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Discovery of 4-(4-(2-((5-Hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)ethyl)piperazin-1-yl)quinolin-8-ol and Its Analogues as Highly Potent Dopamine D2/D3 Agonists and as Iron Chelator: In Vivo Activity Indicates Potential Application in Symptomatic and Neuroprotective Therapy for Parkinson's Disease

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The role of iron in the pathogenesis of Parkinson's disease (PD) has been implicated strongly because of generation of oxidative stress leading to dopamine cell death. In our overall goal to develop bifunctional/multifunctional drugs, we designed dopamine D2/D3 agonist molecules with a capacity to bind to iron. Binding assays were carried out with HEK-293 cells expressing either D2 or D3 receptor with tritiated spiperone to evaluate inhibition constants (K_i). Functional activity of selected compounds was carried out with GTPγS binding assay. SAR results identified compounds (+)-**19a** and (−)-**19b** as two potent agonists for both D2 and D3 receptors (EC_{50} (GTPγS); D2 = 4.51 and 1.69 nM and D3 = 1.58 and 0.74 nM for (−)-**19b** and (+)-**19a**, respectively). In vitro complexation studies with **19b** demonstrated efficient chelation with iron. Furthermore, the deoxyribose assay with **19b** demonstrated potent antioxidant activity. In PD animal model study, (−)-**19b** exhibited potent in vivo activity in reversing locomotor activity in reserpinized rats and also in producing potent rotational activity in 6-OHDA lesioned rats. This reports initial development of unique lead molecules that might find potential use in symptomatic and neuroprotective treatment of PD.

Introduction

Parkinson's disease (PD[a]) is a progressive disorder of the central nervous system that mainly affects motor and other functions.[1] The cardinal clinical features of Parkinson's disease (PD) include resting tremor, rigidity, difficulty in initiating movement, and postural instability.[1,2] These symptoms develop as a result of slow degeneration of dopamine neuron in the substantia niagra resulting in production of less and less dopamine. The loss of dopaminergic neurons in the pars compacta region of the substantia nigra and the inhibition of nigrostriatal dopaminergic pathway result in development of dysfunction of movements. Even though the pathogenesis of PD is poorly understood, studies of the genetic mutations, neuropathology, and other factors of PD have provided much insight into the pathophysiology of PD and the progression of this disease.[3,4] Both oxidative stress and mitochondrial dysfunction have been strongly implicated in cell death.[5−7] The presence of Lewy bodies (LBs) in the surviving neurons of the substantia nigra is the neuropathological hallmark of PD.[8,9] The physical characteristics of LBs are round, eosinophilic, intracytoplasmic proteinaceous inclusions, and they are found to contain principally polymeric α-synuclein proteins.[9]

Evidence from various studies have consistently implicated iron in the pathophysiology of PD. Iron being the most abundant metal in human body is particularly found in higher level in the brain and lever. The role of iron in the pathogenesis of PD has been strengthened by several observations.[10−12] Higher levels of iron is generally found in the brains of PD patients compared to normal brain.[13] Additionally, iron accumulation observed is higher in the substantia nigra region of people afflicted with PD.[12,14] It is well-known that free iron plays a role in generating of oxidative stress leading to dopamine cell death. The generation of hydroxyl radical from free iron occurs by the Fenton reaction (eq 1). It has also been shown that the presence of iron can initiate aggregation of α-synuclein in LBs, implicated in dopamine cell death. The aggregation of α-synuclein possibly takes place via conversion of this molecule into β-pleated sheet. Recent studies have shown that overexpression of α-synuclein can form toxic aggregates in the presence of iron.[15] This is believed to contribute to the formation of LBs via production of oxidative stress.[16] Iron released from neuromelanin has also been reported to cause mitochondrial dysfunction and to reduce proteasomal function.[17] All this evidence has further been corroborated by the fact that iron chelators are neuroprotective.[18] Thus, a crucial role of iron in PD pathogenesis has been emphasized because of its capacity to enhance the production of oxygen radicals and accelerate neuronal degeneration.[19]

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[a]Abbreviations: GTPγS, guanosine 5′-[γ-thio]triphosphate; 5-OH-DPAT, 5-hydroxy-2-(dipropylamino)tetralin; 6-OHDA, 6-hydroxydopamine; CHO, Chinese hamster ovary; HEK, human embryonic kidney; L-DOPA, (*S*)-(3,4 -dihydroxyphenyl)alanine; PD, Parkinson's disease.

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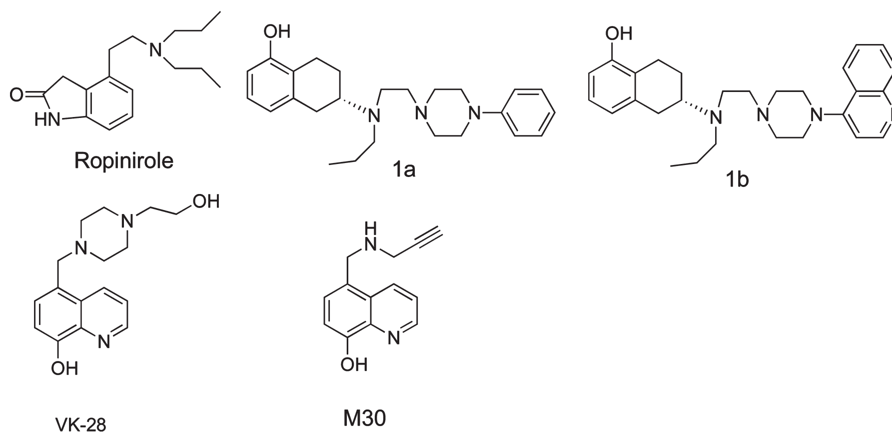
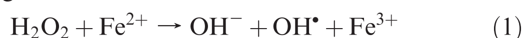


Figure 1. Molecular structures of D3 preferring compounds and iron chelators.

Oxidative stress can facilitate mutant protein aggregation, mimicking proteasomal malfunction.[20] Thus, iron chelators can possibly sequester free iron and thereby prevent its ability to induce oxidative stress as a consequence of reactive hydroxyl radical generation.[21]



$$H_2O_2 + Fe^{2+} \rightarrow OH^- + OH^\bullet + Fe^{3+} \quad (1)$$

Recently, bifunctional iron chelators were developed where an iron binding 8-hydroxyquinoline moiety was attached to *N*-propargylamine and to the piperazine moiety to provide neuroprotective property via reduction of oxidative stress. Two such compounds, 5-((4-(2-hydroxyethyl)piperazin-1-yl)methyl)quinolin-8-ol (VK 28) and 5-((prop-2-ynylamino)methyl)quinolin-8-ol (M30), were shown to be antioxidant and neuroprotective in animal experiments (Figure 1).[22,23]

Given the important role of iron in PD, our overall goal is to develop bifunctional/multifunctional dopamine D2/D3 agonist molecules with a capacity to bind to iron. This paper reports on introducing a metal binding 8-hydroxyquinoline moiety into the piperazine ring of the hybrid template that we developed previously.[24−26] Compounds, e.g., **1a** (D-237) and **1b** (D-354) (Figure 1), derived from this hybrid template displayed agonist interaction with dopamine D2/D3 receptors. Our hypothesis behind designing these bivalent molecules originates from the idea that by maintaining the hybrid template, we should be able to retain affinity for dopamine receptors while the hydroxyquinoline moiety, being located at a distal position with respect to the agonist binding moiety, will participate in binding to iron in the brain without having an impact on agonist activity. In this regard, extensive data are available on metal binding capacity of 8-hydroxyquinoline and its derivatives.[27,28] For proof of concept, following their initial design, these molecules were prepared as described in synthesis Schemes 1−4. We hypothesized that compound with dopamine D2/D3 agonist activity along with a capacity to chelate with iron will not only alleviate motor dysfunction in PD but will also reduce oxidative stress, leading to greater survival of dopamine neurons. Therefore, this approach might provide more desirable therapeutic agents that may slow or even halt the progression of dopamine cell death in PD along with restoration of motor dysfunction.

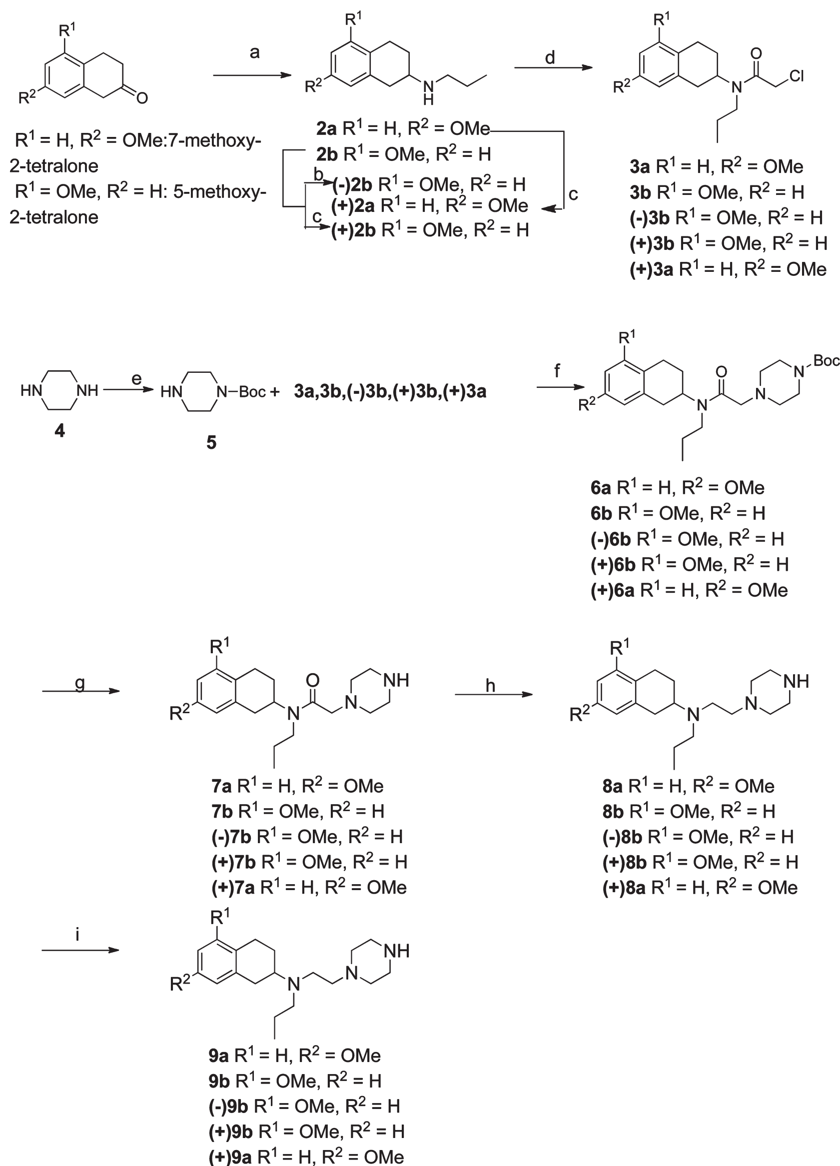
Chemistry

Scheme 1 outlines the syntheses of **9a**, **9b**, and their enantiomers. The starting materials for these compounds were appropriately substituted 7- and 5-methoxy-2-tetralones. These were condensed with propylamine under standard reductive amination conditions to give secondary amines **2a**,**b**. Enantiomerically pure amines were made by using a synthetic chiral resolving agent as described previously by us.[25,29] N-Alkylation of amines using chloroacetyl chloride in the presence of triethylamine produced intermediate α-chloroamides **3a**, **3b**, and their enantiomers. N-Acylation with mono-Boc-protected piperazine gave amides,[30] which were then reduced by lithium aluminum hydride followed by deprotection with trifluoroacetic acid, yielding **8**. Demethylation in the presence of boron tribromide afforded phenols **9a**, **9b**, and their enantiomers.

Scheme 2 depicts the synthesis of two final compounds **12a** and **12b**. Here the starting material is 8-hydroxyquinoline, which was converted into 5-methylene chloride derivative **11** by treating it with formaldehyde and hydrogen chloride gas. N-Alkylation of **11** with two different piperazine fragments **9a** and **9b** provided two final compounds **12a** and **12b** which were then purified by recrystallization of their hydrochloride salts from ethanol.[23]

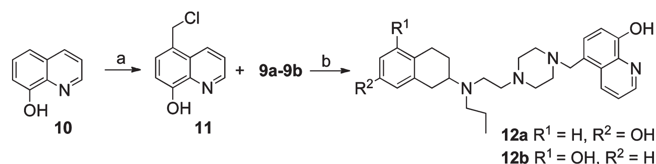
Scheme 3 describes the syntheses of chloride derivative of quinoline component **17**. Most of the current methods for synthesis of quinoline rings are variations of the Skraup method in which an aniline derivative is heated with glycerol and an acid catalyst to form a stable intermediate that undergoes cyclization after a high-temperature Friedel−Crafts acylation. We used a modified method that uses methoxymethylene Meldrum's acid.[31] This has the advantage of giving the same products in two steps rather than four steps. The first step in this sequence is the condensation of *O*-anisidine with Meldrum's acid and trimethyl orthoformate. The Meldrum's acid was refluxed in trimethyl orthoformate to form methoxymethylene Meldrum's acid **14** in situ. Addition of anisidine into the reaction mixture initiated addition−elimination reaction with the methoxymethylene moiety to afford an ene−amine intermediate **15** for cyclization. Addition of an equal volume of DMF to the mixture with increase of reaction temperature overcame sluggishness of the reaction to facilitate the formation of **15**. The ene−amine intermediate was then refluxed at 300 °C in phenyl ether as solvent for 15 min. The cyclized product was isolated by cooling and subsequent precipitation by mixing with hexane followed by filtration, washing with additional hexane, and drying. This compound (**16**) was then purified by column chromatography. The 4-hydroxy-8-methoxyquinoline (**16**) was dissolved in

Scheme 1[a]



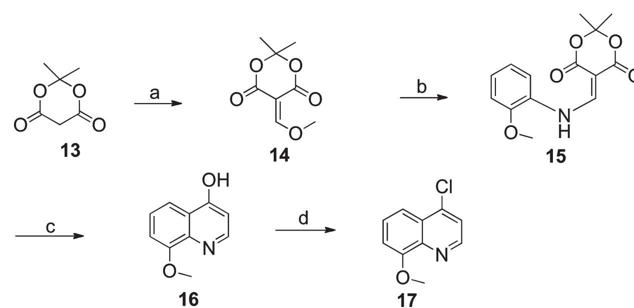
[a] (a) *n*-Propylamine, $NaCNBH_3$, CH_3COOH, dichloroethane, room temp, overnight; (b) (+)-chlocyphos, EtOH; (c) (−)-chlocyphos, EtOH; (d) chloroacetyl chloride, TEA, dichloromethane, 0 °C, 30 min; (e) $(Boc)_2O$, CH2Cl2, 0 °C, 2 h; (f) K_2CO_3, CH_3CN, 80 °C, 2 h; (g) TFA/DCM (1/1), room temp, overnight; (h.) $LiAlH_4$, THF, reflux, 2 h; (i) BBr_3, −40 °C, CH_2Cl_2, overnight.

Scheme 2[a]



[a] (a) HCl (32% water), HCHO (37% in water), 0 °C, room temp, 8 h; (b) N-substitued piperazine (**9a** or **9b**), $(Me_2CH)_2NEt$, $CHCl_3$, room temp, 1 day.

Scheme 3[a]



[a] (a) Trimethyl orthoformate, reflux, 1 h; (b) *o*-anisidine, DMF (cat.), relux, 2 h; (c) diphenyl ether, 300 °C, 15 min; (d) $POCl_3$, reflux, 2 h.

phosphorus oxychloride and heated to reflux for 2 h to give the desired 4-chloroquinoline derivative.[32]

Scheme 4 describes the syntheses of final compounds **19a**, **19b**, and their enantiomers. Intermediates **9a**, **9b**, and their enantiomers were condensed with quinoline component (**17**) under refluxing conditions in 2-propanol in the presence of diisopropylethylamine as base, giving **18**, which was then demethylated under refluxing conditions with 48% aqueous HBr. The final compounds **19a**, **19b**, and their enantiomers were purified by recrystallization of their HCl salt from ethanol.

Discussion

In our approach to designing multifunctional ligands targeting dopamine D2/D3 receptors as agonist and at the same time binding iron to reduce oxidative stress, a hydroxyquinoline moiety was introduced into our hybrid template for D2/D3 receptors. Numerous studies have shown that 8-hydroxyquinoline binds to iron.[27] SAR studies on the hybrid template have indicated that bulky aromatic substitutions in the piperazine ring in a distal location from the aminotetralin moiety are well tolerated by D2/D3 receptors. Our recent SAR studies indicated that different quinoline moieties not only are well tolerated but also produced high agonist activity.[33] Thus, it was reasoned that replacement of the quinoline moiety by 8-hydroxyquinoline should not only retain high affinity for the D2/D3 receptor but also provide potent agonist activity. Preliminary compounds were designed and synthesized to test this rationale.

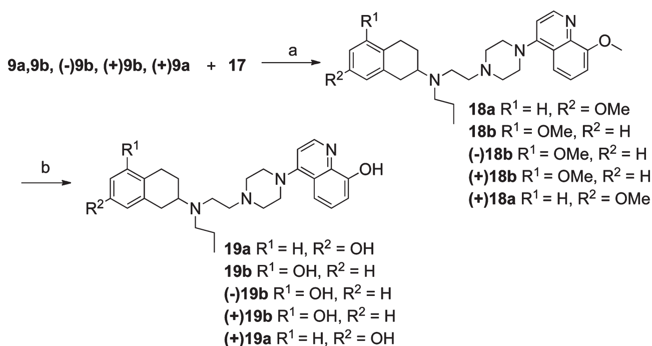
The two compounds that were synthesized first were **12a** and **12b**. In these two compounds, a 5-methylquinoline-8-ol moiety was attached to the piperazine ring. Both compounds exhibited low nanomolar potency for D3 receptor (5.57 and 3.71 nM for **12a** and **12b**, respectively, Table 1). Compound **12b** was twice as potent at D2 receptors compared to **12a** (41 and 86 nM for **12b** and **12a**, respectively). These results indicated that the 5-methylquinoline-8-ol moiety was well tolerated by D2/D3 receptors.

In our next step, we introduced an 8-hydroxyquinoline moiety directly attached to the piperazine ring, which resulted in the development of next five compounds. The two racemic compounds, **19a** and **19b**, designed on the basis of 5-hydroxy and 7-hydroxy templates, exhibited high affinity for both D2 and D3 receptors (K_i of 15.9 and 0.81 nM for **19a** and 13.8 and 1.35 nM for **19b**, respectively). Both these compounds showed moderate preferential affinity at the D3 receptor compared to the D2 receptor (D2/D3; 19.62 and 10.22 for **19a** and **19b**, respectively). These results indicated that introduction of the 8-hydroxyquinoline moiety retained high affinity activity at both D2 and D3 receptors. In our next effort to prepare enantiomerically pure compounds of racemic **19b**, compounds (−)-**19b** and (+)-**19b** were synthesized. As expected from our previous data from 5-hydroxy series hybrid compounds, higher affinity at both D2 and D3 was observed in (−)-**19b** compared to (+)-**19b** (K_i of 3.75 and 1.28 nM for (−)**19b** and 20.7 and 7.73 nM for (+)**19b**, respectively). On the basis of our results from activity of enantiomers of 7-hydroxy series hybrid compounds, we selectively synthesized (+)-**19a**. This compound, like its 5-hydroxy counterpart, exhibited high affinity for D2 and D3 receptors (K_i of 4.55 and 1.27 nM, respectively, Table 1).

Following binding analysis, selected compounds (−)-**19b** and (+)-**19a** were subjected to the [^{35}S]GTPγS functional assay for D2 and D3 receptors and compared with the full agonists dopamine and ropinirole (Table 2). The assays were carried out with the cloned human D2 and D3 receptors expressed in CHO cells.[25] The results indicate that both compounds are quite active in stimulating both D2 and D3 receptors with similar potency; no appreciable selectivity was displayed by these compounds. Both showed full or near-complete agonism at D2 and D3 when compared against the reference substance dopamine, as did ropinirole. Thus, our binding and functional assay results indicated that introduction of an 8-hydroxyquinoline moiety retained not only high affinity for binding to D2/D3 receptors but also potent agonist activity at both receptors. Compound (−)-**19b** was selected for animal study because the 5-hydroxyaminotetralin derived compound, e.g., **1a**, was previously shown to exhibit potent in vivo activity with long duration of action.[25]

pH-Dependent Complexation Studies with Iron(III). Equimolar amounts (600 μM) of **19b** and $FeCl_3$ were mixed together, and complex formation was followed by UV absorption scanned from 200 to 800 nm at different pH values. It is evident from the plot (Figure 2) that **19b** in the

Scheme 4[a]



[a] (a) DIPEA, 2-propanol, relux, overnight; (b) 48% aqueous HBr, reflux, overnight.

Table 1. Inhibition Constants for Competing for [^{3}H]Spiperone Binding to Cloned D_{2L} and D_3 Receptors Expressed in HEK Cells[a]

compd	K_i (nM), D2L [^{3}H]spiperone	K_i (nM), D3 [^{3}H]spiperone	D2L/D3
7-OH-DPAT	202 ± 34	2.35 ± 0.29	86.0
(−)-5-OH-DPAT	58.8 ± 11.0	1.36 ± 0.28	43.2
1a	26.0 ± 7.5	0.825 ± 0.136	31.5
1b	3.74 ± 0.70	0.186 ± 0.030	19.7
12a	86.0 ± 4.1	5.57 ± 1.15	15.4
(+)-**19b**	20.7 ± 1.5	7.73 ± 0.64	2.67
(−)-**19b**	3.75 ± 0.63	1.28 ± 0.08	2.92
19a	15.9 ± 2.1	0.818 ± 0.165	19.6
19b	13.8 ± 0.6	1.35 ± 0.22	10.2
(+)-**19a**	4.55 ± 0.59	1.27 ± 0.15	3.58
12b	41.4 ± 7.1	3.71 ± 0.48	11.2

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

Table 2. Stimulation of [^{35}S]GTPγS Binding to hD2 and hD3 Receptors Expressed in CHO Cells

	CHO-D2		CHO-D3		
compd	[^{35}S]GTPγS EC_{50} (nM)[a]	E_{max} (%)	[^{35}S]GTPγS EC_{50} (nM)[a]	E_{max} (%)	D2/D3
dopamine	209 ± 29	100	4.76 ± 0.87	100	43.9
ropinirole	304 ± 11	73.9 ± 0.9	10.3 ± 1.5	66.6 ± 8.1	29.5
(−)-**19b**	4.51 ± 0.93	106 ± 4	1.58 ± 0.31	92.6 ± 3.6	2.85
(+)-**19a**	1.69 ± 0.16	55.3 ± 4.8	0.74 ± 0.15	99.8 ± 1.4	2.26

[a] EC_{50} values (nM) are the mean ± SEM for three to six experiments each performed in triplicate. 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 the mean ± SEM for three to six experiments each performed in triplicate.

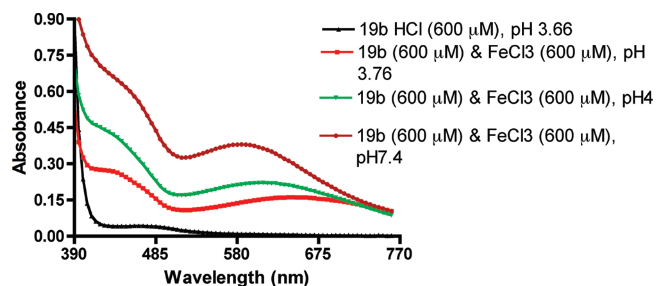


Figure 2. UV−visible absorption spectra of complex formation between racemic **19b** (0.6 mM) and $FeCl_3$ in water at various pH.

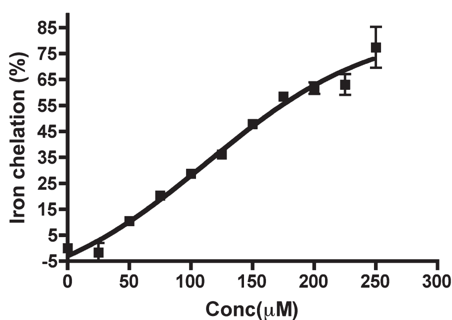


Figure 3. Chelating potency of **19b** via displacement of ferrozine complexed to $FeSO_4$ and expressed as percent of control. Each point represents a value from experiment done in triplicate and is expressed as the mean ± SEM.

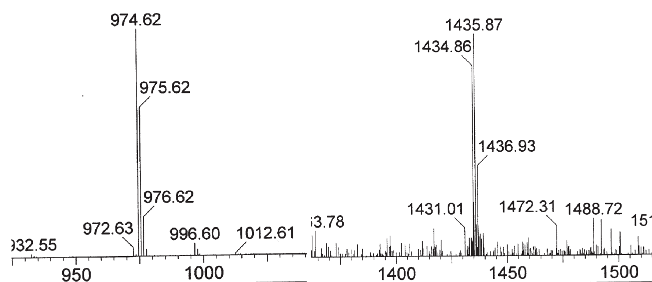


Figure 4. Molecular ion peaks of complexes formed from racemic **19b** and $FeCl_3$ at pH 7.4. Peaks at m/z 975 and 1434 correspond to **19b**−Fe complex stoichiometries 2:1 and 3:1.

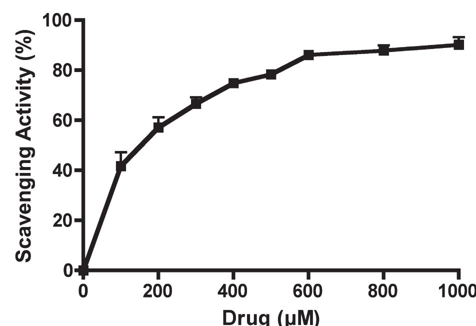


Figure 5. Hydroxyl radical scavenging capacity of **19b** in deoxyribose-containing solution. Values are reported as a percentage versus a blank ± SD.

presence of ferric chloride produced distinctly different UV absorption profiles compared to UV absorption of the compound **19b** alone in the absence of iron chloride. This is indicative of a complex formation. In general a shift in λ_{max} to the left takes place with increase of pH in the solution. Thus, at pH 3.76 the λ_{max} was 647 nm (ε = 567 M^{-1} cm^{-1}) and at pH 7.4 λ_{max} was 580 nm (ε = 1300 M^{-1} cm^{-1}). This observation agrees with the reported data on complexation of 8-hydroxy related compound with iron.[28] Also, the absorption spectra of the solution at pH 7.4 exhibited higher intensity at 580 nm than the spectra at lower pH values. This pH-dependent Fe(III)−**19b** complexation study indicated that the amount of complex formation was favored by neutral pH. Since the brain maintains physiologically a neutral pH, compound **19b** might be a potential candidate to chelate iron in the PD brain.

Evaluation of Fe(II) Chelating Potency of 19b in Ferrozine Assay. We performed an in vitro biochemical iron binding assay, known as the ferrozine assay, to determine the chelation potency of molecule **19b**. We envisioned that a potent iron binding compound will arrest iron in the PD brain from taking part in the Fenton reaction and thereby reduce the formation of hydroxyl radical and oxidative stress. Chelating potency of **19b** was evaluated by the ferrozine assay method, which is a colorimetric assay. Ferrozine is known to bind to iron(II) and forms a characteristics color upon complexation with Fe(II), which can be quantitated at 562 nm.[34,35] In this assay displacement of ferrozine from its complexation to Fe(II) by **19b** in a concentration dependent manner was measured by absorption at 562 nm. It is evident from Figure 3 that at higher concentration of **19b**, complexation almost exclusively takes place with Fe(II). It has been shown in the past that ligands such as DFO complex to Fe(II) to undergo aerobic oxidation to Fe(III).[36] Thus, this process of chelation potentially measures complexation to both Fe(II) and Fe(III). The chelating effect is expressed as a percent of control [80 μM ferrozine, 20 μM ferrous ammonium sulfate in pH 6.9 ammonium acetate buffer (5%)] by using the known equation (shown in the Experimental Section). Inhibition constant (IC_{50}) of this compound was calculated to be 155.56 ± 0.73 μM (n = 3).

Mass Spectroscopy Evidence of Complex Formation. In an effort to demonstrate further formation of iron complexes, we carried out mass spectral analysis of **19b** and $FeCl_3$ solutions used in the UV analysis above to detect any molecular ion peak corresponding to complex molecular ions. As shown in Figure 4, we indeed observed molecular ion peaks corresponding to $L_2{-}Fe^{3+}$ (m/z = 975) and $L_3{-}Fe^{3+}$ (m/z = 1434, 1435) complexe formation (L = ligand molecule). Thus, these results give clear evidence of formation of iron complexes with compound **19b**.

Deoxyribose Antioxidant Assay. Antioxidant activity of **19b** was analyzed by this assay. This is a test tube assay that measures hydroxyl radical scavenging capacity of a test compound by competing with deoxyribose.[37] In this assay, the hydroxyl radical is generated by reaction of the Fe^{3+}−EDTA complex with H_2O_2 (by Fenton reaction) in the presence of ascorbic acid, which then reacts with deoxyribose to form a smaller molecular fragment which upon heating with 2-thiobarbituric acid under acid conditions yields a pink color dye. Test compound(s) with potential radical scavenging capacity will compete with deoxyribose for hydroxyl radical generated by Fenton reaction. Thus, formation of fragment from deoxyribose and the pink color formation will be dictated by the capacity of a test compound to quench the hydroxyl radical. This is a colorimetric assay, and the absorbance is measured at 532 nm. Hydroxyl radical formation by Fenton reaction in the substantia nigral (SN)

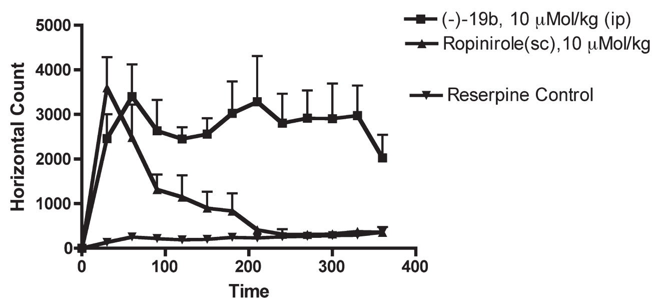


Figure 6. Effect of different drugs upon reserpine (5.0 mg/kg, sc) induced hypolocomotion in rats. Data are the mean ± SEM, $n = 4$ per value. Horizontal activity was measured as described in Experimental Section. Shown is the representation of horizontal locomotor activity at discrete 30 min intervals after the administration of (−)-**19b** (ip) and ropinirole (sc) at a dose of 10 μmol/kg compared to control rats in 18 h after reserpine treatment. One-way ANOVA analysis demonstrates significant effect among treatments $F(3,95) = 31.36$ ($P < 0.0001$). Dunnett's analysis following ANOVA showed that the effects of (−)-**19b** ($P < 0.01$) and ropinirole ($P < 0.05$) were significantly different compared to those of reserpine control.

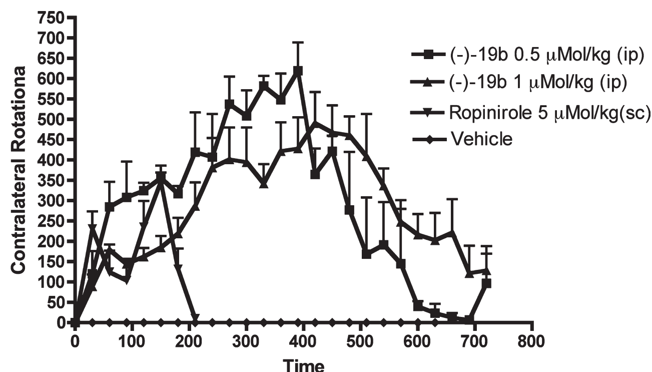


Figure 7. Effect on turning behavior of two different doses of (−)-**19b** (ip) and vehicle in lesioned rats studied for a maximum of 12 h. Each point is the mean ± SEM of three to four rats. The drug (−)-**19b** was administered ip and the ropinirole was administered sc. One-way ANOVA analysis demonstrates significant effect among treatments: $F(4,95) = 21.12$ ($P < 0.0001$). Dunnett's analysis showed that the effect of (−)-**19b** on rotations at two doses was significantly different compared to vehicle ($P < 0.01$) and the effect of ropinirole was significant compared to vehicle ($p < 0.05$).

region of the PD brain might take place, as H_2O_2 is generated in SN by dopamine metabolism and the SN area is rich in iron in the case of PD. It is apparent from Figure 5 that compound **19b** dose-dependently inhibited decomposition of deoxyribose by $OH^•$ with the highest dose exhibiting 80% scavenging activity with respect to control containing deoxyribose alone.

Reversal of Reserpine-Induced Hypolocomotion in Rats by (−)-19b and Ropinirole. Reserpine induces depletion of catecholamines in nerve terminals, resulting in a cataleptic condition in rats, which is a well established animal model for PD.[38] Significant reduction of locomotion of the rats was observed 18 h after the administration of reserpine (5 mg/kg, sc) which indicated the development of akinesia in rats. Compound (−)-**19b** was highly efficacious in reversing the locomotor activity of reserpinized rats (Figure 6). The locomotor activity of (−)-**19b** at the end of 6 h remained very high. The reference drug ropinirole on the other hand exhibited much shorter duration of action compared to (−)-**19b**. Compound (−)-**19b** at a dose of 10 μmol/kg ip not only reversed reserpine induced hypokinesia to the normal level of locomotion found in control animals (vehicle treated reserpinized rats) but also demonstrated significant enhancement of locomotion for the entire duration of study. The mechanism of the locomotor stimulation in the reserpine model is likely to be mediated by postsynaptic D2/D3 receptor activation by (−)-**19b**. Thus, the results suggest that the compound is a potent agonist, which crosses the blood−brain barrier effectively and possesses excellent in vivo stability.

In Vivo Effect of (−)-19b in 6-OHDA Lesioned Rats. Compound (−)-**19b** was tested in vivo in rats carrying an unilateral lesion in the medial forebrain bundle induced by application of the neurotoxin 6-hydroxydopamine (6-OHDA). Development of supersensitivity of dopamine receptors takes place resulting from destruction of dopamine neurons in these surgically modified rats. When these rats are challenged with direct acting dopamine agonists, they produced contralateral rotations away from the lesioned side. This rat model is considered to be one of the standard models for preclinical screening of drugs for possible antiparkinsonian property.[39] Compound (−)-**19b** was highly efficacious in producing a large number of rotations at a smaller dose of 0.5 μmol/kg (0.3 mg/kg), and the activity lasted more than 11 h (number of rotation was 7081). At a higher dose of 1 μmol/kg (0.61 mg/kg), the rotational activity produced by (−)-**19b** was initially less compared to the lowest dose (0.5 μmol/kg) but the activities increased gradually and remained high at the termination of the experiments after 11 h (Figure 7). On the other hand, the reference ropinirole at 5 μmol/kg produced much fewer rotations with shorter duration of action. The efficacy of this compound in producing rotations indicated its excellent brain penetration under ip administration conditions.

Conclusion

In this initial report, we describe the development of unique multifunctional dopamine D2/D3 agonist compounds with a capacity to chelate with iron (Fe^{2+}/Fe^{3+}). Our design of the preliminary compounds originated from observations collected in our earlier SAR studies, which demonstrated the existence of a flexible binding pocket for substitutions on the piperazine ring located in a distal position with respect to the aminotetralin moiety. Thereby, a known iron chelating moiety 8-hydroxyquinoline was introduced into the hybrid structure, which resulted in the development of first-generation multifunctional molecules. Such molecules are not only expected to relieve motor dysfunction in PD but also will have potential to reduce oxidative stress in the PD brain by chelating with iron. Two lead molecules (−)-**19b** and (+)-**19a** identified from the binding study were subjected to the GTPγS functional assay which demonstrated their potent agonist property. Complexation studies with **19b** demonstrated chelation with iron efficiently. Furthermore, the deoxyribose assay with **19b** demonstrated potent antioxidant activity in these compounds. One of the lead molecules was then tested in PD animal models. Compound (−)-**19b** not only reversed the reserpine-induced hypolocomotion in rats but also maintained a significant level of higher activity throughout the study session. In this regard efficacy of (−)-**19b** at an equivalent dose was far greater than the standard reference ropinirole, which exhibited a shorter duration of action. In rotational experiments with 6-OH-DOPA-lesioned rats, two doses of (−)-**19b** were efficacious in producing extensive rotational

activity. Compound (−)-**19b** will be subjected to neuroprotection study to evaluate its potential in protecting against cell death in the near future.

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. The NMR solvent used was $CDCl_3$ or CD_3OD or DMSO-d_6, as indicated. TMS was used as an internal standard. Elemental analyses were performed by Atlantic Microlab, Inc., and were within ±0.4% of the theoretical value.

Procedure A. Preparation of 7-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)propylamine (2a). 7-Methoxy-2-tetralone (10 g, 56.75 mmol) and acetic acid (13.5 mL, 226.9 mmol) were dissolved in dichloroethane (150 mL) and cooled to 0 °C. *n*-Propylamine (11.7 mL, 141.87 mmol) was added and the mixture stirred under a N_2 atmosphere for 30 min. $NaCNBH_3$ (8.915 g, 141.87 mmol) in anhydrous MeOH (15 mL) was then added to the mixture and allowed to stir overnight at ambient temperature. The volatiles were then evaporated, and saturated $NaHCO_3$ solution was added. It was then extracted with dichloromethane, dried over Na_2SO_4, filtered, and concentrated. The crude residue was then taken up in EtOAc, at which time ethereal HCl was added, and the crude salt was filtered and dried over vacuum oven. The crude salt was then recrystallized in ethanol to yield 9.5 g (65%) of white solid and used in the subsequent transformations. ^{1}H NMR (free base) (400 MHz, $CDCl_3$) δ ppm 0.91−0.95 (t, 3H, J = 7.6 Hz), 1.38 (bs, 1H), 1.48−1.60 (m, 3H), 2.04−2.09 (m, 1H), 2.67−2.71 (t, 3H, J = 7.6 Hz), 2.88−2.92 (m, 2H), 2.97−3.04 (m, 1H), 3.81 (s, 3aH), 6.60−6.62 (dd, 1H, J_1 = 1.6 Hz, J_2 = 4.2 Hz), 6.65−6.78 (m, 1H), 6.95−6.98 (d, 1H, J = 8.8 Hz).

(5-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)propylamine (2b). Compound **2b** was prepared following procedure A using 5-methoxy 2-tetralone and purified by recrystallization of its hydrochloride salt from ethanol to get a white salt of **2b** (yield is 64%). ^{1}H NMR (free base) (400 MHz, $CDCl_3$) δ ppm 0.92−0.964 (t, 3H, J = 7.6 Hz), 1.39 (bs, 1H), 1.49−1.61 (m, 3H), 2.05−2.10 (m, 1H), 2.66−2.70 (t, 3H, J = 7.6 Hz), 2.87−2.94 (m, 2H), 2.98−3.03 (m, 1H), 3.81 (s, 3H), 6.65−6.67 (d, 1H, J = 8 Hz), 6.96−6.71 (d, 1H, J = 8 Hz), 7.07−7.11 (t, 1H, J = 8 Hz).

Procedure B. Resolution of 5-Methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine. Racemic (±)-**2b** was resolved into its (+)- and (−)-isomers by using the both (−)- and the (+)-isomers of the synthetic resolving agent 4-(2-chlorophenyl)-5,5-dimethyl-2-hydroxy-1,3,2-dioxaphosphorinane 2-oxide. This optically active resolving agents were prepared according to the published procedure[40] **2b** (free base 14.77 g, 67.36 mmol) and (+)-4-(2-chlorophenyl)-5,5-dimethyl-2-hydroxy-1,3,2-dioxaphosphorinane 2-oxide (20.5 g, 74.1 mmol) were dissolved by warming in 100 mL of ethanol. The solution was cooled to room temperature and then at 0 °C. The precipitated crystals were filtered off and washed with cold ether to yield 17.4 g of the salt ([α]$_D$ −1.2° (*c* 1, methanol)). Further recrystallization two times from hot ethanol yielded the salt (12.9 g, [α]$_D$ −14.1° (*c* 1, methanol)). Further crystallization of the salt from hot ethanol did not change the optical rotation to a significant extent. The salt was then neutralized in the presence of 20% NaOH solution in water under stirred 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 a thick transparent liquid (−)-**2b** (5.8 g). [α]$_D$ of the HCl salt is −71.5° (*c* 1, methanol). Yield 78.5%.

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

Resolution of (*R*)-7-Methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine. This resolution was done according to procedure B, in which (±)-**2a** (5.99 g, 27.31 mmol) was similarly treated using (−)-4-(2-chlorophenyl)-5,5-dimethyl-2-hydroxy-1,3,2-dioxaphosphorinane 2-oxide (7.93 g, 28.68 mmol). Recrystallization from hot ethanol yielded the salt (5.4 g, [α]$_D$ +12.9° (*c* 1, methanol)). Yield is 80%. Further crystallization of the salt from hot ethanol did not change the optical rotation to a significant extent. Hydrolysis of the chlocyphos salt following the above-mentioned procedure yielded (*R*)-(+)-**2a**. [α]$_D$ of the HCl salt is +68.6° (*c* 1, methanol).

Procedure C. Preparation of 2-Chloro-*N*-(7-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylacetamide (3a). Compound **2a** (HCl salt, 3.117 g, 12.18 mmol) and Et_3N (8.4 mL, 60.9 mmol) was stirred at 0 °C in CH_2Cl_2 (75 mL) for 15 min. Chloroacetyl chloride (1.94 mL, 24.37 mmol) was added dropwise, and the resulting solution was stirred at room temperature for 30 min, at which time the reaction mixture was poured into a 1 M solution of NaOH (50 mL). The product was extracted with dichloromethane, dried (Na_2SO_4), filtered, and concentrated. The crude material was purified by column chromatography (Hex/EtOAc, 3:1) to give 3.42 g (95%) of **3a** as a transparent liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.90−0.98 (m, 3H), 1.64−1.72 (m, 2H), 1.83−2.12 (m, 2H), 2.58−2.70 (m, 1H), 2.84−2.89 (dd, 1H, J_1 = 4.8 Hz, J_2 = 16 Hz), 3.00−3.10 (m, 2H), 3.15- 3.26 (m, 2H), 3.82 (s, 3H), 3.95−4.03 (m, 1H), 4.08−4.12 (m, 2H), 6.61−6.62 (dd, 1H, J_1 = 1.6 Hz, J_2 = 4.8 Hz), 6.64−6.77 (m, 1H), 6.96−6.99 (d, 1H, J = 12 Hz).

2-Chloro-*N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylacetamide (3b). This compound was prepared from **2b** following procedure C (yield is 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.92−0.96 (t, 3H, J = 8 Hz), 1.64−1.72 (m, 2H), 1.83−2.12 (m, 2H), 2.58−2.70 (m, 1H), 2.84−2.89 (m 1H), 3.00−3.10 (m, 2H), 3.19−3.27 (m, 2H), 3.86 (s, 3H), 3.95−4.03 (m, 1H), 4.08−4.12 (m, 2H), 6.61−6.68 (m, 2H), 7.07−7.11 (t, 3H, J = 8 Hz).

(−)-2-Chloro-*N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylacetamide, (−)-3b. Compound (−)-**2b** (HCl salt, 6.0 g, 23.46 mmol) was reacted under similar conditions as reported in procedure C to afford the optically pure (−)-**3b** as a transparent liquid (6.52 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.92−0.96 (t, 3H, J = 8 Hz), 1.64−1.72 (m, 2H), 1.83−2.12 (m, 2H), 2.58−2.70 (m, 1H), 2.84−2.89 (m, 1H), 3.00−3.10 (m, 2H), 3.19−3.27 (m, 2H), 3.86 (s, 3H), 3.95−4.03 (m, 1H), 4.08−4.12 (m, 2H), 6.61−6.68 (m, 2H), 7.07−7.11 (t, 1H, J = 8 Hz).

(+)-2-Chloro-*N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylacetamide, (+)-3b. Compound (+)-**2b** (HCl salt, 3.5 g, 13.68 mmol) was reacted under similar conditions as in procedure C to afford the optically pure (+)-**3b** as a transparent liquid (3.9 g, 90.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.92−0.96 (t, 3H, J = 8 Hz), 1.64−1.72 (m, 2H), 1.83−2.12 (m, 2H), 2.58−2.70 (m, 1H), 2.84−2.89 (m, 1H), 3.00−3.10 (m, 2H), 3.19−3.27 (m, 2H), 3.86 (s, 3H), 3.95−4.03 (m, 1H), 4.08−4.12 (m, 2H), 6.61−6.68 (m, 2H), 7.07−7.11 (t, 1H, J = 8 Hz).

(+)-2-Chloro-*N*-(7-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylacetamide, (+)-3a. Compound (+)-**2a** (1.12 g, 5.1 mmol) was prepared following procedure C to afford the optically pure (+)-**3a** as a transparent liquid (1.44 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.90−0.98 (m, 3H), 1.64−1.72 (m, 2H), 1.83−2.12 (m, 2H), 2.58−2.70 (m, 1H), 2.84−2.89 (m, 1H), 3.00−3.10 (m, 2H), 3.15- 3.26 (m, 2H), 3.82 (s, 3H), 3.95−4.03 (m, 1H), 4.08−4.12 (m, 2H), 6.59−6.61 (dd, 1H,

J_1 = 1.6 Hz, J_2 = 4.8 Hz), 6.64−6.77 (m, 1H), 6.96−6.99 (d, 1H, J = 8.8 Hz).

Procedure D. Preparation of *tert*-Butyl 4-(2-((7-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)-2-oxoethyl)piperazine-1-carboxylate (6a). Compound **3a** (3.17 g, 10.72 mmol), compound **5** (1.397 g, 7.5 mmol), and anhydrous K_2CO_3 powder (7.4 g, 53.58 mmol) were refluxed in acetonitrile (100 mL) for 2 h. The solution was cooled, filtered, and concentrated. The crude material was then partitioned between EtOAc and H_2O, and the organic layer was separated, dried (Na_2SO_4), and concentrated. The crude mixture was purified by column chromatography (EtOAc/Hex, 1:1) to give 3.87 g (81%) of **6a** as a thick yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.86−0.90 (t, 3H, J = 8 Hz), 1.45 (s, 9H), 1.59−1.82 (m, 2H), 1.87−1.94 (m, 1H), 1.95−1.97 (m, 3H), 2.420 (bs, 2H), 2.50−2.63 (m, 2H), 2.76−2.82 (m, 4H), 2.96−3.20 (m, 3H), 3.88−3.47 (m, 4H), 3.81 (s, 3H), 6.60−6.61 m, 1H), 6.65−6.78 (m, 1H), 6.95−6.98 (d, 1H, J = 8.8 Hz).

***tert*-Butyl-4-(2-((5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)-2-oxoethyl)piperazine-1-carboxylate (6b).** This compound was prepared from **3b** according to procedure D which yielded **6b** as a thick yellow liquid (77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.87−0.91 (t, 3H, J = 8 Hz), 1.44 (s, 9H), 1.58−1.81 (m, 2H), 1.88−1.95 (m, 1H), 1.96−1.98 (m, 3H), 2.40 (bs, 2H), 2.51−2.63 (m, 2H), 2.78−2.83 (m, 4H), 2.95−3.29 (m, 3H), 3.38−3.47 (m, 4H), 3.81 (s, 3H), 6.63−6.70 (m, 2H), 7.10−7.14 (t, 1H, J = 8 Hz).

(−)-*tert*-Butyl-4-(2-((5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)-2-oxoethyl)piperazine-1-carboxylate, (−)-6b. This compound was prepared from (−)-**3b** (3.5 g, 11.83 mmol) following procedure D to get (−)-**6b** as a thick yellow liquid (4.6 g, 87.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.88−0.92 (t, 3H, J = 8 Hz), 1.45 (s, 9H), 1.59−1.82 (m, 2H), 1.88−1.95 (m, 1H), 1.96−1.98 (m, 3H), 2.40 (bs, 2H), 2.52−2.64 (m, 2H), 2.81−2.84 (m, 4H), 2.95−3.29 (m, 3H), 3.39−3.48 (m, 4H), 3.82 (s, 3H), 6.64−6.71 (m, 2H), 7.11−7.14 (t, 1H, J = 6 Hz).

(+)-*tert*-Butyl-4-(2-((5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)-2-oxoethyl)piperazine-1-carboxylate, (+)-6b. This compound was prepared from (+)-**3b** (4.0 g, 13.52 mmol) according to procedure D to afford (+)-**6b** as a thick yellow liquid (4.44 g, 73.69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.86−0.90 (t, 3H, J = 8 Hz), 1.42 (s, 9H), 1.58−1.81 (m, 2H), 1.88−1.95 (m, 1H), 1.95−1.97 (m, 3H), 2.39 (bs, 2H), 2.51−2.63 (m, 2H), 2.78−2.83 (m, 4H), 2.94−3.28 (m, 3H), 3.88−3.47 (m, 4H), 3.80 (s, 3H), 6.63−6.70 (m, 2H), 7.09−7.13 (t, 1H, J = 8.0 Hz).

(+)-*tert*-Butyl-4-(2-((7-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)-2-oxoethyl)piperazine-1-carboxylate, (+)-6a. This compound was prepared from (+)-**3a** (2.32 g, 7.8 mmol) according to procedure D to afford (+)-**6a** as a thick yellow liquid (2.76 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.86−0.90 (t, 3H, J = 8 Hz), 1.45 (s, 9H), 1.59−1.82 (m, 2H), 1.87−1.94 (m, 1H), 1.95−1.97 (m, 3H), 2.420 (bs, 2H), 2.50−2.63 (m, 2H), 2.76−2.82 (m, 4H), 2.96−3.20 (m, 3H), 3.88−3.47 (m, 4H), 3.81 (s, 3H), 6.60−6.62 (dd, 1H, J_1 = 2.2 Hz, J_2 = 5.2 Hz), 6.65−6.78 (m, 1H), 6.95−6.97 (d, 1H, J = 8 Hz).

Procedure E. Preparation of *N*-(7-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-2-(piperazin-1-yl)-*N*-propylacetamide (7a). Compound **6a** (3.87 g, 8.68 mmol) was dissolved in 40 mL of dichloromethane, and 40 mL of trifluoroacetic acid was added. The mixture was stirred overnight, at which time the solution was concentrated to dryness, dissolved in saturated $NaHCO_3$ solution, and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated to yield 2.91 g (97%) of **7a** as a yellow wax, which was used in the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93−0.96 (t, 3H, J = 12 Hz), 1.62 (m, 3H), 1.85−1.97 (m, 3H), 2.56 (m, 1H), 2.81−2.88 (m, 5H), 2.98−3.34 (m, 9H), 3.81 (s, 3H), 6.60 (s, 1H), 6.65−6.68 (d, 1H, J = 12 Hz), 6.96−6.98 (d, 1H, J = 8 Hz).

***N*-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-2-piperazin-1-yl-*N*-propylacetamide (7b).** This compound was prepared from **6b** as a yellow wax (3.87 g, 8.6 mmol) following procedure E, and the yield of this reaction is 2.76 g (92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.92−0.964 (t, 3H, J = 7.6 Hz), 1.63 (m, 3H), 1.84−1.97 (m, 3H), 2.55 (m, 1H), 2.80−2.87 (m, 5H), 2.97−3.34 (m, 9H), 3.82 (s, 3H), 6.64−6.71 (m, 2H), 7.06−7.15 (m, 1H).

(−)-*N*-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-2-(piperazine-1-yl)-*N*-propylacetamide, (−)-7b. This compound was prepared from (−)-**6b** (4.6 g, 10.32 mmol) following procedure E to get (−)-**7b** as a yellow wax (3.2 g, 89.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.90−0.93 (t, 3H, J = 6.0 Hz), 1.61 (m, 3H), 1.84−1.97 (m, 3H), 2.54 (m, 1H), 2.79−2.86 (m, 5H), 2.97−3.34 (m, 9H), 3.81 (s, 3H), 6.65−6.72 (m, 2H), 7.09−7.16 (m, 1H).

(+)-*N*-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-2-(piperazin-1-yl)-*N*-propylacetamide, (+)-7b. Following the procedure E, this compound was prepared from (+)-**6b** (4.4 g, 9.87 mmol) to afford (+)-**7b** as a yellow wax (3.0 g, 88.23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.90−0.94 (t, 3H, J = 8.0 Hz), 1.66 (m, 3H), 1.84−1.97 (m, 3H), 2.52 (m, 1H), 2.79−2.87 (m, 5H), 2.97−3.34 (m, 9H), 3.84 (s, 3H), 6.65−6.72 (m, 2H), 7.10−7.16 (m, 1H).

(+)-*N*-(7-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-2-(piperazin-1-yl)-*N*-propylacetamide, (+)-7a. This compound was prepared from (*R*)-(+)-**6a** (3.17 g, 7.11 mmol) following procedure E that gave quantitative yield of (*R*)-(+)**7a** as a yellow wax (2.46 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.93−0.96 (t, 3H, J = 6 Hz), 1.62 (m, 3H), 1.85−1.97 (m, 3H), 2.56 (m, 1H), 2.81−2.88 (m, 5H), 2.98−3.34 (m, 9H), 3.81 (s, 3H), 6.60 (s, 1H), 6.65−6.68 (d, 1H, J = 12 Hz), 6.95−6.98 (d, 1H, J = 12.0 Hz).

Procedure F. Preparation of 7-Methoxy-*N*-(2-(piperazin-1-yl)ethyl)-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (8a). To a suspension of $LiAlH_4$ (1.735 g, 45.73 mmol) in THF (100 mL) at 0 °C was added **7a** (3.16 g, 9.15 mmol) in a solution of THF (25 mL). After addition, the mixture was refluxed for 2 h and cooled to 0 °C. Then 15% NaOH was added dropwise to quench the reaction and deactivate the $LiAlH_4$, and the mixture was stirred for 20 min, filtered, and washed with ethyl acetate. The solution was dried over Na_2SO_4, filtered, and concentrated. This crude product was then purified through column chromatography using 20% MeOH in ethyl acetate to get **8a** as a transparent thick liquid (2.23 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.91−0.96 (t, 3H, J = 10 Hz), 1.40−1.6 (m, 3H), 1.97−2.01 (m, 1H), 2.139 (bs, 1H), 2.41−3.11 (m, 18H), 3.82 (s, 3H), 6.61 (s, 1H), 6.66−6.79 (d, 1H, J = 6 Hz), 6.95−6.98 (d, 1H, J = 8.8 Hz).

5-Methoxy-*N*-(2-(piperazin-1-yl)ethyl)-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (8b). This compound was prepared from **7b** following procedure F to get **8b** as a transparent thick liquid (yield is 72.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.92−0.96 (t, 3H, J = 7.6 Hz), 1.41−1.59 (m, 3H), 1.98−2.22 (m, 1H), 2.41−3.1 (m, 19H), 3.81 (s, 3H), 5.2 (bs, 1H), 6.62−6.64 (d, 1H, J = 8 Hz), 6.68−6.69 (d, 1H, J = 4 Hz), 7.05−7.09 (t, 1H, J = 8 Hz).

(−)-5-Methoxy-*N*-(2-(piperazin-1-yl)ethyl)-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine, (−)-8b. This compound was prepared from (−)-**7b** (3.8 g, 11 mmol) following procedure F to get (−)-**8b** as transparent thick liquid (yield is 3.26 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.87−0.91 (t, 3H, J = 8.0 Hz), 1.16−1.19 (t, 3H, J = 6 Hz), 1.98−2.1 (m, 1H), 2.46−3.01 (m, 19H), 3.81 (s, 3H), 5.93 (bs, 1H), 6.64−6.66 (d, 1H, J = 8.0 Hz), 6.70−6.71 (d, 1H, J = 4.0 Hz), 7.07−7.11 (t, 1H, J = 8.0 Hz).

(+)-5-Methoxy-*N*-(2-(piperazin-1-yl)ethyl)-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine, (+)-8b. This compound was prepared from (+)-**7b** (3.5 g, 10.13 mmol) following the above procedure F that yielded 2.48 g (74%) of (+)-**8b** as a transparent thick liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.88−0.91 (t, 3H, J = 6.0 Hz), 1.17−1.20 (t, 3H, J = 6 Hz), 1.97−2.00 (m, 1H), 2.46−3.01 (m, 19H), 3.81 (s, 3H), 5.71 (bs, 1H), 6.65−6.67

(d, 1H, J = 8.0 Hz), 6.71−6.72 (d, 1H, J = 4.0 Hz), 7.06−7.10 (t, 1H, J = 8.0 Hz).

(+)-7-Methoxy-*N*-(2-(piperazin-1-yl)ethyl)-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine, (+)-8a. This compound was prepared from (+)-**7a** (2.46 g, 7.1 mmol) following procedure F, giving (+)-**8a** as a transparent thick liquid (yield is 2.15 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.91−0.96 (t, 3H, J = 10 Hz), 1.40−1.6 (m, 3H), 1.97−2.01 (m, 1H), 2.139 (bs, 1H), 2.41−3.11 (m, 18H), 3.82 (s, 3H), 6.61 (s, 1H), 6.66−6.79 (d, 1H, J = 12 Hz), 6.96−6.98 (d, 1H, J = 8 Hz).

Procedure G. Preparation of 7-[(2-Piperazin-1-ylethyl)-propylamino]-5,6,7,8-tetrahydronaphthalen-2-ol (9a). Compound **8a** (2.23 g, 6.73 mmol) was dissolved in 80 mL of CH_2Cl_2 and cooled to −78 °C. Then 1 M boron tribromide solution in dichloromethane (20 mL) was added dropwise, and the mixture was allowed to warm to ambient temperature and was stirred overnight. Saturated $NaHCO_3$ was added and the product extracted with dichloromethane, dried over Na_2SO_4, filtered, and concentrated to yield the crude product. Column chromatography (7:2:1 CH_2Cl_2/MeOH/Et_3N) afforded 1.62 g (76%) of **9a** as a brown wax. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.84−0.87 (t, 3H, J = 6 Hz), 1.27−1.31 (m, 2H), 1.70−1.82 (m, 3H), 2.25−2.28 (m, 1H), 2.58−2.06 (m, 1H), 2.73−2.78 (m, 4H), 2.97−3.09 (m, 5H), 3.16−3.20 (m, 7H), 6.45 (s, 1H), 6.53−6.55 (d, 1H, J = 9.2 Hz), 6.84−6.86 (d, 1H, J = 8 Hz).

6-[(2-Piperazin-1-ylethyl)propylamino]-5,6,7,8-tetrahydronaphthalen-1-ol (9b). This compound was prepared from **8b** following procedure G (yield is 78%), giving a brown wax. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.99−1.02 (t, 3H, 7.6 Hz), 1.28−1.30 (m, 2H), 1.71−1.83 (m, 3H), 2.26−2.29 (m, 1H), 2.57−2.60 (m, 1H), 2.72−2.77 (m, 4H), 2.97−3.07 (m, 5H), 3.16−3.21 (m, 7H), 6.5−6.52 (d, 1H, J = 8 Hz), 6.55−6.57 (d, 1H, J = 8 Hz), 6.9−6.95 (t, 1H, J = 10 Hz).

(−)-6-((2-(Piperazin-1-yl)ethyl)(propyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol, (−)-9b. This compound was prepared from (−)-**8b** (3.26 g, 9.8 mmol) following the procedure G to make (−)-**9b** as a brown wax (yield is 2.23, 71.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.86−0.89 (t, 3H, 6.0 Hz), 1.08−1.11 (t, 2H, J = 6 Hz), 1.40−1.51 (m, 3H), 1.98−2.01 (m, 1H), 2.46−2.54 (m, 9H), 2.62−2.67 (m, 4H), 2.87−2.96 (m, 4H), 6.47−6.49 (d, 1H, J = 8 Hz), 6.54−6.56 (d, 1H, J = 8 Hz), 6.91−6.95 (t, 1H, J = 8 Hz).

(+)-6-((2-(Piperazin-1-yl)ethyl)(propyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol, (+)-9b. This compound was prepared from (+)-**8b** (2.48 g, 7.48 mmol) following the procedure G which afforded (+)-**9b** as a brown wax (yield 1.74 g, 73.2%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.88−0.91 (t, 3H, 6.0 Hz), 1.10−1.13 (t, 2H, J = 6 Hz), 1.40−1.51 (m, 3H), 1.98−2.01 (m, 1H), 2.48−2.56 (m, 9H), 2.64−2.69 (m, 4H), 2.87−2.96 (m, 4H), 6.48−6.50 (d, 1H, J = 8 Hz), 6.55−6.56 (d, 1H, J = 4 Hz), 6.92−6.95 (t, 1H, J = 6 Hz).

(+)-7-((2-(Piperazin-1-yl)ethyl)(propyl)amino)-5,6,7,8-tetrahydronaphthalen-2-ol, (+)-9a. This compound was prepared from (+)-**8a** (2.15 g, 6.5 mmol) following the procedure G to yield (+)-**9a** as a brown wax (0.39 g, 20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.84−0.87 (t, 3H, J = 6 Hz), 1.70−1.82 (m, 3H), 2.25−2.28 (m, 1H), 2.58−2.06 (m, 1H), 2.73−2.78 (m, 4H), 2.97−3.09 (m, 5H), 3.16−3.20 (m, 9H), 6.45 (s, 1H), 6.53−6.55 (d, 1H, J = 8 Hz), 6.84−6.86 (d, 1H, J = 8 Hz).

5-(Chloromethyl)quinolin-8-ol (11). A mixture of commercially available compound **10**, 8-quinolinol (7.3 g, 50.29 mmol), 8 mL of 32% HCl in water, and 8 mL of 37% formaldehyde in water at 0 °C was treated with hydrogen chloride gas for 6 h. The solution was allowed to stand at room temperature for 2 h without stirring. The yellow solid obtained was collected on a filter, washed with 90% alcohol, and dried under vacuum to give 5- chloromethyl-8-quinolinol hydrochloride **11** as a yellow solid (9.0 g, 77.78%). ^{1}H NMR of HCl salt (400 MHz, DMSO) δ ppm 5.30 (s, 2H), 7.49−7.51 (d, 1H, J = 8 Hz), 7.83−7.85 (d, 1H, J = 8 Hz), 8.08−8.12 (dd, 1H, J_1 = 5.6 Hz, J_2 = 8.8), 9.098−9.110 (d, 1H, J = 4.8 Hz), 9.193−9.213 (d, 1H, J = 8 Hz)

Procedure H. Preparation of 5-((4-(2-((7-Hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)ethyl)piperazin-1-yl)methyl)quinolin-8-ol (12a). To a mixture of 5-chloromethyl-8-quinolinol hydrochloride, **11** (0.20 g, 0.86 mmol), and diisopropylethylamine (0.3 mL, 1.73 mmol, 2.2 equiv) in 25 mL of $CHCl_3$ at 0 °C was added **9a** (0.25 g, 0.78 mmol). The mixture was stirred for 24 h at room temperature. $CHCl_3$ (100 mL) was added, and the solution obtained was washed with 10% $NaHCO_3$, brine and then dried over Na_2SO_4. The solution was filtered and evaporated to dryness. The residue was a hydrochloride salt and crystallized from ethanol to yield **12a** as a yellow solid (0.28 g, 57.3%). ^{1}H NMR of HCl salt (400 MHz, DMSO-d_6) δ ppm 0.88−0.99 (m, 3H), 1.79−1.81 (bs, 4H), 2.298 (bs, 1H), 2.476−2.48 (m, 2H), 2.74 (s, 2H), 2.96−3.02 (t, 1H, J = 12 Hz), 3.122 (bs, 3H), 3.34−3.65 (m, 12H), 6.51−6.56 (m, 2H), 6.86−6.88 (d, 1H, J = 8 Hz), 7.50−7.52 (d, 1H, J = 8 Hz), 7.997−8.008 (m, 2H), 9.06−9.07 (d, 1H, J = 4 Hz), 9.49−9.51 (d, 1H, J = 8 Hz). Hydrochloride salt, mp 242−242 °C. Anal. ($C_{29}H_{40.6}N_4O_{3.3}\cdot 4HCl$) C, H, N

5-((4-(2-((5-Hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)ethyl)piperazin-1-yl)methyl)quinolin-8-ol (12b). This compound was prepared following procedure H in which compounds **11** (0.18 g, 0.8 mmol) and **9b** (0.23 g, 0.72 mmol) were used to afford **12b** as a yellow solid (0.265 g, 59%). ^{1}H NMR of salt (400 MHz, DMSO-d_6) δ ppm 0.84−0.87 (t, 3H, J = 6 Hz), 1.79−1.81 (bs, 4H), 2.298 (bs, 1H), 2.476−2.48 (m, 2H), 2.74 (s, 2H), 2.96−3.02 (t, 1H, J = 12 Hz), 3.122 (bs, 3H), 3.34−3.65 (m, 12H), 6.50−6.52 (d, 1H, J = 8 Hz), 6.55−6.57 (d, 1H, J = 8 Hz), 6.93−6.96 (t, 1H, J = 6 Hz), 7.06−7.08 (d, 1H, J = 8 Hz), 7.32−7.34 (d, 1H, J = 8 Hz), 7.44−7.46 (m, 1H), 8.66−8.68 (d, 1H, J = 8 Hz), 8.77−8.78 (d, 1H, J = 4 Hz). Hydrochloride salt, mp 252−255 °C. Anal. ($C_{29}H_{43}N_4O_{4.5}\cdot 4HCl$) C, H, N

8-Methoxyquinolin-4-ol (16). Trimethyl orthoformate (190 mL, 1.7 mol) and isopropylidine malonate (Meldrum's acid, 5 g, 34.7 mmol) were refluxed for 1 h and then cooled slightly. *O*-Anisidine (3.9 mL, 34.7 mmol) was added to the mixture along with 8 mL of dimethylformamide (DMF), and the resulting mixture was reheated to reflux for 2 h. The mixture was cooled to room temperature, poured into cold water (150 mL), upon which a crystalline solid formed and was filtered and allowed to dry in open air. It was then recrystallized from methanol to get pure white solid **15**. The solid material was then poured into warm diphenyl ether (50 mL) and heated to 300 °C for 15 min under reflux condensor, then cooled to room temperature. The cyclized product was isolated by cooling and subsequent precipitation by mixing with hexane followed by filtration, washing with additional hexane, and drying. It was the purified by column chromatograpy (EtOAc/MeOH, 95:5) to give 2.65 g (overall 44%) of **16** as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.99 (s, 3H), 6.31−6.33(d, 1H, J = 8 Hz), 7.03−7.05 (d, 1H, J = 8 Hz), 7.23−7.27 (t, 1H, J = 8 Hz), 7.64−7.67 (t, 1H, J = 6 Hz), 7.92−7.94 (d, 1H, 8 Hz).

4-Chloro-8-methoxyquinoline (17). Compound **16** (2.65 g, 15.1 mmol) was dissolved in $POCl_3$ (4.2 mL, 45.3 mmol) under nitrogen atmosphere and refluxed for 2 h. It was then cooled and concentrated under vacuum. The solid concentrate was taken in a beaker with 200 mL of water neutralized with $NaHCO_3$ powder and extracted with EtOAc. The solution was dried over Na_2SO_4, filtered, and concentrated. This crude product was then purified through column chromatography using ethyl acetate to get **17** as a brown solid (2.113 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.079 (s, 3H), 7.08−7.1 (d, 1H, J = 8 Hz), 7.49−7.56 (m, 2H), 7.76−7.78 (d, 1H, J = 8 Hz), 8.76−8.77 (d, 1H, J = 4 Hz).

Procedure I. Preparation of 7-((2-(4-(8-Methoxyquinolin-4-yl)piperazin-1-yl)ethyl)(propyl)amino)-5,6,7,8-tetrahydronaphthalen-2-ol (18a). To a mixture of **9a** (0.6 g, 1.89 mmol) and diisopropylethylamine (0.4 mL, 2.08 mmol, 1.1 equiv) in

15 mL of isopropanol was added 4-chloro-8-methoxyquinoline (**17**) (0.366 g, 1.89 mmol, 1 equiv). The mixture was refluxed with stirring for overnight. It was then evaporated, and the concentrate was dissolved in CH_2Cl_2 (50 mL). The solution obtained was washed with 5% $NaHCO_3$ (3 × 50 mL), brine (2 × 50 mL) and then dried over Na_2SO_4. The solution was filtered and evaporated to dryness. The residue was purified through column chromatography using 20% methanol in ethyl acetate to give **18a** as a white wax (0.66 g, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.93−0.95 (t, 3H, 4 Hz), 1.75 (m, 3H), 2.11−2.21 (m, 2H), 2.69−3.07 (m, 13H), 3.23 (s, 4H), 3.47 (s, 1H), 4.02 (s, 3H), 6.60 (s, 1H), 6.66−6.68 (d, 1H, *J* = 8 Hz), 6.82−6.84 (t, 2H, *J* = 4 Hz), 6.98−7.00 (d, 1H, *J* = 8 Hz), 7.36−7.42 (t, 1H, *J* = 12 Hz), 7.50−7.52 (d, 1H, *J* = 8 Hz), 8.67−8.68 (d, 1H, *J* = 4 Hz).

Preparation of 6-((2-(4-(8-Methoxyquinolin-4-yl)piperazin-1-yl)ethyl)(propyl) amino)-5,6,7,8-tetrahydronaphthalen-1-ol (18b). This compound was prepared from **9b** (0.668 g, 2.1 mmol) and **17** (0.4 g, 2.1 mmol) following procedure I to get **18b** as a white wax (yield 0.76 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.92−0.95 (t, 3H, *J* = 6 Hz), 1.58−1.65 (m, 3H), 2.04−2.14 (m, 2H), 2.73−2.96 (m, 13H), 3.25 (bs, 4H), 3.48 (s, 1H), 4.04 (s, 3H), 6.57−6.59 (d, 1H, *J* = 8 Hz), 6.66−6.68 (d, 1H, *J* = 8 Hz), 6.86−6.87(d, 1H, *J* = 4 Hz), 6.92−6.96 (t, 1H, *J* = 8 Hz), 6.99−7.01 (d, 1H, *J* = 8 Hz), 7.37−7.41 (t, 1H, *J* = 8 Hz), 7.54−7.56 (d, 1H, *J* = 8 Hz), 8.72−8.73 (d, 1H, *J* = 4 Hz) .

Preparation of (−)-6-((2-(4-(8-Methoxyquinolin-4-yl)piperazin-1-yl)ethyl)(propyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol, (−)-18b. This compound was prepared from (−)-**9b** (0.50 g, 1.6 mmol) and **17** (0.305 g, 1.6 mmol) following procedure I to afford (−)-**18b** as a white wax (0.419 g, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.98−1.00 (t, 3H, *J* = 4 Hz), 1.58−1.65 (m, 3H), 2.04−2.14 (m, 2H), 2.85−3.12 (m, 13H), 3.25 (bs, 4H), 3.48 (s, 1H), 4.06 (s, 3H), 6.57−6.59 (d, 1H, *J* = 8 Hz), 6.87−6.88 (d, 1H, *J* = 4 Hz), 6.92−6.97 (m, 2H), 7.01−7.03 (d, 1H, *J* = 8 Hz), 7.39−7.43 (t, 1H, *J* = 8 Hz), 7.54−7.57 (t, 1H, *J* = 6 Hz), 8.73−8.74 (d, 1H, *J* = 4 Hz).

(+)-**6-((2-(4-(8-Methoxyquinolin-4-yl)piperazin-1-yl)ethyl)-(propyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol,** (+)-**18b.** This compound was prepared from (+)-**9b** (0.62 g, 1.95 mmol) and **17** (0.378 g, 1.95 mmol) following procedure I to make (+)-**18b** as a white wax (0.565 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.97−0.99 (t, 3H, *J* = 4 Hz), 1.57−1.64 (m, 3H), 2.04−2.14 (m, 2H), 2.85−3.12 (m, 13H), 3.25 (bs, 4H), 3.48 (s, 1H), 4.06 (s, 3H), 6.57−6.59 (d, 1H, *J* = 8 Hz), 6.87−6.88 (d, 1H, *J* = 4 Hz), 6.93−6.97(m, 2H), 7.01−7.03 (d, 1H, *J* = 8 Hz), 7.38−7.42 (t, 1H, *J* = 8 Hz), 7.53−7.56 (t, 1H, *J* = 6 Hz), 8.72−8.73 (d, 1H, 4 Hz).

(+)-**7-((2-(4-(8-Methoxyquinolin-4-yl)piperazin-1-yl)ethyl)-(propyl)amino)-5,6,7,8-tetrahydronaphthalen-2-ol,** (+)-**18a.** This compound was prepared from (+)-**9a** (0.39 g, 1.22 mmol) and **17** (0.214 g, 1.11 mmol) following procedure I to get (+)-**18a** as a white wax (0.110 g, 19%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.93−0.95 (t, 3H, 4 Hz), 1.75 (m, 3H), 2.11−2.21 (m, 2H), 2.69−3.07 (m, 13H), 3.23 (s, 4H), 3.47 (s, 1H), 4.02 (s, 3H), 6.60 (s, 1H), 6.66−6.68 (d, 1H, *J* = 8 Hz), 6.82−6.84 (t, 2H, *J* = 4 Hz), 6.98−7.00 (d, 1H, *J* = 8 Hz), 7.36−7.42 (t, 1H, *J* = 12 Hz), 7.50−7.52 (d, 1H, *J* = 8 Hz), 8.67−8.68 (d, 1H, *J* = 4 Hz).

Procedure J. Preparation of 4-(4-(2-((7-Hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)ethyl)piperazine-1-yl)-quinolin-8-ol (19a, Hydrochloride Salt). Compound **18a** (0.5 g, 1.05 mmol) and 48% aqueous HBr (10 mL) were refluxed for overnight. It was then cooled and concentrated under vacuum, and 50 mL of water was added to the crude residue and made freebase with $NaHCO_3$ powder which was then extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and evaporated. The greenish solid crude product was dissolved in a minimum amount of ethanol, at which time ethereal HCl was added, and the crude salt was filtered and dried over vacuum oven. The crude salt was then purified by recrystallization in ethanol. The HCl salt was filtered and dried to yield 0.329 g (26%) of the final compound as an off-white solid. ^{1}H NMR of HCl salt (400 MHz, DMSO-d_6) δ ppm 0.93−0.95 (t, 3H, *J* = 4 Hz), 1.75 (m, 3H), 2.11−2.21 (m, 2H), 2.69−3.07 (m, 13H), 3.23 (s, 4H), 3.47 (s, 1H), 6.58 (s, 1H), 6.60−6.61 (d, 1H, *J* = 4 Hz), 6.91−6.93 (d, 1H, *J* = 8 Hz), 7.35−7.40 (m, 2H), 7.60−7.68 (m, 2H), 8.60−8.62 (d, 1H, *J* = 8 Hz). Hydrochloride salt, mp 244−246 °C. Anal. ($C_{28}H_{38.8}N_4O_{3.4}\cdot 4HCl$) C, H, N.

4-(4-(2-((5-Hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)ethyl)piperazin-1-yl)quinolin-8-ol (19b, Hydrochloride Salt). This compound was prepared from **18b** following procedure J, giving **19b** as an off-white solid (31%). ^{1}H NMR of HCl salt (400 MHz, DMSO-d_6) δ ppm 0.92−0.95 (t, 3H, *J* = 6 Hz), 1.58−1.65 (m, 3H), 2.04−2.14 (m, 2H), 2.73−2.96 (m, 13H), 3.25 (bs, 4H), 3.48 (s, 1H), 6.55−6.57 (d, 1H, *J* = 8 Hz), 6.62−6.64 (d, 1H, *J* = 8 Hz), 6.92−6.96 (t, 1H, *J* = 8 Hz), 7.31−7.33 (d, 1H, *J* = 8 Hz), 7.39−7.41 (d, 1H, *J* = 8 Hz), 7.55−7.57 (m, 2H), 8.57−8.59 (d, 1H, *J* = 8 Hz). Hydrochloride salt, mp 249−251 °C. Anal. ($C_{28}H_{38.4}N_4O_{3.2}\cdot 4HCl$) C, H, N.

(−)-**4-(4-(2-((5-Hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-(propyl)amino)ethyl)piperazin-1-yl)quinolin-8-ol** ((−)-**19b, Hydrochloride Salt).** This compound was prepared from (−)-**18b** (0.480 g, 1.01 mmol) following procedure J to afford (−)-**19b** as an off-white solid (0.21 g, 35%). ^{1}H NMR (free base, 400 MHz, $CDCl_3$) δ ppm 0.95−0.99 (t, 3H, *J* = 8 Hz), 1.46−1.53 (m, 3H), 2.24−2.50 (m, 2H), 2.84−3.06 (m, 13H), 3.25 (bs, 4H), 3.49−3.67 (m, 1H), 6.52−6.54 (d, 1H, *J* = 8 Hz), 6.60−6.62 (d, 1H, *J* = 8 Hz), 6.85−6.86 (d, 1H, *J* = 4 Hz), 6.95−6.99 (t, 1H, *J* = 8 Hz), 7.10−7.12 (d, 1H, *J* = 8 Hz), 7.35−7.39 (t, 1H, *J* = 8 Hz), 7.44−7.46 (d, 1H, 8 Hz), 8.57−8.58 (d, 1H, *J* = 4 Hz). $[\alpha]^{25}_D$ −36° (*c* 0.5, CH_3OH). Hydrochloride salt, mp 237−240 °C. Anal. ($C_{28}H_{37}N_4O_{2.5}\cdot 4HCl$) C, H, N.

(+)-**4-(4-(2-((5-Hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-(propyl)amino)ethyl)piperazin-1-yl)quinolin-8-ol** ((+)-**19b, Hydrochloride Salt).** This compound was prepared from (+)-**18b** (0.520 g, 1.10 mmol) following procedure J to make (+)-**19b** as an off-white solid (0.26 g, 39%). ^{1}H NMR (free base, 400 MHz, $CDCl_3$) δ ppm 0.96−0.99 (t, 3H, *J* = 6 Hz), 1.47−1.52 (m, 3H), 2.24−2.50 (m, 2H), 2.85−3.05 (m, 13H), 3.25 (bs, 4H), 3.49−3.67 (m, 1H), 6.53−6.55 (d, 1H, *J* = 8 Hz), 6.61−6.63 (d, 1H, *J* = 8 Hz), 6.86−6.88 (d, 1H, *J* = 8 Hz), 6.95−6.99 (t, 1H, *J* = 8 Hz), 7.10−7.12 (d, 1H, *J* = 8 Hz), 7.34−7.38 (t, 1H, *J* = 8 Hz), 7.46−7.48 (d, 1H, 8 Hz), 8.56−8.57 (d, 1H, *J* = 4 Hz). $[\alpha]^{25}_D$ +33.6° (*c* 0.5, CH_3OH). Hydrochloride salt, mp 230−232 °C. Anal. ($C_{28}H_{41}N_4O_{4.5}\cdot 4HCl$) C, H, N.

(+)-**4-(4-(2-((7-Hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-(propyl)amino)ethyl)piperazin-1-yl)quinolin-8-ol** ((+)-**19a, Hydrochloride Salt).** This compound was prepared from (+)-**18a** (0.110 g, 0.232 mmol) following procedure J that yielded (+)-**19a** as an off-white solid (0.05 g, 43%). ^{1}H NMR of HCl salt (400 MHz, DMSO-d_6) δ ppm 0.89−0.91 (t, 3H, *J* = 4 Hz), 1.71 (m, 3H), 2.09−2.19 (m, 2H), 2.67−3.06 (m, 13H), 3.20 (s, 4H), 3.47 (s, 1H), 6.56 (s, 1H), 6.59−6.60 (d, 1H, *J* = 4 Hz), 6.91−6.92 (d, 1H, *J* = 4 Hz), 7.32−7.36 (m, 2H), 7.64−7.68 (m, 2H), 8.59−8.61 (d, 1H, *J* = 8 Hz). $[\alpha]^{25}_D$ +32.4° (*c* 0.5, CH_3OH). Hydrochloride salt, mp 239−241 °C. Anal. ($C_{28}H_{37.4}N_4O_{2.7}\cdot 4HCl$) C, H, N.

Complexation of 19b with Iron(III) Chloride. Compound **19b** (4HCl salt) was dissolved in water to make a 600 μM solution, and the pH of the solution was found to be 3.66. The UV scanned spectra of the solution was taken from 200 to 760 nm. $FeCl_3\cdot 6H_2O$ was next dissolved in water to make a 600 μM colorless solution. The two solutions were mixed together in equal volume, which gave a green solution at pH 3.76. The solution was subjected to UV scan as before. Then the pH of the solution was increased to 4.0 by adding base diisopropylethylamine (DIPEA) (diluted with H_2O) which produced a deep-green color which was followed by UV spectra scan. The pH of the solution was next increased to 7.4 by adding an additional amount of DIPEA which produced a light-brown solution followed by UV scanning from 390 to 770 nm.

Iron-Chelating Capacity. The iron-binding capacity of the test compound **19b** (iron chelating compounds) was determined by assessing their ability to compete with ferrozine (3-[2-pyridyl]-5,6-diphenyl-1,2,4-triazine-4,4′-disulfonic acid) for ferrous ions which result in reduced absorbance of the ferrozine−Fe(II) complex at 562 nm. Complexation reactions were carried out in 5% ammonium acetate buffer (pH 6.9). Various concentrations of the test compound **19b** (25−250 μM) were incubated with $\{[NH_4]_2[Fe][SO_4]_2 \cdot 6H_2O\}$ (20 μM) for 30 min, followed by the addition of 80 μM ferrozine. After incubation at ambient temperature for 1 h, the UV absorbance of the resulting solutions at 562 nm was read. The limitation of this assay is that chelating compound forms complex with iron at higher drug concentration which also gives absorbance reading at 562 nm. We subtracted the absorbance with a blank solution containing only drug and iron without ferrozine (corrected absorbance). The Fe(II) chelating effect was calculated as follows:

$$\text{chelating effect (\%)} = [1 - (\text{Abs}_{562\text{nm}} \text{ of sample})/(\text{Abs}_{562\text{nm}} \text{ of control})] \times 100$$

The chelating effect is expressed as percent of control [80 μM ferrozine, 20 μM ferrous ammonum sulfate in pH 6.9 ammonium acetate buffer (5%)].

Deoxyribose Antioxidant Assay Procedure. The assay was carried out by following the published procedure.[37] Briefly, the reaction mixture, in a final volume of 1.0 mL, contained the following reagents: deoxyribose (2.8 mM), potassium phosphate buffer, pH 7.4 (100 mM), increasing concentrations of test drug (0−1000 μM), ferric chloride (100 μM), ascorbic acid (100 μM), EDTA (100 μM), and H_2O_2 (1 mM). Fresh solutions of deoxyribose, ferric chloridem and H_2O_2 were made prior to use. All solutions were made in degassed water. H_2O_2 solution was added at the end to initiate the reaction to form the hydroxyl radical. The reaction was continued for 30 min at 37 °C. The extent of deoxyribose degradation was monitored by formation of malondialdehyde (a pink chromogen) determined by the addition of 1 mL of 1% (w/v) 2-thiobarbituric acid in 50 mM NaOH (TBA) and 1 mL of 2.8% (w/v) trichloroacetic acid (TCA). After addition of TBA and TCA, the solutions were heated at 85 °C for 20 min. Pink chromogen was formed. The solutions were cooled, and the resultant absorbance was read at 532 nM against appropriate blanks. The intensity of the pink color decreased in the presence of increasing concentrations of hydroxyl radical scavenger.

Dopamine Receptor Affinity and Agonism. Binding affinity was monitored by inhibition of [^{3}H]spiperone (15.0 Ci/mmol, Perkin-Elmer) binding to dopamine rD2 and rD3 receptors expressed in HEK-293 cells, in a buffer containing 0.9% NaCl as described by us previously (Table 1).[26] Functional activity of test compounds in activating dopamine hD2 and hD3 receptors expressed in CHO cells was measured by stimulation of binding of [^{35}S]GTPγS (1250 Ci/mmol, Perkin-Elmer) in comparison to stimulation by the full agonist dopamine as described by us previously.[26]

Animal Experiment. Drugs and Chemicals. The following commercially available drugs were used in the experiment: reserpine hydrochloride (Alfa Aesar), ropinirole (Sigma). The hydrochloride salts of (−)-**19b** and ropinirole were dissolved in water for both locomotor and 6-OH-DA rotational experiments. Reserpine was dissolved in 10−25 μL of glacial acetic acid and further diluted with 5.5% glucose solution. All compounds for this study were administered in a volume of 0.1−0.2 mL for subcutaneous administration and 0.7−0.9 mL for intraperitoneal administration into each rat.

Animals. In rodent studies, animals were male Sprague−Dawley rats from Harlan (Indianapolis, IN) weighing 220−225 g unless otherwise specified. The lesioned rats (290−320 g) were purchased from Taconic Biotechnology (Rensselaer, NY), and their unilateral lesion was checked twice by apomorphine challenge following the surgery. Animals were maintained in sawdust-lined cages in a temperature and humidity controlled environment at 22 ± 1 °C and 60 ± 5%, respectively, with a 12 h light/dark cycle, with lights on from 6:00 a.m. to 6:00 p.m. They were group-housed with unrestricted access to food and water. All experiments were performed during the light component. All animal use procedures were in compliance with the Wayne State University Animal Investigation Committee consistent with AALAC guidelines.

Reversal of Reserpine-Induced Hypolocomotion in Rats. Administration of reserpine induces catalepsy in rodents primarily by blocking the vesicular monoamine trasporter (VMAT) which helps in the internalization of monoamines into vesicles, resulting in metabolism of unprotected monoamines in the cytosol that ultimately causes depletion of monoamines in the synapse of the peripheral sympathetic nerve terminals.[38,41] The ability of the compound (−)-**19b** to reverse the reserpine induced hypolocomotion was investigated.[42] Ropinirole was used as standard reference compound in this study. Reserpine (5.0 mg/kg, sc) or saline (sc) was administered 18 h before the injection of drug or vehicle (ip). The rats were placed individually in chambers for 1 h for acclimatization purposes before the administration of the test drug, standard drug, or vehicle. Immediately after administration of drug or vehicle, animals were individually placed in VersaMax animal activity monitor chamber (45 cm × 30 cm × 20 cm) (AccuScan Instruments, Inc. Columbus, OH) to start measuring locomotor activity. Locomotion was monitored for 6 h. Consecutive interruption of two infrared beams situated 24 cm apart and 4 cm above the cage floor in the monitor chamber recorded movement. The data were presented as horizontal counts (HACTV). The effect of the individual doses of drugs on locomotor activity was compared with respect to saline treated controls (mean ± SEM). The data were analyzed by one way analysis of variance (ANOVA) followed by Dunnett's post hoc test. The effect was considered significant if the difference from control group was observed at $p < 0.05$.

In Vivo Rotational Experiment with 6-OH-DA Lesioned Rats. In the first 14 days postlesion challenge with apomorphine was done with lesioned animals 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 of > 250) indicating successful unilateral lesion. In these rats, lesion was performed on the left side of the medial forebrain bundle in the brain, and the coordinates used from Bregma are the following: AP, −4.3; ML, +1.2; DV, −8.3. The rotations produced upon agonist challenge were clockwise. In this study, apomorphine was also used as a reference compound. The test drugs including ropinirole were dissolved in saline. The drug (−)-**19b** was administered ip and the ropinirole was administered sc. The rotations were measured over 7−10 h. For control, vehicle was administered alone. Rotations were measured in the Rotomax rotometry system (AccuScan Instruments, Inc. Columbus, OH) equipped with Rotomax analyzer, high resolution sensor, and animal chambers with harnesses. Data were analyzed with Rotomax Windows software program. The rotations were measured in a rotational chamber immediately after administration of drugs. The data were collected at every 30 min. Data were analyzed by the GraphPad (version 4, San Diego, CA) program. All drugs produced contralateral rotations in all lesioned rats, which lasted over 3−10 h.

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Supporting Information Available: Elemental analysis data for all final targets. This material is available free of charge via the Internet at http://pubs.acs.org.

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