Design and Synthesis of 2- and 3-Substituted-3-phenylpropyl Analogs of 1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine and 1-[2-(Diphenylmethoxy)ethyl]-4-(3-phenylpropyl)piperazine: Role of Amino, Fluoro, Hydroxyl, Methoxyl, Methyl, Methylene, and Oxo Substituents on Affinity for the Dopamine and Serotonin Transporters

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Novel derivatives of 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine (GBR 12909, **1**) and 1-[2-(diphenylmethoxy)ethyl]-4-(3-phenylpropyl)piperazine (GBR 12935, **2**) with various substituents in positions C2 and C3 of the phenylpropyl side chain were synthesized and evaluated for their ability to bind to the dopamine transporter (DAT) and the serotonin transporter (SERT). In the C2 series, the substituent in the *S*-configuration, with a lone-pair of electrons, significantly enhanced the affinity for DAT, whereas the steric effect of the substituent was detrimental to DAT binding affinity. In the C3 series, neither the lone electron pair nor the steric effect of the substituent seemed to affect DAT binding affinity, while sp^2 hybridized substituents had a detrimental effect on affinity for DAT. In the series, the 2-fluoro-substituted (*S*)-**10** had the highest DAT binding affinity and good DAT selectivity, while the 2-amino-substituted (*R*)-**8** showed essentially the same affinity for DAT and SERT. The oxygenated **16** and **18** possessed the best selectivity for DAT.

Introduction

Cocaine has caused many public health and societal problems[1,2] because of its extensive abuse in many countries throughout the world, exacerbating the spread of HIV-1[3,4] and hepatitis B and C, as well as drug-resistant tuberculosis.[5] Cocaine is known to block the reuptake of several neurotransmitters in the central nervous system, such as dopamine (DA[a]), serotonin (5-HT), and norepinephrine (NE), by interacting with the dopamine transporter (DAT), serotonin transporter (SERT), and norepinephrine transporter (NET) sites, respectively. Abundant studies have indicated that the reinforcing, locomotor-stimulating, and dependence-producing properties of cocaine are mainly mediated by the binding of cocaine to the DAT and subsequent blockade of DA reuptake into presynaptic terminals resulting in increased neurotransmission in the mesolimbic dopaminergic system.[6–12] Therefore, DAT has been considered to be the main target to reduce the effects of cocaine, and DAT ligands with high potency and selectivity have been sought as potential therapeutic agents for cocaine abuse.[13]

Recently, SERT and NET have also been thought to play prominent roles in cocaine addiction.[14–24] Cocaine binds to DAT and SERT with moderate affinity (K_i = 341 and 129 nM, respectively)[15] and blocks the reuptake of [^{3}H]DA and [^{3}H]5-HT (IC_{50} = 478 and 304 nM, respectively).[12,18] In behavioral intervention and knockout mice experiments, the serotonergic system has been found to influence the reinforcing effects of cocaine.[14,25–27] In contrast to the extensive structure–activity relationship (SAR) studies for DAT-selective ligands, fewer SAR studies have been focused on the discovery and development of ligands with a variety of transporter selectivity for both DAT and SERT.[14,28–31] Novel ligands that differ in their transporter affinity and SERT/DAT ratio may help reveal the pharmacological mechanisms relevant to stimulant abuse and also lead to a high efficacy medication for cocaine abuse, with few adverse reactions. Such a medication may also reduce the incidence of HIV infection.[32]

Our research has focused on the discovery of novel analogs of 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine (GBR 12909, **1**) and 1-[2-(diphenylmethoxy)ethyl]-4-(3-phenylpropyl)piperazine (GBR12935, **2**;[33] Chart 1). In an effort to develop long-acting cocaine abuse therapeutic agents, Lewis et al. prepared a series of oxygenated analogs of **1** and **2** and found that a racemic 3-hydroxyl-3-phenyl analog ((±)-**3**) of **1** exhibited a pharmacological profile similar to that of **1**.[34] Later, the decanoate ester of (±)-**3**, prodrug (±)-**4**, was synthesized and formulated as a depot preparation. One dose of (±)-**4** successfully suppressed cocaine-maintained responding in rhesus monkeys without affecting food intake for nearly 30 days.[35] Our continued studies on the SAR of the hydroxyl-containing analogs of **1** and **2** have shown that the *S*- and

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[a] Abbreviations: DA, dopamine; 5-HT, serotonin; NE, norepinephrine; DAT, dopamine transporter; SERT, serotonin transporter; NET, norepinephrine transporter; EDCI, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride; DIPEA, *N*,*N*-diisopropylethylamine.

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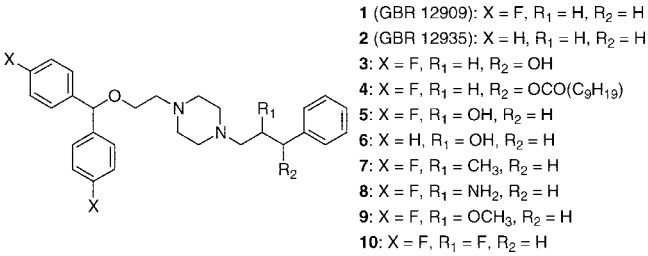
Chart 1



1 (GBR 12909): X = F, R_1 = H, R_2 = H
2 (GBR 12935): X = H, R_1 = H, R_2 = H
3: X = F, R_1 = H, R_2 = OH
4: X = F, R_1 = H, R_2 = OCO(C_9H_{19})
5: X = F, R_1 = OH, R_2 = H
6: X = H, R_1 = OH, R_2 = H
7: X = F, R_1 = CH_3, R_2 = H
8: X = F, R_1 = NH_2, R_2 = H
9: X = F, R_1 = OCH_3, R_2 = H
10: X = F, R_1 = F, R_2 = H

Table 1. Binding Affinities ($K_i \pm$ SD)[a] at the DAT and SERT and K_i Ratios of 2- and 3-Substituted Analogs of **1** and **2**

	binding affinity, K_i (nM)		
no.	DAT	SERT	SERT/DAT ratio
1	3.7 ± 0.4	130 ± 5	35
2	3.7 ± 0.3	620 ± 10	168
(*S*)-**3**	4.4 ± 0.5	135 ± 5	31
(*R*)-**3**	3.0 ± 0.3	85 ± 3	28
(*S*)-**5**	0.75 ± 0.03	230 ± 7	307
(*R*)-**5**	12 ± 1	160 ± 4	13
(*S*)-**6**	2.3 ± 0.07	2200 ± 80	957
(*R*)-**6**	25 ± 0.7	1800 ± 90	72
(+)-**7**	17 ± 1	120 ± 3	7
(−)-**7**	17 ± 1	190 ± 8	11
(*S*)-**8**	39 ± 2	88 ± 5	2
(*R*)-**8**	20 ± 1	22 ± 1	1
(*S*)- **9**	29 ± 3	220 ± 10	8
(*R*)- **9**	27 ± 1	250 ± 20	9
(*S*)-**10**	2.7 ± 0.2	290 ± 10	109
(*R*)-**10**	22 ± 1	540 ± 20	25
11	48 ± 2	220 ± 6	5
12	210 ± 4	1300 ± 30	6
13	18 ± 0.9	190 ± 30	11
14	30 ± 2	1800 ± 180	59
15	4.0 ± 0.4	150 ± 7	39
16	7.0 ± 0.6	1800 ± 60	254
17	6.5 ± 0.4	250 ± 8	38
18	10 ± 1	2500 ± 90	250
19	100 ± 7	430 ± 20	4
20	410 ± 60	3300 ± 160	8
21	57 ± 3	310 ± 30	6
22	150 ± 4	2000 ± 110	14
23	54 ± 6	88 ± 3	2
24	450 ± 50	1400 ± 50	3
(*S*)-**32**	140 ± 4	110 ± 3	0.8
(*R*)-**32**	110 ± 4	190 ± 7	2
38	8.0 ± 0.4	36 ± 2	5

[a] The K_i values of the test ligands were determined in the above assays as described in Biological Methods.

R-enantiomers of the 2-hydroxylated derivatives (e.g., (*S*)-**5** and (*R*)-**5**) possessed quite different pharmacological profiles,[36,37] whereas the 3-hydroxylated enantiomers (e.g., (*S*)-**3** and (*R*)-**3**) displayed very similar biological activities.[34] In the 2-hydroxyl series, the *S*-isomers demonstrated substantially higher affinity for the DAT and were more potent DA reuptake inhibitors than the corresponding *R*-isomers, whereas the *R*-isomers showed higher affinity for the SERT and were more potent in inhibiting the reuptake of 5-HT than the *S*-isomers.[36,37] The alcohols (*S*)-**5** and (*S*)-**6** are among the most potent and selective DAT ligands yet known (Table 1).

Based on these observations that the pharmacological profiles (including DAT and SERT binding affinities, transporter selectivity, and enantioselectivity) could be dramatically changed by minor structural modifications at the 2- and 3-positions of the 3-phenylpropyl side chain of **1** and **2**, we undertook the design and synthesis of novel 2- and 3-substituted analogs of **1** and **2** to more definitively determine the SAR of the 2- and 3-substituted-3-phenylpropyl derivatives of **1** and **2**. This information could help us identify the steric and electronic effects of the 2- and 3-substitutions in analogs of **1** and **2** involved in the binding interaction with DAT and SERT, and may lead to the discovery of novel high-affinity DAT ligands possessing a range of affinities for SERT.

Herein, we report the synthesis and SAR of optically pure 2-substituted-3-phenylpropyl derivatives **7**−**10**, 3-substituted-3-phenylpropyl analogs **13**−**16**, and 2-substituted-3-phenylpropyl derivatives **17**−**22** of **1** and **2** with amino, fluoro, hydroxyl, methoxyl, methyl, methylene, and oxo substituents at the 2- or 3-position of the 3-phenylpropyl moiety (Chart 2). The roles of the 2- and 3-substituents in these transporter ligands on their affinity and selectivity for DAT and SERT are discussed.

Chemistry

The monosubstituted piperazines, 1-[2-[bis(4-fluorophenyl)-methoxy]ethyl]piperazine (**25**) and 1-[2-(diphenylmethoxy)ethyl]piperazine (**26**; Chart 2) were synthesized in two steps according to the literature,[33] with modification.[36] The 2-methyl-, 2-amino-, and 2-methoxy-substituted analogs of **1** were prepared via similar reaction sequences, in which **25** was coupled with an appropriate acid using *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDCI) followed by reduction with a suitable aluminum hydride (Scheme 1).

Coupling of (±)-2-methyl-3-phenylpropionic acid and **25** provided amide (±)- **27**. Compound (±)-**7** was synthesized by reduction of (±)-**27** with $LiAlH_4$. Optically pure (+)-**7** and (−)-**7** were then prepared from (±)-**7** using semipreparative chiral high-performance liquid chromatography (HPLC) followed by recrystallization of their maleate salts.

N-tert-butyloxycarbonyl (Boc)-protected (*S*)-**29** and (*R*)-**29** were prepared starting from commercially available *N*-Boc-protected L- and D-phenylalanines, respectively. EDCI coupling followed by reduction with diisobutylaluminum hydride (DIBALH) yielded (*S*)-**29** and (*R*)-**29** retaining high ee values. Removing the Boc protective groups of (*S*)-**29** and (*R*)-**29** using hydrogen chloride afforded (*S*)-**8** and (*R*)-**8**, respectively.

The optically pure synthons (*S*)-2-methoxy-3-phenylpropanoic acid ((*S*)-**30**) and (*R*)-2-methoxy-3-phenylpropanoic acid ((*R*)-**30**) for the preparation of (*S*)-**31** and (*R*)-**31** were synthesized from L- and D-3-phenyllactic acids, respectively, by selective methylation of the aliphatic hydroxyl groups using an excess amount of NaH in tetrahydrofuran (THF). Alane reduction of (*S*)-**31** and (*R*)-**31** gave (*S*)-**9** and (*R*)-**9**, respectively.

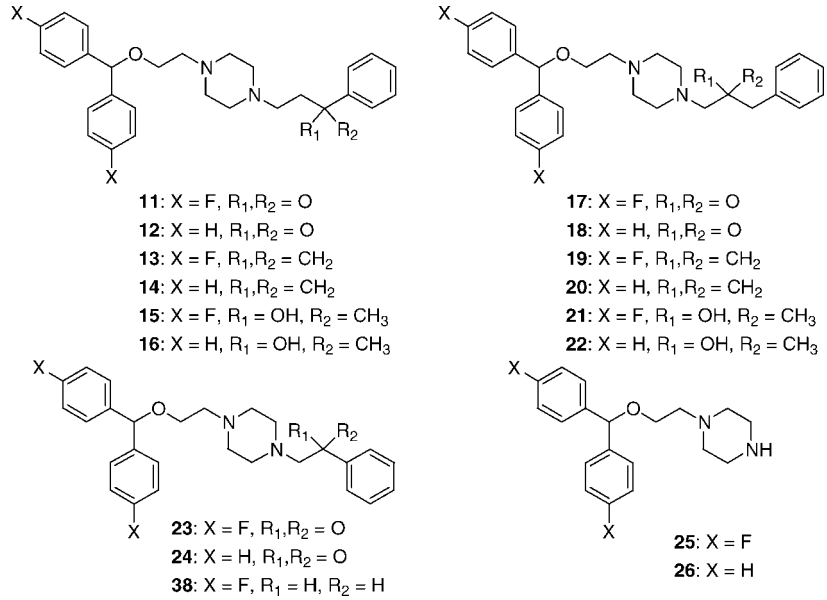
Treatment of enantiomerically pure 2-hydroxyl-substituted (*S*)-**5** and (*R*)-**5**[36] with (diethylamino)sulfur trifluoride (DAST) produced desired 2-fluoro-substituted (*R*)-**10** and (*S*)-**10** and rearranged products (*R*)-**32** and (*S*)-**32**, respectively, in a ratio of 5:3 (Scheme 2). The possible mechanism for this unexpected result is shown in Chart 3. Reaction of (*S*)-**5** with DAST yielded intermediate (*S*)-**I** and hydrogen fluoride (HF). The basic nitrogen atom could be protonated by HF to form (*S*)-**II**, which would be attacked by fluoride ion to provide (*R*)-**10**. On the other hand, the aziridinium intermediate (*S*)-**III** could be formed by anchimeric assistance of the unprotonated nitrogen atom of (*S*)-**I**. Nucleophilic substitution of fluoride ion at the less hindered position of (*S*)-**III** yielded (*R*)-**32**. If the fluoride ion was able to overcome the steric effect to attack the more hindered position of (*S*)-**III**, (*S*)-**10** would be formed and, thus, the ee value of (*R*)-**10** would be substantially reduced. Because both the isolated (*R*)-**10** and (*R*)-**32** showed very high optical purity, the nucleophilic substitution of (*S*)-**III** by fluoride ion was highly regioselective. The ee values of chiral compounds **7**−**10** and **32** were determined by analytical chiral HPLC and were above 98%.

Table 2. Physical Properties

cmpd	empirical formula	mp, °C	$[\alpha]_D^{20}$, deg (solvent)	yield, %[a]
(+)-**7**	$C_{29}H_{34}F_2N_2O \cdot 2C_4H_4O_4$	185–186	+2.3(DMF)	42 (from **27**)
(−)-**7**	$C_{29}H_{34}F_2N_2O \cdot 2C_4H_4O_4$	185–186	−2.5(DMF)	42 (from **27**)
(*S*)-**8**	$C_{28}H_{33}F_2N_3O$	oil	ND[b]	88
(*R*)-**8**	$C_{28}H_{33}F_2N_3O$	oil	ND[b]	91
(*S*)-**9**	$C_{29}H_{34}F_2N_2O_2 \cdot 2C_4H_4O_4$	187–188	+5.4(DMF)	77
(*R*)-**9**	$C_{29}H_{34}F_2N_2O_2 \cdot 2C_4H_4O_4$	187–188	–5.2 (DMF)	94
(*S*)- **10**	$C_{28}H_{31}F_3N_2O \cdot 2C_4H_4O_4$	181–182	+1.0(DMF)	25
(*R*)-**10**	$C_{28}H_{31}F_3N_2O \cdot 2C_4H_4O_4$	180–181	−1.2(DMF)	28
13	$C_{29}H_{32}F_2N_2O \cdot 2C_4H_4O_4$	164–166		52
14	$C_{29}H_{34}N_2O \cdot 2C_4H_4O_4$	168–170		42
15	$C_{29}H_{34}F_2N_2O_2 \cdot 2C_4H_4O_4$	181–182		54
16	$C_{29}H_{36}N_2O_2 \cdot 2C_4H_4O_4$	174–175		25
17	$C_{28}H_{30}F_2N_2O_2 \cdot 2C_4H_4O_4$	166–167		86
18	$C_{28}H_{32}N_2O_2 \cdot 2C_4H_4O_4$	164–165		77
19	$C_{29}H_{32}F_2N_2O \cdot 2C_4H_4O_4$	182–183		70
20	$C_{29}H_{34}N_2O \cdot 2C_4H_4O_4$	186–187		71
21	$C_{29}H_{34}F_2N_2O_2 \cdot 2C_4H_4O_4$	184–185		32
22	$C_{29}H_{36}N_2O_2 \cdot 2C_4H_4O_4$	177–178		75
23	$C_{27}H_{28}F_2N_2O_2 \cdot 2C_4H_4O_4$	176–177		91
24	$C_{27}H_{30}N_2O_2 \cdot 2C_4H_4O_4$	178–179		86
(*S*)-**32**	$C_{28}H_{31}F_3N_2O \cdot 2C_4H_4O_4$	145–146	−17 (DMF)	15
(*R*)-**32**	$C_{28}H_{31}F_3N_2O \cdot 2C_4H_4O_4$	147–148	+15 (DMF)	18

[a] No attempt was made to optimize yields. [b] ND: not determined.

Chart 2



3-Methylene and 3-methyl-3-hydroxyl derivatives of **1** and **2** were synthesized from 3-oxo-substituted **11** and **12**[34] (Scheme 3). Accelerated Wittig-type olefination of **11** and **12** with the $CH_2I_2-TiCl_4-Zn-PbCl_2$ system[38] provided **13** and **14** in moderate yields. Tertiary alcohols **15** and **16** were prepared via Grignard reaction of **11** and **12**, respectively, with methylmagnesium bromide.

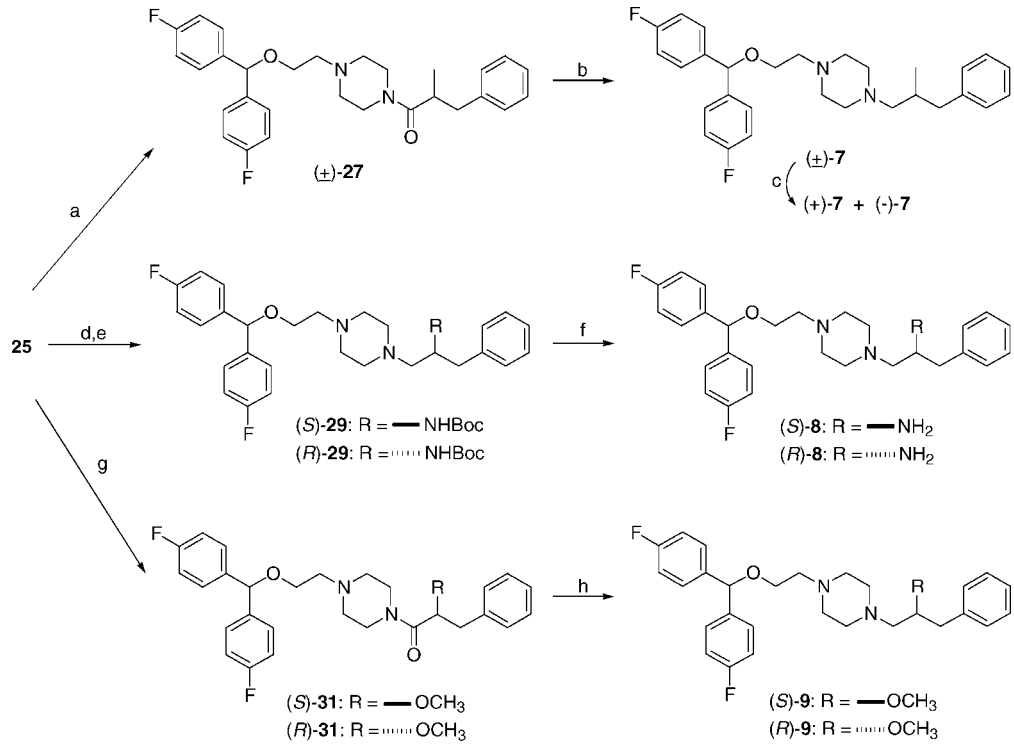
Treatment of **5** and **6**[36] under Swern oxidation conditions afforded 2-oxo-substituted **17** and **18**, as depicted in Scheme 4. Initial attempts to synthesize the 2-methylene analogs **19** and **20** and the 2-methyl-2-hydroxyl derivatives **21** and **22**, following the same reaction conditions for the preparation of the corresponding 3-substituted analogs, failed. We recognized that the 3-positions of ketones **17** and **18** were located between the phenyl and carbonyl functionalities and, therefore, the increased acidity of these positions was detrimental to both the Wittig-type olefination and Grignard reaction. Thus, alternative routes were sought in which the 2-methylene and 2-methyl-2-hydroxyl substitutions were introduced in earlier stages.

Coupling of 2-benzyl-acrylic acid[39,40] with **25** and **26** yielded amides **33** and **34**, respectively (Scheme 5). The 2-methylene analogs **19** and **20** were then produced by reduction of **33** and **34** with alane. *N*-Alkylation of **25** and **26** with 1-chloro-2-methyl-3-phenyl-2-propanol[41] (**35**), using K_2CO_3 and NaI,[34] afforded the desired tertiary alcohols **21** and **22**, respectively. Acetophenones **23**[42] and **24** were prepared in high yields by heating 2-bromoacetophenone with **25** and **26**, respectively, in the presence of diisopropylethylamine (DIPEA) in *N*,*N*-dimethylformamide (DMF).

Results and Discussion

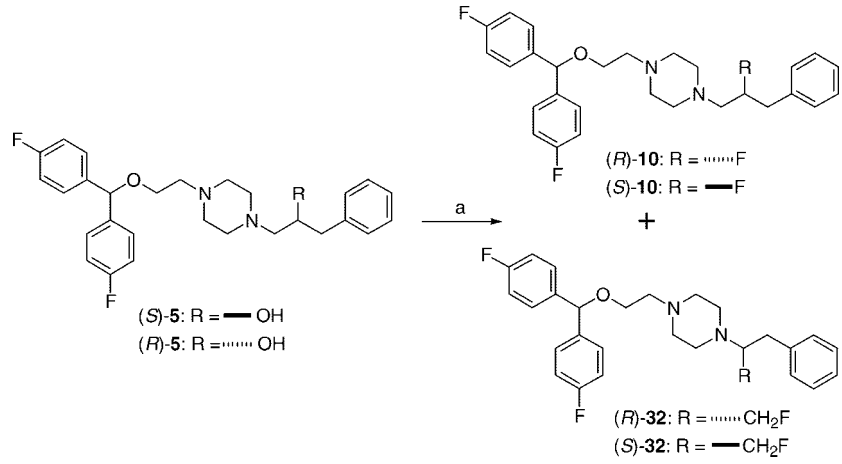
Previous data suggested that the 2-substituted (*S*)-**5** and (*R*)-**5** demonstrated enantioselectivity in DAT and SERT binding, while the corresponding 3-substituted (*S*)-**3** and (*R*)-**3** showed no difference in transporter binding.[34,36] Therefore, the binding affinities of **7**–**10**, the analogs of **5**, for DAT and SERT were determined to investigate the steric and electronic effects of

Scheme 1[a]



[a] Reagents and conditions: (a) (±)-2-methyl-3-phenylpropionic acid, EDCI, CH_2Cl_2, rt; (b) $LiAlH_4$, THF, rt; (c) semipreparative chiral HPLC; (d) *N*-*t*-Boc-L-phenylalanine or *N*-*t*-Boc-D-phenylalanine, EDCI, CH_2Cl_2, rt; (e) DIBAL-H, THF, rt; (f) HCl, MeOH, rt; (g) (*S*)-**30** or (*R*)-**30**, EDCI, CH_2Cl_2, rt; (h) AlH_3, THF, rt.

Scheme 2[a]



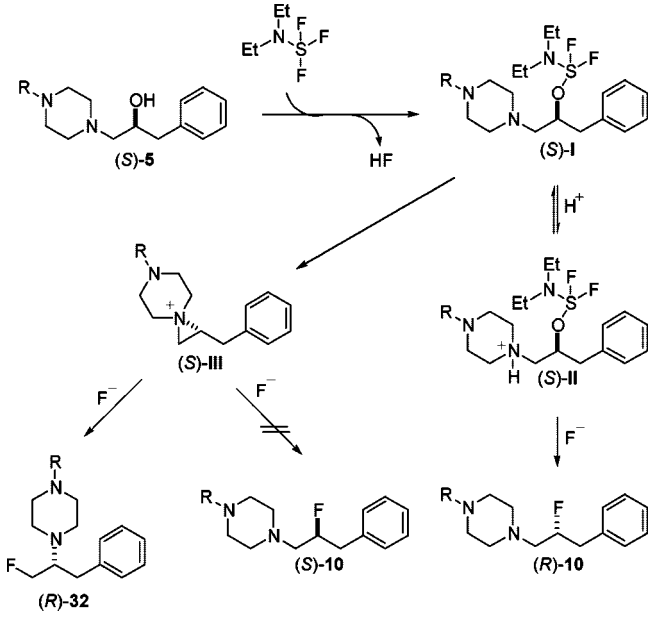
[a] Reagents and conditions: (a) (diethylamino)sulfur trifluoride, CH_2Cl_2, −78 °C−rt.

structural modifications in the 2-position of the phenylpropyl side chain of **1**.

The 2-methyl-substituted analogs (+)-**7** and (−)-**7** had less affinity than **1**, (*S*)-**5**, and (*R*)-**5** in DAT binding, while showing similar SERT affinity as **1** and (*R*)-**5** (Table 1). Curiously, there was no meaningful difference in transporter binding affinities between the two enantiomers (+)-**7** and (−)-**7**. Furthermore, the pharmacological profiles of (+)-**7** and (−)-**7** were quite similar to that of 2-hydroxyl-substituted (*R*)-**5**. To determine whether the 2-hydroxyl group of (*S*)-**5** played an essential role in affinity and selectivity to DAT, the 2-amino-substituted analogs (*S*)-**8** and (*R*)-**8** and 2-methoxy-substituted analogs (*S*)-**9** and (*R*)-**9** were studied. The DAT binding affinities of (*S*)-**8**, (*S*)-**9**, (*R*)-**8**, and (*R*)-**9** were in the range of 20–39 nM, which were lower than that of **1**, (*S*)-**5**, and (*R*)-**5**. Interestingly, the 2-amino-substitution significantly enhanced the binding affinity for SERT. Compound (*R*)-**8** was the most potent SERT ligand in the series and showed approximately the same affinity for DAT and SERT (K_i = 20 and 22 nM, respectively). Hence, (*R*)-**8** may be a potential lead for the development of dual-action transporter ligands.

Methylation of the 2-hydroxyl group not only decreased DAT binding affinity, but also abolished the enantioselectivity of (*S*)-**5** and (*R*)-**5**. The transporter binding patterns of 2-methoxy-substituted analogs (*S*)-**9** and (*R*)-**9** were very similar to that of 2-methyl-substituted analogs (*S*)-**7** and (*R*)-**7**, which implied that the methyl group has an adverse steric effect in DAT binding. To study the role of the lone electron pairs of oxygen in the hydroxyl group of (*S*)-**5** without the interference of steric effects, as in the case of **9**, 2-fluoro-substituted analogs (*S*)-**10** and (*R*)-

Chart 3



10, were examined. In comparison with **1**, (*S*)-**10** showed increased DAT binding affinity and decreased SERT binding affinity and, therefore, much higher DAT selectivity (SERT/DAT ratio = 109). Compound (*S*)-**10** was the most potent DAT ligand (K_i = 2.7 nM)) in this study. On the other hand, (*R*)-**10** showed significantly lower DAT binding affinity and selectivity versus SERT than (*S*)-**10**. Thus, the 2-fluoro-substituted analogs (*S*)-**10** and (*R*)-**10** demonstrated the highest enantioselectivity among this novel series of 2-substituted analogs of **1** and possessed similar pharmacological profiles as that of 2-hydroxyl-substituted analogs (*S*)-**5** and (*R*)-**5**.

The diverse transporter binding affinities, SERT/DAT ratios, and enantioselectivity of these 2-substituted analogs of **1** allowed us to identify the steric and electronic effects of the 2-substituent on the binding interaction to transporters. In previous SAR studies, **36**, a conformational-constrained analog of **1** (Chart 4), demonstrated higher DAT affinity than **1**.[34] Under physiological conditions, the N4-nitrogen atom in piperazine should be protonated. Therefore, the conformer **C-1** with an extended zigzag phenylpropyl side chain might be the active conformation of **1** for DAT binding (Chart 4). A similar conformationally constrained analog of **1**, **37**, in which the potential high-affinity conformer **C-37** was unlikely to be as stable as **C-1** due to the additional steric repulsion, did demonstrate slightly lower DAT and SERT affinities than **1**.[32]

The hydroxyl groups in (*S*)-**5** and (*R*)-**5** could act as a hydrogen bond donor or a hydrogen bond acceptor. The pharmacological similarity between the fluoro- and hydroxyl-substituted analogs led us to hypothesize that its action as a hydrogen bond acceptor played a critical role in the enantioselectivity. As shown in Chart 5, when the oxygen lone pairs in (*S*)-**5** and (*R*)-**5** formed hydrogen bonds with the N4-ammonium groups, conformationally constrained conformers **C-S5** and **C-R5** would be the favorable conformers of (*S*)-**5** and (*R*)-**5**, respectively. As a result, the phenyl ring in (*S*)-**5** and (*R*)-**5** would be forced into opposite directions in space. The position of the phenyl group in **C-1** was between the likely positions of the phenyl groups in **C-S5** and **C-R5**, and this could explain why the DAT affinity of **1** was between that of (*S*)-**5** and (*R*)-**5**. On the other hand, **C-S3-1** could be the corresponding cyclic conformer of (*S*)-**3**. However, the six-membered ring conformation of **C-S3-1** might not be as stable as the five-membered ring conformation of **C-S5** and, therefore, other conformers, such as **C-S3-2**, with an extended zigzag side chain similar to **C-1**, might be the major conformer of (*S*)-**3**. This hypothesis could explain why the transporter binding profiles of **1**, (*S*)-**3**, and (*R*)-**3** were approximately the same. Thus, a proper configuration of substituents with an available lone-pair of electrons, such as 2-(*S*)-OH and 2-(*S*)-F, which would allow the DAT-binding favorable conformer to be stabilized by their electronic effects, was the most critical factor causing the observed increase in DAT affinity. However, these steric and electronic effects did not promote high SERT affinity. Therefore, (*S*)-**5** and (*S*)-**10** are among the most DAT selective ligands that have been found.

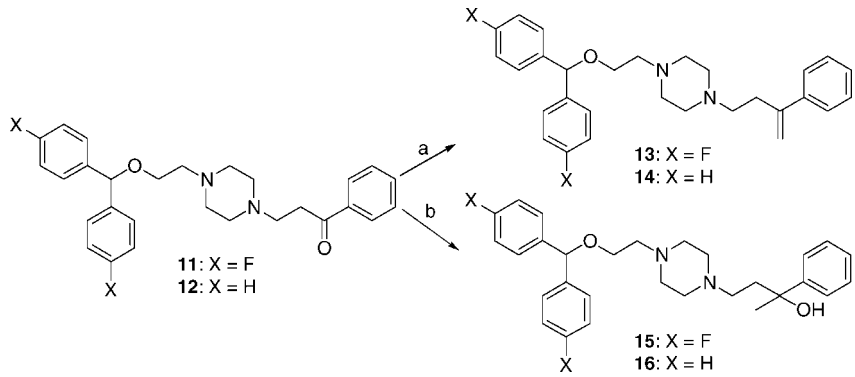
Initially, we thought the 2-amino group would be a strong electron-donating group and, therefore, may result in analogs with high DAT affinity and selectivity. In contrast to the 2-fluoro and 2-hydroxyl analogs, the 2-amino-substituted analogs (*S*)-**8** and (*R*)-**8** had only moderate affinity for DAT. Because the nitrogen lone-pair of electrons in the 2-amino groups of (*S*)-**8** and (*R*)-**8** were protonated under physiological conditions, there was no available electron lone pair to be able to act as a hydrogen bond acceptor. Actually, the protonated 2-ammonium group would be more likely to act as a hydrogen bond donor. Furthermore, the potential electrostatic and steric repulsion between the two cationic N4- and 2-ammonium groups (Chart 5) could substantially destabilize the *syn*-conformers **C-S8-1** and **C-R8-1** and, therefore, force (*S*)-**8** and (*R*)-**8** to adopt other more stable conformations, such as **C-S8-2** and **C-R8-2**, which were significantly different from our postulated conformers with high DAT affinity (e.g., **C-1** and **C-S5**) in this series. Thus, the quite different conformation of **C-R8-2** might be responsible for the high affinity of (*R*)-**8** for SERT. Interestingly, the phenyl groups in **C-S5** and **C-R8-2** were in the same spatial areas, while the phenyl groups in both **C-R5** and **C-S8-2** were in different spatial areas. This observation could help explain why the (*R*)-**8** had higher DAT binding affinity than (*S*)-**8** and the 2-amino-substituted analogs (*S*)-**8** and (*R*)-**8** demonstrated enantioselectivity in both DAT and SERT binding affinities.

Because the 2-fluoro-substituent was not a hydrogen bond donor and 2-fluoro-substituted analogs possessed similar pharmacological profiles as 2-hydroxy-substituted analogs, the ability of the substituent to act as a hydrogen bond donor did not appear to be essential to enantioselectivity. Thus, the lack of enantioselectivity of the 2-methoxy-substituent (*S*)-**9** and (*R*)-**9** could not be ascribed to its inability to act as a hydrogen bond donor, but might be caused by the steric effect of the additional methyl group. Hence, the presence of a small substituent with an available electron lone-pair in a compound with the 2*S* configuration is likely to promote DAT binding affinity. Further work should focus on the influence of steric and electronic effects on transporter binding affinity by the introduction of relatively less hindered sp^2 hybridized oxo and methylene functionalities into **1** and **2**.

Previously, Lewis et al. reported the synthesis and monoamine transporter affinities of 3-oxo-substituted **11** and **12**.[34] In contrast to the unsubstituted **1** and **2**, and 3-hydroxylated (*S*)-**3** and (*R*)-**3**, **11** and **12** demonstrated much lower DAT binding affinity and selectivity. This might be explained by the tendency of the 3-carbonyl group to conjugate with the aromatic phenyl ring, restricting the conformational flexibility of the phenyl group that might be essential for interaction with DAT.

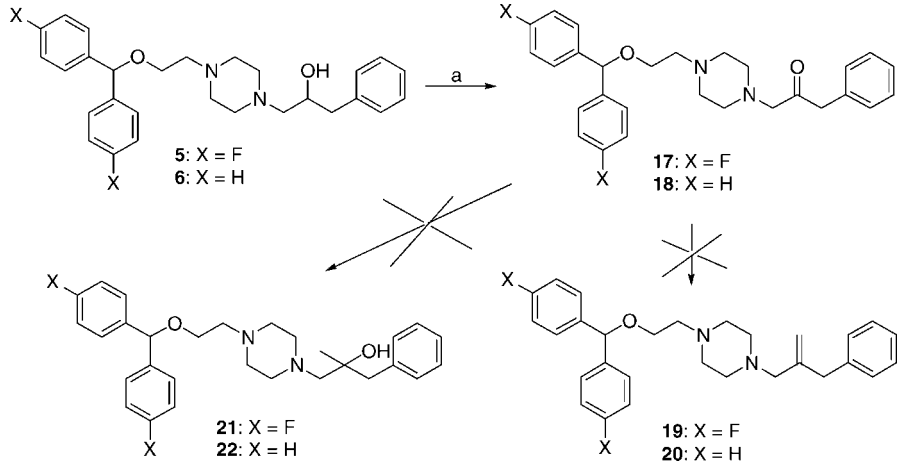
Therefore, the 3-methylene-substituted **13** and **14** and 3-methyl-3-hydroxyl-substituted **15**[42] and **16** were prepared

Scheme 3[a]



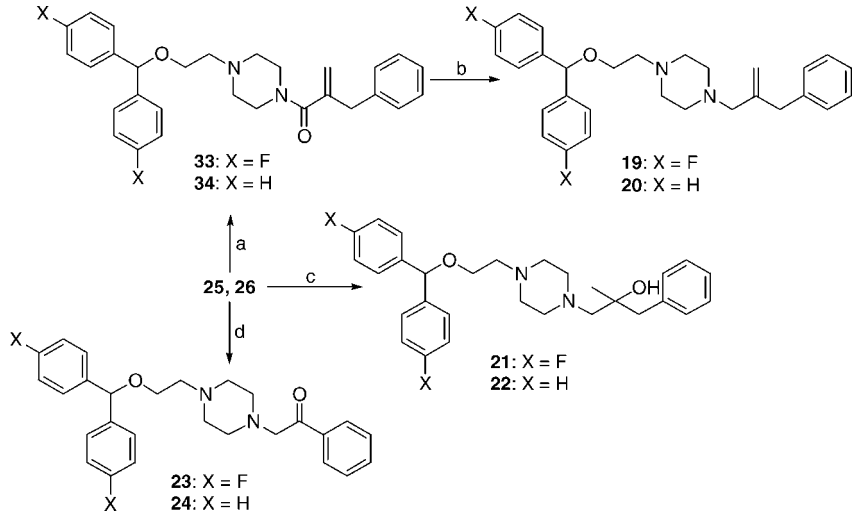
[a] Reagents and conditions: (a) CH_2I_2, Zn, $PbCl_2$, $TiCl_4$, THF, rt; (b) CH_3MgBr, THF, rt.

Scheme 4[a]



[a] Reagents and conditions: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60 °C−rt.

Scheme 5[a]



[a] Reagents and conditions: (a) 2-benzyl-acrylic acid, EDCI, CH_2Cl_2, 0 °C−rt; (b) AlH_3, THF, rt; (c) **35**, NaI, K_2CO_3, DMF, 70−80 °C; (d) 2-bromoacetophenone, DIPEA, DMF, 60 °C.

to explore the "conjugation hypothesis". In terms of interaction with DAT, **13** and **14** had higher affinity than **11** and **12**, but less affinity than **1** and **2**. Although the sp^2 hybridized 3-methylene group in **13** and **14** might also be able to conjugate with the phenyl group, the steric interaction between the hydrogen atoms at the vinyl position and *ortho*-position of the phenyl ring would tend to reduce the activation energy for rotation of the phenyl group (Chart 6). The resultant weaker conjugation resulted in higher DAT binding affinity. The 3-methyl-3-hydroxyl-substituted analogs, **15** and **16**, with quaternary carbon atoms at C3, had almost the same binding affinity as **1** and **2** for DAT and demonstrated greater DAT/SERT selectivity than **1** and **2**. These data indicate that a sp^3 hybridized 3-position is important for high DAT binding

Chart 4

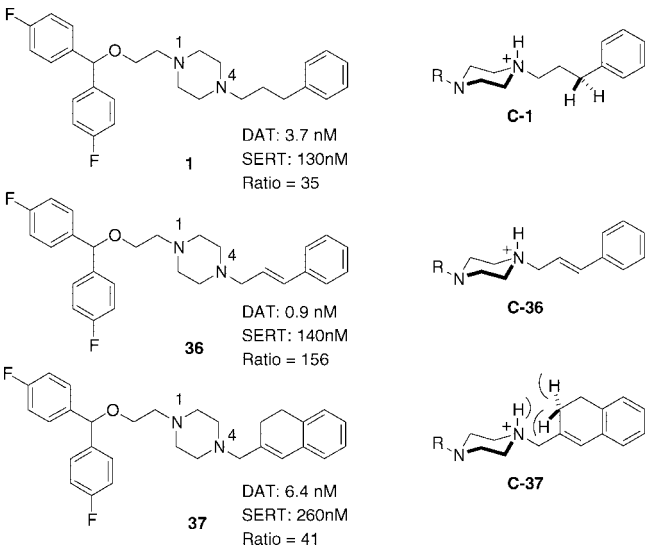
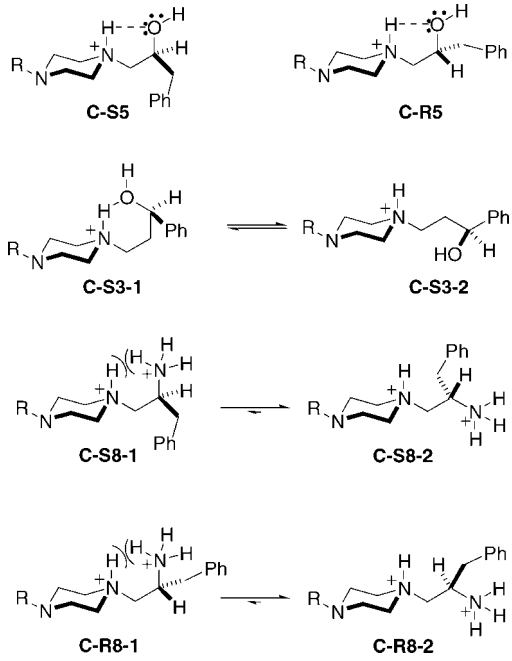


Chart 5

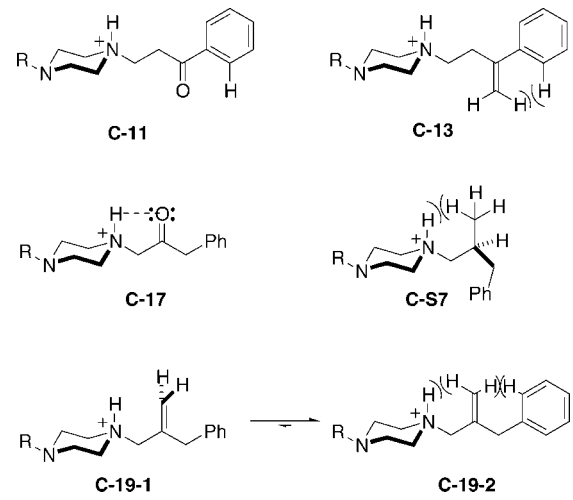


affinity, and the DAT and SERT binding affinities of **1** and **2** are not affected very much by the additional substituent at the 3-position.

In contrast to the 3-oxo-substituted compounds **11** and **12**, which had weak affinity and low selectivity for DAT, the 2-oxo-substituted **17**[42] and **18** showed high DAT binding affinity, and demonstrated higher SERT/DAT ratios than **1** and **2**. The DAT affinity and selectivity of **17** and **18** were higher than that of (*R*)-**5** and (*R*)-**6** and lower than that of (*S*)-**5** and (*S*)-**6**, respectively. Based on our hypothesis, the potential hydrogen bonding between the carbonyl lone-pair of electrons and ammonium groups of **17** and **18** would favor the formation of conformer **C-17**, which was very similar to **C-1** but likely to be more stable (Chart 6). As described earlier, **C-1**-like conformers were poorer SERT ligands, and in agreement with the hypothesis, the SERT binding affinities for **17** and **18** were lower than that of **1** and **2**.

The 2-methylene-substituted analogs **19** and **20**, were then synthesized to explore the electronic effect of the 2-oxo-

Chart 6



substitution and the steric effect of the 2-methyl group. Surprisingly, the DAT binding affinities of **19** and **20** were significantly reduced (27- and 110-fold, respectively) as compared to that of **1** and **2**. Initially, we thought **C-19-1**, which was one of the possible conformers of **19**, should possess less steric hindrance than **C-S7** (i.e., a conformer of (*S*)-**7**) and, therefore, has higher affinity for DAT than the 2-methyl-substituted **7** (Chart 6). However, rotation of the C═C bond to form conformer **C-19-1** is likely to be energetically unfavorable and, thus, **C-19-1** might not exist in a significant amount at room temperature. On the other hand, conformer **C-19-2** should be the more stable conformer of **19**. In the case of **C-19-2**, steric repulsion might occur between the vinyl hydrogen atoms and the proton of the protonated N4-ammonium group. Moreover, the vinyl hydrogen atoms could also interfere with the free rotation of the phenyl group by interaction with the hydrogen atoms at the *ortho*-positions of the phenyl ring. Therefore, high DAT affinity conformations, such as **C-1** and **C-S5**, could not readily be adopted by **19** and **20**. In the 3-phenylpropyl-substituted series, **19** and **20** had the lowest affinity for DAT in the bis(4-fluorophenyl)- and diphenyl-substituted analogs, respectively.

Our hypothesis was supported by the data obtained from the 2-methyl-2-hydroxyl-substituted compounds **21** and **22**. Compared to the 2-methylene-substituted analogs **19** and **20**, compounds **21** and **22**, with crowded tertiary 2-positions, possessed higher binding affinity for both DAT and SERT. Presumably, the postulated unfavorable steric repulsion in **C-19-2** was relieved. Furthermore, **21** demonstrated significantly weaker DAT binding affinity and slightly lower SERT binding affinity than 2-hydroxylated (*S*)-**5** and (*R*)-**5** and 2-methylated (*S*)-**7** and (*R*)-**7**. This indicates that the steric effect produced by additional substitution at the 2-position is more unfavorable to DAT binding affinity than to SERT binding affinity. However, the binding data of **15**, **16**, **21**, and **22** were determined using racemic samples. The possibility that the two enantiomers of these ligands possessed substantially different transporter binding affinities could not be ruled out.

The tremendous differences in DAT binding affinity for 2-oxo-substituted **17** and **18** and 3-oxo-substituted **11** and **12** led us to synthesize acetophenones **23**[42] and **24** in which the 2-oxo-substituents theoretically can conjugate with the phenyl group. Compounds **23** and **24** were similar to **11** and **12** in their weak DAT binding affinities, while the unsubstituted acetophenone **38**[36] (Chart 2) exhibited high binding affinity for DAT

(Table 1). These data further supported the hypothesis that conjugation with the phenyl ring reduces binding affinity for DAT. On the other hand, the 3-oxo-substituted **11** and **12**, 2-oxo-substituted **17** and **18**, and acetophenone **24** demonstrated a similar reduction (1.7∼4.0-fold) in SERT binding affinity as compared to their corresponding unsubstituted analogs.

Interestingly, in the preparation of chiral 2-fluoro-substituted analogs (*S*)-**10** and (*R*)-**10**, the rearranged products (*S*)-**32** and (*R*)-**32**, which could be viewed as 1-fluoromethyl-substituted analogs of **38**, were formed enantioselectively in significant amounts. In contrast to (*S*)-**10** and (*R*)-**10**, in which the chirality was critical to pharmacological activity, the 1-substituted (*S*)-**32** and (*R*)-**32** did not demonstrate meaningful enantioselectivity. Among the bis(4-fluorophenyl)-substituted analogs, (*S*)-**32** and (*R*)-**32** were the weakest DAT ligands. Nevertheless, (*S*)-**32** possessed higher SERT binding affinity than (*R*)-**32** and was the only SERT-selective ligand found in this study (SERT/DAT ratio = 0.8).

Conclusions

In this article, we report SAR studies focused on the 2- and 3-substituted analogs of **1** and **2**. Binding affinities for the DAT and SERT varied depending on the nature of the substituents in the C2- and C3-positions of the phenylpropyl side chain. Steric and electronic effects affected their affinity and selectivity for DAT and SERT. The 2-substituted series showed a quite different SAR than the 3-substituted series. In the C2 series, the substituent in the *S*-configuration with a lone-electron pair significantly enhanced ligand binding affinity for DAT, whereas the steric effect of the substituent was detrimental to DAT binding. In the C3 series, neither the lone-electron pair nor the steric effect of the substituent seemed to affect DAT binding affinity, while compounds with sp^2-hybridized substituents, possibly due to their lessened conformational mobility, had little affinity for DAT. 2-Oxo-substitution retained the DAT binding seen with their parent compound and slightly increased the SERT/DAT ratio, whereas 3-oxo-substitution was detrimental to the affinity and selectivity for DAT. The SERT binding affinity was insensitive to most of the structural modifications in this study, except for 2-amino-substitution, which caused substantially increased SERT binding affinity and selectivity over the DAT.

Novel derivatives with different transporter binding affinities and selectivities were discovered. 2-Fluoro-substituted analogs (*S*)-**10** and (*R*)-**10** displayed substantial enantioselectivity in their binding affinity for the DAT and SERT. Compound (*S*)-**10** had higher affinity and selectivity for DAT than (*R*)-**10**. In the series, (*S*)-**10** had the highest DAT binding affinity and exhibited excellent DAT selectivity over the SERT. Compounds (*R*)-**8** and (*S*)-**32** demonstrated approximately equal affinities for DAT and SERT (SERT/DAT ratio = 1 and 0.8, respectively). Furthermore, (*R*)-**8** demonstrated the highest SERT binding affinity in this series. Thus, the 2-amino-substituted (*R*)-**8** might be a lead compound for the discovery of potent and dual-action ligands able to simultaneously block the DAT and the SERT. As in the previous SAR studies, diphenyl-substituted analogs always showed higher SERT/DAT ratios than the corresponding bis(4-fluorophenyl)-substituted analogs. In the series, **16** and **18** were both oxygenated derivatives of **2** and possessed the highest selectivity for DAT (SERT/DAT ratio = 254 and 250, respectively).

Compounds with customized DAT and SERT binding profiles could be useful research tools to help determine the DAT/SERT ratio needed for the blockade of DAT and SERT that would be more beneficial as a medication for stimulant abuse than the blockade of DAT alone.[43] The affinities of these analogs for the DAT and SERT appeared to be controlled by their electronic and steric effects and by the position of the substituent. Identification of these effects should facilitate the discovery and development of novel ligands with desired monoamine transporter binding patterns, and these may prove to be more effective treatment agents for cocaine abuse with fewer adverse effects.

Experimental Section

Melting points were determined on a MEL-TEMP II apparatus by Laboratory Devices and are uncorrected. NMR spectra were recorded on Bruker DPX-200, Varian XL-300, and AMX-400 FT-NMR spectrometers. Chemical shifts are expressed in parts per million (ppm) on the δ scale relative to a tetramethylsilane (TMS) internal standard. Chemical ionization (CI) mass spectra were obtained using a Finnigan 1015 mass spectrometer. EI mass spectra and high-resolution mass measurements (HRMS) were obtained using a Finnigan MAT 95S mass spectrometer. Elemental analyses were performed with a Heraeus varioIII-NCSH instrument or by Atlantic Microlabs, Atlanta, GA, and were within ±0.4% for the elements indicated. Optical rotations were obtained using a Perkin-Elmer 341 polarimeter and are reported at the sodium D-line (589 nm), unless otherwise noted. Thin-layer chromatography (TLC) was performed on Merck (art. 5715) silica gel plates and visualized under UV light (254 nm), upon treatment with iodine vapor, or upon heating after treatment with 5% phosphomolybdic acid in ethanol. Flash column chromatography was performed with Merck (art. 9385) 40–63 μm silical gel 60. Anhydrous tetrahydrofuran was distilled from sodium-benzophenone prior to use. No attempt was made to optimize yields.

Determination of Enantiomeric Purity by Chiral HPLC Analysis. The free base of the sample was dissolved in 1% isopropanol (IPA) in *n*-hexane. Then the sample solution (10 μL) was eluted using 1–20% IPA in *n*-hexane in the presence of 0.2% diethylamine as mobile phase on the CHIRALCEL OD or AD column (250 × 4 mm, DAICEL). The ee values were calculated based on the UV absorption (254 nm) areas of the two enantiomers.

Synthetic Method A. 1-[4-[2-[Bis(4-fluorophenyl)methoxy]ethyl] piperazinyl]-2-methyl-3-phenylpropan-1-one ((±)-27). To a stirred solution of **25** (740 mg, 2.23 mmol) and (±)-2-methyl-3-phenylpropionic acid (366 mg, 2.23 mmol) in CH_2Cl_2 (10 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI; 469 mg, 2.45 mmol) at 0 °C and then stirred at rt for 1 h. The reaction was quenched with brine and then diluted with CH_2Cl_2. The organic layer was washed with water, saturated $NaHCO_3$ and brine. Then the resultant solution was dried ($MgSO_4$), filtered, evaporated, and chromatographed (silica gel, 5% MeOH in CH_2Cl_2) to afford (±)-**27** (870 mg, 82%) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.28 (m, 9H), 7.16–7.20 (m, 4H), 5.30 (s, 1H), 3.45–3.68 (m, 4H), 3.21–3.32 (m, 2H), 2.94–3.01 (m, 2H), 2.55–2.71 (m, 3H), 2.27–2.46 (m, 3H), 1.93–1.99 (m, 1H), 1.16 (d, J = 5.9 Hz, 3H); CIMS m/z 479 (MH^+).

Synthetic Method B. (*S*)-1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(2-methoxy-3-phenylpropyl)piperazine ((*S*)-9). To a solution of (*S*)-**31** (900 mg, 1.82 mmol) in THF (15 mL) was added a solution of aluminum hydride (alane, 3.6 mmol) in THF (6 mL) dropwise at rt and then stirred for 30 min. The reaction was quenched with water and then 1 M aqueous HCl followed by 1 M aqueous HOAc was added to the solution. The resultant mixture was stirred for 10 min before being extracted with Et_2O. The organic layer was washed with saturated $NaHCO_3$. The aqueous layer was basified to pH = 10 with 10 M NaOH and then extracted with Et_2O. The Et_2O extracts were combined, washed with brine, dried ($MgSO_4$), filtered, and evaporated. The residue was chromatographed (silica gel, 3.5% MeOH in CH_2Cl_2) to afford (*S*)-**9** (676 mg) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21–7.30 (m, 9H), 6.97–7.03 (m, 4H), 5.33 (s, 1H), 3.53–3.57 (m, 3H), 3.36

(s, 3H), 2.83 (d, J = 4.9 Hz, 2H), 2.65 (t, J = 5.9 Hz, 2H), 2.30–2.51 (m, 10H); CIMS m/z 481 (MH^+). Anal. (*S*)-**9**·2 maleate ($C_{29}H_{34}F_2N_2O_2 \cdot 2C_4H_4O_4$) C, H, N.

1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(2-methyl-3-phenylpropyl)piperazine ((±)-7). To a stirred solution of $LiAlH_4$ (2.66 mL, 1.0 M in THF) in THF (10 mL) was added a solution of (±)-**27** (850 mg, 1.78 mmol) in THF (3 mL) at rt and stirred for 10 min. The reaction was quenched with water and stirred for 15 min before 10 M aqueous NaOH was added. The resultant mixture was stirred for another 15 min, and then celite followed by $MgSO_4$ was added to the stirred solution. After 15 min, the mixture was filtered, and evaporated. The residue was chromatographed (silica gel, 4% MeOH in CH_2Cl_2) to afford (±)-**7** (691 mg, 84%) as a colorless oil. mp 185–186 °C (dimaleate salt); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.31 (m, 6H), 7.14–7.19 (m, 3H), 6.98–7.03 (m, 4H), 5.35 (s, 1H), 3.57 (t, J = 5.9 Hz, 2H), 2.82 (dd, J = 13.7, 4.9 Hz, 1H), 2.66 (t, J = 5.9 Hz, 2H), 2.40–2.55 (m, 8H), 2.09–2.33 (m, 3H), 1.91–2.00 (m, 1H), 0.83 (d, J = 6.8 Hz, 3H); CIMS m/z 465 (MH^+). Anal. (±)-**7**·2 maleate ($C_{29}H_{34}F_2N_2O \cdot 2C_4H_4O_4$) C, H, N.

(+)-1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(2-methyl-3-phenylpropyl)piperazine ((+)-7) and (−)-1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(2-methyl-3-phenylpropyl)piperazine ((−)-7). The optically pure compounds (+)-**7** and (−)-**7** were separated from (±)-**7** by HPLC using semipreparative chiral column (Daicel chiralcel OD, 2 cm × 25 cm; UV detection at 254 nm; flow rate 6 mL/min; 2% 2-propanol in *n*-hexane in the presence of 0.2% diethylamine) followed by recrystallization of their maleate salts.

(*R*)-1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(2-amino-3-phenylpropyl)piperazine ((*R*)-8). To a stirred solution of (*R*)-**29** (360 mg, 0.636 mmol) in MeOH (5 mL) was added saturated methanolic HCl (1 mL) at 0 °C, and then the resultant solution was stirred at rt for 90 min. The reaction was quenched with Et_3N, and evaporated. Aqueous NaOH and EtOAc were added to the residue, and the organic layer was washed with brine, dried ($MgSO_4$), filtered, and evaporated. The oily residue was chromatographed (silica gel, MeOH/CH_2Cl_2/NH_4OH = 1:10:0.1) to afford (*R*)-**8** (270 mg) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.32 (m, 9H), 6.97–7.03 (m, 4H), 5.34 (s, 1H), 3.56 (t, J = 5.9 Hz, 2H), 3.14–3.23 (m, 1H), 2.73 (dd, J = 13.2, 4.4 Hz, 1H), 2.65 (t, J = 5.9 Hz, 2H), 2.26–2.53 (m, 11H), 1.59 (broad s, 2H); EIHRMS calcd for $C_{28}H_{33}F_2N_3O$ $[M]^+$, 465.2592; found, 465.2588.

(*S*)-1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(2-amino-3-phenylpropyl)piperazine ((*S*)-8). Compound (*S*)-**8** was synthesized using (*S*)-**29** according to the procedure for the preparation of (*R*)-**8** and afforded an oil. EIHRMS calcd for $C_{28}H_{33}F_2N_3O$ $[M]^+$, 465.2592; found, 465.2579.

(*R*)-1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(2-methoxy-3-phenylpropyl)piperazine ((*R*)-9). Compound (*R*)-**9** was synthesized from (*R*)-**31** according to the synthetic method B and yielded a yellow oil. Anal. (*R*)-**9**·2 maleate ($C_{29}H_{34}F_2N_2O_2 \cdot 2C_4H_4O_4$) C, H, N.

(*S*)-1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]->4-(2-fluoro-3-phenylpropyl)piperazine ((*S*)-10) and (*S*)-1-(1-Benzyl-2-fluoroethyl)-4-[2-[bis(4-fluorophenyl)methoxy]ethyl]piperazine ((*S*)-32). To a stirred solution of (diethylamino)sulfur trifluoride (0.53 mL, 4.0 mmol) in CH_2Cl_2 (8 mL) was added a solution of (*R*)-**5**[36] (1247 mg, 2.67 mmol) in CH_2Cl_2 (8 mL) at −78 °C, and then the resultant mixture was stirred and warmed to rt over 5 h. The solution was washed with aqueous $NaHCO_3$ followed by brine, and then the organic layer was dried ($MgSO_4$), filtered, evaporated, and chromatographed (silica gel, 80–100% EtOAc in *n*-hexane) to afford (*S*)-**10** (305 mg) and (*S*)-**32** (185 mg) as colorless oils. (*S*)-**10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21–7.32 (m, 9H), 6.97–7.03 (m, 4H), 5.33 (s, 1H), 4.77–4.99 (m, 1H), 3.55 (t, J = 6.4 Hz, 2H), 2.99 (d, J = 5.9 Hz, 1H), 2.92 (dd, J = 6.8, 2.9 Hz, 1H), 2.65 (t, J = 5.9 Hz, 2H), 2.48–2.61 (m, 10H); EIMS m/z 468 (M^+). Anal. (*S*)-**10**·2 maleate ($C_{28}H_{31}F_3N_2O \cdot 2C_4H_4O_4$) C, H, N. (*S*)-**32**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.31 (m, 9H), 6.97–7.03 (m, 4H), 5.34 (s, 1H), 4.27–4.60 (m, 2H), 3.57 (t, J = 5.9 Hz, 2H), 2.49–3.00 (m, 13H); EIMS m/z 468 (M^+). Anal. (*S*)-**32**·2 maleate ($C_{28}H_{31}F_3N_2O \cdot 2C_4H_4O_4$) C, H, N.

(*R*)-1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(2-fluoro-3-phenylpropyl)piperazine ((*R*)-10) and (*R*)-1-(1-Benzyl-2-fluoroethyl)-4-[2-[bis(4-fluorophenyl)methoxy]ethyl]piperazine ((*R*)-32). Compounds (*R*)-**10** and (*R*)-**32** were synthesized using (*S*)-**5**[36] according to the procedure for the preparation of (*S*)-**10** and (*S*)-**32** and yielded (*R*)-**10** and (*R*)-**32** as colorless oils. Anal. (*R*)-**10**·2 maleate ($C_{28}H_{31}F_3N_2O \cdot 2C_4H_4O_4$) C, H, N. Anal. (*R*)-**32**·2 maleate ($C_{28}H_{31}F_3N_2O \cdot 2C_4H_4O_4$) C, H, N.

1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenyl-but-3-enyl)piperazine (13). To a stirred suspension of activated zinc (620 mg, 9.48 mmol) and lead(II) chloride (11 mg, 0.04 mmol) in THF (8 mL) was added diiodomethane (0.32 mL, 3.95 mmol) at rt under an argon atmosphere. This reaction was a slightly exothermic process. After 1 h, $TiCl_4$ (0.79 mL, 1 M in CH_2Cl_2) was added at 0 °C, and the resultant dark brown mixture was stirred at rt for 30 min. A solution of **11**[34] (369 mg, 0.79 mmol) in THF (2 mL) was added dropwise at rt and stirred for 2 h. The mixture was diluted with ether (140 mL), and the organic layer was washed with aqueous $NaHCO_3$ (150 mL) and brine, dried ($MgSO_4$), filtered, and evaporated. The residue was chromatographed (silica gel; Et_2O/CH_2Cl_2 = 1/2) to afford **13** (191 mg) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.96–7.43 (m, 13H), 5.34 (s, 1H), 5.31 (s, 1H), 5.10 (s, 1H), 3.57 (t, J = 5.8 Hz, 2H), 2.64–2.76 (m, 4H), 2.44–2.54 (m, 10H); MS (EI, 70 eV) m/z 462 (M^+), 203 (base); EIHRMS calcd for $C_{29}H_{32}F_2N_2O$ $[M]^+$, 462.2483; found, 462.2475. Anal. **13**·2 maleate ($C_{29}H_{32}F_2N_2O \cdot 2C_4H_4O_4$) C, H, N.

1-[2-(Diphenylmethoxy)ethyl]-4-(3-phenyl-but-3-enyl)piperazine (14). Compound **14** was synthesized using **12**[34] according to the procedure for the preparation of **13** and yielded an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.26–7.39 (m, 15H), 5.37 (s, 1H), 5.30 (s, 1H), 5.09 (s, 1H), 3.60 (t, J = 6.0 Hz, 2H), 2.66–2.76 (m, 4H), 2.44–2.56 (m, 10H); EIHRMS calcd for $C_{29}H_{34}N_2O$ $[M]^+$, 426.2671; found, 426.2654. Anal. **14**·2 maleate ($C_{29}H_{34}N_2O \cdot 2C_4H_4O_4$) C, H, N.

4-[4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]piperazinyl]-2-phenylbutan-2-ol (15). To a solution of **11**[34] (379 mg, 0.816 mmol) in THF (5 mL) was added methylmagnesium bromide (3.96 mL, 1 M in THF) and stirred for 17 h at rt. The mixture was quenched with water and evaporated. The residue was treated with CH_2Cl_2 and water. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and evaporated. The crude product was chromatographed (silica gel; Et_2O/CH_2Cl_2 = 1/2) to afford **15** (213 mg) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.96–7.46 (m, 13H), 5.32 (s, 1H), 3.55 (t, J = 5.9 Hz, 2H), 1.80–2.69 (m, 15H), 1.49 (s, 3H); EIHRMS calcd for $C_{29}H_{34}F_2N_2O_2$ $[M]^+$, 480.2588; found, 480.2588. Anal. **15**·2 maleate ($C_{29}H_{34}F_2N_2O_2 \cdot 2C_4H_4O_4$) C, H, N.

4-[4-[2-(Diphenylmethoxy)ethyl]piperazinyl]-2-phenylbutan-2-ol (16). Compound **16** was synthesized using **12**[34] according to the procedure for the preparation of **15** and yielded an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.21–7.46 (m, 15H), 5.36 (s, 1H), 3.58 (t, J = 5.8 Hz, 2H), 1.79–2.70 (m, 15H), 1.49 (s, 3H); EIHRMS calcd for $C_{29}H_{36}N_2O_2$ $[M]^+$, 444.2777; found, 444.2760. Anal. **16**·2 maleate ($C_{29}H_{36}N_2O_2 \cdot 2C_4H_4O_4$) C, H, N.

1-[4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]piperazinyl]-3-phenylpropan-2-one (17). To a stirred solution of oxalyl chloride (584 mg, 4.60 mmol) in CH_2Cl_2 (4 mL) was added dropwise a solution of DMSO (0.72 mL, 10 mmol) in CH_2Cl_2 (3 mL) at −60 °C. The reaction mixture was warmed to −20 °C before a solution of (±)-**5**[36] (980 mg, 2.10 mmol) in CH_2Cl_2 (3 mL) was added. After the reaction mixture was stirred and allowed to warm to −10 °C, triethylamine (1.06 g, 10.5 mmol) was added. The resultant mixture was warmed to rt and stirred for an additional 2 h, and then water was added. The aqueous layer was extracted with CH_2Cl_2, and the organic layers were combined, washed with brine, dried ($MgSO_4$), filtered, and evaporated. The oily residue was chromatographed (silica gel, 3% MeOH in CH_2Cl_2) to afford **17** (837 mg) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22–7.32 (m, 9H), 7.00 (t, J = 8.8 Hz, 4H), 5.33 (s, 1H), 3.74 (s, 2H), 3.55 (t, J = 6.4 Hz, 2H), 3.20 (s, 2H), 2.67 (t, J = 5.9 Hz,

2H), 2.47–2.56 (m, 8H); CIMS *m/z* 465 (MH^+). Anal. **17**·2 maleate ($C_{28}H_{30}F_2N_2O_2 \cdot 2C_4H_4O_4$) C, H, N.

1-[4-[2-(Diphenylmethoxy)ethyl]piperazinyl]-3-phenylpropan-2-one (18). Compound **18** was synthesized using (±)-**6**[36] according to the procedure for the preparation of **17** and afforded a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22–7.34 (m, 15H), 5.36 (s, 1H), 3.74 (s, 2H), 3.59 (t, J = 6.4 Hz, 2H), 3.19 (s, 2H), 2.69 (t, J = 6.4 Hz, 2H), 2.46–2.58 (m, 8H); CIMS *m/z* 429 (MH^+). Anal. **18**·2 maleate ($C_{28}H_{32}N_2O_2 \cdot 2C_4H_4O_4$) C, H, N.

1-(2-Benzyl-allyl)-4-[2-(diphenylmethoxy)ethyl] piperazine (19). To a stirred solution of AlH_3 (1.4 mmol) in THF (6 mL) was added **33** (270 mg, 0.57 mmol) in THF (3 mL) dropwise at rt. The solution was stirred for 15 min and then quenched with 1 M NaOH. The mixture was extracted with ether (50 mL × 3), and the organic layers were combined, washed with brine, dried ($MgSO_4$), filtered, and evaporated. The crude residue was chromatographed (silica gel; 3% MeOH in CH_2Cl_2) to afford **19** (185 mg) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.19–7.31 (m, 9H), 6.95–7.04 (m, 4H), 5.34 (s, 1H), 4.97 (s, 1H), 4.84 (s, 1H), 3.57 (t, J = 6.0 Hz, 2H), 3.37 (s, 2H), 2.79 (s, 2H), 2.67 (t, J = 6.0 Hz, 2H), 2.39 (bs, 4H), 2.27 (bs, 4H); EIHRMS calcd for $C_{29}H_{32}F_2N_2O$ $[M]^+$, 462.2483; found, 462.2489. Anal. **19**·2 maleate ($C_{29}H_{32}F_2N_2O \cdot 2C_4H_4O_4$) C, H, N.

1-(2-Benzyl-allyl)-4-[2-[bis(4-fluorophenyl)methoxy]ethyl] piperazine (20). Compound **20** was synthesized using **34** according to the procedure for the preparation of **19** and yielded an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.18–7.33 (m, 15H), 5.38 (s, 1H), 4.97 (s, 1H), 4.84 (s, 1H), 3.62 (t, J = 5.9 Hz, 2H), 3.37 (s, 2H), 2.80 (s, 2H), 2.72 (t, J = 5.9 Hz, 2H), 2.58 (bs, 4H), 2.41 (bs, 4H); EIHRMS calcd for $C_{29}H_{34}N_2O$ $[M]^+$, 426.2671; found, 426.2656. Anal. **20**·2 maleate ($C_{29}H_{34}N_2O \cdot 2C_4H_4O_4$) C, H, N.

1-[4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]piperazinyl]-2-methyl-3-phenylpropan-2-ol (21). To a stirred solution of **25** (472 mg, 1.42 mmol) in DMF (3 mL) was added 1-chloro-2-methyl-3-phenyl-2-propanol[41] (**35**, 1071 mg, 5.68 mmol). Potassium carbonate (590 mg, 4.26 mmol) was added, followed by sodium iodide (426 mg, 2.84 mmol). The reaction was stirred at 70–80 °C for 18–24 h, cooled to rt, and poured into water (20 mL). The mixture was extracted with ether (50 mL × 3), and the organic layers were combined, washed with brine, dried ($MgSO_4$), filtered, and evaporated. The crude residue was chromatographed (silica gel; MeOH/CH_2Cl_2 = 1/30) to afford **21** (215 mg) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.96–7.30 (m, 13H), 5.33 (s, 1H), 3.57 (t, J = 5.8 Hz, 2H), 2.30–2.83 (m, 15H), 1.09 (s, 3H); EIHRMS calcd for $C_{29}H_{32}F_2N_2O_2$ $[M - 2H]^+$, 478.2432; found, 478.2433. Anal. **21**·2 maleate ($C_{29}H_{34}F_2N_2O_2 \cdot 2C_4H_4O_4$) C, H, N.

1-[4-[2-(Diphenylmethoxy)ethyl]piperazinyl]-2-methyl-3-phenylpropan-2-ol (22). Compound **22** was synthesized using **26** and **35** according to the procedure for the preparation of **21** and yielded an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.20–7.36 (m, 15H), 5.37 (s, 1H), 3.59 (t, J = 5.9 Hz, 2H), 3.13 (bs, 1H), 2.28–2.82 (m, 14H), 1.07 (s, 3H); EIHRMS calcd for $C_{29}H_{34}N_2O_2$ $[M - 2H]^+$, 442.2620; found, 442.2612. Anal. **22**·2 maleate ($C_{29}H_{36}N_2O_2 \cdot 2C_4H_4O_4$) C, H, N.

2-[4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]piperazinyl]-1-phenylethanone (23). A mixture of **25** (2.00 g, 6.02 mmol), 2-bromoacetophenone (1.56 g, 7.82 mmol), and *N*-ethyldiisopropylamine (2.1 mL, 12 mmol) in DMF (20 mL) was stirred at 60 °C under argon for 15 h. The reaction was quenched with water, and then the resultant mixture was extracted with diethyl ether. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and evaporated. The oily residue was chromatographed (silica gel, 3% MeOH in CH_2Cl_2) to afford **23** (2.47 g) as a light brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98–8.01 (m, 2H), 7.55–7.60 (m, 1H), 7.44–7.48 (m, 2H), 7.25–7.30 (m, 4H), 6.97–7.04 (m, 4H), 5.34 (s, 1H), 3.82 (s, 2H), 3.57 (t, J = 5.9 Hz, 2H), 2.69 (t, J = 5.9 Hz, 2H), 2.62 (broad s, 8H); CIMS *m/z* 451 (MH^+). Anal. **23**·2 maleate ($C_{27}H_{28}F_2N_2O_2 \cdot 2C_4H_4O_4$) C, H, N.

2-[4-[2-(Diphenylmethoxy)ethyl]piperazinyl]-1-phenylethanone (24). Compound **24** was synthesized using **26** according to the procedure for the preparation of **23** and afforded a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98–8.01 (m, 2H), 7.23–7.57 (m, 13H), 5.37 (s, 1H), 3.81 (s, 2H), 3.61 (t, J = 5.9 Hz, 2H), 2.71 (t, J = 6.4 Hz, 2H), 2.64 (m, 8H); CIMS *m/z* 415 (MH^+). Anal. **24**·2 maleate ($C_{27}H_{30}N_2O_2 \cdot 2C_4H_4O_4$) C, H, N.

(*S*)-1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-[2-(*tert*-butyloxycarbonylamino)-3-phenylpropyl]piperazine ((*S*)-29). The intermediate (*S*)-1-[4-[2-[bis(4-fluorophenyl)methoxy]ethyl]piperazinyl]-2-(*tert*-butyloxycarbonylamino)-3-phenylpropan-1-one ((*S*)-**28**) was synthesized using **25** and *N*-*t*-Boc-L-phenylalanine according to the synthetic method A and yielded a white glassy solid in a yield of 90%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17–7.29 (m, 9H), 6.98–7.03 (m, 4H), 5.45 (d, J = 8.8 Hz, 1H), 5.29 (s, 1H), 4.82 (dd, J = 14.3, 8.3 Hz, 1H), 3.47–3.58 (m, 4H), 3.26–3.32 (m, 1H), 2.94–3.02 (m, 3H), 2.55 (t, J = 5.4 Hz, 2H), 2.27–2.43 (m, 3H), 1.83–1.88 (m, 1H), 1.42 (s, 9H); CIMS *m/z* 580 (MH^+). To a solution of diisobutylaluminum hydride (DIBALH, 10 mmol) in THF (20 mL) was added (*S*)-**28** (1.20 g, 2.07 mmol) in THF (5 mL) dropwise at rt and then stirred for 3 h. The reaction was quenched with water, and then 1 M HCl followed by 1 M aqueous HOAc was added to the solution. The resultant mixture was stirred for 10 min and then extracted with Et_2O. The organic layer was washed with saturated $NaHCO_3$. The aqueous layer was basified to pH = 10 with 10 M NaOH and then extracted with Et_2O. The Et_2O extracts were combined, washed with brine, dried ($MgSO_4$), filtered, and evaporated. The residue was chromatographed (silica gel, 3.5% MeOH in CH_2Cl_2) to afford (*S*)-**29** (910 mg, 78%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17–7.31 (m, 9H), 6.97–7.03 (m, 4H), 5.34 (s, 1H), 4.61 (d, J = 6.0 Hz, 1H), 3.90–3.98 (m, 1H), 3.55 (t, J = 5.9 Hz, 2H), 2.85–2.87 (m, 2H), 2.64 (t, J = 5.9 Hz, 2H), 2.20–2.50 (m, 10H), 1.43 (s, 9H); CIMS *m/z* 566 (MH^+).

(*R*)-1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-[2-(*tert*-butyloxycarbonylamino)-3-phenylpropyl]piperazine (*R*)-29. The intermediate (*R*)-1-[4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]piperazinyl]-2-(*tert*-butyloxycarbonylamino)-3-phenylpropan-1-one ((*R*)-**28**) was synthesized using **25** and *N*-*t*-Boc-D-phenylalanine according to the synthetic method A and yielded a white glassy solid in 82% yield. Compound (*R*)-**29** was then synthesized using (*R*)-**28** according to the procedure for the preparation of (*S*)-**29** and afforded an oil in 79% yield.

(*S*)-2-Methoxy-3-phenylpropanoic acid ((*S*)-30). To a stirred solution of NaH (28.8 mmol) in THF (10 mL) was added a solution of L-3-phenyllactic acid (2.00 g, 12.0 mmol) in THF (40 mL) at rt and stirred for 10 min before iodomethane (1.5 mL, 24.0 mmol) was added to the reaction mixture. After stirred at rt for 5 h, 1 M aqueous HCl was added and the resultant mixture was evaporated. The residue was treated with additional 1 M aqueous HCl and extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$), filtered, and evaporated to afford (*S*)-**30** (2.10 g, 97%) as an oil, which was used for the following synthesis without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23–7.34 (m, 5H), 4.03 (dd, J = 7.9, 3.9 Hz, 1H), 3.40 (s, 3H), 3.14 (dd, J = 14.2, 4.4 Hz, 1H), 3.02 (dd, J = 14.2, 8.3 Hz, 1H), 1.26 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 136.7, 129.4, 128.5, 126.9, 81.2, 58.5, 38.6; CIMS *m/z* 198 (MNH_4^+).

(*R*)-2-Methoxy-3-phenylpropanoic acid ((*R*)-30). Compound (*R*)-**30** was synthesized from D-3-phenyllactic acid according to the procedure for the preparation of (*S*)-**30** and afforded an oil in 93% yield, which was used for the following synthesis without further purification.

(*S*)-1-[4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]piperazinyl]-2-phenylpropan-1-one ((*S*)-31). Compound (*S*)-**31** was synthesized using **25** and (*S*)-**30** according to the synthetic method A and yielded a light yellow oil in 96% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22–7.32 (m, 9H), 6.99–7.04 (m, 4H), 5.32 (s, 1H), 4.27 (t, J = 6.9 Hz, 1H), 3.44–3.64 (m, 6H), 3.32 (s, 3H), 3.02–3.05 (m, 2H), 2.61 (t, J = 5.9 Hz, 2H), 2.34–2.51 (m, 3H), 2.16–2.23 (m, 1H); CIMS *m/z* 495 (MH^+).

(*R*)-1-[4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]piperazinyl]-2-methoxy-3-phenylpropan-1-one ((*R*)-31). Compound (*R*)-**31** was synthesized using **25** and (*R*)-**30** according to the synthetic method A and yielded a light yellow oil in 82% yield.

2-Benzyl-1-[4-[2-[bis(4-fluorophenyl)methoxy]ethyl] piperazinyl]propenone (33). Compound **33** was synthesized using **25** and 2-benzyl-acrylic acid[40] according to the synthetic method A and yielded an oil in 55% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.18−7.28 (m, 9H) 7.00 (t, J = 8.6 Hz, 4H), 5.28 (s, 1H), 5.19 (s, 1H), 4.98 (s, 1H), 3.62 (s, 2H), 3.58 (bs, 2H), 3.48 (t, J = 5.8 Hz, 2H), 3.27 (bs, 2H), 2.52 (t, J = 5.8 Hz, 2H), 2.33 (bs, 2H), 1.19 (bs, 2H); EIHRMS calcd for $C_{29}H_{28}F_2N_2O_2$ $[M - 2H]^+$, 474.2119; found, 474.2131.

2-Benzyl-1-[4-[2-(diphenylmethoxy)ethyl]piperazinyl] propenone (34). Compound **34** was synthesized using **26** and 2-benzyl-acrylic acid[40] according to the synthetic method A and yielded an oil in 77% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.18–7.30 (m, 15H), 5.33 (s, 1H), 5.18 (s, 1H), 4.98 (s, 1H), 3.62 (s, 2H), 3.58 (bs, 2H), 3.51 (t, J = 5.8 Hz, 2H), 3.26 (bs, 2H), 2.54 (t, J = 5.8 Hz, 2H), 2.35 (bs, 2H), 1.94 (bs, 2H).

Biological Methods. Binding assays for the DAT and SERT followed published procedures[44] and used 0.01 nM [^{125}I]RTI-55[45] (s.a. = 2200 Ci/mmol). Briefly, 12 mm × 75 mm polystyrene test tubes were prefilled with 100 μL of drugs, 100 μL of radioligand ([^{125}I]RTI-55), and 50 μL of a "blocker" or buffer. Drugs and blockers were made up in 55.2 mM sodium phosphate buffer, pH 7.4 (BB), containing 1 mg/mL bovine serum albumin (BB/BSA). Radioligands were made up in a protease inhibitor cocktail containing 1 mg/mL BSA [BB containing chymostatin (25 μg/mL), leupeptin (25 μg/mL), ethylenediaminetetraacetic acid (100 μM), and EGTA (100 μM)]. The samples were incubated in triplicate for 18–24 h at 4 °C (equilibrium) in a final volume of 1 mL. Brandel cell harvesters were used to filter the samples over Whatman GF/B filters, which were presoaked in wash buffer (ice-cold 10 mM Tris-HCl/150 mM NaCl, pH 7.4) containing 2% poly(ethylenimine).

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Supporting Information Available: Theoretical and experimental elemental analyses for compounds (±)-**7**, (*S*)-**9**, (*R*)-**9**, (*S*)-**10**, (*R*)-**10**, **13**−**24**, (*S*)-**32**, and (*R*)-**32**. This material is available free of charge via the Internet at http://pubs.acs.org.

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