Potent and Selective Ligands for the Dopamine Transporter (DAT): Structure−Activity Relationship Studies of Novel 4-[2-(Diphenylmethoxy)ethyl]-1-(3-phenylpropyl)piperidine Analogues

Aloke K. Dutta,*,† Lori L. Coffey,‡ and Maarten E. A. Reith‡

Organix Inc., 65 Cummings Park, Woburn, Massachusetts 01801, and Department of Biomedical and Therapeutic Sciences, University of Illinois, College of Medicine, P.O. Box 1649, Peoria, Illinois 61656

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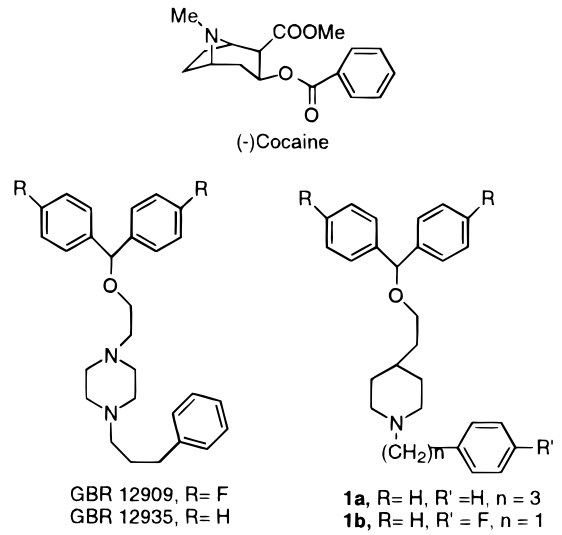
Molecular structural modifications of 4-[2-(diphenylmethoxy)ethyl]-1-(3-phenylpropyl)piperidine (**1a**), a dopamine transporter (DAT)-specific ligand, generated several novel analogues. Biological activities of these new molecules for their binding to the DAT and serotonin transporter (SERT) were evaluated in rat striatal membranes. Some of these new analogues were more potent and selective than GBR 12909 when their binding to the DAT relative to SERT was compared. Thus compounds **9** and **19a** were among the most potent (IC_{50} = 6.6 and 6.0 nM, respectively) and selective (DAT/SERT = 33.8 and 30.0, respectively) compounds in this series, and they were more active than GBR 12909 (IC_{50} = 14 nM, DAT/SERT = 6.1). Introduction of a double bond in the *N*-propyl side chain of these molecules did not influence their activities to a great extent. Bioisosteric replacement of the aromatic phenyl group by a thiophene moiety produced some of the most potent compounds in this series.

Introduction

Cocaine is a strong reinforcer and has great abuse potential in humans.[1−3] Cocaine use has reached an epidemic proportion in the last two decades in the United States. There is an urgent need to develop a pharmacotherapeutic agent to treat cocaine addiction, since currently there is no medication available to treat this addiction. Cocaine binds to all three monoamine transporter systems in the brain which mediate the neuronal uptake of dopamine (dopamine transporter, DAT), serotonin (SERT), and norepinephrine (NET).[4−6] The central mechanism of cocaine addiction is attributed to its binding to the DAT which is located presynaptically in the dopaminergic neuron.[7−9] Binding of cocaine to the DAT leads to an elevated level of dopamine in the synapse and is the underlying reason for cocaine's stimulatory and perhaps addictive effect.[7] A significant correlation exists between the potencies of various cocaine-like compounds binding to the DAT and the potencies of these same compounds producing self-administration behavior. In a recent study, it has also been demonstrated that knockout mice without the DAT were not stimulated by cocaine which further reinforces the dopaminergic hypothesis of cocaine addiction.[10]

Drug development targeting the DAT resulted in the generation of some very potent and selective molecules of diverse structural backgrounds.[11−13] Comprehensive structure−activity relationship (SAR) studies based on the phenyl tropane class of compounds provided many potent and selective molecules for this transpoprter.[14−16] GBR compounds, which are disubstituted piperazine derivatives, were shown to display high affinity and selectivity for the DAT. Some well-known GBR compounds, GBR 12935 and its bisfluorinated analogue GBR 12909 (Chart 1), were shown to have high potency for the DAT.[17,18] Recent evidence suggests that GBR 12935-like compounds might have efficacy of potential pharmacotherapeutic agents as cocaine antagonists. Thus in locomotor-stimulating activity, GBR 12909 was found to be less potent than cocaine in rats.[19] Other recent experiments further demonstrated that GBR 12909 could decrease cocaine-maintained responding without having an effect on food-maintained responding in monkeys.[20,21] In human studies GBR 12909 was found to have nonstimulant properties, and in microdialysis studies in rats GBR 12909 could attenuate the enhancement of the level of extracellular dopamine in the striatum induced by cocaine.[22,23] All of this information strengthened the notion that a suitable derivative of a GBR-type analogue may have the potential to antagonize cocaine action.

Chart 1



* To whom correspondence should be addressed.
† Organix Inc.
‡ University of Illinois.

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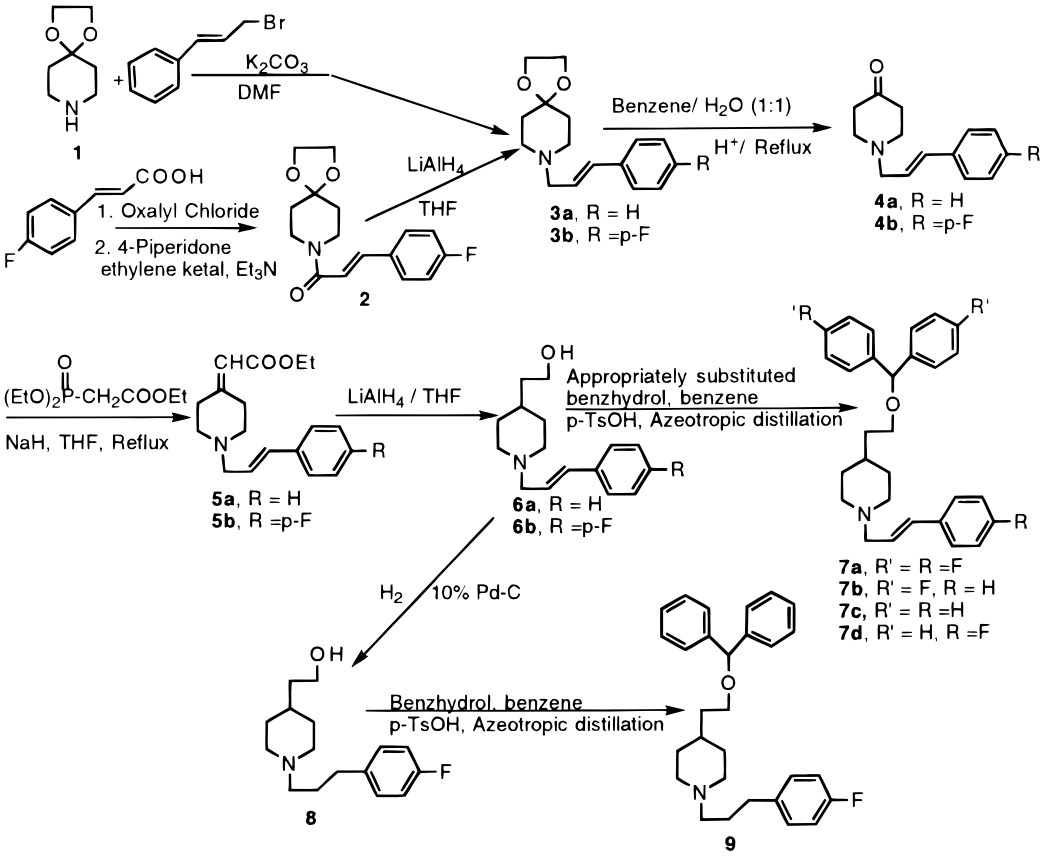
Scheme 1



Our ongoing SAR studies with the novel 4-[2-(diphenylmethoxy)ethyl]-1-(3-phenylpropyl)piperidine analogues resulted in the generation of potent and selective molecules for this transporter.[24−26] These compounds are structurally similar to GBR 12935 molecules differing only with the presence of a piperidine moiety instead of a piperazine ring located in the original GBR structures, **1a** (Chart 1). These new analogues of GBR-type compounds turned out to be even more selective since they did not have nonspecific piperazine acceptor site binding activity which is present in the original GBR molecules.[27] We have demonstrated in our previous SAR studies that some of the key structural features, which are needed for good potency and selectivity in these molecules for the DAT, are the following: (a) The unsubstituted and fluoro-substituted aromatic rings in the diphenylmethoxy moiety were best tolerated. (b) Different *N*-benzyl substitutions, where the different electronegative, electron-withdrawing, and neutral groups were introduced in the aromatic ring of the benzyl group, at the piperidine ring of the molecule produced some of the most potent and selective molecules for the DAT, **1b** (Chart 1).[26] (c) Different alkyl chain lengths connected to the 1- and 4-positions of the piperidine ring played important roles in the activities. One of our important findings from these SAR studies showed that replacement of the *N*-propyl-3-phenyl moiety in these molecules by a *N*-benzyl group resulted in the generation of highly selective molecules for the DAT mainly due to the reduction of affinity for the SERT.

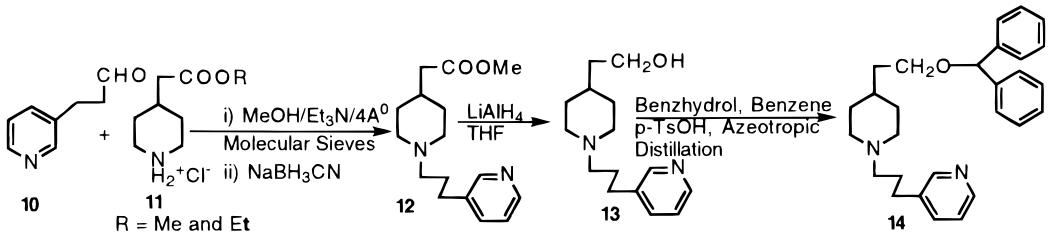
Past and recent SAR studies in the GBR series of molecules were carried out with different structural variations introduced into the molecule which resulted in the development of a number of potent analogues.[28,29] In some of these analogues the piperazine ring was altered while maintaining their high affinity and potency for the DAT.[30,31] Also, some recent reports described the synthesis of different series of novel benztropine derivatives structurally resembling GBR-type compounds and their binding affinity for the DAT.[32,33]

To understand the mode of binding of our piperidine analogues of GBR 12935 and to make a comparison with conventional GBR compounds, further structural variations of the compound 4-[2-(diphenylmethoxy)ethyl]-1-(3-phenylpropyl)piperidine, **1a**, were undertaken by introducing a double bond in the *N*-propyl side chain and also by replacing the aromatic phenyl moiety with bioisosteric thiophene and pyridine rings. It is of interest to assess whether there is a differential binding activity in these compounds as compared with their corresponding conventional GBR analogues and also to compare the binding results with those obtained by us previously for other compounds in this class.

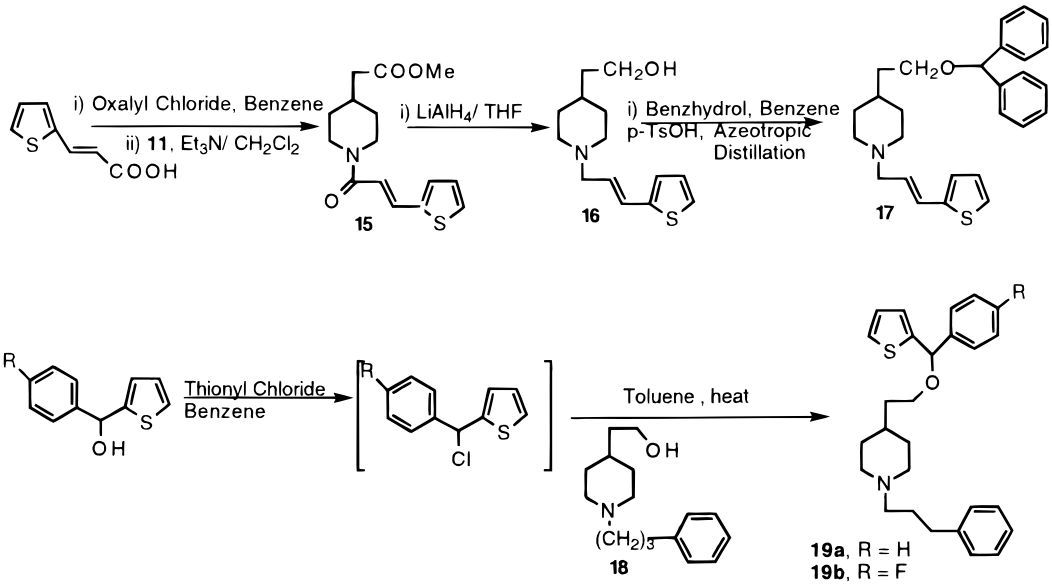
Chemistry

Syntheses of **7a**−**d** and **9** were accomplished by following our previous synthetic route as shown in Scheme 1.[25] Thus N-alkylation of ketal amine **1** with *trans*-cinnamyl bromide furnished **3a**, and similarly N-acylation of **1** with *trans*-cinnamoyl chloride followed by reduction with lithium aluminum hydride (LAH) produced **3b**. Deketalization of **3a,b** under acidic conditions yielded piperidinones **4a,b** which on Wittig reaction provided unsaturated esters **5a,b**. Reduction of the

Scheme 2



Scheme 3



esters with LAH provided alcohols **6a,b** and hydrogenation of **6b** yielded saturated alcohol **8**. Final compounds **7a**−**d** and **9** were synthesized by reacting alcohols **6a,b** and **8** with appropriate benzhydrols under azeotropic distillation conditions.[25,26,34]

Syntheses of **14** and **17** are described in Schemes 2 and 3 which followed our earlier procedure. Reductive amination of aldehyde **10** with amine **11** in the presence of sodium cyanoborohydride produced ester **12** which upon reduction with LAH and reaction with benzhydrol produced the final compound **14**.[35] Similarly acylation of amine **11** with the acid chloride of *trans*-thienylacrylic acid provided **15** which on reduction and followed by reaction with benzhydrol provided final target **17**. Syntheses of **19a**,**b** were carried out from a common known intermediate (**18**) in the same way as described before.[26]

Biochemistry

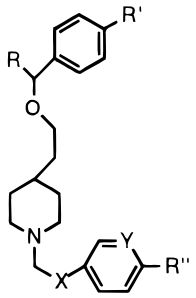
Biological studies of the newly synthesized compounds were carried out with membranes prepared from rat brain striatum as described earlier.[25,26] Binding analyses were performed to determine their activity at the DAT and SERT in brain. The DAT in the rat striatal tissue was labeled with a tritiated potent analogue of cocaine, [^{3}H]WIN 35,428, and the SERT was labeled with [^{3}H]citalopram.

Results and Discussion

Our previous SAR studies on GBR-type molecules resulted in the identification of active molecular determinants, some of which are different from the original GBR molecules. One of the important differences that emerged from these SAR studies between these two similar classes of molecules was evident from the effect of the introduction of different *N*-alkyl side chains. Thus, in the original GBR molecules, the 3-phenylpropyl side chain produced optimum activity and selectivity. On the contrary, in our case different benzylic substitutions produced highly selective molecules for the DAT. These divergent results may be indicative of the existence of different binding sites for these two classes of compounds, or of different conformations induced by these compounds in a single binding site.

Introduction of a double bond in the propyl side chain as shown in **7a**−**d** and **17** maintained the potency and selectivity for the DAT in these compounds. Trisubstituted fluoro compound **7a** showed good potency but relatively less selectivity for the DAT (SERT/DAT = 5) (Table 1). This observation is inconsistent with our previous results which demonstrated that, in general, fluoro substitutions on the aromatic ring of the diphenylmethoxy moiety decrease the selectivity without compromising the potencies of these compounds at the DAT. On the other hand, disubstituted compound **7b** was unexpectedly somewhat less potent and selective indicating the contribution of unfavorable electronegative F atom interactions. Compounds **7c,d** turned out to have similar potency and selectivity. Thus the presence of a fluorine atom in the aromatic ring of the *N*-phenylpropylene part of **7d** did not make any difference in its activity. On the other hand, compound **9**, the saturated version of compound **7d**, was almost twice as potent and more selective than **7d** (IC_{50} = 6.6 vs 10.8

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



						IC_{50} (nM)		
compd	R	R′	R″	X	Y	DAT,[^{3}H]WIN 35,428[a]	SERT, [^{3}H]citalopram[a]	SERT/DAT
GBR 12 909						14.0 ± 0.6	86.6 ± 10.2	6.2
7a	Ph-pF	F	F	CH=CH	CH	15.1 ± 2.0	75.8 ± 22.1	5.00
7b	Ph-pF	F	H	CH=CH	CH	41.4 ± 8.0	271.2 ± 18.4	6.5
7c	Ph	H	H	CH=CH	CH	10.1 ± 1.6	231.8 ± 4.5	22.9
7d	Ph	H	F	CH=CH	CH	10.8 ± 3.2	205.2 ± 13.3	19
9	Ph	H	F	$(CH_2)_2$	CH	6.6 ± 1.4	223.4 ± 32.2	33.8
14	Ph	H	H	$(CH_2)_2$	N	29.9 ± 0.3	194.1 ± 20.0	6.5
17	Ph	H		CH=CH	Th[b]	9.8 ± 2.4	290.8 ± 63	29.6
19a	Th[b]	H	H	$(CH_2)_2$	CH	6.0 ± 0.5	180.4 ± 21.6	30.00
19b	Th[b]	F	H	$(CH_2)_2$	CH	11.7 ± 1.0	85.7 ± 2.6	7.3

[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. [b] Thiophene.

19nM and SERT/DAT = 33.8 vs 19), which might indicate the important contribution of conformational flexibilities in **9**. It was previously reported by others that in the GBR 12935 series the double-bond unsaturation in the *N*-propyl side chain yielded slightly more potent compounds than their saturated counterparts when their affinities to the DAT were compared.[13,29] In our case, we saw a reverse trend with the saturated version being more potent. Thus, compounds **9** and GBR 12909 were more potent than the unsaturated versions **7d,b**, respectively. More elaborate future SAR studies will help to reach a more firm conclusion regarding this trend.

Bioisosteric replacement of the phenyl ring in these compounds by thiophene and pyridine rings retained their biological activity.[36] Thus, compounds **19a,b** where one of the phenyl groups in the diphenylmethoxy moiety was replaced with a thiophene group, retained the potency and selectivity. **19a** and **9** were equally active and were the most potent and selective compounds in this series. In compounds **14** and **17**, the aromatic ring of the *N*-alkyl side chain was replaced by pyridine and thiophene rings, respectively, and **17** was the most potent and selective of the two. Our previous SAR studies on derivatives containing *N*-benzyl substitutions demonstrated that bioisosteric replacement at a certain position maintained the activity but at a different position diminished it[26] and thus show a pattern different from our current results. The data taken together suggest the importance of the length of the *N*-alkyl chain between the piperidine ring and the aromatic moiety. The present results are consonant with recently published SAR studies on GBR 12935 derivatives where it was demonstrated that a thiophene moiety was a more potent bioisosteric replacer than a pyridyl moiety.[29]

Conclusion

In this report, we have described the synthesis and biological studies of potent and specific molecules for the DAT. Selectivity of these molecules for the DAT were measured by comparing their binding relative to SERT. Future binding characterization of these compounds with the NET will enable us to assess their selectivity with respect to NET as well. Some of these compounds described here are among the most potent GBR-type compounds known. In general, introduction of a double bond in the *N*-propyl side chain did not have a major effect on the biological activity. Nevertheless, the greater conformational flexibility in the saturated *N*-propyl chain versions as in **9** and **19a,b** resulted in a more favorable interaction with the DAT. Our current results also reestablished our previous finding concerning the role of *N*-benzyl substitutions in the maximal selectivity for the DAT since these current compounds with *N*-propyl substitutions are not as selective. On the other hand, some of these current compounds are more potent than GBR 12909 and also are more potent than the previously reported most active piperidine class of GBR-type compounds for their binding to the DAT.[25,26] Replacement with a thiophene ring produced the most active compound indicating more tolerance for the thiophene ring by the DAT compared to the pyridine moiety. It is important to note that **19a**,**b** as reported here are a racemic mixture. It will be interesting to find out in future studies whether one of the optical antipodes is mostly responsible for the potency and selectivity for the DAT.

Experimental Detail

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 Bruker WP-100-SY spectrometer. 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-(3-Phenyl-2-propenyl)-4-piperidone Ethylene Ketal (3a). 4-Piperidone ethylene ketal (3 g, 20.8 mmol) and cinnamyl bromide (5.2 g, 26 mmol) were dissolved in 35 mL of DMF. Potassium carbonate (8 g) was then added, and the mixture was heated overnight in an oil bath at 70 °C under nitrogen. The reaction mixture was brought to room temperature, and water (100 mL) was added. The product was extracted into an ether layer (250 mL) and dried over Na_2SO_4. The crude product was collected and purified by flash column chromatography (silica gel). Elution with EtOAc/hexane (1:1) provided pure compound **3a**, 4 g (74% yield), as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ .80 (4H, t, J = 3 Hz, -(CH_2)-CH_2-N-), 2.60 (4H, t, J = 3 Hz, -CH_2-(CH_2)-N-), 3.18 (2H, d, J = 4.5 Hz, -(CH_2)-CH=CH-), 3.95 (4H, s, -O-$(CH_2)_2$-O-), 6.12−6.60 (2H, m, -(CH=CH)-CH_2-), 7.15−7.40 (5H, m, -Ph). Anal. ($C_{16}H_{21}NO_2$·0.15H_2O) C, H, N.

Procedure B: Synthesis of 1-(4′-Fluorocinnamoyl)-4-piperidone Ethylene Ketal (2). *trans*-4-Fluorocinnamic acid (4 g, 2.4 mmol) was suspended in 150 mL of dry methylene chloride, and into it was added a couple of drops of DMF. Oxalyl chloride was then added, and the solution was stirred at room temperature for 8 h. Solvent was removed in vacuo, and the residue was dried in the pump. The residue was redissolved in methylene chloride containing triethylamine (20 g) and cooled in an ice bath. Into the cold solution was added dropwise a solution of ketal **1** (3.09 g, 2.16 mmol) dissolved in methylene chloride. The solution was brought back to room temperature and stirred for an additional 2 h. The solution was diluted with water, and the product was extracted into the EtOAc layer. The crude product was chromatographed over a silica gel column, and the pure product was eluted with a EtOAc/hexane (1:1) mixture, 5.72 g (83% yield), as an oil. ^{1}H NMR ($CDCl_3$): δ 1.78 (4H, t, J = 3.0 Hz, -(CH_2)-CH_2-N-), 3.65−3.90 (4H, m, -(CH_2)-CH_2-N-), 4.00 (4H, s, -(CH_2)-O-), 6.82 (1H, d, -CH=(CH)-, J = 15 Hz, trans coupling), 7.0−7.72 (5H, m, -(CH)=CH- + -Ph). Anal. ($C_{16}H_{18}NFO_3$) C, H, N.

Procedure C: Synthesis of 1-[3-(4′-Fluorophenyl)-2-propenyl]-4-piperidone Ethylene Ketal (3b). Lithium aluminum hydride (LAH) (3 g, 79 mmol) was suspended in 100 mL of dry THF, and the solution was cooled in an ice bath. The amide **2** (4 g, 13.7 mmol), dissolved in 25 mL of THF, was added dropwise into the cold solution. The solution was refluxed for 2 h, and after cooling (ice bath) unreacted LAH was quenched by careful addition of an excess amount of 10% NaOH solution. The solution was filtered, and THF was removed in vacuo. The product was partitioned between water and the ethyl acetate layer. Organic layer was dried over Na_2SO_4, and the product **3b** was collected, 3 g (79% yield), as a viscous liquid. ^{1}H NMR ($CDCl_3$): δ 1.80 (4H, t, J = 3 Hz, -(CH_2)-CH_2-N-), 2.30−2.65 (4H, m), 3.15 (2H, d, J = 4.5 Hz, -(CH_2)-CH=CH-), 3.95 (4H, s, -O-$(CH_2)_2$-O-), 6.05−6.56 (2H, m, -(CH=CH)-), 6.85−7.45 (4H, m, Ph-F). Anal. ($C_{16}H_{20}NFO_2$) C, H, N.

Procedure D: Synthesis of 1-(3-Phenyl-2-propenyl)-4-piperidone (4a). 1-(3-Phenyl-2-propenyl)-4-piperidone ethylene ketal, **3a** (3.8 g, 17.6 mmol), was dissolved in 100 mL of benzene/water (3:1) containing 15% HCl. The solution was refluxed for 24 h, and benzene was removed in vacuo. The acid was neutralized by adding an excess amount of solid $NaHCO_3$, and the crude product was extracted into the ethyl acetate (250 mL) layer. The organic layer was dried over Na_2SO_4. The crude product was purified by flash column chromatography over a silica gel column, and the pure product **4a** was eluted with EtOAc/hexane (1:1), 1.5 g (48% yield), as an oil. ^{1}H NMR ($CDCl_3$): δ 2.50 (4H, t, J = 3 Hz, -(CH_2)-CH_2-N-), 2.84 (4H, t, J = 3 Hz, -CH_2-(CH_2)-N-), 3.25 (2H, d, J = 4.5 Hz, -(CH_2)-N-), 6.12−6.65 (2H, m, -(CH=CH)-), 7.18−7.45 (5H, m, -Ph). Anal. ($C_{14}H_{17}NO$·0.15H_2O) C, H, N.

Procedure E: Synthesis of 1-(3-Phenyl-2-propenyl)-4-[(ethoxycarbonyl)methylene]piperidine (5a). Into a suspension of NaH (60% oil dispersion, 0.24 g, 5 mmol) in 25 mL of THF was added triethyl phosphonoacetate (1.1 g, 4.8 mmol) dissolved in 20 mL of THF. The solution was stirred at room temperature for 10 min followed by refluxing for 15 min. After cooling, a solution of compound **4a** (0.87 g, 4.0 mmol), in 20 mL of THF, was added dropwise. The reaction mixture was heated to reflux for 1.5 h, and THF was removed in vacuo. The product was partitioned between ether and water. The organic layer was dried over Na_2SO_4, and the crude material was flash-chromatographed (silica gel). The pure compound **5a** was eluted with EtOAc/hexane (2:3), 0.9 g (78% yield), as an oil. ^{1}H NMR ($CDCl_3$): δ 1.27 (3H, t, J = 4.5 Hz, (CH_3)-CH_2-), 2.25−2.62 (6H, m), 3.07 (2H, t, J = 3 Hz, -N-(CH_2)-CH_2-), 3.28 (2H, d, J = 4.5 Hz, -N-(CH_2)-CH=), 4.16 (2H, q, J = 4.5 Hz, CH_3-(CH_2)-), 5.65 (1H, s, (CH)-COOEt), 6.12−6.62 (2H, m, -(CH=CH)-), 7.2−7.45 (5H, m, -Ph). Anal. ($C_{18}H_{23}$-NO_2) C, H, N.

Procedure F: Synthesis of 4-[2-(Diphenylmethoxy)-ethyl]-1-(3-phenyl-2-propenyl)piperidine (7c). Benzhydrol (0.9 g, 4.7 mmol), 1-(3-phenyl-2-propenyl)-4-(2-hydroxyethyl)piperidine, **6a** (0.33 g, 1.34 mmol), and *p*-toluenesulfonic acid (0.33 g, 1.73 mmol) were mixed together in 65 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 ether (100 mL) and saturated $NaHCO_3$. The ether layer was separated and dried over Na_2SO_4. The crude mixture was chromatographed over a silica gel column, and **7c** was eluted with a EtOAc/hexane (1:1) mixture, 0.1 g (20% yield), as a viscous oil. ^{1}H NMR ($CDCl_3$): δ 1.25−2.05 (9H, m), 2.90−3.00 (2H, m), 3.12 (2H, d, J = 4.5 Hz, -(CH_2)-CH=CH-), 3.48 (2H, t, J = 3.0 Hz, -CH_2-(CH_2)-O-), 5.3 (1H, s, -O-(CH)-Ph_2), 6.12−6.60 (2H, m, -(CH=CH)-Ph), 7.15−7.45 (15H, m, 3Ph). Free base was converted into its oxalate salt, mp 161−162.1 °C. Anal. ($C_{29}H_{33}NO$·$(COOH)_2$·H_2O) C, H, N.

Synthesis of 1-[3-(3′-Pyridyl)propyl]-4-[(ethoxycarbonyl)methyl]piperidine (12). Amine hydrochloride **11** (0.25 g, 1.6 mmol), which was obtained as a predominantly methyl ester, and 3-pyridinepropionaldehyde, **10** (0.2 g, 1.4 mmol), were dissolved in 25 mL of dry MeOH with 0.3 g of triethylamine. Into the solution was added 4 Å molecular sieves (2.5 g), and the reaction mixture was stirred at room temperature for 1.5 h. Sodium cyanoborohydride (0.13 g, 2.1 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 a 30% MeOH/EtOAc mixture, 0.22 g (48% yield), as a colorless liquid. ^{1}H NMR showed the presence of the methyl ester. ^{1}H NMR ($CDCl_3$): δ 1.35−2.10 (9H, m), 2.20−2.44 (4H, m), 2.64 (2H, t, J = 4.5 Hz, -CH_2-(CH_2)-pyridyl), 2.84−2.96 (2H, m), 3.66 (3H, s, $COO(CH_3)$-), 7.14−8.45 (4H, m, pyridyl). Anal. ($C_{16}H_{24}N_2O_2$·0.4H_2O) C, H, N.

Synthesis of *N*-[3-(4′-Fluorophenyl)-2-propenyl]-4-piperidone (4b). Ketal **3b** (2.2 g, 7.9 mmol) was converted into **4b**, 1.1 g (61% yield), as a colorless oil (procedure D). ^{1}H NMR ($CDCl_3$): δ 2.4−2.58 (4H, m, 2-N-CH_2-(CH_2)-), 2.68−2.88 (4H, m, 2-N-(CH_2)-CH_2-), 3.25 (2H, d, J = 4.5 Hz, -(CH_2)-CH=CH-), 6.05−6.62 (2H, m, -(CH=CH)-Ph), 6.85−7.45 (4H, m, -PhF). Anal. ($C_{14}H_{16}NFO$·0.1H_2O) C, H, N.

Synthesis of 1-[3-(4′-Fluorophenyl)-2-propenyl]-4-[(ethoxycarbonyl)methylene]piperidine (5b). Keto compound **4b** (1 g, 4.2 mmol) was converted into **5b**, 1.1 g (85% yield), as a colorless oil (procedure E). ^{1}H NMR ($CDCl_3$): δ 1.27 (3H, t, J = 4.5 Hz, (CH_3)-CH_2-), 2.25−2.68 (6H, m), 2.95−3.18 (4H, m, -N-(CH_2)-CH_2- + -(CH_2)-CH=CH-), 4.16 (2H, q, J = 4.5 Hz, CH_3-(CH_2)-), 5.65 (1H, s, =(CH)-COOEt), 6.04−6.58 (2H, m, -(CH=CH)-), 6.90−7.40 (4H, m, -PhF). Anal. ($C_{18}H_{22}NFO_2$·0.1H_2O) C, H, N.

Synthesis of 1-(3-Phenyl-2-propenyl)-4-(2-hydroxyethyl)piperidine (6a). Compound **5a** (0.76 g, 2.6 mmol) was converted into alcohol **6a**, 0.6 g (95% yield), as a colorless viscous liquid (procedure C). ^{1}H NMR ($CDCl_3$): δ 1.19−2.53 (9H, m), 2.91−3.18 (4H, m, -N-(CH_2)-CH_2- + -(CH_2)-CH=CH-),

3.69 (2H, t, J = 3.0 Hz, -CH_2-(CH_2)-O-), 6.29−6.61 (2H, m, Ph-(CH=CH)-CH_2-), 7.23−7.41 (5H, m, -Ph). MS (CI): *m/e* 246.2 $(M + H)^+$.

Synthesis of 1-[3-(4′-Fluorophenyl)-2-propenyl]-4-(2-hydroxyethyl)piperidine (6b). Compound **5b** (1.27 g, 4.19 mmol) was converted into alcohol **6b**, 1.06 g (96% yield), as a colorless viscous liquid (procedure C). ^{1}H NMR ($CDCl_3$): δ 1.10−2.66 (9H, m), 2.83−3.17 (4H, m, -N-(CH_2)-CH_2- + -(CH_2)-CH=CH-), 3.69 (2H, t, J = 3.0 Hz, -CH_2-(CH_2)-O-), 6.10−6.56 (2H, m, Ph-(CH=CH)-CH_2-), 6.85−7.40 (4H, m, -PhF). MS (CI): *m/e* 264.2 $(M + H)^+$.

Synthesis of 1-[3-(4′-Fluorophenyl)propyl]-4-(2-hydroxyethyl)piperidine (8). Compound **6b** (0.5 g, 1.9 mmol) was dissolved in 50 mL of ethanol, and 10% Pd/C was then added into the solution. The solution was then hydrogenated in a Parr hydrogenation apparatus for 8 h. The solution was filtered through Celite, and the filtrate was collected. Ethanol was removed in vacuo, and the product **8** was collected and dried in the pump, 0.45 g (90% yield). ^{1}H NMR ($CDCl_3$): δ 1.08−2.45 (13H, m), 2.61 (2H, t, J = 4.5 Hz, -(CH_2)-Ph), 2.85−2.96 (2H, m), 3.67 (2H, t, J = 3.0 Hz, -CH_2-(CH_2)-O-), 6.85−7.28 (4H, m, -PhF). MS (CI): *m/e* 266.3 $(M + H)^+$.

Synthesis of 4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-1-(3-phenyl-2-propenyl)piperidine (7b). Compound **6a** (0.27 g, 1.1 mmol) was reacted with 4,4′-difluorobenzhydrol (0.72 g, 3.3 mmol) to produce **7b**, 0.1 g (20% yield). ^{1}H NMR ($CDCl_3$): δ 1.15−2.05 (9H, m), 2.90−3.02 (2H, m), 3.14 (2H, d, J = 4.5 Hz, -(CH_2)-CH=CH-), 3.45 (2H, t, J = 3.0 Hz, -CH_2-(CH_2)-O-), 5.28 (1H, s, -O-(CH)-Ph_2), 6.15−6.62 (2H, m, -(CH=CH)-Ph), 6.92−7.40 (13H, m, 2Ph-F + Ph). Free base was converted into its oxalate salt, mp 162.7−163.5 °C. Anal. ($C_{29}H_{31}NFO$·$(COOH)_2$·H_2O) C, H, N.

Synthesis of 4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-1-[3-(4′-fluorophenyl)-2-propenyl]piperidine (7a). Compound **6b** (0.3 g, 1.14 mmol) was reacted with 4,4′-difluorobenzhydrol (0.82 g, 3.76 mmol) to produce **7a**, 0.3 g (57% yield). ^{1}H NMR ($CDCl_3$): δ 1.20−2.68 (11H, m), 2.88−3.05 (2H, m), 3.10 (2H, d, J = 4.5 Hz, -(CH_2)-CH=CH-), 3.44 (2H, t, J = 3.0 Hz, -CH_2-(CH_2)-O-), 5.28 (1H, s, -O-(CH)-FPh_2), 6.05−6.55 (2H, m, -(CH=CH)-Ph), 6.92−7.40 (12H, m, 3Ph-F). Free base was converted into its oxalate salt, mp 172.5−173.5 °C. Anal. ($C_{29}H_{30}NF_3O$·$(COOH)_2$) C, H, N.

Synthesis of 4-[2-(Diphenylmethoxy)ethyl]-1-[3-(4′-fluorophenyl)-2-propenyl]piperidine (7d). Compound **6b** (0.2 g, 1.14 mmol) was reacted with benzhydrol (0.5 g, 2.66 mmol) to produce **7d**, 0.23 g (38% yield). ^{1}H NMR ($CDCl_3$): δ 1.15−2.70 (11H, m), 3.08−3.35 (4H, m, -N-(CH_2)-CH_2- + -(CH_2)-CH=CH-), 3.50 (2H, t, J = 3.0 Hz, -CH_2-(CH_2)-O-), 5.31 (1H, s, -O-(CH)-Ph_2), 6.05−6.62 (2H, m, -(CH=CH)-PhF), 6.94−7.50 (14H, m, 2Ph + Ph-F). Free base was converted into its oxalate salt, mp 141.5−143.1 °C. Anal. ($C_{29}H_{32}NFO$·$(COOH)_2$·$0.5H_2O$) C, H, N.

Synthesis of 4-[2-(Diphenylmethoxy)ethyl]-1-[3-(4′-fluorophenyl)propyl]piperidine (9). Compound **8** (0.36 g, 1.35 mmol) was reacted with benzhydrol (0.9 g, 4.37 mmol) to produce **9**, 0.28 g (48% yield). ^{1}H NMR ($CDCl_3$): δ 1.15−2.40 (13H, m), 2.61 (2H, t, J = 4.5 Hz, -(CH_2)-Ph), 2.80−2.95 (2H, m), 3.49 (2H, t, J = 3.0 Hz, -CH_2-(CH_2)-O-), 5.30 (1H, s, -O-(CH)-Ph_2), 6.85−7.35 (14H, m, 2Ph + Ph-F). Free base was converted into its oxalate salt, mp 164.9−165.8 °C. Anal. ($C_{29}H_{34}NFO$·$(COOH)_2$) C, H, N.

Synthesis of 1-[3-(3′-Pyridyl)propyl]-4-(2-hydroxyethyl)piperidine (13). Compound **12** (0.5 g, 1.81 mmol) was converted into **13**, 0.40 g (95% yield), as a viscous oil (procedure C). ^{1}H NMR ($CDCl_3$): δ 1.10−2.55 (13H, m), 2.67 (2H, t, J = 4.5 Hz, -CH_2-(CH_2)-pyridyl), 2.86−2.98 (2H, m), 3.65 (2H, t, J = 3.0 Hz, -CH_2-(CH_2)-O-), 6.98−8.44 (4H, m, pyridyl). MS (CI): *m/e* 249.2 $(M + H)^+$.

Synthesis of 4-[2-(Diphenylmethoxy)ethyl]-1-[3-(3′-pyridyl)propyl]piperidine (14). Compound **13** (0.2 g, 0.8 mmol) was reacted with benzhydrol (0.5 g, 2.66 mmol) to produce **14**, 0.24 g (72% yield). ^{1}H NMR ($CDCl_3$): δ 1.05−2.44 (13H, m), 2.64 (2H, t, J = 4.5 Hz, -CH_2-(CH_2)-pyridyl), 2.82−2.95 (2H, m), 3.50 (2H, t, J = 3.0 Hz, -CH_2-(CH_2)-O-), 5.34 (1H, s, -(CH)-O-), 7.15−8.50 (14H, m, 2Ph- + pyridyl). Free base was converted into its oxalate salt, mp 126−130.3 °C. Anal. ($C_{28}H_{34}N_2O$·$2(COOH)_2$·$1.3H_2O$·$0.1(COOH)_2$) C, H, N.

Synthesis of 1-[3-(2′-Thienyl)acryloyl]-4-[(ethoxycarbonyl)methyl]piperidine (15). Acid chloride of thienyl acrylic acid (0.43 g, 2.49 mmol) was reacted with amine **11** (0.4 g, 2.5 mmol) to produce ethyl ester **15a**, 0.23 g, and methyl ester **15**, 0.17 g (76% yield combined), as a colorless oil. Compound **15** was further characterized. ^{1}H NMR ($CDCl_3$): δ 1.00−2.35 (11H, m), 3.68 (3H, s, (CH_3)OOC-), 6.70 (1H, d, -CH=(CH)-, J = 15 Hz, trans coupling), 7.00−7.35 (3H, m, thienyl), 7.80 (1H, d, -CO-(CH)=CH-, J = 15 Hz, trans coupling). Anal. ($C_{15}H_{19}NSO_3$) C, H, N.

Synthesis of 1-[3-(2′-Thienyl)-2-propylene]-4-(2-hydroxyethyl)piperidine (16). Compound **15** (0.15 g, 0.74 mmol) was converted into **16**, 0.14 g (77% yield), as a viscous liquid (procedure C). ^{1}H NMR ($CDCl_3$): δ 1.10−1.48 (9H, m), 2.94−3.15 (4H, m), 3.71 (2H, t, J = 3.0 Hz, -CH_2-(CH_2)-O-), 5.95−7.20 (5H, m, -(CH=CH)- + thienyl). MS (CI): *m/e* 252.1 $(M + H)^+$.

Synthesis of 4-[2-(Dihenylmethoxy)ethyl]-1-[3-(2′-thienyl)-2-propylene]piperidine (17). Compound **16** (0.16 g, 0.63 mmol) was converted into the final product **17**, 0.13 g (50% yield), as a viscous liquid. ^{1}H NMR ($CDCl_3$): δ 1.18−1.95 (9H, m), 2.90−3.15 (4H, m, -(CH_2)-CH=CH- + -CH_2-(CH_2)-N-), 3.50 (2H, t, J = 3.0 Hz, -CH_2-(CH_2)-O-), 5.34 (1H, s, -(CH)-O-), 5.96−6.70 (2H, m, -(CH=CH)-), 6.95−7.40 (13H, m, 2Ph- + thienyl). Free base was converted into its oxalate salt, mp 151.7−153.6 °C. Anal. ($C_{29}H_{33}O_5NS$·$0.4H_2O$) C, H, N.

Synthesis of 4-[2-[(2-Thienyl)phenylmethoxy]ethyl]-1-(3-phenylpropyl)piperidine (19a). Phenyl(2-thienyl)methanol (0.5 g, 2.6 mmol) was dissolved in 25 mL of dry benzene, and into it was added thionyl chloride (0.37 g). 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, **18** (0.18 g, 0.72 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 the ethyl acetate layer and dried over Na_2SO_4. Crude product was chromatographed over a silica gel column, and the pure product was eluted with a 1:1 EtOAc/hexane mixture to give **19a**, 0.12 g (40% yield), as a viscous liquid. ^{1}H NMR ($CDCl_3$): δ 1.10−2.05 (11H, m), 2.25−2.45 (2H, m), 2.64 (2H, t, J = 4.5 Hz, -CH_2-(CH_2)-Ph), 2.85−2.98 (2H, m), 3.49 (2H, t, J = 3 Hz, -CH_2-(CH_2)-O-), 5.55 (1H, s, -(CH)-O-), 6.78−7.45 (13H, m, 2Ph + thienyl). Free base was converted into its oxalate salt, mp 197.1−197.9 °C. Anal. ($C_{27}H_{33}ONS$·$(COOH)_2$·$0.3H_2O$) C, H, N.

Synthesis of 4-[2-[(2-Thienyl)(4-fluorophenyl)methoxy]-ethyl]-1-(3-phenylpropyl)piperidine (19b). (4-Fluorophenyl)(2-thienyl)methanol (0.5 g, mmol) was reacted with **18** (0.3 g, 1.2 mmol) in the same way as described for **19a** to produce **19b**, 0.15 g (30% yield). ^{1}H NMR ($CDCl_3$): δ 1.0−1.85 (11H, m), 2.25−2.42 (2H, m), 2.61 (2H, t, J = 4.5 Hz, -CH_2-(CH_2)-Ph), 2.84−3.00 (2H, m), 3.45 (2H, t, J = 3 Hz, -CH_2-(CH_2)-O-), 5.12 (1H, s, -(CH)-O-), 6.72−7.48 (12H, m, Ph + Ph-F + thienyl). Free base was converted into its oxalate salt, mp 116.1−119.2 °C. Anal. ($C_{27}H_{32}NSO$·$(COOH)_2$·$0.5H_2O$) C, H, N.

Biological Methods. The DAT was labeled with [^{3}H]WIN 35,428 and the SERT with [^{3}H]citalopram as described by us previously.[26] Both binding assays were carried out under the same conditions with striatal tissue from male, young adult Sprague−Dawley rats, exactly as described in our previous work.[26] All compounds were dissolved in dimethyl sulfoxide (DMSO) and diluted out in 10% (v/v) DMSO. Additions from the latter stocks resulted in a final concentration of DMSO of 0.5%, which by itself did not interfere with radioligand binding. After initial range-finding experiments, at least five concentrations of the test compound were studied spaced evenly around

its IC_{50} value. The latter was estimated by nonlinear computer curve-fitting procedures as described by us previously.[25]

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