 2.41–2.45 (t, $J = 7.0$ Hz, 2H), 2.60–2.63 (t, $J = 4.5$ Hz, 4H, $N(CH_2)_2$), 2.67–2.71 (t, $J = 6.2$ Hz, 2H), 2.76–2.80 (m, 4H), 2.89–2.92 (m, 1H) 3.51–3.52 (d, $J = 2.1$ Hz, 2H, $CH_2C{\equiv}CH$), 3.20–3.24 (t, $J = 4.6$ Hz, 4H, $N(CH_2)_2$), 6.56–6.61 (m, 2H, Ar-H), 6.88–6.95 (m, 4H, Ar-H), 7.24–7.29 (m, 2H, Ar-H),). Free base was converted into its HBr salt. Mp = 182–186 °C. Anal. Calcd for ($C_{27}H_{35}N_3O{\cdot}3HBr{\cdot}0.75H_2O$) C, H, N.

### 11.3. 7-({4-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-butyl}-prop-2-ynyl-amino)-5,6,7,8-tetrahydro-naphthalen-2-ol (7c)

Compound **6c** (0.28 g, 0.70 mmol) was reacted with $BBr_3/CH_2Cl_2$ (1.50 mL, 1.50 mmol) (Procedure E) to give pure product **7c**, 0.23 g (84%). $^1$H NMR ($CDCl_3$) 1.48–1.56 (m, 4H), 2.09–2.13 (m, 2H), 2.17–2.18 (t, $J = 1.8$ Hz, 1H, C≡CH), 2.45–2.47 (t, $J = 6.6$ Hz, 2H), 2.66–2.68 (br s, 4H, $N(CH_2)_2$), 2.71–2.80 (m, 5H), 2.89–2.96 (m, 2H), 3.09–3.10 (br s, 4H, $N(CH_2)_2$), 3.51–3.52 (d, $J = 1.5$ Hz, 2H, $CH_2C{\equiv}CH$), 6.57–6.61 (m, 2H, Ar-H), 6.92–6.98 (m, 2H, Ar-H), 7.14–7.16 (m, 2H, Ar-H). Free base was converted into its HCl salt, mp = 180–183 °C and analysis demonstrated partial hydrochloride salt formation. Anal. Calcd for ($C_{27}H_{33}N_3OCl_2{\cdot}2.70HCl{\cdot}0.06H_2O$) C, H, N.

### 11.4. 7-{[2-(4-Phenyl-piperazin-1-yl)-ethyl]-propyl-amino}-5,6,7,8-tetrahydro-naphthalen-2-ol (10a)

Compound **9a** (0.60 g, 0.88 mmol) was reacted with 1 M $BBr_3/CH_2Cl_2$ (1.60 mL, 1.60 mmol) in $CH_2Cl_2$ (20 mL) to furnish **10a**, 0.29 g (83%) (Procedure E). $^1$H NMR ($CDCl_3$) 0.86–0.91 (t, $J = 7.2$ Hz, 3H, $CH_3CH_2CH_2N$), 1.43–1.50 (m, 4H), 1.89–1.93 (m, 2H), 2.46–2.51 (t, $J = 7.5$ Hz, 2H, $NCH_2$), 2.53–2.68 (m, 6H), 2.70–2.74 (t, $J = 4.8$ Hz, 4H, $N(CH_2)_2$), 2.83–2.88 (m, 1H), 3.23–3.26 (t, $J = 4.8$ Hz, 4H, $N(CH_2)_2$), 6.45–6.56 (m, 2H, Ar-H), 6.83–6.93 (m, 4H, Ar-H), 7.23–7.26 (m, 2H, Ar-H). Free base was converted into its HCl salt, mp = 143–146 °C. Anal. Calcd for ($C_{27}H_{35}N_3O{\cdot}3HCl{\cdot}0.9H_2O$) C, H, N.

### 11.5. 7-{[4-(4-Phenyl-piperazin-1-yl)-butyl]-propyl-amino}-5,6,7,8-tetrahydro-naphthalen-2-ol (10b)

Compound **9b** (0.30 g, 0.69 mmol) was reacted with 1 M $BBr_3/CH_2Cl_2$ (1.3 mL) to give **10b**, 0.25 g (87%) (Procedure E). $^1$H NMR($CDCl_3$) 0.86–0.91 (t, $J = 7.2$ Hz, 3H), 1.40–1.82 (m, 7H), 1.93–2.05 (m, 1H), 2.39–2.44 (t, $J = 7.2$ Hz, 2H), 2.44–2.50 (t, $J = 7.5$ Hz, 2H), 2.56–2.51(t, $J = 6.6$ Hz, 2H), 2.60–2.63 (t, $J = 4.2$ Hz, 4H, $N(CH_2)_2$), 2.75–2.80 (m, 4H), 2.92–2.99 (m, 1H), 3.20–3.23 (t, $J = 4.2$ Hz, 4H, $N(CH_2)_2$), 6.54–6.60 (m,

2H, Ar-H), 6.83–6.95 (m, 4H, Ar-H), 7.24–7.29 (m, 2H, Ar-H). Free base was converted into its HBr salt. Mp = 152–156 °C. Anal. Calcd for ($C_{27}H_{42}N_3OBr_3 \cdot 0.30H_2O$) C, H, N.

### 11.6. 7-({2-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-ethyl}-propyl-amino)-5,6,7,8-tetrahydro-naphthalen-2-ol (10c)

Compound **9c** (0.23 g, 0.47 mmol) in $CH_2Cl_2$ (20 mL) was demethylated with $BBr_3/CH_2Cl_2$ (2.0 mL, 2.0 mmol) (Procedure E) to give **7c** as a thick oil 0.19 g (87%). $^1$H NMR (300 MHz, $CDCl_3$) 0.86–0.91 (t, $J = 7.2$ Hz, 3H, $CH_3CH_2CH_2N$), 1.44–1.50 (m, 4H), 1.90–1.94 (m, 2H), 2.46–2.51 (t, $J = 7.5$ Hz, 2H, $NCH_2$), 2.53–2.68 (m, 6H), 2.70–2.74 (t, $J = 4.8$ Hz, 4H, $N(CH_2)_2$), 2.83–2.88 (m, 1H), 3.25–3.27 (t, $J = 4.8$ Hz, 4H, $N(CH_2)_2$), 6.40–6.54 (m, 2H, Ar-H), 6.87–6.93 (m, 2H, Ar-H), 7.08–7.15 (m, 2H, Ar-H). Anal. Calcd for ($C_{25}H_{36}N_3OCl_5 \cdot 1.9H_2O$) C, H, N.

### 11.7. 7-({4-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-butyl}-propyl-amino)-5,6,7,8-tetrahydro-naphthalen-2-ol (10d)

Compound **9d** (0.36 g, 0.71 mmol) was reacted with 1 M $BBr_3/CH_2Cl_2$ (1.5 mL, 1.5 mmol) (Procedure E) to give **10d** (0.29 g, 83%). $^1$H NMR ($CDCl_3$) 0.85–0.90 (t, $J = 7.2$ Hz, 3H, $CH_3$), 1.43–1.58 (m, 6H), 1.96–2.00 (m, 2H), 2.44–2.55 (m, 6H, $CH_2NN(CH_2)_2$), 2.69–2.77 (m, 8H), 2.94–2.95 (m, 1H), 3.08–3.09 (br s, 4H, $N(CH_2)_2$), 6.51–6.57 (m, 2H, Ar-H), 6.88–6.93 (m, 2H, Ar-H), 7.09–7.15 (m, 2H, Ar-H). Free base was converted into its HCl salt, mp = 155–159 °C. Anal. Calcd for ($C_{27}H_{37}N_3OCl_2 \cdot 3HCl \cdot 0.8H_2O$) C, H, N.

## 12. Procedure F

### 12.1. *N*-(7-Methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-*N*-[2-(4-phenyl-piperazin-1-yl)-ethyl]-propionamide (8a)

Propionyl chloride (0.2 g, 2.16 mmol) was added to a solution of compound **5a** (0.36 g, 0.97 mmol) and $Et_3N$ (1.0 mL) in anhydrous methylene chloride at 0 °C under $N_2$ atmosphere and then stirred at room temperature for 2 h. The reaction was diluted with $CH_2Cl_2$, washed with water, brine, and the organic layer was dried over $Na_2SO_4$, evaporated, and purified by flash chromatography. (EtOAc/MeOH/$Et_3N$ = 95:5:0.5) to give **8a**, 0.42 g (93%). $^1$H NMR ($CDCl_3$) 1.14–1.20 (t, $J = 6.6$ Hz, 3H, $CH_3CH_2CO$), 1.63–1.70 (m, 2H), 1.90–2.04 (m, 2H), 2.40–2.50 (m, 4H), 2.66–2.74 (t, $J = 4.8$ Hz, 4H, $N(CH_2)_2$) 2.76–2.91 (m, 5H), 3.20–3.22 (t, $J = 4.8$ Hz, 4H, $N(CH_2)_2$), 3.78 (s, 3H, $CH_3O$), 6.60–6.70 (m, 2H, Ar-H), 6.91–7.01 (m, 4H, Ar-H), 7.25–7.29 (m, 2H, Ar-H).

### 12.2. *N*-(7-Methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-*N*-[4-(4-phenyl- piperazin-1-yl)-butyl]-propionamide (8b)

Compound **5b** (0.28 g, 0.71 mmol) was reacted with propionyl chloride (0.25 g, 3.57 mmol) and $Et_3N$ (1.0 mL) in $CH_2Cl_2$ (10 mL) (Procedure F) to give pure compound **8b**, 0.32 g (99%). $^1$H NMR ($CDCl_3$) 1.11–1.26 (t, $J = 6.6$ Hz, 3H), 1.52–1.74 (m, 6H), 1.89–1.98 (m, 2H), 2.35–2.45(m, 4H), 2.58–2.61 (t, $J = 4.5$ Hz, 4H, $N(CH_2)_2$), 2.78–3.05 (m, 4H), 3.18–3.23 (t, $J = 4.5$ Hz, 4H, $N(CH_2)_2$), 3.15–3.56 (m, 1H), 3.76 (s, 3H, $CH_3O$–), 6.58–6.73 (m, 2H, Ar-H), 6.85–7.03 (m, 4H, Ar-H), 7.23–7.28 (t, $J = 7.6$ Hz, 2H, Ar-H).

## 13. Procedure G

### 13.1. (7-Methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-[2-(4-phenyl-piperazin-1-yl)-ethyl]-propyl-amine (9a)

Compound **8a** (0.38 g, 0.90 mmol) in anhydrous THF (15 mL) was added dropwise into a suspension of $LiAlH_4$ (0.15 g, 4.41 mmol) in anhydrous THF at 0 °C under $N_2$ atmosphere. The reaction mixture was refluxed for 8 h, cooled to room temperature and saturated $NaOH/H_2O$ (1 mL) was added dropwise. The mixture was filtered and the solution was dried over $Na_2SO_4$. The solvent was removed under vacuo to afford a white solid **9a**, 0.36 g (97%). $^1$H NMR ($CDCl_3$) 0.87–0.93 ( t, $J = 7.2$ Hz, 3H, $CH_3CH_2CH_2N$), 1.46–1.53 (m, 4H), 1.88–2.07 (m, 2H), 2.51–2.55 (t, $J = 7.2$ Hz, 2H, $CH_2N$), 2.64–2.68 (t, $J = 4.8$ Hz, 4H, $N(CH_2)_2$), 2.72–2.83 (m, 6H), 2.90–3.06 (m, 1H), 3.19–3.22 (t, $J = 4.8$ Hz, 4H, $N(CH_2)_2$), 3.77 (s, 3H, $CH_3O$), 6.62–6.70 (m, 2H, Ar-H), 6.85-7.00 (m, 4H, Ar-H), 7.24-7.29 (m, 2H, Ar-H).

### 13.2. (7-Methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-[4-(4-phenyl-piperazin-1-yl)-butyl]-propyl-amine (9b)

Compound **8b** (0.30 g, 0.71 mmol) was reacted with $LiAlH_4$ (0.25 g, 7.57 mmol) in THF (20 mL) (Procedure G) to give **9b** 0.28 g (99%). $^1$H NMR ($CDCl_3$) 0.86–0.91 (t, $J = 7.2$ Hz, 3H), 1.40–1.66 (m, 7H), 1.98–2.05(m, 1H), 2.38–2.43 (t, $J = 7.2$ Hz, 2H), 2.45–2.50 (t, $J = 7.2$ Hz, 2H), 2.52–2.56 (t, $J = 6.8$ Hz, 2H), 2.59–2.62 (t, $J = 4.8$ Hz, 4H, $N(CH_2)_2$), 2.69–2.88 (m, 4H), 2.91–3.02 (m, 1H), 3.20–3.22 (t, $J = 4.5$ Hz, 4H, $N(CH_2)_2$), 3.77 (s, 3H, $CH_3O$), 6.62–6.69 (m, 2H, Ar-H), 6.83–7.00 (m, 4H, Ar-H), 7.24–7.29 (m, 2H, Ar-H).

### 13.3. {2-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-ethyl}-(7-methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-propyl-amine (9c)

A mixture of amine **5c** (1.47 g, 3.39 mmol), 1-bromopropane (2.08 g, 15.40 mmol), and $K_2CO_3$ (3.0 g, 21.74 mmol) in dry DMF (40 mL) was stirred at 60 °C for 20 h. The reaction mixture was poured into water (100 mL) and extracted with $Et_2O$ (3 × 200 mL). The combined organic phase was washed with brine and dried over $Na_2SO_4$ (Procedure D). The solvent was removed by evaporation and residue was purified by flash chromatography (EtOAc/$Et_3N$ = 100:1) to a thick oil 1.32 g (82%). $^1$H NMR (300 MHz, $CD_3Cl$) 0.87–0.93 ( t, $J = 7.2$ Hz, 3H, $CH_3CH_2CH_2N$), 1.46–1.53 (m, 4H), 1.88–2.07 (m, 2H), 2.51–2.55 (t, $J = 7.2$ Hz, 2H, $CH_2N$),

2.64–2.68 (t, $J = 4.8$ Hz, 4H, $N(CH_2)_2$), 2.71–2.83 (m, 6H), 2.90–3.06 (m, 1H), 3.21–3.24 (t, $J = 4.8$ Hz, 4H, $N(CH_2)_2$), 3.78 (s, 3H, $CH_3O$), 6.64–6.71 (m, 2H, Ar-H), 6.95–7.01 (m, 2H, Ar-H), 7.14–7.15 (m, 2H, Ar-H).

### 13.4. {4-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-butyl}-(7-methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-propyl-amine (9d)

Compound **9d** was synthesized from **5d** by following the Procedures F and G (92%, two steps). $^1$H NMR($CDCl_3$) 0.89–0.93 (t, $J = 7.2$ Hz, 3H, $CH_3CH_2$), 1.47–1.61 (m, 6H), 2.02–2.05 (m, 2H), 2.44–2.49 (t, $J = 7.2$ Hz, 2H, $NCH_2$), 2.52–2.65 (m, 8H), 2.76–2.87 (m, 5H), 3.07–3.08 (br s, 4H, $N(CH_2)_2$), 3.77 (s, 3H, $CH_3O$), 6.63–6.70 (m, 2H, Ar-H), 6.95–7.00 (m, 2H, Ar-H), 7.14–7.19 (t, $J = 2.7$ Hz, 2H, Ar-H).

## 14. Synthesis of 14 and 15

### 14.1. (1,4-Dioxa-spiro[4.5]dec-8-yl)-[2-(4-phenyl-piperazin-1-yl)-ethyl]-amine (11)

A mixture of amine **4a** (2.21 g, 10.8 mmol), cyclohexanedione monoethylene ketal (1.68 g, 10.8 mol), $Na(OAc)_3BH$ (3.24 g, 15.12 mmol), and HOAc(0.65 g, 10.8 mol) in $ClCH_2CH_2Cl$ (40 mL) was stirred overnight at room temperature. The reaction mixture was diluted with EtOAc (200 mL), washed with saturated $NaHCO_3$ solution, water, and brine. The organic layer was dried over $Na_2SO_4$, evaporated and the crude product was purified by flash chromatography (EtOAc/MeOH/$Et_3N$ = 100:5:1) to give **11** as a white solid 3.55 g (91%). $^1$H NMR (300 MHz, $CDCl_3$) 1.52–1.56 (m, 6H), 1.74–1.79 (m, 2H), 1.91–1.96 (m, 2H), 2.57–2.66 (m, 7H, $N(CH_2)_2$, $CHNHCH_2$), 2.80–2.84 (t, $J = 6.0$ Hz, 2H), 3.14–3.18 (t, $J = 48$ Hz, 4H, $N(CH_2)_2$), 3.90 (s, 4H, $OCH_2CH_2O$), 6.83–6.91 (m, 3H, Ar-H), 7.21–7.25 (m, 2H, Ar-H).

### 14.2. (1,4-Dioxa-spiro[4.5]dec-8-yl)-[2-(4-phenyl-piperazin-1-yl)-ethyl]-propyl-amine (12)

Compound **11** (1.0 g, 2.94 mmol), 1-bromopropane (1.45 g, 11.80 mol), and $K_2CO_3$ (1.22 g, 8.70 mmol) in dry DMF (20 mL) was stirred at 60 °C for 10 h and the mixture was poured into water (50 mL) and extracted with $Et_2O$ (3 × 100 mL). The combined organic layer was washed with brine, dried over $Na_2SO_4$ evaporated and the residue was purified by flash chromatography (EtOAc/MeOH/$Et_3N$ = 100:2:1) to give **12** as a thick oil 0.80 g (70%). $^1$H NMR (300 MHz, $CDCl_3$) 0.83–0.88 (t, $J = 7.2$ Hz, 3H, $CH_3$), 1.40–1.47 (m, 2H), 1.52–1.58 (m, 4H), 1.73–1.80 (m, 4H), 2.41–2.50 (m, 4H), 2.58–2.65 (m, 7H), 3.17–3.20 (t, $J = 5.2$ Hz, 4H, $N(CH_2)_2$), 3.17–3.20 (t, $J = 5.2$ Hz, 4H, $N(CH_2)_2$), 3.92 (s, 4H, $OCH_2CH_2O$), 6.82–6.86 (t, $J = 7.2$ Hz, 1H, Ar-H), 6.90–6.93 (d, $J = 7.8$ Hz, 2H, Ar-H), 7.22–7.28 (m, 2H, Ar-H).

### 14.3. 4-{[2-(4-Phenyl-piperazin-1-yl)-ethyl]-propyl-amino}-cyclohexanone (13)

A solution of ketal **12** (2.00 g, 5.17 mmol) in THF (20 mL) and 1 N HCl (20 mL) was stirred at 80 °C under $N_2$ for 2 h. THF was removed under vacuo and saturated $NaHCO_3$ solution was added slowly. The mixture was extracted with EtOAc (3 × 100 mL) and the combined organic layer was washed with brine, dried over $Na_2SO_4$, and evaporated to give the crude product, which was purified by flash chromatography (EtOAc/$Et_3N$ = 100:1) to afford **13** 1.31 g (99%). $^1$H NMR (300 MHz, $CDCl_3$) 0.87–0.90 (t, $J = 5.7$ Hz, 3H, $CH_3$), 1.43–1.51 (dt, $J = 5.7$, 6.0 Hz, 2H, $NCH_2CH_2CH_3$), 1.70–1.79 (m, 2H), 2.04–2.07 (m, 2H), 2.30–2.52 (m, 8H), 2.64–2.70 (m, 6H), 2.97–3.03 (t, $J = 10.4$ Hz, 1H, $NCH(CH_2)_2$), 3.19–3.21 (t, $J = 4.4$ Hz, 4H, $N(CH_2)_2$), 6.83–6.87 (t, $J = 7.2$ Hz, 1H, Ar-H), 6.91–6.93 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.24–7.28 (m, 2H, Ar-H).

### 14.4. *N*6-[2-(4-Phenyl-piperazin-1-yl)-ethyl]-*N*6-propyl-4,5,6,7-tetrahydro-benzothiazole-2,6-diamine (14)

Compound **13** (0.50 g, 1.45 mmol) and pyrrolidine (0.13 mL, 1.52 mmol) in anhydrous benzene was heated to reflux in a Dean–Stark apparatus for 1.5 h. The mixture was then cooled to room temperature and concentrated in vacuo. The residue was dissolved in anhydrous MeOH. Sulfur powder (0.046 g, 0.1812 mmol, of $S_8$) was added at room temperature, stirred for 20 min and then cooled to 0 °C. Cyanamide (0.061 g, 1.45 mmol) in MeOH was added to the reaction mixture and stirred overnight at rt. Methanol was evaporated on the rotavapor, the residue dissolved in EtOAc, washed with water, brine, dried, concentrated, and purified by column chromatography (0.5% MeOH and 1% $Et_3N$ in EtOAc) to afford the title product **14** (0.385 g, 66%) as a thick yellow solid.

$^1$H NMR (400 MHz, $CDCl_3$): 0.88 (t, 3H, $J = 7.4$ Hz), 1.42–1.51 (m, 2H), 1.71 (dq, 1H, $J = 5.6$, 12.0 Hz), 1.97–1.99 (m, 1H), 2.45–2.59 (m, 6H), 2.63 (−2.72 (m, 8H), 3.00–3.05 (m, 1H), 3.19 (t, 4H, $J = 4.8$ Hz), 4.84 (s, 2H), 6.85 (t, 1H, $J = 7.2$ Hz), 6.92 (d, 2H, $J = 8.0$ Hz), 7.23–7.27 (m, 2H). The product was converted into the corresponding trioxalate salt. Anal. Calcd for ($C_{28}H_{39}N_5SO_{12}\cdot 1.55H_2O$) C, H, N.

### 14.5. *N*6-[2-(4-Phenyl-piperazin-1-yl)-ethyl]-*N*6-propyl-5,6,7,8-tetrahydro-quinazoline-2,6-diamine (15)

Into a solution of ketone **13** (0.60 g, 1.75 mmol) in dry toluene (20 mL), tris(dimethylamino)methane (1.27 g, 8.76 mmol) was added and the mixture was stirred under nitrogen at 90 °C for 4 h. The solvent was removed under vacuo and the residue was dissolved in EtOH (25 mL). Guandine carbonate (0.78 g, 4.33 mmol) was added next. The mixture was then refluxed for 17 h. The solvent was evaporated in vacuo and the residue was diluted with $CH_2Cl_2$ and washed with brine. The organic layer was dried over $Na_2SO_4$ and evaporated to give the

crude product, which was purified by flash chromatography (EtOAc/MeOH/$Et_3N$ = 25:1:1) to Give **15** as a yellow solid, 0.61 g (88%). $^1H$ NMR (300 MHz, $CDCl_3$) 0.86–0.91 (t, $J = 7.2$ Hz, 3H, $CH_3$), 1.44–1.52 (dt, $J = 7.2, 7.2$ Hz, 2H, $NCH_2CH_2CH_3$), 1.61–1.74 (m, 1H), 2.03–2.10 (m, 1H), 2.49–2.56 (m, 4H), 2.64–2.67 (t, $J = 5.0$ Hz, 4H, $N(CH_2)_2$), 2.69–2.75 (m, 4H), 2.79–2.81(dd, $J = 2.8, 6.0$ Hz, 1H), 2.85–2.95 (m, 1H), 3.18–3.21 (t, $J = 5.0$ Hz, 4H, $N(CH_2)_2$), 4.88 (s, 2H, $NH_2$), 6.82–6.87 (t, $J = 7.2$ Hz, 1H, Ar-H), 6.90–6.93 (d, $J = 8.4$ Hz, 2H, Ar-H), 8.01 (s, 1H, H-pyrimidine). Free base was converted into its HCl salt. Mp = 97–102 °C. Anal. Calcd for ($C_{23}H_{34}N_6 \cdot 4HCl \cdot 1.5H_2O$) C, H, N.

## 15. Synthesis of enantiomers of 10a

### 15.1. 2-Methoxy-*N*-(7-methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-2- phenyl-*N*-[2-(4-phenyl-piperazin-1-yl)-ethyl]-acetamide (16)

A mixture of (*R*)-(−)-α-methoxyphenylacetic acid (0.456 g, 2.74 mmol), EDCI (0.58 g, 3.02 mmol), HOBT (0.40 g, 3.02 mmol), and $Et_3N$ (0.38 mL, 2.75 mmol) in anhydrous methylene chloride was stirred at room temperature under nitrogen atmosphere for 1 h. A solution of amine **5a** (0.5 g, 1.374 mmol) in anhydrous methylene chloride was added to the reaction mixture under $N_2$ at room temperature and stirred for 20 h. The mixture was diluted with $CH_2Cl_2$, washed with 5% citric acid solution, sodium bicarbonate, and brine. The solvent was removed and the residue was purified by column chromatography (1% MeOH, 3% $Et_3N$ in EtOAc) to afford a diastereomeric mixture of **16** (0.57 g, 81%).

### 15.2. Separation of diastereomers

The diastereoisomers were separated by semi-preparative HPLC using a normal phase column (Nova-Pack Silica 6 μm). The mobile phase used was 3% isopropanol in hexane with a flow rate of 18 mL/min. The two fractions were eluted with retention time of 18.76 min for the (+)-isomer **16a** and 23 min for (−)-isomer **16b**. Final purity of the separated diastereoisomers was checked by an analytical normal phase column (Nova-Pack Silica 60 Å 4 μm) using the same mobile phase with a flow rate of 1 mL/min. Pure diastereomers **16a** (+)-isomer and **16b** (−)-isomer were eluted at 10.96 and 13.43 min, respectively.

Compound **16a** (+)-isomer was isolated in 0.20 g, 30% yield.

Compound **16b** (−)-isomer was isolated in 0.20 g, 30% yield.

$^1H$ NMR (400 MHz, $CDCl_3$) of **16a**: 1.24–1.29 (m, 2H), 2.33–2.43 (m, 2H), 2.50–2.74 (m, 8H), 2.82–2.89 (m, 2H), 3.19 (t, 4H, $J = 4.8$ Hz), 3.52 (s, 3H), 3.75 (s, 3H), 4.26–4.34 (m, 1H), 5.10 (s, 1H), 6.51 (d, 1H, $J = 2.4$ Hz), 6.68 (dd, 1H, $J = 2.4, 8.0$ Hz), 6.84 (t, 1H, $J = 7.2$ Hz), 6.92 (d, 2H, $J = 8.8$ Hz), 7.23–7.27 (m, 2H), 7.28–7.36 (m, 3H), 7.38–7.40 (m, 2H), 7.47–7.49 (m, 1H).

$^1H$ NMR (400 MHz, $CDCl_3$) of **16b**: 1.24–1.28 (m, 2H), 2.34–2.44 (m, 2H), 2.58–2.74 (m, 8H), 2.80–2.87 (m, 2H), 3.19 (t, 4H, $J = 4.8$ Hz), 3.46 (s, 3H), 3.75 (s, 3H), 4.19–4.21 (m, 1H), 5.04 (s, 1H), 6.46 (d, 1H, $J = 2.4$ Hz), 6.69 (dd, 1H, $J = 2.4, 8.0$ Hz), 6.85 (t, 1H, $J = 7.2$ Hz), 6.92 (d, 2H, $J = 8.8$ Hz), 7.24–7.29 (m, 2H), 7.31–7.35 (m, 3H), 7.38–7.40 (m, 2H), 7.48–7.50 (m, 1H).

### 15.3. (7-Methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-[2-(4-phenyl-piperazin-1-yl)ethyl]-amine: (+)-isomer-(17a)

Potassium *t*-butoxide (0.26 g, 2.34 mmol) was added to a solution of **16a** (0.20 g, 0.39 mmol) in THF at room temperature under nitrogen atmosphere and stirred overnight. TLC revealed complete consumption of the starting material and formation of a mixture of the free amine and N-formyl derivative. The solvent was removed, the residue suspended in EtOAc, washed with water, $NH_4Cl$ solution, brine, dried, and concentrated.

Into a solution of this mixture in dry THF, a solution of MeLi (0.56 mL, 0.78 mmol) was added at rt under $N_2$ atmosphere and stirred for approximately 0.5 h when TLC revealed completion of the reaction. The mixture was quenched with water, the solvent evaporated, and the residue suspended in EtOAc. The organic layer was washed with water, brine, dried, concentrated, and purified by column chromatography (10% MeOH, 1% $Et_3N$ in EtOAc) to afford the optically pure amine (+)**17a** (0.13 g, 88%).

$^1H$ NMR (400 MHz, $CDCl_3$): 1.60–1.68 (m, 2H), 2.60–2.63 (m, 6H), 2.76—3.04 (m, 7H), 3.18 (t, 4H, $J = 4.8$ Hz). 3.78 (s, 3H), 6.51 (d, 1H, $J = 2.4$ Hz), 6.68 (dd, 1H, $J = 2.4, 8.0$ Hz), 6.84 (t, 1H, $J = 7.2$ Hz), 6.92 (d, 2H, $J = 8.8$ Hz), 7.28–7.36 (m, 3H).

### 15.4. (7-Methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-[2-(4-phenyl-piperazin-1-yl)ethyl]-amine: (−)-isomer-(17b)

Amide **16b** (0.200 g, 0.39 mmol) was hydrolyzed under similar conditions as reported above to afford the optically pure amine **17b** (0.13 g, 88%).

$^1H$ NMR identical is identical with that of **17a**.

The amines (+)-**17a** and (−)-**17b** were converted to the final products (+)-**10a** and (−)-**10a** in three steps as described in Scheme 2 (Procedures F, G, and E) in 81% and 82% yield, respectively.

*7-{[2-(4-Phenyl-piperazin-1-yl)-ethyl]-propyl-amino}-5,6,7,8-tetrahydro-naphthalen-2-ol (+)*-**10a**

Optical rotation: $[\alpha]_D$+8.21 (*c* 2, MeOH)

$^1H$ NMR (400 MHz, $CDCl_3$): 0.90 (t, 3H, $J = 7.2$ Hz), 1.43–1.51 (m, 4H), 1.88–1.95 (m, 2H), 2.49 (t, 2H,

$J = 7.2$ Hz), 2.52–2.69 (m, 6H), 2.72 (t, 4H, $J = 4.8$ Hz), 2.84–2.89 (m, 1H), 3.21 (t, 4H, $J = 4.8$ Hz), 6.51 (d, 1H, $J = 2.4$ Hz), 6.68 (dd, 1H, $J = 2.4$, 8.0 Hz), 6.85 (t, 1H, $J = 7.2$ Hz), 6.91 (d, 2H, $J = 8.8$ Hz), 7.27–7.37 (m, 3H).

The product was converted into the corresponding trihydrochloride salt. Anal. Calcd for ($C_{25}H_{38}N_3Cl_3O$ $0.5H_2O$) C, H, N.

*7-{[2-(4-Phenyl-piperazin-1-yl)-ethyl]-propyl-amino}-5,6,7,8-tetrahydro-naphthalen-2-ol (−)*-**10a**

Optical rotation: $[\alpha]_D$ −11.06 (*c*2, MeOH)

$^1$H NMR (400 MHz, $CDCl_3$): 0.90 (t, 3H, $J = 7.2$ Hz), 1.43–1.51 (m, 4H), 1.88–1.95 (m, 2H), 2.49 (t, 2H, $J = 7.2$ Hz), 2.52–2.69 (m, 6H), 2.72 (t, 4H, $J = 4.8$ Hz), 2.84–2.89 (m, 1H), 3.21 (t, 4H, $J = 4.8$ Hz), 6.51 (d, 1H, $J = 2.4$ Hz), 6.68 (dd, 1H, $J = 2.4$, 8.0Hz), 6.85 (t, 1H, $J = 7.2$ Hz), 6.91 (d, 2H, $J = 8.8$ Hz), 7.27–7.37 (m, 3H).

The product was converted into the corresponding trihydrochloride salt. Anal. Calcd for ($C_{25}H_{38}N_3Cl_3O\cdot$ $0.85H_2O$) C, H, N.

## 16. Biological experiments

### 16.1. Potencies at dopamine D2 and D3 receptors

Binding affinities were assessed according to previously published procedures.[38–40] Human embryonic kidney (HEK) 293 cells, stably transfected with cDNA for the human D2L and D3 receptors[39] were the source for membranes prepared as described previously.[38,40] Approximately 50 (for D2L) or 135 (for D3) mg of protein was incubated with each test compound and [$^3$H]spiperone (0.49 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 2 mL. (+)-Butaclamol (2 mM) was used to define nonspecific binding. As in our previous study,[40] assays were terminated by addition of ice-cold buffer and washing with a 24-pin Brandel harvester. $IC_{50}$ values were estimated by nonlinear regression analysis with the ALLFIT equation, which is equivalent to the logistic model in the least squares fitting program ORIGIN, and converted to inhibition constants ($K_i$) by the Cheng–Prusoff equation.[41] In this conversion, the $K_d$ values for [$^3$H]spiperone binding were 0.18 nM for D2-receptors and 0.40 nM for D3-receptors as measured in our previous experiments.[40]

### 16.2. D2 and D3 mitogenesis functional assay

To measure D2L and D3 stimulation of mitogenesis (agonists assay), CHOp-cells (human receptor) were seeded in a 96-well plate at a concentration of 5,000 cells/well. The cells were incubated at 37 °C in α-MEM with 10% FBS, 0.05% penicillin–streptomycin, and 200 mg/mL of G418. After 48 h, the cells were rinsed twice with serum-free α-MEM and incubated for 24 h at 37 °C. To initiate the functional agonism assay, the medium was removed and replaced with 90 mL of serum-free α-MEM and 10 mL of test compounds in sterile water. After another 24 h incubation at 37 °C, 0.25 mCi of [$^3$H]thymidine was added to each well and the plates were further incubated for 2 h at 37 °C. The cells were then trypsinized and the plates were filtered and counted as usual. Quinpirole was run on every plate as an internal standard. Intrinsic activity relative to quinpirole was calculated as the ratio of the EC50 of test drug over that of quinpirole. This was done because some test compounds were evaluated at a much later point in time when the test system gave higher EC50 values for quinpirole at both D2 and D3. Computation of the D2/D3 selectivity ratio also took into account these quinpirole shifts occurring in the latter assays by including normalization to the quinpirole selectivity observed in the early assays (9.98 nM at D2 and 2.91 nM at D3).

## 17. 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 post-lesion challenge with apomorphine was done to observe a complete rotation session post administration. In the second challenge with apomorphine (0.05 mg/kg) 21 days post lesion, 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 this 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 6 h. For control, vehicle was administered alone. Rotations were measured in the Rotomax Rotometry System (AccuScan Instruments, Inc. Columbus, Ohio) equipped with Rotomax Analyser, high resolution sensor and animal chambers with harnesses. Data were analyzed with Rotomax Window software program. Test drugs (−)-**10a** (10 mM/kg) was 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 at every 30 min. Data were analyzed with the microsoft excel program. Compound (−)-**10a** produced contralateral rotations in all four lesioned rats which lasted over 6 h. The peak effect was observed between 2 and 3 h. The reference drug apomorphine exhibited a fast onset of action with the peak effect occurring within the first 30 min. It exhibited a short duration of action. Each point on the graphs represents the mean results from four rats with the corresponding standard mean error (SEM).

## Acknowledgements

We thank Janet Berfield for conducting the binding assays. We are also grateful to the NIDA medication department for carrying out the functional mitogenesis experiments under NIDA contract no. N01DA-1-8816. We acknowledge Dr. Hanley Abramson for careful reading of the manuscript.

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