Highly Selective, Novel Analogs of 4-[2-(Diphenylmethoxy)ethyl]-1-benzylpiperidine for the Dopamine Transporter: Effect of Different Aromatic Substitutions on Their Affinity and Selectivity

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Several analogs of the potent and selective dopamine transporter (DAT) ligand 4-[2-(diphenylmethoxy)ethyl]-1-benzylpiperidine, **1a**, were prepared and biologically evaluated at the dopamine and serotonin transporter (SERT) sites. Several substituents were introduced in the aromatic rings to evaluate the influences of electronic and steric interactions in their binding to the DAT. All the novel analogs showed preferential interaction at the DAT compared with the SERT. Different aromatic substitutions in the phenyl ring of the *N*-benzyl part of the molecule played a key role in the selectivity. In general, compounds with strong electron-withdrawing substituents were most active and selective at the DAT. Thus, compounds **5a** (R = F) and **11b** (R = NO_2) were among the most potent (IC_{50} = 17.2 and 16.4 nM, respectively) and most selective (SERT/DAT = 112 and 108, respectively) and were far more selective than GBR 12909 (SERT/DAT = 6). Bioisosteric replacement of one of the phenyl rings of the diphenylmethoxy moiety by a thiophene ring was tolerated well and produced the most potent compound **13b** (IC_{50} = 13.8 nM) in the series. Our current structure−activity studies of these piperidine analogs resulted in the generation of second generation of GBR-type compounds, and all of these new compounds reported here were more selective than GBR 12909 in interacting with the DAT over the SERT.

Introduction

Cocaine is a strong reinforcer[1−3] in humans, and its great abuse potential causes an economic burden to the society. The role of the dopamine transporter (DAT) has been implicated in the central mechanism of cocaine addiction[4−6] and has been studied intensely to understand the neurochemical actions of cocaine associated with this transporter.[7−9] DAT is a presynaptically located macromolecule which regulates the concentration of dopamine in the synaptic junction by translocating it into the presynaptic neurons.[10] Furthermore, in recent experiments involving knockout mice without the DAT, cocaine had no stimulating effect in these mice, consonant with a crucial role of the DAT in cocaine action.[11] Studies aimed at developing drugs targeted at this transporter produced wide varieties of compounds including some very potent cocaine derivatives.[12−15] Similarly, several DAT-specific radioligands have been developed to characterize the cocaine binding sites and to act as probes for the transporter.[16−18]

GBR compounds, which were originally discovered by Van der Zee et al.,[19] have been shown to have high affinity and selectivity for the DAT. Some of the well-known compounds in this class are GBR 12909 and 12935 (Figure 1),[20,21] and they have been used widely to study many neurochemical actions in the central nervous system (CNS). GBR compounds have been described to have a high affinity for the DAT and slow dissociation from the transporter, resulting in long duration of action.[22] It has been shown that GBR 12909 can attenuate the increase in extracellular concentration of dopamine level (ECDA) induced by cocaine in microdialysis experiments in the rat brain, which might indicate its possible partial agonist properties against cocaine action.[22,23] A recent study showed that GBR 12909 in low doses is not self-administered, while another study demonstrated that GBR 12909 has much less reinforcing potential when compared to cocaine.[24,25] Furthermore, GBR 12909 was shown to be effective in suppressing cocaine self-administration in monkey experiments and was nonstimulant in human studies.[26,27] Taken together, these experimental lines of evidence

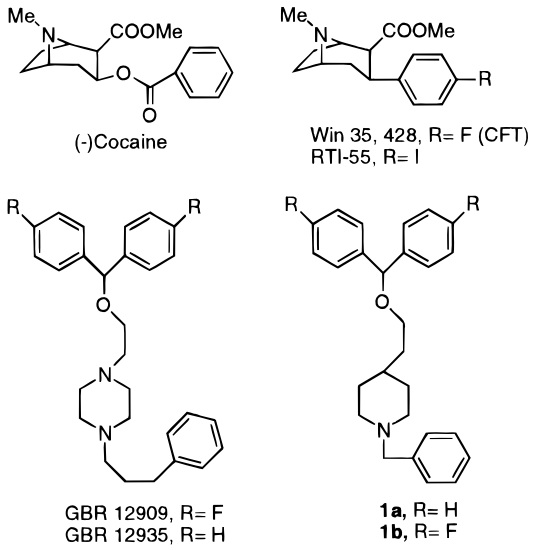

Figure 1.

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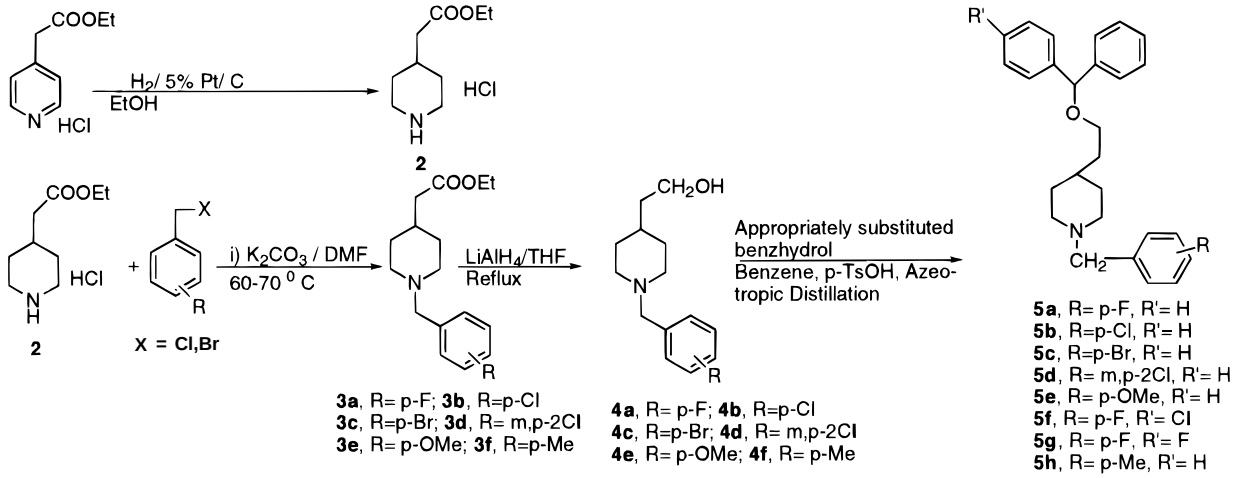
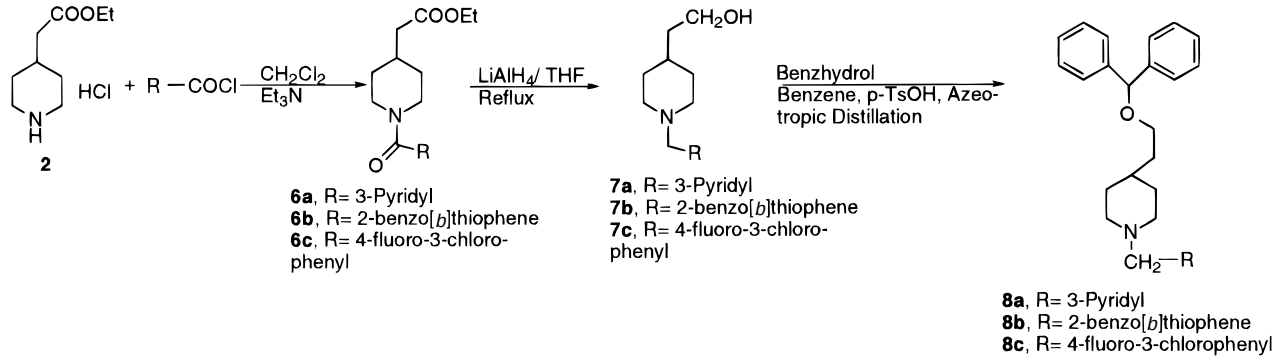
Scheme 1



Scheme 2



suggest that a suitable GBR-type compound might have the potential to act as a pharmacotherapeutic agent in the treatment of cocaine addiction.

Our ongoing study to design and develop suitable GBR-type compounds to investigate the macromolecular DAT structure led to the development of a series of compounds described earlier.[28,29] In our structure−activity relationship (SAR) studies it was shown that piperidine analogs of GBR compounds retain the potency and selectivity for the DAT, and some of these novel compounds were more selective than GBR 12909.[29,30] Furthermore, our SAR studies showed that the fluorinated and unsubstituted versions of these analogs had interesting opposite effects in terms of their selectivity and potency for the DAT. Thus our lead compound from this study, 4-[2-(diphenylmethoxy)-ethyl]-1-benzylpiperidine, **1a** (Figure 1), was shown to have the highest selectivity for the DAT while the fluorinated version **1b** was more potent but less selective than **1a**. Both **1a** and **1b** were more selective than GBR 12909. Other workers have demonstrated that alternating the piperazine ring to homopiperazine or into substituted chiral piperazine structures retains the potency and specificity in these compounds for the DAT.[31,32] Recently 2-carbomethoxybenztropine analogs of tropane compounds bearing GBR-like diphenylmethoxy moieties were predicted to more closely resemble GBR compounds in their mode of binding with the DAT.[33]

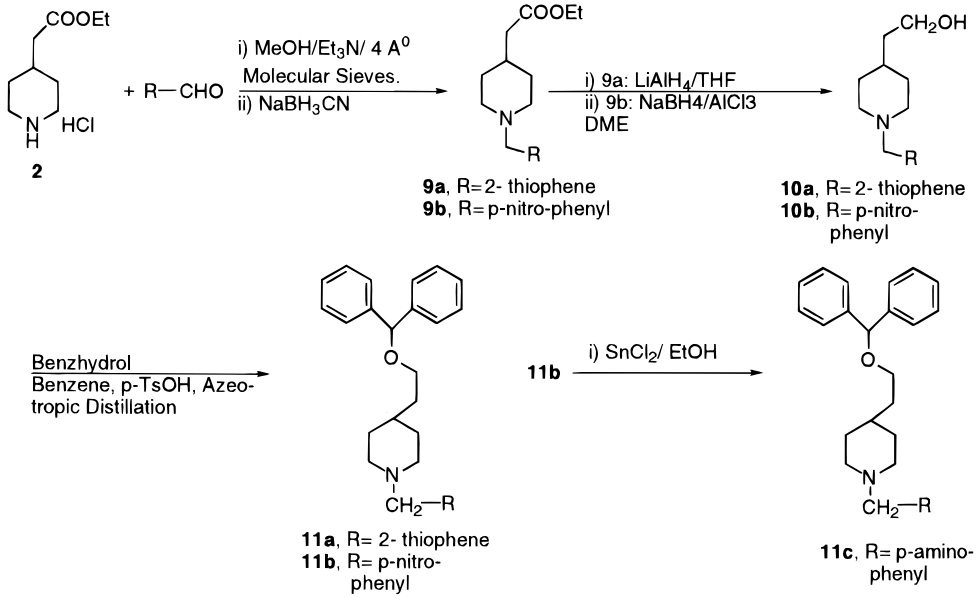
Extensive SAR studies have been done on different analogs of 3β-phenyltropane-2β-carboxylic acid methyl ester, WIN 35,428, a cocaine analog originally reported by Clarke and co-workers.[34] These resulted in the generation of a wealth of structural information about the binding of these compounds to the DAT.[12−15,35−37] In comparison, even though there are SAR data available from the original GBR series and from recent reports,[19,38] GBR-type compounds have not been studied in great detail with respect to the influences of different stereoelectronic effects and other aspects of their binding to the DAT. In our objective to gain further insight into the pharmacophore for binding of these compounds with the DAT, several analogs were designed and synthesized. In this report we describe the syntheses of analogs of our lead compound **1a** and their biological activity at the DAT and the SERT.

Chemistry

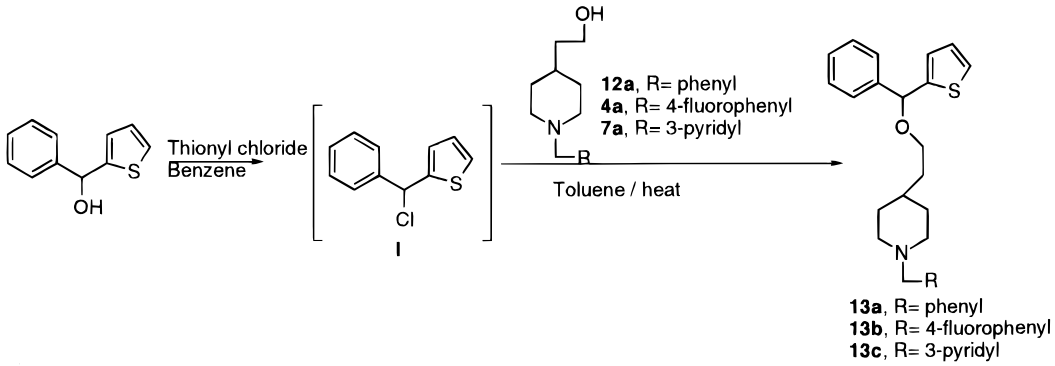
The synthesis of compounds **5a**−**h** is described in Scheme 1. In this synthetic scheme, the common intermediate amino ester **2** was prepared by hydrogenation of commercially available ethyl 4-pyridylacetate in the presence of 5% Pt/C as catalyst. This amine was N-alkylated with the appropriate benzyl halide under standard conditions to produce compounds **3a**−**f**, which on reduction with lithium aluminum hydride (LAH) gave the corresponding alcohols **4a**−**f**. Final compounds **5a**−**h** were synthesized by reacting alcohols **4a**−**f** with the appropriate benzhydrol in a manner described earlier.[29,39]

The synthesis of **8a**−**c** is described in Scheme 2. Reaction of amine **2** with the appropriate acid chloride produced amides **6a**−**c**, which on reduction with excess LAH yielded **7a**−**c**. Similarly the reaction of **7a**−**c** with the benzhydrol produced **8a**−**c**.

Scheme 3



Scheme 4



Synthesis of compounds **11a**−**c** was accomplished in a manner as shown in Scheme 3. Reaction of amine **2** with suitable aldehydes, in a reductive amination reaction procedure, produced **9a**,**b**.[40] The reduction of **9b** was carried out in the presence of $NaBH_4/AlCl_3$ to ensure selective reduction of the ester group only, while avoiding the reduction of the nitro functionality.[41] Alcohols **10a**,**b** were then converted into final compounds **11a**,**b** in a similar way. Compound **11c** was synthesized from **11b** via the reduction of the nitro group in the presence of $SnCl_2$ in ethanol.

Compounds **13a**−**c** were synthesized in a slightly different manner as shown in Scheme 4 where intermediate chloride **I** was treated with already synthesized alcohols **12a**,[29] **4a**, and **7a** to produce the final products **13a**−**c**.

Biochemistry

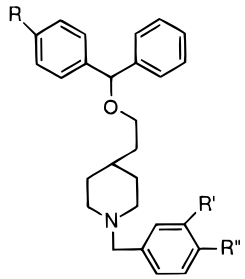
Biological studies of the newly synthesized compounds were carried out with rat brain striatal membrane tissue as described earlier.[29] Binding analyses were performed to determine their activity at the DAT and SERT in the brain tissues. The DAT in the rat striatal tissue was labeled with a tritiated potent analog of cocaine, [^{3}H]WIN 35,428, and the SERT was labeled with [^{3}H]citalopram.

Results and Discussion

The selective lead compound **1a** for the DAT developed from our earlier SAR studies was the starting point for investigating different novel analogs as to their activity at the DAT and SERT. Specifically, we wanted to explore the influence of different steric and electronic effects on their interaction with the DAT. It was evident from our previous SAR studies that substitutions, with the exception of fluoro, on the aromatic rings of the diphenylmethoxy part of the molecule resulted in lower binding affinity and selectivity.[29] The same SAR study also revealed that the introduction of a *N*-benzyl substitution in the molecule, as in **1a**, was responsible for a marked decrease in its potency for the SERT without affecting its affinity for the DAT. In our current study, we wanted to extend and explore these findings by particularly incorporating different electron-withdrawing, electron-donating, and hydrophobic substituents into the phenyl ring of the *N*-benzyl group of the lead molecule **1a**. It is noteworthy that subtitutions on the 3β-phenyl ring of the tropane compound, WIN 35,428 (Figure 1), had a profound effect on its activity, and in this context, it will also be interesting to observe whether a similar trend exists for the current series of compounds.[13] We also wanted to observe the effect on the biological activitiy of replacing the aromatic phenyl rings with bioisosteric heterocyclic rings.

In our first series of compounds, **5a**−**h**, **8c**, and **11b**,**c**, different electron-withdrawing (NO_2, F, Cl, Br), electron-donating (NH_2, OCH_3), and neutral (CH_3) groups were introduced (Table 1). The results indicated no significant direct correlation between the activities and the

Table 1. Affinity and Selectivity of Drugs at the Dopamine and Serotonin Transporters in Rat Striatum



				IC_{50} (nM)[b]		
compound	R	R′	R″	DAT, [^{3}H]WIN 35,428	SERT, [^{3}H]citalopram	SERT/DA
GBR 12909				14.0 ± 0.6	82 ± 4[a]	6
1a[a]	H	H	H	15.2 ± 2.8	743 ± 6	49
5a	H	H	F	17.2 ± 4.7	1920 ± 233	112
5b	H	H	Cl	24.7 ± 5.5	1610 ± 119	65.1
5c	H	H	Br	31.1 ± 2.9	1490 ± 319	48
5d	H	Cl	Cl	85.7 ± 4.7	2880 ± 281	33.6
5e	H	H	OCH_3	27.8 ± 6.8	1240 ± 342	45
5f	Cl	H	F	52.4 ± 7.8	1810 ± 107	34.4
5g	F	H	F	14.0 ± 3.3	1260 ± 72	89
5h	H	H	CH_3	23.0 ± 3.7	1390 ± 240	60.4
8c	H	Cl	F	28.2 ± 3.1	2530 ± 50	90
11b	H	H	NO_2	16.4 ± 3.0	1770 ± 305	108
11c	H	H	NH_2	101 ± 13	1570 ± 201	15.6

[a] See ref 28. [b] The DAT was labeled with [^{3}H]WIN 35,428, and the SERT was labeled with [^{3}H]citalopram. Results are average ± SEM of three independent experiments assayed in triplicate.

nature of the substitutions in these compounds even though the compounds with the two strongest electronegative and electron-withdrawing substituents (NO_2, F) were among the most potent and selective for the DAT. The compounds **5a** (R = F) and **11b** (R = NO_2) showed maximum preferential interaction at the DAT by exhibiting IC_{50} values of 17.2 and 16.4 nM for the DAT vs 1919 and 1774 nM for the SERT. Thus, compared to GBR 12909, compounds **5a** and **11b** were almost equipotent in interacting with the DAT but they were about 19-fold more selective for the DAT (SERT/DAT, 112 and 108 for **5a** and **11b** vs 6 for GBR 12909, Table 1). The selectivity of compound **5a** was the highest in this series of compounds and is also, to our knowledge, the most selective GBR-type compound known to date when tested under similar assay conditions. Compounds with chloro and bromo substituents, as in **5b** and **5c**, were slightly less potent than **5a** but were still very selective for the DAT. The reduction in potency may be attributed to the presence of unfavorable steric and electronic interactions as observed previously.[29] The 3,4-dichloro analog **5d** was relatively less potent compared to other analogs. This is in contrast to the results found in the tropane series of compounds where 3,4-dichloro substitutions in 3β-phenyl ring of WIN 35,428 produced one of the most potent tropane analogs.[13] This suggests different sites of interaction of the phenyl rings with the DAT for these two different classes of compounds. Interestingly the 3-chloro-4-fluoro-substituted compound **8c** (IC_{50} = 28.2 nM) was more potent than the dichloro compound **5d** (IC_{50} = 85.7 nM), which indicates an unfavorable interaction originating from the presence of 3-chloro substitution in **5d** which is also supported by relative higher potency of 4-chloro substitution in **5b** (IC_{50} = 24.7 nM). In compounds **5f** and **5g**, substitutions in one of the aromatic rings of the diphenylmethoxy moiety of the molecule resulted in one of the most potent and selective compounds, fluoro-substituted **5g** (IC_{50} = 14.0 nM, SERT/DAT = 89), and a relatively weaker compound, chloro-substituted **5f** (IC_{50} = 52.4 nM, SERT/DAT = 34.4). These observations are in agreement with our previous findings which demonstrated that a fluoro-substituted diphenylmethoxy moiety always increases the potency at the DAT in this class of compounds whereas other halogen substitutions generally lead to a decrease.[28,29]

The introduction of an electron-donating methoxy group, as in **5e**, did not influence the overall activity to a significant extent, whereas the amino derivative **11c** turned out to be relatively weak and less selective. The analog bearing a methyl group, **5h**, was more potent and selective than **5e** and **11c**.

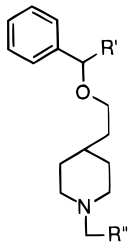
The next series of compounds, **8a**,**b**, **11a**, and **13a**−**c**, present structural modifications where one of the aromatic rings is replaced by a bioisosteric equivalent thienyl or pyridyl ring (Table 2). Our objectives behind introducing polar bioisosteric moieties were the following: (a) to examine the effect on activity since it is a valuable tool in elucidating SAR studies[42] and (b) to decrease the lipophilicity in these molecules without compromising activity since the high lipophilicity in GBR molecules requires great caution in carrying out biological assays due to the tendency of adsorption to the walls of the tubes used for incubation. Compound **8a**, in which the phenyl ring of the *N*-benzyl group is replaced by a pyridine ring, exhibited reduced potency and selectivity (Table 2) compared to other analogs **5a**−**h**, whereas **8b** and **11a** replaced with benzo[*b*]thiophene and thiophene groups were quite inactive at the DAT. These results indicated that the exchange of phenyl ring in the *N*-benzyl part of the molecule by the above aromatic heterocyclic rings did not result in a good bioisosteric replacement. They were not tolerated very well in terms of DAT activity.

In contrast, compounds **13a**−**c** exhibited interesting activity. The most potent and one of the most selective compounds generated from this series was **13b** (IC_{50} = 13.8 nM for the DAT, SERT/DAT= 100.5), which was 17-fold more selective compared to GBR 12909. The potency and selectivity of compounds **13a** and **13c** were moderate compared to **13b**. These results demonstrate that the replacement of the phenyl ring in the diphenylmethoxy part of the molecule by a thiophene ring does not impede interaction with the DAT and does not impact negatively on the DAT selectivity. It is also important to note that compounds **5f**,**g** and **13a**−**c** were synthesized and biologically evaluated in their racemic forms. It will be interesting to observe any differences in binding activities among the pure enantiomeric forms of these racemic compounds as it was observed previously in this class of compound.[32]

Conclusion

In this report we have demonstrated the development of some very potent and highly selective ligands for the DAT. The current results have provided us with some additional information about the pharmacophore of selective binding of these compounds with the DAT.

Table 2. Affinity and Selectivity of Drugs at the Dopamine and Serotonin Transporters in Rat Striatum



			IC_{50} (nM)[a]		
compound	R′	R″	DAT, [^{3}H]WIN 35,428	SERT, [^{3}H]citalopram	SERT/DA
8a	Ph	3-pyridyl	48.6 ± 8.4	680.0 ± 12.0	13.9
8b	Ph	2-benzo[*b*]thiophenyl	172.1 ± 16.4	1540 ± 251	8.9
11a	Ph	2-thienyl	59.3 ± 5.8	1250 ± 87	21
13a	2-thienyl	Ph	27.2 ± 0.1	741 ± 108	27
13b	2-thienyl	4-fluorophenyl	13.8 ± 3.4	1390 ± 243	100
13c	2-thienyl	3-pyridyl	58.3 ± 5.7	927 ± 34	15.9

[a] The DAT was labeled with [^{3}H]WIN 35,428, and the SERT was labeled with [^{3}H]citalopram. Results are average ± SEM of three independent experiments assayed in triplicate.

Practically all of the compounds were more selective than GBR 12909, whereas some were as potent as GBR 12909 itself. Compounds **5a**, **11b**, and **13b** were found to be equipotent with GBR 12909 and had the highest selectivity for the DAT (SERT/DAT = 112, 108, and 100.5). The influence of electronic factors was indicated to some extent by these results since the compounds containing the most electronegative atom **5a** (R = F) and electron-withdrawing group **11b** (R = NO_2) showed maximal preferential interaction at the DAT. Furthermore, these results also may indicate the possible existence of complimentary electropositive/electron accepting sites on the DAT to favor the observed interaction and vice versa on SERT.

Replacement of the phenyl ring of the *N*-benzyl group of **1a** by a bioisosteric moiety was not tolerated very well, which might indicate an unfavorable electronic interaction. However, higher activity was achieved when the bioisosteric thiophene ring replaced one of the phenyl rings of the diphenylmethoxy part of the molecule, thus indicating a positive interaction with the transporter. The current work has resulted in the development of a number of highly DAT-selective GBR-type piperidine analogs and with selectivities many times greater than that of the conventional GBR compounds. Finally, substitution at the N atom of the piperidine ring with different derivatives of the benzyl group resulted in the generation of optimum potency and high selectivity in the current series, whereas 3-phenylpropyl substitution as in GBR 12909 and 12935 conferred the maximum potency in the GBR series of compounds.[19] These structural dissimilarities coupled with differences in the pK_a values of the N atoms between the piperidine and piperazine rings may suggest a different mode of binding between these two classes of compounds with the DAT.

Experimental Details

Analytical silica gel coated TLC plates (Si 250F) were purchased from Baker, Inc and were visualized with UV light or by treatment with phosphomolybdic acid (PMA). Flash chromatography was carried out on Baker silica gel 40 μM. ^{1}H NMR spectra were routinely obtained at 100 MHz on a Brucker WP-100-SY. The NMR solvent used was $CDCl_3$ as indicated. TMS was used as an internal standard. Elemental analyses were performed by Atlantic Microlab, Inc. and were within ±0.4% of the theoretical value.

[^{3}H]CFT (83.5 Ci/mmol) and [^{3}H]citalopram (85.7 Ci/mmol) were obtained from Dupont-New England Nuclear (Boston, MA). Cocaine hydrochloride was purchased from Mallinckrodt Chemical Corp. (St. Louis, MO). CFT naphthalenesulfonate was purchased from Research Biochemicals, Inc. (Natick, MA).

Procedure A: Synthesis of 1-[(4-Fluorophenyl)methyl]-4-[(ethoxycarbonyl)methyl]piperidine (3a). Amine salt **2** (0.4 g, 1.9 mmol) and 4-fluorobenzyl chloride (0.41 g, 2.8 mmol) were dissolved in 15 mL of dry *N*,*N*-dimethylformamide (DMF). Finely ground anhydrous potassium carbonate (1.9 g) was added into the solution, and the mixture was warmed to 65 °C overnight under nitrogen. The reaction mixture was cooled, diluted with water, extracted with ether, and dried over Na_2SO_4. The crude product was isolated and then purified by flash column chromatography (silica gel). Elution with EtOAc/hexane (1:3) provided the desired compound as a colorless oil: 0.3 g (57% yield); ^{1}H NMR ($CDCl_3$) 1.17−1.31 (3H, t, J = 7.1 Hz, CH_3CH_2), 1.47−2.09 (7H, m), 2.19−2.25 (2H, d, J = 6.6 Hz, CH_2CH), 2.77−2.89 (2H, m), 3.44 (2H, s, NCH_2), 4.01−4.22 (2H, q, J = 7.1 Hz, CH_2CH_3), 6.88−7.33 (4H, m, *Ph*F). Anal. ($C_{16}H_{22}FNO_2$) C, H, N.

Procedure B: Synthesis of 1-[(4-Fluorophenyl)methyl]-4-(2-hydroxyethyl)piperidine (4a). Lithium aluminum hydride (0.18 g, 4.8 mmol) was suspended in 30 mL of dry THF, and the solution was cooled in an ice bath. Ester **3a** (0.27 g, 0.96 mmol), dissolved in 10 mL of tetrahydrofuran (THF), was added dropwise into the cold solution. The solution was refluxed for 2 h, and after cooling (ice bath), unreacted lithium aluminum hydride was quenched by careful addition of an excess amount of 10% NaOH solution. The solution was filtered, and the residue was repeatedly washed with an excess amount of ethyl acetate (EtOAc). The combined extract was dried over Na_2SO_4, and the product was collected, 0.23 g (91% yield), as a colorless liquid. This product was used in the next reaction without any further purification: ^{1}H NMR ($CDCl_3$) 1.25−2.18 (9H, m), 2.77−2.89 (2H, m), 3.43 (2H, s, NCH_2), 3.60−3.72 (2H, t, J = 6.3 Hz, CH_2CH_2O), 6.88−7.33 (4H, m, *Ph*F); CI-MS *m*/*e* 238.13 $(M + H)^+$.

Procedure C: Synthesis of 4-[2-(Diphenylmethoxy)-ethyl]-1-[(4-fluorophenyl)methyl]piperidine (5a). Benzhydrol (0.5 g, 2.7 mmol), 1-[(4′-fluorophenyl)methyl]-4-(2-hydroxyethyl)piperidine (**4a**) (0.2 g, 0.84 mmol) and *p*-toluenesulfonic acid (0.20 g, 1.0 mmol) were mixed together in 60 mL of benzene, and the solution was heated to reflux under azeotropic distillation conditions overnight under nitrogen. Benzene was removed in vacuo, and the residue was partitioned between EtOAc and saturated $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4, and the crude material was flash chromatographed (silica gel). **5a** was eluted with

EtOAc/hexane (1:4) mixture, 0.2 g (60%, yield); ^{1}H NMR ($CDCl_3$) 1.19−2.01 (9H, m), 2.75−2.86 (2H, bd), 3.41−3.51 (4H, m, NCH_2 and OCH_2CH_2), 5.30 (1H, s, Ph_2CHO), 6.88−7.60 (14H, m, 2*Ph* + *Ph*F). Free base was converted into its oxalate salt, mp 168.8−169.9 °C. Anal. [$C_{27}H_{30}FNO\cdot(COOH)_2$] C, H, N.

Procedure D: Synthesis of 1-Nicotinoyl-4-[(ethoxycarbonyl)methyl]piperidine (6a). Hydrochloride salt of amine ester **2** (0.47 g, 2.3 mmol) was added into 15 mL of dry methylene chloride solution with triethylamine (1.3 g). Nicotinoyl chloride (0.83 g, 4.6 mmol) was then added into the solution in a portionwise manner. The solution was stirred under nitrogen overnight. The crude product was collected by removing methylene chloride and was chromatographed over a silica gel column. Pure product was eluted with EtOAc/MeOH (1%) solvent mixture, 0.55 g (87% yield), as a colorless viscous liquid: ^{1}H NMR ($CDCl_3$) 1.18−1.32 (3H, t, J = 7.1 Hz, CH_3CH_2), 1.43−2.31 (7H, m), 2.74−3.18 (2H, m), 4.03−4.24 (2H, q, J = 7.0 Hz, CH_2CH_3), 4.59−4.76 (2H, m), 7.28−8.66 (4H, m, *aromatic-CH*). Anal. ($C_{15}H_{20}N_2O_3\cdot 0.2H_2O$) C, H, N.

Procedure E: Synthesis of 1-[(2-Thienyl)methyl]-4-[(ethoxycarbonyl)methyl]piperidine (9a). Amine hydrochloride **2** (0.2 g, 0.96 mmol) and 1-thiophenecarbomethoxaldehyde (0.15 g, 1.3 mmol) were dissolved in 25 mL of dry MeOH with 0.4 g of triethylamine. Into the solution was added 4A molecular sieves (4 g), and the reaction mixture was stirred at room temperature for 1.5 h. Sodium cyanoborohydride (0.15 gm, 2.38 mmol) was added into the solution, and the reaction was continued for an additional 12 h. The reaction mixture was filtered through Celite, and the filtrate was collected. Crude material was chromatographed over a silica gel column. Pure compound was eluted with 30% EtOAc/hexane mixture, 0.17 g (68% yield), as a colorless liquid: ^{1}H NMR ($CDCl_3$) 1.16−1.31 (3H, t, J = 7.0 Hz, CH_3CH_2), 1.36−2.25 (7H, m), 2.84−2.95 (2H, m), 3.70 (2H, s, NCH_2), 4.00−4.22 (2H, q, J = 7.1 Hz, CH_3CH_2), 6.89−7.25 (3H, m, *aromatic-CH*). Anal. ($C_{14}H_{21}NO_2S$) C, H, N.

Procedure F: Synthesis of 4-[2-[(2-Thienyl)phenylmethoxy]ethyl]-1-(phenylmethyl)piperidine (13a). Phenyl(2-thienyl)methanol (0.39 g, 2 mmol) was dissolved in 25 mL of dry benzene, and into it was added thionyl chloride (0.39 g, 2 mmol). The solution was refluxed for 1 h, and benzene along with excess thionyl chloride was removed in vacuo. The residue was dried in the pump. Crude chloride was dissolved in toluene, and into it was added 1-benzyl-4-(2-hydroxyethyl)-piperidine (**12a**) (0.15 g, 0.68 mmol). The solution was refluxed under nitrogen for 1.5 h, and thin layer chromatography showed the formation of a new product. Solvent was removed in vacuo, and the crude compound was taken in saturated $NaHCO_3$ solution. Crude product was extracted into ethyl acetate layer and was dried over Na_2SO_4. Crude product was chromatographed over a silica gel column, and the pure product was eluted with (1:1) EtOAc/hexane mixture to give **13a**, 0.2 g (77% yield), as a viscous liquid: ^{1}H NMR ($CDCl_3$) 1.10−1.75 (7H, m), 1.82−2.05 (2H, t, J = 10.8 Hz, NCH_2CH_2), 2.75−2.95 (2H, m), 3.40−3.60 (4H, m), 5.52 (1H, s, Ph(2-thiophene)*CH*), 6.75−7.50 (13H, m, *aromatic-CH*). Free base was converted into its oxalate salt, mp 171.9−173 °C. Anal. [$C_{25}H_{29}NOS\cdot(COOH)_2\cdot 0.3H_2O$] C, H, N.

Synthesis of 1-[(4-Chlorophenyl)methyl]-4-[(ethoxycarbonyl)methyl]piperidine (3b). 4-Chlorobenzyl chloride (0.27 g, 1.7 mmol) was reacted with amine hydrochloride **2** (0.3 g, 1.4 mmol) in the presence of K_2CO_3 to furnish **3b**, 0.3 g (73%), as a colorless oil (procedure A): ^{1}H NMR ($CDCl_3$) 1.17−1.31 (3H, t, J = 7.1 Hz, CH_3CH_2), 1.43−2.09 (5H, m), 2.18−2.25 (2H, d, J = 6.7 Hz, CH_2CH), 2.75−2.87 (2H, m), 3.42 (2H, s, NCH_2), 4.01−4.22 (2H, q, J = 7.0 Hz, CH_2CH_3), 7.24−7.31 (4H, m, *Ph*Cl). Anal. ($C_{16}H_{22}NO_2Cl$) C, H, N.

Synthesis of 1-[(4-Bromophenyl)methyl]-4-[(ethoxycarbonyl)methyl]piperidine (3c). 4-Bromobenzyl bromide (0.9 g, 3.6 mmol) was reacted with amine hydrochloride **2** (0.3 g, 1.4 mmol) in the presence of K_2CO_3 to furnish **3c**, 0.38 g (88% yield), as a colorless oil (procedure A): ^{1}H NMR ($CDCl_3$) 1.17−1.31 (3H, t, J = 7.1 Hz, CH_3CH_2), 1.61−2.09 (5H, m), 2.18−2.25 (2H, d, J = 6.6 Hz, CH_2CH), 2.75−2.87 (2H, m), 3.41 (2H, s, NCH_2), 4.01−4.22 (2H, q, J = 7.0 Hz, CH_2CH_3), 7.13−7.46 (4H, m, *Ph*Br). Anal. ($C_{16}H_{22}NO_2Br$) C, H, N.

Synthesis of 1-[(3,4-Dichlorophenyl)methyl]-4-[(ethoxycarbonyl)methyl]piperidine (3d). α,3,4-Trichlorotoluene (0.96 g, 4.9 mmol) was reacted with amine hydrochloride **2** (0.6 g, 2.8 mmol) in the presence of K_2CO_3 to furnish **3d**, 0.72 g (78% yield), as a colorless oil (procedure A): ^{1}H NMR ($CDCl_3$) 1.17−1.31 (3H, t, J = 7.1 Hz, CH_3CH_2), 1.45−2.11 (5H, m), 2.19−2.26 (2H, d, J = 6.6 Hz, CH_2CH), 2.75−2.86 (2H, m), 3.41 (2H, s, NCH_2), 4.01−4.23 (2H, q, J = 7.0 Hz, CH_2CH_3), 7.17−7.42 (3H, m, *Ph*Cl_2). Anal. ($C_{16}H_{21}NO_2Cl_2$) C, H, N.

Synthesis of 1-[(4-Methoxyphenyl)methyl]-4-[(ethoxycarbonyl)methyl]piperidine (3e). Amine hydrochloride **2** (0.15 g, 0.72 mmol) was reacted with *p*-methoxy-α-chlorotoluene (0.15 g, 0.95 mmol) to give **3e**, 0.09 g (45% yield), as a colorless oil (procedure A): ^{1}H NMR ($CDCl_3$) 1.17−1.31 (3H, t, J = 7.1 Hz, CH_3CH_2), 1.63−2.07 (5H, m), 2.18−2.25 (2H, d, J = 6.6 Hz, CH_2CH), 2.78−2.90 (2H, m), 3.42 (2H, s, NCH_2), 3.79 (3H, s, CH_3O), 4.00−4.22 (2H, q, J = 7.0 Hz, CH_2CH_3), 6.79−7.26 (4H, m, *Ph*OCH_3). Anal. ($C_{17}H_{25}NO_3$) C, H, N.

Synthesis of 1-[(4-Methylphenyl)methyl]-4-[(ethoxycarbonyl)methyl]piperidine (3f). Amine hydrochloride **2** (0.3 g, 1.44 mmol) was reacted with 4-methylbenzyl chloride (0.32 g, 2.3 mmol) to give **3f**, 0.28 g (72% yield), as a colorless oil (procedure A): ^{1}H NMR ($CDCl_3$) 1.16−1.34 (3H, t, J = 7.1 Hz, CH_3CH_2), 1.61−2.06 (5H, m), 2.18−2.24 (2H, d, J = 6.6 Hz, CH_2CH), 2.32 (3H, s, CH_3Ph), 2.79−2.90 (2H, m), 3.44 (2H, s, NCH_2), 4.00−4.22 (2H, q, J = 7.0 Hz, CH_2CH_3), 7.13−7.25 (4H, m, *Ph*CH_3). Anal. ($C_{17}H_{25}NO_2$) C, H, N.

Synthesis of 1-[(4-Chlorophenyl)methyl]-4-(2-hydroxyethyl)piperidine (4b). Ester **3b** (0.46 g, 1.5 mmol) was converted into product **4b**, 0.36 g (92% yield), as a colorless oil (procedure B): ^{1}H NMR ($CDCl_3$) 1.25−2.03 (9H, m), 2.75−2.86 (2H, m), 3.41 (2H, s, NCH_2), 3.56−3.68 (2H, t, J = 6.3 Hz, CHCH_2O), 7.23−7.27 (4H, m, *Ph*Cl); MS (CI) *m/e* 253.59 $(M + H)^+$.

Synthesis of 1-[(4-Bromophenyl)methyl]-4-(2-hydroxyethyl)piperidine (4c). Ester **3c** (0.3 g, 0.92 mmol) was converted into product **4c**, 0.22 g (82% yield), as a colorless viscous oil (procedure B): ^{1}H NMR ($CDCl_3$) 1.10−2.08 (9H, m), 2.75−2.95 (2H, m), 3.45 (2H, s, NCH_2), 3.60−3.75 (2H, t, J = 6.3 Hz, CHCH_2O), 7.15−7.52 (4H, m, *Ph*Br); MS (CI) *m/e* 299.04 $(M + H)^+$.

Synthesis of 1-[(3,4-Dichlorophenyl)methyl]-4-(2-hydroxyethyl)piperidine (4d). Ester **3d** (0.43 g, 1.3 mmol) was converted into product **4d**, 0.3 g (81% yield), as a colorless oil (procedure B): ^{1}H NMR ($CDCl_3$) 1.10−2.05 (9H, m), 2.74−2.86 (2H, m), 3.58−3.70 (2H, t, J = 6.3 Hz, CHCH_2O), 4.62-(2H, s, NCH_2), 7.19−7.44 (3H, m, *Ph*Cl_2); MS (CI) *m/e* 289.03 $(M + H)^+$.

Synthesis of 1-[(4-Methoxyphenyl)methyl]-4-(2-hydroxyethyl)piperidine (4e). Ester **3e** (0.08 g, 0.27 mmol) was converted into product **4e**, 0.065 g (95% yield), as a viscous liquid (procedure B): ^{1}H NMR ($CDCl_3$) 1.23−2.00 (9H, m), 2.80−2.91 (2H, m), 3.42 (2H, s, CH_2N), 3.61−3.74 (2H, t, J = 6 Hz, CH_2CH_2O), 3.79 (3H, s, CH_3O), 6.79−7.26 (4H, m, *Ph*OCH_3); MS (CI) *m/e* 250.15 $(M + H)^+$.

Synthesis of 1-[(4-Methylphenyl)methyl]-4-(2-hydroxyethyl)piperidine (4f). Ester **3f** (0.2 g, 0.72 mmol) was converted into product **4f**, 0.13 g (81%, yield), as a colorless oil (procedure B): ^{1}H NMR ($CDCl_3$) 1.10−2.08 (9H, m), 2.35 (3H, s, CH_3Ph), 2.85−2.95 (2H, m), 3.45 (2H, s, NCH_2), 3.60−3.80 (2H, t, J = 6.3 Hz, CHCH_2O), 7.00−7.28 (4H, m, *Ph*CH_3); MS (CI) *m/e* 234.16 $(M + H)^+$.

Synthesis of 4-[2-(Diphenylmethoxy)ethyl]-1-[(4-chlorophenyl)methyl]piperidine (5b). Compound **4b** (0.3 g, 1.18 mmol) was reacted with benzhydrol (0.71 g, 3.9 mmol) to give **5b**, 0.3 g (62% yield), as a viscous liquid (procedure C): ^{1}H NMR ($CDCl_3$) 1.12−2.01 (9H, m), 2.73−2.84 (2H, m), 3.39−3.51 (4H, m, CH_2CH_2O + NCH_2), 5.30 (1H, s, Ph_2CH), 7.22−7.59 (14H, m, 2*Ph* + *Ph*Cl). Free base was converted into its oxalate salt, mp 179.6−181.6 °C. Anal. [$C_{27}H_{30}NOCl\cdot(COOH)_2$] C, H, N.

Synthesis of 4-[2-(Diphenylmethoxy)ethyl]-1-[(4-bromophenyl)methyl]piperidine (5c). Compound **4c** (0.2 g,

0.67 mmol) was reacted with benzhydrol (0.43 g, 2.3 mmol) to give **5c**, 0.19 g (61% yield), as a viscous liquid (procedure C): ^{1}H NMR ($CDCl_3$) 1.22−2.03 (9H, m), 2.74−2.86 (2H, bd), 3.40−3.53 (4H, m, CH_2CH_2O + NCH_2), 5.31 (1H, s, Ph_2CH), 7.22−7.59 (14H, m, 2*Ph* + *Ph*Br). Free base was converted into its oxalate salt, mp 180.5−181.9 °C. Anal. [$C_{27}H_{30}NOBr\cdot(COOH)_2$] C, H, N.

Synthesis of 4-[2-(Diphenylmethoxy)ethyl]-1-[(3,4-dichlorophenyl)methyl]piperidine (5d). Compound **4d** (0.26 g, 0.9 mmol) was reacted with benzhydrol (0.5 g, 2.8 mmol) to give **5d**, 0.11 g (28% yield), as a viscous liquid (procedure C): ^{1}H NMR ($CDCl_3$) 1.22−2.03 (9H, m), 2.73−2.84 (2H, bd), 3.39−3.53 (4H, m, CH_2CH_2O + NCH_2), 5.30 (1H, s, Ph_2CH), 7.09−7.40 (13H, m, 2*Ph* + *Ph*Cl_2). Free base was converted into its oxalate salt, mp 171.8−172.8 °C. Anal. [$C_{27}H_{29}NOCl_2\cdot(COOH)_2$] C, H, N.

Synthesis of 4-[2-(Diphenylmethoxy)ethyl]-1-[(4-methoxyphenyl)methyl]piperidine (5e). Compound **4e** (0.3 g, 1.2 mmol) was reacted with benzhydrol (0.71 g, 3.8 mmol) to give **5e**, 0.31 g (63% yield), as a viscous liquid (procedure C): ^{1}H NMR ($CDCl_3$) 1.16−2.01 (9H, m), 2.76−2.87 (2H, bd), 3.39−3.51 (4H, m, CH_2CH_2O + NCH_2), 3.75 (3H, s, CH_3O), 5.29 (1H, s, Ph_2CH), 6.78−7.34 (14H, m, 2*Ph* + *Ph*OCH_3). Free base was converted into its oxalate salt, mp 151.9−153.4 °C. Anal. [$C_{28}H_{33}NO_2\cdot(COOH)_2\cdot0.3\ H_2O$] C, H, N.

Synthesis of 4-[2-[(4-Chlorophenyl)phenylmethoxy]-ethyl]-1-[(4-fluorophenyl)methyl]piperidine (5f). 4-Chlorobenzhydrol (0.38 g, 1.7 mmol) was reacted with compound **4a** (0.12 g, 0.5 mmol) to give **5f**, 0.11 g (52% yield), as a viscous liquid (procedure C): ^{1}H NMR ($CDCl_3$) 1.24−2.04 (9H, m), 2.75−2.87 (2H, m), 3.38−3.51 (4H, m, CH_2CH_2O + NCH_2), 5.27 (1H, s, Ph_2CH), 6.88−7.28 (13H, m, *Ph* + *Ph*F + *Ph*Cl). Free base was converted into its oxalate salt, mp 164.5−165.8 °C. Anal. [$C_{27}H_{29}NOFCl\cdot(COOH)_2$] C, H, N.

Synthesis of 4-[2-[(4-Fluorophenyl)phenylmethoxy]-ethyl]-1-[(4-fluorophenyl)methyl]piperidine (5g). 4-Fluorobenzhydrol (0.42 g, 2 mmol) was reacted with compound **4a** (0.15 g, 0.63 mmol) to give **5g**, 0.17 g (65% yield), as a viscous liquid (procedure C): ^{1}H NMR ($CDCl_3$) 1.19−2.02 (9H, m), 2.75−2.87 (2H, m), 3.39−3.51 (4H, m, CH_2CH_2O + NCH_2), 5.28 (1H, s, Ph_2CH), 6.89−7.36 (13H, m, *Ph* + *Ph*F + *Ph*F). Free base was converted into its oxalate salt, mp 153.9−155.8 °C. Anal. [$C_{27}H_{29}NF_2O\cdot(COOH)_2$] C, H, N.

Synthesis of 4-[2-(Diphenylmethoxy)ethyl]-1-[(4-methylphenyl)methyl]piperidine (5h). Compound **4f** (0.1 g, 0.42 mmol) was reacted with benzhydrol (0.23 g, 1.2 mmol) to produce **5h**, 0.11 g (69% yield), as a viscous liquid (procedure C): ^{1}H NMR ($CDCl_3$) 1.25−2.02 (9H, m), 2.32 (3H, s, CH_3Ph), 2.77−2.90 (2H, m), 3.43−3.52 (4H, m, CH_2CH_2O + NCH_2), 5.30 (1H, s, Ph_2CH), 7.05−7.35 (14H, m, *2Ph* + *Ph*CH_3). Free base was converted into its oxalate salt. Anal. [$C_{28}H_{33}NO\cdot(COOH)_2$] C, H, N.

Synthesis of 1-(2-Benzo[*b*]thiopheneyl)-4-[(ethoxycarbonyl)methyl]piperidine (6b). Amine hydrochloride **2** (0.22 g, 1.1 mmol) was reacted with acid chloride of benzo[b]-thiophene-2-carboxylic acid (1.1 mmol) to give product **6b**, 0.31 g (86% yield), as a viscous liquid (procedure D): ^{1}H NMR ($CDCl_3$) 1.17−1.31 (3H, t, J = 7.1 Hz, CH_3CH_2), 1.55−2.40 (7H, m), 2.75−3.20 (2H, t, J = 8 Hz, CH_2CH_2NCO), 4.05−4.26 (2H, q, J = 7.0 Hz, CH_2CH_3), 4.35−4.60 (2H, bd, CH_2NCO), 7.25−7.95 (5H, m, *aromatic-CH*). Anal. ($C_{18}H_{21}NO_3S$) C, H, N.

Synthesis of 1-(3-Chloro-4-fluorobenzoyl)-4-[(ethoxycarbonyl)methyl]piperidine (6c). Amine hydrochloride **2** (0.3 g, 1.4 mmol) was reacted with 3-chloro-4-fluorobenzoyl chloride (1.7 mmol) to give product **6c**, 0.5 g (91% yield), as an oil (procedure D): ^{1}H NMR ($CDCl_3$) 1.17−1.31 (3H, t, J = 7.1 Hz, CH_3CH_2), 1.55−2.36 (7H, m), 2.65−3.20 (2H, m), 4.02−4.26 (2H, q, J = 7.0 Hz, CH_2CH_3), 4.40−4.60 (2H, m), 7.05−7.55 (3H, m, *Ph*ClF). Anal. ($C_{16}H_{19}NO_3ClF$) C, H, N.

Synthesis of 1-[(3-Pyridyl)methyl]-4-(2-hydroxyethyl)-piperidine (7a). Ester **6a** (0.45 g, 1.6 mmol) was converted into product **7a**, 0.32 g (91% yield), as a viscous liquid (procedure B): ^{1}H NMR ($CDCl_3$) 1.00−2.15 (9H, m), 2.50−3.05 (2H, m), 3.50 (2H, s, NCH_2), 3.55−3.80 (2H, t, J = 6 Hz, CH_2CH_2O), 7.15−8.55 (3H, m, *aromatic-CH*); MS (CI) *m/e* 221.14 $(M + H)^+$.

Synthesis of 1-[(2-Benzo[*b*]thiopheneyl)methyl]-4-(2-hydroxyethyl)piperidine (7b). Ester **6b** (0.09 g, 0.27 mmol) was converted into product **7a**, 0.085 g (93% yield), as a viscous liquid (procedure B): ^{1}H NMR ($CDCl_3$) 1.00−2.20 (9H, m), 2.85−3.10 (2H, m), 3.60−3.85 (4H, m, NCH_2 + CH_2CH_2O), 7.12−7.85 (5H, m, *aromatic-CH*); MS *m/e* (CI) 276.12 $(M + H)^+$.

Synthesis of 1-[(3-Chloro-4-fluorophenyl)methyl]-4-(2-hydroxyethyl)piperidine (7c). Ester **6c** (0.45 g, 1.3 mmol) was converted into product **7c**, 0.3 g (86% yield), as an oil (procedure B): ^{1}H NMR ($CDCl_3$) 1.08−2.08 (9H, m), 2.75−2.90 (2H, m), 3.45 (2H, s, NCH_2), 3.60−3.78 (2H, t, J = 6 Hz, CH_2CH_2O), 6.98−7.45 (3H, m, *Ph*ClF); MS (CI) *m/e* 272.57 $(M + H)^+$.

Synthesis of 4-[2-(Diphenylmethoxy)ethyl]-1-(3-pyridylmethyl)piperidine (8a). Compound **7a** (0.17 g, 0.77 mmol) was reacted with benzhydrol (0.5 g, 2.6 mmol) to give product **8a**, 0.12 g (42% yield), as a viscous liquid (procedure C): ^{1}H NMR ($CDCl_3$) 1.22−1.66 (7H, m), 1.83−2.05 (2H, t, J = 11.2 Hz, NCH_2CH_2), 2.74−2.85 (2H, m), 3.40−3.51 (4H, m, NCH_2 + CH_2CH_2O), 5.29 (1H, s, Ph_2CHO), 7.20−8.51 (14H, m, 2*Ph* + *aromatic-CH*). Free base was converted into its oxalate salt, mp 150.5−151.6 °C. Anal. [$C_{26}H_{30}N_2O\cdot2(COOH)_2\cdot0.6H_2O$] C, H, N.

Synthesis of 4-[2-(Diphenylmethoxy)ethyl]-1-[(2-benzo[*b*]thiopheneyl)methyl]piperidine (8b). Compound **7b** (0.085 g, 0.3 mmol) was reacted with benzhydrol (0.17 g, 0.92 mmol) to give product **8b**, 0.05 g (39% yield), as a viscous liquid (procedure C): ^{1}H NMR ($CDCl_3$) 1.15−1.67 (7H, m), 1.90−2.11 (2H, t, J = 11.2 Hz, NCH_2CH_2), 2.86−2.98 (2H, m), 3.40−3.52 (2H, t, J = 6 Hz, CH_2CH_2O), 3.74 (2H, s, NCH_2), 5.30 (1H, s, Ph_2CHO), 7.11−7.88 (15H, m, 2*Ph* + *aromatic-CH*). Free base was converted into its oxalate salt, mp 171.8−172.8 °C. Anal. [$C_{29}H_{31}NOS\cdot(COOH)_2\cdot0.25\ H_2O$] C, H, N.

Synthesis of 4-[2-(Diphenylmethoxy)ethyl]-1-[(4-fluoro-3-chlorophenyl)methyl]piperidine (8c). Compound **7c** (0.23 g, 0.84 mmol) was reacted with benzhydrol (0.72 g, 3.9 mmol) to give product **8c**, 0.25 g (68%, yield), as a viscous liquid (procedure C): ^{1}H NMR ($CDCl_3$) 1.24−2.03 (9H, m), 2.73−2.84 (2H, m), 3.38−3.53 (4H, m, NCH_2 + CH_2CH_2O), 5.30 (1H, Ph_2CHO), 7.02−7.38 (13H, m, 2*Ph* + *Ph*ClF). Free base was converted into its oxalate salt, mp 201.9−203 °C. Anal. [$C_{27}H_{29}FNOCl\cdot(COOH)_2$] Anal. C, H, N.

Synthesis of 1-[(4-Nitrophenyl)methyl]-4-[(ethoxycarbonyl)methyl]piperidine (9b). Amine hydrochloride **2** (0.5 g, 2.4 mmol) was reacted with *p*-nitrobenzaldehyde (0.6 g, 3.9 mmol) to give product **9b**, 0.23 g (33% yield), as a reddish oil (procedure E): ^{1}H NMR ($CDCl_3$): 1.18−1.32 (3H, t, J = 7.0 Hz, CH_3CH_2), 1.36−2.27 (7H, m), 2.74−2.87 (2H, m), 3.56 (2H, s, NCH_2), 4.02−4.84 (2H, q, J = 7.1 Hz, CH_2CH_3), 7.45−8.21 (4H, m, *Ph*NO_2). Anal. ($C_{16}H_{22}N_2O_4\cdot0.1H_2O$) C, H, N.

Synthesis of 1-(2-Thienylmethyl)-4-(2-hydroxyethyl)-piperidine (10a). Ester **9a** (0.2 g, 0.79 mmol) was converted into product **10a**, 0.16 g (94% yield), as a viscous liquid (procedure B): ^{1}H NMR ($CDCl_3$) 1.10−2.26 (9H, m), 2.80−3.02 (2H, m), 3.55−3.75 (4H, m, NCH_2 + CH_2CH_2O), 6.90−7.25 (3H, m, *aromatic-CH*); MS (CI) *m/e* 226.13 $(M + H)^+$.

Synthesis of 1-[(4-Nitrophenyl)methyl]-4-(2-hydroxyethyl)piperidine (10b). Ester **9b** (0.1 g, 0.3 mmol) was dissolved in 10 mL of the dimethyl ether of glycol, and $NaBH_4$ (20 mg, 0.4 mmol) was added. The solution was warmed to 45 °C, and $AlCl_3$ (20 mg, 0.14 mmol) was added next. The reaction was then continued at 55 °C for 1 h and was brought back to room temperature. The reaction was quenched with ice cold 1 N HCl solution, and the acidic solution was neutralized by NaOH solution. The product was extracted into EtOAc layer and was dried over Na_2SO_4. The amount of alcohol **10b** isolated was 0.065 g (82% yield) as a viscous liquid: ^{1}H NMR ($CDCl_3$) 1.10−3.20 (11H, m), 3.65−4.15 (4H, m, NCH_2 + CH_2CH_2O), 7.55−8.30 (4H, m, *Ph*NO_2); MS (CI) *m/e* 265.12 $(M + H)^+$.

Synthesis of 4-[2-(Diphenylmethoxy)ethyl]-1-(2-thienylmethyl)piperidine (11a). Compound **10a** (0.15 g, 0.66 mmol) was reacted with benzhydrol (0.51 g, 2.8 mmol) to give **8b**, 0.15 g (60% yield), as a viscous liquid (procedure C): ^{1}H NMR ($CDCl_3$) 1.25−1.68 (7H, m), 1.86−2.04 (2H, t, J = 10.8

Hz, NCH_2CH_2), 2.83−2.94 (2H, m), 3.40−3.52 (2H, t, J = 6.1 Hz, CH_2CH_2O), 3.69 (2H, s, NCH_2), 5.30 (1H, s, Ph_2CH), 6.89−7.42 (13H, m, 2*Ph* + *aromatic-CH*). Free base was converted into its oxalate salt, mp 145.9−149 °C. Anal. [$C_{25}H_{29}NSO\cdot(COOH)_2$] C, H, N.

Synthesis of 4-[2-(Diphenylmethoxy)ethyl]-1-[(4-nitrophenyl)methyl]piperidine (11b). Compound **10b** (0.09 g, 0.34 mmol) was reacted with benzhydrol (0.18 g, 1 mmol) to give **11b**, 0.08 g (57% yield), as a viscous liquid (procedure C): ^{1}H NMR ($CDCl_3$) 1.11−1.72 (7H, m), 1.86−2.10 (2H, t, J = 10.9 Hz, NCH_2CH_2), 2.74−2.88 (2H, m), 3.41−3.55 (4H, m, CH_2CH_2O + NCH_2), 5.32 (1H, s, Ph_2CH), 7.20−8.24 (14H, m, 2*Ph* + *Ph*NO_2). Free base was converted into its oxalate salt, mp 95.2−96.5 °C. Anal. [$C_{27}H_{30}N_2O_3\cdot(COOH)_2\cdot0.6H_2O$] C, H, N.

Synthesis of 4-[2-(Diphenylmethoxy)ethyl]-1-[(4-aminophenyl)methyl]piperidine (11c). Compound **11b** (0.08 g, 0.18 mmol) was dissolved in 10 mL of ethanol, and to it was added a solution of 200 mg of $SnCl_2$ dissolved in a minimum volume of ethanol. The solution was stirred at room temperature for 3 h, and TLC revealed completion of the reaction. Ethanol was removed in vacuo, and the residue was partitioned between EtOAc and water. The organic layer was dried over Na_2SO_4, and crude product collected was chromatographed over a silica gel column. Pure product **11c** came out with EtOAc (0.5% Et_3N), 0.04 g (57% yield), as a viscous liquid: ^{1}H NMR ($CDCl_3$) 1.25−2.00 (9H, m), 2.78−2.90 (2H, m), 3.37−3.59 (6H, m), 5.31 (1H, s, Ph_2CH), 6.59−7.35 (14H, m, 2*Ph* + *Ph*NH_2). Free base was converted into its oxalate salt, mp 160.8−163.4 °C. Anal. [$C_{27}H_{32}N_2O\cdot2(COOH)_2$] C, H, N.

Synthesis of 4-[2-[(2-Thienyl)phenylmethoxy]ethyl]-1-[(4′-fluorophenyl)methyl]piperidine (13b). Phenyl(2-thienyl)methanol (0.51 g, 2.7 mmol) was reacted with alcohol **4a** (0.2 g, 0.84 mmol) to give product **13b**, 0.11 g (33% yield), as a viscous liquid (procedure F): ^{1}H NMR ($CDCl_3$) 1.21−1.79 (7H, m), 1.80−2.03 (2H, t, J = 10.8 Hz, NCH_2CH_2), 2.76−2.88 (2H, m), 3.42−3.56 (4H, m), 5.52 (1H, s, Ph(2-thienyl)*CH*), 6.77−7.43 (12H, m, *Ph* + *aromatic-CH* + *Ph*F). Free base was converted into its oxalate salt, mp 187.1−188.2 °C.

Anal. [$C_{25}H_{28}NSOF\cdot(COOH)_2\cdot H_2O$] C, H, N.

Synthesis of 4-[2-[(2-Thienyl)phenylmethoxy]ethyl]-1-(3-pyridylmethyl)piperidine (13c). Phenyl(2-thienyl)methanol (0.9 g, 4.0 mmol) was reacted with alcohol **7a** (0.28 g, 1.2 mmol) to give product **13b**, 0.05 g (11% yield), as a viscous liquid (procedure F): ^{1}H NMR ($CDCl_3$) 1.10−1.75 (7H, m), 1.85−2.10 (2H, t, J = 10.8 Hz, NCH_2CH_2), 2.75−2.94 (2H, m), 3.36−3.56 (4H, m), 5.40 (1H, s, Ph(2-thiophene)*CH*), 6.75−8.55 (12H, m, *Ph* + *aromatic-CH*). Free base was converted into its oxalate salt, mp 135.9−137.8 °C. Anal. [$C_{24}H_{26}N_2OS\cdot2(COOH)_2\cdot0.5H_2O$] C, H, N.

Biological Methods. Binding of [^{3}H]WIN 35,428 to the DAT and [^{3}H]citalopram to the SERT was measured exactly as described by us previously.[29] Rat striatal tissue was the source of transporters, and both assays were carried out under the same conditions. All compounds were dissolved in 10% dimethyl sulfoxide, and IC_{50} values were determined as described in our previous report.[29] The only difference was that the binding assays were terminated by filtration with MACH3−96 Tomtee harvester (Wallac Inc., Gaithersburg, MO), and the filter mats (glan fibre, Wallac Inc.) were assayed for radioactivity with Betaplate Scint liquid scintillation cocktail (Wallac Inc.) in a Microbeta Plus liquid scintillation counter (Wallac Inc.), at an efficiency for ^{3}H of approximately 35%.

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