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Structure−Activity Relationship Study of N^6-(2-(4-(1*H*-Indol-5-yl) piperazin-1-yl)ethyl)-N^6-propyl-4,5,6,7-tetrahydrobenzo[*d*]thiazole-2,6-diamine Analogues: Development of Highly Selective D3 Dopamine Receptor Agonists along with a Highly Potent D2/D3 Agonist and Their Pharmacological Characterization

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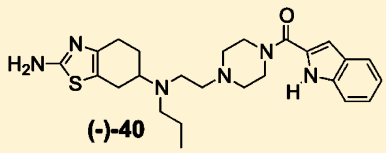
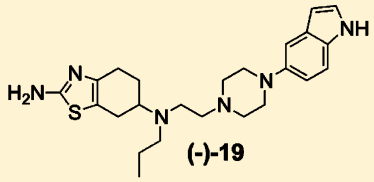
Supporting Information



EC50: D2 = 114 nM, % *Emax* = 101 & D3 = 0.26 nM, % *Emax* = *103* D2/D3 = 438



EC50: D2 = 2.96 nM, % *Emax* = 107 & D3 = 1.26 nM, % *Emax* = 93 D2/D3 = 2.35

ABSTRACT: In our effort to develop multifunctional drugs against Parkinson's disease, a structure−activity-relationship study was carried out based on our hybrid molecular template targeting D2/D3 receptors. Competitive binding with [^{3}H]spiroperidol was used to evaluate affinity (K_i) of test compounds. Functional activity of selected compounds in stimulating [^{35}S]GTPγS binding was assessed in CHO cells expressing either human D2 or D3 receptors. Our results demonstrated development of highly selective compounds for D3 receptor (for (−)-**40** K_i, D3 = 1.84 nM, D2/D3 = 583.2; for (−)-**45** K_i, D3 = 1.09 nM, D2/D3 = 827.5). Functional data identified (−)-**40** (EC_{50}, D2 = 114 nM, D3 = 0.26 nM, D2/D3 = 438) as one of the highest D3 selective agonists known to date. In addition, high affinity, nonselective D3 agonist (−)-**19** (EC_{50}, D2 = 2.96 nM and D3 = 1.26 nM) was also developed. Lead compounds with antioxidant activity were evaluated using an in vivo PD animal model.

INTRODUCTION

Dopaminergic receptor systems have been targeted for the development of pharmacotherapeutic agents for a number of CNS related disorders, including drug addiction, schizophrenia, depression, and Parkinson's disease (PD). Dopamine (DA) receptor agonists have been employed more extensively in the treatment of Parkinson's disease than any other type of pharmacotherapy. Levodopa (L-dopa), the immediate precursor to endogenous DA, is the current gold-standard treatment option for PD. DA receptors belong to the family of transmembrane proteins known as G-protein-coupled receptors (GPCRs). DA receptors are widely distributed in the CNS, are also present in the periphery, and are divided into five subtypes. On the basis of the stimulatory action on adenylyl cyclase, D1 and D5 are grouped together as D1 type. D2−D4 receptors are classified as D2 type because of their inhibitory action on adenylyl cyclase activity.[1−7] Interestingly, the D3 receptor was found to have a distribution in the brain that is somewhat different from that of the D2 receptor. The highest levels of D3 receptor expression were found to be in the limbic region of the brain, while D2 receptor expression is most dense in the striatum of the midbrain.[8] D2 and D3 receptor subtypes occur post- and presynaptically. In the latter location they function as autoreceptors that regulate DA synthesis, metabolism, and release.[9] It is noteworthy that D2 and D3 receptor subtypes share 50% overall amino acid sequence homology and 75−80% in their agonist binding sites. As a result, development of ligands selective for either subtype is a challenging task.[10,11]

Parkinson's disease (PD) is a progressive, neurodegenerative disorder that results from the death of DA-producing cells in the substantia nigra region of the midbrain. Common symptoms include resting tremor, muscular rigidity, bradykinesia, postural instability, and cognitive psychiatric complications.[12−14] Although the etiology of PD is not yet clear and may be multifactorial, oxidative stress and mitochondrial dysfunction are thought to play a central role in the pathology of the disease. Recent studies on various genetic mutations have provided new insights into the disease process.[15−17] Oxidative

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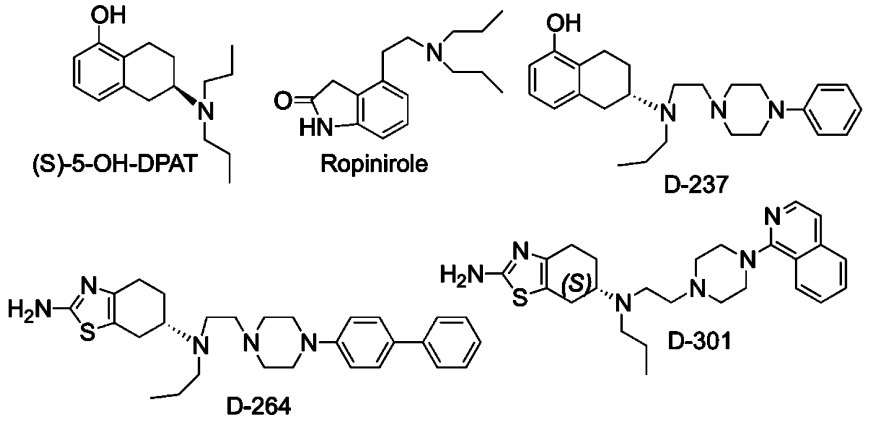
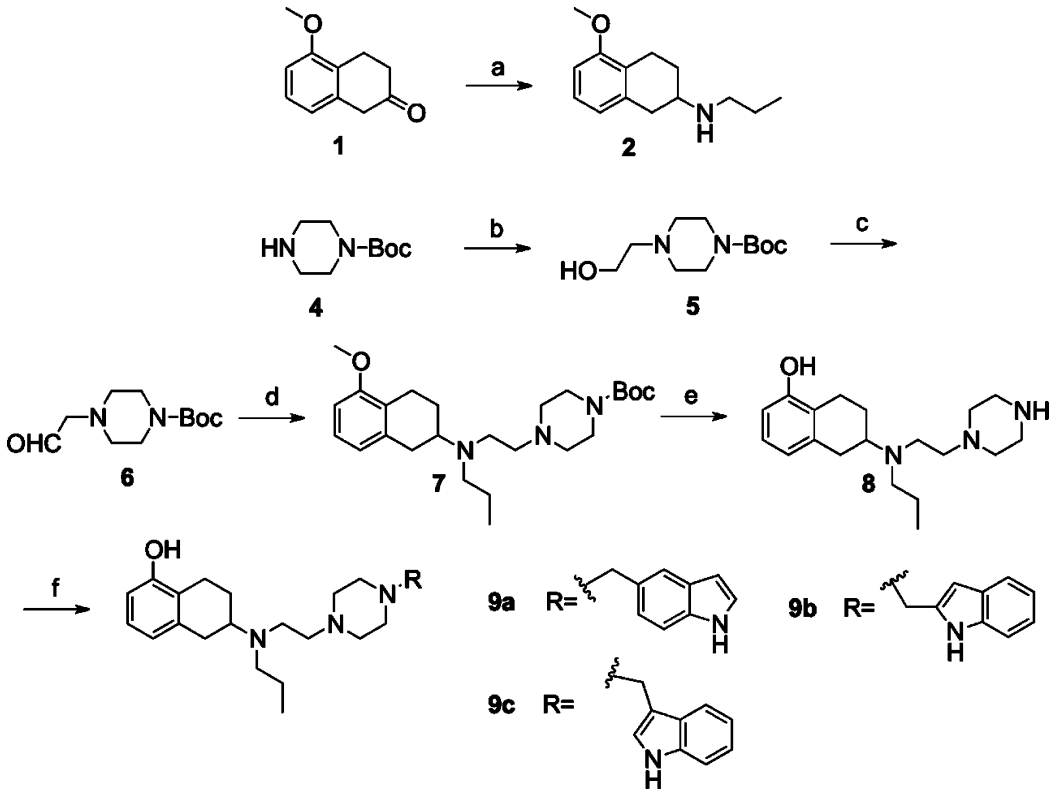


Figure 1. Molecular structure of dopamine D3-receptor-preferring agonists.

Scheme 1[a]



[a]Reagents and conditions: (a) *n*-propylamine, $NaCNBH_3$, AcOH, CH_2Cl_2; (b) 2-bromoethanol, K_2CO_3, CH_3CN reflux; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt; (d) **2**, $Na(OAc)_3BH$, CH_2Cl_2; (e) aq HBr (48%), reflux; (f) indole-5-, -2- or -3-carbaldeyde, $Na(OAc)_3BH$, CH_2Cl_2.

stress has been strongly implicated in midbrain dopaminergic cell death.[15] Toxicity from endogenous and exogenous origins, caused by oxidative mechanisms, has been implicated as a fundamental process in progressive nigral cell loss.[18] Along with motor fluctuations and wearing off after long-term treatment, side effects associated with L-dopa treatment and the eventual oxidation of DA derived from L-dopa have been speculated to produce further oxidative stress.[19]

In addition, α-synuclein, a presynaptic protein involved in fibrillization, has been implicated in the pathogenesis of PD.[20,21] A recent report demonstrated that in cultured human dopaminergic neurons, accumulation of α-synuclein induces apoptosis in the presence of DA and reactive oxygen species.[22] Furthermore, an interaction between calcium, cytosolic DA, and α-synuclein has been implicated in the loss of DA neurons in the substantia nigra.[23] In this case, DA-dependent neurotoxicity is mediated by a soluble protein complex containing α-synuclein.[24] Therefore, α-synuclein, together with oxidized DA, could have synergistic effects in terms of disease susceptibility and progression.

It is increasingly evident that for a complex disease such as PD, a drug aimed at one target site will only partially address the therapeutic need of the disease. Thus, it is hypothesized that multifunctional drugs, having multiple pharmacological activities, will be more effective in the case of PD.[25] Our approach in developing such agents involves alleviating symptoms of the disease, along with preventing or halting the neurodegeneration process. Our drug development approach

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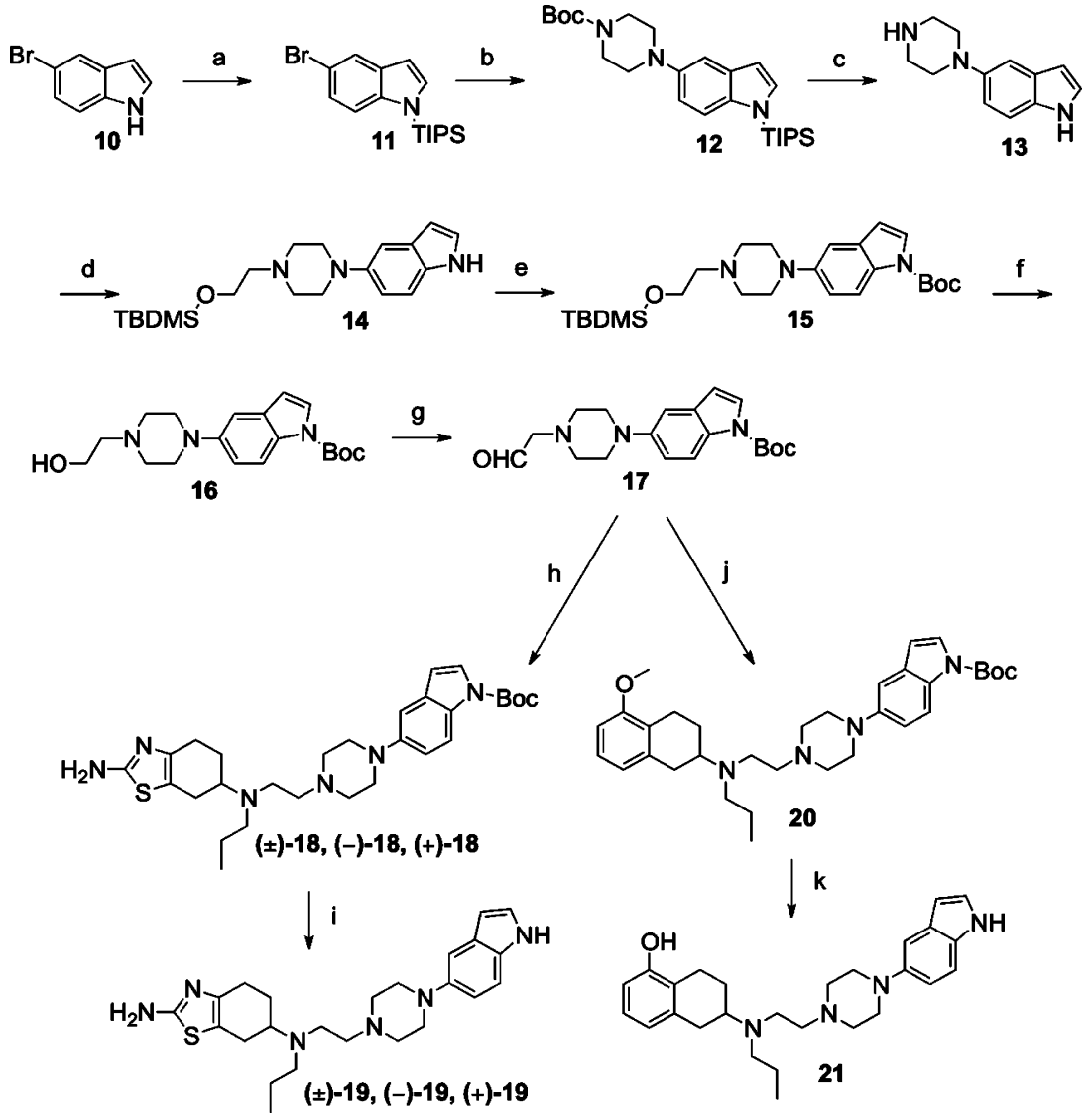
Scheme 2[a]



[a]Reagents and conditions: (a) triisopropylsilyl chloride, NaH, THF; (b) **4**, $PdCl_2[P(o\text{-tol})_3]_2$, NaO*t*-Bu, xylenes, reflux; (c) CF_3COOH, CH_2Cl_2; (d) (2-bromoethoxy)-*tert*-butyldimethylsilane, K_2CO_3, CH_3CN, reflux; (e) $(Boc)_2O$, DMAP, THF; (f) *n*-Bu_4NF, THF; (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt; (h) (±)-, (−)-, or (+)-pramipexole, $Na(OAc)_3BH$, CH_2Cl_2; (i) CF_3COOH, CH_2Cl_2; (j) **2**, $Na(OAc)_3BH$, CH_2Cl_2; (k) aq HBr (48%), reflux.

encompasses and incorporates some of the critical pathogenic factors implicated in PD.[26,27] We have designed a novel, hybrid, molecular template by combining known D2/D3 agonists with D2/D3 antagonist fragments, which led to the development of a number of D3-preferring agonists.[28−33] One such compound, D-264, was shown to be neuroprotective in two PD animal models.[34] Furthermore, we demonstrated that our D3-preferring agonist, D-264, significantly improved behavioral syndromes in both acute MPTP and progressive lactacystin mouse models of PD.[34] Moreover, D-264 exhibited pronounced neuroprotection in both MPTP- and lactacystin-lesioned animal models, in which degeneration of dopaminergic pathways is known to occur. The neuroprotective effect of D-264 was attributed, in part, to activation of the D3 receptor. Structural flexibility in the D2/D3 antagonist fragment of our hybrid molecular template has allowed us to design and develop new DA agonists with the capacity to bind iron. Iron has been implicated in the pathogenesis of PD, likely via increasing oxidative stress levels.[31] In our recent study, we have demonstrated development of brain penetrant, multifunctional compounds with agonist activity at D2/D3 receptors along with capacity to chelate iron. One of our lead compounds in this series exhibited in vivo neuroprotection in a mouse MPTP model.[31,35]

As mentioned above, we have previously reported a hybrid structure approach as part of our ongoing effort to design and develop selective agonists for the DA D3 receptor. Our hybrid approach combines, via suitable linker length, an agonist binding moiety (aminotetralin or bioisosteric equivalent) with arylpiperazine fragments. This approach has yielded molecules that retain agonist activity while exhibiting varying selectivity for the D3 receptor (Figure 1). Our current structure−activity-relationship study is focused on introducing several indole derivatives on the piperazine ring. Our goal is to assess indole substitution in terms of its effect on selectivity and affinity for the D3 receptor. It is important to mention that indole

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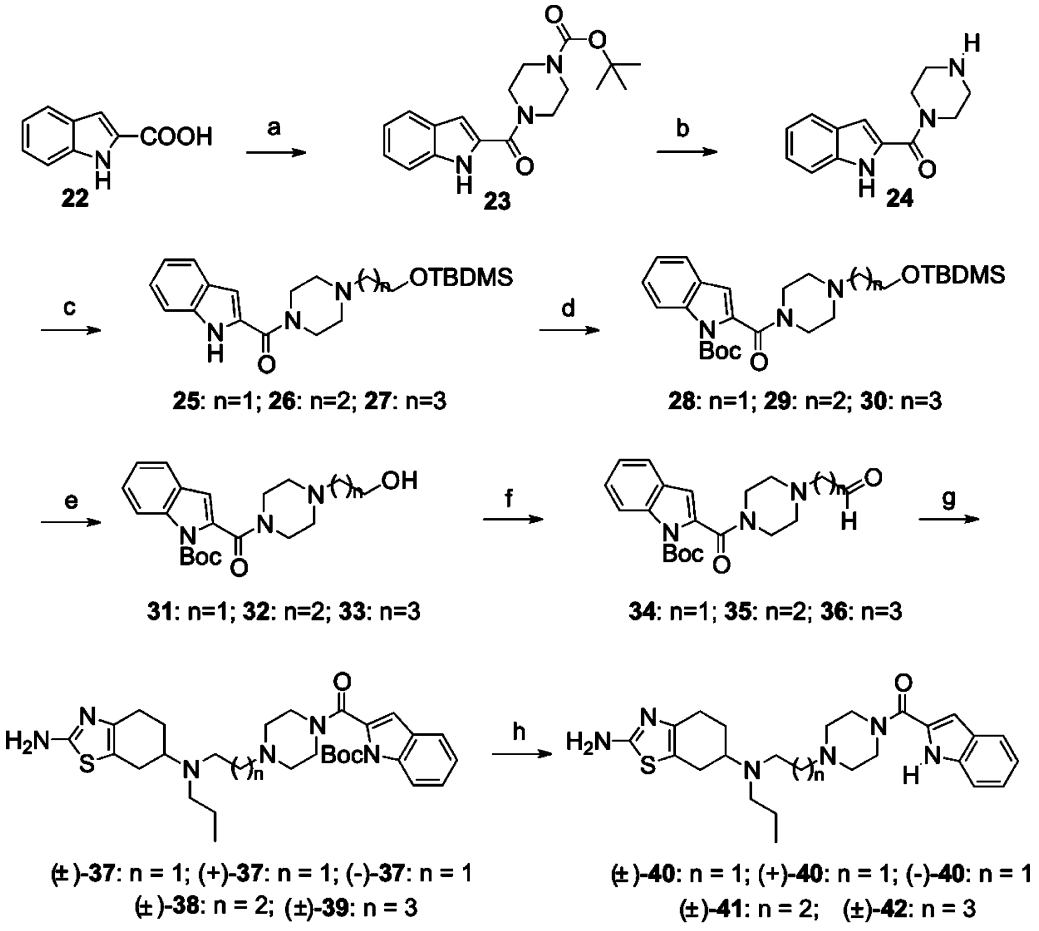
Scheme 3[a]



[a]Reagents and conditions: (a) **4**, EDCl, HOBT, Et_3N, CH_2Cl_2; (b) CF_3COOH, CH_2Cl_2; (c) (2-bromoethoxy)(*tert*-butyl)dimethylsilane, (3-bromopropoxy)(*tert*-butyl)dimethylsilane or (bromobutoxy)(*tert*-butyl)dimethylsilane, K_2CO_3, CH_3CN, reflux; (d) $(Boc)_2O$, 4-DMAP, THF; (e) *n*-Bu_4NF, THF; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt; (g) (±), (+), or (−)-pramipexole, $Na(OAc)_3BH$, CH_2Cl_2; (h) CF_3COOH, CH_2Cl_2.

derivatives are well-known for their potent antioxidant activity.[36,37] Another goal is to produce synergistic, antioxidant activity by combining the 2-aminothiazole moiety with an indole functionality.[38]

CHEMISTRY

Scheme 1 outlines the synthesis of **9a**, **9b**, and **9c**. 5-Methoxy-2-tetralone was first condensed with *n*-propylamine in the presence of sodium cyanoborohydride under reductive amination conditions to yield secondary amine **2**. In preparation of **7**, amine **4** was N-alkylated using 2-bromoethanol to provide alcohol **5**. Alcohol **5** was converted, under Swern oxidation conditions, to its aldehyde derivative. Condensation of aldehyde **6** with amine **2**, using sodium triacetoxyborohydride as reducing agent, yielded compound **7**. Treatment of intermediate **7** with aqueous HBr (48%) provided amine **8**. Finally, condensation of secondary amine **8** with properly substituted indolecarbaldehydes afforded final compounds **9a**−**c**.

Scheme 2 describes the synthesis of final compounds (±)-**19**, (+)-**19**, (−)-**19**, and **21**. Commercially available 5-bromoindole was N-protected using triisopropylsilyl chloride in the presence of NaH to give intermediate **11**. Palladium-catalyzed cross-coupling of **11** with amine **4**, using $PdCl_2[P(o\text{-tol})_3]_2$ and NaO-*t*-Bu in xylenes at reflux, yielded intermediate **12**. Successive deprotection of TIPS and Boc groups with trifluoroacetic acid gave amine **13**, which on selective N-alkylation with (2-bromoethoxy)-*tert*-butyldimethylsilane yielded compound **14**. The indole moiety of intermediate **14** was N-protected giving compound **15**, which on TBDMS deprotection yielded alcohol **16**. Compound **16** was converted to its aldehyde derivative **17**, under Swern oxidation conditions. Aldehyde **17** was subsequently condensed with (±)-, *S*-(−)-, or *R*-(+)-pramipexole to yield intermediates (±)-**18**, *S*-(−)-**18**, and *R*-(+)-**18**, which were each treated with trifluoroacetic acid to afford final compounds (±)-**19**, *S*-(−)-**19**, and *R*-(+)-**19**. Aldehyde **17** was further condensed with 5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)propylamine under reductive amination conditions and subsequently treated with aqueous HBr (48%) to furnish final compound **21**.

Scheme 3 depicts the synthesis of final compounds (±)-**40**, *R*-(+)-**40**, *S*-(−)-**40**, **41**, and **42**. Indole-2-carboxylic acid was reacted with amine **4**, under amide coupling conditions, to yield intermediate **23**. Deprotection, followed by selective N-alkylation with appropriately substituted TBDMS-protected alkyl halides afforded intermediates **25**−**27**. Protection of the indole moiety, followed by selective deprotection of the hydroxyl functionality, gave alcohols **31**−**33**. Alcohols **31**−**33**

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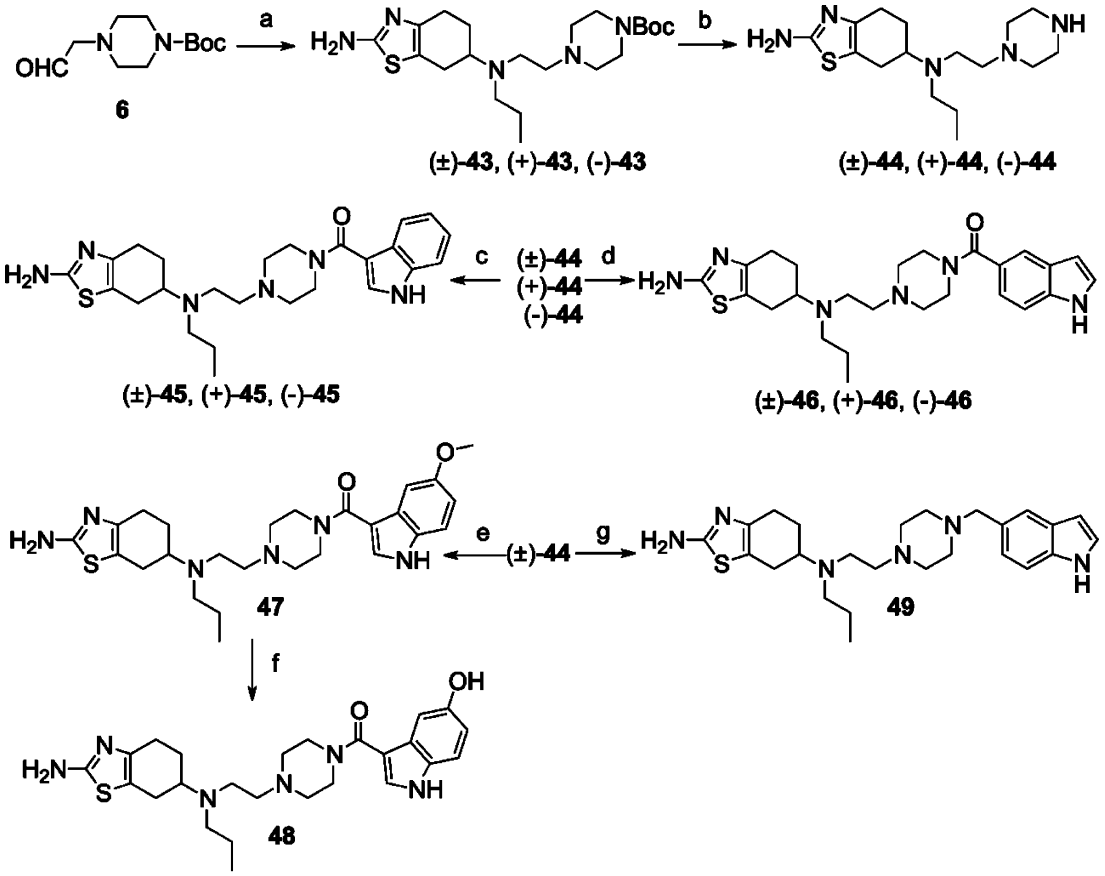
Scheme 4[a]



[a]Reagents and conditions: (a) (±)-, (+)-, or (−)-pramipexole, $Na(OAc)_3BH$, CH_2Cl_2; (b) CF_3COOH, CH_2Cl_2; (c) indole-3-carboxylic acid, EDCl, HOBT, Et_3N, CH_2Cl_2; (d) indole-5-carboxylic acid, EDCl, HOBT, Et_3N, CH_2Cl_2; (e) 5-methoxy-1*H*-indole-3-carboxylic acid, EDCl, HOBT, Et_3N, CH_2Cl_2; (f) BBr_3, CH_2Cl_2, −78 °C to rt; (g) 1*H*-indole-5-carbaldehyde, $Na(OAc)_3BH$, CH_2Cl_2.

were subsequently converted to their aldehyde derivative, under Swern oxidation conditions, to yield **34**−**36**. Aldehyde **34** was coupled with (±)-, *R*-(+), and *S*-(−)-pramipexole, under reductive amination conditions, to give condensed products (±)-**37**, *R*-(+)-**37**, and *S*-(−)-**37**. Deprotection of the indole moiety afforded final compounds (±)-**40**, *R*-(+)-**40**, and *S*-(−)-**40**. Aldehydes **35** and **36** were condensed with (±)-pramipexole to yield intermediates **38** and **39**, which were deprotected under acidic conditions to furnish final compounds **41** and **42**.

Scheme 4 outlines the synthesis of final compounds (±)-**45**, *R*-(+)-**45**, *S*-(−)-**45**, (±)-**46**, *R*-(+)-**46**, *S*-(−)-**46**, **48**, and **49**. Aldehyde **6** was coupled with (±)-, (+)-, or (−)-pramipexole to yield condensed products (±)-**43**, *R*-(+)-**43**, and *S*-(−)-**43**. Subsequent treatment with trifluoroacetic acid yielded deprotected intermediates (±)-**44**, *R*-(+)-**44**, and *S*-(−)-**44**. Separately, under amide coupling conditions, (±)-**44**, *R*-(+)-**44**, and *S*-(−)-**44** were reacted with either indole-3-carboxylic acid or indole-5-carboxylic acid to yield final compounds (±)-**45**, *R*-(+)-**45**, *S*-(−)-**45**, (±)-**46**, *R*-(+)-**46**, and *S*-(−)-**46**. Reaction of (±)-**44** with 5-methoxy-1*H*-indole-3-carboxylic acid, under amide coupling conditions, or 1*H*-indole-5-carbaldehyde under reductive amination conditions afforded intermediate **47** and final compound **49**. Finally, demethylation of **47** with boron tribromide furnished final compound **48**.

RESULTS AND DISCUSSION

Our current study is aimed at investigating the molecular and chemical flexibility, along with basicity, of the arylpiperazine fragment of our hybrid template as it relates to D2/D3 receptor binding and functional activity. The present series of compounds comprise various indole derivatives, as our previous studies have indicated that an indole substituent in the arylpiperazine region is well tolerated, producing molecules with high D2/D3 affinity and preference for D3 receptor.[32] We have carried out our binding studies with rat dopamine D2 and D3 (rD2 and rD3) receptors expressed in HEK-293 cells and functional characterization with human D2 and D3 receptors (hD2 and hD3) expressed in CHO cells. In our own findings, we did not see any significant difference of affinity of compounds interacting with either rat or human dopamine D2 and D3 receptors. An overall high degree of homology exists between the two species, 95% for D2 and greater than 78% for D3 with somewhat shorter third intracellular loop in the human version of the D3 receptor.[2,39]

Table 1 summarizes the binding data for analogues that were synthesized. Compounds **9a**−**c**, which incorporate the 5-hydroxyaminotetralin headgroup and a methylene unit connecting piperazine to indole at various positions, displayed high affinity for D3 and moderate affinity for D2 receptors. Among this series of analogues, the 5-substituted indole derivative **9a** displayed the highest selectivity for D3 (K_i, D2 = 269 nM, D3 = 4.17 nM, D2/D3 = 64.5), while **9c** (K_i, D2 =

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Table 1. Inhibition Constants for Competition with [^{3}H]Spiroperidol Binding to Cloned Rat D2L and D3 Receptors Expressed in HEK-293 Cells[a]

	K_i (nM)		
compd	rD2L, [^{3}H]spiroperidol	rD3, [^{3}H]spiroperidol	D2L/D3
(−)-5-OH-DPAT	58.8 ± 11.0	1.36 ± 0.28	43.2
D-237	26.0 ± 7.5	0.83 ± 0.13	31.5
D-301	269 ± 16	2.23 ± 0.60	121
D-264	264 ± 40	0.92 ± 0.23	253
9a	269 ± 183	4.17 ± 0.36	64.5
9b	183 ± 26	5.48 ± 0.86	33.4
9c	82.1 ± 7.1	3.20 ± 0.32	25.6
(±)-**19**	46.7 ± 6.6	1.92 ± 0.38	24.3
(−)-**19**	39 ± 5	2.19 ± 0.39	17.8
(+)-**19**	134 ± 12	15.9 ± 3.6	8.46
21	76.4 ± 2.4	10.4 ± 1.6	7.3
(±)-**40**	852 ± 209	4.59 ± 0.15	185.6
(−)-**40**	1,073 ± 92	1.84 ± 0.51	583
(+)-**40**	2,558 ± 112	54.1 ± 4.2	47.3
41	928 ± 152	2.78 ± 0.25	334
42	531 ± 119	1.74 ± 0.25	305
(±)-**45**	1,503 ± 67	4.17 ± 0.30	360
(−)-**45**	902 ± 130	1.09 ± 0.14	828
(+)-**45**	1,316 ± 244	48.2 ± 8.6	27.3
(±)-**46**	1,243 ± 130	4.10 ± 0.57	303
(−)-**46**	1,031 ± 182	1.40 ± 0.29	736
(+)-**46**	2,626 ± 229	52.8 ± 8.3	49.7
48	1,079 ± 139	16.8 ± 0.6	64.2
49	132 ± 22	8.07 ± 0.93	16.4

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

82.1 nM, D3 = 3.20 nM, D2/D3 = 25.6) proved to be the most potent and least selective. Analogues **9a−c** exhibited lower affinity for D2 and in the case of **9a**, higher selectivity for D3 compared to parent compound D-237 (**9a** K_i, D2 = 269 nM, D2/D3 = 64.5 vs D-237 K_i, D2 = 26.0 nM, D2/D3 = 31.5). A similar 5-substituted indole derivative, **21**, lacks a linking carbon between piperazine and indole and displayed low selectivity and lost some potency (K_i, D2 = 76.4 nM, D3 = 10.4 nM, D2/D3 = 7.3) for the D3 receptor compared to counterparts **9a−c**. Compound **49**, analogous to **9a−c**, with 2-aminothiazole substitution in the agonist headgroup maintained D2 receptor affinity within the range displayed by **9a−c**, while D3 affinity decreased by approximately 2-fold (K_i, D2 = 132 nM, D3 = 8.07 nM, D2/D3 = 16.4).

Previous and current results consistently demonstrate that in the 2-aminothiazole series of hybrid compounds, the (−)-isomeric version exhibits the highest affinity for the D3 receptor compared to the (+)-isomer. Bioisosteric equivalent molecules were synthesized with the aminotetralin headgroup replaced with 2-aminothiazole. The first of these analogues incorporated a bond that linked the piperazine moiety directly to the indole group. The most active optical isomer of this molecule, (−)-**19**, displayed the highest affinity for the D2 receptor among the compounds in our study, along with low selectivity (K_i, D2 = 39 nM, D3 = 2.19 nM, D2/D3 = 17.8). In contrast, one of the parent compounds, D-301, displayed lower D2 affinity and higher D3 selectivity (K_i, D2 = 269 nM, D3 = 2.23 nM, D2/D3 = 121) compared to (−)-**19**. This suggests that the indole moiety alone does not give rise to selectivity for either receptor subtype. In order to investigate the effect of lowering the basicity of the piperazine ring, we synthesized a number of analogues that incorporate an amide bond at the piperazine nitrogen atom, distal to the agonist headgroup. Interestingly, in these molecules, D3 receptor affinity was maintained in the low nanomolar range, while D2 affinity dropped significantly to the low micromolar range. The 2-aminothiazole derived, 3-substituted indoleacyl derivative (−)-**45** displayed the highest selectivity in binding (K_i, D2 = 902 nM, D3 = 1.09 nM, D2/D3 = 828) to D3 receptor in our current series of molecules. A more than 3-fold increase in D3 selectivity was observed for (−)-**45** when compared to previous lead and parent compound D-264 (D2/D3, 828 vs 253 for (−)-**45** vs D-264). Compound (−)-**45** was also more selective than another lead compound, D-301 (D2/D3, 828 vs 121 for (−)-**45** vs D-301). Our next goal was to synthesize isomeric, 2-substituted indoleacyl derivative (±)-**40**, connected to the piperazine ring via amide linkage. The most active enantiomer, (−)-**40**, exhibited high affinity and selectivity for D3 receptor (K_i, D3 = 1.84 nM, D2/D3 = 583). Next, the isomeric, 5-substituted, indoleacyl derivative (±)-**46** was prepared. The most active enantiomer, (−)-**46**, produced a similar high affinity and selectivity profile for D3 receptor (K_i, D3 = 1.40 nM, D2/D3 = 736). Thus, affinity and selectivity for D3 receptor were similar in isomeric compounds (−)-**40**, (−)-**45**, and (−)-**46**.

Next, to determine the impact of the linker length on D2/D3 receptor binding, we varied the length of the two-carbon tether between the agonist headgroup and the arylpiperazine fragment. The two-carbon linker of (±)-**40** was increased to three and four carbons. Compound **41** (K_i, D2 = 928 nM, D3 = 2.78 nM, D2/D3 = 333.8) contained a three-carbon linker and displayed an almost 2-fold increase in D3 selectivity compared to the parent compound (±)-**40** (K_i, D2 = 852 nM, D3 = 4.59 nM, D2/D3 = 186). Compound **42** contained a four-carbon

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Table 2. Stimulation of [^{35}S]GTPγS Binding to Cloned Human D2 Receptor and D3 Receptor Expressed in CHO Cells[a]

	hCHO-D2		hCHO-D3		
compd	[^{35}S]GTPγS EC_{50} (nM)	E_{max} (%)	[^{35}S]GTPγS EC_{50} (nM)	E_{max} (%)	D2/D3
DA	227 ± 11	100	8.57	100	26.5
D-301	116 ± 16	88.4 ± 3.9	0.82 ± 0.20	102 ± 2	141
D-264	33.1 ± 6.6	104 ± 5	1.51 ± 0.22	90.0 ± 4.3	22.1
(−)-**40**	114 ± 12	101 ± 5	0.26 ± 0.07	103 ± 10	438
(−)-**45**	86.4 ± 6.2	91.6 ± 5.9	0.87 ± 0.11	100 ± 6	99.3
(−)-**46**	70.7 ± 14.9	107 ± 4	0.56 ± 0.14	98.1 ± 3.3	126
(−)-**19**	2.96 ± 0.3	107 ± 3	1.26 ± 0.2	93.1 ± 4.4	2.35

[a] EC_{50} is the concentration producing half-maximal stimulation. For each compound, maximal stimulation (E_{max}) is expressed as a 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 independent experiments, each performed in triplicate.

linker, which increased affinity for both D2 and D3 receptors (K_i, D2 = 531 nM, D3 = 1.74 nM, D2/D3 = 305) compared to (±)-**40** and **41**. Finally, we modified (±)-**45** to incorporate a hydroxyl substituent at the 5-position of the indole moiety. Hydroxyl substitution helped us to study the electronic effects of an electron-releasing group on the indole nucleus and a possible contribution of hydrogen-bond interactions in this region of D2 and D3 receptors. This modification produced compound **48**, which maintained micromolar D2 affinity of the parent compound, while D3 affinity decreased 4-fold (K_i, D2 = 1,079 nM, D3 = 16.8 nM, D2/D3 = 64.2). This result indicated that introduction of a 5-hydroxyl group on the indole nucleus did not have a significant effect on D2 affinity, while D3 affinity and selectivity were impacted unfavorably.

The next goal of our study was to investigate the functional activity of selected compounds at D2/D3 receptors. The most and least selective D3 ligands, based on binding results, were selected for functional activity evaluation. Optically active lead compounds (−)-**19**,(−)-**40**, (−)-**45**, and (−)-**46** were tested in the [^{35}S]GTPγS functional assay to characterize their ability to stimulate D2/D3 receptors in comparison to the endogenous ligand DA and to the parent compounds D-264 and D-301. (−)-**40**, (−)-**45**, and (−)-**46** each of the three compounds tested displayed higher functional selectivity and potency for D3 receptor in comparison to D-264 and DA (Table 2). In particular, (−)-**40** maintained high functional selectivity for D3 receptor (EC_{50}, D2 = 114 nM, D3 = 0.26 nM, D2/D3 = 438), correlating well with binding data, and exhibited full agonist activity at both D2 and D3 receptors (E_{max} close to 100%). Compound (−)-**40** demonstrated a 5-fold increase in functional potency (EC_{50}, D3 = 1.51 vs 0.26 for D-264 vs (−)-**40**) and an almost 20-fold increase in functional selectivity (D2/D3 22.1 vs 438 nM for D-264 vs (−)-**40**) for the D3 receptor when compared to D-264. On the other hand, in comparison to D-301, the selectivity was 3-fold higher (EC_{50} D2/D3 = 438 vs 141). Compounds (−)-**45** (EC_{50}, D2 = 86.4 nM, D3 = 0.87 nM, D2/D3 = 99.3) and (−)-**46** (EC_{50}, D2 = 70.7 nM, D3 = 0.56 nM, D2/D3 = 126) each exhibited full agonist activity (E_{max} not significantly different from 100%) at D2 and D3 receptors, while their selectivity for D3 receptor dropped considerably when compared to binding data. In contrast to the above-mentioned indoleacyl derivatives, compound (−)-**19** was exceptionally potent at D2 receptor (EC_{50}, D2 = 2.96 nM and D3 = 1.26 nM), while also exhibiting high potency for D3 receptor. Thus, (−)-**19** was indiscriminate in its binding to D2 and D3 receptors.

Evaluation of Free Radical Scavenging Activity. Scavenging of the DPPH (1,1-diphenyl-2-picrylhydrazyl) radical by (±)-**40**, (±)-**45**, (±)-**46**, (±)-**19**, and ascorbic acid is shown in Figure 2.[40] The scavenging effect is expressed as

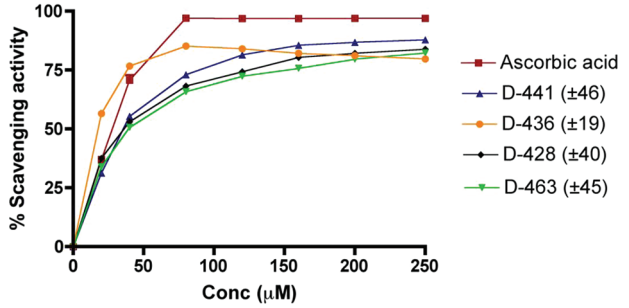

Figure 2. DPPH radical scavenging activity by (±)-**19**, (±)-**40**, (±)-**45**, (±)-**46**, and ascorbic acid.

percent of control. As shown in Figure 2, each compound inhibited DPPH radical activity dose dependently. The standard compound, ascorbic acid, had an IC_{50} of 24.9 μM in this assay procedure, whereas the IC_{50} for (±)-**19** was 14.5 μM (n = 3−4 for all compounds tested). All other compounds exhibited potencies comparable to that of ascorbic acid. It is clear from the data that compound (±)-**19** is nearly twice as potent as ascorbic acid in quenching the DPPH radical.

Reversal of Reserpine-Induced Hypolocomotion in Rats by (−)-19, (−)-46, (−)-40, 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.[41] 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 (Figure 3). Compound (−)-**19** (5 μmol/kg, sc) was efficacious in significantly reversing akinesia in rats, compared to reserprine treatment alone, over a 6 h period. Similarly, treatment with the reference drug ropinirole (5 μmol/kg, sc) produced a significant locomotor activation compared to control, reaching higher levels of locomotion but with a much shorter duration of action compared with (−)-**19**. On the other hand, compounds (−)-**46** and (−)-**40** (10 μmol/kg, sc) failed to produce any appreciable effect in reversing akinesia in reserpine-treated rats.

CONCLUSION

Results from binding and functional activity studies indicate that we have developed a novel class of D3-selective agonists, based on our hybrid template. Our current series of compounds include those with low, moderate, and high selectivity for D3

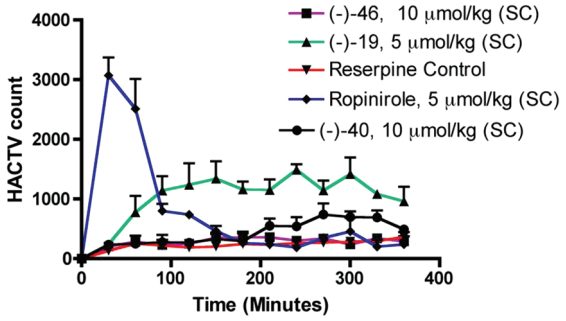

Figure 3. Effects of different drugs (administered sc) upon reserpine (5.0 mg/kg, sc, 18 h pretreatment) induced hypolocomotion in rats. Each point represents the mean ± SEM for three to six rats. Horizontal activity was measured as described in Experimental Section. Representation of horizontal locomotor activity is at discrete 30 min intervals after the administration of (−)-**19** (5 μmol/kg), (−)-**46** (10 μmol/kg), (−)-**40** (10 μmol/kg), and ropinirole (5 μmol/kg) compared to control rats, 18 h after reserpine treatment. Differences among treatments were significant by one-way ANOVA analysis ($F(4.95) = 6.69$ ($P < 0.0001$)): (**) $P < 0.01$ ((−)-**19**) or (*) $P < 0.05$ (ropinirole) compared to reserpine control (Dunnett's analysis after one-way ANOVA).

receptor. D3 selectivity, according to our SAR results, is influenced by three factors: linker length, molecular structure, and basicity of the arylpiperazine fragment. Our results indicate a correlation between basicity of the nitrogen atom that connects piperazine to the indole ring, with D2/D3 selectivity and potency. In the case of compound **49**, piperazine and indole are connected via a methylene unit, giving rise to high basicity of the piperazine nitrogen atom and low selectivity for D3 receptor (D2/D3 = 16.4 for **49**). On the other hand, when the connecting carbon is a planar sp^2 hybridized carbonyl group, the basicity of the nitrogen atom is low and much higher selectivity is observed for the D3 receptor (D2/D3 = 583, 828, and 736 for (−)-**40**, (−)-**45**, and (−)-**46**, respectively). It is also possible that an electronic effect of carbonyl group on the indole ring might also additionally play an important role in selectivity for D3 receptor. In the GTPγS functional assay, compound (−)-**40** exhibited high selectivity for the D3 receptor and is one of the most selective D3 agonists known to date (D2/D3 = 438). These results indicate that amide linkage, connecting the piperazine ring to the indole moiety, is unfavorable in terms of binding to the D2 receptor while affinity for the D3 receptor remains high. In this regard, in a recent publication, the importance of the presence of amide linkage has been shown in highly selective D3 antagonist compounds.[42] The length of the tether between the agonist headgroup and the arylpiperazine fragment affects the affinity and selectivity for D2 and D3 receptors. In the series (±)-**40**, **41**, and **42**, in which the linker length is increased from $n = 2$ to $n = 4$, an increase in D3 affinity and selectivity occurs.

Furthermore, radical quenching study indicates that compound (±)-**19** has potent antioxidant activity. Antioxidant activity is highly relevant, as there has been a strong implication of oxidative stress in the pathogenesis of PD. Further evaluation of the antioxidant activity of these compounds is underway. In the present in vivo PD animal model, compound (−)-**19** produced a significant, long-lasting reversal of hypolocomotion in reserpinized rats. Our ongoing studies with (−)-**19** are directed at evaluating the full potential of this compound as a multifunctional, neuroprotective agent against PD.

EXPERIMENTAL SECTION

Reagents and solvents were purchased from commercial suppliers and used as received unless otherwise noted. Dry solvent was obtained following the standard procedure. All reactions were performed under N_2 atmosphere unless otherwise indicated. Analytical silica gel 60 F_{254}-coated TLC plates were purchased from EMD Chemicals, Inc. and were visualized with UV light or by treatment with phosphomolybdic acid (PMA), Dragendorff's reagent, or ninhydrin. Whatman Purasil 60A silica gel 230−400 mesh was used for flash column chromatographic purifications. Proton nuclear magnetic resonance (^{1}H NMR) spectra were measured on a Varian 400 MHz FT NMR spectrometer, using tetramethylsilane (TMS) as an internal standard. The NMR solvent used was $CDCl_3$ unless otherwise indicated. Optical rotations were recorded on Perkin-Elmer 241 polarimeter. Mass spectra were recorded on Micromass QuattroLC triple quadrupole mass spectrometer. Melting points were recorded using a MEL-TEMP II (Laboratory Devices Inc., U.S.) capillary melting point apparatus and were uncorrected. Elemental analyses were performed by Atlantic Microlab, Inc. and were within ±0.4% of the theoretical value.

5-Methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (2). Into a stirring solution of *n*-propylamine (14.9 mL, 181.6 mmol) and ketone **1** (12.8 g, 72.6 mmol) in CH_2Cl_2 (70 mL) was added glacial acetic acid (17.3 mL, 290.5 mmol). After the mixture was stirred for 0.5 h, $NaCNBH_3$ (11.4 g, 181.6 mmol) was added portionwise at 0 °C, followed by methanol (20 mL). The mixture was allowed to reach room temperature and stirred overnight. The reaction mixture was quenched with a saturated $NaHCO_3$ solution at 0 °C and extracted with ethyl acetate (3 × 100 mL). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Solvent was removed under reduced pressure. Crude product was purified by column chromatography (EtOAc/MeOH, 9:1) to give compound **2** (11.1 g, 70%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.96 (t, $J = 7.2$ Hz, 3H), 1.54−1.65 (m, 3H), 2.09−2.16 (m, 1H), 2.52−2.74 (m, 4H), 2.88−3.07 (m, 3H), 3.81 (s, 3H), 6.66 (d, $J = 8.0$ Hz, 1H), 6.71 (d, $J = 8.4$ Hz, 1H), 7.09 (t, $J = 8.4$ Hz, 1H).

4-(2-Hydroxyethyl)piperazine-1-carboxylic Acid *tert*-Butyl Ester (5). A mixture of compound **4** (10.0 g, 53.7 mmol), 2-bromoethanol (10.1 g, 80.6 mmol), and K_2CO_3 (22.3 g, 161.1 mmol) in CH_3CN (100 mL) was refluxed for 14 h according to procedure D. The crude material was purified by silica gel column chromatography (EtOAc/MeOH, 20:1) to give compound **5** (7.12 g, 58%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.40 (s, 9H), 2.40 (t, $J = 4.8$ Hz, 4H), 2.50 (t, $J = 5.2$, 2H), 3.38 (t, $J = 4.8$ Hz, 4H), 3.58 (t, $J = 5.2$ Hz, 2H).

Procedure A. 4-(2-Oxoethyl)piperazine-1-carboxylic Acid *tert*-Butyl Ester (6). Into a stirring solution of oxalyl chloride (5.5 g, 43.3 mmol) in CH_2Cl_2 (80 mL) at −78 °C was added DMSO (6.2 mL, 78.7 mmol). The reaction mixture was stirred for 0.5 h, followed by addition of compound **5** (5.0 g, 21.7 mmol, in 20 mL of CH_2Cl_2). The reaction mixture was stirred at the same temperature for 0.5 h, followed by addition of Et_3N (18.2 mL, 179.4 mmol), and stirring was continued for 1.5 h while allowing the reaction mixture to reach room temperature. The reaction mixture was quenched by addition of a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layer was dried using Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (EtOAc/MeOH, 20:1) to give compound **6** (4.96 g, ∼100%).

Procedure B. 4-{2-[(5-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)propylamino]ethyl}piperazine-1-carboxylic Acid *tert*-Butyl Ester (7). Into a stirring solution of amine **2** (4.76 g, 21.7 mmol) in CH_2Cl_2 (50 mL) was added aldehyde **6** (4.96 g, 21.7 mmol). After the mixture was stirred for 1 h, $NaBH(OAc)_3$ (8.29 g, 39.1 mmol) was added portionwise and the mixture was stirred for 48 h at room temperature. The reaction mixture was quenched with a saturated solution of $NaHCO_3$ at 0 °C and extracted with ethyl acetate (3 × 100 mL). The combined organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. Crude product was purified by column chromatography (EtOAc/MeOH, 20:1) to give compound **7** (6.46 g, 69%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.86 (t, $J = 7.6$ Hz, 3H), 1.20 (s, 9H), 1.30−1.52 (m, 3H), 1.90−2.12 (m,

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1H), 2.20−3.06 (m, 13H), 3.20−3.60 (m, 6H), 3.77 (s, 3H), 6.61 (d, J = 8 Hz, 1H), 6.67 (d, J = 8 Hz, 1H), 7.05 (t, J = 7.6 Hz, 1H).

6-[(2-Piperazin-1-ylethyl)propylamino]-5,6,7,8-tetrahydronaphthalen-1-ol (8). A mixture of compound **7** (6.46 g, 14.9 mmol) and 48% aqueous HBr (40 mL) was refluxed at 125 °C for 12 h. The reaction mixture was evaporated to dryness, and a saturated solution of $NaHCO_3$ was added to it at 0 °C. The reaction mixture was then extracted with ethyl acetate (3 × 100 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield compound **8** (3.80 g, 80%). ^{1}H NMR (CD_3OD, 400 MHz): δ 1.06 (t, J = 7.2 Hz, 3H), 1.80−2.02 (m, 3H), 2.36−2.48 (m, 1H), 2.60- 2.80 (m, 1H), 2.96−4.02 (m, 18H), 6.61 (d, J = 8 Hz, 1H), 6.66 (d, J = 8 Hz, 1H), 6.96 (t, J = 8 Hz, 1H).

6-({2-[4-(1*H*-Indol-5-ylmethyl)piperazin-1-yl]ethyl}-propylamino)-5,6,7,8-tetrahydronaphthalen-1-ol (9a). Amine **8** (200 mg, 0.63 mmol) was reacted with 1*H*-indole-5-carbaldehyde (91 mg, 0.63 mmol) and $NaBH(OAc)_3$ (240 mg, 1.13 mmol) in CH_2Cl_2 (15 mL) using procedure B. The crude residue was purified by column chromatography (MeOH/EtOAc, 1:6) to afford compound **9a** (220 mg, 79%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.86 (t, J = 7.2 Hz, 3H), 1.30−1.52 (m, 3H), 1.90−2.10 (m, 1H), 2.46−3.02 (m, 19H), 3.76 (s, 2H), 6.51 (d, J = 8 Hz, 1H), 6.67 (d, J = 8 Hz, 1H), 6.94 (t, J = 7.6 Hz, 1H), 7.06−7.25 (m, 3H), 7.36 (d, J = 8 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H), 8.26 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.0, 22.3, 24.0, 25.7, 29.9, 32.4, 47.9, 52.8, 53.5, 53.6, 53.8, 57.4, 58.7, 111.2, 112.2, 119.6, 121.4, 122.1, 123.6, 124.2, 126.3, 128.2, 136.5, 138.5, 154.2, 171.4. The free base was converted to its hydrochloride salt. Mp 165−169 °C. Anal. ($C_{30}H_{46.5}Cl_{3.5}N_4O$) C, H, N.

6-({2-[4-(1*H*-Indol-2-ylmethyl)piperazin-1-yl]ethyl}-propylamino)-5,6,7,8-tetrahydronaphthalen-1-ol (9b). Amine **8** (200 mg, 0.63 mmol) was reacted with 1*H*-indole-2-carbaldehyde (91 mg, 0.63 mmol) and $NaBH(OAc)_3$ (240 mg, 1.13 mmol) in CH_2Cl_2 (15 mL) using procedure B. The crude residue was purified by column chromatography (MeOH/EtOAc, 1:6) to afford compound **9b** (225 mg, 81%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.90 (t, J = 7.2 Hz, 3H), 1.40−1.71 (m, 3H), 1.96−2.10 (m, 1H), 2.36−3.08 (m, 19H), 3.77 (s, 2H), 5.36 (bs, 2H), 6.39 (s, 1H), 6.60 (dd, J = 7.2 Hz, 1H), 6.95 (t, J = 7.6 Hz, 1H), 7.04−7.12 (m, 2H), 7.17 (t, J = 7.6 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.1, 21.6, 24.0, 25.4, 28.4, 30.0, 31.8, 47.5, 52.5, 52.8, 53.2, 53.6, 55.5, 57.2, 57.8, 103.0, 111.3, 119.9, 120.5, 122.0, 123.7, 126.0, 128.3, 133.8, 136.7, 137.6, 154.6, 178.0. The free base was converted to its hydrochloride salt. Mp 180−185 °C. Anal. ($C_{28}H_{47}Cl_4N_4O_{3.5}$) C, H, N.

6-({2-[4-(1*H*-Indol-3-ylmethyl)piperazin-1-yl]ethyl}-propylamino)-5,6,7,8-tetrahydronaphthalen-1-ol (9c). Amine **8** (200 mg, 0.63 mmol) was reacted with 1*H*-indole-3-carbaldehyde (91 mg, 0.63 mmol) and $NaBH(OAc)_3$ (240 mg, 1.13 mmol) in CH_2Cl_2 (15 mL) using procedure B. The crude residue was purified by column chromatography (MeOH/EtOAc, 1:6) to afford compound **9c** (213 mg, 77%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.85 (t, J = 7.2 Hz, 3H), 1.20−1.56 (m, 2H), 1.80−2.04 (m, 1H), 2.20−3.00 (m, 18H), 3.20−3.45 (m, 2H), 3.74 (s, 2H), 6.48 (d, J = 7.6 Hz, 1H), 6.57 (d, J = 7.6 Hz, 1H), 6.93 (t, J = 7.2 Hz, 1H), 7.02−7.25 (m, 3H), 7.35 (d, J = 7.6 Hz, 1H), 7.71 (d, J = 7.6 Hz, 1H), 8.24 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.0, 22.5, 25.4, 26.0, 26.7, 29.9, 48.4, 52.9, 53.7, 58.3, 58.6, 63.6, 102.6, 111.0, 117.5, 121.7, 124.0, 124.7, 128.1, 128.8, 135.5, 145.2, 165.9. The free base was converted to its hydrochloride salt. Mp 180−185 °C. Anal. ($C_{28}H_{47}Cl_4N_4O_{3.5}$) C, H, N.

5-Bromo-1-(triisopropylsilyl)-1*H*-indole (11). Into a stirring solution of NaH (4.03 g, 170.0 mmol) in dry THF (150 mL) was added compound **10** (16.44 g, 83.9 mmol) portionwise at 0 °C. The reaction mixture was allowed to stir at room temperature for 1 h, followed by dropwise addition of triisopropylsilyl chloride (20 g, 103.7 mmol). The reaction mixture was stirred for 12 h and then filtered through Celite. The crude residue was purified by column chromatography using hexane as solvent to afford compound **11** (22 g, 75%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.23 (s, 18H), 1.74 (heptet, J = 7.6 Hz, 3H), 6.64 (d, J = 3.2 Hz, 1H), 7.07 (d, J = 6 Hz, 1H), 7.14 (s, 1H), 7.31 (d, J = 3.2 Hz, 1H), 7.45 (d, J = 8.8, 1H).

***tert*-Butyl 4-(1-(Triisopropylsilyl)-1*H*-indol-5-yl)piperazine-1-carboxylate (12).** A mixture of **11** (22.0 g, 63.0 mmol), **4** (11.71 g, 63.0 mmol), $PdCl_2[P(O\text{-}tol)_3]_2$ (2.47 g, 3.1 mmol), and NaO-*t*-Bu (9.08 g, 94.4 mmol) in xylenes (175 mL) was heated at 110 °C for 12 h. The reaction mixture was filtered through Celite and concentrated in vacuo. The crude residue was purified by column chromatography (EtOAc/hexane, 1:20) to afford compound **12** (13.22 g, 46%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.19 (s, 18H), 1.55 (s, 9H), 1.74 (heptet, J = 6.8 Hz, 3H), 3.14 (bs, 4H), 3.67 (bs, 4H), 6.60 (t, J = 6 Hz, 1H), 6.94 (d, J = 8.8 Hz, 1H), 7.19 (s, 1H), 7.26 (t, J = 2.8 Hz, 1H), 7.47 (d, J = 8.8 Hz, 1H).

Procedure C. 5-Piperazin-1-yl-1*H*-indole (13). To a stirring solution of compound **12** (7.70 g, 16.8 mmol) in CH_2Cl_2 (15 mL) was added TFA (15 mL) slowly at room temperature, and the reaction mixture was stirred for 2 h. Unreacted TFA and solvent were removed under reduced pressure, and the salt was washed with diethyl ether. A saturated solution of $NaHCO_3$ was added to the salt, followed by extraction with CH_2Cl_2 (3 × 50 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo to provide compound **13** (2.88 g, 85%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.85 (bs, 1H), 2.80−3.28 (m, 8H), 6.85−7.10 (m, 1H), 7.02−7.40 (m, 4H), 8.31 (bs, 1H).

Procedure D. 5-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]-piperazin-1-yl}-1*H*-indole (14). A mixture of compound **13** (2.88 g, 14.3 mmol), (2-bromoethoxy)-*tert*-butyldimethylsilane (3.42 g, 14.3 mmol), and K_2CO_3 (5.93 g, 42.9 mmol) in CH_3CN (50 mL) was refluxed for 14 h. After filtration, acetonitrile was evaporated under reduced pressure and the crude material was purified by silica gel column chromatography (EtOAc/hexane, 3:1) to give compound **14** (4.01 g, 78%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.02 (s, 6H), 0.83 (s, 9H), 2.30−2.80 (m, 6H), 2.82−3.30 (m, 4H), 3.52−3.82 (m, 2H), 6.25−6.48 (m, 1H), 6.75−7.30 (m, 4H), 8.09 (s, 1H).

5-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]piperazin-1-yl}-indole-1-carboxylic Acid *tert*-Butyl Ester (15). Amine **14** (4.0 g, 11.1 mmol) was reacted with $(Boc)_2O$ (2.68 g, 12.2 mmol) and DMAP (1.49 g, 12.2 mmol) in THF (50 mL) at room temperature using procedure G. The crude material was purified by column chromatography over silica gel (EtOAc/hexane, 1:1) to give compound **15** (5.2 g, ∼100%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.08 (s, 6H), 0.95 (s, 9H), 1.65 (s, 9H), 2.61 (t, J = 6.4 Hz, 2H), 2.73 (t, J = 4.8 Hz, 4H), 3.19 (t, J = 4.8 Hz, 4H), 3.81 (t, J = 6.4 Hz, 2H), 6.47 (d, J = 3.6 Hz, 1H), 7.01 (dd, J = 6.4, 2.4 Hz, 1H), 7.06 (dd, J = 6.4, 2.4 Hz, 1H), 7.53 (s, 1H), 8.00 (s, 1H).

Procedure E. 5-[4-(2-Hydroxyethyl)piperazin-1-yl]indole-1-carboxylic Acid *tert*-Butyl Ester (16). Into a stirring solution of compound **15** (2.0 g, 4.3 mmol) in THF (30 mL) was added *n*-tetrabutylammonium fluoride (1.14 g, 4.3 mmol, 1.0 M solution in THF) at 0 °C. The reaction mixture was then stirred at room temperature for 1 h. THF was evaporated in vacuo, and the residue was diluted with CH_2Cl_2 (50 mL) and washed with water. The water layer was extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The crude product was purified by silica gel column chromatography (EtOAc/MeOH, 20:1) to yield compound **16** (1.49 g, 99%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.65 (s, 9 H), 2.61 (t, J = 5.2 Hz, 2H), 2.70 (t, J = 4.8 Hz, 4H), 3.19 (t, J = 4.8 Hz, 4H), 3.67 (t, J = 5.2 Hz, 2H), 6.47 (d, J = 3.6 Hz, 1H), 7.01 (dd, J = 6.8, 2 Hz, 1H), 7.06 (d, J = 2 Hz, 1H), 7.53 (s, 1H), 8.00 (s, 1H).

5-[4-(2-Oxoethyl)piperazin-1-yl]indole-1-carboxylic Acid *tert*-Butyl Ester (17). Compound **16** (1.49 g, 4.3 mmol) was reacted with oxalyl chloride (0.75 mL, 8.6 mmol), DMSO (1.23 mL, 17.3 mmol), and Et_3N (3.6 mL, 25.8 mmol) in CH_2Cl_2 (40 mL) using procedure A. The crude residue was purified by column chromatography using ethyl acetate as solvent to afford compound **17** (1.23 g, 83%).

5-(4-{2-[(2-Amino-4,5,6,7-tetrahydrobenzothiazol-6-yl)-propylamino]ethyl}piperazin-1-yl)indole-1-carboxylic Acid *tert*-Butyl Ester [(±)-18]. Compound **17** (175 mg, 0.51 mmol) was reacted with (±)-pramipexole (108 mg, 0.51 mmol) and $NaBH(OAc)_3$ (194 mg, 0.92 mmol) in CH_2Cl_2 (15 mL) according

to procedure B. The crude product was purified by silica gel column chromatography (EtOAc/MeOH, 20:1) to yield compound (±)-**18** (150 mg, 55%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.91 (t, J = 6.8 Hz, 1H), 1.35−1.60 (m, 2H), 1.67 (s, 9H), 1.89−2.10 (m, 1H), 2.30−3.30 (m, 20H), 4.94 (bs, 2H), 6.67 (t, J = 3.2 Hz, 1H), 7.09 (dd, J = 8.8, 2.8 Hz, 1H), 7.28 (dd, J = 3.2 Hz, 1H), 7.59 (s, 1H), 7.97 (d, J = 6.4 Hz, 1H).

(*S*)-5-(4-{2-[(2-Amino-4,5,6,7-tetrahydrobenzothiazol-6-yl)-propyl amino]ethyl}piperazin-1-yl)indole-1-carboxylic Acid *tert*-Butyl Ester [(−)-18]. Compound **17** (175 mg, 0.51 mmol) was reacted with *S*-(−)-pramipexole (108 mg, 0.51 mmol) and $NaBH(OAc)_3$ (194 mg, 0.92 mmol) in CH_2Cl_2 (15 mL) using procedure B. The crude residue was purified by column chromatography (EtOAc/MeOH, 20:1) to afford compound *S*-(−)-**18** (161 mg, 59%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.93 (t, J = 6.8 Hz, 1H), 1.35−1.60 (m, 2H), 1.68 (s, 9H), 1.89−2.10 (m, 1H), 2.30−3.30 (m, 20H), 4.94 (bs, 2H), 6.67 (t, J = 3.2 Hz, 1H), 7.09 (dd, J = 8.8, 2.8 Hz, 1H), 7.28 (dd, J = 3.2 Hz, 1H), 7.60 (s, 1H), 7.97 (d, J = 6.4 Hz, 1H).

(*R*)-5-(4-{2-[(2-Amino-4,5,6,7-tetrahydrobenzothiazol-6-yl)-propyl amino]ethyl}piperazin-1-yl)indole-1-carboxylic Acid *tert*-Butyl Ester [(+)-18]. Compound **17** (175 mg, 0.51 mmol) was reacted with *R*-(+)-pramipexole (108 mg, 0.51 mmol) and $NaBH(OAc)_3$ (194 mg, 0.92 mmol) in CH_2Cl_2 (15 mL) using procedure B. The crude residue was purified by column chromatography using (EtOAc/MeOH, 20:1) to afford compound *R*-(+)-**18** (164 mg, 60%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.91 (t, J = 6.8 Hz, 1H), 1.37−1.60 (m, 2H), 1.67 (s, 9H), 1.89−2.10 (m, 1H), 2.30−3.30 (m, 20H), 4.94 (bs, 2H), 6.67 (t, J = 3.2 Hz, 1H), 7.10 (dd, J = 8.8, 2.8 Hz, 1H), 7.28 (dd, J = 3.2 Hz, 1H), 7.59 (s, 1H), 7.98 (d, J = 6.4 Hz, 1H).

N^6-{2-[4-(1*H*-Indol-5-yl)piperazin-1-yl]ethyl}-N^6-propyl-4,5,6,7-tetrahydrobenzothiazole-2,6-diamine [(±)-19]. Compound (±)-**18** (150 mg, 0.28 mmol) was reacted with TFA (10 mL) in CH_2Cl_2 (10 mL) using procedure C. Unreacted TFA and solvent were removed in vacuo and the salt was washed with diethyl ether and recrystallized from ethanol to afford compound (±)-**19** (106 mg, 38%). ^{1}H NMR (CD_3OD, 400 MHz): δ 0.99 (t, J = 7.2 Hz, 3H), 1.52−1.74 (m, 2H), 1.76−2.04 (m, 1H), 2.19 (d, J = 9.2 Hz, 1H), 2.52−2.84 (m, 6H), 3.10−3.58 (m, 13H), 6.50 (d, J = 3.2 Hz, 1H), 7.05 (d, J = 8.8 Hz, 1H), 7.29 (d, J = 3.2 Hz, 1H), 7.34 (d, J = 8.8 Hz, 2H). ^{13}C NMR (CD_3OD, 100 MHz): δ 12.0, 22.2, 24.0, 25.1, 47.0, 51.1, 54.4, 54.8, 59.2, 101.4, 101.5, 111.8, 115.3, 116.1, 127.8, 129.7, 135.1, 136.0, 140.7, 171.0. Mp 110−115 °C. Anal. ($C_{30}H_{40}F_9N_6O_{7.5}S$) C, H, N.

(*S*)-N^6-{2-[4-(1*H*-Indol-5-yl)piperazin-1-yl]ethyl}-N^6-propyl-4,5,6,7-tetrahydrobenzothiazole-2,6-diamine [(−)-19]. Compound (−)-**18** (150 mg, 0.28 mmol) was reacted with TFA (10 mL) in CH_2Cl_2 (10 mL) using procedure C. Unreacted TFA and solvent were removed in vacuo and the salt was washed with diethyl ether and recrystallized from ethanol to afford compound *S*-(−)-**19** (120 mg, 43%). ^{1}H NMR (CD_3OD, 400 MHz): δ 0.98 (t, J = 7.2 Hz, 3H), 1.54−1.74 (m, 2H), 1.76−2.04 (m, 1H), 2.19 (d, J = 9.2 Hz, 1H), 2.52−2.84 (m, 6H), 3.10−3.58 (m, 13H), 6.51 (d, J = 3.2 Hz, 1H), 7.05 (d, J = 8.8 Hz, 1H), 7.29 (d, J = 3.2 Hz, 1H), 7.34 (d, J = 8.8 Hz, 2H). ^{13}C NMR (CD_3OD, 100 MHz): δ 12.0, 22.3, 24.0, 25.1, 47.0, 51.1, 54.5, 54.8, 59.2, 101.4, 101.6, 111.8, 115.3, 116.1, 127.8, 129.7, 135.1, 136.0, 140.8, 171.0. $[\alpha]^{25}_D$ −11.0° (c 1.0, CH_3OH). Mp 115−120 °C. Anal. ($C_{31}H_{37.5}F_{10.5}N_6O_7S$) C, H, N.

(*R*)-N^6-{2-[4-(1*H*-Indol-5-yl)piperazin-1-yl]ethyl}-N^6-propyl-4,5,6,7-tetrahydrobenzothiazole-2,6-diamine [(+)-19]. Compound (+)-**18** (150 mg, 0.28 mmol) was reacted with TFA (10 mL) in CH_2Cl_2 (10 mL) using procedure C. Unreacted TFA and solvent were removed in vacuo and the salt was washed with diethyl ether and recrystallized from ethanol to afford compound *R*-(+)-**19** (140 mg, 50%). ^{1}H NMR (CD_3OD, 400 MHz): δ 0.98 (t, J = 7.2 Hz, 3H), 1.54−1.78 (m, 2H), 1.76−2.04 (m, 1H), 2.20 (d, J = 9.2 Hz, 1H), 2.52−2.84 (m, 6H), 3.10−3.58 (m, 13H), 6.51 (d, J = 3.2 Hz, 1H), 7.05 (d, J = 8.8 Hz, 1H), 7.29 (d, J = 3.2 Hz, 1H), 7.34 (d, J = 8.8 Hz, 2H). ^{13}C NMR (CD_3OD, 100 MHz): δ 12.2, 22.3, 24.0, 25.1, 47.0, 51.2, 54.5, 54.8, 59.2, 101.4, 101.6, 111.8, 115.3, 116.1, 127.8, 129.7, 135.1, 136.2, 140.8, 171.0. $[\alpha]^{25}_D$ +15.5° (c 1.0, CH_3OH). Mp 115−120 °C. Anal. ($C_{31}H_{37.9}F_{10.5}N_6O_{7.2}S$) C, H, N.

***tert*-Butyl 5-(4-(2-((5-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)ethyl)piperazin-1-yl)-1*H*-indole-1-carboxylate (20).** Aldehyde **17** (320 mg, 0.93 mmol) was reacted with amine **2** (204 mg, 0.93 mmol) and $NaBH(OAc)_3$ (355 mg, 1.68 mmol) in CH_2Cl_2 (20 mL) using procedure B. The crude material was purified by column chromatography over silica gel (EtOAc/hexane, 1:1) to give compound **20** (190 mg, 38%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.91 (t, J = 7.2 Hz, 3H), 1.33−1.75 (m, 13H), 1.95−2.13 (m, 1H), 2.35−3.23 (m, 18H), 3.81 (s, 3H), 6.55−6.77 (m, 3H), 7.03−7.15 (m, 3H), 7.58 (d, J = 2.4 Hz, 1H), 7.96 (d, J = 6.8 Hz, 1H).

6-({2-[4-(1*H*-Indol-5-yl)piperazin-1-yl]ethyl}propylamino)-5,6,7,8-tetrahydronaphthalen-1-ol (21). A mixture of compound **20** (60 mg, 0.11 mmol) and 48% aqueous HBr (10 mL) was refluxed for 5 h. The reaction mixture was evaporated to dryness, and the residue was washed with diethyl ether. Finally, the HBr salt was recrystallized from ethanol to furnish compound **21** (50 mg, 60%). ^{1}H NMR (CD_3OD, 400 MHz): δ 0.95 (t, J = 7.2 Hz, 3H), 1.41−1.57 (m, 3H), 2.00−2.22 (m, 1H), 2.58−3.18 (m, 19H), 6.61 (d, J = 8 Hz, 1H), 6.75 (d, J = 8 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 7.19−7.38 (m, 3H), 7.51 (d, J = 8 Hz, 1H), 7.90 (d, J = 8.2 Hz, 1H), 8.50 (bs, 1H). Mp 250−260 °C. Anal. ($C_{27}H_{41.4}Br_4N_4O_{1.7}$) C, H, N.

Procedure F. 4-(1*H*-Indole-2-carbonyl)piperazine-1-carboxylic Acid *tert*-Butyl Ester (23). To a stirring solution of EDCI·HCl (15.45 g, 80.6 mmol) in CH_2Cl_2 (150 mL) was added acid derivative **22** (10.39 g, 64.5 mmol) at room temperature. The reaction mixture was stirred for 0.5 h, followed by addition of amine **4** (10.0 g, 53.7 mmol), HOBT (10.89 g, 80.6 mmol), and Et_3N (22.46 g, 161.2 mmol). The reaction mixture was stirred for 3 h, followed by addition of a saturated solution of $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layer was dried over Na_2SO_4, evaporated under reduced pressure and the crude product was purified by flash column chromatography (CH_2Cl_2/MeOH, 50:1) to afford compound **23** (15.6 g, 88%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.49 (s, 9H), 3.56 (t, J = 5.6 Hz, 4H), 3.74−4.04 (m, 4H), 6.78 (s, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.30 (t, J = 7.6 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 9.14 (bs, 1H).

(1*H*-Indol-2-yl)piperazin-1-ylmethanone (24). Compound **23** (12 g, 36.4 mmol) was reacted with TFA (20 mL) in CH_2Cl_2 (20 mL) using procedure C to provide compound **24** (7.85 g, 94%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.52−3.04 (m, 4H), 3.60−4.06 (m, 4H), 6.77 (s, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.27 (d, J = 6.8 Hz, 1H), 7.43 (d, J = 6.8 Hz, 1H), 7.65 (d, J = 6.8 Hz, 1H), 9.50 (bs, 1H).

{4-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]piperazin-1-yl}-(1*H*-indol-2-yl)methanone (25). Compound **24** (2.50 g, 10.9 mmol) was reacted with (2-bromoethoxy)-*tert*-butyldimethylsilane (3.13 g, 13.1 mmol) and K_2CO_3 (4.52 g, 32.7 mmol) in CH_3CN (50 mL) using procedure D. The crude material was purified by silica gel column chromatography using ethyl acetate as solvent to give compound **25** (3.55 g, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.09 (s, 6H), 0.92 (s, 9H), 2.02−2.80 (m, 6H), 3.01−4.20 (m, 6H), 6.77 (s, 1H), 7.11 (t, J = 7.6 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8 Hz, 1H), 10.4 (bs, 1H).

{4-[3-(*tert*-Butyldimethylsilanyloxy)propyl]piperazin-1-yl}-(1*H*-indol-2-yl)methanone (26). Compound **24** (2.50 g, 10.9 mmol) was reacted with (3-bromopropoxy)-*tert*-butyldimethylsilane (3.31 g, 13.1 mmol) and K_2CO_3 (4.52 g, 32.7 mmol) in CH_3CN (50 mL) using procedure D. The crude material was purified by silica gel column chromatography (EtOAc/hexane, 1:1) to give compound **26** (3.33 g, 76%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.06 (s, 6H), 0.90 (s, 9H), 1.52−1.86 (m, 2H), 2.45−2.70 (m, 6H), 3.68 (t, J = 12 Hz, 2H), 3.72−4.20 (m, 4H), 6.78 (s, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.20−7.32 (m, 2H), 7.43 (d, J = 7.6 Hz, 1H), 7.64 (d, J = 7.6 Hz, 1H), 9.35 (s, 1H).

{4-[4-(*tert*-Butyldimethylsilanyloxy)butyl]piperazin-1-yl}-(1*H*-indol-2-yl)methanone (27). Compound **24** (2.50 g, 10.9 mmol) was reacted with (4-bromobutoxy)-*tert*-butyldimethylsilane (3.50 g, 13.1 mmol) and K_2CO_3 (4.52 g, 32.7 mmol) in CH_3CN (50

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mL) using procedure D. The crude material was purified by silica gel column chromatography (EtOAc/hexane, 2:3) to give compound **27** (4.31 g, 95%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.05 (s, 6H), 0.90 (s, 9H), 1.47−1.75 (m, 4H), 2.40 (t, J = 6.4 Hz, 2H), 2.53 (t, J = 4.4 Hz, 4H), 3.64 (t, J = 5.6 Hz, 2H), 3.80−4.05 (m, 4H), 6.77 (s, 1H), 7.12 (t, J = 6.8 Hz, 1H), 7.26 (t, J = 7.2 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 8 Hz, 1H), 10.00 (s, 1H).

Procedure G. 2-{4-[3-(*tert*-Butyldimethylsilanyloxy)ethyl]-piperazine-1-carbonyl}indole-1-carboxylic Acid *tert*-Butyl Ester (28). To a stirring solution of amine **25** (3.55 g, 9.2 mmol) in THF (50 mL) were added $(Boc)_2O$ (2.21 g, 10.1 mmol) and DMAP (1.23 g, 10.1 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 12 h. The crude mixture was evaporated under reduced pressure, followed by extraction with CH_2Cl_2 (3 × 100 mL) in water. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by column chromatography over silica gel using ethyl acetate as solvent to give compound **28** (4.46 g, ∼100%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.05 (s, 6H), 0.09 (s, 9H), 1.62 (s, 9H), 2.48 (t, J = 4 Hz, 2H), 2.56 (t, J = 6 Hz, 2H), 2.63 (t, J = 4 Hz, 2H), 3.38 (t, J = 4 Hz, 2H), 3.76 (t, J = 6 Hz, 4H), 6.60 (s, 1H), 7.20−7.28 (m, 1H), 7.34 (t, J = 7.2 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 8.16 (d, J = 7.6 Hz, 1H).

2-{4-[3-(*tert*-Butyldimethylsilanyloxy)propyl]piperazine-1-carbonyl}indole-1-carboxylic Acid *tert*-Butyl Ester (29). Amine **26** (3.33 g, 8.3 mmol) was reacted with $(Boc)_2O$ (2.00 g, 9.1 mmol) and DMAP (1.11 g, 9.1 mmol) in THF (50 mL) using procedure G. The crude material was purified by column chromatography over silica gel (EtOAc/hexane, 1:1) to give compound **29** (4.04 g, 97%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.002 (s, 6H), 0.84 (s, 9H), 1.57 (s, 9H), 1.50−1.80 (m, 2H), 2.20−2.70 (m, 6H), 3.30−3.45 (m, 2H), 3.62 (t, J = 12 Hz, 2H), 3.66−3.80 (m, 2H), 6.55 (s, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H).

2-{4-[4-(*tert*-Butyldimethylsilanyloxy)butyl]piperazine-1-carbonyl}indole-1-carboxylic Acid *tert*-Butyl Ester (30). Amine **27** (4.31 g, 10.4 mmol) was reacted with $(Boc)_2O$ (2.50 g, 11.4 mmol) and DMAP (1.39 g, 11.4 mmol) in THF (50 mL) using procedure G. The crude material was purified by column chromatography over silica gel (EtOAc/hexane, 1:3) to give compound **30** (4.92 g, 92%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.001 (s, 6H), 0.84 (s, 9H), 1.25−1.70 (m, 13H), 2.15−2.40 (m, 4H), 2.42−2.55 (m, 2H), 3.25−3.45 (m, 2H), 3.47−3.65 (m, 2H), 3.67−3.85 (m, 2H), 6.54 (s, 1H), 7.18 (t, J = 7.2 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H).

2-[4-(2-Hydroxyethyl)piperazine-1-carbonyl]indole-1-carboxylic Acid *tert*-Butyl Ester (31). Compound **28** (4.46 g, 9.2 mmol) was reacted with *n*-tetrabutylammonium fluoride (2.39 g, 9.2 mmol, 1.0 M solution in THF) in THF (30 mL) using procedure E. The crude product was purified by silica gel column chromatography (EtOAc/MeOH, 9:1) to yield compound **31** (3.08 g, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.62 (s, 9H), 2.46 (t, J = 4.8 Hz, 2H), 2.54−2.68 (m, 4H), 3.41 (t, J = 5.2 Hz, 2H), 3.64 (t, J = 5.2 Hz, 2H), 3.72−3.78 (m, 2H), 6.60 (s, 1H), 7.21−7.28 (m, 1H), 7.35 (t, J = 8.4 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 8.14 (d, J = 7.6 Hz, 1H).

2-[4-(3-Hydroxypropyl)piperazine-1-carbonyl]indole-1-carboxylic Acid *tert*-Butyl Ester (32). Compound **29** (4.04 g, 8.1 mmol) was reacted with *n*-tetrabutylammonium fluoride (2.11 g, 8.1 mmol, 1.0 M solution in THF) in THF (30 mL) using procedure E. The crude product was purified by silica gel column chromatography (EtOAc/MeOH, 9:1) to yield compound **32** (2.84 g, 91%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.30−1.75 (m, 11H), 2.33 (m, 2H), 2.47 (t, J = 4.4 Hz, 4H), 3.29 (m, 2H), 3.63 (t, J = 4.8 Hz, 4H), 6.50 (s, 1H), 7.13 (t, J = 7.6 Hz, 1H), 7.24 (t, J = 7.2 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H).

2-[4-(4-Hydroxybutyl)piperazine-1-carbonyl]indole-1-carboxylic Acid *tert*-Butyl Ester (33). Compound **30** (4.92 g, 9.5 mmol) was reacted with *n*-tetrabutylammonium fluoride (2.50 g, 9.5 mmol, 1.0 M solution in THF) in THF (30 mL) using procedure E. The crude product was purified by silica gel column chromatography (EtOAc/MeOH, 9:1) to yield compound **33** (3.72 g, 97%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.95−1.70 (m, 13H), 2.30 (t, J = 6 Hz, 4H), 2.37−2.65 (m, 2H), 3.15−3.36 (m, 2H), 3.37−3.55 (m, 2H), 3.55−3.82 (m, 2H), 6.48 (s, 1H), 7.12 (t, J = 7.6 Hz, 1H), 7.23 (t, J = 8 Hz, 1H), 7.42 (d, J = 8 Hz, 1H), 8.05 (d, J = 8 Hz, 1H).

2-[4-(2-Oxoethyl)piperazine-1-carbonyl]indole-1-carboxylic Acid *tert*-Butyl Ester (34). Compound **31** (1.0 g, 2.7 mmol) was reacted with oxalyl chloride (0.47 mL, 5.4 mmol), DMSO (0.76 mL, 10.7 mmol), and Et_3N (2.2 mL, 16.1 mmol) in CH_2Cl_2 (40 mL) using procedure A. The crude residue was purified by column chromatography (EtOAc/MeOH, 20:1) to afford compound **34** (0.81 g, 81%).

2-[4-(3-Oxopropyl)piperazine-1-carbonyl]indole-1-carboxylic Acid *tert*-Butyl Ester (35). Compound **32** (0.8 g, 2.1 mmol) was reacted with oxalyl chloride (0.36 mL, 4.1 mmol), DMSO (0.59 mL, 8.3 mmol), and Et_3N (1.73 mL, 12.4 mmol) in CH_2Cl_2 (40 mL) using procedure A. The crude residue was purified by column chromatography (EtOAc/MeOH, 20:1) to afford compound **35** (0.62 g, 78%).

2-[4-(4-Oxobutyl)piperazine-1-carbonyl]indole-1-carboxylic Acid *tert*-Butyl Ester (36). Compound **33** (1.0 g, 2.5 mmol) was reacted with oxalyl chloride (0.43 mL, 5.0 mmol), DMSO (0.71 mL, 10.0 mmol), and Et_3N (2.08 mL, 15.0 mmol) in CH_2Cl_2 (40 mL) using procedure A. The crude residue was purified by column chromatography (EtOAc/MeOH, 20:1) to afford compound **36** (0.75 g, 75%).

2-(4-{2-[(2-Amino-4,5,6,7-tetrahydrobenzothiazol-6-yl)-propylamino]ethyl}piperazine-1-carbonyl)indole-1-carboxylic Acid *tert*-Butyl Ester [(±)-37]. Aldehyde **34** (480 mg, 1.3 mmol) was reacted with (±)-pramipexole (273 mg, 1.3 mmol) and $NaBH(OAc)_3$ (451 mg, 2.3 mmol) in CH_2Cl_2 (25 mL) using procedure B. The crude material was purified by column chromatography over silica gel (EtOAc/MeOH, 9:1) to give compound (±)-**37** (0.52 g, 71%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.85 (t, J = 3.6 Hz, 3H), 1.30−1.65 (m, 2H), 1.60 (s, 9H), 1.95 (d, J = 10.8 Hz, 1H), 2.20−3.10 (m, 16H), 3.15−3.82 (m, 4H), 4.94 (bs, 2H), 6.58 (s, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.33 (t, J = 6.8 Hz, 1H), 7.53 (d, J = 6 Hz, 1H), 8.13 (d, J = 6 Hz, 1H).

(*R*)-2-(4-{2-[(2-Amino-4,5,6,7-tetrahydrobenzothiazol-6-yl)-propylamino]ethyl}piperazine-1-carbonyl)indole-1-carboxylic Acid *tert*-Butyl Ester [(+)-37]. Aldehyde **34** (200 mg, 0.54 mmol) was reacted with *R*-(+)-pramipexole (114 mg, 0.54 mmol) and $NaBH(OAc)_3$ (205 mg, 0.97 mmol) in CH_2Cl_2 (25 mL) using procedure B. The crude material was purified by column chromatography over silica gel (EtOAc/MeOH, 9:1) to yield compound *R*-(+)-**37** (186 mg, 61%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.86 (t, J = 3.6 Hz, 3H), 1.30−1.65 (m, 2H), 1.61 (s, 9H), 1.95 (d, J = 10.8 Hz, 1H), 2.20−3.10 (m, 16H), 3.15−3.82 (m, 4H), 4.94 (bs, 2H), 6.58 (s, 1H), 7.25 (d, J = 8.4 Hz, 1H), 7.33 (t, J = 6.8 Hz, 1H), 7.53 (d, J = 6 Hz, 1H), 8.13 (d, J = 6 Hz, 1H).

(*S*)-2-(4-{2-[(2-Amino-4,5,6,7-tetrahydrobenzothiazol-6-yl)-propylamino]ethyl}piperazine-1-carbonyl)indole-1-carboxylic Acid *tert*-Butyl Ester [(−)-37]. Aldehyde **34** (300 mg, 0.81 mmol) was reacted with *S*-(−)-pramipexole (170 mg, 0.81 mmol) and $NaBH(OAc)_3$ (308 mg, 1.45 mmol) in CH_2Cl_2 (25 mL) using procedure B. The crude material was purified by column chromatography over silica gel (EtOAc/MeOH, 9:1) to yield compound *S*-(−)-**37** (284 mg, 62%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.83 (t, J = 3.6 Hz, 3H), 1.30−1.65 (m, 2H), 1.61 (s, 9H), 1.95 (d, J = 10.8 Hz, 1H), 2.20−3.10 (m, 16H), 3.15−3.82 (m, 4H), 4.94 (bs, 2H), 6.58 (s, 1H), 7.25 (d, J = 8.4 Hz, 1H), 7.33 (t, J = 6.8 Hz, 1H), 7.53 (d, J = 6 Hz, 1H), 8.14 (d, J = 6 Hz, 1H).

2-(4-{3-[(2-Amino-4,5,6,7-tetrahydrobenzothiazol-6-yl)-propylamino]propyl}piperazine-1-carbonyl)indole-1-carboxylic Acid *tert*-Butyl Ester (38). Aldehyde **35** (220 mg, 0.57 mmol) was reacted with (±)-pramipexole (121 mg, 0.57 mmol) and $NaBH(OAc)_3$ (218 mg, 1.03 mmol) in CH_2Cl_2 (25 mL) using procedure B. The crude material was purified by column chromatography over silica gel (EtOAc/MeOH, 9:1) to give compound **38** (215 mg, 65%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.86 (t, J = 7.2 Hz, 3H), 1.15−1.85 (m, 13H), 1.96 (d, J = 7.2 Hz, 1H), 2.10−2.85 (m, 15H), 2.90−3.15 (m, 1H), 3.20−3.50 (m, 2H), 3.55−

3.95 (m, 2H), 6.58 (s, 1H), 7.23 (t, J = 7.6 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.52 (d, J = 7.6 Hz, 1H), 8.13 (d, J = 8 Hz, 1H).

2-(4-{4-[(2-Amino-4,5,6,7-tetrahydrobenzothiazol-6-yl)-propylamino]butyl}piperazine-1-carbonyl)indole-1-carboxylic Acid *tert*-Butyl Ester (39). Aldehyde **36** (233 mg, 0.58 mmol) was reacted with (±)-pramipexole (123 mg, 0.58 mmol) and $NaBH(OAc)_3$ (222 mg, 1.05 mmol) in CH_2Cl_2 (25 mL) using procedure B. The crude material was purified by column chromatography over silica gel (EtOAc/MeOH, 20:1) to yield compound **39** (190 mg, 55%). ^1H NMR ($CDCl_3$, 400 MHz): δ 0.87 (t, J = 7.2 Hz, 3H), 1.10−1.78 (m, 15H), 1.96 (d, J = 11.2 Hz, 1H), 2.12−2.85 (m, 15H), 2.90−3.15 (m, 1H), 3.25−3.50 (m, 2H), 3.65−3.92 (m, 2H), 4.78 (s, 2H), 6.60 (s, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 8.15 (d, J = 8.4 Hz, 1H).

(4-{2-[(2-Amino-4,5,6,7-tetrahydrobenzothiazol-6-yl)-propylamino]ethyl}piperazin-1-yl)-(1*H*-indol-2-yl)methanone [(±)-40]. Compound (±)-**37** (200 mg, 0.35 mmol) was reacted with TFA (20 mL) in CH_2Cl_2 (20 mL) using procedure C. Unreacted TFA and solvent were removed under reduced pressure. The TFA salt was converted to the free base by extraction using CH_2Cl_2 (3 × 100 mL) and a saturated solution of $NaHCO_3$. The crude material was purified by column chromatography over silica gel to afford compound (±)-**40** (228 mg, 80%). ^1H NMR (CD_3OD, 400 MHz): δ 1.04 (t, J = 7.2 Hz, 3H), 1.70−1.88 (m, 2H), 2.01−2.18 (m, 1H), 2.32 (d, J = 10.8 Hz, 1H), 2.60−3.60 (m, 13H), 3.72−4.20 (m, 6H), 6.85 (s, 1H), 7.07 (t, J = 8 Hz, 1H), 7.23 (t, J = 8 Hz, 1H), 7.44 (d, J = 8 Hz, 1H), 7.62 (d, J = 8 Hz, 1H). ^{13}C NMR (CD_3OD, 100 MHz): δ 14.1, 23.0, 26.0, 26.7, 27.0, 56.6, 57.0, 57.8, 63.1, 109.2, 115.7, 116.3, 124.1, 125.4, 127.9, 131.3, 132.7, 137.4, 137.5, 167.8, 174.4. The free base was converted to its hydrochloride salt. Mp 270−275 °C. Anal. ($C_{25}H_{40}Cl_4N_6O_2S$) C, H, N.

(*R*)-(4-{2-[(2-Amino-4,5,6,7-tetrahydrobenzothiazol-6-yl)-propylamino]ethyl}piperazin-1-yl)-(1*H*-indol-2-yl)methanone [(+)-40]. Compound (+)-**37** (150 mg, 0.26 mmol) was reacted with TFA (15 mL) in CH_2Cl_2 (15 mL) using procedure C. Unreacted TFA and solvent were removed in vacuo and the salt was washed with diethyl ether and recrystallized from ethanol to afford compound *R*-(+)-**40** (160 mg, 75%). ^1H NMR (CD_3OD, 400 MHz): δ 1.05 (t, J = 7.2 Hz, 3H), 1.70−1.88 (m, 2H), 2.01−2.18 (m, 1H), 2.34 (d, J = 10.8 Hz, 1H), 2.60−3.60 (m, 13H), 3.72−4.20 (m, 6H), 6.85 (s, 1H), 7.07 (t, J = 8 Hz, 1H), 7.23 (t, J = 8 Hz, 1H), 7.44 (d, J = 8 Hz, 1H), 7.63 (d, J = 8 Hz, 1H). ^{13}C NMR (CD_3OD, 100 MHz): δ 14.1, 23.0, 26.2, 26.7, 27.0, 56.6, 57.0, 57.8, 63.1, 109.3, 115.7, 116.3, 124.1, 125.4, 127.9, 131.3, 132.7, 137.4, 137.6, 167.8, 174.4. $[\alpha]^{25}_D$ +25.2° (c 1.0, CH_3OH). Mp 100−110 °C. Anal. ($C_{31}H_{38.2}F_9N_6O_{7.6}S$) C, H, N.

(*S*)-(4-{2-[(2-Amino-4,5,6,7-tetrahydrobenzothiazol-6-yl)-propylamino]ethyl}piperazin-1-yl)-(1*H*-indol-2-yl)methanone [(−)-40]. Compound (−)-**37** (200 mg, 0.35 mmol) was reacted with TFA (20 mL) in CH_2Cl_2 (20 mL) using procedure C. Unreacted TFA and solvent were removed in vacuo and the salt was washed with diethyl ether and recrystallized from ethanol to afford compound *S*-(−)-**40** (237 mg, 83%). ^1H NMR (CD_3OD, 400 MHz): δ 1.02 (t, J = 7.2 Hz, 3H), 1.73−1.88 (m, 2H), 2.01−2.18 (m, 1H), 2.32 (d, J = 10.8 Hz, 1H), 2.60−3.60 (m, 13H), 3.72−4.20 (m, 6H), 6.85 (s, 1H), 7.08 (t, J = 8 Hz, 1H), 7.23 (t, J = 8 Hz, 1H), 7.44 (d, J = 8 Hz, 1H), 7.62 (d, J = 8 Hz, 1H). ^{13}C NMR (CD_3OD, 100 MHz): δ 14.3, 23.0, 26.2, 26.7, 27.0, 56.6, 57.0, 57.8, 63.1, 109.3, 115.7, 116.3, 124.1, 125.4, 127.9, 131.3, 132.7, 137.4, 137.5, 167.8, 174.4. $[\alpha]^{25}_D$ −31.2° (c 1.0, CH_3OH). Mp 110−115 °C. Anal. ($C_{31}H_{40}F_9N_6O_{8.5}S$) C, H, N.

(4-{3-[(2-Amino-4,5,6,7-tetrahydrobenzothiazol-6-yl)-propylamino]propyl}piperazin-1-yl)-(1*H*-indol-2-yl)methanone (41). Compound **38** (200 mg, 0.34 mmol) was reacted with TFA (20 mL) in CH_2Cl_2 (20 mL) using procedure C. Unreacted TFA and solvent were removed under reduced pressure, followed by washing of the salt with diethyl ether and recrystallization from ethanol to afford compound **41** (266 mg, 94%). ^1H NMR (CD_3OD, 400 MHz): δ 1.04 (t, J = 7.6 Hz, 3H), 1.65−1.90 (m, 2H), 1.95−2.18 (m, 1H), 2.20−2.48 (m, 3H), 2.56−3.70 (m, 12H), 3.78−4.40 (m, 5H), 6.90 (s, 1H), 7.08 (t, J = 8 Hz, 1H), 7.23 (t, J = 8 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H). ^{13}C NMR (CD_3OD, 100 MHz): δ 10.0, 18.4, 20.1, 21.8, 22.3, 22.7, 51.8, 53.1, 53.6, 59.2, 104.4, 105.7, 111.8, 120.2, 121.6, 124.2, 127.4, 128.2, 133.7, 136.9, 163.8, 170.5. Mp 115−120 °C. Anal. ($C_{32}H_{42}F_9N_6O_{8.5}S$) C, H, N.

(4-{4-[(2-Amino-4,5,6,7-tetrahydrobenzothiazol-6-yl)-propylamino]butyl}piperazin-1-yl)-(1*H*-indol-2-yl)methanone (42). Compound **39** (175 mg, 0.29 mmol) was reacted with TFA (20 mL) in CH_2Cl_2 (20 mL) using procedure C. Unreacted TFA and solvent were removed under reduced pressure, followed by washing of the salt with diethyl ether and recrystallization from ethanol to afford compound **42** (175 mg, 71%). ^1H NMR (CD_3OD, 400 MHz): δ 1.03 (t, J = 7.2 Hz, 3H), 1.50−2.02 (m, 6H), 2.03−2.20 (m, 1H), 2.35 (d, J = 10.8 Hz, 1H), 2.54−3.70 (m, 18H), 3.74−4.01 (m, 1H), 6.90 (s, 1H), 7.08 (t, J = 7.6 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H). ^{13}C NMR (CD_3OD, 100 MHz): δ 10.0, 18.4, 21.0, 21.7, 22.0, 22.2, 22.7, 51.6, 56.0, 59.1, 105.7, 105.7, 111.8, 120.3, 121.6, 124.2, 127.4, 128.2, 133.2, 136.9, 163.8, 170.6. Mp 100−105 °C. Anal. ($C_{35}H_{43.6}F_{12}N_6O_{9.8}S$) C, H, N.

4-{2-[(2-Amino-4,5,6,7-tetrahydrobenzothiazol-6-yl)-propylamino]ethyl}piperazine-1-carboxylic Acid *tert*-Butyl Ester [(±)-43]. Aldehyde **6** (2.4 g, 10.5 mmol) was reacted with (±)-pramipexole (2.22 g, 10.5 mmol) and $NaBH(OAc)_3$ (4.01 g, 18.9 mmol) in CH_2Cl_2 (40 mL) using procedure B. The crude material was purified by column chromatography over silica gel (EtOAc/MeOH, 20:1) to yield compound (±)-**43** (3.34 g, 75%). ^1H NMR ($CDCl_3$, 400 MHz): δ 0.81 (t, J = 7.2 Hz, 3H), 1.10−1.75 (m, 10H), 1.91 (d, J = 9.6 Hz, 1H), 2.10−2.75 (m, 15H), 2.97 (m, 1H), 3.36 (m, 4H), 5.29 (bs, 2H).

(*R*)-4-{2-[(2-Amino-4,5,6,7-tetrahydrobenzothiazol-6-yl)-propylamino]ethyl}piperazine-1-carboxylic Acid *tert*-Butyl Ester [(+)-43]. Compound **6** (1.2 g, 5.25 mmol) was reacted with (*R*)-(+)-pramipexole (1.11 g, 5.25 mmol) and $NaBH(OAc)_3$ (2.0 g, 9.46 mmol) in CH_2Cl_2 (25 mL) using procedure B. The crude material was purified by column chromatography over silica gel (EtOAc/MeOH, 20:1) to give compound *R*-(+)-**43** (1.63 g, 73%). ^1H NMR ($CDCl_3$, 400 MHz): δ 0.83 (t, J = 7.2 Hz, 3H), 1.10−1.75 (m, 10H), 1.91 (d, J = 9.6 Hz, 1H), 2.10−2.75 (m, 15H), 2.98 (m, 1H), 3.36 (m, 4H), 5.29 (bs, 2H).

(*S*)-4-{2-[(2-Amino-4,5,6,7-tetrahydrobenzothiazol-6-yl)-propylamino]ethyl}piperazine-1-carboxylic Acid *tert*-Butyl Ester [(−)-43]. Compound **6** (1.2 g, 5.25 mmol) was reacted with (*S*)-(−)-pramipexole (1.11 g, 5.25 mmol) and $NaBH(OAc)_3$ (2.0 g, 9.46 mmol) in CH_2Cl_2 (25 mL) using procedure B. The crude material was purified by column chromatography over silica gel (EtOAc/MeOH, 20:1) to give compound *S*-(−)-**43** (1.61 g, 71%). ^1H NMR ($CDCl_3$, 400 MHz): δ 0.80 (t, J = 7.2 Hz, 3H), 1.10−1.75 (m, 10H), 1.91 (d, J = 9.6 Hz, 1H), 2.12−2.75 (m, 15H), 2.97 (m, 1H), 3.36 (m, 4H), 5.29 (bs, 2H).

***N*^{6}-(2-Piperazin-1-ylethyl)-*N*^{6}-propyl-4,5,6,7-tetrahydrobenzothiazole-2,6-diamine [(±)-44].** Compound (±)-**43** (3.34 g, 7.88 mmol) was reacted with TFA (20 mL) in CH_2Cl_2 (20 mL) using procedure C to give compound (±)-**44** (2.30 g, 90%). ^1H NMR ($CDCl_3$, 400 MHz): δ 0.79 (t, J = 7.2 Hz, 3H), 1.25−1.48 (m, 2H), 1.50−1.72 (m, 1H), 1.88 (d, J = 11.2 Hz, 1H), 2.08−3.07 (m, 19H), 5.40 (bs, 2H).

(*R*)-*N*^{6}-(2-Piperazin-1-ylethyl)-*N*^{6}-propyl-4,5,6,7-tetrahydrobenzothiazole-2,6-diamine [(+)-44]. Compound (+)-**43** (1.63 g, 3.84 mmol) was reacted with TFA (15 mL) in CH_2Cl_2 (15 mL) using procedure C to yield compound *R*-(+)-**44** (1.16 g, 93%). ^1H NMR ($CDCl_3$, 400 MHz): δ 0.80 (t, J = 7.2 Hz, 3H), 1.25−1.48 (m, 2H), 1.52−1.72 (m, 1H), 1.88 (d, J = 11.2 Hz, 1H), 2.08−3.07 (m, 19H), 5.40 (bs, 2H).

(*S*)-*N*^{6}-(2-Piperazin-1-ylethyl)-*N*^{6}-propyl-4,5,6,7-tetrahydrobenzothiazole-2,6-diamine [(−)-44]. Compound (−)-**43** (1.61 g, 3.80 mmol) was reacted with TFA (15 mL) in CH_2Cl_2 (15 mL) using procedure C to afford compound *S*-(−)-**44** (1.16 g, 94%). ^1H NMR ($CDCl_3$, 400 MHz): δ 0.79 (t, J = 7.2 Hz, 3H), 1.25−1.48 (m, 2H), 1.50−1.72 (m, 1H), 1.89 (d, J = 11.2 Hz, 1H), 2.08−3.07 (m, 19H), 5.41 (bs, 2H).

(4-{2-[(2-Amino-4,5,6,7-tetrahydrobenzothiazol-6-yl)-propylamino]ethyl}piperazin-1-yl)-(1*H*-indol-3-yl)methanone [(±)-45]. Indole-3-carboxylic acid (54 mg, 0.33 mmol) was reacted with compound (±)-**44** (90 mg, 0.28 mmol) in the presence of

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EDCI.HCl (80 mg, 0.42 mmol), TEA (0.12 mL, 0.83 mmol), and HOBT (56 mg, 0.41 mmol) in CH_2Cl_2 (10 mL) using procedure F. The crude product was purified by flash column chromatography (EtOAc/MeOH, 4:1) to afford compound (±)-**45** (83 mg, 64%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.87 (t, J = 7.6 Hz, 3H), 1.30−1.52 (m, 2H), 1.55−1.80 (m, 1H), 1.95 (d, J = 11.6 Hz, 1H), 2.20−2.80 (m, 13H), 2.85−3.10 (m, 1H), 3.50−3.82 (m, 4H), 4.86 (bs, 2H), 7.0−7.38 (m, 4H), 7.60−7.76 (m, 1H), 9.77 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.0, 14.4, 21.3, 22.5, 25.4, 26.1, 26.8, 48.6, 53.7, 54.2, 58.3, 58.8, 60.6, 111.5, 112.1, 117.6, 120.4, 121.2, 122.8, 125.6, 127.5, 135.9, 145.3, 165.8, 167.2. The free base was converted to its hydrochloride salt. Mp 170−175 °C. Anal. ($C_{25}H_{38.6}Cl_4N_6O_{1.3}S$) C, H, N.

(*R*)-(4-{2-[(2-Amino-4,5,6,7-tetrahydrobenzothiazol-6-yl)-propylamino]ethyl}piperazin-1-yl)-(1*H*-indol-3-yl)methanone [(+)-45)]. Indole-3-carboxylic acid (54 mg, 0.33 mmol) was reacted with compound (+)-**44** (90 mg, 0.28 mmol) in the presence of EDCI·HCl (80 mg, 0.42 mmol), TEA (0.12 mL, 0.83 mmol), and HOBT (56 mg, 0.41 mmol) in CH_2Cl_2 (10 mL) using procedure F. The crude material was purified by column chromatography over silica gel (EtOAc/MeOH, 4:1) to yield compound *R*-(+)-**45** (87 mg, 67%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.89 (t, J = 7.6 Hz, 3H), 1.30−1.52 (m, 2H), 1.57−1.80 (m, 1H), 1.95 (d, J = 11.6 Hz, 1H), 2.20−2.80 (m, 13H), 2.85−3.10 (m, 1H), 3.50−3.82 (m, 4H), 4.87 (bs, 2H), 7.0−7.38 (m, 4H), 7.60−7.76 (m, 1H), 9.77 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.0, 14.4, 21.4, 22.5, 25.4, 26.1, 26.9, 48.6, 53.7, 54.2, 58.3, 58.8, 60.6, 111.6, 112.1, 117.6, 120.4, 121.2, 122.8, 125.6, 127.5, 135.9, 145.3, 165.9, 167.2. $[\alpha]^{25}_D$ +37.4° (*c* 1.0, CH_3OH). The free base was converted to its hydrochloride salt. Mp 185−190 °C. Anal. ($C_{25}H_{40}Cl_4N_6O_2S$) C, H, N.

(*S*)-(4-{2-[(2-Amino-4,5,6,7-tetrahydrobenzothiazol-6-yl)-propylamino]ethyl}piperazin-1-yl)-(1*H*-indol-3-yl)methanone [(−)-45)]. Indole-3-carboxylic acid (54 mg, 0.33 mmol) was reacted with compound (−)-**44** in the presence of EDCI·HCl (80 mg, 0.42 mmol), TEA (0.12 mL, 0.83 mmol), and HOBT (56 mg, 0.41 mmol) in CH_2Cl_2 (10 mL) using procedure F. The crude material was purified by column chromatography over silica gel (EtOAc/MeOH, 4:1) to give compound *S*-(−)-**45** (93 mg, 72%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.85 (t, J = 7.6 Hz, 3H), 1.30−1.52 (m, 2H), 1.55−1.80 (m, 1H), 1.95 (d, J = 11.6 Hz, 1H), 2.20−2.80 (m, 13H), 2.85−3.10 (m, 1H), 3.50−3.82 (m, 4H), 4.86 (bs, 2H), 7.0−7.38 (m, 4H), 7.60−7.76 (m, 1H), 9.77 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.0, 14.4, 21.3, 22.5, 25.4, 26.1, 26.8, 48.6, 53.8, 54.2, 58.3, 58.8, 60.6, 111.5, 112.1, 117.7, 120.4, 121.2, 122.8, 125.6, 127.5, 135.9, 145.3, 165.8, 167.2. $[\alpha]^{25}_D$ −33.6° (*c* 1.0, CH_3OH). The free base was converted to its hydrochloride salt. Mp 205−210 °C. Anal. ($C_{25}H_{41.5}Cl_{4.5}N_6O_{2.5}S$) C, H, N.

(4-{2-[(2-Amino-4,5,6,7-tetrahydrobenzothiazol-6-yl)-propylamino]ethyl}piperazin-1-yl)-(1*H*-indol-5-yl)methanone [(±)-46]. Indole-5-carboxylic acid (60 mg, 0.37 mmol) was reacted with compound (±)-**44** (100 mg, 0.31 mmol) in the presence of EDCI·HCl (89 mg, 0.46 mmol), TEA (0.13 mL, 0.93 mmol), and HOBT (63 mg, 0.46 mmol) in CH_2Cl_2 (15 mL) using procedure F. The crude material was purified by column chromatography over silica gel (EtOAc/MeOH, 4:1) to yield compound (±)-**46** (102 mg, 71%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, J = 7.2 Hz, 1H), 1.40−1.54 (m, 2H), 1.60−1.81 (m, 1H), 1.97 (d, J = 11.2 Hz, 1H), 2.20−2.72 (m, 14H), 2.90−3.15 (m, 1H), 3.30−4.02 (m, 4H), 4.89 (bs, 2H), 6.57 (s, 1H), 7.15−7.29 (m, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.71 (s, 1H), 8.84 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.0, 22.5, 25.3, 26.0, 26.7, 48.5, 53.7, 58.3, 58.7, 103.1, 111.4, 117.3, 120.4, 121.4, 125.9, 127.0, 127.5, 136.7, 145.1, 166.1, 172.2. The free base was converted to its hydrochloride salt. Mp 185−190 °C. Anal. ($C_{25}H_{41}Cl_4N_6O_{2.5}S$) C, H, N.

(*R*)-(4-{2-[(2-Amino-4,5,6,7-tetrahydrobenzothiazol-6-yl)-propylamino]ethyl}piperazin-1-yl)-(1*H*-indol-5-yl)methanone [(+)-46]. Indole-5-carboxylic acid (60 mg, 0.37 mmol) was reacted with compound (+)-**44** (100 mg, 0.31 mmol) in the presence of EDCI·HCl (89 mg, 0.46 mmol), TEA (0.13 mL, 0.93 mmol), and HOBT (63 mg, 0.46 mmol) in CH_2Cl_2 (15 mL) using procedure F. The crude material was purified by column chromatography over silica gel (EtOAc/MeOH, 4:1) to furnish compound *R*-(+)-**46** (94 mg, 65%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.89 (t, J = 7.2 Hz, 1H), 1.40−1.54 (m, 2H), 1.60−1.81 (m, 1H), 1.97 (d, J = 11.2 Hz, 1H), 2.20−2.72 (m, 14H), 2.90−3.15 (m, 1H), 3.30−4.03 (m, 4H), 4.89 (bs, 2H), 6.57 (s, 1H), 7.16−7.29 (m, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.71 (s, 1H), 8.84 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.0, 22.5, 25.3, 26.0, 26.7, 48.5, 53.7, 58.3, 58.7, 103.1, 111.4, 117.3, 120.4, 121.4, 125.9, 127.0, 127.5, 136.7, 145.1, 166.1, 172.2. $[\alpha]^{25}_D$ +38.6° (*c* 1.0, CH_3OH). The free base was converted to its hydrochloride salt. Mp 200−205 °C. Anal. ($C_{25}H_{40}Cl_4N_6O_2S$) C, H, N.

(*S*)-(4-{2-[(2-Amino-4,5,6,7-tetrahydrobenzothiazol-6-yl)-propylamino]ethyl}piperazin-1-yl)-(1*H*-indol-5-yl)methanone [(−)-46]. Indole-5-carboxylic acid (60 mg, 0.37 mmol) was reacted with compound (−)-**44** (100 mg, 0.31 mmol) in the presence of EDCI·HCl (89 mg, 0.46 mmol), TEA (0.13 mL, 0.93 mmol), and HOBT (63 mg, 0.46 mmol) in CH_2Cl_2 (15 mL) using procedure F. The crude material was purified by column chromatography over silica gel (EtOAc/MeOH, 4:1) to yield compound *S*-(−)-**46** (95 mg, 66%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.86 (t, J = 7.2 Hz, 1H), 1.40−1.54 (m, 2H), 1.62−1.81 (m, 1H), 1.97 (d, J = 11.2 Hz, 1H), 2.20−2.72 (m, 14H), 2.90−3.15 (m, 1H), 3.30−4.02 (m, 4H), 4.89 (bs, 2H), 6.58 (s, 1H), 7.15−7.29 (m, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.71 (s, 1H), 8.84 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.2, 22.5, 25.3, 26.1, 26.7, 48.5, 53.7, 58.3, 58.9, 103.1, 111.4, 117.3, 120.4, 121.4, 125.9, 127.1, 127.5, 136.7, 145.1, 166.1, 172.2. $[\alpha]^{25}_D$ −34.4° (*c* 1.0, CH_3OH). The free base was converted to its hydrochloride salt. Mp 200−205 °C. Anal. ($C_{25}H_{42.1}Cl_{4.5}N_6O_{2.8}S$) C, H, N.

(4-{2-[(2-Amino-4,5,6,7-tetrahydrobenzothiazol-6-yl)-propylamino]ethyl}piperazin-1-yl)-(5-methoxy-1*H*-indol-3-yl)-methanone (47). 5-Methoxy-1*H*-indole-3-carboxylic acid (213 mg, 1.11 mmol) was reacted with compound (±)-**44** (300 mg, 0.93 mmol) in the presence of EDCI·HCl (267 mg, 1.40 mmol), TEA (0.39 mL, 2.78 mmol), and HOBT (188 mg, 1.40 mmol) in CH_2Cl_2 (25 mL) using procedure F. The crude material was purified by column chromatography over silica gel (EtOAc/MeOH, 6:1) to give compound **47** (280 mg, 61%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.85 (t, J = 7.2 Hz, 3H), 1.32−1.48 (m, 2H), 1.56−1.76 (m, 1H), 1.93 (d, J = 10 Hz, 1H), 2.26−2.78 (m, 1H), 2.90−3.10 (m, 1H), 3.52−3.77 (m, 4H), 3.77 (s, 3H), 5.21 (bs, 2H), 6.77 (d, J = 8.4 Hz, 1H), 6.90−7.22 (m, 3H), 10.3 (bs, 1H).

(4-{2-[(2-Amino-4,5,6,7-tetrahydrobenzothiazol-6-yl)-propylamino]ethyl}piperazin-1-yl)-(5-hydroxy-1*H*-indol-3-yl)-methanone (48). Compound **47** (140 mg, 0.28 mmol) was brought to −78 °C in CH_2Cl_2 (15 mL), followed by dropwise addition of BBr_3 (0.13 mL, 1.41 mmol). The reaction mixture was allowed to stir for 12 h while gradually attaining room temperature. The reaction was quenched by the addition of a saturated solution of $NaHCO_3$, and extraction was with CH_2Cl_2 (2 × 100 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by flash column chromatography over silica gel (EtOAc/MeOH, 2:1) to give compound **48** (80 mg, 59%). ^{1}H NMR (CD_3OD, 400 MHz): δ 0.91 (t, J = 7.6 Hz, 3H), 1.42−1.58 (m, 2H), 1.62−1.80 (m, 1H), 2.00 (d, J = 8.8 Hz, 1H), 2.40−2.85 (m, 15H), 3.00−3.22 (m, 1H), 3.60−3.88 (m, 4H), 6.74 (dd, J = 8, 1.6 Hz, 1H), 7.04 (d, J = 2.4 Hz, 1H), 7.24 (s, 1H), 7.53 (s, 1H). The free base was converted to its hydrochloride salt. Mp 210−215 °C. Anal. ($C_{25.8}H_{43.4}Cl_4N_6O_{3.9}S$) C, H, N.

***N*^{6}-{2-[4-(1*H*-Indol-5-ylmethyl)piperazin-1-yl]ethyl}-*N*^{6}-propyl-4,5,6,7-tetrahydrobenzothiazole-2,6-diamine (49).** Amine (±)-**44** (80 mg, 0.25 mmol) was reacted with 1*H*-indole-5-carbaldehyde (36 mg, 0.25 mmol) and $NaBH(OAc)_3$ (94 mg, 0.45 mmol) in CH_2Cl_2 (15 mL) using procedure B. The crude residue was purified by column chromatography (EtOAc/MeOH, 4:1) to afford compound **49** (71 mg, 63%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.86 (t, J = 7.2 Hz, 3H), 1.32−1.54 (m, 2H), 1.60−1.78 (m, 1H), 1.95 (d, J = 10.4 Hz, 1H), 2.20−2.80 (m, 18H), 2.90−3.10 (m, 1H), 3.63 (s, 2H), 4.87 (bs, 2H), 6.51 (s, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.19 (s, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.55 (s, 1H), 8.45 (s, 1H). The free base was

converted to its hydrochloride salt. Mp 230−235 °C. Anal. ($C_{27}H_{49}Cl_5N_6O_2S$) C, H, N.

Evaluation of Potency in Binding to and Activating Dopamine D2 and D3 Receptors. Binding potency was monitored by inhibition of [^{3}H]spiroperidol (15.0 Ci/mmol, Perkin-Elmer) binding to DA rD2 and rD3 receptors expressed in HEK-293 cells in a buffer containing 0.9% NaCl. Functional activity of test compounds in activating dopamine hD2 and hD3 receptors expressed in CHO cells was measured by stimulation of [^{35}S]GTPγS (1250 Ci/mmol, Perkin-Elmer) binding in comparison to stimulation by the full agonist DA as described by us previously.[29]

Evaluation of Antioxidant Activity. DPPH Radical Scavenging Assay. To a 96-well plate, an amount of 100 μL of methanolic drug solutions ranging from 20 to 250 μM was added. Next 100 μL of 200 μM methanolic solution of DPPH (1,1-diphenyl-2-picrylhydrazyl) was added and the plate was shaken vigorously at 30 °C for 20 min. Control wells received 100 μL of methanol and 100 μL of 200 μM methanolic DPPH solution. Wells containing only 200 μL of methanol served as a background correction. The change in absorbance of all samples and standard (ascorbic acid) was measured at 517 nm. Radical scavenging activity was expressed as inhibition percentage and was calculated using the following formula: % scavenging activity = [(absorbance of control − absorbance of sample)/(absorbance of control)] × 100.[40]

Animal Experiments. Drugs and Chemicals. The following commercially available drugs were used in the experiment: reserpine hydrochloride (Alfa Aesar) and ropinirole (Sigma Aldrich). The trifluoroacetate salt of (−)-**19** and (−)-**40** and the hydrochloride salt of (−)-**46** and ropinirole were dissolved in water. 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 subcutaneously (sc) in a volume of 0.1−0.3 mL to each rat.

Animals. In rodent studies, animals were male and female Sprague-Dawley rats from Harlan (Indianapolis, IN) weighing 220−225 g unless otherwise specified. Animals were maintained in sawdust-lined cages in a temperature and humidity controlled environment at 22 ± 1 °C and 60 ± 5% humidity, respectively. A 12 h light/dark cycle was maintained, 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 assists in the internalization of monoamines into vesicles. VMAT inhibition results in metabolism of unprotected monoamines in the cytosol, ultimately causing depletion of monoamines in the synapses of the peripheral sympathetic nerve terminals.[41,43] The ability of compounds (−)-**19**, (−)-**40**, and (−)-**46** to reverse reserpine-induced hypolocomotion was investigated.[44] Ropinirole was used as a standard reference compound in this study. Reserpine (5.0 mg/kg, sc) was administered 18 h before the injection of drug or vehicle (sc). The rats were placed individually in the chambers for 1 h for acclimatization before 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 activity (HACTV). The effect of 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 the control group was observed at $p < 0.05$.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

GTPγS, guanosine 5′-[γ-thio]triphosphate; 5-OH-DPAT, 5-hydroxy-2-(dipropylamino)tetralin; CHO, Chinese hamster ovary; HEK, human embryonic kidney; L-DOPA, (*S*)-(3,4-dihydroxyphenyl)alanine; DPPH, 1,1-diphenyl-2-picrylhydrazyl; PD, Parkinson's disease; DA, dopamine; sc, subcutaneous

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