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Novel Diphenylalkyl Piperazine Derivatives with High Affinities for the Dopamine Transporter

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Abstract—The novel diphenyl piperazine derivatives containing the phenyl substituted aminopropanol moiety, including 1-[4,4-bis(4-fluorophenyl)butyl]-4-[2-hydroxy-3-(phenylamino)propyl]piperazine **1**, which were modified at the connective between the diphenyl and piperazine moieties, have been found to be potent dopamine uptake inhibitors. To study the further structure–activity relationship (SAR) of these compounds, a new series was synthesized, with modifications at the 2-hydroxy-3-phenylaminopropyl moiety of 1. The series was evaluated for dopamine transporter (DAT) binding affinity with [^{3}H]GBR12935 in rat striatal membranes. Most of the compounds showed moderate to high DAT binding affinities and some were approximately equivalent in activity to compound **1** or GBR12909 as a dopamine uptake inhibitor, with IC_{50} values of nanomolar range. The SAR suggested that on exhibiting a potent interaction with the DAT, there is probably a steric limitation around the benzene ring of the phenylamino moiety of **1**, allowing only small-sized substituents with the exception of basic moieties at the 4-position. In addition, the SAR at the 3-amino-2-propanol moiety of **1** suggested that either the nitrogen atom with an electron donating substituent or the unsubstituted nitrogen atom and also the hydroxy group are desirable for elicitation of a potent DAT binding affinity.

Introduction

Dopamine (DA) is a neurotransmitter involved in many biological processes in the central nervous system (CNS) and the dopaminergic neurotransmission is terminated by a uptake mechanism through the DAT located in the dopaminergic nerves terminals.[1] Dopaminergic neurotransmission has been reported to be closely associated with CNS disorders such as Parkinson's disease,[2] depression,[3] and cocaine abuse,[4] therefore much effort has been focused on the research of the DAT, which has been one of the most attractive targets for the treatment of these CNS disorders. In the last two decades, great interest and effort have been focused on the SARs of DA uptake inhibitors, which have led mainly two types of them, tropane and diphenyl piperazine derivatives represented respectively by Win 35,428[5] and GBR12909[6] (Fig. 1). They have included potent and selective DA uptake inhibitors and some have been in preclinical development or clinical trials. They have shown great promise as treatments of CNS disorders such as Parkinson's disease,[7] depression,[3] or cocaine addiction,[8] and have also helped to characterize biological and pharmacological profiles of the DAT.

In our previous study,[9] we found that the novel diphenyl piperazine derivatives containing the phenyl substituted aminopropanol moiety, including 1-[4,4-bis(4-fluorophenyl)butyl]-4-[2-hydroxy-3-(phenylamino)propyl]piperazine **1** (Fig. 1), which were modified at the

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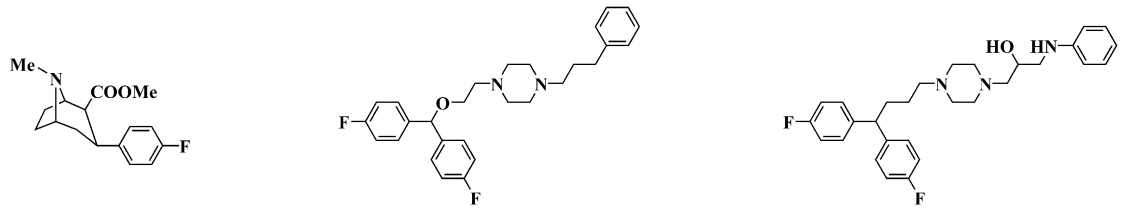


Win 35,428 GBR12909 1

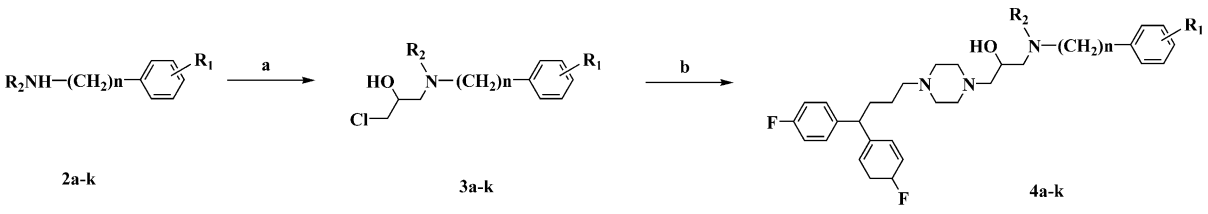
Figure 1.

connective between the diphenyl and piperazine moieties, exhibited moderate to high DAT binding affinities in rat striatal membranes. Furthermore, from an in vivo pharmacological study, compound **1** was also found to produce significant and dose-dependent increases of rat striatal extracellular DA levels, which were much greater than those by GBR12909. These findings suggested that these diphenyl piperazine derivatives are potent DA uptake inhibitors in the CNS and can serve as new structural molecules as DA uptake inhibitors different from GBR12909 analogues with the diphenylmethoxyalkyl and phenylalkyl moieties at the 1- and 4-position of the piperazine or piperizine ring and their bioisosteric moieties.[10–16] Therefore, we attempted to study further their SARs as DA uptake inhibitors. In this paper, we describe the syntheses of a new series of diphenylalkyl piperazine derivatives, which were modified at the 2-hydroxy-3-(phenylamino)propyl moiety in compound **1**, and their DAT binding affinities using [^{3}H]GBR12935 in rat striatal membranes.

Chemistry

The diphenylalkyl piperazine derivatives **4a–h**, **5**, and **6** containing various substituents on the benzene ring of the phenylamino moiety, *N*-methyl derivative **4j**, and benzylamino derivative **4k** were synthesized as shown in Schemes 1 and 2. Treatment of epichlorohydrin with the corresponding aniline derivatives **2a–j** and benzylamine **2k** in ethanol, followed by alkylation of 1-[4,4-bis(4-fluorophenyl)butyl]piperazine with the resultant chlorohydrin derivatives **3a–k** in the presence of potassium carbonate and potassium iodide in ethanol, afforded the desirable diphenylalkyl piperazine derivatives **4a–k** (Scheme 1). Reduction of the 4-nitro derivative **4e** with tin(II) chloride gave the amine derivative **5** (Scheme 2). Deprotection of the benzyl group in the 4-benzyloxy derivative **4i** using palladium catalyst in methanol containing formic acid gave the 4-hydroxy derivative **6** (Scheme 2). The *N*-acetyl **9a** and *N*-mesyl **9b** derivatives, 4-pyridyl derivative **10a**, 3,5-di-*tert*-butyl-4-hydroxy derivative **10b**, and 2-acetoxy **12** and 2-methoxy **13** propanol derivatives were synthesized as shown in Schemes 3 and 4. Alkylation of *N*-substituted anilines **7a–e** with epibromohydrin using sodium hydride (NaH) in *N*,*N*-dimethylformamide (DMF), followed by the treatment of the resultant epoxides **8a–e** with 1-[4,4-bis(4-fluorophenyl)butyl]piperazine in ethanol, afforded the desirable diphenylalkyl piperazine derivatives **9a–e** (Scheme 3). Deprotection of the *tert*-butoxycarbonyl (Boc) groups in **9c** and **9d** with hydrogen chloride in ethyl acetate gave the 4-pyridyl derivative **10a** and the 3,5-di-*tert*-butyl-4-hydroxy derivative **10b**, respectively (Scheme 3). Acetylation of **9e** with acetic anhydride in pyridine, followed by deprotection of the Boc group in the resultant compound **11** with hydrogen chloride in ethyl acetate, afforded an acetate **12** (Scheme 4). Alkylation of **1** with iodomethane in the presence of NaH in DMF gave a methoxide **13** as a sole product (Scheme 4).

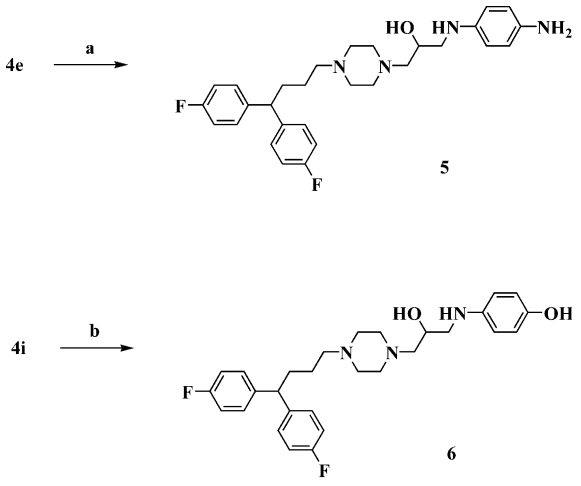
All of the final compounds synthesized as described above were used for the pharmacological evaluations in the forms of their corresponding salts listed in Table 1.



2a-k 3a-k 4a-k

a: R_1=4-F, R_2=H, n=0; b: R_1=4-OMe, R_2=H, n=0; c: R_1=4-Me, R_2=H, n=0; d: R_1=4-Cl, R_2=H, n=0; e: R_1=4-NO_2, R_2=H, n=0; f: R_1=4-$N(CH_3)_2$, R_2=H, n=0; g: R_1=3,4-diCl, R_2=H, n=0; h: R_1=3,4,5-triOMe, R_2=H, n=0; i: R_1=4-OBn, R_2=H, n=0; j: R_1=H, R_2=Me, n=0; k: R_1=H, R_2=H, n=1

Scheme 1. Reagents and conditions: (a) epichlorohydrin, EtOH, reflux, 42–72%; (b) 1-[4,4-bis(4-fluorophenyl)butyl]piperazine, K_2CO_3, KI, EtOH, reflux, 31–78%.



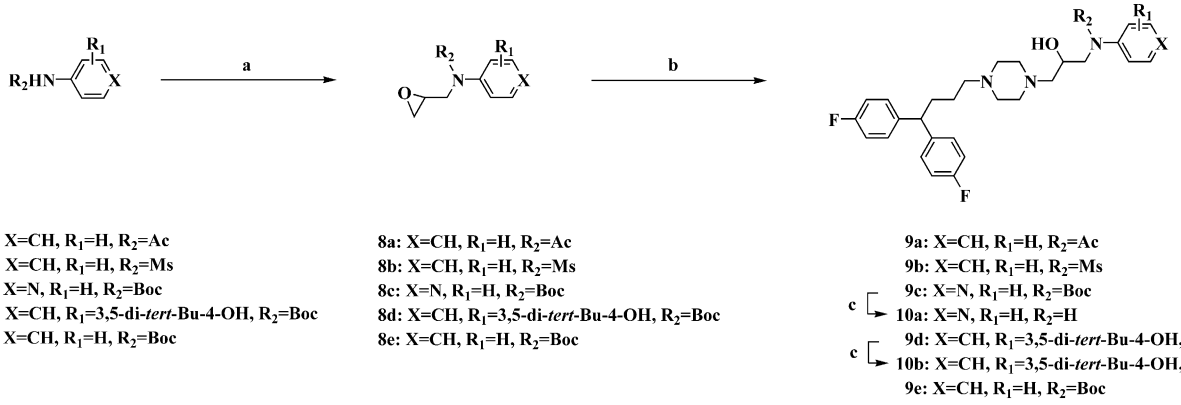
Scheme 2. Reagents and conditions: (a) $SnCl_2$, EtOH, heat, 81%; (b) 10% Pd-black, HCOOH, MeOH, room temperature, 95%.

Results and Discussion

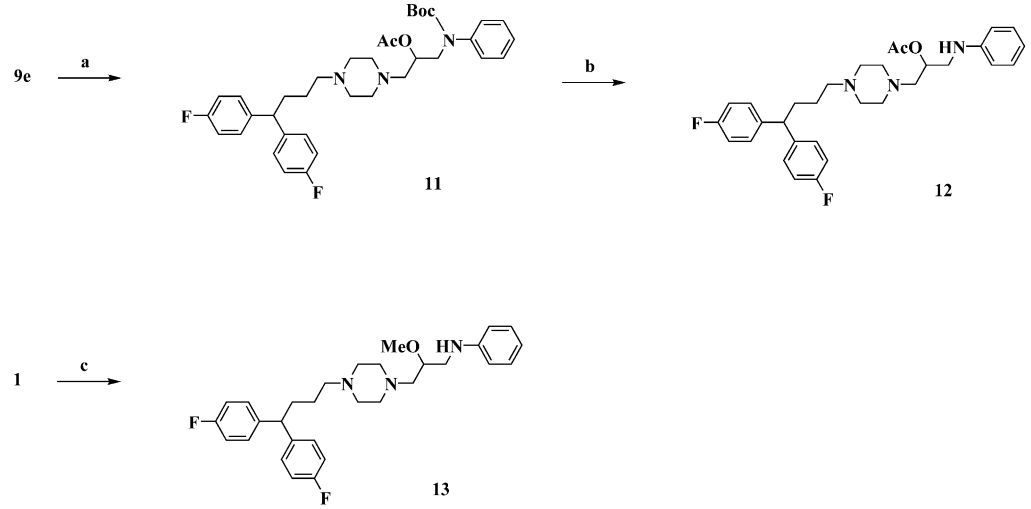
[^{3}H]GBR12935 binding studies

Diphenylalkyl piperazine derivatives synthesized as described above were evaluated for their competitive binding assays using [^{3}H]GBR12935 to label the DAT in rat striatal membranes.[17] The results are shown in Table 1.

At first, diphenylalkyl piperazine derivatives **4a–h**, **5**, **6**, and **10b** having the mono-, di-, and tri-substituents with various physico-chemical properties at the *meta*- and/or *para*-position of the benzene ring in the phenylamino moiety were evaluated, including 4-pyridyl **10a** and benzyl **4k** derivatives. The 4-fluoro **4a**, 4-methoxy **4b**, 4-methyl **4c**, and 4-chloro **4d** derivatives showed potent binding affinities for the DAT with IC_{50} values of low nanomolar range, which were similar to **1** or GBR12909, a known potent DA uptake inhibitor. These findings suggest that the electronic and hydrophobic properties of the substitutent at the 4-position have no great influence on these affinities. This possibility is supported by the

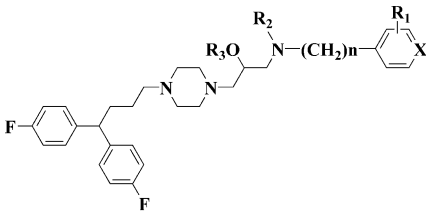


Scheme 3. Reagents and conditions: (a) NaH, epibromohydrin, DMF, room temperature, 34–100%; (b) 1-[4,4-bis(4-fluorophenyl)butyl]piperazine, EtOH, room temperature, 18–74%; (c) HCl/AcOEt, room temperature, 50%.



Scheme 4. Reagents and conditions: (a) Ac_2O, pyridine, room temperature, 89%; (b) HCl/AcOEt, room temperature, 91%; (c) NaH, CH_3I, DMF, room temperature, 29%.

Table 1. DAT binding affinities of diphenylalkyl piperazine derivatives



Compd	R_1	R_2	R_3	*n*	X	Salt[a]	IC_{50} (nM)[b]
4a	4-F	H	H	0	CH	A	4.00±0.23
4b	4-OMe	H	H	0	CH	A	3.00±0.16
4c	4-Me	H	H	0	CH	A	4.00±0.41
4d	4-Cl	H	H	0	CH	B	3.00±0.32
4e	4-NO_2	H	H	0	CH	C	8.00±0.50
4f	4-$N(CH_3)_2$	H	H	0	CH	B	109.00±19.00
4g	3,4-diCl	H	H	0	CH	C	12.00±0.72
4h	3,4,5-triOMe	H	H	0	CH	B	43.00±5.00
4j	H	Me	H	0	CH	D	3.00±0.21
4k	H	H	H	1	CH	A	18.00±4.00
5	4-NH_2	H	H	0	CH	B	37.00±9.00
6	4-OH	H	H	0	CH	B	10.00±3.00
9a	H	Ac	H	0	CH	C	38.00±4.00
9b	H	Ms	H	0	CH	D	10.00±0.78
10a	H	H	H	0	N	B	34.00±2.00
10b	3,5-di-*tert*-Bu-4-OH	H	H	0	CH	B	87.00±7.00
12	H	H	Ac	0	CH	D	14.00±1.00
13	H	H	Me	0	CH	A	17.00±4.00
1	H	H	H	0	CH	A	2.00±0.29
GBR12909						C	2.00±0.35

[a]A, trihydrochloride; B, trimaleate; C, dihydrochloride; D, dimaleate.
[b]The DAT was labeled with [^{3}H]GBR12935. IC_{50} values represent the concentrations inhibiting 50% of specific bindings and were calculated by non-linear regression fitting. Each value indicates a mean ±standard error from three experiments conducted in duplicates.

finding that the 4-nitro derivative **4e** with an electron withdrawing group and the 4-hydroxy derivative **6** with an electron donating group both kept potent binding affinities, although the activities were slightly less potent than those of **4a–d**. On the other hand, the 4-amino derivative **5** and 4-pyridyl derivative **10a** apparently decreased the binding affinities as compared with other 4-substituted derivatives described above. The results suggest that the basic property at the 4-position decreases the interaction with the binding site at the DAT, probably due to the ionization of the group through its strong basicity. The 4-dimethylamino derivative **4f** showed dramatically reduced binding affinity with IC_{50} value of 109 nM, which might be due to either excessive bulkiness or basicity or their combination. Concerning the 3,4-di- and 3,4,5-tri-substituted derivatives, 3,4-dichloro **4g**, 3,4,5-tri-methoxy **4h**, and 3,5-di-*tert*-butyl-4-hydroxy **10b** derivatives, they all caused decrease of binding affinity as compared with the corresponding 4-mono-substituted derivatives (**4g** vs **4d**), (**4h** vs **4b**), and (**10b** vs **6**), implying that there is probably an adverse steric effect including the bulkiness at the *meta*-position in interacting with the binding site at the DAT. The benzyl derivative **4k** also induced a slight decrease of binding affinity compared with **1**, which might indicate the involvement of less favorable interaction of this compound with the DAT. Namely, it is suggested that the appropriate location of the benzene ring of **1** for the binding site at the DAT sterically shifted to less favorable location due to the introduction of the methylene group between the benzene ring and the nitrogen atom. Thus, the results of the modifications of the benzene ring in the phenylamino moiety of compound **1** including the benzyl derivative described above suggest that on showing a potent interaction with the binding site at the DAT, there is probably a steric limitation around the benzene ring and only small-sized substitutents with the exception of basic moieties at the 4-position are allowed.

Next, diphenylalkyl piperazine derivatives **4j**, **9a**, **9b**, **12**, and **13**, which were modified at the 3-amino-2-propanol moiety of compound **1**, were evaluated. The *N*-methyl derivative **4j** exhibited a potent binding affinity comparable to **1**, while *N*-acetyl **9a** and *N*-mesyl **9b** derivatives decreased the binding affinities compared with **1**, showing IC_{50} values of 38 and 10 nM, respectively. Thus, the results of the modifications on the nitrogen atom of **1** indicate that an electron donating substituent such as a methyl group or the unsubstituted nitrogen atom is more favorable for a potent binding affinity for the DAT compared with an electron withdrawing substituent such as an acetyl or a mesyl group. Since a hydroxy group has been known to be often important for molecular recognition through the hydrophilic or hydrogen-bonded interaction, the modification of the hydroxy group of **1** was attempted. Replacement of the hydroxy group by the acetoxy group **12** and the methoxy group **13** induced slight reductions of binding affinity. These findings suggest that the 2-propanol moiety of **1** may exhibit a potent DAT binding affinity through the hydrophilic or hydrogen-bonded interaction, or there may be a steric limitation in the interaction of this moiety with the binding site at the DAT.

In conclusion, we have synthesized a new series of diphenylalkyl piperazine derivatives modified at the 2-hydroxy-3-(phenylamino)propyl moiety of compound **1** and evaluated them for DAT binding affinities with [^{3}H]GBR12935. Most of the compounds showed moderate to high DAT binding affinities and some were approximately equivalent in activity to **1** or GBR12909. The SAR through the modifications of the benzene ring in the phenylamino moiety of **1** suggested that on exhibiting a potent interaction with the DAT, there is a probably steric limitation around the benzene ring, allowing only small-sized substituents except for basic moieties at the 4-position. In addition, the SAR at the 3-amino-2-propanol moiety of **1** suggested that the nitrogen atom having an electron donating substituent or the unsubstituted nitrogen atom is more preferable for a potent DAT binding affinity compared with that having an electron withdrawing substituent, and that the hydroxy group also favors potent DAT binding affinity. Combined with the previous results of the modifications in the diphenylalkyl moiety of **1**, we have selected compound **1** as a representative for further biological and pharmacological evaluations and now continue these studies.

Experimental

All melting points were determined using a Büchi micromelting point apparatus without correction. IR

spectra were measured with a Nicolet FT-IR 205 spectrometer. ^{1}H NMR spectra were recorded on a JEOL GSX spectrometer (270 MHz). Chemical shifts were reported in ppm (δ) values, based on tetramethylsilane as an internal standard. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet, dt = double triplet, brs = broad singlet. MS spectra were recorded using a JEOL SX-102 mass spectrometer. Elemental analyses were performed by Yanaco CHN CORDER MT-5 (C, H, N) and Flask Combustion (Cl). Column chromatography were performed on silica gel (BW-200, Fuji Silisia Chemical, Ltd., 100–200 mesh).

***N*-(3-Chloro-2-hydroxypropyl)-4-fluoroaniline (3a)**. A mixture of 4-fluoroaniline (2.00 g, 18.0 mmol) and epichlorohydrin (0.83 g, 8.97 mmol) in EtOH (25 mL) was heated under reflux for 5 h. The mixture was cooled to room temperature and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3/CH_3OH$ = 99:1 as an eluent) to give **3a** (0.82 g, 45%) as a colorless oil. IR (KBr) cm^{-1}: 3398, 1508, 1220. ^{1}H NMR ($CDCl_3$) δ 2.82 (1H, brs), 3.18 (1H, dd, J = 7.0, 13.5 Hz), 3.34 (1H, dd, J = 4.6, 13.5 Hz), 3.61–3.74 (2H, m), 3.97–4.12 (1H, m), 6.61–6.73 (2H, m), 6.92–7.04 (2H, m). FAB-MS m/z 204 $[M+H]^+$.

Using this procedure, the following compounds **3b–k** were synthesized.

***N*-(3-Chloro-2-hydroxypropyl)-4-methoxyaniline (3b)**. A colorless oil. Yield 52%. IR (KBr) cm^{-1}: 3394, 1513, 1237, 1097, 824, 753. ^{1}H NMR ($CDCl_3$) δ 3.07 (1H, brs), 3.15 (1H, dd, J = 7.3, 12.7 Hz), 3.31 (1H, dd, J = 4.0, 12.7 Hz), 3.61–3.70 (2H, m), 3.71(3H, s), 3.74–3.79 (1H, m), 6.59–6.72 (2H, m), 6.76–6.92 (2H, m). HRFAB-MS calcd for $C_{10}H_{15}ClNO_2$ $[M+H]^+$: 216.0791. Found: 216.0789.

***N*-(3-Chloro-2-hydroxypropyl)-4-methylaniline (3c)**. A pale yellow oil. Yield 72%. IR (KBr) cm^{-1}: 3402, 1615, 1519, 1241, 1089, 914, 821, 742. ^{1}H NMR ($CDCl_3$) δ 2.28 (3H, s), 3.10 (1H, brs), 3.18 (1H, dd, J = 7.3, 13.5 Hz), 3.33 (1H, dd, J = 4.1, 13.5 Hz), 3.62–3.69 (2H, m), 3.98–4.13 (1H, m), 6.58 (2H, dd, J = 2.7, 11.7 Hz), 7.00 (2H, d, J = 8.4 Hz). FAB-MS m/z 200 $[M+H]^+$.

4-Chloro-*N*-(3-chloro-2-hydroxypropyl)aniline (3d). A colorless oil. Yield 72%. IR (KBr) cm^{-1}: 3390, 1597, 1498, 1241, 1084, 828, 744, 667. ^{1}H NMR ($CDCl_3$) δ 3.19 (1H, dd, J = 7.3, 13.2 Hz), 3.35 (1H, dd, J = 4.3, 13.2 Hz), 3.62–3.72 (2H, m), 3.96–4.13 (1H, m), 6.57–6.71 (2H, m), 7.11–7.24 (2H, m). FAB-MS m/z 220 $[M+H]^+$.

***N*-(3-Chloro-2-hydroxypropyl)-4-nitroaniline (3e)**. A yellow oil. Yield 45%. IR (KBr) cm^{-1}: 3340, 1603, 1507. ^{1}H NMR ($CDCl_3$) δ 2.57 (1H, d, J = 5.7 Hz), 3.41–3.47 (1H, m), 3.53–3.60 (1H, m), 3.62–3.74 (2H, m), 4.11–4.24 (1H, m), 4.77–4.92 (1H, m), 6.58–6.72 (2H, m), 7.93–8.14 (2H, m). FAB-MS m/z 231 $[M+H]^+$.

***N*-(3-Chloro-2-hydroxypropyl)-4-(dimethylamino)aniline (3f)**. A dark brown oil. Yield 42%. IR (KBr) cm^{-1}: 3420, 1604, 1507. ^{1}H NMR ($CDCl_3$) δ 2.81 (6H, s), 3.19–3.42 (2H, m), 3.52–3.64 (2H, m), 3.87–4.03 (1H, m), 6.61–6.83 (4H, m). FAB-MS m/z 229 $[M+H]^+$.

***N*-(3-Chloro-2-hydroxypropyl)-3,4-dichloroaniline (3g)**. A colorless oil. Yield 64%. IR (KBr) cm^{-1}: 3409, 1599, 1496, 1240, 1134, 1090, 846, 806, 751. ^{1}H NMR ($CDCl_3$) δ 3.18 (1H, dd, J = 7.6, 13.5 Hz), 3.33 (1H, dd, J = 4.1, 13.5 Hz), 3.62–3.74 (2H, m), 3.97–4.13 (1H, m), 6.48 (1H, dd, J = 2.4, 8.4 Hz), 6.71 (1H, d, J = 3.0 Hz), 7.19 (1H, d, J = 8.4 Hz). FAB-MS m/z 254 $[M+H]^+$.

***N*-(3-Chloro-2-hydroxypropyl)-3,4,5-trimethoxyaniline (3h)**. A colorless oil. Yield 63%. IR (KBr) cm^{-1}: 3398, 1612, 1511, 1235, 805, 775. ^{1}H NMR ($CDCl_3$) δ 3.21 (1H, dd, J = 6.8, 13.5 Hz), 3.37 (1H, dd, J = 3.8, 13.5 Hz), 3.72–3.82 (2H, m), 3.76 (3H, s), 3.84 (6H, s), 3.98–4.12 (1H, m), 5.91 (2H, s). FAB-MS m/z 276 $[M+H]^+$.

4-Benzyloxy-*N*-(3-chloro-2-hydroxypropyl)aniline (3i). A colorless oil. Yield 62%. IR (KBr) cm^{-1}: 3411, 1603, 1254. ^{1}H NMR ($CDCl_3$) δ 3.24 (1H, dd, J = 7.0, 13.2 Hz), 3.39 (1H, dd, J = 4.9, 13.2 Hz), 3.58–3.82 (2H, m), 4.01–4.14 (1H, m), 5.07 (2H, s), 6.71 (2H, t, J = 7.8 Hz), 6.76–6.91 (2H, m), 7.32–7.54 (5H, m). HRFAB-MS calcd for $C_{16}H_{19}ClNO_2$ $[M+H]^+$: 292.1104. Found: 292.1098.

***N*-(3-Chloro-2-hydroxypropyl)-*N*-methylaniline (3j)**. A yellow oil. Yield 59%. IR (KBr) cm^{-1}: 3413, 1602, 1507, 751. ^{1}H NMR ($CDCl_3$) δ 2.45 (1H, d, J = 4.9 Hz), 2.99 (3H, s), 3.45 (2H, d, J = 4.9 Hz), 3.60 (1H, dd, J = 5.4, 11.4 Hz), 3.70 (1H, dd, J = 4.1, 11.4 Hz), 4.08–4.23 (1H, m), 6.69–6.93 (3H, m), 7.21–7.33 (2H, m). FAB-MS m/z 200 $[M+H]^+$.

***N*-(3-Chloro-2-hydroxypropyl)benzylamine (3k)**. A pale yellow oil. Yield 46%. IR (KBr) cm^{-1}: 3392, 1603, 1507. ^{1}H NMR ($CDCl_3$) δ 2.66 (1H, dd, J = 7.8, 11.9 Hz), 2.78 (1H, dd, J = 4.1, 10.5 Hz), 3.52 (2H, d, J = 5.9 Hz), 3.78 (2H, s), 3.89–4.04 (1H, m), 7.18–7.42 (5H, m). FAB-MS m/z 200 $[M+H]^+$.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[3-[(4-fluorophenyl)amino]-2-hydroxypropyl]piperazine (4a). A mixture of **3a** (0.82 g, 4.03 mmol), 1-[4,4-bis(4-fluorophenyl)butyl] piperazine (1.33 g, 4.03 mmol), potassium carbonate (0.67 g, 4.85 mmol), and potassium iodide (0.07 g, 0.422 mmol) in EtOH (25 mL) was heated under reflux for 5 h. After removal of insoluble materials by filtration, the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3/CH_3OH$ = 99:1 as an eluent) to give **4a** (1.55 g, 78%) as a pale yellow oil. IR (KBr) cm^{-1}: 3387, 1603, 1508, 1222. ^{1}H NMR ($CDCl_3$) δ 1.41–1.52 (2H, m), 1.92–2.03 (2H, m), 2.31-2.48 (10H, m), 2.63–2.69 (2H, m), 2.98 (1H, dd, J = 5.9, 11.9 Hz), 3.19 (1H, dd, J = 4.1, 11.9 Hz), 3.86 (1H, t, J = 8.1 Hz), 3.87–4.02 (1H, m), 6.51–6.64 (2H, m), 6.77–7.03 (6H, m), 7.07–7.23 (4H, m). FAB-MS m/z 498 $[M+H]^+$.

Using this procedure, the following compounds **4b–k** were synthesized.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[2-hydroxy-3-[(4-methoxyphenyl)amino]propyl]piperazine (4b). A pale yellow oil. Yield 44%. IR (KBr) cm^{-1}: 3440, 1604, 1512, 1235. ^1H NMR ($CDCl_3$) δ 1.38–1.52 (2H, m), 1.87–2.13 (2H, m), 2.32–2.57 (10H, m), 2.63–2.72 (2H, m), 2.98 (1H, dd, $J=6.5$, 12.4 Hz), 3.20 (1H, dd, $J=3.5$, 12.4 Hz), 3.74 (3H, s), 3.82–4.04 (2H, m), 6.60 (2H, dd, $J=2.2$, 6.5 Hz), 6.77 (2H, dd, $J=1.9$, 6.5 Hz), 6.87–7.02 (4H, m), 7.08–7.23 (4H, m). FAB-MS m/z 510 $[M+H]^+$.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[2-hydroxy-3-[(4-methylphenyl)amino]propyl]piperazine (4c). A pale yellow oil. Yield 72%. IR (KBr) cm^{-1}: 3420, 1604, 1506, 1221. ^1H NMR ($CDCl_3$) δ 1.37–1.51 (2H, m), 1.96–2.12 (2H, m), 2.23 (3H, s), 2.28–2.54 (10H, m), 2.61–2.74 (2H, m), 3.01 (1H, dd, $J=6.2$, 12.2 Hz), 3.22 (1H, dd, $J=3.2$, 12.2 Hz), 3.83 (1H, t, $J=7.8$ Hz), 3.92–4.03 (1H, m), 6.65 (2H, d, $J=8.4$ Hz), 6.91–7.04 (5H, m), 7.12–7.23 (3H, m), 7.36 (2H, s). FAB-MS m/z 494 $[M+H]^+$.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[3-[(4-chlorophenyl)amino]-2-hydroxypropyl]piperazine (4d). A colorless oil. Yield 72%. IR (KBr) cm^{-1}: 3440, 1603, 1506, 1220. ^1H NMR ($CDCl_3$) δ 1.38–1.52 (2H, m), 1.97–2.11 (2H, m), 2.21–2.54 (10H, m), 2.62–2.74 (2H, m), 2.99 (1H, dd, $J=5.9$, 12.4 Hz), 3.21 (1H, dd, $J=3.5$, 12.4 Hz), 3.86 (1H, t, $J=7.3$ Hz), 3.88–4.02 (1H, m), 6.54 (2H, dd, $J=1.9$, 7.0 Hz), 6.95 (4H, dt, $J=1.9$, 7.0 Hz), 7.08–7.22 (4H, m), 7.36 (2H, s). FAB-MS m/z 514 $[M+H]^+$.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[2-hydroxy-3-[(4-nitrophenyl)amino]propyl]piperazine (4e). A yellow oil. Yield 69%. IR (KBr) cm^{-1}: 3420, 1605, 1508, 1229. ^1H NMR ($CDCl_3$) δ 1.38–1.51 (2H, m), 1.89–2.02 (2H, m), 2.31–2.58 (10H, m), 2.64–2.72 (2H, m), 3.11 (1H, dd, $J=5.9$, 11.3 Hz), 3.29–3.41(1H, m), 3.89 (1H, t, $J=7.8$ Hz), 3.89–4.03 (1H, m), 6.54 (2H, d, $J=6.8$ Hz), 6.95 (4H, dt, $J=2.4$, 6.8 Hz), 7.07–7.21 (4H, m), 8.08 (2H, dd, $J=1.9$, 7.3 Hz). HRFAB-MS calcd for $C_{29}H_{35}F_2N_4O_3$ $[M+H]^+$: 525.2677. Found: 525.2674.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[3-[(4-dimethylaminophenyl)amino]-2-hydroxypropyl]piperazine (4f). A dark brown oil. Yield 31%. IR (KBr) cm^{-1}: 3407, 1602, 1507, 1223. ^1H NMR ($CDCl_3$) δ 1.32–1.47 (2H, m), 1.92–2.04 (2H, m), 2.21–3.83 (14H, m), 2.85 (6H, s), 3.85 (1H, t, $J=7.4$ Hz), 3.92–4.03 (1H, m), 6.61 (2H, d, $J=7.4$ Hz), 6.72 (2H, d, $J=7.4$ Hz), 7.01 (4H, t, $J=7.4$ Hz), 7.11–7.23 (4H, m). FAB-MS m/z 523 $[M+H]^+$.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[3-[(3,4-dichlorophenyl)amino]-2-hydroxypropyl]piperazine (4g). A colorless oil. Yield 54%. IR (KBr) cm^{-1}: 3388, 1601, 1507, 1223. ^1H NMR ($CDCl_3$) δ 1.37–1.52 (2H, m), 1.96–2.13 (2H, m), 2.31–2.58 (10H, m), 2.64–2.71 (2H, m), 2.96 (1H, dd, $J=5.9$, 11.8 Hz), 3.20 (1H, d, $J=11.8$ Hz), 3.86 (1H, t, $J=8.1$ Hz), 3.88–4.01 (1H, m), 6.44 (1H, dd, $J=2.4$, 8.9 Hz), 6.67 (1H, d, $J=8.1$ Hz), 6.98 (4H, dt, $J=2.2$, 8.9 Hz), 7.08–7.22 (5H, m). HRFAB-MS calcd for $C_{29}H_{34}Cl_2F_2N_3O$ $[M+H]^+$: 548.2047. Found: 548.2052.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[2-hydroxy-3-[(3,4,5-trimethoxyphenyl)amino]propyl]piperazine (4h). A pale yellow oil. Yield 48%. IR (KBr) cm^{-1}: 3390, 1607, 1509, 1221. ^1H NMR ($CDCl_3$) δ 1.37–1.51 (2H, m), 1.98–2.13 (2H, m), 2.27–2.63 (10H, m), 2.64–2.73 (2H, m), 3.01 (1H, dd, $J=6.5$, 11.9 Hz), 3.23 (1H, dd, $J=3.8$, 11.9 Hz), 3.76 (3H, s), 3.82 (6H, s), 3.87 (1H, t, $J=8.1$ Hz), 3.91–4.02 (1H, m), 5.91 (2H, s), 6.98 (3H, t, $J=6.5$ Hz), 7.07–7.21 (3H, m), 7.36 (2H, s). FAB-MS m/z 570 $[M+H]^+$.

1-[3-[(4-Benzyloxyphenyl)amino]-2-hydroxypropyl]-4-[4,4-bis(4-fluorophenyl)butyl]piperazine (4i). A pale purple oil. Yield 47%. IR (KBr) cm^{-1}: 3420, 1602, 1507, 1221. ^1H NMR ($CDCl_3$) δ 1.37–1.51 (2H, m), 1.89–2.04 (2H, m), 2.27–2.52 (10H, m), 2.54–2.64 (2H, m), 2.95 (1H, dd, $J=7.0$, 12.4 Hz), 3.16 (1H, d, $J=3.2$, 12.4 Hz), 3.83 (1H, t, $J=7.8$ Hz), 3.88–4.03 (1H, m), 4.98 (2H, s), 6.51 (2H, d, $J=8.9$ Hz), 6.63 (6H, d, $J=8.9$ Hz), 6.92 (4H, dt, $J=2.2$, 7.8 Hz), 7.08–7.23 (5H, m). FAB-MS m/z 586 $[M+H]^+$.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[2-hydroxy-3-(*N*-methyl-*N*-phenylamino)propyl]piperazine (4j). A yellow oil. Yield 54%. IR (KBr) cm^{-1}: 3425, 1601, 1507, 1223. ^1H NMR ($CDCl_3$) δ 1.38–1.52 (2H, m), 1.88–2.03 (2H, m), 2.32–2.54 (10H, m), 2.59–2.72 (2H, m), 2.98 (3H, s), 3.22 (2H, d, $J=8.4$ Hz), 3.85 (1H, t, $J=7.8$ Hz), 3.89–4.02 (1H, m), 6.68–6.82 (5H, dt, $J=1.9$, 6.2 Hz), 7.16–7.32 (8H, m). FAB-MS m/z 494 $[M+H]^+$.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[2-hydroxy-3-(phenylmethylamino)propyl]piperazine (4k). A yellow oil. Yield 62%. IR (KBr) cm^{-1}: 3448, 1604, 1508, 1223. ^1H NMR ($CDCl_3$) δ 1.37–1.52 (2H, m), 1.88–2.03 (2H, m), 2.31–2.84 (14H, m), 3.78–3.93 (2H, m), 3.83 (2H, s), 6.95 (4H, t, $J=6.5$ Hz), 7.18–7.28 (4H, m), 7.33–7.44 (5H, m). FAB-MS m/z 494 $[M+H]^+$.

1-[3-[(4-Aminophenyl)amino]-2-hydroxypropyl]-4-[4,4-bis(4-fluorophenyl)butyl]piperazine (5). A mixture of **4e** (0.30 g, 0.572 mmol) and tin (II) chloride (0.48 g, 2.53 mmol) in EtOH (1 mL) was heated in an oil bath of 90 °C for 6 h under a nitrogen atmosphere. The mixture was cooled to room temperature, poured into aqueous saturated $NaHCO_3$ (30 mL), and extracted with two 40 mL portions of AcOEt. The extracts were combined, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3/CH_3OH=99:1$ as an eluent) to give **5** (0.23 g, 81%) as a yellow oil. IR (KBr) cm^{-1}: 3433, 1508, 1230. ^1H NMR ($CDCl_3$) δ 1.37–1.51 (2H, m), 1.96–2.12 (2H, m), 2.28–2.58 (10H, m), 2.63–2.72 (2H, m), 2.95 (1H, dd, $J=5.4$, 11.9 Hz), 3.18 (1H, dd, $J=3.2$, 11.8 Hz), 3.86 (1H, t, $J=7.8$ Hz), 3.88–4.03 (1H, m), 6.48–6.72 (3H, m), 6.87–7.03 (5H, m), 7.08–7.21 (4H, m). HRFAB-MS calcd for $C_{29}H_{37}F_2N_4O$ $[M+H]^+$: 495.2935. Found: 495.2943.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[3-[(4-hydoxyphenyl)amino]-2-hydroxypropyl]piperazine (6). A solution of **4i** (2.98 g, 5.09 mmol) in MeOH (16 mL) was added to a suspension of 10% Pd-black (0.82 g) in MeOH (20 mL)

containing formic acid (1.1 mL) and the mixture was stirred for 3 h at room temperature under a nitrogen atmosphere. After removal of insoluble materials by filtration, the filtrate was poured into a mixture of benzene (40 mL) and H_2O (40 mL). The organic layer was separated and the aqueous layer was extracted with two 40 mL portions of benzene. The organic layer and the extracts were combined, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3/CH_3OH = 99:1$ as an eluent) to give **6** (2.39 g, 95%) as a pale purple oil. IR (KBr) cm^{-1}: 3440, 1617, 1508, 1222. ^1H NMR ($CDCl_3$) δ 1.37–1.52 (2H, m), 1.88–2.03 (2H, m), 2.26–2.48 (10H, m), 2.53–2.62 (2H, m), 2.95 (1H, dd, $J = 7.0$, 12.4 Hz), 3.16 (1H, dd, $J = 3.2$, 12.4 Hz), 3.83 (1H, t, $J = 7.8$ Hz), 3.86–4.03 (1H, m), 6.51 (2H, d, $J = 8.9$ Hz), 6.63 (2H, d, $J = 8.9$ Hz), 6.92 (4H, dt, $J = 2.2$, 7.8 Hz), 7.07–7.24 (4H, m). FAB-MS m/z 496 $[M+H]^+$.

***N*-Acetyl-*N*-(2,3-epoxypropyl)aniline (8a)**. NaH (60% in mineral oil, 0.59 g, 14.8 mmol) was added to a solution of acetanilide **7a** (2.00 g, 14.8 mmol) in DMF (30 mL) under ice bath cooling and the mixture was stirred for 15 min. To the mixture was added dropwise a solution of epibromohydrin (2.03 g, 14.8 mmol) in DMF (5 mL) over a period of 20 min with stirring under ice bath cooling and the mixture was stirred for 4 h at room temperature. The mixture was poured into a mixture of benzene (50 mL) and H_2O (50 mL) and the organic layer was separated, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3/CH_3OH = 99:1$ as an eluent) to give **8a** (2.78 g, 98%) as a pale yellow oil. IR (KBr) cm^{-1}: 1631, 1602, 1501, 1263. ^1H NMR ($CDCl_3$) δ 1.85 (3H, s), 2.44 (1H, dd, $J = 2.4$, 4.3 Hz), 2.76 (1H, dd, $J = 4.3$, 4.9 Hz), 3.19–3.32 (1H, m), 3.60 (1H, dd, $J = 6.2$, 14.0 Hz), 4.01 (1H, dt, $J = 6.2$, 14.0 Hz), 7.18–7.33 (2H, m), 7.42–7.54 (3H, m). FAB-MS m/z 192 $[M+H]^+$.

Using this procedure, the following compounds **8b–e** were synthesized.

***N*-(2,3-Epoxypropyl)-*N*-methansulfonylaniline (8b)**. A pale yellow oil. Yield 34%. IR (KBr) cm^{-1}: 1597, 1494, 1332. ^1H NMR ($CDCl_3$) δ 2.52 (1H, q, $J = 2.4$ Hz), 2.75 (1H, q, $J = 4.6$ Hz), 3.02 (3H, s), 3.12–3.28 (1H, m), 3.37 (1H, dd, $J = 2.4$, 4.6 Hz), 3.84 (1H, dd, $J = 6.8$, 13.7 Hz), 7.28–7.53 (5H, m). FAB-MS m/z 228 $[M+H]^+$.

4-[*N*-*tert*-Butoxycarbonyl-*N*-(2,3-epoxypropyl)amino]pyridine (8c). This compound was used for the next reaction without purification by silica gel column chromatography.

***N*-*tert*-Butoxycarbonyl-3,5-di-*tert*-butyl-*N*-(2,3-epoxypropyl)-4-hydroxyaniline (8d)**. This compound was used for the next reaction without purification by silica gel column chromatography.

***N*-*tert*-Butoxycarbonyl-*N*-(2,3-epoxypropyl)aniline (8e)**. A colorless oil. Yield 100%. IR (KBr) cm^{-1}: 1699, 1598, 1497, 1379. ^1H NMR ($CDCl_3$) δ 1.52 (9H, s), 2.50 (1H, q, $J = 2.4$ Hz), 2.79 (1H, t, $J = 4.3$ Hz), 3.18–3.32 (1H, m), 3.62 (1H, dd, $J = 5.4$, 14.9 Hz), 3.86 (1H, dd, $J = 4.1$, 14.9 Hz), 7.18–7.54 (5H, m). FAB-MS m/z 250 $[M+H]^+$.

1-[3-(*N*-Acetyl-*N*-phenylamino)-2-hydroxypropyl]-4-[4,4-bis(4-fluorophenyl)butyl]piperazine (9a). A mixture of **8a** (2.78 g, 14.5 mmol) and 1-[4,4-bis(4-fluorophenyl)-butyl]piperazine (4.81 g, 14.6 mol) in EtOH (120 mL) was stirred for 18 h at room temperature. After removal of EtOH, the residue was purified by silica gel column chromatography ($CHCl_3/CH_3OH = 99:1$ as an eluent) to give **9a** (1.33 g, 18%) as a pale yellow oil. IR (KBr) cm^{-1}: 3420, 1654, 1597, 1508, 1222. ^1H NMR ($CDCl_3$) δ 1.36–1.51 (2H, m), 1.86 (3H, s), 1.86–2.03 (2H, m), 2.27–2.47 (10H, m), 2.52–2.61 (2H, m), 3.67 (1H, dd, $J = 7.8$, 13.8 Hz), 3.81–4.03 (3H, m), 6.94 (4H, t, $J = 8.4$ Hz), 7.08–7.16 (4H, m), 7.22–7.31 (2H, m), 7.32–7.43 (3H, m). FAB-MS m/z 522 $[M+H]^+$.

Using this procedure, the following compounds **9b–e** were synthesized.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[2-hydroxy-3-(*N*-methanesulfonyl-*N*-phenylamino)propyl]piperazine (9b). A pale yellow oil. Yield 29%. IR (KBr) cm^{-1}: 3442, 1602, 1508, 1340, 1222. ^1H NMR ($CDCl_3$) δ 1.56–1.72 (2H, m), 2.09–2.22 (2H, m), 3.11 (3H, s), 3.21–3.84 (14H, m), 4.07–4.22 (1H, m), 4.10 (1H, t, $J = 7.8$ Hz), 7.07–7.23 (4H, m), 7.39–7.64 (9H, m). HRFAB-MS calcd for $C_{30}H_{38}F_2N_3O_3S$ $[M+H]^+$: 558.2602. Found: 558.2596.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[3-[*N*-*tert*-butoxycarbonyl-*N*-(4-pyridyl)amino]-2-hydroxypropyl]piperazine (9c). A yellow oil. Yield 18%. IR (KBr) cm^{-1}: 3423, 1706, 1593, 1508, 1223. ^1H NMR ($CDCl_3$) δ 1.27–1.43 (2H, m), 1.53 (9H, s), 1.92–2.13 (2H, m), 2.17–2.48 (10H, m), 2.53–2.63 (2H, m), 3.54 (1H, dd, $J = 7.6$, 14.9 Hz), 3.82–4.03 (3H, m), 6.95 (4H, dt, $J = 1.9$, 8.9 Hz), 7.07–7.22 (4H, m), 7.26–7.43 (2H, m), 8.51 (2H, dd, $J = 1.9$, 4.9 Hz). FAB-MS m/z 581 $[M+H]^+$.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[3-[*N*-*tert*-butoxycarbonyl-*N*-(3,5-di-*tert*-butyl-4-hydroxyphenyl)amino]-2-hydroxypropyl]piperazine (9d). A pale yellow oil. Yield 28%. IR (KBr) cm^{-1}: 3440, 1689, 1603, 1508, 1224. ^1H NMR ($CDCl_3$) δ 1.38–1.47 (2H, m), 1.41 (18H, s), 1.43 (9H, s), 1.93–2.01 (2H, m), 2.16–2.37 (10H, m), 2.51–2.62 (2H, m), 3.53 (1H, dd, $J = 6.5$, 13.2 Hz), 3.73 (1H, dd, $J = 9.1$, 13.2 Hz), 3.78–4.02 (3H, m), 5.13 (1H, s), 6.87–7.03 (4H, m), 7.12–7.23 (4H, m), 7.36 (2H, s). FAB-MS m/z 708 $[M+H]^+$.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[3-(*N*-*tert*-butoxycarbonyl-*N*-phenylamino)-2-hydroxypropyl]piperazine (9e). A colorless oil. Yield 74%. IR (KBr) cm^{-1}: 3433, 1697, 1508, 1223. ^1H NMR ($CDCl_3$) δ 1.38–1.52 (2H, m), 1.42 (9H, s), 1.97–2.11 (2H, m), 2.29–2.53 (12H, m), 3.75 (1H, dd, $J = 8.4$, 14.9 Hz), 3.85 (1H, t, $J = 8.1$ Hz), 3.97 (1H, dd, $J = 3.0$, 14.9 Hz), 5.26–5.41 (1H, m), 6.96 (4H, dt, $J = 3.0$, 8.4 Hz), 7.13–7.22 (5H, m), 7.24–7.34 (4H, m). FAB-MS m/z 580 $[M+H]^+$.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[2-hydroxy-3-[(4-pyridyl)amino]propyl]piperazine (10a). A solution of 4.0 N

HCl in AcOEt (3.0 mL) was added dropwise over a period of 5 min to a solution of **9c** (1.00 g, 1.72 mmol) in AcOEt (36 mL) with stirring under ice bath cooling and the mixture was stirred at room temperature for 48 h. After removal of the solvent, the residue was solidified with Et_2O and filtered. The solids were dissolved in a mixture of benzene (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated in vacuo to give **10a** (0.41 g, 50%) as a yellow oil, which was used for the next reaction without further purification. IR (KBr) cm^{-1}: 3423, 1607, 1508, 1221. ^1H NMR ($CDCl_3$) δ 1.38–1.51 (2H, m), 1.93–2.12 (2H, m), 2.27–2.49 (10H, m), 2.54–2.63 (2H, m), 3.07 (1H, dd, $J=5.7$, 12.7 Hz), 3.21–3.33 (1H, m), 3.86 (1H, t, $J=7.8$ Hz), 3.89–4.02 (1H, m), 4.61–4.73 (1H, m), 6.44 (1H, dd, $J=1.4$, 5.1 Hz), 6.94 (4H, dt, $J=2.4$, 4.9 Hz), 7.06–7.22 (5H, m), 8.18 (2H, dd, $J=1.4$, 4.9 Hz). HRFAB-MS calcd for $C_{28}H_{35}F_2N_4O$ $[M+H]^+$: 481.2779. Found: 481.2783.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[3-[(3,5-di-*tert*-butyl-4-hydroxyphenyl)amino]-2-hydroxypropyl]piperazine (10b). This compound was prepared according to the procedure described for **10a** and used for the next reaction without further purification.

1-[2-Acetoxy-3-(*N*-*tert*-butoxycarbonyl-*N*-phenylamino)-propyl]-4-[4,4-bis(4-fluorophenyl)butyl]piperazine (11). A mixture of **9e** (6.60 g, 11.4 mmol) and acetic anhydride (3.49 g, 34.2 mmol) in pyridine (85 mL) was stirred for 60 h at room temperature. After removal of the solvent, the residue was dissolved in a mixture of benzene (50 mL) and H_2O (50 mL), the organic layer was separated, and the aqueous layer was extracted with two portions of benzene. The organic layer and the extracts were combined, washed with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/CH_3OH = 97:3 as an eluent) to give **11** (6.28 g, 89%) as a pale yellow oil. IR (KBr) cm^{-1}: 1740, 1699, 1508, 1223, 1158. ^1H NMR ($CDCl_3$) δ 1.37–1.51 (2H, m), 1.52 (9H, s), 1.86 (3H, s), 1.87–2.03 (2H, m), 2.26–2.54 (12H, m), 3.75 (1H, dd, $J=7.8$, 14.6 Hz), 3.85 (1H, t, $J=7.6$ Hz), 4.00 (1H, dd, $J=3.0$, 14.6 Hz), 5.21–5.33 (1H, m), 6.95 (4H, dt, $J=2.2$, 6.5 Hz), 7.08–7.22 (6H, m), 7.29–7.43 (3H, m). FAB-MS m/z 622 $[M+H]^+$.

1-[2-Acetoxy-3-(phenylamino)propyl]-4-[4,4-bis(4-fluorophenyl)butyl]piperazine (12). A solution of 4.0 N HCl in AcOEt (18 mL) was added dropwise to a solution of **11** (7.40 g, 11.9 mol) in AcOEt (36 mL) over a period of 5 min with stirring under ice bath cooling, and then the mixture was stirred for 7 h at room temperature. The mixture was poured into a mixture of AcOEt (50 mL) and saturated aqueous $NaHCO_3$ (50 mL), the organic layer was separated, and the aqueous layer was extracted with two portions of AcOEt. The organic layer and the extracts were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/CH_3OH = 99:1 as an eluent) to give **12** (5.66 g, 91%) as a pale yellow oil. IR (KBr) cm^{-1}: 1736, 1603, 1508, 1236. ^1H NMR ($CDCl_3$) δ 1.37–1.51 (2H, m), 1.88–2.03 (2H, m), 2.03 (3H, s), 2.27–2.63 (12H, m), 3.35 (2H, m), 3.86 (1H, t, $J=8.1$ Hz), 4.34–4.43 (1H, brs), 5.16 (1H, t, $J=7.6$ Hz), 6.63(2H, d, $J=7.6$ Hz), 6.70 (1H, t, $J=7.6$ Hz), 6.88–7.04 (5H, m), 7.21–7.24 (5H, m). HRFAB-MS calcd for $C_{31}H_{38}F_2N_3O_2$ $[M+H]^+$: 522.2932. Found: 522.2940.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[2-methoxy-3-(phenylamino)propyl]piperazine (13). NaH (60% in mineral oil, 1.74 g, 43.5 mmol) was added to a solution of **1** (17.4 g, 36.3 mmol) in DMF (40 mL) and the mixture was stirred for 1 h at room temperature. A solution of iodomethane (5.68 g, 40.0 mmol) in DMF (10 mL) was added dropwise over a period of 30 min and the mixture was stirred for 5 h at room temperature. The mixture was poured into ice water (100 mL) and extracted with two portions of AcOEt (80 mL). The extracts were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/CH_3OH = 99:1 as an eluent) to give **13** (5.12 g, 29%) as a pale yellow oil. IR(KBr) cm^{-1}: 1603, 1508, 1227. ^1H NMR ($CDCl_3$) δ 1.37–1.52 (2H, m), 1.87–2.03 (2H, m), 2.32–2.74 (12H, m), 3.17 (1H, dd, $J=5.1$, 12.4 Hz), 3.27 (1H, dd, $J=5.1$, 12.4 Hz), 3.41 (3H, s), 3.49–3.61 (1H, m), 3.86 (1H, t, $J=7.8$ Hz), 4.41–4.53 (1H, m), 6.52–6.72 (3H, m), 6.88–7.03 (4H, m), 7.07–7.22 (6H, m). HRFAB-MS calcd for $C_{30}H_{38}F_2N_3O$ $[M+H]^+$: 494.2983. Found: 494.2976.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[3-[(4-fluorophenyl)amino]-2-hydroxypropyl]piperazine trihydrochloride (4a·3HCl). A solution of 7.0 N HCl in EtOH (2.5 mL) was added dropwise to a solution of **4a** (1.55 g, 3.11 mmol) in EtOH (10 mL) under ice bath cooling and the mixture was stirred for 1 h at room temperature. The resultant precipitates were collected by filtration and recrystallized from EtOH to give **4a·3HCl** (1.58 g, 84%) as white crystals. Mp 208–211 °C. IR (KBr) cm^{-1}: 3377, 1510, 1236, 1226. ^1H NMR (DMSO-d_6) δ 1.47–1.62 (2H, m), 1.97–2.13 (2H, m), 3.15–3.83 (14H, m), 4.03 (1H, t, $J=8.1$ Hz), 4.23–4.32 (1H, m), 6.97–7.24 (8H, m), 7.28–7.43 (4H, m). Anal. calcd for $C_{29}H_{34}F_3N_3O·3HCl$: C, 57.39; H, 6.14; N, 6.92; Cl, 17.52. Found: C, 57.29; H, 6.12; N, 6.79; Cl, 17.31.

Using this procedure, the following diphenylalkyl piperazine derivatives (**4b**, **4c**, **4k**, and **13**) were converted to their trihydrochlorides.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[2-hydroxy-3-[(4-methoxyphenyl)amino]propyl]-piperazine trihydrochloride (4b·3HCl). White crystals. Yield 75%. Mp 207–210 °C. IR (KBr) cm^{-1}: 3442, 1606, 1511, 1256, 1226. ^1H NMR (DMSO-d_6) δ 1.47–1.62 (2H, m), 1.97–2.13 (2H, m), 3.07–3.83 (14H, m), 3.76 (3H, s), 4.02 (1H, t, $J=7.3$ Hz), 4.32–4.43 (1H, m), 7.00 (2H, d, $J=8.6$ Hz), 7.02–7.14 (4H, m), 7.26–7.43 (6H, m). Anal. calcd for $C_{30}H_{37}F_2N_3O_2·3HCl·2H_2O$: C, 55.01; H, 6.77; N, 6.41; Cl, 16.24. Found: C, 55.28; H, 6.59; N, 6.43; Cl, 16.27.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[2-hydroxy-3-[(4-methylphenyl)amino]propyl]piperazine trihydrochloride (4c·3HCl). White crystals. Yield 96%. Mp 210–213 °C. IR (KBr)

cm^{-1}: 3420, 1603, 1508, 1227. ^1H NMR (DMSO-d_6) δ 1.48–1.63 (2H, m), 1.95–2.13 (2H, m), 2.27 (3H, s), 3.18–3.92 (14H, m), 4.00 (1H, t, $J=7.8$ Hz), 4.32–4.41 (1H, m), 7.07–7.24 (8H, m), 7.32–7.44 (4H, m). Anal. calcd for $C_{30}H_{37}F_2N_3O{\cdot}3HCl$: C, 59.75; H, 6.69; N, 6.97; Cl, 17.64. Found: C, 59.57; H, 6.70; N, 6.88; Cl, 17.57.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[2-hydroxy-3-(phenylmethylamino)propyl]piperazine trihydrochloride (4k·3HCl). White crystals. Yield 72%. Mp 235–238 °C. IR (KBr) cm^{-1}: 3498, 1508, 1222. ^1H NMR (DMSO-d_6) δ 1.57–1.73 (2H, m), 2.09–2.23 (2H, m), 2.85–3.84 (14H, m), 4.10 (1H, t, $J=7.8$ Hz), 4.26 (2H, s), 4.31–4.43 (1H, m), 7.20 (4H, t, $J=8.9$ Hz), 7.37–7.61 (7H, m), 7.64–7.72 (2H, m). Anal. calcd for $C_{30}H_{37}F_2N_3O{\cdot}3HCl$: C, 59.75; H, 6.69; N, 6.97; Cl, 17.64. Found: C, 59.59; H, 6.74; N, 6.90; Cl, 17.69.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[2-methoxy-3-(phenylamino)propyl]piperazine trihydrochloride (13·3HCl). White crystals. Yield 70%. Mp 181–184 °C. IR (KBr) cm^{-1}: 1602, 1507, 1159, 1222. ^1H NMR (DMSO-d_6) δ 1.58–1.73 (2H, m), 2.06–2.22 (2H, m), 3.17–3.84 (14H, m), 3.50 (3H, s), 3.97–4.12 (1H, m), 4.10 (1H, t, $J=8.1$ Hz), 6.57 (1H, t, $J=7.3$ Hz), 6.74 (2H, d, $J=7.3$ Hz), 7.08–7.23 (6H, m), 7.41–7.54 (4H,m). Anal. calcd for $C_{30}H_{37}F_2N_3O{\cdot}3HCl$: C, 59.75; H,6.69; N, 6.97; Cl, 17.64. Found: C, 59.97; H, 6.69; N, 6.97; Cl, 17.82.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[3-[(4-chlorophenyl)amino]-2-hydroxypropyl]piperazine trimaleate (4d·3$C_4H_4O_4$). A solution of maleic acid (2.50 g, 21.5 mmol) in Et_2O (125 mL) was added dropwise to a solution of **4d** (3.60 g, 7.00 mmol) in Et_2O (65 mL) under ice bath cooling, and the mixture was stirred for 1 h at room temperature. The resultant precipitates were collected by filtration and recrystallized from EtOH to give **4**·3$C_4H_4O_4$ (4.16 g, 69%) as white crystals. Mp 170–173 °C. IR (KBr) cm^{-1}: 3438, 1602, 1578, 1508, 1223. ^1H NMR (DMSO-d_6) δ 1.37–1.52 (2H, m), 1.98–2.13 (2H, m), 2.61–3.34 (14H, m), 3.87–4.03 (1H, m), 4.06 (1H, t, $J=8.1$ Hz), 6.23 (6H, s), 6.65 (2H, dd, $J=1.9$, 6.8 Hz), 7.06–7.23 (6H, m), 7.37–7.53 (4H, m). Anal. calcd for $C_{29}H_{34}ClF_2N_3O{\cdot}3C_4H_4O_4$: C, 57.11; H, 5.38; N, 4.87; Cl, 4.11. Found: C, 57.28; H, 5.34; N, 4.83; Cl, 4.09.

Using this procedure, the following diphenylalkyl piperazine derivatives (**4f**, **4h**, **5**, **6**, **10a**, and **10b**) were converted to their trimaleates.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[3-[(4-dimethylaminophenyl)amino]-2-hydroxypropyl]piperazine trimaleate (4f·3$C_4H_4O_4$). A brown powder. Yield 70%. Mp 170–173 °C. IR (KBr) cm^{-1}: 3427, 1608, 1503, 1224. ^1H NMR (DMSO-d_6) δ 1.37–1.52 (2H, m), 1.92–2.03 (2H, m), 2.50 (6H, s), 2.52–3.54 (14H, m), 3.92–4.01 (1H, m), 3.99 (1H, t, $J=7.3$ Hz), 6.14 (6H, s), 6.72–6.81 (2H, m), 6.98–7.11 (2H, m), 7.12 (4H, t, $J=8.4$ Hz), 7.27–7.43 (4H, m). Anal. calcd for $C_{31}H_{40}F_2N_4O{\cdot}3C_4H_4O_4$: C, 59.30; H, 6.02; N, 6.43. Found: C, 59.02; H, 6.01; N, 6.39.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[2-hydroxy-3-[(3,4,5-trimethoxyphenyl)amino]propyl]piperazine trimaleate (4h·3$C_4H_4O_4$). White crystals. Yield 49%. Mp 163–164 °C. IR (KBr) cm^{-1}: 3442, 1604, 1509, 1217. ^1H NMR (DMSO-d_6) δ 1.38–1.52 (2H, m), 1.92–2.03 (2H, m), 2.61–3.12 (14H, m), 3.55 (3H, s), 3.76 (6H, s), 3.94–4.02 (1H, m), 4.00 (1H, t, $J=7.8$ Hz), 5.97 (2H, s), 6.15 (6H, s), 7.12 (4H, t, $J=8.4$ Hz), 7.33 (4H, dd, $J=5.9$, 8.4 Hz). Anal. calcd for $C_{32}H_{41}F_2N_3O_4{\cdot}3C_4H_4O_4$: C, 57.57; H, 5.82; N, 4.58. Found: C, 57.88; H, 5.71; N, 4.50.

1-[3-[(4-Aminophenyl)amino]-2-hydroxypropyl]-4-[4,4-bis(4-fluorophenyl)butyl]piperazine trimaleate (5·3$C_4H_4O_4$). A dark brown powder. Yield 72%. Mp 153–155 °C. IR (KBr) cm^{-1}: 3451, 1617, 1508, 1231. ^1H NMR (DMSO-d_6) δ 1.37–1.52 (2H, m), 1.97–2.13 (2H, m), 2.51–3.64 (14H, m), 3.92–4.03 (1H, m), 4.03 (1H, t, $J=7.6$ Hz), 6.15 (6H, s), 6.69 (2H, d, $J=7.8$ Hz), 7.03 (2H, d, $J=8.4$ Hz), 7.16 (4H, t, $J=8.4$ Hz), 7.32–7.43 (4H, m). Anal. calcd for $C_{29}H_{36}F_2N_4O{\cdot}3C_4H_4O_4$: C, 58.43; H, 5.74; N, 6.65. Found: C, 58.71; H, 5.71; N, 6.83.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[3-[(4-hydoxyphenyl)amino]-2-hydroxypropyl]piperazine trimaleate (6·3$C_4H_4O_4$). Pale yellow crystals. Yield 69%. Mp 160–162 °C. IR (KBr) cm^{-1}: 3401, 3223, 1617, 1508, 1222. ^1H NMR (DMSO-d_6) δ 1.38–1.51 (2H, m), 1.93–2.11 (2H, m), 2.57–3.04 (13H, m), 3.05 (1H, dd, $J=4.9$, 12.4 Hz), 3.81–3.93 (1H, m), 4.00 (1H, t, $J=8.1$ Hz), 6.17 (6H, s), 6.60 (4H, s), 7.12 (4H, t, $J=8.9$ Hz), 7.27–7.43 (4H, m). Anal. calcd for $C_{29}H_{35}F_2N_3O_2{\cdot}3C_4H_4O_4$; C, 58.36; H, 5.61; N, 4.98. Found: C, 58.15; H, 5.58; N, 5.12.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[2-hydroxy-3-[(4-pyridyl)amino]propyl]piperazine trimaleate (10a·3$C_4H_4O_4$). A dark brown powder. Yield 70%. Mp 169–170 °C. IR (KBr) cm^{-1}: 3449, 1578, 1509, 1224. ^1H NMR (DMSO-d_6) δ 1.48–1.57 (2H, m), 2.11–2.23 (2H, m), 2.82–3.24 (12H, m), 3.34 (1H, dd, $J=6.2$, 13.2 Hz), 3.47 (1H, dd, $J=5.9$, 13.2 Hz), 3.92–4.03 (1H, m), 4.09 (1H, t, $J=7.8$ Hz), 6.19 (6H, s), 7.00 (2H, d, $J=7.3$ Hz), 7.19 (4H, t, $J=8.9$ Hz), 7.38-7.52 (4H, m), 8.11–8.32 (1H, m), 8.62 (1H, t, $J=5.9$ Hz). Anal. calcd for $C_{28}H_{34}F_2N_4O{\cdot}3C_4H_4O_4$: C, 57.97; H, 5.59; N, 6.76. Found: C, 57.94; H, 5.57; N, 6.75.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[3-[(3,5-di-*tert*-butyl-4-hydroxyphenyl)amino]-2-hydroxypropyl]piperazine trimaleate (10b·3$C_4H_4O_4$). White crystals. Yield 27%. Mp 179–180 °C. IR (KBr) cm^{-1}: 3448, 1619, 1509, 1223. ^1H NMR (DMSO-d_6) δ 1.38–1.51 (2H, m), 1.40 (18H, s), 1.92–2.03 (2H, m), 2.57–3.82 (14H, m), 3.83–3.95 (1H, m), 4.00 (1H, t, $J=8.4$ Hz), 6.17 (6H, s), 6.52 (2H, s), 7.12 (4H, t, $J=8.9$ Hz), 7.32–7.43 (4H, m). Anal. calcd for $C_{37}H_{51}F_2N_3O_2{\cdot}3C_4H_4O_4$: C, 61.56; H, 6.64; N, 4.40. Found: C, 61.72; H, 6.43; N, 4.28.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[2-hydroxy-3-[(4-nitrophenyl)amino]propyl]piperazine dihydrochloride (4e·2HCl). A solution of 7.0 N HCl in EtOH (1.2 mL) was added dropwise to a solution of **4e** (0.52 g, 0.991 mmol) in EtOH (10 mL) under ice bath cooling and the mixture was stirred for 1 h at room temperature. The resultant precipitates were collected by filtration and recrystallized

from EtOH to give **4e·2HCl** (0.44 g, 70%) as yellow crystals. Mp 145–148 °C. IR (KBr) cm^{-1}: 3387, 1605, 1508, 1229. ^1H NMR (DMSO-d_6) δ 1.57–1.72 (2H, m), 2.13–2.24 (2H, m), 3.16–3.92 (14H, m), 4.10 (1H, t, $J=7.8$ Hz), 4.32–4.44 (1H, m), 6.82 (2H, d, $J=9.5$ Hz), 7.20 (4H, t, $J=9.5$ Hz), 7.42–7.53 (4H, m), 8.07 (2H, d, $J=9.5$ Hz). Anal. calcd for $C_{29}H_{34}F_2N_4O_3\cdot 2HCl\cdot 2H_2O$: C, 54.98; H, 6.36; N, 8.84; Cl, 11.19. Found: C, 55.21; H, 6.24; N, 8.89; Cl, 11.20.

Using this procedure, the following diphenylalkyl piperazine derivatives (**4g** and **9a**) were converted to their dihydrochlorides.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[3-[(3,4-dichlorophenyl)amino] - 2 - hydroxypropyl]piperazine dihydrochloride (4g·2HCl). White crystals. Yield 53%. Mp 148–150 °C. IR (KBr) cm^{-1}: 3452, 1604, 1509, 1217, 707. ^1H NMR (DMSO-d_6) δ 1.52–1.63 (2H, m), 2.11–2.23 (2H, m), 3.24–4.07 (14H, m), 4.10 (1H, t, $J=7.8$ Hz), 4.23–4.34 (1H, m), 6.71 (1H, dd, $J=2.7$, 8.9 Hz), 6.92 (1H, d, $J=2.4$ Hz), 7.20 (4H, t, $J=8.9$ Hz), 7.34 (1H, d, $J=8.9$ Hz), 7.38–7.52 (4H, m). Anal. calcd for $C_{29}H_{33}Cl_2F_2N_3O\cdot 2HCl$: C, 56.05; H, 5.68; N, 6.76; Cl, 22.82. Found: C, 56.32; H, 5.67; N, 6.54; Cl, 22.76.

1-[3-(*N*-Acetyl-*N*-phenylamino)-2-hydroxypropyl]-4-[4,4-bis(4 - fluorophenyl)butyl]piperazine dihydrochloride (9a·2HCl). White crystals. Yield 66%. Mp 210–212 °C. IR (KBr) cm^{-1}: 3420, 1652, 1595, 1225. ^1H NMR (DMSO-d_6) δ 1.58–1.73 (2H, m), 1.81 (3H, s), 2.21–2.35 (2H, m), 3.14–3.96 (14H, m), 4.01–4.13 (1H, m), 4.10 (1H, t, $J=8.1$ Hz), 7.22–7.34 (4H, m), 7.36–7.54 (5H, m), 7.55–7.64 (4H, m). Anal. calcd for $C_{31}H_{37}F_2N_3O_2\cdot 2HCl\cdot 2H_2O$: C, 59.05; H, 6.87; N, 6.66; Cl, 11.24. Found: C, 58.96; H, 6.82; N, 6.62; Cl, 11.32.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[2-hydroxy-3-(*N*-methyl-*N*-phenylamino)propyl]piperazine dimaleate (4j·2C4H4O4). A solution of maleic acid (3.23 g, 27.8 mmol) in Et_2O (60 mL) was added dropwise to a solution of **4j** (3.45 g, 6.99 mmol) in Et_2O (65 mL) under ice bath cooling, and the mixture was stirred for 1 h at room temperature. The resultant precipitates were collected by filtration and recrystallized from EtOH to give **4j·2C4H4O4** (5.02 g, 99%) as white crystals. Mp 180–182 °C. IR (KBr) cm^{-1}: 3399, 1601, 1578, 1508, 1225. ^1H NMR (DMSO-d_6) δ 1.38–1.53 (2H, m), 2.14–2.23 (2H, m), 2.71–3.23 (12H, m), 3.00 (3H, s), 3.28 (1H, dd, $J=7.3$, 14.9 Hz), 3.45 (1H, dd, $J=4.9$, 14.9 Hz), 4.06 (2H, t, $J=7.8$ Hz), 6.21 (4H, s), 6.67 (1H, t, $J=7.3$ Hz), 6.77 (2H, m), 7.12–7.33 (6H, m), 7.38–7.53 (4H, m). Anal. calcd for $C_{30}H_{37}F_2N_3O\cdot 2C_4H_4O_4$: C, 62.89; H, 6.25; N, 5.79. Found: C, 62.77; H, 6.19; N, 5.69.

Using this procedure, the following diphenylalkyl piperazine derivatives (**9b** and **12**) were converted to their dimaleates.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-[2-hydroxy-3-(*N*-methanesulfonyl - *N* - phenylamino)propyl]piperazine dimaleate (9b·2C4H4O4). White crystals. Yield 66%. Mp.195–198 °C. IR (KBr) cm^{-1}: 3424, 1602, 1334, 1223. ^1H NMR (DMSO-d_6) δ 1.38–1.54 (2H, m), 2.02–2.14 (2H, m), 2.42–3.15 (12H, m), 2.99 (3H, s), 3.61–3.72 (3H, m), 3.99 (1H, t, $J=7.8$ Hz), 6.14 (4H, s), 7.09 (4H, t, $J=7.8$ Hz), 7.32–7.46 (5H, m), 7.48–7.54 (4H, m). Anal. calcd for $C_{30}H_{37}F_2N_3O_3S\cdot 2C_4H_4O_4$: C, 57.79; H, 5.74; N, 5.32. Found: C, 57.62; H, 5.80; N, 5.24.

1-[2-Acetoxy-3-(phenylamino)propyl]-4-[4,4-bis(4-fluorophenyl)butyl]piperazine dimaleate (12·2C4H4O4). White crystals. Yield 58%. Mp 159–160 °C. IR (KBr) cm^{-1}: 1736, 1605, 1225. ^1H NMR (DMSO-d_6) δ 1.62–1.74 (2H, m), 2.19 (3H, s), 2.82–3.64 (16H, m), 4.14 (1H, t, $J=8.1$ Hz), 5.15 (1H, t, $J=5.4$ Hz), 6.31 (4H, s), 6.67 (1H, t, $J=7.3$ Hz), 6.75 (4H, d, $J=7.3$ Hz), 7.22–7.44 (8H, m). Anal. calcd for $C_{31}H_{37}F_2N_3O_2\cdot 2C_4H_4O_4$: C, 62.14; H, 6.02; N, 5.57. Found: C, 62.02; H,6.02; N, 5.48.

[^{3}H]GBR12935 binding studies

Binding assays for the DAT were determined according to the published procedure.[17] Briefly, the rat striatal membranes were incubated with [^{3}H]GBR12935 (1 nM final concentration) and test compounds (final concentration range: 10^{-11}–10^{-5} M), which were diluted with dimethyl sulfoxide solution (final dimethyl sulfoxide concentration was less than 0.1%), for 60 min at 4 °C in 50 mM Tris–citrate (pH 7.4) buffer containing 120 mM NaCl and 4 mM $MgCl_2$. [^{3}H]GBR12935 (53 Ci/mmol) was purchased from Du Pont-NEN (Boston, MA, USA). The assay was terminated by filtration through Whatman GB/F glass fiber filtermats, persoaked with 0.1% bovine serum albumin solution, with a Brandel Cell Harvester (Gaithersberg, MD, USA). Filters were assayed for radioactivity with Packard Tris-Carb Liquid Scintillation Counter (Meriden, CT, USA) in 4 mL Aquasol-2.

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