Development of Novel, Potent, and Selective Dopamine Reuptake Inhibitors through Alteration of the Piperazine Ring of 1-[2-(Diphenylmethoxy)ethyl]- and 1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazines (GBR 12935 and GBR 12909)

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Received April 24, 1996⊗

The design, synthesis, and biological evaluation of compounds related to the dopamine (DA) uptake inhibitors: 1-[2-(diphenylmethoxy)ethyl]-4-(3-phenylpropyl)piperazine (**1**) and 1-[2-[bis-(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine (**2**) (GBR 12395 and GBR 12909, respectively), directed toward the development and identification of new ligands interacting with high potency and selectivity at the dopamine transporter (DAT) is reported. The substitution of the piperazine ring in the GBR structure with other diamine moieties resulted in the retention of the high affinity of new ligands for the DAT. Some of the modified GBR analogs (e.g. **8**, **10**, **(−)-49**, or **(−)-50**) displayed substantially higher selectivity (4736- to 693-fold) for the dopamine (DA) versus the serotonin (5HT) reuptake site than the parent compounds. The bis(p-fluoro) substitution in the (diphenylmethoxy)ethyl fragment slightly increased the affinity of the ligands at the DA reuptake site but reduced their selectivity at this site (e.g. **9** and **8**, **11** and **10**, or **17** and **16**, respectively). Congeners, such as the series of monosubstituted and symmetrically disubstituted piperazines and *trans*-2,5-dimethylpiperazines, which lack the (diphenylmethoxy)ethyl substituent lost the affinity for the DAT yet exhibited very high potency for binding to the σ receptors (e.g. **28**). The chiral pyrrolidine derivatives of **1**, **(−)-49**, and **(+)-49**, exhibited an enantioselectivity ratio of 181 and 146 for the inhibition of DA reuptake and binding to the DAT, respectively.

Introduction

The current epidemic of cocaine abuse is a major international problem which continues to be exacerbated by the appearance of cocaine base ("crack") smoking, an extremely reinforcing route of self-administration.[1−6] The heightened health and social problems in many United States areas related to cocaine have encouraged new efforts toward the development of pharmacotherapies for the treatment and prevention of cocaine abuse. Such efforts, including the National Institute on Drug Abuse Medications Development Program, have benefited from intensive studies of the mechanism of action of this drug. Although cocaine potently inhibits the reuptake of both norepinephrine (NE) and serotonin (5HT), many lines of evidence indicate that its ability to increase dopaminergic transmission by inhibiting the reuptake of dopamine (DA) into dopaminergic neurons is the prevailing neurochemical pathway responsible for its reinforcing effects.[7−13] Cocaine exerts this effect via specific interaction with DA transporter (DAT) proteins (cocaine receptor) located on DA nerve terminals. This increase of dopaminergic transmission in the reward mediating brain mesolimbic system is the essence of the dopamine hypothesis of reinforcement advanced by Wise[10] and his associates and elaborated for cocaine by Kuhar.[8] Although no pure cocaine antagonist (analogous to the opioid antagonist naloxone) is known, the dopamine hypothesis leaves open the possibility that such a drug may ultimately be identified.

A number of drugs from a variety of pharmacological classes have been tested in both clinical and preclinical studies as potential medications for the treatment of cocaine abuse.[1,14−19] These include opioid receptor agonists[15,20] and antagonists,[18,20] antidepressants,[1,14] dopamine antagonists[21,22] and agonists.[23] dopamine reuptake inhibitors,[12,24] and many others. Since the dopamine transporter seems to play an essential role in the mechanism of cocaine action in the brain, a variety of structurally diverse DAT ligands have been subjected to a number of pharmacological studies.[7,25−29] Disubstituted piperazines **1** and **2** (Chart 1) proved to be among the most potent and selective DA reuptake inhibitors.[30−32] It has been hypothesized that the development of a high-affinity, low intrinsic activity partial cocaine agonist, which noncompetitively inhibits the DA reuptake but does not produces euphoria (the DA reuptake blocker type 2[33,34]), might be a suitable approach to treat cocaine addiction in humans. In microdialysis experiments, the slowly dissociating DAT ligand, 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine (**2**, GBR 12909), was shown to attenuate the extracellular DA (ECDA) levels enhanced by cocaine in rat striatum[35] and nucleus accumbens.[36] Glowa et al. recently showed that **2** decreases the cocaine-maintained responding without decreasing the food-maintained responding in cocaine and food self-administration studies in rhesus monkeys.[37,38] These

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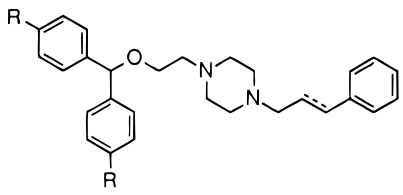
⊗ Abstract published in *Advance ACS Abstracts,* October 15, 1996.

S0022-2623(96)00305-6

Chart 1



1 (GBR 12935) R=H (single bond)
2 (GBR 12909) R=F (single bond)
3 (GBR 12783) R=H (double bond)

results and other characteristics of **2** including its slow onset, long duration of action, lower *in vivo* efficacy as a motoric stimulant in rats as compared to cocaine[39] and nonstimulant profile of action in normal human volunteers following oral administration[40] suggest that GBR-type of agents may be useful for the treatment of cocaine abuse.[12,24]

Our studies have been focused on the development and identification of novel compounds in the GBR series, which interact with high affinity and selectivity at dopaminergic sites. It had been shown earlier that it was possible to retain the high affinity of new ligands at the DAT by several modifications in (diphenylmethoxy)ethyl and phenylpropyl moieties of the GBR molecule.[32,41,42] Other researchers showed that one nitrogen atom attached to the phenylpropyl chain of **2** is sufficient for the retention of high affinity for the binding to the DAT[43] and recently synthesized a series of piperidine-based, GBR related, compounds.[44] Our primary experiments involved the expansion of the piperazine ring of **1**, which dramatically improved the selectivity of a new GBR analog, homopiperazine **8** (LR-1111),[45,46] at the DA reuptake site. As a continuation of these studies, we reported also the synthesis and evaluation *in vitro* of chiral *trans*-2,5-dimethylpiperazines, which displayed a 35-fold enantioselectivity ratio for the binding to the DAT.[47] In this paper we describe the design, synthesis, and biological evaluation of "GBR related" congeners with further modifications in the piperazine moiety as high-affinity and selectivity DAT ligands.

Design Rationale

Our initial synthetic plan was to modify the piperazine moiety of **1** without significantly changing the rest of the molecule. These modifications included (a) alteration of the steric bulk of the piperazine moiety (i.e. seven-[45] and eight-membered-ring analogs **8** and **36** or *trans*-2,5-dimethylpiperazine **14** and dimethylhomopiperazine **33**; Schemes 1 and 2), (b) opening the piperazine ring (e.g. congener **30**; Scheme 2), and (c) changes in the dihedral angle between the C−N bonds (e.g. homopiperidines **40** and **43**; Scheme 3). Initially, we tried to preserve the ethylenediamine moiety of piperazine ring as a basic and important pharmacophore for effective binding. Eventually, we also tested precursors such as **32** and **35** (Scheme 2), which represent further examples of ring-opened analogs of **1** with three and four carbon atoms between two nitrogen atoms, respectively. The homopiperazine and *trans*-2,5-dimethylpiperazine series (Scheme 1) include analogs with the bis(4-fluoro) substitution in the (diphenylmethoxy)ethyl fragment (e.g. compounds **9** and **15**, analogs of **2**) and/or the double bond in the phenylpropyl chain (e.g. compounds **10** and **16**, analogs of 1-[2-[bis(4-fluorophenyl)methoxy]-ethyl]-4-(3-phenyl-2-propenyl)piperazine (**3**, GBR 12783[48]). Subsequently, since one of the intermediates in the *trans*-2,5-dimethylpiperazine series, **13** (Scheme 1), exhibited a relatively high affinity and selectivity at the DA reuptake site, and **19** (Table 4) was practically inactive at this site, we decided to expand this series of ligands. We synthesized monosubstituted and symmetrically disubstituted *trans*-2,5-dimethylpiperazines and piperazines **20**−**28** (Table 5) in order to confirm the hypothesis that the (diphenylmethoxy)ethyl fragment attached to a diamine moiety is an essential or even sufficient pharmacophore to retain the high affinity of these ligands at the dopaminergic site.

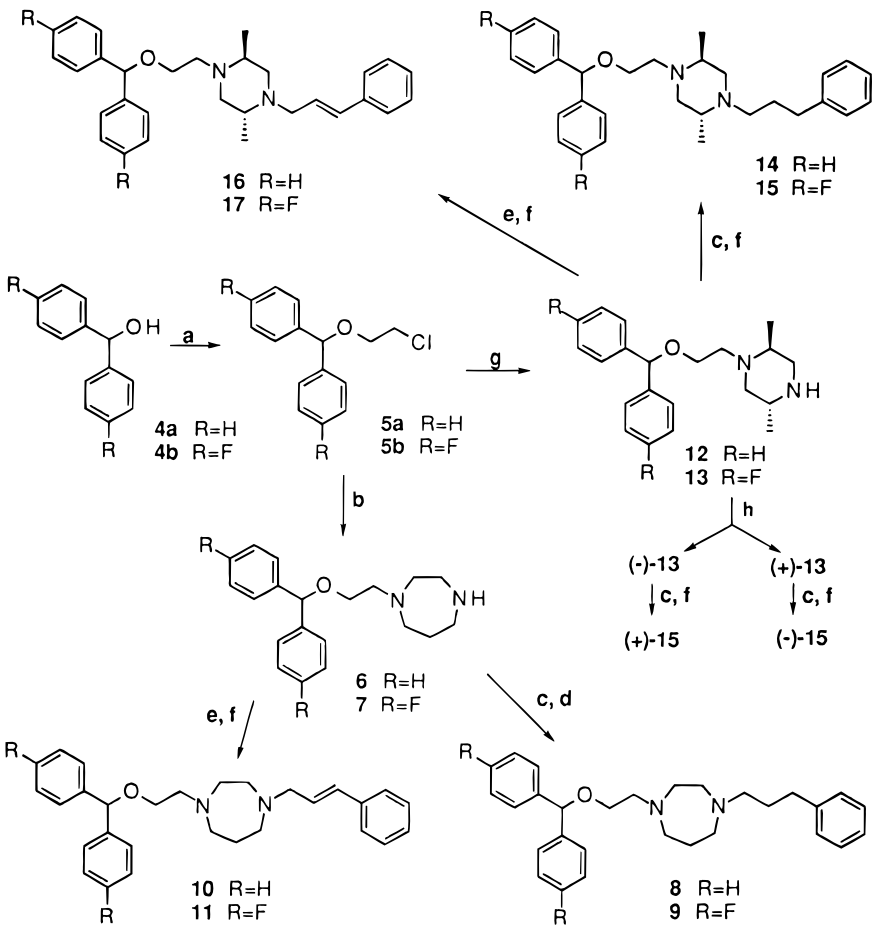
In order to study the effect of chirality in this series we obtained earlier, as mentioned above, **(−)-** and **(+)-13** by optical resolution of **(±)-13** and converted these enantiomers to **(+)-** and **(−)-15**, respectively.[47] Further alteration of the piperazine ring in the GBR structure provided chiral pyrrolidines: **(−)-** and **(+)-49** (Scheme 4). Although the attempt to further improve the potency of the more active enantiomer **(−)-49** by preparing its bis(*p*-fluoro) or hydroxy derivatives, **(−)-50** and **(−)-52**, respectively, was not successful, this series of chiral congeners may be a very useful research tool for the study of the DA transporter since the potential problems of biological study of racemates is well-known.[49]

The novel GBR analogs were evaluated *in vitro* at the DA transporter of rat striatum labeled with [^{3}H]GBR 12935 or [^{125}I]RTI 55. Their inhibitory effect on [^{3}H]-DA reuptake into striatal synaptosomes and [^{3}H]5HT reuptake into whole brain synaptosomes was also evaluated. Furthermore, *in vitro* binding affinity of new GBR derivatives for the σ receptors was assessed. As a result of these studies it was possible to distinguish the main structural elements responsible for the binding to the dopaminergic versus σ sites.

Chemistry

New analogs of **1** and **2** were prepared by standard chemical routes illustrated in Schemes 1-4. Initially, we used the general method of Van der Zee et al.[32] Reaction of benzhydrol or 4,4′-difluorobenzhydrol with 2-chloroethanol in toluene in the presence of sulfuric acid afforded 2-chloroethyl diphenylmethyl ether **5a** or its bis(4-fluoro) derivative **5b**, respectively, in 95% yield. The monoalkylation of commercially available homopiperazine (method A; Table 1) or *trans*-2,5-dimethylpiperazine followed by coupling with the appropriate acid chloride and reduction of the resulting amides (method B; Table 2) yielded the target GBR analogs **9**−**11** or **14**−**17**, respectively (Scheme 1). The same synthetic route afforded opened-ring analogs of **1**: **30**, **32**, and **35** (Scheme 2). The diamine monoalkylation yielded monosubstituted piperazines: **6**, **7**, **29**, **31**, and **34** (method A; Table 1) or **12**, **13**, **23**, and **24** (method C), whereas symmetrically disubstituted **20** and **21** or **26** and **27** (Table 5) were obtained as products of dialkylation of *trans*-2,5-dimethylpiperazine and piperazine, respectively (method C). Similarly, **19** and **25** or **22** and **28** (Table 5) were synthesized by mono- or diacylation of *trans*-2,5-dimethylpiperazine and piperazine (method D), respectively, followed by the lithium aluminum hydride or aluminum hydride reduction of the mono- or diamide precursors. Amides obtained in the coupling reaction of a diamine with the acid chloride were generally used in the following step without further purification. The synthesis of 3,3-dimethylhomopipera-

Scheme 1[a]



[a] (a) $HOCH_2CH_2Cl$, H_2SO_4, $PhCH_3$; (b) homopiperazine, K_2CO_3, $PhCH_3$; (c) $PhCH_2CH_2COCl$, $CHCl_3$; (d) LAH, THF; (e) PhCH=CHCOCl, $CHCl_3$; (f) AlH_3, THF; (g) *trans*-2,5-dimethylpiperazine, K_2CO_3, $PhCH_3$; (h) optical resolution with (−)- and (+)-dibenzoyltartaric acids, 2-PrOH.

zine **33** or 1,4-diazaoctane **36** (Scheme 2), was achieved by refluxing of their precursors **32** or **35**, respectively, with the excess 1,2-dibromoethane and K_2CO_3 in xylenes (method E). α-Amino-ϵ-caprolactam was transformed into **40** or **43** by a sequence of several standard steps depicted in Scheme 3.

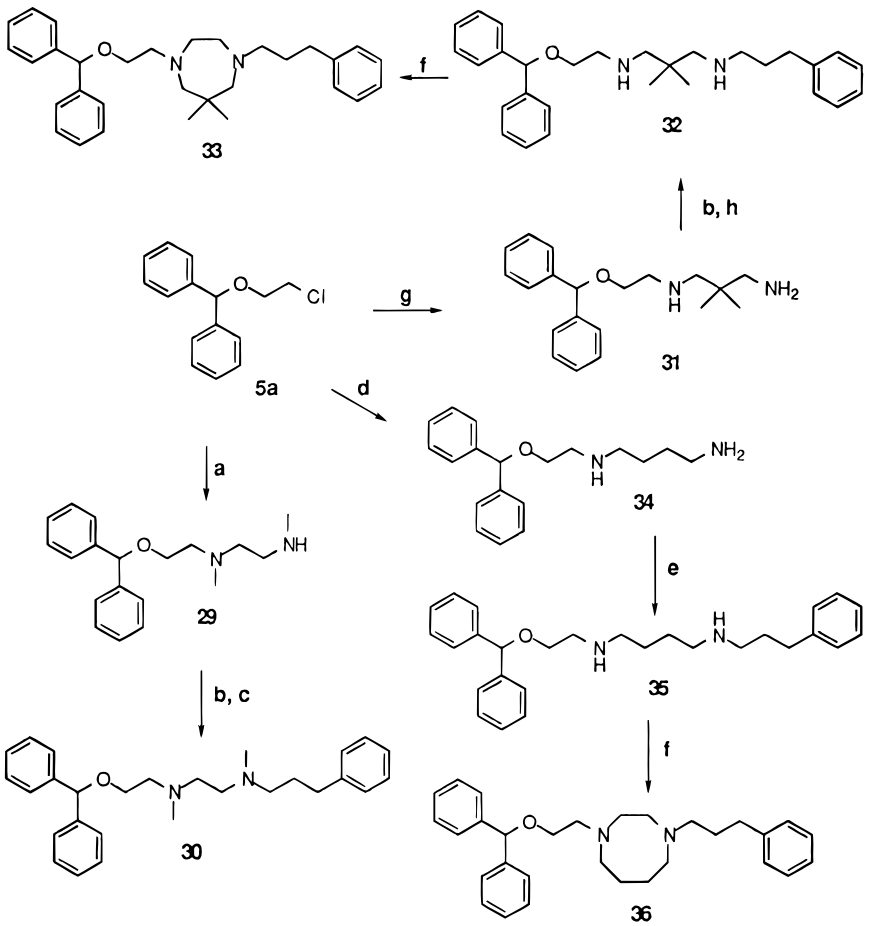
The synthesis of optically pure enantiomeric *trans*-2,5-dimethylpiperazines **(−)-** and **(+)-13** or **(+)-** and **(−)-15** (Scheme 1) has been described in detail elsewhere.[47] Commercially available L-(−)-prolinamide and *N*-Boc-D-(+)-proline were used as starting materials in the synthesis of the chiral pyrrolidines **(−)-** and **(+)-49**, **(−)-50** and **(−)-52** (Scheme 4). Substituted amines **(−)-46** and **(−)-48** were prepared by treatment of L-(−)-prolinamide with **5a** or **5b**, respectively (method A; Table 1) followed by reduction of the amide function. Coupling of **(−)-46** and **(−)-48** with hydrocinnamoyl chlorides followed by amide reduction afforded **(−)-49** and **(−)-50**, respectively. 2-(Aminomethyl)pyrrolidine **(−)-46** was then reacted with *m*-(benzyloxy)cinnamic acid (prepared by O-benzylation of commercially available *m*-hydroxycinnamic acid with benzyl bromide in DMF) in the presence of 1,3-dicyclohexylcarbodiimide (DCC) to yield **(−)-51**. The double bond in **(−)-51** was reduced and the protecting benzyl group was removed by hydrogenation in the presence of 10% Pd/C. The reduction of the carbonyl group with AlH_3 afforded the target amine **(−)-52**. The synthesis of **(+)-49** involved the condensation of *N*-Boc-D-(+)-proline with 3-phenylpropylamine in the presence of water soluble 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide as a coupling agent to yield **(+)-54**, which was followed by its *N*-Boc deprotection with trifluoroacetic acid, then alkylation of **(+)-55** with **5a**, and finally the reduction of the resulting amide **(+)-56**.

Results and Discussion

This series of GBR-related compounds was synthesized and evaluated *in vitro* to determine the SAR requirements for high affinity binding to the DAT and inhibition of [^{3}H]DA reuptake. The data in Tables 3 and 4 indicate that replacement of the piperazine ring in **1** and **2** with another diamine moiety can result in the retention of high affinity of the new ligands for binding to the DAT and essential improvement of their selectivity at this site versus 5HT site. The expansion of the piperazine ring of **1** to the seven-membered ring in the structure of **8** did not significantly change the affinity for inhibition of [^{3}H]DA, but greatly improved its selectivity at this site (>4700-fold).[45] However, further increase of the bulk of the piperazine moiety by incorporation of another methylene group in the homopiperazine ring in eight-membered-ring analog **36** or addition of two methyl groups to this ring in case of congener **33**, attenuated both affinity and selectivity of these ligands at the DAT site in comparison to **1** and **8**.

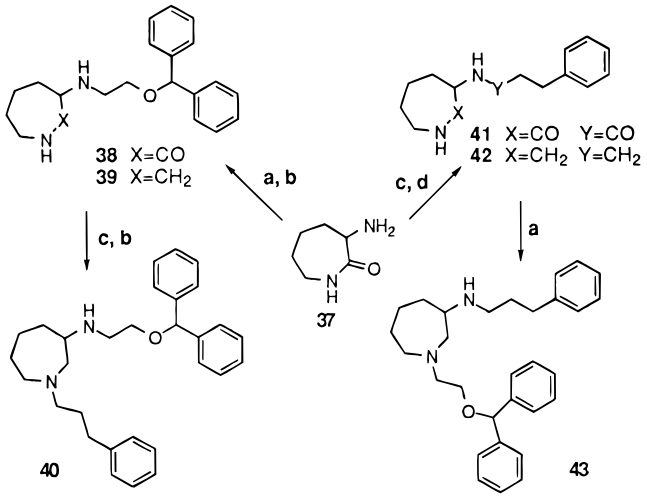
The ring-opened ethylenediamine analog **30** retained high affinity for binding to the DAT (IC_{50} = 18 nM) and inhibition of [^{3}H]DA reuptake (Table 3: IC_{50} = 27 nM). It also exhibited a 2-fold improvement in selectivity over

Scheme 2[a]



[a] (a) $MeNHCH_2CH_2NHMe$, K_2CO_3, $PhCH_3$; (b) $Ph(CH_2)_2COCl$, $CHCl_3$; (c) LAH, THF; (d) $H_2N(CH_2)_4NH_2$, K_2CO_3, $PhCH_3$; (e) $Ph(CH_2)_3Cl$, K_2CO_3, $PhCH_3$; (f) $BrCH_2CH_2Br$, K_2CO_3, $Ph(CH_3)_2$; (g) $H_2NCH_2C(Me)_2CH_2NH_2$, K_2CO_3, $PhCH_3$; (h) AlH_3, THF.

Scheme 3[a]

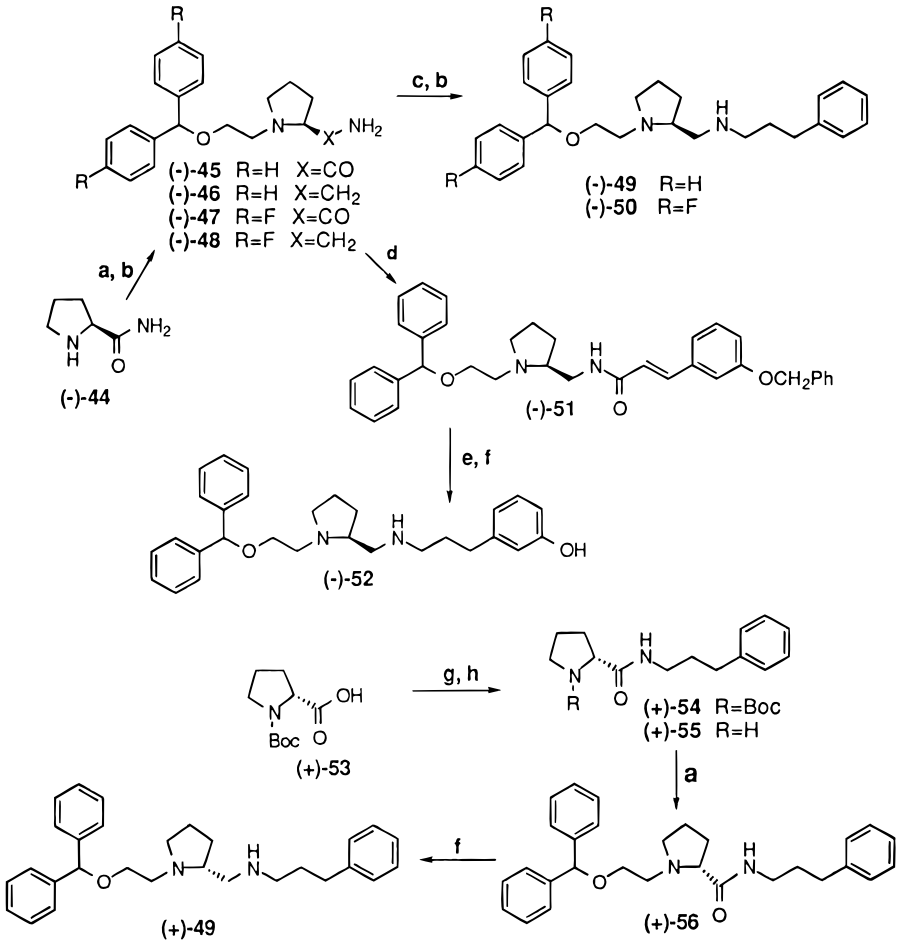


[a] (a) **5a**, K_2CO_3, $PhCH_3$; (b) AlH_3, THF; (c) $Ph(CH_2)_2COCl$, $CHCl_3$; (d) LAH, THF.

1 at the DA versus 5HT site. These results suggest that high-affinity binding to the DAT of GBR-type ligands does not require a conformationally restricted piperazine ring and that some degree of structural flexibility is allowed at this site. However, other ring-opened congeners such as **32** and **35** were less potent and much less selective than **30** at the DAT site (compare 23-, 11-, and 136-fold ratio of IC_{50} for inhibition of [^{3}H]DA versus [^{3}H]5HT reuptake for **32**, **35**, and **30**, respectively). It is difficult to make any further conclusions at this point because of other structural differences among these compounds. However, the ethylene moiety seems to be the optimal linkage between two nitrogen atoms in the GBR structure. Interestingly, both ring-opened analogs **32** and **35** as well as other intermediates such as **29**, **31**, and **34**, which were practically inactive for binding to the DAT (Table 3: IC_{50} > 800 nM for all three), contain in their structures at least one primary or secondary amine function, in contrast to tertiary diamine **30** (Scheme 2), which retains high affinity at this site. The semirigid GBR derivatives, homopiperidines **40** and **43** (Scheme 3), represent a very interesting pair of regioisomers that exhibit a 6-fold difference in affinity for the inhibition of [^{3}H]DA reuptake as well as a 3-fold difference in selectivity at this site in favor of **43** (Table 3).

In the homopiperazine and *trans*-2,5-dimethylpiperazine series of GBR derivatives (Table 4), bis(4-fluoro)-substituted congeners were slightly more potent than their desfluoro analogs for binding to the DAT labeled with [^{3}H]GBR 12935, except for one pair (**14** and **15**). However, the desfluoro analogs displayed greatly improved selectivity in inhibiting [^{3}H]DA reuptake (versus [^{3}H]5HT reuptake), mainly due to their significantly lower affinity at the 5HT sites (compare **8** and **9**, **10** and **11**, **14** and **15**, or **16** and **17**). Addition of a double bond increased affinity for inhibition of [^{3}H]DA reuptake 13 times (e.g. compare **8** and **10**). However, this correlation was not the same for other, similarly substituted pairs of homologs in this series (Table 4). In contrast to our previous observation with the other partial structures (**29**, **31**, or **34**, Table 3), both mono-

Scheme 4[a]



[a] (a) **5a** or **5b**, K_2CO_3, $PhCH_3$; (b) LAH, THF; (c) $Ph(CH_2)_2COCl$, $CHCl_3$; (d) *m*-(benzyloxy)cinnamic acid, DCC, CH_2Cl_2; (e) H_2, 10% Pd−C, MeOH; (f) AlH_3, THF; (g) $Ph(CH_2)_3NH_2$, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide, CH_2Cl_2; (h) CF_3COOH, CH_2Cl_2.

Table 1. Method A: Reaction Conditions

compd	starting amine	ratio (chloride:amine:K_2CO_3)	reaction time (h)	mp (salt)[a] (°C)	crystallization solvent	yield (%)
6	homopiperazine	1:7:2	24	134−134.5	MeOH	71
7	homopiperazine	1:5:2	12	128.5−129.5	MeOH	61
29	N,N′-dimethyl-ethylenediamine	1:7:2	18	128−129.5	MeOH	79
31	2,2-dimethyl-1,3-propanediamine	1:5:2	8	144.5−146	2-PrOH:MeOH	82
34	1,4-diaminobutane	1:5:3	12	168−170	2-PrOH:MeOH	51
38	α-amino-ϵ-caprolactam	1:1.2:2	45	115−117[b]	Et_2O	83
43	**42**	1:1.2:2	48	110−112	2-PrOH:MeOH	74
(−)-45	L-(−)-prolinamide	1:1.2:2	24	187.5−188.5	2-PrOH:MeOH	36
(−)-47	L-(−)-prolinamide	1:1.2:2	24	230−231 dec	MeOH	32
(+)-56	**(+)-55**	1:1:5	48			60

[a] Salt form of the base indicated in the Experimental Section. [b] Free base.

substituted homopiperazine and *trans*-2,5-dimethylpiperazine **7** and **13** exhibited high potency for the inhibition of [^{3}H]DA reuptake. Furthermore, in contrast to fully substituted diamines in the homopiperazine and *trans*-2,5-dimethylpiperazine series, both partial fluoro derivatives **7** and **13** were not only more potent binding ligands and [^{3}H]DA reuptake inhibitors but also more selective than their desfluoro homologs **6** and **12**, respectively. On the other hand, two diamines monosubstituted with the phenylpropyl moiety of the GBR molecule **18** and **19** were inactive at the DAT site (Table 4). These observations prompted us to synthesize a series of monosubstituted and symmetrically disubstituted *trans*-2,5-dimethylpiperazines and piperazines (Table 5). The SAR studies in this group of congeners provided interesting relations between dopaminergic and σ binding properties of GBR related ligands. Compounds with at least one (diphenylmethoxy)ethyl substituent retain good affinity for the inhibition of [^{3}H]-DA reuptake from high (**26**, IC_{50} = 12 nM) to modest (**12**, IC_{50} = 138 nM) degrees, and for binding to the DAT, whereas mono- or disubstituted piperazines with phenylpropyl chain **19**, **22**, **25**, and **28**, practically lost all affinity at this site. On the other hand, these four ligands displayed very high affinity for binding to the σ receptors (Table 5). σ binding was tested because **1** and **2**[50] as well as some of their new analogs (Table 3) displayed relatively high affinity at this site. The significance of affinity for binding to the σ receptors of these and other DA reuptake inhibitors (e.g. BTCP, 1-[1-(2-benzo[*b*]thienyl)cyclohexyl]piperidine[51]) is still unclear. It has been known, however, that cocaine binds to the σ receptors with a weak affinity.[52] Other studies have shown that several σ ligands antagonized some of

Table 2. Method B: Reaction Conditions

product	acid chloride	reducing agent	reduction time (h)	reduction temp (°C)	mp (salt)[a] (°C)	crystallization solvent	yield[b] (%)
8	H[c]	L[d]	24	rt	143.5−144.5	MeOH	71
9	H	A[e]	24	rt	137.5−138	2-PrOH	62
10	C[f]	A	24	rt	141−142.5	2-PrOH	56
11	C	A	0.25	rt	146−147	2-PrOH	77
14	H	A	1	rt	149−151	2-PrOH:MeOH	70
15	H	A	2	rt	154−157	2-PrOH:MeOH	58
16	C	A	1	0−5	171−173	2-PrOH	63
17	C	A	3	0−5	179−180	MeOH	49
18	C	A	0.5	0−5	155−158	MeOH	74
30	H	L	24	rt	137−138	MeOH	45
32	H	A	48	rt	159−160	2-PrOH:MeOH	48
35	H	A	8	reflux	170−172	2-PrOH	23
40	H	A	1	rt	159−162	2-PrOH:MeOH	28
42	H	L	2	reflux	145−146	2-PrOH	43
(−)-49	H	L	4	reflux	155−156	2-PrOH	57
(−)-50	H	L	3	reflux	138−140	2-PrOH:EtOAc	63

[a] Salt form of the base indicated in the Experimental Section. [b] Total yield for two steps. [c] H = hydrocinnamoyl chloride. [d] L = lithium aluminum hydride. [e] A = aluminum hydride. [f] C = cinnamoyl chloride.

Table 3. DA and 5HT Reuptake Inhibition and Binding Affinities at the DAT and σ Receptors: GBR 12935 Analogs with Modified Diamine Moiety

	$IC_{50} \pm SD$ (nM)[a]				
compound	[^{3}H]DA reuptake	[^{3}H]GBR 12935 binding (DAT)	[^{3}H]5HT reuptake	[^{3}H]-(+)-pentaz binding (σ)	ratio ([^{3}H]5HT/[^{3}H] DA reuptake)
1 (GBR 12935)	3.7 ± 0.4	4.1 ± 0.6	289 ± 29	17 ± 2	78
8	7.2 ± 0.5	7.9 ± 1.7	34100 ± 3590	26 ± 2	4736
14	9.6 ± 1.5	21 ± 1.0	1730 ± 70	8.6 ± 0.1	180
29	545 ± 38	834 ± 31	>10000	231 ± 13	
30	18 ± 1	27 ± 4	2450 ± 57	34 ± 2	136
31	453 ± 20	1460 ± 90	>10000	n/d	
32	83 ± 7	169 ± 5	1890 ± 268	n/d	23
33	87 ± 5	286 ± 8	3150 ± 491	n/d	36
34	510 ± 19	9780 ± 4090	6830 ± 1502	>10000	13
35	35 ± 2	80 ± 6	376 ± 19	1050 ± 35	11
36	93 ± 6	864 ± 91	1590 ± 60	180 ± 9	17
40	57 ± 10	74 ± 5	2860 ± 45	78 ± 13	50
43	9.3 ± 1.8	20 ± 0.7	1480 ± 69	83 ± 11	159
cocaine	478 ± 25	660 ± 30[b]	304 ± 10	n/d	0.6

[a] The IC_{50} values of the test agents were determined in the above assays as described in Methods; n/d, not done. [b] Published data; K_i value (nM).[60]

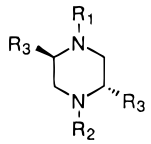
Table 4. DA and 5HT Reuptake Inhibition and Binding Affinities at the DAT Labeled by [^{3}H]GBR 12935: Homopiperazine and *trans*-2,5-Dimethylpiperazine Series

	$IC_{50} \pm SD$ (nM)[a]			
compound	[^{3}H]DA reuptake	[^{3}H]GBR 12935 binding (DAT)	[^{3}H]5HT reuptake	ratio ([^{3}H]5HT/[^{3}H]DA reuptake)
1 (GBR 12935)	3.7 ± 0.4	4.1 ± 0.6	289 ± 29	78
2 (GBR 12909)	4.3 ± 0.3	5.5 ± 0.4	73 ± 1.5	17
6	651 ± 82	1360 ± 316	14300 ± 90	22
7	17 ± 1.6	143 ± 17	2080 ± 96	122
8 (LR-1111)	7.2 ± 0.5	7.9 ± 1.7	34100 ± 3590	4736
9	3.4 ± 0.4	4.4 ± 0.4	112 ± 24	33
10	0.6 ± 0.1	8.6 ± 1.1	503 ± 103	838
11	3.4 ± 0.4	2.6 ± 0.4	234 ± 10	69
12	138 ± 43	1000 ± 65	25300 ± 1180	183
13	30 ± 5	106 ± 9	8940 ± 317	298
14	9.6 ± 1.5	21 ± 1.0	1720 ± 70	180
15	15 ± 2	40 ± 1	459 ± 26	31
16	20 ± 4	103 ± 13	2680 ± 122	134
17	28 ± 5	23 ± 3	1180 ± 404	42
18[b]	252 ± 16	1730 ± 141	20 ± 0.9	0.08
19[c]	>30000	>30000	12200 ± 429	

[a] The IC_{50} values of the test agents were determined in the above assays as described in Methods. [b] **18** [1-(3-phenyl-2-propenyl)homopiperazine]. [c] **19** [*trans*-2,5-dimethyl-1-(3-phenylpropyl)piperazine].

the behaviors induced by cocaine in animals,[53,54] suggesting their potential therapeutic usage for the treatment of cocaine abuse.[55] In the series of congeners shown in Table 5, compound **28** exhibited the highest (IC_{50} = 0.5 nM) affinity for displacement of σ_1 selective [^{3}H]-(+)-pentazocine.[56] It should be pointed out that **28** highly resembles the structures of some of the compounds belonging to the piperazine class of σ ligands.[57] It is also noteworthy that piperazines which are symmetrically disubstituted only with the (diphenylmethoxy)-ethyl moiety (**20**, **21**, **26**, and **27**) displayed dramatically lower, micromolar affinity at σ site.

Table 5. DA and 5HT Reuptake Inhibition and Binding Affinities at the DAT and σ Receptors: Monosubstituted and Symmetrically Disubstituted Piperazines



				$IC_{50} \pm SD$ (nM)[a]					
ligand	R_1	R_2	R_3	[^{3}H]DA reuptake	[^{3}H]GBR 12935 binding (DAT)	[^{125}I]RTI 55 binding (DAT)	[^{3}H]5HT reuptake	[^{3}H]-(+)-pentaz binding (σ)	ratio ([^{3}H]DA reuptake/ DAT binding)
GBR 12935				3.7 ± 0.4	4.1 ± 0.6	3.7 ± 0.3	289 ± 29	17 ± 2	0.9 1[b]
12	A[c]	H	Me	138 ± 43	1000 ± 65	n/d	>25000	67 ± 9	0.4
13	B[c]	H	Me	30 ± 5	106 ± 9	44 ± 1	8940 ± 317	65 ± 16	0.3 0.7[b]
19	C[c]	H	Me	>30000	>30000	n/d	12200 ± 429	8.5 ± 0.1	
20	A	A	Me	35 ± 9	33 ± 16	n/d	6220 ± 465	4001 ± 338	1.1
21	B	B	Me	86 ± 31	36 ± 5	n/d	4240 ± 313	3640 ± 541	2.4
22	C	C	Me	1330 ± 418	9940 ± 666	n/d	2530 ± 116	8.5 ± 0.6	0.1
23	A	H	H	124 ± 25	110 ± 7	n/d	9570 ± 1111	1480 ± 119	1.1
24	B	H	H	71 ± 12	104 ± 13	n/d	1400 ± 58	965 ± 114	0.7
25	C	H	H	>30000	>30000	n/d	361 ± 12	109 ± 20	
26	A	A	H	12 ± 0.4	9.3 ± 1.7	1.6 ± 0.04	1710 ± 234	>10000	1.3 7.5[b]
27	B	B	H	40 ± 2	7.3 ± 1	1.1 ± 0.02	278 ± 32	>10000	5.5 36.4[b]
28	C	C	H	1640 ± 433	7760 ± 654	n/d	1340 ± 81	0.5 ± 0.1	0.2
cocaine				478 ± 25	660 ± 30	341 ± 25[d]	304 ± 10	n/d	

[a] The IC_{50} values of the test agents were determined in the above assays as described in Methods. [b] Ratio of IC_{50} for [^{3}H]DA reuptake over IC_{50} for the displacement of [^{125}I]RTI 55 at the DAT. [c] Substituents: A, 2-(diphenylmethoxy)ethyl; B, 2-[bis(*p*-fluorophenyl)methoxy-]ethyl; C, 3-phenylpropyl; n/d, not done. [d] Published data; K_i value (nM).[61]

It is interesting to note the improved ratios of IC_{50} for [^{3}H]DA reuptake inhibition to IC_{50} for [^{3}H]GBR 12935 displacement for the series of GBR derivatives reported in Table 5. All the piperazines symmetrically disubstituted with the diphenylmethoxyethyl moiety, i.e. **20**, **21**, **26**, and **27**, exhibited a ratio between 1 and 5.5 in contrast to **1** with a ratio of 0.9. The ratio for **27** increases to 36 when the calculation involves the IC_{50} value for the binding to the DAT labeled with [^{125}I]RTI 55 instead of [^{3}H]GBR 12935 (Table 5). Some investigators suggest that this ratio may offer a strategy for the identification of a potential cocaine antagonist.[42] However, since the ratio may vary with the conditions of the assay,[58] and since this hypothesis has not been validated with bioassays, the results produced for the present series of GBR analogs should be viewed cautiously.

We have previously reported the first example of enantioselective binding in the GBR series of DA reuptake ligands.[47] The optical resolution of racemic *trans*-2,5-dimethylpiperazine **13** was performed with (−)- and (+)-dibenzoyltartaric acids and enantiomers of **13** were then used to obtain **(+)-** and **(−)-15**. These two pairs of enantiomers, **(−)-** and **(+)-13** and **(−)-** and **(+)-15** exhibited a 7-fold and a 35-fold enantioselectivity ratio of IC_{50} for the inhibition of [^{3}H]DA reuptake, respectively, in favor of the *2S,5R* absolute configuration in both cases,[47] which suggested some degree of structural homology at this site. As shown in Scheme 4, the enantiospecific synthesis of the second type of chiral GBR derivatives **(+)-49**, **(−)-49**, **(−)-50**, and **(−)-52** avoided frequently cumbersome optical resolution by utilization of chiral starting materials **(−)-44** and **(+)-53**. Two pyrrolidine derivatives **(−)-49** and **(+)-49** displayed a 181- and a 146-fold enantioselectivity for the inhibition of [^{3}H]DA reuptake and binding to the DA transporter labeled with [^{3}H]GBR 12935, respectively (Table 6). There was also a striking difference in the ratio of IC_{50} for the inhibition of [^{3}H]5HT versus [^{3}H]DA reuptake inhibition for these two isomers (1409- versus 25-fold). However, the aromatic bis(4-fluoro) or *m*-hydroxy substitution did not improve the affinity of the more potent enantiomer for the inhibition of [^{3}H]-DA reuptake or binding to the DAT site. In fact, the phenolic derivative **(−)-52** proved to be dramatically less selective at the DA versus the 5HT reuptake site than its precursor **(−)-49** (28- versus 1409-fold, respectively). These compounds represent a new generation of optically active GBR-type ligands which may be very useful in the studies of structure and function of DAT.

Table 6. DA and 5HT Reuptake Inhibition and Binding Affinities at the DAT: Chiral Pyrrolidines

	$IC_{50} \pm SD$ (nM)[a]			
compound	[^{3}H]DA reuptake	[^{3}H]GBR 12935 binding (DAT)	[^{3}H]5HT reuptake	ratio ([^{3}H]5HT/ [^{3}H]DA reuptake)
1 (GBR 12935)	3.7 ± 0.4	4.1 ± 0.6	289 ± 29	78
2 (GBR 12909)	4.3 ± 0.3	5.5 ± 0.6	73 ± 1.5	17
(−)-49	0.7 ± 0.05	5.1 ± 0.4	986 ± 34	1409
(+)-49	127 ± 10	747 ± 163	3210 ± 450	25
(−)-50	29 ± 2	104 ± 8	20100 ± 2400	693
(−)-52	31 ± 0.1	222 ± 13	857 ± 17	28

[a] The IC_{50} values of the test agents were determined in the above assays as described in Methods.

The preliminary *in vivo* studies have shown that several new, modified GBR derivatives were inactive in rats at doses up to 30 mg/kg injected ip (Figure 1; graphs show the effect of only one dose 30 mg/kg of each GBR analog; ip injection), in contrast to **1** and **2** which produced strong stimulation of motoric behavior following the same route of administration. For example, **8** failed to stimulate locomotor activity in rats at doses of up to 40 mg/kg following ip injection[45] and also failed

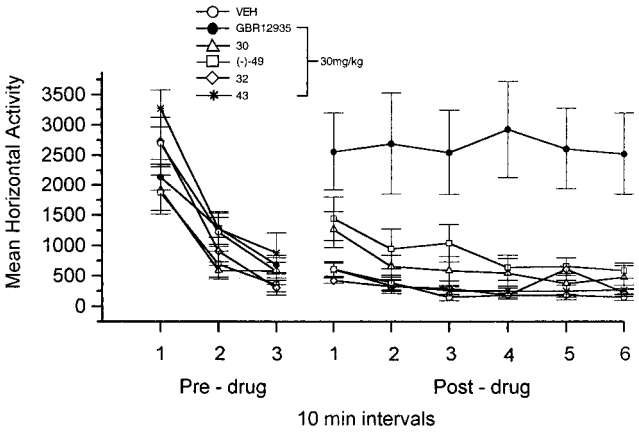


Figure 1. Effects of several GBR analogs on horizontal locomotor activity in rats following ip injection (30 mg/kg). Repeated measures analyses of variance revealed a significant postdrug treatment effect only between the vehicle group and the group injected with GBR 12935.

to decrease either food intake or cocaine self-administration (5.6−10 μg/kg per injection) in rhesus monkeys at doses of up to 5.6 mg/kg, iv (data not shown). However, **8** caused long-lasting stimulation of locomotor activity in rats when administered intravenously.[45] These results suggest that GBR analogs with the modified diamine moiety may exhibit a poor blood-brain barrier permeability and/or be subjected to degradative metabolic processes in the liver. Additional experiments are required to explain the differences in pharmacological profile of the new GBR analogs from cocaine and the parent compounds.

Conclusions

New GBR derivatives were synthesized and evaluated at the DA reuptake site. These studies have shown that significant structural variations are permitted in the GBR series of compounds and that the conformationally restricted piperazine ring may be substituted by other, more flexible or more bulky, diamine moieties and still retain the high affinity for both binding to the DAT and inhibition of [^{3}H]DA reuptake. At least one (diphenylmethoxy)ethyl substituent in the GBR structure is required for high-affinity binding to the DAT. Several new, modified analogs reported here are among the ligands of the highest selectivity at the DA versus 5HT reuptake site known to date within the class of GBR compounds as well as the other structurally different DA reuptake inhibitors. Further *in vivo* studies of novel, potent, and selective DAT ligands are being conducted and will be reported in due course. These compounds as well as the enantiomeric GBR analogs provide novel probes and leads for the development of research tools to study the structure and functions of the DA transporter. They may be also useful in the identification of successful therapeutics for the treatment and prevention of cocaine abuse.

Experimental Section

Chemical Methods. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Determination of specific rotation at the sodium-D line were obtained in a 1 dm cell using a Perkin-Elmer 241-MC polarimeter. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA, and were within ±0.4% for the elements indicated. Chemical ionization mass spectra (CIMS) were obtained using a Finnigan 1015 mass spectrometer. Electron ionization mass spectra (EIMS) and high-resolution mass measurements (HRMS) were obtained using a V. G. Micro Mass 7070F mass spectrometer. ^{1}H NMR spectra were recorded on the free bases in $CDCl_3$ or $CDCl_3$ plus D_2O using a Varian XL-300 spectrometer. Chemical shifts are expressed in parts per million (ppm) on the δ scale relative to a TMS internal standard. Thin layer chromatography (TLC) was performed on 250 μm Analtech GHLF silica gel plates. The following TLC systems were employed: A, $CHCl_3$:MeOH = 19:1; B, $CHCl_3$:MeOH = 9:1; C, $CHCl_3$:MeOH:NH_4OH = 90:9:1; D, $CHCl_3$:MeOH:NH_4OH = 80:18:2. No attempt was made to optimize the yields reported.

Method A. General procedure (yields and reaction conditions are reported in Table 1). 2-(Diphenylmethoxy)ethyl or 2-[bis(4-fluorophenyl)methoxy]ethyl chloride (**5a**) or (**5b**), respectively, was added dropwise to a refluxing solution of a diamine in toluene. Anhydrous K_2CO_3 was then added, and the mixture was refluxed for the indicated number of hours (Table 1). The reaction mixture was cooled to room temperature and washed with water (3×), and then toluene was removed in vacuum. The resulting substituted diamine, isolated as an oil, was either transformed directly into a salt or chromatographed on silica gel using the specified eluent and then converted into a salt with the indicated acid.

Method B. General procedure (yields and reaction conditions are reported in Table 2). The acid chloride (1.2 equiv) was added dropwise to the vigorously stirred solution of monosubstituted diamine (1 equiv) in chloroform at room temperature. After the reaction was complete (typically 24 h; monitored by TLC; solvent system A, B, C, or D), the organic layer was washed with saturated $NaHCO_3$ solution (3×) and water (1×) and dried (anhydrous Na_2SO_4) and solvent removed in vacuum to afford an amide. This crude product was usually employed without further purification. A solution of an amide in THF was added dropwise to a 1 M solution of LAH or AlH_3 (2−5 equiv excess) in THF, and the mixture was stirred at room temperature or refluxed for the indicated number of hours (Table 2) until completion (TLC). Workup: (1) (LAH reduction) water, 10% NaOH and again water was carefully added; the reaction mixture was filtered, the filter cake was washed with Et_2O and organic solvents removed in vacuum; (2) (AlH_3 reduction) the reaction mixture was treated with 10% NaOH and extracted with Et_2O (3×). Organic extracts were combined, dried (Na_2SO_4), and evaporated to give an oily product. The final diamine was purified (silica gel chromatography using the specified eluent), if required, and (or) directly transformed into a salt.

1-[2-(Diphenylmethoxy)ethyl]homopiperazine (6) was synthesized following method A (Table 1). ^{1}H NMR ($CDCl_3$ plus D_2O) δ 1.70−1.78 (m, 2H), 2.71−2.78 (m, 10H), 3.58 (t, J = 6.1 Hz, 2H), 5.35 (s, 1H), 7.21−7.37 (m, 10H); MS (CI-NH_3) m/z 311 (MH^+). Anal. **6**·2maleate ($C_{20}H_{26}N_2O$·$2C_4H_4O_4$) C, H, N.

1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]homopiperazine (7) was synthesized following method A (Table 1): ^{1}H NMR ($CDCl_3$ plus D_2O) δ 2.65−2.69 (m, 2H), 2.69−2.93 (m, 10H), 3.52 (t, J = 5.8 Hz, 2H), 5.32 (s, 1H), 6.95−7.05 (m, 4H), 7.20−7.34 (m, 4H); MS (CI-NH_3) m/z 347 (MH^+). Anal. **7**·2maleate ($C_{20}H_{24}F_2N_2O$·$2C_4H_4O_4$) C, H, N.

1-[2-(Diphenylmethoxy)ethyl]-4-(3-phenylpropyl)homopiperazine (8) was synthesized from **6** following method B (Table 2). ^{1}H NMR ($CDCl_3$) δ 1.72−1.84 (m, 4H), 2.48 (t, J = 6.9 Hz, 2H), 2.59−2.78 (m, 10H), 2.82 (t, J = 6.3 Hz, 2H), 3.57 (t, J = 6.2 Hz, 2H), 5.35 (s, 1H), 7.17−7.37 (m, 15H); MS (CI-NH_3) m/z 429 (MH^+). Anal. **8**·2maleate ($C_{29}H_{36}N_2O$·$2C_4H_4O_4$·$0.5H_2O$) C, H, N.

1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)homopiperazine (9) was synthesized from **7** following method B (Table 2): ^{1}H NMR ($CDCl_3$) δ 1.70−1.85 (m, 4H), 2.48 (t, J = 7.3 Hz, 2H), 2.58−2.76 (m, 10H), 2.80 (t, J = 6.2 Hz, 2H), 3.52 (t, J = 6.1 Hz, 2H), 5.32 (s, 1H), 6.96−7.03 (m, 3H), 7.16−7.19 (m, 2H), 7.24−7.30 (m, 8H); MS (CI-NH_3) m/z 465 (MH^+). Anal. **9**·2maleate ($C_{29}H_{34}F_2N_2O$·$2C_4H_4O_4$) C, H, N.

1-[2-(Diphenylmethoxy)ethyl]-4-(3-phenyl-2-propenyl-)homopiperazine (10) was synthesized from **6** following method B (Table 2). ^{1}H NMR ($CDCl_3$) δ 1.76−1.84 (m, 2H), 2.68−2.87 (m, 10H), 3.27 (dd, J = 0.7, 6.8 Hz, 2H), 3.58 (t, J

= 5.9 Hz, 2H), 5.36 (s, 1H), 6.29 (dt, J = 6.8, 15.8 Hz, 1H), 6.49 (d, J = 15.8 Hz, 1H), 7.18−7.40 (m, 15H); MS (CI-NH_3) m/z 427 (MH^+). Anal. **10**·2maleate ($C_{29}H_{34}N_2O$·$2C_4H_4O_4$) C, H, N.

1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenyl-2-propenyl)homopiperazine (11) was synthesized from **7** following method B (Table 2): ^{1}H NMR ($CDCl_3$) δ 1.75−1.86 (m, 2H), 2.62−2.85 (m, 10H), 3.25−3.35 (m, 2H), 3.45−3.60 (t, J = 6.4 Hz, 2H), 5.34 (s, 1H), 6.25−6.45 (m, 1H), 6.50 (d, J = 15.0 Hz, 1H), 6.95−7.05 (m, 4H), 7.15−7.45 (m, 9H); MS (CI-NH_3) m/z 463 (MH^+). Anal. **11**·2maleate ($C_{29}H_{32}F_2N_2O$·$2C_4H_4O_4$) C, H, N.

Method C. *trans*-2,5-Dimethyl-1-[2-(diphenylmethoxy)-ethyl]piperazine (12) and *trans*-2,5-Dimethyl-1,4-bis[2-(diphenylmethoxy)ethyl]piperazine (20). *trans*-2,5-Dimethylpiperazine (20.0 g, 175 mmol) was refluxed in toluene (70 mL), and a solution of **5a** (14.4 g, 58 mmol) in toluene (30 mL) was added dropwise. Anhydrous K_2CO_3 (16.2 g, 116 mmol) was added, and the reaction mixture was refluxed for 36 h. The organic phase was washed with water to remove the unreacted *trans*-2,5-dimethylpiperazine and then extracted with 10% citric acid to separate the mono- from the disubstituted product.

1. The toluene was removed from the organic phase under vacuum to yield the disubstituted piperazine **20** (1.2 g), which had higher R_f value (TLC, system C). The product was crystallized as the oxalate salt from MeOH: mp 178.5−180 °C; ^{1}H NMR ($CDCl_3$) δ 0.99 (s, 3H), 1.01 (s, 3H), 2.12 (t, J = 10.5 Hz, 2H), 2.39−2.41 (m, 2H), 2.56−2.64 (m, 2H), 2.76 (dd, J = 2.5, 11.2 Hz, 2H), 2.95−3.04 (m, 2H), 3.51−3.59 (m, 4H), 5.36 (s, 2H), 7.20−7.35 (m, 20H); MS (CI-NH_3) m/z 535 (MH^+). Anal. **20**·2oxalate ($C_{36}H_{42}N_2O_2$·$2C_2H_2O_4$) C, H, N.

2. The citric acid layer was neutralized with 15% NaOH and extracted with CH_2Cl_2. The organic phase was dried (anhydrous Na_2SO_4), and the solvent was evaporated under vacuum to give **12** (17.8 g) as an oily residue. This compound was purified as the fumarate salt from 2-PrOH; mp 185−187 °C dec; ^{1}H NMR ($CDCl_3$ plus D_2O) δ 1.01 (d, J = 6.2 Hz, 3H), 1.03 (d, J = 6.3 Hz, 3H), 1.97 (t, J = 11.2 Hz, 1H), 2.29−2.31 (m, 1H), 2.49−2.57 (m, 1H), 2.63−2.70 (m, 1H), 2.80−2.88 (m, 3H), 2.99−3.04 (m, 1H), 3.55−3.60 (m, 2H), 5.36 (s, 1H), 7.21−7.33 (m, 10H); MS (CI-NH_3) m/z 325 (MH^+). Anal. **12**·0.5fumarate ($C_{21}H_{28}N_2O$·$0.5C_4H_4O_4$) C, H, N.

***trans*-2,5-Dimethyl-1-[2-[bis(4-fluorophenyl)methoxy]-ethyl]piperazine (13) and *trans*-2,5-dimethyl-1,4-bis[2-[bis(4-fluorophenyl)methoxy]ethyl]piperazine (21)** were prepared from *trans*-2,5-dimethylpiperazine (9.2 g, 81 mmol) and **5b** (7.6 g, 27 mmol) and purified following method C.

1. The monosubstituted amine **13** (7.5 g) was converted into the fumarate salt (2-PrOH:MeOH = 3:1): mp 121−123 °C; ^{1}H NMR ($CDCl_3$ plus D_2O) δ 0.99 (d, J = 6.2 Hz, 3H), 1.02 (d, J = 6.3 Hz, 3H), 1.94 (t, J = 10.7 Hz, 1H), 2.18−2.26 (m, 1H), 2.49−2.65 (m, 2H), 2.78−2.89 (m, 3H), 2.98−3.03 (m, 1H), 3.51−3.57 (m, 2H), 5.33 (s, 1H), 6.98−7.03 (m, 3H), 7.25−7.31 (m, 5H); MS (CI-NH_3) m/z 361 (MH^+). Anal. **13**·2fumarate ($C_{21}H_{26}N_2F_2O$·$2C_4H_4O_4$·$0.5H_2O$) C, H, N.

2. Compound **21** (2.2 g) was purified as the fumarate salt by crystallization from MeOH:2-PrOH = 2:1; mp 164−167 °C; ^{1}H NMR ($CDCl_3$) δ 1.01 (s, 3H), 1.02 (s, 3H), 2.12−3.02 (m, 10H), 3.52 (s, broad, 4H), 5.32 (s, 2H), 6.96−7.04 (m, 6H), 7.23−7.29 (m, 10H); MS (CI-NH_3) m/z 607 (MH^+). Anal. **21**·-2fumarate ($C_{36}H_{38}N_2F_4O_2$·$2C_4H_4O_4$·H_2O) C, H, N.

***trans*-2,5-Dimethyl-1-[2-(diphenylmethoxy)ethyl]-4-(3-phenylpropyl)piperazine (14)** was synthesized from **12** following method B (Table 2). The crude product was chromatographed on a silica gel column (CH_2Cl_2:MeOH = 100:2): ^{1}H NMR ($CDCl_3$) δ 0.98 (d, J = 5.9 Hz, 3H), 1.04 (d, J = 6.1 Hz, 3H), 1.78−1.83 (m, 2H), 1.96−2.05 (m, 1H), 2.18−2.84 (m, 10H), 2.96−3.04 (m, 1H), 3.54−3.60 (m, 2H), 5.38 (s, 1H), 7.15−7.35 (m, 15H); MS (CI-NH_3) m/z 443 (MH^+). Anal. **14**·-2fumarate ($C_{30}H_{38}N_2O$·$2C_4H_4O_4$) C, H, N.

***trans*-2,5-Dimethyl-1-[2-[bis(4-fluorophenyl)methoxy]-ethyl]-4-(3-phenylpropyl)piperazine (15)** was synthesized from **13** following method B (Table 2). The crude product was chromatographed on a silica gel column (CH_2Cl_2:MeOH = 100:5): ^{1}H NMR ($CDCl_3$) δ 0.97 (d, J = 6.1 Hz, 3H), 1.02 (d, J = 6.2 Hz, 3H), 1.75−1.81 (m, 2H), 1.93−2.02 (m, 1H), 2.11−2.79 (m, 10H), 2.97−3.02 (m, 1H), 3.52−3.55 (m, 2H), 5.32 (s, 1H), 6.97−7.03 (m, 3H), 7.15−7.19 (m, 2H), 7.22−7.30 (m, 8H); MS (CI-NH_3) m/z 479 (MH^+). Anal. **15**·2fumarate ($C_{30}H_{36}N_2F_2O$·-$2C_4H_4O_4$) C, H, N.

***trans*-2,5-Dimethyl-1-[2-(diphenylmethoxy)ethyl]-4-(3-phenyl-2-propenyl)piperazine (16)** was synthesized from **12** following method B (Table 2): ^{1}H NMR ($CDCl_3$) δ 1.04 (d, J = 6.1 Hz, 3H), 1.09 (d, J = 6.1 Hz, 3H), 2.05−2.09 (m, 1H), 2.26−2.29 (m, 1H), 2.43−2.55 (m, 2H), 2.61−2.69 (m, 1H), 2.83 (d, J = 10.4 Hz, 2H), 2.96−3.07 (m, 2H), 3.54−3.67 (m, 3H), 5.36 (s, 1H), 6.26−6.34 (m, 1H), 6.57 (d, J = 15.8 Hz, 1H), 7.21−7.38 (m, 15H); MS (CI-NH_3) m/z 441 (MH^+). Anal. **16**·-2fumarate ($C_{30}H_{36}N_2O$·$2C_4H_4O_4$) C, H, N.

***trans*-2,5-Dimethyl-1-[2-[bis(4-fluorophenyl)methoxy]-ethyl]-4-(3-phenyl-2-propenyl)piperazine (17)** was obtained from **13** as described in procedure B (Table 2). ^{1}H NMR ($CDCl_3$) δ 1.01−1.09 (m, 6H), 1.21−1.30 (m, 2H), 2.00−3.03 (m, 8H), 3.49−3.68 (m, 3H), 5.32 (s, 1H), 6.51 (d, J = 15.9 Hz, 1H), 6.97−7.03 (m, 2H), 6.20−7.38 (m, 11H); MS (CI-NH_3) m/z 477 (MH^+). Anal. **17**·2fumarate ($C_{30}H_{34}N_2F_2O$·$2C_4H_4O_4$) C, H, N.

1-(3-Phenyl-2-propenyl)homopiperazine (18) was obtained from homopiperazine as described in procedure B (Table 2). ^{1}H NMR ($CDCl_3$ plus D_2O) δ 1.72−1.81 (m, 2H), 2.65−2.73 (m, 4H), 2.88−2.95 (m, 4H), 3.35 (d, J = 7.2 Hz, 2H), 6.26 (dt, J = 7.1, 16.5 Hz, 1H), 6.47 (d, J = 16.5 Hz, 1H), 7.15−7.37 (m, 5H); MS (CI-NH_3) m/z 217 (MH^+). Anal. **18**·2fumarate ($C_{14}H_{20}N_2$·$2C_4H_4O_4$·$0.25H_2O$) C, H, N.

Method D. *trans*-2,5-Dimethyl-1-(3-phenylpropyl)piperazine (19) and *trans*-2,5-Dimethyl-1,4-bis(3-phenylpropyl)piperazine (22). *trans*-2,5-Dimethylpiperazine (5.0 g, 44 mmol) and hydrocinnamoyl chloride (7.4 g, 44 mmol) were stirred in chloroform at room temperature overnight. The reaction mixture was then washed with saturated $NaHCO_3$ and water and extracted with 10% citric acid. The organic layer yielded diamide **I** (4.5 g) as an oily residue which solidified after treatment with ethyl ether. The acidic layer was basified with 15% NaOH and extracted with CH_2Cl_2. The combined organic extracts yielded monosubstituted amide **II** (0.6 g).

1. Diamide **I** (1.9 g, 5 mmol) was then reduced with AlH_3 (workup according to method B) to afford **22** (1.5 g, 88% yield) which was transformed into the fumarate salt from MeOH:2-PrOH = 1:3: mp 195−196 °C; ^{1}H NMR ($CDCl_3$) δ 0.99 (d, J = 6.2 Hz, 6H), 1.77−1.81 (m, 4H), 1.95−2.05 (m, 2H), 2.22−2.38 (m, 4H), 2.55−2.64 (m, 4H), 2.74−2.80 (m, 4H), 7.15−7.19 (m, 4H), 7.25−7.30 (m, 6H); MS (CI-NH_3) m/z 351 (MH^+). Anal. **22**·2fumarate ($C_{24}H_{34}N_2$·$2C_4H_4O_4$) C, H, N.

2. Monoamide **II** (0.6 g, 2.3 mmol) was reduced with LAH (workup according to method B) to yield the monoamine **19** (0.45 g, 85%) which was converted to the 2fumarate salt from MeOH:2-PrOH = 1:2: mp 154−156 °C; ^{1}H NMR ($CDCl_3$ plus D_2O) δ 0.99 (d, J = 6.2 Hz, 3H), 1.05 (d, J = 6.3 Hz, 3H), 1.76−1.89 (m, 3H), 2.24−2.33 (m, 2H), 2.54−2.64 (m, 4H), 2.74−2.92 (m, 4H), 7.18−7.31 (m, 5H); MS (CI-NH_3) m/z 233 (MH^+). Anal. **19**·2fumarate ($C_{15}H_{24}N_2$·$2C_4H_4O_4$·$0.5H_2O$) C, H, N.

1-[2-(Diphenylmethoxy)ethyl]piperazine (23)[32] was prepared according to method C.

1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]piperazine (24)[32] was prepared according to method C.

1,4-Bis[2-(diphenylmethoxy)ethyl]piperazine (26) was obtained from piperazine (0.43 g, 5 mmol), **5a** (2.5 g, 10 mmol), and K_2CO_3 (1.4 g, 10 mmol) as described in method C (compound with a higher R_f; TLC system B) as an oily residue (0.6 g, 24%) which formed the maleate salt from MeOH: mp 194−195 °C; ^{1}H NMR ($CDCl_3$) δ 2.53 (s, broad, 8H), 2.66 (t, J = 6.1 Hz, 4H), 3.59 (t, J = 6.1 Hz, 4H), 5.37 (s, 2H), 7.24−7.36 (m, 20H); MS (CI-NH_3) m/z 507 (MH^+). Anal. **26**·-2maleate ($C_{34}H_{38}N_2O_2$·$2C_4H_4O_4$) C, H, N.

1,4-Bis[2-[bis(4-fluorophenyl)methoxy]ethyl]piperazine (27) was obtained from piperazine (0.26 g, 3 mmol), **5b** (1.7 g, 6 mmol), and K_2CO_3 (0.84 g, 6 mmol) as described in method C (compound with a higher R_f; TLC system B) as an oily residue (1.26 g, 73%) which formed the 2maleate from MeOH: mp 199−200 °C; ^{1}H NMR ($CDCl_3$) δ 2.52 (s, broad, 8H), 2.65 (t, J = 6.1 Hz, 4H), 3.55 (t, J = 6.1 Hz, 4H), 5.33 (s,

2H), 6.97−7.03 (m, 6H), 7.25−7.29 (m, 10H); MS (CI-NH_3) *m/z* 579 (MH^+). Anal. **27**·2maleate ($C_{34}H_{34}N_2F_4O_2·2C_4H_4O_4$) C, H, N.

1-(3-Phenylpropyl)piperazine (25) and 1,4-bis(3-phenylpropyl)piperazine (28) were synthesized according to the procedure and separation technique described in method D. The monosubstituted amine **25** was purified as the maleate salt from MeOH: mp 154−156 °C; ^{1}H NMR ($CDCl_3$ plus D_2O) δ 1.83 (quintet, J = 7.7 Hz, 2H), 2.28−2.41 (m, complex, 6H), 2.63 (t, J = 7.8 Hz, 2H), 2.88 (t, J = 4.9 Hz, 4H), 7.18−7.31 (m, 5H); MS (CI-NH_3) *m/z* 205 (MH^+). Anal. **25**·2maleate ($C_{13}H_{20}N_2·2C_4H_4O_4·0.5H_2O$) C, H, N. The disubstituted amine **28** was transformed into the hydrochloride salt (2-PrOH); mp >245 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.21 (t, J = 6.9 Hz, 2H), 1.82 (quintet, J = 7.7 Hz, 4H), 2.35−2.48 (m, complex, 8H), 2.63 (t, J = 7.8 Hz, 4H), 3.48 (q, J = 6.9 Hz, 2H), 7.15−7.30 (m, 10H); MS (CI-NH_3) *m/z* 323 (MH^+). Anal. **28**·2hydrochloride ($C_{22}H_{30}N_2·2HCl$) C, H, N.

***N,N′*-Dimethyl-*N*-[2-(diphenylmethoxy)ethyl]ethylenediamine (29)** was synthesized following method A (Table 1). ^{1}H NMR ($CDCl_3$ plus D_2O) δ 2.28 (s, 3H), 2.36 (s, 3H), 2.50−2.70 (m, 6H), 3.55 (t, J = 6.0 Hz, 2H), 5.38 (s, 1H), 7.18−7.42 (m, 10H); MS (CI-NH_3) *m/z* 299 (MH^+). Anal. **29**·2maleate ($C_{19}H_{26}N_2O·2C_4H_4O_4$) C, H, N.

***N,N′*-Dimethyl-*N*-[2-(diphenylmethoxy)ethyl]-*N′*-(3-phenylpropyl)ethylenediamine (30)** was synthesized from **29** according to method B (Table 2): ^{1}H NMR ($CDCl_3$) δ 1.78 (m, 2H), 2.22 (s, 3H), 2.29 (s, 3H), 2.38 (dd, J = 7.2, 8.6 Hz, 2H), 2.44−2.65 (m, 6H), 2.70 (t, J = 6.2 Hz, 2H), 3.58 (t, J = 6.2 Hz, 2H), 5.38 (s, 1H), 7.12−7.40 (m, 15H); MS (CI-NH_3) *m/z* 417 (MH^+). Anal. **30**·2maleate ($C_{28}H_{36}N_2O·2C_4H_4O_4$) C, H, N.

2,2-Dimethyl-*N*-[2-(diphenylmethoxy)ethyl]-1,3-propanediamine (31) was synthesized following method A (Table 1): ^{1}H NMR ($CDCl_3$ plus D_2O) δ 0.87 (s, 6H), 2.41 (s, 2H), 2.50 (s, 2H), 2.82 (t, J = 5.3 Hz, 2H), 3.58 (t, J = 5.3 Hz, 2H), 5.37 (s, 1H), 7.22−7.35 (m, 10H); MS (CI-NH_3) *m/z* 313 (MH^+). Anal. **31**·2fumarate ($C_{20}H_{28}N_2O·2C_4H_4O_4·C_3H_8O$) C, H, N.

2,2-Dimethyl-*N*-[2-(diphenylmethoxy)ethyl]-*N′*-(3-phenylpropyl)-1,3-propanediamine (32) was obtained from **31** following procedure B (Table 2): ^{1}H NMR ($CDCl_3$ plus D_2O) δ 0.91 (s, 6H), 1.75−1.80 (m, 2H), 2.42−2.44 (m, 4H), 2.55−2.63 (m, 4H), 2.83 (t, J = 5.2 Hz, 2H), 3.57 (t, J = 5.2 Hz, 2H), 5.36 (s, 1H), 7.14−7.34 (m, 15H); MS (CI-NH_3) *m/z* 431 (MH^+). Anal. **32**·2maleate ($C_{29}H_{38}N_2O·2C_4H_4O_4$) C, H, N.

Method E. 3,3-Dimethyl-1-[2-(diphenylmethoxy)ethyl]-5-(3-phenylpropyl)homopiperazine (33). The free base **32** (0.2 g, 0.47 mmol), 1,2-dibromoethane (0.176 g, 0.94 mmol), and K_2CO_3 (0.26 g, 1.88 mmol) were stirred and refluxed in xylenes (10 mL) for 72 h. The reaction mixture was then cooled down and washed with water (3×). The organic solvent was removed under vacuum, and the residue was chromatographed (silica gel column; CH_2Cl_2:MeOH = 40:1) to afford the pure diamine **33** (0.1 g, 47%) as an oil, which was isolated as a powder by lyophilization of the HCl salt from water: ^{1}H NMR ($CDCl_3$) δ 0.81 (s, 6H), 1.73−1.77 (m, 2H), 2.27 (s, broad, 2H), 2.42 (s, broad, 4H), 2.55−2.65 (m, 6H), 2.77−2.79 (m, 2H), 3.54 (t, J = 6.1 Hz, 2H), 5.36 (s, 1H), 7.17−7.36 (m, 15H); MS (CI-NH_3) *m/z* 457 (MH^+); HRMS MH^+ (calcd for $C_{31}H_{40}N_2O$) = 457.3219; MH^+ (found) = 457.3234.

***N*-[2-(Diphenylmethoxy)ethyl]-1,4-diaminebutane (34)** was synthesized following method A (Table 1); ^{1}H NMR ($CDCl_3$ plus D_2O) δ 1.46−1.53 (m, 4H), 2.60 (t, J = 6.8 Hz, 2H), 2.68 (t, J = 6.6 Hz, 2H), 2.82 (t, J = 5.2 Hz, 2H), 3.59 (t, J = 5.2 Hz, 2H), 5.37 (s, 1H), 7.24−7.34 (m, 10H); MS (CI-NH_3) *m/z* 299 (MH^+). Anal. **34**·2maleate ($C_{19}H_{26}N_2O·2C_4H_4O_4·0.5H_2O$) C, H, N.

***N*-[2-(Diphenylmethoxy)ethyl]-*N′*-(3-phenylpropyl)-1,4-butanediamine (35)** was obtained from **34** following procedure B (Table 2). ^{1}H NMR ($CDCl_3$ plus D_2O) δ 1.43−1.49 (m, 4H), 1.81 (quintet, J = 7.5 Hz, 2H), 2.58−2.67 (m, complex, 8H), 2.82 (t, J = 5.1 Hz, 2H), 3.58 (t, J = 5.2 Hz, 2H), 5.36 (s, 1H), 7.18−7.33 (m, 15H); MS (CI-NH_3) *m/z* 417 (MH^+). Anal. **35**·2maleate ($C_{28}H_{36}N_2O·2C_4H_4O_4$) C, H, N.

1-[2-(Diphenylmethoxy)ethyl]-4-(3-phenylpropyl)-1,4-diazaoctane (36) was prepared using the conditions described in method E. The crude product was chromatographed (silica gel column, $CHCl_3$:MeOH = 9:1) to give pure and oily **36** (28% yield), which was isolated as a powder by lyophilization of the hydrochloride salt from water. ^{1}H NMR ($CDCl_3$) δ 1.60−1.79 (m, 6H), 2.46 (t, J = 7.1 Hz, 2H), 2.54−2.57 (m, 2H), 2.61−2.79 (m, 6H), 2.79−2.83 (m, 4H), 3.53 (t, J = 6.2 Hz, 2H), 5.37 (s, 1H), 7.15−7.36 (m, 15H); MS (CI-NH_3) *m/z* 443 (MH^+); HRMS: MH^+ (calcd for $C_{30}H_{38}N_2O$) = 443.3060; MH^+ (found) = 443.3062.

α-[N-[2-(Diphenylmethoxy)ethyl]amino]-ε-caprolactam (38) was synthesized following method A (Table 1). ^{1}H NMR ($CDCl_3$ plus D_2O) δ 1.38−1.99 (m, 6H), 2.76−2.82 (m, 1H), 2.91−2.99 (m, 1H), 3.13−3.18 (m, 2H), 3.35−3.39 (m, 1H), 3.57−3.61 (m, 2H), 5.39 (s, 1H), 5.85 (s, broad, 1H), 7.20−7.37 (m, 10H); MS (CI-NH_3) *m/z* 339 (MH^+). Anal. **38** base ($C_{21}H_{26}N_2O_2$) C, H, N.

3-[*N*-[2-(Diphenylmethoxy)ethyl]amino]homopiperidine (39) was obtained by AlH_3 reduction of **38** in THF in 79% yield (workup according to method B). The final amine was converted into the maleate salt and crystallized from MeOH: mp 152−54 °C; ^{1}H NMR ($CDCl_3$ plus D_2O) δ 1.65−1.93 (m, 6H), 2.73−2.93 (m, complex, 7H), 3.58 (t, J = 5.2 Hz, 2H), 5.37 (s, 1H), 7.23−7.33 (m, 10H); MS (CI-NH_3) *m/z* 325 (MH^+). Anal. **39**·2maleate ($C_{21}H_{28}N_2O·2C_4H_4O_4$) C, H, N.

3-[*N*-[2-(Diphenylmethoxy)ethyl]amino]-1-(3-phenylpropyl)homopiperidine (40) was obtained from **39** following method B (Table 2): ^{1}H NMR ($CDCl_3$ plus D_2O) δ 1.63−1.80 (m, complex, 10H), 2.52−2.92 (m, complex, 7H), 3.30−3.48 (m, 2H), 3.60−3.89 (m, 2H), 5.30 (s, 1H), 7.11−7.31 (m, 15H); MS (CI-NH_3) *m/z* 443 (MH^+). Anal. **40**·2fumarate ($C_{30}H_{38}N_2O·2C_4H_4O_4·0.5H_2O$) C, H, N.

3-[*N*-(3-Phenylpropyl)amino]homopiperidine (42) was synthesized from **37** according to method B (Table 2): ^{1}H NMR ($CDCl_3$ plus D_2O) δ 1.23 (t, J = 6.9 Hz, 2H), 1.44−1.49 (m, 2H), 1.52−1.71 (m, 2H), 1.80 (quintet, J = 7.5 Hz, 2H), 2.58−2.76 (m, complex, 4H), 2.76−2.91 (m, 3H), 3.48 (q, J = 7.1 Hz, 2H), 7.16−7.31 (m, 5H); MS (CI-NH_3) *m/z* 233 (MH^+). Anal. **42**·2maleate ($C_{15}H_{24}N_2·2C_4H_4O_4$) C, H, N.

1-[2-(Diphenylmethoxy)ethyl]-3-[*N*-(3-phenylpropyl)-amino]homopiperidine (43) was synthesized according to method A (Table 1): ^{1}H NMR ($CDCl_3$ plus D_2O) δ 1.63−1.79 (m, 10H), 2.49−2.79 (m, complex, 7H), 2.83 (t, J = 5.8 Hz, 2H), 3.55 (t, J = 5.8 Hz, 2H), 5.30 (s, 1H), 7.12−7.37 (m, 15H); MS (CI-NH_3) *m/z* 443 (MH^+). Anal. **43**·2oxalate ($C_{30}H_{38}N_2O·2C_2H_2O_4$) C, H, N.

(*S*)-(−)-*N*-[2-(Diphenylmethoxy)ethyl]prolinamide [(−)-45] was prepared from (*S*)-(−)-prolinamide **[(−)-44]** following the procedure described in method A (Table 1): $[\alpha]^{23}_D = -11.8°$ (hydrobromide, MeOH, c = 1.14); ^{1}H NMR ($CDCl_3$ plus D_2O) δ 1.71−1.82 (m, complex, 2H), 1.88−1.98 (m, 1H), 2.11−2.25 (m, 1H), 2.30−2.39 (m, 1H), 2.70 (dt, J = 3.8, 13.3 Hz, 1H), 2.96−3.04 (m, complex, 1H), 3.09−3.28 (m, 2H), 3.46−3.61 (m, 2H), 5.36 (s, 1H), 7.21−7.36 (m, 10H); MS (CI-NH_3) *m/z* 325 (MH^+). Anal. **(−)-45**·hydrobromide ($C_{20}H_{24}N_2O_2·HBr$) C, H, N.

(*S*)-(−)-2-(Aminomethyl)-*N*-[2-(diphenylmethoxy)ethyl]pyrrolidine [(−)-46] was obtained as a product of LAH reduction of **(−)-45** in THF in 93% yield (workup according to method B). The final amine was purified as the oxalate salt and crystallized from MeOH: mp 130−130.5 °C; $[\alpha]^{23}_D = -8.4°$ (2oxalate, MeOH, c = 1.05); ^{1}H NMR ($CDCl_3$ plus D_2O) δ 1.52−1.65 (m, 1H), 1.65−1.78 (m, 2H), 1.78−1.90 (m, 1H), 2.26 (q, J = 8.2 Hz, 1H), 2.40−2.60 (m, 2H), 2.66 (d, J = 4.9 Hz, 2H), 2.98−3.09 (m, 1H), 3.09−3.17 (m, 1H), 3.58 (t, J = 5.9 Hz, 2H), 5.38 (s, 1H), 7.20−7.40 (m, 10H); MS (CI-NH_3) *m/z* 311 (MH^+). Anal. **(−)-46**·2oxalate ($C_{20}H_{26}N_2O·2C_2H_2O_4·H_2O$) C, H, N.

(*S*)-(−)-*N*-[2-[Bis(4-fluorophenyl)methoxy]ethyl]prolinamide [(−)-47] was prepared from L-(−)-prolinamide **[(−)-44]** following the procedure described in method A (Table 1): $[\alpha]^{23}_D = -13.9°$ (hydrobromide, MeOH, c = 0.51); ^{1}H NMR ($CDCl_3$ plus D_2O) δ 1.22 (t, J = 6.9 Hz, 2H), 1.76−1.84 (m, 1H), 1.89−1.99 (m, complex, 1H), 2.14−2.24 (m, 1H), 2.33−2.42 (m, 1H), 2.73 (dt, J = 4.1, 13.3 Hz, 1H), 2.96−3.04 (m, complex, 1H), 3.12−3.21 (m, 1H), 3.45−3.59 (m, 2H), 5.33 (s, 1H), 7.03−7.07 (m, 4H), 7.25−7.32 (m, 4H); MS (CI-NH_3) *m/z* 361 (MH^+). Anal. **(−)-47**·hydrobromide ($C_{20}H_{22}N_2F_2O_2·HBr$) C, H, N.

(*S*)-(−)-2-(Aminomethyl)-*N*-[2-[bis(4-fluorophenyl)-methoxy]ethyl]pyrrolidine [(−)-48] was obtained as a product of LAH reduction of **(−)-47** in THF in 93% yield (workup according to method B). The final amine was purified on a silica gel column (CH_2Cl_2:MeOH = 100:15) and used as an oil in the next step: $[\alpha]^{23}_D = -25.8°$ (free base, $CHCl_3$, c = 0.43); ^{1}H NMR ($CDCl_3$ plus D_2O) δ 1.57−1.69 (m, complex, 1H), 1.71−1.78 (m, complex, 2H), 1.82−1.91 (m, complex, 1H), 2.28 (q, J = 8.5 Hz, 1H), 2.48−2.58 (m, 2H), 2.68 (d, J = 4.5 Hz, 2H), 3.05 (quintet, J = 6.4 Hz, 1H), 3.11−3.17 (m, 1H), 3.55 (t, J = 5.9 Hz, 2H), 5.36 (s, 1H), 7.03 (t, J = 8.6 Hz, 4H), 7.28−7.34 (m, 4H); MS (CI-NH_3) m/z 347 (MH^+); HRMS: MH^+ (calcd for $C_{20}H_{24}N_2F_2O$) = 347.1935; MH^+ (found) = 347.1922.

(*S*)-(−)-1-[2-(Diphenylmethoxy)ethyl]-2-[[*N*-(3-phenylpropyl)amino]methyl]pyrrolidine [(−)-49] was synthesized from **(−)-46** according to method B (Table 2): $[\alpha]^{22}_D$ = −5.7° (2oxalate, MeOH, c = 0.67); ^{1}H NMR ($CDCl_3$ plus D_2O) δ 1.54−1.78 (m, 6H), 1.81−1.91 (m, 1H), 2.22−2.32 (m, 2H), 2.51−2.64 (m, 6H), 3.02−3.16 (m, 2H), 3.55 (t, J = 5.8 Hz, 2H), 5.41 (s, 1H), 7.09−7.38 (m, 15H); MS (CI-NH_3) m/z 429 (MH^+). Anal. **(−)-49**·2oxalate ($C_{29}H_{36}N_2O{\cdot}2C_2H_2O_4$) C, H, N.

(*S*)-(−)-1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-2-[[*N*-(3-phenylpropyl)amino]methyl]pyrrolidine [(−)-50] was synthesized from **(−)-48** according to method B (Table 2): $[\alpha]^{23}_D = -2.3°$ [2(L-tartate), MeOH, c = 0.49]; ^{1}H NMR ($CDCl_3$ plus D_2O) δ 1.19−1.25 (m, 1H), 1.58−1.62 (m, complex, 1H), 1.64−1.79 (m, complex, 4H), 1.82-1.91 (m, complex, 1H), 2.23 (q, J = 8.7 Hz, 1H), 2.47−2.65 (m, 7H), 2.99−3.12 (m, 2H), 3.47−3.53 (m, 2H), 5.33 (s, 1H), 6.95−7.01 (m, 4H), 7.14−7.30 (m, 9H); MS (CI-NH_3) m/z 465 (MH^+). Anal. **(−)-50**·2(L-tartate) ($C_{29}H_{34}N_2F_2O{\cdot}2C_4H_6O_6{\cdot}0.5H_2O$) C, H, N.

(*S*)-(−)-1-[2-(Diphenylmethoxy)ethyl]-2-[[*N*-[3-(*m*-hydroxyphenyl)propyl]amino]methyl]pyrrolidine [(−)-52].

1. (−)-51. To a solution of *m*-(benzyloxy)cinnamic acid (2.54 g, 10 mmol) stirred under nitrogen in CH_2Cl_2 (50 mL) was added a solution of dicyclohexylcarbodiimide (DCC) (2.06 g, 10 mmol) in CH_2Cl_2 (20 mL). After 40 min of stirring, a solution of **(−)-46** (1.55 g, 5 mmol) in CH_2Cl_2 (20 mL) and pyridine (0.15 mL) were added. This mixture was stirred for 5 h until the reaction was complete (TLC, system A). The precipitated solid material was filtered off, and the solvent was evaporated. The crude product was chromatographed (silica gel, short column, CH_2Cl_2) to yield **(−)-51** (2.3 g, 82% yield) as an oil, which was used without further purification in the next step; $[\alpha]^{21}_D = -31.8°$ (free base, MeOH, c = 0.32); ^{1}H NMR ($CDCl_3$) δ 1.58−1.95 (m, 3H), 2.35−2.82 (m, 3H), 3.15−3.42 (m, 5H), 3.60 (s, broad, 2H), 5.02 (s, 2H), 5.40 (s, 1H), 6.85−6.95 (m, 2H), 7.12−7.40 (m, complex, 19H); MS (CI-NH_3) m/z 547 (MH^+).

2. (−)-52. The amide **(−)-51** (2.0 g, 3.66 mmol) was hydrogenated (H_2, atmospheric pressure) with 5% Pd−C in MeOH (30 mL) at room temperature for 24 h until the reaction was complete (TLC, system B). The reaction mixture was then filtered through a pad of Celite and the solvent evaporated to give an oily product (1.56 g, 93%), MS (CI-NH_3) m/z 459 (MH^+). This amide was then directly reduced with AlH_3 to afford the final phenolic amine **(−)-52** which was chromatographed (silica gel column, CH_2Cl_2:MeOH:NH_4OH = 100:10:1) (0.85 g, 58%), and converted to the amorphous dihydrochloride by lyophilization from water; $[\alpha]^{23}_D = -21.9°$ (free base, $CHCl_3$, c = 0.75); ^{1}H NMR ($CDCl_3$ plus D_2O) δ 1.20−1.26 (m, 1H), 1.57−1.88 (m, 6H), 2.25−2.36 (m, 2H), 2.48−2.65 (m, 6H), 3.04−3.13 (m, 2H), 3.56 (t, J = 5.9 Hz, 2H), 5.38 (s, 1H), 6.60−6.67 (m, 2H), 7.08−7.36 (m, 12H); MS (CI-NH_3) m/z 445 (MH^+). Anal. **(−)-52**·2hydrochloride ($C_{29}H_{36}N_2O_2{\cdot}2HCl$) C, H, N.

(*R*)-(+)-1-[2-(Diphenylmethoxy)ethyl]-2-[[*N*-(3-phenylpropyl)amino]methyl]pyrrolidine [(+)-49].

1. (+)-54. To a solution of *N*-Boc-D-proline **[(+)-53]** (0.65 g, 3 mmol) in CH_2Cl_2 (10 mL), a solution of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (0.77 g, 3.6 mmol, 1.2 equiv) in CH_2Cl_2 (10 mL) followed by 1-hydroxybenzotriazole[59] (0.49 g, 3.6 mmol, 1.2 equiv) was added and stirred for 40 min. A solution of 3-phenyl-1-propylamine (0.6 g, 4.5 mmol, 1.5 equiv) in CH_2Cl_2 (5 mL) was then added dropwise, and the reaction mixture was stirred at room temperature overnight. The solvent was then removed under vacuum, and the residue was dissolved in ethyl acetate. The organic solution was extracted with 10% citric acid (3×), and the acidic extracts were discarded. The organic phase was washed with saturated solution of sodium bicarbonate and water, dried (Na_2SO_4), and evaporated to dryness to afford pure **(+)-54** as a colorless oil: $[\alpha]^{21}_D = +69.2°$ (free base, CH_2Cl_2, c = 0.57); ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9H), 1.78−1.88 (m, 6H), 2.65 (t, J = 7.5 Hz, 2H), 3.24−3.39 (m, 5H), 4.23 (s, broad, 1H), 7.16−7.19 (m, 3H), 7.21−7.31 (m, 2H); MS (CI-NH_3) m/z 333 (MH^+).

2. (+)-55. A solution of **(+)-54** (0.84 g, 2.53 mmol) in CH_2Cl_2 (10 mL) and trifluoroacetic acid (5 mL) were stirred at room temperature until the reaction was complete (2 h, TLC system A). The reaction mixture was then quenched with a saturated solution of potassium carbonate, stirred for 0.5 h, and extracted with CH_2Cl_2. The organic extracts were combined and dried (Na_2SO_4) and the solvent removed under vacuum to afford 0.58 g (97% yield) of pure **(+)-55** (TLC system A): $[\alpha]^{21}_D = +43.9°$ (free base, CH_2Cl_2, c = 0.31); ^{1}H NMR ($CDCl_3$) δ 1.66−1.75 (m, 2H), 1.76−1.96 (m, 3H), 2.08−2.20 (m, 1H), 2.65 (t, J = 7.7 Hz, 2H), 2.89 (dt, J = 6.3, 10.2 Hz, 1H), 3.01 (dt, J = 6.8, 10.2 Hz, 1H), 3.27 (dd, J = 7.0, 13.3 Hz, 2H), 3.74 (dd, J = 5.3, 9.2 Hz, 1H), 7.16−7.19 (m, 3H), 7.21−7.31 (m, 2H), 7.63 (s, broad, 1H); MS (CI-NH_3) m/z 233 (MH^+).

3. (+)-56. The *N*-[2-(diphenylmethoxy)ethyl]-substituted pyrrolidine **(+)-56** was obtained from pyrrolidine **(+)-55** according to method A (Table 1). The pure oily **(+)-56** was used in the next step without further purification: $[\alpha]^{21}_D$ = +26.8° (free base, CH_2Cl_2, c = 0.23); ^{1}H NMR ($CDCl_3$) δ 1.57 (quintet, J = 7.5 Hz, 2H), 1.69−1.79 (m, 2H), 1.83−1.92 (m, 1H), 2.14−2.21 (m, 1H), 2.29−2.38 (m, 1H), 2.45 (t, J = 7.9 Hz, 2H), 2.66 (dt, J = 3.9, 13.2 Hz, 1H), 2.90−3.03 (m, 2H), 3.10−3.22 (m, 3H), 3.47−3.56 (m, 2H), 5.36 (s, 1H), 7.08 (d, J = 7.1 Hz, 1H), 7.17−7.35 (m, 14H), 7.80 (s, broad, 1H); MS (CI-NH_3) m/z 443 (MH^+).

4. (+)-49. A 1 M solution of AlH_3 in THF (10 mL) was added to the solution of **(+)-56** (0.6 g, 1.35 mmol) in THF (10 mL) and refluxed with stirring for 5 h. After usual workup (see method B), the pure oily amine **(+)-57** (0.49 g, 84% yield) was converted into the oxalate salt from 2-PrOH: mp 162−164 °C; $[\alpha]^{23}_D$ = +8.5° (2oxalate, MeOH, c = 0.44); ^{1}H NMR ($CDCl_3$ plus D_2O) δ 1.58−1.79 (m, 6H), 1.81−1.96 (m, 1H), 2.31−2.45 (m, 2H), 2.45−2.56 (m, 2H), 2.58−2.68 (m, 4H), 3.04−3.17 (m, 2H), 3.53−3.63 (m, 2H), 5.45 (s, 1H), 7.08 (d, J = 6.9 Hz, 1H), 7.17−7.37 (m, 14H); MS (CI-NH_3) m/z 429 (MH^+). Anal. **(+)-49**·2oxalate ($C_{29}H_{36}N_2O{\cdot}2C_2H_2O_4$) C, H, N.

Biological Methods. 1. Binding and Reuptake Inhibition Assays. Binding assays for the DAT followed published procedures and used 2 nM [^{3}H]GBR 12935[60] (SA = 42.5 Ci/mmol) and 0.01 nM [^{125}I]RTI 55[61] (SA = 2200 Ci/mmol). Briefly, 12 × 75 mm polystyrene test tubes were prefilled with 100 μL of drug, 100 μL of radioligand ([^{3}H]GBR 12935 or [^{125}I]-RTI 55), and 50 μL of a "blocker" or buffer. Drugs and blockers were made up in 55.2 mM sodium phosphate buffer, pH 7.4 (BB) containing 1 mg/mL bovine serum albumin (BB/BSA). Radioligands were made up in a protease inhibitor cocktail containing 1 mg/mL BSA {BB containing chymostatin (25 μg/mL), leupeptin (25 μg/mL), EDTA (100 μM), and EGTA (100 μM)}. The samples were incubated in triplicate for 18−24 h at 4 °C (equilibrium) in a final volume of 1 mL. Brandel cell harvesters were used to filter the samples over Whatman GF/B filters, which were presoaked in wash buffer (ice-cold 10 mM TRIS-HCl/150 mM NaCl), pH 7.4) containing 2% polyethylenimine.

The [^{3}H]DA and [^{3}H]5HT uptake assays also proceeded according to published procedures.[45] Briefly, synaptosomes were prepared by homogenization of rat caudate (for [^{3}H]DA reuptake) or whole rat brain minus cerebellum (for [^{3}H]5HT reuptake) in ice-cold 10% sucrose, using a Potter-Elvehjem homogenizer. After a 1000*g* centrifugation for 10 min at 4 °C, the supernatants were retained on ice. The uptake assays were initiated by the addition of 100 μL of synaptosomes to 12 × 75 mm polystyrene test tubes, which were prefilled with 750 μL of [^{3}H]ligand (5 nM and 2 nM final concentration for [^{3}H]DA and [^{3}H]5HT, respectively) in a Krebs-phosphate buffer (pH 7.4), which contained ascorbic acid (1 mg/mL) and pargyline (50 μM) (buffer), 100 μL of test drugs made up in buffer, and 50 μL of buffer. The nonspecific uptake

of each [^{3}H]ligand was measured by incubations in the presence of 1 μM GBR 12909 ([^{3}H]DA) and 10 μM fluoxetine ([^{3}H]5HT). The incubations were terminated after a 15 min ([^{3}H]DA) or 30 min ([^{3}H]5HT) incubation at 25 °C by adding 4 mL of wash buffer (10 mM Tris-HCl, pH 7.4 containing 0.9% NaCl at 25 °C), followed by rapid filtration over Whatman GF/B filters and one additional wash cycle. The Krebs-phosphate buffer contained 154.5 mM NaCl, 2.9 mM KCl, 1.1 mM $CaCl_2$, 0.83 mM $MgCl_2$, and 5 mM glucose. The tritium retained on the filters was counted, in a Taurus beta counter, after an overnight extraction into ICN Cytoscint cocktail.

For the [^{3}H]-(+)-pentazocine (σ) binding assay large batches of frozen membranes were prepared from frozen guinea pig brains (Pel Freeze) as previously described.[62] The [^{3}H]-(+)-pentazocine binding assay proceeded with minor modifications of previously published procedures.[63] Briefly, incubations proceeded for 3−4 h at 25 °C (steady state) in 5 mM Tris-HCl, pH 8.2, with a protease inhibitor cocktail (chymostatin [10 μg/mL], leupeptin [10 μg/mL], EDTA [10 μM], EGTA [10 μM]). The incubations were terminated by rapid filtration over Whatman GF/B filters presoaked in 1% polyethylenimine, followed by two 4 mL washes with ice-cold 5 mM Tris-HCl, pH 8.0. The tritium on the filters was measured after an overnight extraction in 5 mL of ICN Cytoscint coctail, using standard liquid scintillation counting methods. Nonspecific binding was determined by incubations in the presence of 10 μM DTG.

For the structure−activity study, initial experiments were conducted to determine the appropriate concentration range of each test agent at each binding site. After this, ten-point inhibition curves, ranging from 90% to 10% of control, were generated. The data of two separate experiments were pooled, and fit, using the nonlinear least-squares curve-fitting language MLAB-PC,[64] (Civilized Software, Bethesda, MD) to the two parameter logistic equation[63] for the best-fit estimates o the IC_{50} and slope factor. The data are reported as IC_{50} values. As reported elsewhere,[45] the K_m values for [^{3}H]5HT and [^{3}H]DA reuptake were 17.4 ± 0.8 nM and 38.3 ± 1.6 nM, respectively. The K_d values for [^{3}H]-GBR 12935, [^{125}I]RTI 55 binding, and [^{3}H]-(+)-pentazocine were 1.35 ± 0.14 nM, 0.91 ± 0.04 and 4.9 ± 0.1 nM, respectively.[60,61,65]

Materials. The sources of radioligands and reagents have been published.[45,60,61,65]

2. Behavioral Analysis of GBR Analogs. Subjects. Male Sprague−Dawley rats weighting between 250 and 300 g were group housed and maintained on a 12 h light−dark cycle (lights on 0600−1800 h) with food and water available *ad libitum* in the home cage. All the animals were adapted to the vivarium conditions for at least one week before experimentation was begun. Behavioral testing was always performed between 1000 and 1700 h.

Apparatus. Locomotor activity was assessed in photocell activity monitors (Omnitech Electronics, Columbus, OH) which were constructed from clear Plexiglas (30.5 cm high × 42 cm long). The activity monitors were enclosed in sound-attenuating compartments equipped with a 15 W fluorescent light, a ventilating fan that also provides masking noise, and a one-way mirror (21 × 21 cm) mounted in the door to allow visual observation of the animals during testing. A series of 16 equally spaced infrared photocell detectors were located along two adjacent walls of the chamber 4 cm from the floor surface. Interruptions of the infrared light source by the animals were recorded and stored by an IBM AT computer.

Drugs. The drugs were dissolved in a solution comprised of 25% propylene glycol and 75% sterile water in a concentration of 30 mg/mL. It was necessary to slightly heat some of the drug solutions. Drugs were injected in a volume of 1 mL/kg.

Procedure. All rats were placed in the locomotor activity chambers for 30 min. Data were collected in 10 min intervals. The animals were then removed from the apparatus and injected with the appropriate drugs or vehicle and returned to the activity monitors for an additional 60 min. Data were collected again in 10 min intervals.

Acknowledgment. We would like to thank Noel Whittaker and Wesley White of the Laboratory of Analytical Chemistry for mass spectral data and acknowledge the National Institute on Drug Abuse, Medications Development Division for partial financial support of this work.

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JM960305H