# Structure−Activity Relationship Studies of Novel 4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-1-(3-phenylpropyl)piperidine Analogs: Synthesis and Biological Evaluation at the Dopamine and Serotonin Transporter Sites

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*Received September 5, 1995*⊗

Several analogs of the potent dopamine (DA) transporter ligand 4-[2-[bis(4-fluorophenyl)-methoxy]ethyl]-1-(3-phenylpropyl)piperidine, **1b**, were made and biologically evaluated for their binding at the DA and serotonin (5HT) transporters in rat striatal membranes. Different alkyl chain lengths and substitutions were introduced in these molecules to generate an optimum activity and selectivity for the DA transporter. In general, unsubstituted and fluoro-substituted compounds were the most active and selective for the DA transporter. The compound 4-[2-(diphenylmethoxy)ethyl]-1-benzylpiperidine, **9a**, showed high potency and was the most selective for the DA transporter (5HT/DA = 49) in this series of compounds. Some of these novel analogs were found to be more selective in binding at the DA transporter than the original GBR 12909 molecule, 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperidine.

The dopamine (DA) transporter, a presynaptically located macromolecule, terminates dopaminergic neurotransmission by reaccumulation of released dopamine into presynaptic neurons[1] and plays an important role in some pathophysicological processes in the central nervous system (CNS). Cocaine, a powerful drug of abuse,[2] is known to bind to various neurotransporter systems in the brain,[3−5] but the reinforcing effect of cocaine is believed to be initiated by binding to the DA transporter causing inhibition of DA transport;[6−8] important factors also are the rapid uptake and clearance of cocaine.[9] Phenylcyclidine (PCP), a psychoactive drug of abuse, exhibits some of its behavioral effects through binding to the DA transporter.[10,11] This transporter also plays a crucial role in the neurotoxic action of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) which induces idiopathic Parkinsonian syndrome in humans.[12,13] The DA transporter, which is localized presynaptically, is found to be absent in tissue sections of Parkinson's diseased putamen, and its measurement can be used as a probe for this disease.[14,15]

Different classes of compounds have been developed in the past to characterize cocaine-[3,16,17] and PCP[18,19]-binding sites at the DA transporter. Extensive studies on structure−activity relationships (SAR) in the series of cocaine 3$\beta$-(aryltropanyl)-2$\beta$-(carboxylic acid methyl ester) analogs resulted in the development of some very potent and selective tropane derivatives for the DA transporter.[20−22] Some of the well-known compounds in this class are CFT (WIN 35, 428) and RTI-55 (Figure 1), and they are more potent and selective than cocaine in their action at the DA transporter.[3,23,24] Recent reports describe the discovery of some even more potent and selective tropane classes of compounds for this transporter.[25,26] Such analogs will help to establish and characterize the putative binding site of cocaine at the DA transporter. Similarly the modification of PCP molecule, which induces behavioral effect in the CNS, led to the development of a more potent compound, BTCP (Figure 1), and its analogs for the DA transporter.[18,19,27]

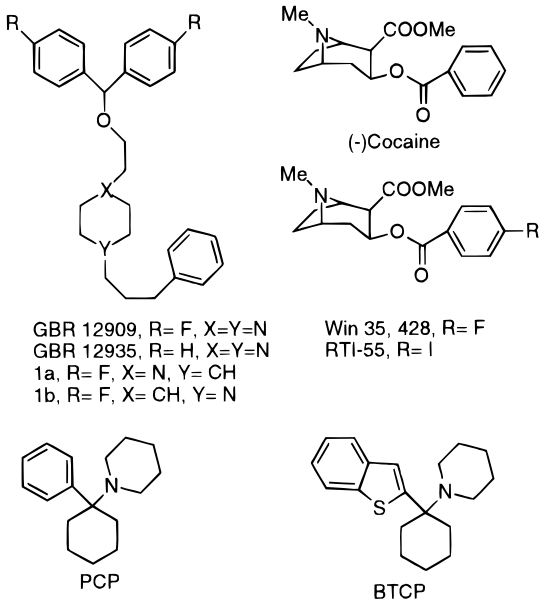


**Figure 1.**

The GBR classes of compounds, originally developed by Van der Zee et al.,[28] are known for their unusual high selectivity and potency for the DA transporter. Two of the most widely used GBR compounds, GBR 12909 and 12935 (Figure 1), have affinities in the low-nanomolar range.[29,30] An extensive SAR study was conducted in the GBR series of compounds by Van der Zee et al. which produced some very potent compounds for the DA transporter. Consequently some of these potent compounds have been radiolabeled, and detailed neuropharmacological actions have been carried out with these radioligands.[31−33] GBR 12909 dissociates very slowly from the DA transporter,[34] attenuates the in-

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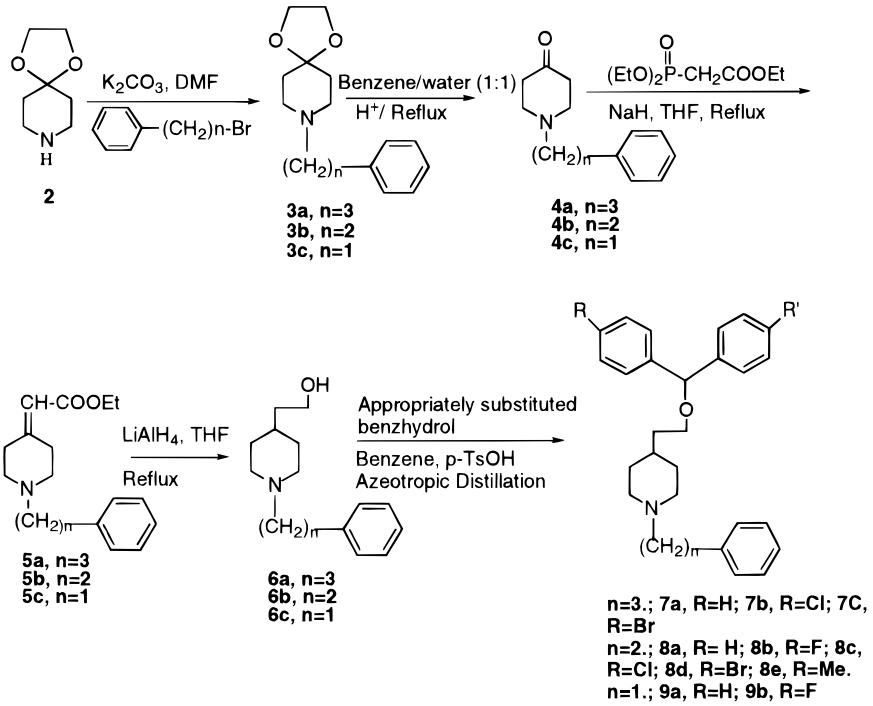
⊗ Abstract published in *Advance ACS Abstracts,* January 15, 1996.

0022-2623/96/1839-0749$12.00/0 

**Scheme 1**




crease in extracellular dopamine level induced by cocaine as measured in microdialysis experiments,[34,35a] and exhibits nonstimulant properties in human volunteers.[35b] It is also shown recently that GBR 12909 selectively blocks cocaine self-administration behavior in rhesus monkey.[35c] These intriguing results have raised the possibility that a suitable GBR derivative or related compounds can act as a cocaine antagonist.[34,35a]

Our interest in GBR molecules began with the exploration and identification of molecular determinants needed in these molecules to confer their strong selective affinity for the DA transporter. In our previous study, we demonstrated that the replacement of the piperazine ring of GBR 12909 by a piperidine group maintains the same activity of GBR 12909 in the new molecule, **1b** (Figure 1), when the nitrogen atom is in the correct position.[36] In addition, this new molecule was shown to have more selectivity since it did not have the nonselective piperazine binding activity[37] which contributes as much as 30% to binding of conventional GBR compounds to brain preparations under commonly used assay conditions.[29] In this regard it has been shown by other workers that changing the piperazine ring to a homopiperazine moiety in the GBR 12935 molecule produces a highly selective compound for the DA transporter.[38]

We embarked upon several structural modifications of our lead compound **1b** in an effort to establish a SAR among these compounds. One of our goals is to develop potent and selective compounds for the DA transporter which will help to characterize the molecular structure of this macromolecule further. A suitable compound found in these studies might also be developed as a radioligand to study the DA transporter; it would have the advantage of lacking the nonspecific piperazine binding activity relative to [$^3$H]GBR 12935. Such a compound might also be tested for use as a potential cocaine antagonist in treatment programs. In this report, we are describing the synthesis and biological characterization of a series of analogs from the structural modifications of the lead compound **1b**.

## Chemistry

The synthesis of **7a**−**c**, **8a**−**e**, and **9a**,**b** is described in Scheme 1. The commercially available ketal **2** was N-alkylated with 1-bromo-3-phenylpropane in the presence of $K_2CO_3$ to give compound **3a** in excellent yield. Deketalization of compound **3a** in acidic THF (5% HCl) produced **4a** in good yield (65%). A modified Wittig reaction of **4a** with triethyl phosphonoacetate produced **5a** in very good yield, which on reduction with lithium aluminum hydride gave **6a** in quantitative yield. Final compounds **7a**−**c** were prepared by acid-catalyzed reaction of **6a** with commercially available appropriately substituted benzhydrols via azeotropic distillation.[39] Similarly compounds **8a**−**e** and **9a**,**b** were prepared in an identical fashion by following the same reaction conditions applied to prepare **7a**−**c**.

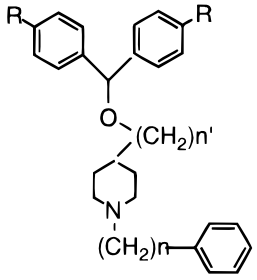
Compound **7d** was prepared in a slightly different way. Here 4,4′-dimethoxybenzhydrol was converted into the corresponding chloride which was then converted into the final compound by treatment with alcohol **6a** in good yield. The synthesis is shown in Scheme 2.

Scheme 3 describes the synthesis of **15a**,**b**, **16a**,**b**, and **17a**,**b**. The common commercially available starting material ethyl isonipecotate was N-alkylated in the presence of a base with 1-bromo-3-phenylpropane to give **13a** in excellent yield. The reduction of ester **13a** gave alcohol **14a** which on reaction with benzhydrol furnished **15a** in good yield. Compounds **15b**, **16a**,**b**, and **17a**,**b** were also made by following the same procedure.

## Biochemistry

Biological studies of the newly synthesized compounds were carried out with rat brain striatal membrane tissue. Binding analyses were performed to determine

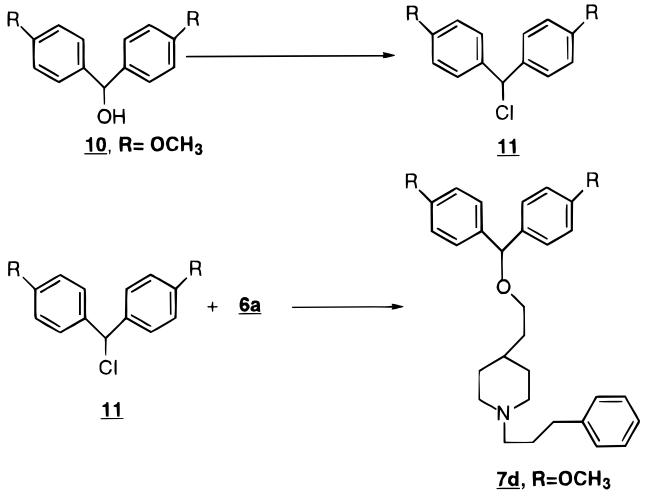
**Table 1.** Affinity and Receptor Selectivity of Drugs at the Dopamine and Serotonin Transporters in Rat Striatum




| | | | | $IC_{50}$ (nM)[a] | | |
|---|---|---|---|---|---|---|
| compd | R | *n* | *n'* | DA, [$^3$H]CFT | 5HT, [$^3$H]citalopram | 5-HT/DA |
| GBR 12909 | F | 3 | 2 | 6.0 ± 0.7 | 82 ± 4 | 13.7 |
| **1b** | F | 3 | 2 | 16.7 ± 4.0 | 55 ± 10 | 3.3 |
| **7a** | H | 3 | 2 | 12.0 ± 0.4 | 232 ± 28 | 20 |
| **7b** | Cl | 3 | 2 | 65 ± 12 | 224 ± 10 | 3.5 |
| **7c** | Br | 3 | 2 | 159 ± 56 | 835 ± 142 | 5.2 |
| **7d** | $OCH_3$ | 3 | 2 | 255 ± 32 | 340 ± 24 | 1.3 |
| **8a** | H | 2 | 2 | 10.6 ± 0.85 | 102 ± 5 | 9.7 |
| **8b** | F | 2 | 2 | 19.9 ± 9.5 | 31.9 ± 7.1 | 1.6 |
| **8c** | Cl | 2 | 2 | 115 ± 22 | 414 ± 32 | 3.6 |
| **8d** | Br | 2 | 2 | 382 ± 167 | 638 ± 71 | 1.6 |
| **8e** | Me | 2 | 2 | 311 ± 71 | 888 ± 58 | 2.8 |
| **9a** | H | 1 | 2 | 15.2 ± 2.8 | 743 ± 6 | 49 |
| **9b** | F | 1 | 2 | 9.7 ± 0.4 | 198 ± 7 | 20 |
| **15a** | H | 3 | 1 | 14.5 ± 1.9 | 58 ± 7 | 4 |
| **15b** | F | 3 | 1 | 13.0 ± 2.5 | 112 ± 4 | 8.6 |
| **16a** | H | 2 | 1 | 108 ± 14 | 456 ± 90 | 4.2 |
| **16b** | F | 2 | 1 | 13.5 ± 2.6 | 237 ± 53 | 17.5 |
| **17a** | H | 1 | 1 | 702 ± 34 | 544 ± 91 | 0.7 |
| **17b** | F | 1 | 1 | 126 ± 13 | 761 ± 101 | 6 |

[a] The DA transporter was labeled with [$^3$H]CFT, and the 5HT transporter was labeled with [$^3$H]citalopram. Results are average ± SEM of three to five (DA) or two to three (5-HT) independent experiments assayed in triplicate.

**Scheme 2**




their activity at the DA and serotonin (5HT) transporters in the brain tissues. The DA transporter in the rat striatal tissue was labeled with a tritiated analog of a potent cocaine analog, [$^3$H]CFT, and the 5HT transporter was labeled with [$^3$H]citalopram. Table 1 shows the $IC_{50}$ values of the compounds, i.e., the concentrations needed to inhibit binding by 50%.

## Results and Discussion

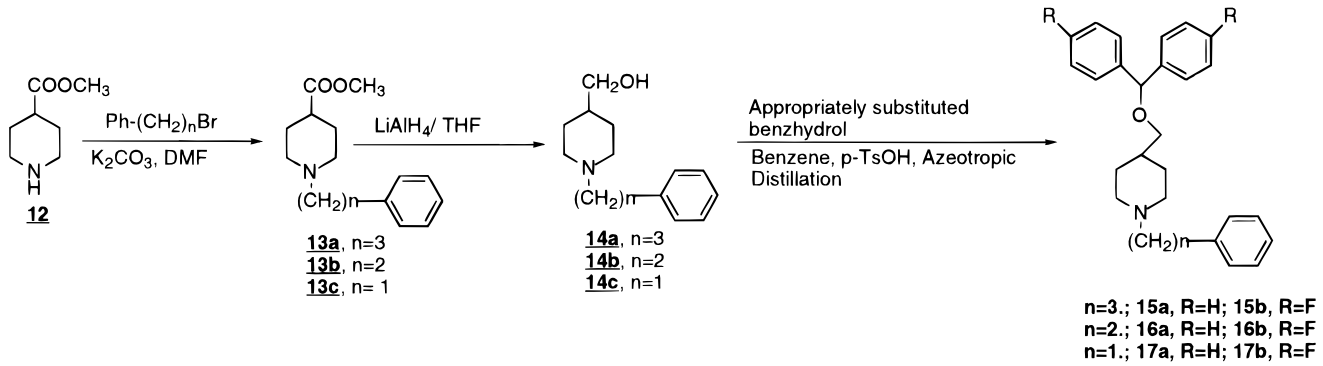
Some of the modifications of our lead compound **1b** (R = F) involve the variations of the length of methylene connectivities attached to the 1 and 4 positions of the piperidine ring in these molecules. Various substitutions in the aromatic rings were also tried to determine the role of electronic and steric environments in the potency of these molecules for the DA transporter. In order to assess their dopaminergic selectivity, we tested the compounds also for their activity at the 5HT transporter.

Compounds **7a**−**d** represent the analogs of **1b** with different halogens and methoxy substitutions in the diphenylmethoxy moiety. The most potent and selective compound in this particular series was **7a** (R = H, 5HT/DA = 20) where the F atoms of **1b** were replaced by H atoms. In this case, due to the changes in aromatic substitution, the selectivity of **7a** increased by 6-fold when compared to **1b** (5HT/DA = 3.3). It is noteworthy to mention that **1b** showed higher selectivity for the DA transporter when measured originally in monkey (*Macaca fascicularis*) brain striatum ([$^3$H]CFT $IC_{50}$ = 24 nM, 5HT/DA = 10).[36] Among the other substitutions, the dichloro compound **7b** showed 3.4 times less potency than **1b**, while the dibromo and dimethoxy compounds **7c** (R = Br) and **7d** (R = $OCH_3$) were much less potent and selective for the DA transporter which might indicate the involvement of unfavorable steric and electronic interactions of these compounds with the receptor.

Replacement of the propyl side chain connected to the N atom in compound **7a** by an ethyl linkage resulted in the development of the next series of compounds, **8a**−**e**. Their pattern of biological activities was parallel to that of **7a**−**d**. Compounds **8a** (R = H) and **8b** (R = F) exhibited almost the same potency when compared with their counterparts **7a** and **1b**. Thus, the $IC_{50}$ values of **8a**,**b** for displacing [$^3$H]CFT at the DA transporter, 10.6 and 19.9 nM, are comparable with the values of 12.0 and 16.7 nM for **7a** and **1b**. But the selectivity of **8a**,**b** for the DA transporter was lower than that of **7a** and **1b** (5HT/DA, 9.7 and 1.6 vs 20 and 3.3). These results reflect the fact that the replacement of the propyl chain by an ethyl chain did not alter the potency in these compounds at the DA transporter but enhanced the affinity for the 5HT transporter by ca. 2-fold. Reduced dopaminergic selectivity of the substituted compounds **8c**−**e** may be due again to a combination of unfavorable electronic and steric interactions with the receptors.

Continuing along the same experimental pathways, compounds **9a** (R = H) and **9b** (R = F) were synthesized where the *N*-propylphenyl side chain of the original compound **1b** was replaced by a benzyl group. This modification resulted in compounds with potent activity at the DA transporter and the highest selectivity for the DA transporter as compared with 5HT observed in the present series. Thus, compound **9a**, which had an $IC_{50}$ value of 15.2 nM and a 5HT/DA ratio of 49, showed 15 and 2.5 times more selectivity when compared to our previous lead compound **1b** and the compound **7a** in the current series, whereas compound **9b** turned out to be as selective as **7a**. Compound **9a**, when compared to the original GBR 12909, was much more selective at the DA transporter (Table 1, see also ref 36). In addition, while the potencies of compounds **9a**,**b** at the DA transporter did not change significantly, like their previous counterparts **7a**, **1b**, and **8a**,**b**, their affinities

**Scheme 3**




for the 5HT transporter were reduced significantly. Enhanced selectivity of **9a**,**b** for the DA transporter could not be rationalized completely since initial reduction in chain length from *N*-propyl to *N*-ethyl yielded less selective compounds. A further structure−activity exploration of **9a** currently is in progress to develop more selective compounds in this category.

The next series of compounds, **15a**,**b**, **16a**,**b**, and **17a**,**b**, represents the structural modifications in the alkyl chain length connected to the O atom of diarylmethoxy moiety as well as to the N atom of the piperidine ring. It was observed that the reduction of ethylene linkage connected to O atom of the diphenylmethoxy moiety into a methylene unit, as shown in these structures, did not change the high potency of the compounds **15a**,**b** and **16b** (R = F) at the DA transporter. On the other hand, compounds **17a**,**b** turned out to be much less potent at the DA transporter which reflects the low tolerance of the DA transporter for *N*-benzyl substitution in these molecules. The most potent and selective compound in this particular series was found to be **16b** (5HT/DA = 17.5). These results suggest that the activities in this series of molecules with a connection of one methylene unit ($n' = 1$) were more dependent on the variation of the *N*-alkyl chain length showing the weakest activity for compounds with the shortest chain length ($n = 1$, **17a**,**b**). There was an interesting contrast between the effect of fluorination in all these compounds and that in **1b**/**7a** and **8a**/**8b**. Only in the latter pairs were the fluoro-substituted compounds slightly less potent than their hydrogen counterparts in inhibiting the DA transporter, suggesting a complex interaction between substitutions at one end of the molecule and alkyl chain length changes at distal portions. A similar complexity probably underlies the abrupt drop in potency in the unsubstituted compounds **16a** (R = H) and **17a** (R = H).

## Conclusion

In this report we describe the development of novel potent and selective compounds for the DA transporter. Compound **9a** turned out to be the most DA transporter selective compound in this series, while **9b** was the most potent at the DA transporter. These results reflect that the benzyl substitution at the N atom of the piperidine ring in **9a**,**b** is optimally tolerated and recognized potently and selectively by the DA transporter. This, however, stands in contrast to the work of Van der Zee et al., where the 3-phenylpropyl substitution was shown to confer maximum potency.[28] Most likely, the factor underlying this difference is the substitution of a piperidine for the piperazine ring in the current series of compounds. It is known that the p$K_a$ value of the piperazine derivative is lower than that of the piperidine derivative which might be responsible for the better selectivity for the DA transporter in the case of the current piperidine derivatives.

Our present work is an extension of our initial work on the modification of the piperazine ring in these molecules. Some of these new analogs were shown to have more DA transporter selectivity than GBR 12909 (5HT/DA, 13.7 for GBR 12909 vs 49, 20, 20, and 17.5 for **9a**,**b**, **7a**, and **16b**). In addition, it was shown by us previously that these new analogs lacked the nonspecific piperazine site binding activity unlike conventional GBR compounds.[37] It is interesting to observe that variations of the alkyl chain length were allowed without compromising the activity of these compounds appreciably. This is encouraging since one of our goals is to reduce the lipophilicity in these new molecules in the light of the fact that high lipophilicity imposes considerable difficulty in handling GBR compounds. Further SAR studies in these classes of compounds in the future will enable us to characterize the DA transporter complex in greater detail.

## Experimental Details

Analytical silica gel-coated TLC plates (Si 250F) were purchased from Baker, Inc., and visualized with UV light or by treatment with phosphomolybdic acid (PMA). Flash chromatography was carried out on Baker silica gel (40 $\mu$M). $^1$H NMR spectra were routinely obtained at 100 MHz on a Brucker WP-100-SY spectrometer. The NMR solvents used were $CDCl_3$ and $CD_3OD$ as indicated; resonances are reported in $\delta$ units. TMS was used as an internal standard. Elemental analyses were performed by Atlantic Microlab, Inc., and are within ±0.4% of the theoretical values.

[$^3$H]CFT (84.5 Ci/mmol) and [$^3$H]citalopram (81 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 from Research Biochemicals, Inc. (Natick, MA).

**Procedure A: Synthesis of 1-(3-Phenylpropyl)-4-piperidone Ethylene Ketal (3a).** 4-Piperidone ethylene ketal (3 g, 20.8 mmol) and 1-bromo-3-phenylpropane (5 g, 24.2 mmol) were dissolved in 35 mL of DMF. Potassium carbonate (8 g) was then added, and the mixture was warmed 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**, 4.8 g (88% yield), as a colorless liquid. $^1$H NMR ($CDCl_3$): 1.62−2.00 (6H, complex m), 2.30−2.75 (8H, complex m), 3.92 (4H, s, -2O-($CH_2$)-), 7.20 (5H, bs, Ph). Anal. ($C_{16}H_{23}NO_2$) C, H, N.

**Procedure B: Synthesis of 1-(3-Phenylpropyl)-4-piperidone (4a).** *N*-(3-Phenylpropyl)-4-piperidone ethylene ketal, **3a** (4.6 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 excess amount of solid $NaHCO_3$, and the crude product was extracted into 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), 2.47 g (64.6% yield), as an oil. $^1$H NMR ($CDCl_3$): 1.65−2.05 (2H, m), 2.32−2.82 (12H, complex m), 7.20 (5H, bs, Ph). Anal. ($C_{14}H_{19}NO$) C, H, N.

**Procedure C: Synthesis of 1-(3-Phenylpropyl)-4-[(ethoxycarbonyl)methylene]piperidine (5a).** Into a suspension of NaH (60% oil dispersion, 0.41 g, 0.90 mmol) in 25 mL of THF was added triethyl phosphonoacetate (1.9 g, 0.86 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** (1.5 g, 6.9 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. 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 (1:1), 1.14 g (74% yield), as an oil. $^1$H NMR ($CDCl_3$): 1.15−1.36 (3H, t, $J$ = 4.5 Hz, $(CH_3)$-$CH_2$-O-), 1.65−2.00 (2H, m), 2.25−2.75 (10H, complex m), 2.90−3.10 (2H, t, $J$ = 3 Hz, -N-$(CH_2)$-$CH_2$), 4.00−4.25 (2H, q, $J$ = 4.5 Hz, $CH_3$-$(CH_2)$-O-), 5.65 (1H, s, =(CH)-COOEt), 7.20 (5H, bs, Ph). Anal. ($C_{18}H_{25}NO_2$) C, H, N.

**Procedure D: Synthesis of 1-(3-Phenylpropyl)-4-(2-hydroxyethyl)piperidine (6a).** Lithium aluminum hydride (LAH) (0.09 g, 2.37 mmol) was suspended in 25 mL of dry THF, and the solution was cooled in an ice bath. The ester **5a** (0.22 g, 0.76 mmol), dissolved in 10 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 excess amount of 10% NaOH solution. The solution was filtered, and THF was removed in vacuo. The product was partioned between water and ether layer. Organic layer was dried over $Na_2SO_4$, and the product **6a** was collected, 0.17 g (91% yield). This product was used in the next reaction without any further purification. $^1$H NMR ($CDCl_3$): 1.20−2.05 (9H, complex m), 2.10−3.20 (9H, complex m), 3.50−3.72 (2H, t, $J$ = 3 Hz, -$(CH_2)$-O-), 7.20 (5H, bs, Ph). MS (CI): *m/e* 248.2 $(M + H)^+$.

**Procedure E: Synthesis of 4-[2-(Diphenylmethoxy)ethyl]-1-(3-phenylpropyl)piperidine Hydrochloride (7a).** Benzhydrol (0.17 g, 0.92 mmol), *N*-(3-phenylpropyl)-4-(2-hydroxyethyl)piperidine (0.17 g, 0.68 mmol), and *p*-tolunesulfonic acid (0.17 g, 0.85 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 seperated and dried over $Na_2SO_4$. Crude mixture was chromatographed over a silica gel column, and **7a** was eluted with EtOAc/hexane (1:1) mixture, 0.05 g (17% yield), as a viscous oil. $^1$H NMR ($CDCl_3$): 1.00−2.05 (11H, complex m), 2.24−2.45 (2H, m), 2.50−2.75 (2H, t, $J$ = 4.5 Hz, -$(CH_2)$-Ph), 2.80−3.00 (2H, m), 3.40−3.60 (2H, t, $J$ = 3 Hz, -$CH_2$-$(CH_2)$-O-), 5.35 (1H, s, -(CH)-O-), 7.12−7.45 (15H, m, 3Ph).

Free base was converted into its hydrochloride salt, mp 125.9−126.4 °C. Anal. ($C_{29}H_{36}NOCl$) C, H, N.

**Synthesis of 4-[2-[Bis(4-chlorophenyl)methoxy]ethyl]-1-(3-phenylpropyl)piperidine Hydrochloride (7b).** Starting from 4,4′-dichlorobenzhydrol, the final compound **7b** was synthesized (procedure E). Thus an excess amount of 4,4′-dichlorobenzhydrol (1 g, 3.9 mmol) was reacted with alcohol **6a** (0.4 g, 1.6 mmol) to produce **7b**, 0.68 g (88% yield), as an oil. $^1$H NMR ($CDCl_3$): 1.10−2.05 (11H, complex m), 2.25−2.45 (2H, m), 2.50−2.70 (2H, t, $J$ = 4.5 Hz, -$(CH_2)$-Ph), 2.75−3.00 (2H, m), 3.30−3.54 (2H, t, $J$ = 3 Hz, -$CH_2$-$(CH_2)$-O-), 5.25 (1H, s, -(CH)-O-), 7.05−7.35 (13H, m, Ph + 2(Ph)-Cl).

Free base was converted into its hydrochloride salt, mp 164.5−165.8 °C. Anal. ($C_{29}H_{34}NOCl_3$) C, H, N.

**Synthesis of 4-[2-[Bis(4-bromophenyl)methoxy]ethyl]-1-(3-phenylpropyl)piperidine Hydrochloride (7c).** An excess amount of 4,4′-dibromobenzhydrol (1 g, 3 mmol) was reacted with alcohol **6a** (0.4 g, 1.6 mmol) to give product **7c**, 0.24 g (42% yield), as a viscous oil (procedure E). $^1$H NMR ($CDCl_3$): 1.10−2.00 (11H, complex m), 2.25−2.45 (2H, m), 2.50−2.74 (2H, t, $J$ = 4.5 Hz, -$(CH_2)$-Ph), 2.78−3.00 (2H, m), 3.35−3.55 (2H, t, $J$ = 3 Hz, $CH_2$-$(CH_2)$-O-), 5.20 (1H, s, -(CH)-O-), 7.05−7.55 (13H, m, Ph + 2(Ph)-Br).

Free base was converted into its solid hydrochloride salt, mp 94.6−96.9 °C. Anal. ($C_{29}H_{34}NOClBr_2$) C, H, N.

**Synthesis of 1-(2-Phenylethyl)-4-piperidone Ethylene Ketal (3b).** 4-Piperidone ethylene ketal (5 g, 35 mmol) was reacted with (2-bromoethyl)benzene (7.4 g, 40 mmol) to yield **3b**, 6.28 g (73% yield), as a colorless oil (procedure A). $^1$H NMR ($CDCl_3$): 1.66−1.90 (4H, t, $J$ = 4.5 Hz, 2-$(CH_2)$-C-O-), 2.50−2.95 (8H, complex m), 3.95 (4H, s, 2-O-$(CH_2)$-), 7.25 (5H, bs, Ph). Anal. ($C_{15}H_{21}NO_2$) C, H, N.

**Synthesis of 1-(2-Phenylethyl)-4-piperidone (4b).** Ketal **3b** (5.38 g, 21.7 mmol) after hydrolysis furnished 3.6 g (81% yield) of **4b** as a colorless solid, mp 79−82 °C (procedure B). $^1$H NMR ($CDCl_3$): 2.35−2.58 (4H, t, $J$ = 4.5 Hz, 2-$(CH_2)$-C=O), 2.60−3.00 (8H, complex m), 7.12−7.45 (5H, m, Ph). Anal. ($C_{13}H_{17}NO$) C, H, N.

**Synthesis of 1-(2-Phenylethyl)-4-[(ethoxycarbonyl)-methylene]piperidine (5b). 4b** (5.5 g, 27 mmol) was converted into the product **5b**, 1.7 g (24% yield), as an oil (procedure C). $^1$H NMR ($CDCl_3$): 1.15−1.40 (3H, t, $J$ = 4.5 Hz, $(CH_3)$-$CH_2$-O-), 2.25−2.90 (10H, complex m), 2.95−3.15 (2H, t, $J$ = 4.5 Hz, -N-$(CH_2)$-), 4.00−4.30 (2H, q, $J$ = 4.5 Hz, -O-$(CH_2)$-$CH_3$), 5.65 (1H, s, =(CH)-COOEt), 6.10−6.40 (5H, m, Ph). Anal. ($C_{17}H_{23}NO_2$) C, H, N.

**Synthesis of 1-(2-Phenylethyl)-4-(2-hydroxyethyl)piperidine (6b).** Ester **5b** (1.67 g, 6.1 mmol) was converted into **6b**, 1.31 g (92% yield), mp 79−81 °C (procedure D). $^1$H NMR ($CDCl_3$): 1.10−3.10 (15H, complex m), 3.60−3.80 (2H, t, $J$ = 4.5 Hz, -$CH_2$-$(CH_2)$-O-), 7.05−7.40 (5H, m, Ph). MS (CI): *m/e* 234.1 $(M + H)^+$.

**Synthesis of 4-[2-(Diphenylmethoxy)ethyl]-1-(2-phenylethyl)piperidine Hydrochloride (8a).** Benzhydrol (0.51 g, 2.7 mmol) and alcohol **6b** (0.26 g, 1.1 mmol) were reacted to give **8a**, 0.18 g (42% yield), as a viscous liquid (procedure E). $^1$H NMR ($CDCl_3$): 1.10−2.15 (9H, complex m), 2.42−3.10 (6H, complex m), 3.40−3.58 (2H, t, $J$ = 3 Hz, -$CH_2$-$(CH_2)$-O-), 5.32 (1H, s, -(CH)-O-), 7.10−7.45 (15H, m, 3Ph).

Free base was converted into its solid hydrochloride salt, mp 172−174.2 °C. Anal. ($C_{28}H_{34}NOCl$) C, H, N.

**Synthesis of 4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-1-(2-phenylethyl)piperidine Hydrochloride (8b).** 4,4′-Difluorobenzhydrol (0.55 g, 2.5 mmol) was reacted with alcohol **6b** (0.24 g, 1.3 mmol) to furnish **8b**, 0.2 g (45% yield), as a viscous liquid (procedure E). $^1$H NMR ($CDCl_3$): 1.05−2.15 (9H, complex m), 2.45−3.10 (6H, complex m), 3.35−3.55 (2H, t, $J$ = 3 Hz, -$CH_2$-$(CH_2)$-O-), 5.25 (1H, s, -(CH)-O-), 6.85−7.40 (13H, m, Ph + 2(Ph)-F).

Free base was converted into its solid hydrochloride salt, mp 146.9−148.8 °C. Anal. ($C_{28}H_{32}NOF_2Cl$) C, H, N.

**Synthesis of 4-[2-[Bis(4-chlorophenyl)methoxy]ethyl]-1-(2-phenylethyl)piperidine Hydrochloride (8c).** 4,4′-Dichlorobenzhydrol (0.75 g, 3 mmol) and alcohol **6b** (0.28 g, 1.2 mmol) were reacted to give compound **8c**, 0.33 g (59% yield), as a viscous liquid (procedure E). $^1$H NMR ($CDCl_3$): 1.10−2.20 (9H, complex m), 2.45−3.15 (6H, complex m), 3.35−3.55 (2H, t, $J$ = 3 Hz, -$CH_2$-$(CH_2)$-O-), 5.25 (1H, s, -(CH)-O-), 7.10−7.40 (13H, m, Ph + 2(Ph)-Cl).

Free base was converted into its solid hydrochloride salt, mp 123−126.5 °C. Anal. ($C_{28}H_{32}NOCl_3$) C, H, N.

**Synthesis of 4-[2-[Bis(4-bromophenyl)methoxy]ethyl]-1-(2-phenylethyl)piperidine Hydrochloride (8d).** 4,4′-Dibromobenzhydrol (1.02 g, 3 mmol) and alcohol **6b** (0.28 g, 1.2 mmol) were reacted to give compound **8d**, 0.33 g (50% yield), as a viscous liquid (procedure E). $^1$H NMR ($CDCl_3$): 1.10−2.15 (9H, complex m), 2.45−3.10 (6H, complex m), 3.35−

3.60 (2H, t, $J$ = 3 Hz, -$CH_2$-($CH_2$)-O-), 5.24 (1H, s, -(CH)-O-), 7.05−7.60 (13H, m, Ph + 2(Ph)-Br).

Free base was converted into its hydrochloride salt, mp 121.8−125 °C. Anal. ($C_{28}H_{32}NOClBr_2$) C, H, N.

**Synthesis of 4-[2-[Bis(4-methylphenyl)methoxy]ethyl]-1-(2-phenylethyl)piperidine Hydrochloride (8e).** Reaction between 4,4′-dimethylbenzhydrol (0.87 g, 4.1 mmol) and alcohol **6b** (0.3 g, 1.2 mmol) was carried out to give **8e**, 0.25 g (49% yield), as a viscous liquid (procedure E). $^1$H NMR ($CDCl_3$): 1.20−2.15 (9H, complex m), 2.30 (6H, s, 2($CH_3$)-Ph), 2.40−3.10 (6H, complex m), 3.35−3.55 (2H, t, $J$ = 3 Hz, -$CH_2$-($CH_2$)-O-), 5.26 (1H, s, -(CH)-O-), 6.00−6.35 (13H, m, Ph + 2(Ph)-$CH_3$).

Free base was converted into its hydrochloride salt, mp 159.3−160.9 °C. Anal. ($C_{30}H_{38}NOCl$) C, H, N.

**Synthesis of 1-Benzyl-4-[(ethoxycarbonyl)methylene]-piperidine (5c).** The compound **4c** (1.5 g, 7.9 mmol) was reacted with triethyl phosphonoacetate (2 g, 9.1 mmol) to give product **5c**, 0.52 g (26% yield), as an oil (procedure C). $^1$H NMR ($CDCl_3$): 1.15−1.35 (3H, t, $J$ = 4.5 Hz, ($CH_3$)-$CH_2$-O-), 2.20−2.60 (6H, complex m), 2.90−3.05 (2H, t, $J$ = 3 Hz, -N-($CH_2$)-), 3.50 (2H, s, -N-($CH_2$)-Ph), 4.00−4.25 (2H, q, $J$ = 4.5 Hz, $CH_3$-($CH_2$)-O-), 5.64 (1H, s, ═(CH)-COOEt), 7.30 (5H, bs, Ph). Anal. ($C_{16}H_{21}NO_2$) C, H, N.

**Synthesis of 1-Benzyl-4-(2-hydroxyethyl)piperidine (6c).** The compound **5c** (0.4 g, 1.5 mmol) was converted into alcohol **6c**, 0.29 g (91% yield), as an oil (procedure D). $^1$H NMR ($CDCl_3$): 1.10−3.00 (12H, complex m), 3.50 (2H, s, -N-($CH_2$)-Ph), 3.55−3.75 (2H, t, $J$ = 3 Hz, -($CH_2$)-O-), 7.30 (5H, bs, Ph). MS (CI): *m/e* 220.2 $(M + H)^+$.

**Synthesis of 4-[2-(Diphenylmethoxy)ethyl]-1-benzylpiperidine Hydrochloride (9a).** Alcohol **6c** (0.15 g, 0.68 mmol) was reacted with benzhydrol (0.44 g, 2.39 mmol) to give product **9a**, 0.12 g (46% yield), as a viscous liquid (procedure E). $^1$H NMR ($CDCl_3$): 1.10−1.74 (7H, complex m), 1.78−2.05 (2H, t, $J$ = 4.5 Hz, -N($CH_2$)-), 2.75−2.95 (2H, m), 3.35−3.55 (4H, m, -N-($CH_2$)-Ph + -($CH_2$)-O-), 5.30 (1H, s, -(CH)-O-), 7.15−7.40 (15H, m, 3Ph).

Free base was converted into its foamy hydrochloride salt. Anal. ($C_{27}H_{32}NOCl·0.2H_2O$) C, H, N.

**Synthesis of 4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-1-benzylpiperidine Hydrochloride (9b).** Alcohol **6c** (0.24 g, 1.09 mmol) was reacted with 4,4′-difluorobenzhydrol (0.96 g, 4.35 mmol) to give product **9b**, 0.1 g (23% yield), as a viscous liquid (procedure E). $^1$H NMR ($CDCl_3$): 1.10−1.75 (7H, complex m), 1.78−2.10 (2H, t, $J$ = 4.5 Hz, -N-($CH_2$)-), 2.70−3.00 (2H, m), 3.30−3.54 (4H, m, -N-($CH_2$)Ph + -($CH_2$)-O-), 5.25 (1H, s, -(CH)-O-), 6.85−7.40 (13H, m, Ph + 2Ph-F).

Free base was converted into its oxalate salt, mp 145.5−147.4 °C. Anal. ($C_{29}H_{32}NO_6F_2·0.1(COOH)_2·0.8H_2O$) C, H, N.

**Synthesis of 4-[2-[Bis(4-methoxyphenyl)methoxy]ethyl]-1-(3-phenylpropyl)piperidine Hydrochloride (7d).** A 50 mL flask equipped with a magnetic stirrer was charged with 4,4′-dimethoxybenzhydrol (1 g, 4 mmol) dissolved in 20 mL of dry benzene. Excess amount of thionyl chloride (1 g, 8 mmol) was added, and the solution was refluxed for 1 h. After cooling benzene and excess thionyl chloride were removed in vacuo. The crude chloride was used in the next reaction without any further purification. Chloride **11** (4 mmol) and the alcohol **6a** (0.3 g, 1.2 mmol) were dissolved in 25 mL of toluene, and the solution was refluxed for 3 h. Toluene was removed in vacuo, and the residue was partitioned between EtOAc (100 mL) and excess saturated $NaHCO_3$ solution. Crude product was chromatographed over a silica gel column, and the pure product **7d** was eluted with EtOAc/hexane (1:1) mixture, 0.36 g (64% yield), as a solid, mp 74−75.8 °C. $^1$H NMR ($CDCl_3$): 1.10−2.20 (11H, complex m), 2.25−2.45 (2H, m), 2.50−2.74 (2H, t, $J$ = 4.5 Hz, -($CH_2$)-Ph), 2.76−3.00 (2H, m), 3.35−3.54 (2H, t, $J$ = 3 Hz, -O-($CH_2$)-), 3.80 (6H, s, -2$OCH_3$), 5.24 (1H, s, -O-(CH)-), 6.75−7.35 (13H, m, Ph + 2Ph-$OCH_3$). Anal. ($C_{31}H_{39}O_3N$) C, H, N.

**Synthesis of 1-(3-Phenylpropyl)-4-carbethoxypiperidine (13a).** Ethyl isonipecotate, **12** (6 g, 38 mmol), and 1-bromo-3-phenylpropane (9.5 g, 47 mmol) were reacted in the presence of $K_2CO_3$ to furnish **13a**, 9.1 g (87% yield), as an oil (procedure A). $^1$H NMR ($CDCl_3$): 1.14−1.32 (3H, t, $J$ = 4.4 Hz, ($CH_3$)-$CH_2$-O-), 1.60−2.45 (11H, complex m), 2.54−2.72 (2H, t, $J$ = 4.5 Hz, -($CH_2$)-Ph), 2.76−3.00 (2H, m), 4.00−4.25 (2H, q, $J$ = 4.5 Hz, -O-($CH_2$)-$CH_3$), 7.05−7.40 (5H, m, Ph). Anal. ($C_{16}H_{23}NO_2$) C, H, N.

**Synthesis of 1-(3-Phenylpropyl)-4-(hydroxymethyl)-piperidine (14a).** Ester **13a** (5.17 g, 18.8 mmol) was converted to alcohol **14a**, 4 g (93% yield), as an oil (procedure B). $^1$H NMR ($CDCl_3$): 1.20−2.45 (11H, complex m), 2.50−2.70 (2H, t, $J$ = 4.5 Hz, -($CH_2$)-Ph), 2.80−3.10 (3H, m), 3.30−3.50 (2H, d, $J$ = 3 Hz, -($CH_2$)-O-), 7.00−7.40 (5H, m, Ph). MS (CI): *m/e* 234.2 $(M + H)^+$.

**Synthesis of 4-[(Diphenylmethoxy)methyl]-1-(3-phenylpropyl)piperidine Hydrochloride (15a).** Alcohol **14a** (0.7 g, 3 mmol) and benzhydrol (1.6 g, 9 mmol) were reacted to give product **15a**, 0.6 g (50% yield), as a viscous liquid (procedure E). $^1$H NMR ($CDCl_3$): 1.20−1.90 (9H, complex m), 2.25−2.46 (2H, m), 2.50−2.72 (2H, t, $J$ = 4.5 Hz, -($CH_2$)-Ph), 2.80−3.00 (2H, m), 3.25−3.35 (2H, d, $J$ = 3 Hz, -($CH_2$)-O-), 5.30 (1H, s, -(CH)-O-), 7.10−7.45 (15H, m, 3Ph).

Free base was converted into its solid hydrochloride salt, mp 178−181.2 °C. Anal. ($C_{28}H_{34}NOCl·0.25H_2O$) C, H, N.

**Synthesis of 4-[[Bis(4-fluorophenyl)methoxy]methyl]-1-(3-phenylpropyl)piperidine Hydrochloride (15b).** Alcohol **14a** (0.7 g, 3 mmol) and 4,4′-difluorobenzhydrol (1.9 g, 8.6 mmol) were reacted to give product **15b**, 0.9 g (69% yield), as an oil (procedure E). $^1$H NMR ($CDCl_3$): 1.10−2.05 (9H, complex m), 2.25−2.45 (2H, m), 2.50−2.74 (2H, t, $J$ = 4.5 Hz, -($CH_2$)-Ph), 2.80−3.05 (2H, m), 3.15−3.35 (2H, d, $J$ = 3 Hz, -($CH_2$)-O-), 5.25 (1H, s, -(CH)-O-), 6.85−7.40 (13H, m, Ph + 2Ph-F).

Free base was converted into its hydrochloride salt, mp 173.3−176.3 °C. Anal. ($C_{28}H_{32}NOF_2Cl$) C, H, N.

**Synthesis of 1-(2-Phenylethyl)-4-carbethoxypiperidine (13b).** Ethyl isonipecotate, **12** (6 g, 38 mmol), and 2-(bromoethyl)benzene (8.47 g, 45 mmol) were treated to produce **13b**, 6.55 g (66% yield), as an oil (procedure A). $^1$H NMR ($CDCl_3$): 1.14−1.35 (3H, t, $J$ = 4.5 Hz, ($CH_3$)-$CH_2$-O-), 1.55−3.10 (13H, complex m), 4.00−4.26 (2H, q, $J$ = 4.5 Hz, $CH_3$-($CH_2$)-O-), 7.05−7.40 (5H, m, Ph). Anal. ($C_{16}H_{23}NO_2$) C, H, N.

**Synthesis of 1-(2-Phenylethyl)-4-(hydroxymethyl)piperidine (14b).** Ester **13b** (5 g, 15 mmol) was converted to alcohol **14b**, 3.14 g (95% yield), mp 101−104 °C (procedure B). $^1$H NMR ($CDCl_3$): 1.10−2.18 (8H, complex m), 2.45−3.15 (6H, complex m), 3.48−3.58 (2H, d, $J$ = 3 Hz, CH-($CH_2$)-O-), 7.10−7.40 (5H, m, Ph). MS (CI): *m/e* 220.2 $(M + H)^+$.

**Synthesis of 4-[(Diphenylmethoxy)methyl]-1-(2-phenylethyl)piperidine Hydrochloride (16a).** Alcohol **14b** (0.7 g, 3.1 mmol) and benzhydrol (1.8 g, 10 mmol) were treated to give product **16a**, 0.7 g (59% yield), as a colorless solid, mp 67.3−68.9 °C (procedure E). $^1$H NMR ($CDCl_3$): 1.10−2.15 (7H, complex m), 2.45−3.12 (6H, m), 3.24−3.38 (2H, d, $J$ = 3 Hz, -CH-($CH_2$)-O-), 5.30 (1H, s, -(CH)-O-), 7.10−7.40 (15H, m, 3Ph).

Free base was converted into its hydrochloride salt, mp 220−222.5 °C. Anal. ($C_{27}H_{32}NOCl$) C, H, N.

**Synthesis of 4-[[Bis(4-fluorophenyl)methoxy]methyl]-1-(2-phenylethyl)piperidine Hydrochloride (16b).** Alcohol **14b** (0.7 g, 3 mmol) and 4,4′-difluorobenzhydrol (2.2 g, 9.9 mmol) were reacted to give product **16b**, 0.85 g (66% yield), as a viscous liquid (procedure E). $^1$H NMR ($CDCl_3$): 1.20−2.15 (7H, complex m), 2.45−3.14 (6H, complex m), 3.20−3.35 (2H, d, $J$ = 3 Hz, CH-($CH_2$)-O-), 5.25 (1H, s, -(CH)-O-), 6.85−7.40 (13H, m, Ph + 2Ph-F).

Free base was converted into its solid hydrochloride salt, mp 225.5−226.7 °C. Anal. ($C_{27}H_{30}NOClF_2$) C, H, N.

**Synthesis of 1-Benzyl-4-carbethoxypiperidine (13c).** Ethyl isonipecotate, **12** (2.75 g, 17.5 mmol), and benzyl bromide were reacted to produce **13c**, 3 g (70% yield), as an oil (procedure A). $^1$H NMR ($CDCl_3$): 1.14−1.35 (3H, t, $J$ = 4.5 Hz, ($CH_3$)-CH2-O-), 1.60−2.45 (7H, complex m), 2.70−3.00 (2H, m), 3.50 (2H, s, -N-($CH_2$)-Ph), 4.00−4.25 (2H, q, $J$ = 4.5 Hz, -O-($CH_2$)-$CH_3$), 7.30 (5H, bs, Ph). Anal. ($C_{14}H_{19}NO_2$) C, H, N.

**Synthesis of 1-Benzyl-4-(hydroxymethyl)piperidine (14c).** Ester **13c** (2 g, 8 mmol) was converted to alcohol **14c**, 1.53 g (93% yield), as a viscous oil (procedure B). $^1$H NMR

($CDCl_3$): 1.10−2.10 (6H, m), 2.70−3.00 (4H, m), 3.35−3.50 (4H, m), 7.30 (5H, bs, Ph). MS (CI): *m/e* 206.1 $(M + H)^+$.

**Synthesis of 4-[(Diphenylmethoxy)methyl]-1-benzylpiperidine Hydrochloride (17a).** Alcohol **14c** (0.4 g, 1.9 mmol) and benzhydrol (1.07 g, 5.8 mmol) were reacted to give product **17a**, 0.6 g (85% yield), as a viscous liquid (procedure E). $^1H$ NMR ($CDCl_3$): 1.10−2.10 (7H, complex m), 2.75−3.00 (2H, m), 3.22−3.35 (2H, d, $J = 3$ Hz, -CH-($CH_2$)-O-), 3.45 (2H, s, -N-($CH_2$)-Ph), 5.25 (1H, s, -(CH)-O-), 7.25 (15H, bs, 3Ph).

Free base was converted into its oxalate salt, mp 175.6−177.1 °C. Anal. ($C_{28}H_{31}NO_5$) C, H, N.

**Synthesis of 4-[[Bis(4-fluorophenyl)methoxy]methyl]-1-benzylpiperidine Hydrochloride (17b).** Alcohol **14c** (0.4 g, 1.9 mmol) and 4,4′-difluorobenzhydrol (1.3 g, 5.8 mmol) were reacted to give product **17b**, 0.6 g (78% yield), as a viscous liquid (procedure E). $^1H$ NMR ($CDCl_3$): 1.04−2.10 (7H, complex m), 2.76−3.00 (2H, m), 3.15−3.30 (2H, d, $J = 3$ Hz, -CH-($CH_2$)-O-), 3.48 (2H, s, -N-($CH_2$)-Ph), 5.25 (1H, s, -(CH)-O-), 6.85−7.40 (13H, m, Ph + 2Ph-F).

Free base was converted into its oxalate salt, mp 161.5−162.9 °C. Anal. ($C_{28}H_{29}NF_2O_5 \cdot 0.4H_2O$) C, H, N.

**Biological Methods.** Binding of [$^3$H]CFT (2$\beta$-carbomethoxy-3$\beta$-(4-fluorophenyl)tropane, also known as WIN 35, 428) to the DA transporter and of [$^3$H]citalopram to the 5HT transporter was measured in rat striatal $P_2$ membrane preparations as described previously.[40] Briefly, rat striatal tissue was homogenized in 0.32 M sucrose, the $P_2$ pellet was polytronned in ice-cold 35 mM sodium phosphate buffer (final $[Na^+]$ of 35 mM by mixing 35 mM $NaH_2PO_4$ and 17.5 mM $Na_2HPO_4$ to obtain a pH of 7.4 at room temperature), and the binding assays were carried out for 2 h on ice at a final sodium phosphate concentration of 30 mM. The compounds were dissolved in dimethyl sulfoxide and diluted out into 10% (v/v) dimethyl sulfoxide solution. Additions from the later stocks resulted in a final concentration of dimethyl sulfoxide of 0.5%, which by itself did not interfere with the binding of [$^3$H]CFT or [$^3$H]-citalopram. After initial range-finding experiments, typical inhibition curves consisted of five different concentrations of compounds spaced evenly around the $IC_{50}$ value. Computation of $IC_{50}$ values was carried out with the equation of the ALLFIT program[41] entered into the Biosoft ORIGIN curve-fitting and plotting software.

**Acknowledgment.** This work was supported by the National Institute on Drug Abuse Grant No. DA08647. We thank Lori L. Coffey for excellent assistance.

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JM9506581