Design and Synthesis of Promiscuous High-Affinity Monoamine Transporter Ligands: Unraveling Transporter Selectivity

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A series of 4-[2-[bis(4-fluorophenyl)methoxy]ethyl]-piperidines and 4-[2-[(bisphenyl)methoxy]ethyl]-piperidines with different types of substituents in the phenylpropyl side-chain were synthesized and examined for their ability to bind to the dopamine transporter (DAT), the serotonin transporter (SERT), and the norepinephrine transporter (NET). All of the compounds showed high binding affinities for the DAT in the low to subnanomolar range. Their ability to bind to the SERT and the NET, while maintaining their high affinity for the DAT, could be altered by substitution in positions C2 and C3 of the phenylpropyl side-chain. This approach gave rise to a new set of compounds with selectivity for the DAT, the DAT and the SERT, or the DAT and the NET. Six compounds (**7**, **9**, **11**, **12**, **14**, and **20**) with relatively low SERT/DAT ratios were selected for additional study in biogenic amine uptake inhibition assays based on the biogenic amine transporter binding results. Some of the new ligands can serve as pharmacological tools to block DAT or DAT and another transporter simultaneously.

Introduction

Cocaine is known to be one of the most widely abused drugs because of its powerful reinforcing properties. Its abuse has had great effects on public health, exacerbating the spread of HIV-1, hepatitis B and C, and drug resistant tuberculosis.[1] Cocaine binds with moderate and roughly equal affinities to dopamine transporters (DATs) and serotonin transporters (SERTs), which are monoamine transporters (K_i = 341 ± 25, 129 ± 9, and 13 038 ± 983 nM for DAT, SERT, and norepinephrine transporter (NET) binding, respectively, using [^{125}I]RTI-55 for DAT and SERT, and [^{3}H]nisoxetine for NET).[2] Cocaine inhibits the presynaptic reuptake of neurotransmitters, such as dopamine (DA), serotonin (5-HT), and norepinephrine (NE) (e.g., [^{3}H]DA = 478 ± 25, [^{3}H]5-HT = 304 ± 10, and [^{3}H]NE = 779 ± 30 nM).[3,4] However, the main target for cocaine has been considered to be the dopamine transporter (DAT). The mesolimbic dopaminergic system has been said to mediate reinforcement and the dependence-producing properties of abused drugs,[3,5−8] and drug-induced changes in this system may be one of the factors that can drive the compulsive use of cocaine.[8,9] Recent work[2,10,11] suggests that both the serotonin transporter (SERT) and the norepinephrine transporter (NET) may also play prominent roles in cocaine addiction.[4,12−17] Results from experiments with knock-out mice and behavioral intervention experiments indicated that the serotonergic system might further the reinforcing effect of cocaine.[18−20] NET plays an important role in the regulation of cardiac function, and perinatal exposure to cocaine was shown to produce impaired myocardial NET function in rats.[12]

1-{2-[Bis(4-fluorophenyl)methoxy]ethyl}-4-(3-phenylpropyl)-piperazine (**1**) (GBR 12 909, Scheme 1), which is currently being tested in phase I clinical trials, was one of the first high-affinity DAT inhibitors. To date, most analogues of **1**[21] have been synthesized with two general goals in mind: to determine structure−activity relationships (SAR) at the DAT and to identify ligands with high affinity and selectivity for the DAT (e.g., compound **2** (Scheme 1), the 2-hydroxy derivative of **1**). In contrast to the extensive studies on DAT-selective ligands, fewer studies have focused on the SAR relevant to the development of ligands with diverse levels of transporter selectivity for two of the three or all of the three transporter types.[22−25] New ligands with high DAT affinity combined with affinity and selectivity for the SERT, for example, could have potential as treatment agents for stimulant abuse.[4] Recently, we reported on a series of ligands that completely lacked selectivity, thus blocking all three transporter types simultaneously.[22] Compounds that vary in their transporter affinity and selectivity may help unravel the pharmacological mechanisms relevant to stimulant abuse. To further elucidate the role of the different transporter systems in cocaine reward and craving, novel ligands with different selectivities for each of the three transporter sites must be obtained.[4] We have now explored a new series of analogues of **1** in which we altered the phenylpropyl side-chain with the hope of modifying their selectivity. If this could be accomplished, it might provide a framework for the customization of transporter selectivity. A compound with appropriate affinity for each transporter might lead to an optimized medication for stimulant abuse with the highest efficacy and fewest side effects. A single drug with the desired profile would have the advantage of incorporating the effects of multiple drugs

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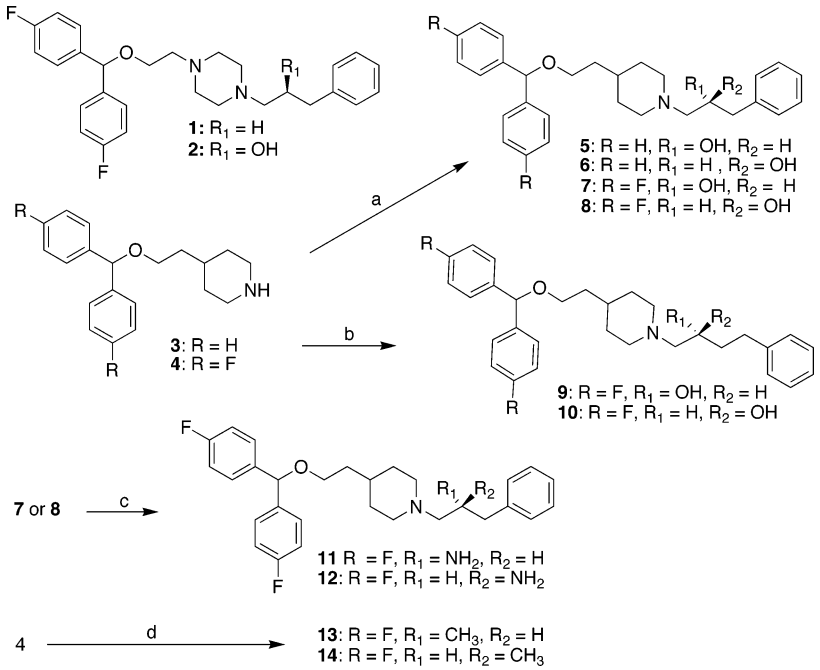
Scheme 1[a]



[a] Reagents: (a) ((*R*)-(+)- or (*S*)-(−))-3-Chloro-1-phenylpropanol, K_2CO_3, and MeOH; (b) ((*R*)-(+) or (*S*)-(−))-1-chloro-4-phenyl-propan-2-ol, K_2CO_3, NaI, and EtOH; (c) HN_3, DIAD, $(C_6H_5)_3P$, and THF; and (d) (1) ((*S*)-(+) or (*R*)-(−))-α-methylhydrocinnamic acid, EDCI, and CH_2Cl_2 (2) $LiAlH_4$, H_2SO_4, and THF.

that, if needed, would multiply the potential of pharmacokinetic complications.

Chemistry

The key intermediates, 4-[2-[(bisphenyl)methoxy]ethyl-piperidine (**3**) and 1-[2-[bis(4-fluorophenyl)methoxy]ethyl-piperidine (**4**), were synthesized in three steps from commercially available 1-piperidineethanol.[26] N-protection with benzoyl chloride and ether formation using benzhydrol or 4,4′-difluorobenzhydrol, respectively, in toluene, under azeotropic distillation conditions was followed by N-deprotection under basic conditions to give **3** and **4**, respectively (Scheme 1).[26] C2-hydroxylated analogues **5**−**10** were prepared from chiral synthons according to the literature, with modifications.[21] The (*S*)-(+)/(*R*)-(−)-1-chloro-3-phenylpropan-2-ol and (*S*)-(+)/(*R*)-(−)-1-chloro-3-phenylbutan-2-ol isomers were synthesized via regioselective epoxide ring opening by a Grignard reagent, phenylmagnesium bromide or benzylmagnesium bromide, and CuI in THF at −40 °C. Compounds **3** and **4** were alkylated with (*S*)-(+)/ (*R*)-(−)-1-chloro-3-phenylpropan-2-ol and (*S*)-(+)/(*R*)-(−)-1-chloro-3-phenylbutan-2-ol, respectively, in MeOH under reflux conditions using K_2CO_3 and NaI to afford the appropriate *R* or *S* isomers. Analogous amino-derivatives **11** and **12** were synthesized from **7** and **8** in two steps. In a one-pot reaction, a stereospecific transformation of the hydroxyl derivatives to an azide by a modified Mitsunobu reaction was followed by a Staudinger reduction to the amine with inversion of the configuration at the stereochemical center.[27,28] C2-methylated enantiomers **13** and **14** were synthesized by coupling **4** with (+)-α-methylhydrocinnamic acid and (−)-α-methyl hydrocinnamic acid,[29] respectively, using EDCI, and subsequently reducing the amide functionality by treatment with $LiAlH_4$. Derivatives **19**, **20**, **22**, and **23** (Scheme 2**)** were synthesized by a similar procedure, including a coupling reaction with the appropriate acid followed by $LiAlH_4$ reduction. 3,4-Dihydro-2-naphthoic acid, which was synthesized in three steps from 4-phenylbutyric acid ethyl ester, following a published procedure,[30] was reacted with **4** followed by a $LiAlH_4$ reduction to afford **21**. Phenylcyclopropyl compounds **22** and **23** were prepared from the *R,R*- and *S,S-trans*-2-phenylcarboxylic acids obtained through optical resolution using dehydroabietylamine.[31]

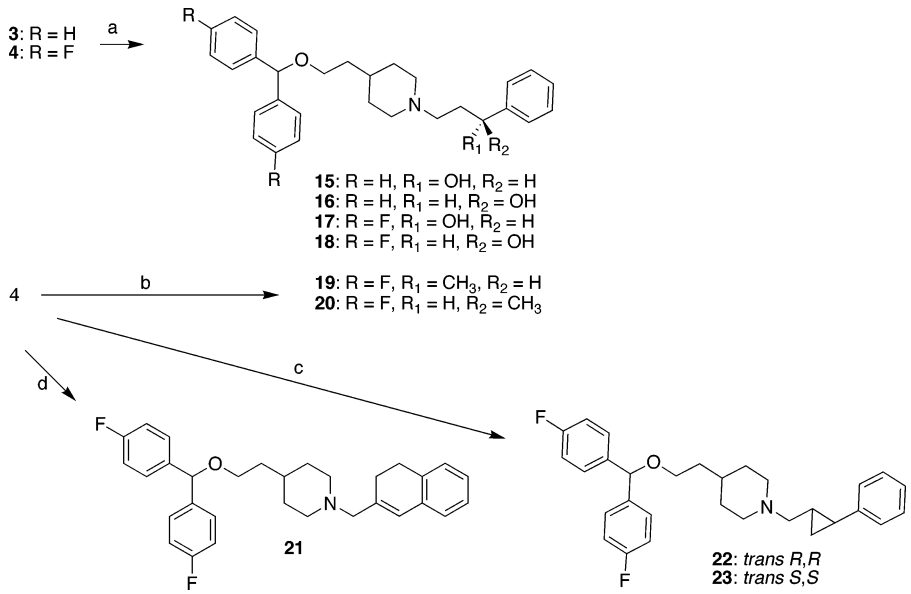
Results and Discussion

Our goal for this study was to find compounds with high affinity for the DAT (preferably with *K*i < 10 nM), combined with an affinity for either the SERT or the NET. Compound **1** (Scheme 1), a nonselective monoamine transporter inhibitor, served as the basic template. Previous data[21] suggested that enantioselectivity in transporter binding could be achieved with a hydroxy-substituted derivative of **1**, when the hydroxy group is in the C2 position. Compound **2** (Scheme 1), the C2-hydroxy substituted analogue of **1**, was among the most selective DAT ligands.[21] Hence, it seems that the substitution pattern in the side chain of the ligand might have a distinct influence on its ability to bind to the different transporters. Thus, in our attempt to improve the affinity for a second transporter for ligands with good affinity for DATs, we examined the following effects of modifications in the phenylpropyl moiety: (A) substitution (OH, NH_2, and CH_3) in the side chain in positions C2 and C3; (B) the effect of chirality; and (C) the conformational constraint of side-chain flexibility through the incorporation of a double-bond or additional rings.

We started our study with the synthesis of C2 and C3 hydroxy-substituted 4-[2-[bis(4-fluorophenyl)methoxyethyl]-piperidines (**7**, **8**, **13**, and **14**, Scheme 1) and 4-[2-bisphenyl]-methoxyethyl]piperidines (**5**, **6**, **15**, and **16**, Schemes 1 and 2). This resulted in a set of compounds with high binding affinity for the DAT, comparable to those of their respective analogues from the piperazine series (Table 1).[21]

In accordance with our previous findings,[21] desfluoro analogues **5**, **6**, **15**, and **16** were generally more selective for binding to the DAT than the bis-4-fluorophenyl analogues. Bis-4-fluorophenyl analogues **7**, **8**, **17**, and **18** displayed a somewhat higher affinity for the DAT and improved affinity for the SERT.

Scheme 2[a]



[a] Reagents: (a) ((*R*)-(+) or (*S*)-(−))-3-Chloro-1-phenylpropanol, K_2CO_3, and DMF; (b) (1) ((*S*)- or (*R*)-)-3-phenylbutyric acid, EDCI, and CH_2Cl_2 (2) $LiAlH_4$, H_2SO_4, and THF; (c) as in method b, using 3,4-dihydro-2-naphthoic acid; and (d) as in method b, using (*R*,*R*)- or (*S*,*S*)-*trans*-2-phenylcyclopropanecarboxylic acid.

Table 1. Binding Affinities at the DAT, SERT, and NET

		(*K*i ± SD, nM)				
compd[a]	*R*/*S*	DAT[b]	SERT[b]	NET[b]	SERT/DAT	NET/DAT
1[c]		3.7 ± 0.4	126 ± 5	426 ± 33	34	115
2[d]	*S*	0.75 ± 0.03	230 ± 7		307	
5	*R*	6.9 ± 0.3	286 ± 22	785 ± 36	42	114
6	*S*	1.4 ± 0.2	450 ± 30	485± 19	332	359
7	*R*	5.1 ± 0.6	91 ± 9	1221 ± 99	18	240
8	*S*	0.4 ± 0.1	82 ± 5	361 ± 16	205	902
9	*R*	2.1 ± 0.2	13 ± 1	460 ± 41	6	215
10	*S*	1.6 ± 0.2	38 ± 4	736 ± 97	24	457
11	*R*	12 ± 1	68 ± 5	941 ± 45	6	78
12	*S*	6.3 ± 0.5	76 ± 5	851 ± 102	12	135
13	*R*	0.9 ± 0.14	53 ± 2	103 ± 13	61	118
14	*S*	8 ± 0.9	100 ± 6	380 ± 45	13	47
15	*R*	1.8 ± 0.2	280 ± 15	>5600	158	3200
16	*S*	2.1 ± 0.2	230 ± 35	210 ± 12	107	101
17	*R*	0.8 ± 0.1	43 ± 3	330 ± 15	51	394
18	*S*	0.9 ± 0.1	22 ± 0.8	440 ± 15	26	515
19	*R*	2.2 ± 0.2	58 ± 3	560 ± 75	26	253
20	*S*	1.3 ± 0.14	30 ± 2	340 ± 30	22	259
21		1.1 ± 0.1	127 ± 7	43 ± 4	118	40
22		0.5 ± 0.02	16 ± 1	947 ± 52	32	1894
23		1.4 ± 0.2	136 ± 5	359 ± 41	97	256

[a] Prepared and tested as oxalate salts. [b] Values determined as in Lewis et al.[36] Binding affinities at the DAT and SERT are labeled with [^{125}I]RTI-55 and at the NET with [^{3}H]nisoxetine. [c] Data from Boos et al.[37] [d] Data from Hsin et al.[21]

Desfluoro analogues **5**, **6**, **15**, and **16** displayed SERT/DAT selectivity ratios up to 330-fold (**6**), whereas corresponding bis-4-fluorophenyl analogues **7**, **8**, **17**, and **18** showed generally lower SERT/DAT selectivity (Table 1). Chirality had a distinct influence on SERT/DAT selectivity in both the bis-4-fluorophenyl and in the desfluoro series. The *S* isomers with the hydroxy group in the C2 position showed higher SERT/DAT selectivity than their *R* configured analogues (**6** is 8-fold more selective than **5**, and **8** is 11-fold more selective than **7**). Shifting the substituent to the C3 position (**15**−**18**, Scheme 2) mostly abolished this effect, and the enantiomeric differences in SERT/DAT selectivity were less pronounced. None of these analogues showed high affinity for the NET. Side-chain elongation to four carbon atoms with a hydroxy group in the C2 position gave rise to enantiomers **9** and **10**. Altthough their binding affinities for the DAT are similar to those of their counterparts **7** and **8**, SERT affinity was, as we desired, further increased by this modification. The *R* isomer **9** is much less selective for DATs and SERTs than **7**, **8**, and **10**. Compound **9** had good affinity for DAT (*K*i = 2 nM) and reasonable affinity for SERT (*K*i = 13 nM, Table 1).

Because the bis-4-fluorophenyl compounds proved to be more active at the DAT and the bis-4-fluorophenyl moiety of the molecule seemed to be slightly better tolerated at the NET, we decided to use the 4-[2-[bis(4-fluorophenyl)methoxy]ethyl-1-phenylpropylpiperidine backbone for further modifications (Scheme 1). Introduction of an amino group into the C2 position resulted in compounds **11** and **12**. These compounds show slightly lower DAT affinities than their hydroxy substituted analogues **7** and **8**, whereas their SERT affinities were in the

Table 2. Uptake-Inhibition Studies for Selected Compounds

		(*K*i ± SD, nM)				
compd[a]	*R*/*S*	[^{3}H]DA[b]	[^{3}H]5-HT[b]	[^{3}H]NE[b]	5-HT/DA	NE/DA
7	*R*	1.7 ± 0.14	41 ± 2.3	143 ± 14	24	84
9	*R*	1.4 ± 0.05	19 ± 0.9	79 ± 8.6	14	56
11	*R*	17 ± 1.4	229 ± 10	402 ± 37	13	24
12	*S*	13 ± 0.9	228 ± 8	338 ± 32	18	26
14	*S*	3.8 ± 0.23	124 ± 5	160 ± 18	33	42
20	*S*	2.1 ± 0.14	75 ± 5.9	40 ± 3.6	36	19

[a] Prepared and tested as oxalate salts. [b] Values determined as in refs 32−34.

same range (Table 1). Their enantioselectivity was in accordance with the trend we observed in the hydroxy substituted series. *R* isomer **11** was less SERT/DAT selective. However, the amino group seemed to be even less tolerated at the NET than the hydroxy substituent, so we continued by exploring other substituents.

Substitution of the hydroxy group with a methyl group in positions C2 and C3 did not affect DAT binding, and all of the compounds displayed DAT binding affinities in the low nanomolar to subnanomolar range (e.g., *K*i = 0.9 nM for **11**, Table 1). C3-substituted, S-configured analogue **20** displayed the highest SERT affinity (*K*i = 30 nM) in this set, whereas the other analogues, **13**, **14**, and **19**, showed only moderate affinity for the SERT. The absolute configuration of the methyl group was more important for the affinity of the C2-substituted isomers at the DAT and SERT than for the C3-methylated analogues. Unlike the corresponding hydroxy analogue, C2-methyl substituted *R* isomer **13** was significantly more SERT/DAT selective than its *S* isomer 14 (Table 1). Although **13** had a higher affinity than that of **14** for SERTs, the SERT/DAT ratio (61, Table 1) was higher than that for **14** because of the exceptionally high affinity of **15** at the DAT. The SERT/DAT ratio of ca. 13 for analogue **16** was much better for our purposes, although the affinities of **14** for both transmitters (DAT *K*i = 8, SERT *K*i = 100 nM) was not very high. The binding affinities of the methyl-substituted analogues at the NET were generally poor, but a methyl substituent anywhere in the side chain seemed to improve NET affinity or decrease DAT/NET selectivity.

Because the polar, electrophilic hydroxy substituent in the side chain was not needed to maintain the high binding affinity at the DAT, we thought it would be of interest to investigate the effect of substituents that, perhaps like the methyl and hydroxyl moieties, might influence the interaction of the ligand with DATs, SERTs, and/or NETs through a steric effect. We decided to increase the steric effect by reducing the flexibility of the side chain through an additional ring.[21−23] The introduction of an unsaturated six-membered ring with a double bond between C2 and C3 resulted in compound **21** with a high affinity for the DAT (*K*i = 1 nM) and moderate affinity for the SERT (*K*i = 127 nM). Because **21** displayed the highest affinity for the NET (*K*i = 43 nM) in this series, it might prove useful as a prototype for compounds able to simultaneously block the DAT and the NET. The *trans*-cyclopropylmethyl derivatives **22** and **23** also showed a high affinity for the DAT (*K*i = 0.5 and 1.4 nM, respectively). Their binding affinities for the SERT were comparable to those of the methylated analogues. However, NET affinity seemed to be decreased by this modification.

On the basis of the biogenic amine transporter binding results (Table 1), we selected six compounds (**7**, **9**, **11**, **12**, **14**, and **20**) with relatively low SERT/DAT ratios for additional study in biogenic amine uptake inhibition assays, conducted as described.[32−34] The results (see Table 2) showed that the *K*i values for the inhibition of DAT binding was generally similar to the *K*i values for the inhibition of [^{3}H]DA uptake. The *K*i values for the inhibition of SERT binding were also similar to the *K*i values for the [^{3}H]5-HT uptake inhibition, except for those of **11** and **12**, which were about 3 times less potent in the uptake inhibition assay than in the SERT binding assay. Greater discrepancies were observed in the NET assays. In this case, all agents were between 2.3-fold and 10-fold more potent in the [^{3}H]NE uptake inhibition assay than in the NET binding assay. The discrepant results in the NET assays likely result from the use of [^{3}H]nisoxetine to label the NET because recent studies showed that this ligand generally yields *K*i values significantly higher than that observed in [^{3}H]NE uptake assays.[33] The use of [^{125}I]RTI-55 to label NET in HEK cells that express the NET, which is now our current practice, helps to resolve this problem. An additional factor that can contribute to the differences between binding and functional *K*i values is the fact that the assays are done under very different conditions.[34] Thus, in agreement with the findings of Reith et al.,[33] in cases where it is critical to determine the functional selectivity of biogenic amine transporter ligands, uptake inhibition assays are probably superior to biogenic amine transporter binding assays.

Conclusions

Some of the compounds listed in Table 1 (**8**, **13**, **17**, **18**, and **22**) had exceptionally high, subnanomolar affinity for DAT, whereas the others showed a high affinity for the DAT in the low nanomolar range. Their binding affinities for the SERT and the NET varied, depending on the nature of the substituent in the C2 position of the phenylpropyl side chain, and could be further affected by the remote introduction of chirality. Introduction of a hydroxy substituent with an *S* configuration in the C2 position (**6**, **8**) led to highly selective DAT ligands. Two compounds with an *R*-hydroxy group (**9**) or an *R*-amino group (**11**) in the C2 position showed high affinities for DATs and good affinities for the SERT. The binding data indicate that these compounds might be useful for determining the effects of the simultaneous blockade of two transporters, DATs and SERTs. However, functional data from uptake-inhibition studies clearly suggest that **9** would be more efficacious than **11** for that purpose. The highest binding affinity for the NET was observed with a compound where the movement of the side-chain was restrained by an additional ring system (**22**). Although progress was made toward finding ligands able to interact with both DATs and SERTs or DATs and NETs, their affinities for the SERTs and NETs need to be increased. Our results are consistent with the following hypotheses: (1) the steric effects of the substituent influence the binding of a ligand at the SERT and the NET, as may hydrogen bonding (e.g., compound **9**), (2) the restrictions in the flexibility of the side chain have a lesser influence, and (3) the electronic effects of polar substituents in these positions apparently interfere with NET binding. Compounds with customized transporter properties could serve as pharmacological tools to determine to what extent the blockade of two of the three transporters is beneficial as a medication for cocaine abuse, as compared to the blockade of DATs alone. A better understanding of these effects may facilitate the development of more effective treatment agents with fewer side effects.

Experimental Section

All melting points were determined on a Thomas-Hoover melting-point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a Varian XL-300 instrument with DMSO-d_6 as

solvent, with the values given in ppm (TMS as internal standard) and *J* (Hz) assignments of ^{1}H resonance coupling. Chemical ionization mass spectra (CIMS) were obtained using a Finnigan 1015 mass spectrometer. Electron ionization (EIMS) mass spectra were obtained using a VG-Micro Mass 7070F mass spectrometer. Thin-layer chromatography (TLC) was performed on 250 mm Analtech GHLF silica gel plates using *n*-hexane/EtOAc, 7:3, as the solvent system. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. (*S*)-(+)-1-Chloro-3-phenylpropan-2-ol and (*R*)-(−)-1-chloro-3-phenylpropan-2-ol were purchased from Aldrich Chemical Co., Milwaukee, WI. Enantiomeric purity was assessed by HPLC (Shimadzu LC-6A with a Shimadzu SPD-6AV UM detector (at 254 nm) using Daicel's Chiralcel OD column (0.46 × 5 cm^2 coupled to 0.46 × 25 cm^2). The mobile phase was hexanes/2-propanol/diethylamine (95:5:0.1) at a flow rate of 0.7−1 mL/min. The chiral compounds (all of the hydroxy- and amino-substituted compounds) were either found to be optically pure (>99%) by chiral HPLC or were prepared from optically pure starting material.

(*R*)-(−)-4-(2-Benzhydryloxyethyl)-1-(3-phenylpropan-2-ol)-piperidine Oxalate (5). A mixture of **3** (1.8 g, 0.0047 mol, free base), (*R*)-(−)-3-chloro-1-phenylpropanol[35] (0.8 g, 0.005 mol), and K_2CO_3 (1.9 g, 0.0141 mol) in MeOH (30 mL) was heated to reflux for 12 h. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with saturated NaCl (2 × 50 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded a crude oil that was purified by column chromatography (silica gel, CH_2CH_2/MeOH, 9:1). The resulting oil was dissolved in Et_2O (50 mL), and oxalic acid (1.1 equiv) was added. The mixture was cooled in an ice bath to induce crystallization. The precipitate was collected and dried to afford 1.2 g (44%) of a white solid: mp 156−158 °C; $[\alpha]_D^{20}$ −8.7 (*c* 0.975, MeOH); ^{1}H NMR (DMSO-d_6): δ 7.2−7.4 (m, 15H), 5.4 (s, 1H, CH−O), 2.8−3.2 (m, 5H), 2.7 (d, 2H, J = 6); MS *m*/*z* (CI): 430.3 [M + 1]$^+$. Anal. ($C_{29}H_{35}NO_2 \cdot C_2H_2O_4$): C, H, N.

(*S*)-(+)-4-(2-Benzhydryloxyethyl)-1-(3-phenylpropan-2-ol)-piperidine Oxalate (6). Compound **6** was prepared in 34% yield using the procedure described for **5**, as colorless crystals: mp 156−158 °C; $[\alpha]_D^{20}$ +8.5 (*c* 1.05, MeOH); ^{1}H NMR (DMSO-d_6): δ 7.2−7.4 (m, 15H); 5.4 (s, 1H, CH−O); 2.7 (d, 2H, J = 6); MS *m*/*z* (CI): 430.3 [M + 1]$^+$. Anal. ($C_{29}H_{35}NO_2 \cdot C_2H_2O_4$): C, H, N.

(*R*)-(−)-4-[2-[Bis-(4-fluorophenyl)methoxy]ethyl]-1-(3-phenylpropan-2-ol)-piperidine Oxalate (7). A mixture of **4** (2.0 g, 0.0047 mol, free base), K_2CO_3 (1.9 g, 0.0141 mol), catalytic amounts of NaI, and (*R*)-(−)-3-chloro-1-phenylpropanol[35] (0.8 g, 0.005 mol) in abs EtOH (30 mL) was heated at reflux for 12 h. The solvent was removed under reduced pressure, and H_2O (150 mL) was added to the residue. The mixture was extracted with Et_2O (3 × 50 mL). The combined Et_2O layers were washed with saturated NaCl (2 × 100 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded a crude oil that was purified by column chromatography (silica gel, CH_2Cl_2/MeOH, 9:1). The product was dissolved in 2-propanol. Oxalic acid (1.1 equiv) and H_2O (0.5 mL) were added, the solution was cooled in an ice bath, and the precipitate was collected to afford **7** (2.0 g, 77%) as a colorless solid: mp 72−75 °C; $[\alpha]_D^{20}$ −8.5 (*c* 1.13, MeOH); ^{1}H NMR (DMSO-d_6): δ 7.1−7.4 (m, 13H), 5.5 (s, 1H, CH−O), 4.2 (m, 1H, CH−OH), 3.4 (m, 4H), 2.7 (d, 2H, J = 6.0 Hz); MS *m*/*z* (CI): 466.2 [M + 1]$^+$. Anal. ($C_{29}H_{33}NO_2F_2 \cdot C_2H_2O_4 \cdot 0.25H_2O$): C, H, N.

(*S*)-(+)-4-[2-[Bis-(4-fluorophenyl)methoxy]ethyl]-1-(3-phenylpropan-2-ol)-piperidine Oxalate (8). Compound **8** was prepared in 66% yield using the procedure described for **7** from **4** (2.0 g, 0.0047 mol) and (*S*)-(+)-3-chloro-1-phenylpropanol (0.8 g, 0.005 mol) as colorless crystals: mp 73−76 °C; $[\alpha]_D^{20}$ +8.0 (*c* 1.15, MeOH); ^{1}H NMR (DMSO-d_6): δ 7.1−7.4 (m, 13H), 5.5 (s, 1H, CH−O), 4.2 (m, 1H, CH−OH), 3.4 (m, 4H), 2.7 (d, 2H, J = 6.6 Hz); MS *m*/*z* (CI): 466.2 [M + 1]$^+$. Anal. ($C_{29}H_{33}NO_2F_2 \cdot C_2H_2O_4 \cdot 0.25H_2O$): C, H, N.

(*R*)-(+)-4-[2-[Bis-(4-fluorophenyl)methoxy]ethyl]-1-(4-phenylbutan-2-ol)-piperidine Oxalate (9). Into a suspension of Mg (0.54 g, 0.0222 mol) and catalytic amounts of I_2 in Et_2O (25 mL) was added about a quarter of the total amount of benzyl bromide (total of 3.8 g, 0.0222 mol) in Et_2O (10 mL), and the reaction was initiated by slight heating. The rest of the benzyl bromide solution was added dropwise to maintain a gentle reflux. After addition, the mixture was heated to efflux for 30 min before the Grignard reagent was transferred into a dry flask. CuI (1.6 g, 0.0083 mol) was added, and the solution was cooled to −78 °C. (*R*)-(−)-Epichlorohydrin (0.5 g, 0.0056 mol) was added in a dropwise manner. The mixture was warmed to 0 °C and stirred for 1 h before NH_4Cl (saturated solution, 100 mL) was added. The mixture was extracted with EtOAc (2 × 60 mL). The combined organic layers were washed with H_2O (3 × 50 mL) and brine (3 × 50 mL), and dried over Na_2SO_4. The solvent was removed under reduced pressure, affording a crude oil. Purification by column chromatography (silica gel, hexanes/EtOAc, 85:15) yielded 1-chloro-4-phenylpropan-2-ol as a clear oil. Compound **9** was prepared in 66% yield using the procedure described for **7** from **4** as colorless crystals: mp 144−145 °C; $[\alpha]_D^{20}$ +1.9 (*c* 1.06, MeOH); ^{1}H NMR (DMSO-d_6): δ 7.1−7.4 (m, 13H), 5.5 (s, 1H, CH−O), 4.3 (d, 1H, CH−OH, J = 3.6), 3.4 (m, 4H); MS *m*/*z* (CI): 480.3 [M + 1]$^+$. Anal. ($C_{30}H_{35}NO_2F_2 \cdot C_2H_2O_4$): C, H, N.

(*S*)-(−)-4-[2-[Bis-(4-fluorophenyl)methoxy]ethyl]-1-(4-phenylbutan-2-ol)-piperidine Oxalate (10). Compound **10** was prepared in 49% yield using the procedure described for **7** from **5** (2.5 g, 0.0075 mol) and (*S*)-1-chloro-4-phenyl-butan-2-ol as colorless crystals: mp 146−147 °C; $[\alpha]_D^{20}$ −1.6 (*c* 1.20, MeOH); ^{1}H NMR (DMSO-d_6): δ 7.1−7.4 (m, 13H), 5.5 (s, 1H, CH−O), 4.3 (d, 1H, CH−OH, J = 3.6), 3.4 (m, 4H); MS *m*/*z* (CI): 480.3 [M + 1]$^+$. Anal. ($C_{30}H_{35}NO_2F_2 \cdot C_2H_2O_4$): C, H, N.

(*R*)-(−)-1-(2-Amino-3-phenylpropyl)-4-[2-[bis-(4-fluorophenyl)methoxy]ethyl]piperidine Dioxalate (11). NaN_3 (6.5 g, 0.100 mol) was suspended into warm H_2O. Benzene (100 mL) was added, and the mixture was cooled to 0 °C. H_2SO_4 (4.9 g, 0.05 mol) was added in a dropwise manner while the temperature was kept below 10 °C. After the mixture was cooled to 0 °C, the organic layer was decanted and dried over Na_2SO_4. Diisopropylazodicarboxylate (DIAD, 0.42 g, 0.0021 mol) was added dropwise to a solution of **7** (1.0 g, 0.0021 mol), triphenylphosphine (660 mg, 0.0025 mol), and hydrazoic acid/benzene (2.5 mL, 4%) in THF (50 mL) at 5 °C. This mixture was stirred at room temperature for 3 h, and triphenylphosphine (0.55 g, 0.0021 mol) was added in one portion. The solution was heated to 40 °C, until the evolution of gas ceased. H_2O (1 mL) was added, and the solution was stirred for an additional 3 h. The solvents were removed under reduced pressure, and the residue was dissolved in CH_2Cl_2/2N HCl (100 mL, 1:1). The aqueous layer was separated, basified, and extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with H_2O (1 × 100 mL) and brine (1 × 100 mL) and dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded a crude oil that was purified by column chromatography (silica gel, hexane/EtOAc, 9:1). The resulting oil was dissolved in Et_2O (50 mL), and oxalic acid (1.1 equiv) was added. The mixture was cooled in an ice bath to induce crystallization. The precipitate was collected and dried to afford 1.2 g (80%) of colorless crystals: mp 145−147 °C; $[\alpha]_D^{20}$ −7.3 (*c* 1.04, MeOH); ^{1}H NMR (DMSO-d_6): δ 7.1−7.4 (m, 13H), 5.4 (s, 1H, CH−O); MS *m*/*z* (CI): 465 [M + 1]$^+$. Anal. ($C_{29}H_{34}N_2OF_2 \cdot 2C_2H_2O_4$): C, H, N.

(*S*)-(+)-1-(2-Amino-3-phenylpropyl)-4-[2-[bis-(4-fluorophenyl)-methoxy]ethyl]piperidine Dioxalate (12). Compound **12** was prepared in 70% yield using the procedure described for **11** from **7** (2.0 g, 0.0044 mol) as colorless crystals: mp 147−148 °C; $[\alpha]_D^{20}$ +7.6 (*c* 1.03, MeOH); ^{1}H NMR (DMSO-d_6): δ 7.1−7.4 (m, 13H), 5.4 (s, 1H, CH−O); MS *m*/*z* (CI): 465 [M + 1]$^+$. Anal. ($C_{29}H_{34}N_2OF_2 \cdot 2C_2H_2O_4$): C, H, N.

***R*-(−)-4-[2-[Bis-(4-fluorophenyl)methoxy]ethyl]-1-(2-methyl-3-phenylpropyl)piperidine Oxalate (13).** A solution of **4** (1.3 g, 0.0039 mol, free base), (*S*)-(+)-α-methylhydrocinnamic acid[29] (0.7 g, 0.0039 mol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodi-

imide hydrochloride (EDCI) (0.9 g, 0.005 mol) in dry CH_2Cl_2 (25 mL) was stirred at room temperature for 12 h. The solvent was removed under reduced pressure, and EtOAc (125 mL) was added to the residue. The combined EtOAc layers were washed successively with 1 M HCl (2 × 50 mL), 10% K_2CO_3 (2 × 50 mL), and saturated NaCl (50 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford 1.8 g (95%) of the corresponding amide as an oil, which was used without further characterization. To a suspension of $LiAlH_4$ (0.7 g, 0.0195 mol) in dry THF (100 mL) at 0 °C, 100% H_2SO_4 (d = 1.84, 0.9 g, 0.009 mol) was cautiously added. Upon completion of the addition, the mixture was stirred at room temperature for 1 h. A solution of the crude amide in dry THF (50 mL) was added in a dropwise manner. The resulting mixture was stirred for 2 h, and then 10% NaOH (150 mL) was added cautiously. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with H_2O (100 mL) and saturated NaCl (2 × 100 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded a crude oil that was purified by chromatography (silica gel, EtOAc/*n*-hexane, 3:7). The product was dissolved in Et_2O, and an excess of oxalic acid was added. The precipitate was collected and dried to afford **13** (1.0 g, 56%), as colorless crystals: mp 118−122 °C; $[\alpha]_D^{20}$ −1.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR (DMSO-d_6): δ 7.1−7.4 (m, 13H), 5.5 (s, 1H, CH−O), 0.8 (d, 3H, J = 6.3 Hz); MS *m*/*z* (CI): 464.1 $[M + 1]^+$. Anal. ($C_{30}H_{35}NOF_2 \cdot C_2H_2O_4 \cdot 0.5H_2O$): C, H, N.

***S*-(+)-4-[2-[Bis-(4-fluorophenyl)methoxy]ethyl]-1-(2-methyl-3-phenylpropyl)piperidine Oxalate (14).** Compound **14** was prepared in 67% yield using the procedure described for **13** from **4** (1.3 g, 0.0039 mol, free base) and *(R)*-(−)-α-methylhydrocinnamic acid[29] (0.7 g, 0.0039 mol) as colorless crystals: mp 120−124 °C; $[\alpha]_D^{20}$ +1.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR (DMSO-d_6): δ 7.1−7.4 (m, 13H), 5.4 (s, 1H, CH−O), 0.7 (d, 3H, J = 6.3 Hz); MS *m*/*z* (CI): 464.1 $[M + 1]^+$. Anal. ($C_{30}H_{35}NOF_2 \cdot C_2H_2O_4 \cdot 0.5H_2O$): C, H, N.

(*R*)-(+)-4-(2-Benzhydryloxyethyl)-1-(3-phenylpropan-3-ol)-piperidine Oxalate (15). A mixture of **3** (1.5 g, 0.0039 mol), K_2CO_3 (1.6 g, 0.0117 mmol), and (*R*)-(+)-3-chloro-1-phenylpropanol (0.7 g, 0.0041 mol) in DMF (30 mL) was heated for 12 h at 85 °C. H_2O (200 mL) was added, and the mixture was extracted with EtOAc (3 × 70 mL). The combined EtOAc layers were washed with H_2O (2 × 100 mL) and saturated NaCl (2 × 50 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded a crude oil that was dissolved in Et_2O. An excess of oxalic acid was added, and the precipitate was collected, washed with Et_2O (100 mL) and dried to afford **15 (**1.5 g, 74%), as a colorless solid: mp 98−102 °C; $[\alpha]_D^{20}$ +15.6 (*c* 1.05, MeOH); ^{1}H NMR (DMSO-d_6): δ 7.1−7.4 (m, 15H), 5.5 (s, 1H, CH−O), 4.6 (m, 1H, CH−OH), 3.4 (m, 4H), 2.8−3.2 (m, 4H), 2.1−1.8 (m, 5H), 1.2−1.6 (m, 4H); MS *m*/*z* (CI): 430.3 $[M + 1]^+$. Anal. ($C_{29}H_{35}NO_2 \cdot C_2H_2O_4 \cdot 0.25H_2O$): C, H, N.

(*S*)-(−)-4-(2-Benzhydryloxyethyl)-1-(3-phenylpropan-3-ol)-piperidine Oxalate (16). Compound **16** was prepared in 84% yield using the procedure described for **15** from **3** (1.3 g, 0.0039 mol, free base) and (*S*)-(−)-3-chloro-1-phenyl-propanol (0.7 g, 0.0041 mol) as colorless crystals: mp 97−101 °C; $[\alpha]^{20}_D$ −16.7 (*c* 1.07, MeOH); ^{1}H NMR (DMSO-d_6): δ 7.2−7.4 (m, 5H), 5.4 (s, 1H, CH−O), 4.6 (t, 1H, J = 6.9 Hz); MS *m*/*z* (EI): 429.3 $[M]^+$. Anal. ($C_{29}H_{35}NO_2 \cdot C_2H_2O_4 \cdot 0.25\ H_2O$): C, H, N.

(*R*)-(+)-4-[2-[Bis-(4-fluorophenyl)methoxy]ethyl]-1-(3-phenylpropan-3-ol)-piperidine Oxalate (17). Compound **17** was prepared in 95% yield using the procedure described for **15** from **4** (1.5 g, 0.0036 mol) and (*R*)-(+)-3-chloro-1-phenyl-propanol (0.7 g, 0.0041 mol), as colorless crystals: mp 98−103 °C; $[\alpha]_D^{20}$ +16.0 (*c* 1.08, MeOH); ^{1}H NMR (DMSO-d_6): δ 7.0−7.5 (m, 13H), 5.5 (s, 1H, CH−O), 4.6 (m, 1H, J = 5.7 Hz); MS *m*/*z* (EI): 465.3 $[M]^+$. Anal. ($C_{29}H_{35}NO_2 \cdot C_2H_2O_4$): C, H, N.

(*S*)-(−)-4-[2-[Bis-(4-fluorophenyl)methoxy]ethyl]-1-(3-phenylpropan-3-ol)-piperidine Oxalate (18). Compound **18** was prepared in 95% yield using the procedure described for **15** from **4** (1.5 g, 0.0036 mol) and (*S*)-(−)-3-chloro-1-phenyl-propanol (0.7 g, 0.0041 mol) as colorless crystals: mp 97−102 °C; $[\alpha]_D^{20}$ −16.4 (*c* 1.07, MeOH); ^{1}H NMR (DMSO-d_6): δ 7.1−7.4 (m, 13H), 5.4 (s, 1H, CH−O), 4.6 (m, 1H, CH−OH); MS *m*/*z* (CI): 466.3 $[M + 1]^+$. Anal. ($C_{29}H_{35}NO_2 \cdot C_2H_2O_4$): C, H, N.

***R*-(−)-4-[2-[Bis-(4-fluorophenyl)methoxy]ethyl]-1-(3-phenylbutyl)-piperidine Oxalate (19).** Compound **19** was prepared in 60% yield using the procedure described for **13** from **4** (2.0 g, 0.0060 mol, free base) using (*R*)-3-phenylbutyric acid (1.0 g, 0.0061 mol) to give colorless crystals: mp 154−156 °C; $[\alpha]_D^{20}$ −2.93 (*c* 1.09, MeOH); ^{1}H NMR (DMSO-d_6): δ 7.1−7.4 (m, 13H), 5.4 (s, 1H, CH−O), 0.7 (d, 3H, J = 6.3 Hz); MS *m*/*z* (CI): 464.3 $[M + 1]^+$. Anal. ($C_{30}H_{35}F_2NO \cdot C_2H_2O_4$): C, H, N.

***S*-(+)-4-[2-[Bis-(4-fluorophenyl)methoxy]ethyl]-1-(3-phenylbutyl)-piperidine (20).** Compound **20** was prepared in 40% yield using the procedure described for **15** from **4** (2.0 g, 0.0060 mol, free base) and (*S*)-3-phenylbutyric acid (1.0 g, 0.0061 mol), as colorless crystals: mp 155−157 °C; $[\alpha]_D^{20}$ +2.80 (*c* 1.00, MeOH); ^{1}H NMR (DMSO-d_6): δ 7.1−7.4 (m, 13H), 5.4 (s, 1H, CH−O), 1.2 (d, 3H, J = 7.2 Hz); MS *m*/*z* (CI): 464.3 $[M + 1]^+$. Anal. ($C_{30}H_{35}F_2NO \cdot C_2H_2O_4 \cdot 0.5H_2O$): C, H, N.

4-[2-[Bis-(4-fluorophenyl)methoxy]ethyl]-1-(3,4-dihydronaphthalen-2-ylmethyl)-piperidine Oxalate (21). Compound **21** was prepared in 64% yield using the procedure described for **13** from **4** (1.5 g, 0.0047 mol, free base), 3,4-dihydro-2-naphthoic acid (0.8 g, 0.0047 mol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI, 1.0 g, 0.002 mol). The crude oil was dissolved in Et_2O, and an excess of oxalic acid was added. The precipitate was collected and recrystallized from 2-propanol to afford **21** as colorless crystals: mp 157−161 °C; ^{1}H NMR (DMSO-d_6): δ 7.0−7.4 (m, 12H), 6.6 (s, 1H, olefinic), 5.5 (s, 1H, CH−O); MS *m*/*z* (CI): 474.4 $[M + 1]^+$. Anal. ($C_{31}H_{33}NOF_2 \cdot C_2H_2O_4 \cdot 0.5H_2O$): C, H, N.

***trans*-(*R*,*R*)-4-[2-[Bis-(4-fluorophenyl)methoxy]ethyl]-1-(2-phenyl-cyclopropylmethyl)-piperidine Oxalate (22).** Compound **22** was prepared in 92% yield using the procedure described for **13**, with (*R*,*R*)-*trans*-2-phenylcyclopropanecarboxylic acid: mp 129−130 °C; $[\alpha]_D^{20}$ −42.2 (*c* 1.01, MeOH); ^{1}H NMR (DMSO-d_6): δ 7.1−7.4 (m, 13H), 5.5 (s, 1H, CH−O); MS *m*/*z* (CI): 462 $[M + 1]^+$. Anal. ($C_{30}H_{33}F_2NO \cdot C_2H_2O_4 \cdot 0.25H_2O$): C, H, N.

***trans*-(*S*,*S*)-4-[2-[Bis-(4-fluorophenyl)methoxy]ethyl]-1-(2-phenyl-cyclopropylmethyl)-piperidine Oxalate (23).** Compound **23** was prepared in 93% yield using the procedure described for **13** with (*S*,*S*)-*trans*-2-phenylcyclopropanecarboxylic acid: mp 123−126 °C; $[\alpha]_D^{20}$ +39.03 (*c* 1.03, MeOH); ^{1}H NMR (DMSO-d_6): δ 7.1−7.4 (m, 13H), 5.5 (s, 1H, CH−O); MS *m*/*z* (CI): 462 $[M + 1]^+$. Anal. ($C_{30}H_{33}F_2NO \cdot C_2H_2O_4$): C, H, N.

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Supporting Information Available: Table of elemental analyses for purified products described in this article. This material is available free of charge via the Internet at http://pubs.acs.org.

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