Synthesis and Transporter Binding Properties of Bridged Piperazine Analogues of 1-{2-[Bis(4-fluorophenyl)methoxy]ethyl}-4-(3-phenylpropyl)piperazine (GBR 12909)

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A series of analogues related to 1-[2-(diphenylmethoxy)ethyl]-4-(3-phenylpropyl)piperazine (**2**) and 1-{2-[bis(4-fluorophenyl)methoxy]ethyl}-4-(3-phenylpropyl)piperazine (**3**) (GBR 12935 and GBR 12909, respectively), in which the piperazine moiety was replaced by bridged piperazines for structural rigidity, has been designed, synthesized, and evaluated for their ability to bind to the dopamine transporter (DAT) and to inhibit the uptake of ^{3}H-labeled dopamine (DA). The binding data indicated that compounds **7** and **11**, the *N*-methyl- and *N*-propylphenyl-3,8-diaza[3.2.1]bicyclooctane analogues of **3**, showed high affinity for the DAT (IC_{50} = 8.0 and 8.2 nM, respectively), and **7** had high selectivity at the DAT relative to the serotonin transporter (SERT) (88- and 93-fold for binding and reuptake, respectively). They also displayed linear activity in DA uptake inhibition, possessing a similar binding and reuptake inhibition profile to **3**. The *N*-indolylmethyl analogue **16** showed the highest affinity (IC_{50} = 1.4 nM) of the series, with a 6-fold increase over its corresponding *N*-phenypropyl derivative **11**. Interestingly, this compound exhibited a high ratio (29-fold) of IC_{50} for the inhibition of DA reuptake versus binding to the DAT. Replacing the piperazine moiety of **2** and **3** with (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]-heptane resulted in compounds **23**−**26**, which showed moderate to poor affinity (IC_{50} = 127−1170 nM) for the DAT. Substitution of the homopiperazine moiety of **4** with a more rigid 3,9-diazabicyclo[4.2.1]nonane gave compounds **28**−**33**. However, the binding data showed that compound **32** displayed a 10-fold decrease in affinity at the DAT and a 100-fold decrease in selectivity at the DAT relative to the SERT compared to its corresponding homopiperazine compound **4**.

Introduction

Cocaine (**1**) is one of the most powerfully addictive drugs known, exerting its effect by acting directly on the reward or pleasure centers of the brain.[1] Cocaine abuse has imposed a great burden on public health and public safety worldwide, by playing an important role in the rapid spread of acquired immune deficiency syndrome (AIDS) and drug-resistant tuberculosis and in drug-related violent and nonviolent crimes.[2,3] Although smoking cocaine base (crack) and other forms of its abuse appear to have stabilized at a high level, various forms of cardiovascular, respiratory, and neurological morbidity and mortality continue to present a formidable public health problem.[4−6] Therefore, study of the mechanism of action of cocaine with the goals of development of strategies for the treatment and prevention of cocaine abuse has become a major goal of the National Institute on Drug Abuse through the Medications Development Program and numerous groups worldwide.

Cocaine inhibits the presynaptic reuptake of neurotransmitters such as dopamine (DA), serotonin (5-HT), and norepinephrine (NE). However, evidence suggests that its binding to the dopamine transporter (DAT) and subsequent inhibition of DA reuptake may be responsible for its reinforcing property and locomotor activity.[7−11] Further evidence supporting this DAT hypothesis has emerged from recent studies on knockout mice lacking the DAT gene. Treatment of homozygote mice with high doses of cocaine resulted in no increase of locomotor activity, suggesting that the DAT is the molecular target of cocaine responsible for its abuse potential.[12]

However, several lines of evidence suggest that the strategy of developing selective and high-affinity DA uptake inhibitors for the treatment of cocaine abuse may be misplaced. Recent studies showed that DAT knockout mice self-administer cocaine[13] and demonstrate cocaine conditioned place preference,[14] indicating that in the absence of the DAT, cocaine can still establish rewarding effects. Although these data suggest that the DAT is not critical for mediating cocaine reward, the data do not rule out a role for mesolimbic DA as a mediator of cocaine reward. Since DA is a substrate of the NE transporter,[15] DA could be accumulated by NE nerves. This has been shown to occur in both the medial frontal cortex[16] and nucleus accumbens, but not in the striatum

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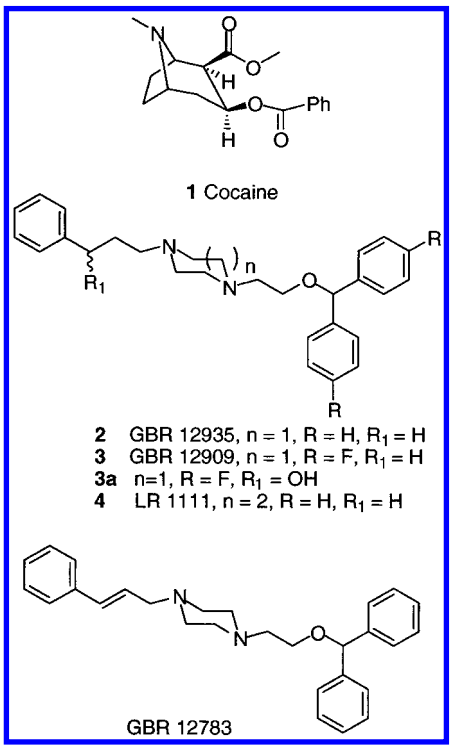
of rats,[17] which lacks noradrenergic innervation.[18] The inability of cocaine to elevate extracellular DA in the striatum of DAT knockout mice[13] is consistent with the lack of NE transporters in this brain region. Thus, in the absence of the DAT, it is reasonable to assume that some of the extracellular DA in the nucleus accumbens would be accumulated by NE nerves. Since cocaine is a potent inhibitor of the NE transporter,[19] administration of cocaine would block DA accumulation and increase extracellular DA, triggering the cocaine reward.

Second, although, as noted above, the evidence that DA mediates the reinforcing effect of cocaine in rodent models is overwhelming, published data strongly suggest that DA is not the sole mediator of the acute euphoric effects of cocaine in humans. These data, as reviewed in detail elsewhere,[20−23] include the observations: (1) that DA receptor antagonists do not block the subjective effects of cocaine[20,24] or amphetamine,[25,26] (2) that administration of pharmacologically active doses of bromocriptine did not produce or block cocaine-like subjective effects,[27] and (3) that inhibition of DA synthesis by α-methyparatyrosine failed to significantly block cocaine-induced subjective effects.[28] Third, other studies indicate that cocaine withdrawal causes a dual neurochemical deficit of dopaminergic and serotonergic function and that pharmacotherapy for cocaine dependence will have to normalize both deficits.[29,30]

Viewed collectively, these data indicate the need to further test the clinical relevance of the DA hypothesis of cocaine reward. One approach to test the DA hypothesis is to develop appropriate pharmacological tools such as high-affinity slowly dissociating DAT ligands with low intrinsic activity.[31,32] The DA hypothesis predicts that such an agent would have efficacy in treating cocaine addiction. The present study focuses not on the ultimate goal of testing the clinical relevance of the DA hypothesis but rather on developing potential medications with which to test the hypothesis.

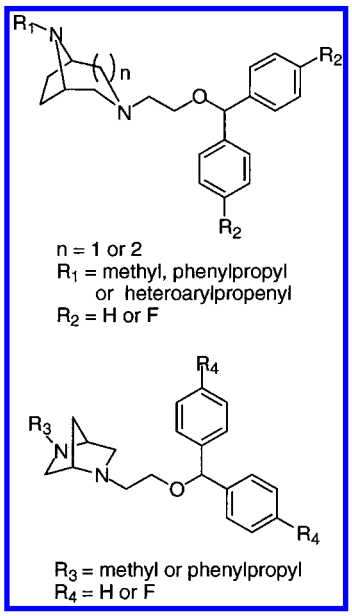
One of the approaches to develop a potential therapeutic agent for the treatment of cocaine abuse proposed by Rothman et al. in 1991 is to develop an agent which binds with high affinity to and dissociates slowly from the DAT.[33] This strategy assumes that if the dissociation rate of such a ligand from the transporter is slow enough, the agent will behave as a noncompetitive inhibitor, creating an insurmountable inhibition of the effects of cocaine mediated via elevation of extracellular DA. Such an agent may also provide cocaine addicts with some relief from cocaine craving, thereby reducing cocaine self-administration behavior.[33] Aryl-1,4-dialk(en)ylpiperazines including: GBR 12935 (1-[2-(diphenylmethoxy)ethyl]-4-(3-phenylpropyl)piperazine) (**2**), GBR 12909 (1-{2-[bis(4-fluorophenyl)]methoxy]ethyl}-4-(3-phenylpropyl)piperazine) (**3**), and GBR 12783 (1-[2-(diphenylmethoxyl)ethyl]-4-(3-phenyl-2-propenyl)piperazine) (Chart 1), were among the first agents characterized as high-affinity and selective inhibitors of DA reuptake.[34,35] GBR 12909 (**3**) produces only a modest increase in extracellular DA levels;[36,37] however, it attenuates the ability of cocaine to increase extracellular DA levels in rat caudate.[33] It binds tightly to the DAT but is less efficient than cocaine in increasing DA-mediated motoric behaviors.[32] It has been shown in cocaine and food self-administration studies that **3** decreases cocaine-maintained responding without affecting food-maintained responding in rhesus monkeys.[38,39] It has also been reported that **3** attenuates cocaine-induced activation of mesolimbic DA neurons, as measured by in vivo microdialysis.[40] Recently, a behavioral study of rhesus monkeys administered the decanoate ester of a racemic benzylic hydroxyl derivative of **3** (**3a**) was carried out.[41] The benzylic hydroxyl derivative **3a** was selected for conversion to the decanoate ester prodrug after preliminary in vivo and in vitro studies revealed its profile to be similar to that of **3**.[41] Preliminary data showed that a single treatment with this prodrug **3a** as an extended action formulation resulted in a sustained and selective effect on cocaine-maintained responding for almost 30 days without affecting the normal food-seeking behavior of rhesus monkeys. Later studies with the enantiomers of **3a** showed that these compounds were nearly equipotent, but twice as potent as **3** in preventing cocaine-maintained responding in rhesus monkeys.[42] Given the promising neurochemical and behavioral properties of **3**, this compound and its analogues have been identified as novel compounds potentially useful for the pharmacotherapy of cocaine abuse in humans.

Chart 1

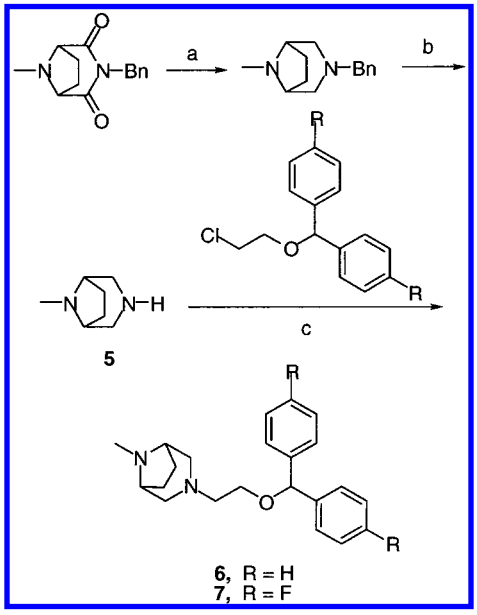


An early SAR study on **2**, replacing the piperazine moiety with homopiperazine, resulted in the identification of LR 1111 (**4**, Chart 1) as a highly selective DA uptake inhibitor. This compound has been reported to show similar binding affinity to **2** for the DAT but with greater than 4000-fold selectivity for inhibition of [^{3}H]-DA uptake relative to [^{3}H]5-HT uptake.[43] Other studies have also shown that modifying the central piperazine ring of the GBR molecule significantly alters the affinity and selectivity of the analogues at the DAT site.[44,45] We have utilized these findings in the development of a new series of GBR-related ligands, in which the piperazine fragment was replaced by a bridged piperazine or bridged homopiperazine moiety (Chart 2), and we report

Chart 2



Scheme 1. Synthesis of *N*-Methyl Bridged Piperazine GBR Analogues[a]



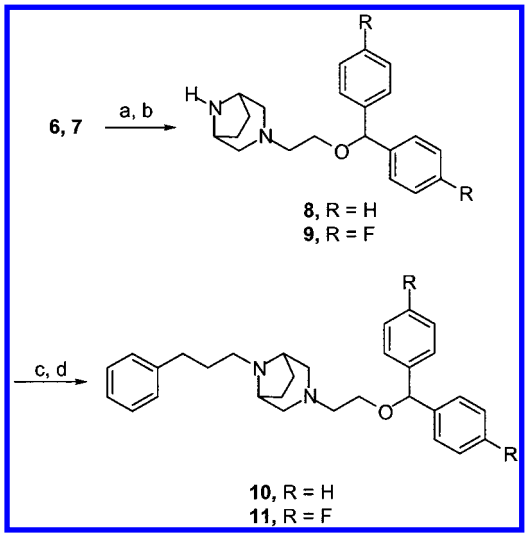
[a] (a) 0.5 M AlH_3 in THF, 0 °C; (b) H_2, ethanol, 10% Pd/C; (c) K_2CO_3, toluene, reflux.

here the binding affinity of these novel ligands for the DAT and serotonin transporter (SERT) and their ability to inhibit the reuptake of DA and 5-HT. Additionally, an earlier study on **3** showed that modification of the phenylpropyl "tail" portion of the molecule by incorporation of a heteroaromatic moiety resulted in an increase of the binding affinity and selectivity at DAT binding site.[46] Therefore, it was also our intention to synthesize a series of bridged piperazine derivatives of **3** with a heteroaromatic "tail" (Chart 2) in order to evaluate their biological activities.

Chemistry

The bridged piperazine 8-methyl-3,8-diaza[3.2.1]-bicyclooctane (**5**) was prepared (Scheme 1) in two steps from 3-benzyl-8-methyl-3,8-diaza[3.2.1]bicyclooctane-2,4-dione according to the literature method with modifications.[47−49] The imide was reduced by 0.5 M aluminum hydride in THF at 0 °C to afford the diamine, which was then followed by an *N*-debenzylation using catalytic hydrogenation to afford **5** in 54% yield. *N*-Alkylation of **5** with 2-(diphenylmethoxy)ethyl chloride or 2-[bis(4-fluorophenyl)methoxy]ethyl chloride, prepared as previously described,[34] afforded *N*-methyl analogues **6** and **7** (Scheme 1).

Scheme 2. Synthesis of Bridged Piperazine GBR Derivatives[a]



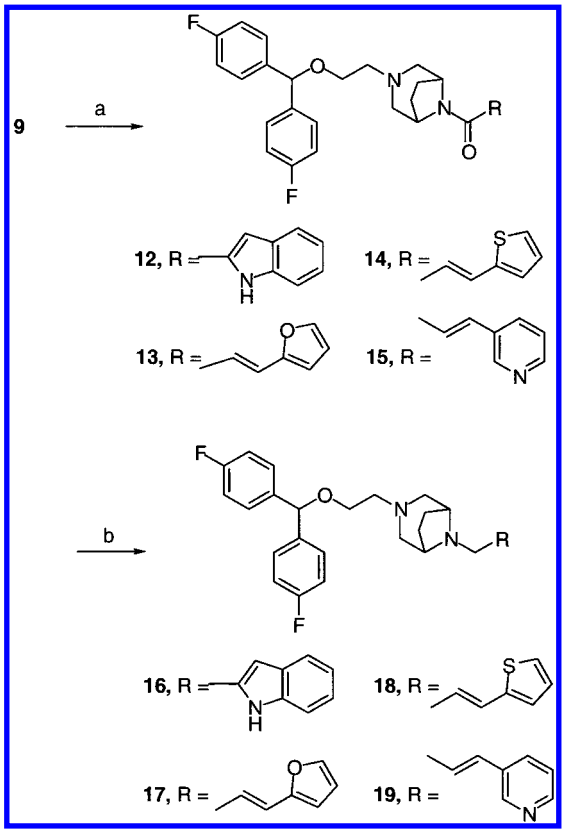
[a] (a) 2,2,2-Trichloroethyl chloroformate, toluene, reflux; (b) Zn, acetic acid, rt; (c) hydrocinnamoyl chloride, methylene chloride, rt; (d) 1.0 M AlH_3 in THF, rt.

N-Demethylation of **6** and **7** was then carried out under mild reaction conditions[50] (method A, Scheme 2). Compounds **6** and **7** were converted into carbamates with 2,2,2-trichloroethyl chloroformate in toluene, followed by a treatment with zinc powder in acetic acid at room temperature to give **8** and **9**, respectively. The obtained *N*-demethylated compounds **8** and **9** were acylated with hydrocinnamoyl chloride in dichloromethane, and the resulting amides underwent alane reduction (method C) to afford the target amines **10** and **11**. *N*-Acylation of **9** with indole-2-carboxylic acid, 2-furylacrylic acid, 3-(2-thienyl)acrylic acid, or *trans*-3-(3-pyridyl)acrylic acid, followed by alane reduction at 0 °C, afforded the unsaturated final products **16**−**19** respectively (Scheme 3, methods B and C).

The synthesis of **23** and **24** (Scheme 4) proceeded from the *N*-alkylation of the commercially available (1*S*,4*S*)-*N*-*t*-Boc-2,5-diazabicyclo[2.2.1]heptane with diarylmethoxyethyl iodide (method D) to form **21** and **22**, followed by a reduction of the *N*-Boc protecting group with 1.0 M lithium aluminum hydride (LAH) in THF. Deprotection of *N*-Boc in 88% of formic acid at room temperature, followed by *N*-alkylation with 1-iodo-3-phenylpropane in THF, gave the desired compounds **25** and **26**.

The bridged homopiperazine 9-methyl-3,9-diazabicyclo-[4.2.1]nonane (**27**) was prepared according to the literature method in two steps with minor modifications.[51] Treatment of 3-tropinone with hydrazoic acid gave the bicyclic lactam, which was then reduced with lithium aluminum hydride under refluxing conditions for 2 days to afford **27** in 73% overall yield (Scheme 5). This *N*-methyl bridged homopiperazine was then alkylated

Scheme 3. Synthesis of Bridged Piperazine GBR Derivatives with Heterocyclic Aromatic Tail[a]



[a] (a) Carboxylic acid, EDCI, methylene chloride, rt; (b) 1.0 M AlH_3 in THF, 0 °C for 2 min.

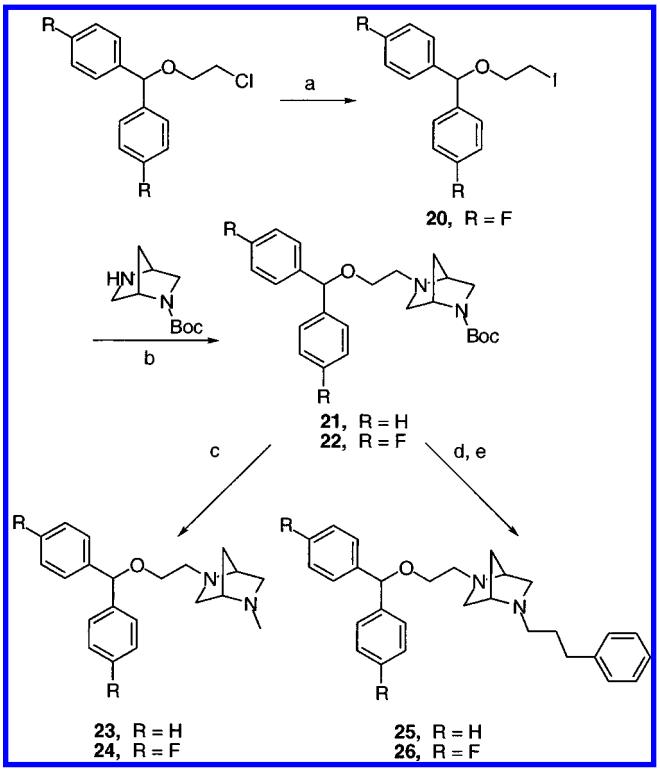
with diarylmethoxyethyl iodide to give the *N*-methyl compounds **28** and **29** (method D). *N*-Demethylation of **28** and **29** (method A) resulted in **30** and **31**, followed by *N*-alkylation with 1-iodo-3-phenylpropane in THF (method D) to afford the target compounds **32** and **33** (Scheme 5).

All final products were purified and crystallized as salts with organic or inorganic acids as listed in Table 1.

Results and Discussion

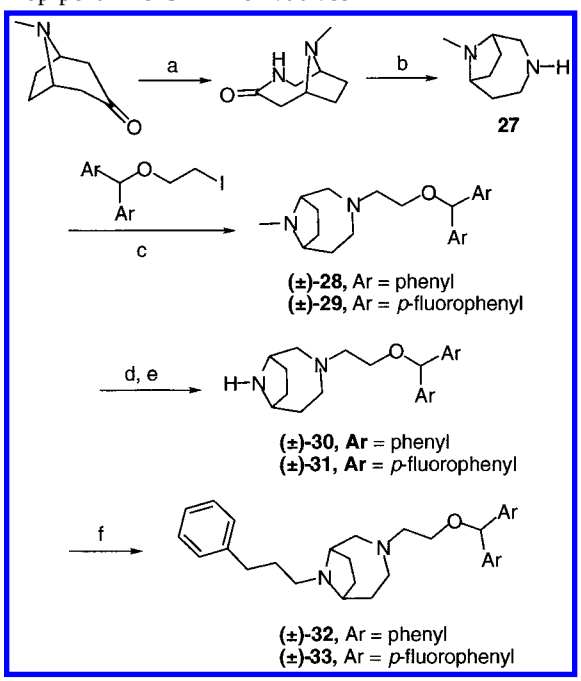
The bridged piperazine series of compounds were designed to introduce some rigidity to the piperazine ring of the analogues of **3** and to force these analogues to adopt a conformation similar to cocaine. Replacement of the C-3 carbon in the tropane skeleton of cocaine with a basic nitrogen results in the analogues **6**, **7**, **10**, and **11** with a two-carbon bridge in the piperazine ring, as shown in Scheme 1. The binding data in Table 2 indicated that both **7** and **11**, the compounds with *p*-fluoro substitution in the aromatic region, showed high activity in DA reuptake inhibition with high affinity for the DAT. Compound **7** possessed an affinity of 8.0 nM at DAT binding and 9.6 nM in DA reuptake inhibition. It exhibits an 88-fold selectivity for the DAT relative to the SERT, as well as a 93-fold selectivity at reuptake inhibition for DA relative to 5-HT. Replacing the phenylpropyl side chain of the bridged piperazine derivative **11** with a heteroaromatic "tail" resulted in compounds **16**−**19**. An earlier study by Matecka et al. showed that the binding affinity of the corresponding unbridged series of compounds benefited from the

Scheme 4. Synthesis of One-Carbon Bridged (1*S*,4*S*)-Piperazine GBR Derivatives[a]



[a] (a) NaI, acetone, reflux overnight; (b) K_2CO_3, THF, reflux; (c) 1 M $LiAlH_4$ in THF, reflux; (d) 88% formic acid, rt; (e) 1-iodo-3-phenylpropane, K_2CO_3, THF, reflux.

Scheme 5. Synthesis of Racemic Bridged Homopiperazine GBR Derivatives[a]



[a] (a) Concd H_2SO_4, NaN_3, −5 to 50 °C; (b) 1 M $LiAlH_4$ in THF, reflux 2 days; (c) K_2CO_3, THF, reflux; (d) 2,2,2-trichloroethyl chloroformate, K_2CO_3, toluene; (e) Zn, acetic acid, rt; (f) 1-iodo-3-phenylpropane, K_2CO_3, THF, reflux.

incorporation of a heteroaromatic moiety such as furan or thiophene into the *N*-phenylpropyl side chain.[46] We observed the same effects in our bridged series (Table 2) in that compounds containing indole, furan, and

Table 1. Physical Properties of the Ligands

no.[a]	salt	solvent	mp (°C)	CI-MS (*m*/*z*)	analysis[b]
6	HBr	ethanol	221−2	336	$C_{22}H_{28}N_2O\cdot 2HBr$
7	oxalate	acetone	154−5	372	$C_{22}H_{26}N_2OF_2\cdot 2C_2H_2O_4$
10	oxalate	acetone	143−4	440	$C_{30}H_{36}N_2O\cdot 2C_2H_2O_4$
11	oxalate	acetone	155−6	476	$C_{30}H_{34}N_2OF_2\cdot 2C_2H_2O_4$
16	oxalate	acetone	203−4	487	$C_{30}H_{31}N_3OF_2\cdot C_2H_2O_4$
17	oxalate	acetone	195−6	478	$C_{28}H_{30}N_2O_2F_2\cdot 2C_2H_2O_4\cdot 0.5H_2O$
18	oxalate	acetone	194−5	494	$C_{28}H_{30}N_2OF_2S\cdot 2C_2H_2O_4$
19	oxalate	acetone	151−3	489	$C_{29}H_{31}N_3OF_2\cdot 2C_2H_2O_4\cdot 1.25H_2O$
23	oxalate	ethanol	160−1	322	$C_{21}H_{26}N_2O\cdot 2C_2H_2O_4$
24	oxalate	ethanol	167−9	358	$C_{21}H_{24}N_2OF_2\cdot 2C_2H_2O_4\cdot 0.5H_2O$
25	oxalate	methanol	188−9	426	$C_{29}H_{34}N_2O\cdot 2C_2H_2O_4$
26	oxalate	methanol	185−6	462	$C_{29}H_{32}N_2OF_2\cdot 2C_2H_2O_4$
28	HCl[c]	ether	70[d]	350	$C_{23}H_{30}N_2O\cdot 2HCl\cdot H_2O$
29	HCl[c]	ether	81[d]	386	$C_{23}H_{28}N_2OF_2\cdot 2HCl\cdot 0.5H_2O$
30	HCl[c]	ether	93[d]	336	$C_{22}H_{28}N_2O\cdot 2HCl\cdot 0.25H_2O$
32	HCl[c]	ether	85[d]	454	$C_{31}H_{38}N_2O\cdot 2HCl\cdot 0.5H_2O$
33	HCl[c]	ether	67[d]	490	$C_{31}H_{36}N_2OF_2\cdot 2HCl\cdot H_2O$

[a] The ^{1}H NMR data for the free base of these compounds are shown in the Experimental Section. [b] Elemental compositions (%) were found to be within ±0.4% of the theoretical values of C, H, and N. [c] HCl salt was tritiated from ether. [d] Softening point.

thiophene moieties showed low-nanomolar affinity at the DAT binding, while the pyridine-containing analogue exhibited a slightly lower affinity. The indole-containing compound **16** displayed the highest affinity (IC_{50} = 1.4 nM) for DAT binding, a 6-fold increase over the corresponding phenylpropyl derivative **11**, while retaining high binding selectivity (74-fold) over the SERT. However, it is interesting to note that this compound displayed a relatively lower activity (IC_{50} = 40 nM) in DA reuptake inhibition and exhibited a high ratio (29-fold) of IC_{50} for the inhibition of DA reuptake versus binding to the DAT. Recently, attention has been drawn toward the design of compounds that show high affinity for the DAT and relatively low inhibitory activity for DA reuptake as potential therapeutic agents for cocaine abuse.[52−54] It has been proposed that such a compound could be an effective therapeutic agent because it would serve to block cocaine from binding to the transporter while not interfering with DA transport. Although the biological significance of such an agent has not been fully studied, the development of novel agents such as **16** will allow further functional studies to be performed to test this hypothesis.

As mentioned earlier, modification of **2** by replacement of the piperazine with a homopiperazine moiety resulted in **4**, a compound that exhibited a similar binding profile as **2** for the DAT while having a much higher selectivity (4000-fold) at the DAT relative to the SERT. Therefore, it was of interest to prepare a group of bridged homopiperazine compounds to compare their binding properties with **4**. The binding data in Table 2 show that among this series (**28**−**33**), compound **32** displayed the highest affinity for the DAT (IC_{50} = 32 nM), a 10-fold decrease in affinity versus **4**. This compound differs from **4** only by a two-carbon bridge over C-2 and C-7. However it shows a 100-fold decrease in selectivity versus **4** at the DAT relative to SERT. The nor-compound **30** showed the lowest affinity of the series with IC_{50} = 0.4 μM, indicating that a tertiary amine center may be important for high-affinity binding at the DAT.

The design of compounds **23**−**26** was intended to provide some view into the geometry of the piperazine moiety of GBR analogues upon binding. Although a variety of studies have been carried out in the modification of both *N*- and *N*′-substitution of the piperazine ring, studies on the piperazine moiety itself have remained minimal. Among the few, a study by Matecka et al.[44] showed that the (±)-2,5-dimethylpiperazine derivative of **3** had a comparable affinity to **3 (**GBR 12909) for the DAT labeled by [^{125}I]RTI-55. In addition, the compound exhibited enantioselectivity at the DAT as well as DA uptake inhibition in favor of the 2*S*,5*R* absolute configuration [IC_{50}(DAT) = 2.9 nM].[44] In our bridged piperazine series, the methylene group locks the six-membered ring into a more rigid geometry with the bridge heads existing in an *S*,*S* configuration. The binding data of compounds **23**−**26** (Table 2) showed that these compounds displayed only moderate affinity for DAT binding as well as moderate inhibitory activity for DA reuptake. Within this series, compound **26** possesses the closest structural similarity to the Matecka et al. compound, the 2,5-dimethylpiperazine derivative of **3**.[44] Interestingly, **26** exhibited a binding affinity of 127 nM for the DAT and 203 nM for the SERT, similar to the binding property of the (2*R*,5*S*)-(+)-dimethylpiperazine derivative [IC_{50}(DAT labeled by [^{125}I]RTI-55) = 99 nM, IC_{50}(SERT labeled by [^{125}I]RTI-55) = 298 nM] in Matecka's series, while the corresponding 2*S*,5*R* compound showed high affinity and selectivity at the DAT.[44] This suggests that the 2*S*,5*R* absolute configuration is one of the important criteria for the interaction of the GBR type of compounds with the binding domain of the DAT site. The increased bulk of the bridged piperazines and their increased molecular volume did not prevent binding.

In summary, we have synthesized a series of novel bridged piperazine analogues corresponding to the unbridged compounds **2** and **3**. The preliminary binding study showed that compound **16**, a bridged piperazine derivative with an *N*-indolylmethyl, displayed high binding affinity and selectivity for the DAT. Compounds such as **2** and **3** usually show a linear correlation between the binding affinity and reuptake inhibition activity (by IC_{50} value). However, **16** was 29-fold (by IC_{50} value) less active in DA reuptake inhibition. The interesting binding profile of **16** will lead to further investigation of its behavioral profile.

Experimental Section

Chemical Methods. Melting points were determined on a Mel-Temp II capillary apparatus and are reported uncorrected. Elemental analyses were obtained from Atlantic Microlabs, Atlanta, GA, and were determined to be within ±0.4% of the theoretical values for carbon, hydrogen, and nitrogen. CI-MS (chemical ionization mass spectra) was performed using a Finnigan 1015 mass spectrometer. ^{1}H NMR spectra were obtained on a Varian XL-300 spectrometer using $CDCl_3$ solutions of free bases. All the chemical shifts reported are relative to a tetramethylsilane (TMS) internal reference in ppm on the δ scale. Thin-layer chromatography (TLC) was performed on Analtech GHLF silica gel plates (250 microns) with a solvent system of 90:9:1 $CHCl_3$/MeOH/concentrated NH_4OH unless otherwise indicated. No attempt was made to optimize the reaction yields reported. The physical properties of the ligands synthesized are given in Table 1.

Method A: *N*-Demethylation. A solution of the *N*-methyl compound, 1.2 equiv of 2,2,2-trichloroethyl chloroformate, and

Table 2. Binding Affinities at the DAT and SERT Labeled with [^{125}I]RTI-55 and DA and 5-HT Reuptake Inhibition of GBR Analogues

	binding IC_{50} (±SEM, nM)		reuptake (±SEM, nM)		5-HT/DA ratio	
no.	DAT	5-HT	[^{3}H]DA	[^{3}H]5-HT	binding	reuptake
6	111 ± 6	6400 ± 600	1140 ± 190	13700 ± 930	58	12
7	8.0 ± 0.2	705 ± 24	9.6 ± 0.2	898 ± 51	88	93
10	18 ± 1	740 ± 19	24 ± 1	1390 ± 70	42	58
11	8.2 ± 0.2	277 ± 7	19 ± 1	506 ± 20	34	27
16	1.4 ± 0.1	104 ± 4	40 ± 7	645 ± 27	74	16
17	5.5 ± 0.4	146 ± 4	24 ± 1	299 ± 8	27	13
18	4.0 ± 0.2	46 ± 1	28 ± 1	268 ± 8	12	10
19	12 ± 0.5	395 ± 23	24 ± 2	968 ± 30	33	40
23	1170 ± 30	33 ± 5 (μM)	830 ± 37	28 ± 1 (μM)	29	33
24	121 ± 4	1697 ± 108	125 ± 10	2150 ± 70	14	17
25	223 ± 8	720 ± 38	198 ± 15	912 ± 34	3	5
26	127 ± 3	203 ± 33	113 ± 6	173 ± 7	1.6	1.5
28	307 ± 19	17 ± 2 (μM)	928 ± 48	6154 ± 375	56	6.6
29	89 ± 4	1903 ± 71	36 ± 2	1667 ± 117	21	47
30	431 ± 12	6060 ± 230	260 ± 8	3960 ± 120	14	15
32	32 ± 1	1320 ± 40	87 ± 8	2300 ± 100	41	26
33	130 ± 6	843 ± 25	47 ± 1	2080 ± 130	6.5	44
3 (GBR 12909)[a]	3.7 ± 0.4	126 ± 5	7.3 ± 0.2	73 ± 2	25	46

[a] Data from ref 46.

1.5 equiv of K_2CO_3 in dry toluene (10 mmol of *N*-methyl compound in 100 mL of solvent) was heated at reflux overnight. The light brown colored solution was washed with water, extracted with 15% aqueous citric acid solution twice, washed with water and brine, dried over Na_2SO_4 and evaporated to give a dark brown colored oil. The oil was dissolved in CH_2Cl_2 and filtered through a silica gel plug to remove polar, colored impurities, and a light yellow oil was collected after evaporation of the filtrate. To the obtained oil in acetic acid (10 mmol of carbamate in 100 mL of 99.7% HOAc) was added zinc powder (50 mmol), and the suspension was allowed to stir at room temperature vigorously until TLC showed the disappearance of the carbamate. The solvent was evaporated on a rotavapor with an equal volume of toluene, and the residue was dissolved in methylene chloride. The solution containing a small amount of zinc powder was extracted three times with 15% aqueous citric acid. The combined aqueous layer was washed once with CH_2Cl_2, basified with concentrated NH_4OH, and extracted three times with CH_2Cl_2. The organic layer was washed with water, brine, dried over Na_2SO_4, and evaporated to give the *N*-demethylated product as light yellow oil.

Method B: *N*-Acylation. A solution of the carboxylic acid and dimethylaminopropylethylcarbodiimide (EDCI) in CH_2Cl_2 was allowed to stir at room temperature for 5 min before a solution of the amino compound in CH_2Cl_2 was added. The mole ratio of amine to acid to EDCI was approximately 1:1.25:1.5. The reaction mixture was stirred at room temperature, overnight, at which time TLC showed the completion of the reaction. The mixture was then washed with saturated aqueous $NaHCO_3$ twice, water once, brine once and dried over Na_2SO_4. A yellow oil was obtained after the solution was evaporated. The crude product was then purified on a silica gel column with 15:1 $CHCl_3$/MeOH to give the desired amide as light yellow oil.

Method C: Amide Reduction. A solution of the amide in the minimum amount of THF was added dropwise to a stirred, freshly prepared solution of 1 M AlH_3 in THF.[55] The molar ratio of amide to AlH_3 was about 1:5. The reaction mixture was stirred at room temperature or in an ice water bath until TLC showed the disappearance of the amide (<0.5 h). The mixture was then poured slowly into a 15% aqueous NaOH solution in an ice−water bath. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layer was then washed with water and brine, dried over Na_2SO_4, and evaporated to give the corresponding amino compound in free base form. The crude product was then purified through crystallization of the salt in a specified solvent (Table 1). Column chromatography was performed (with 150:10:1 $CHCl_3$/MeOH/concentrated NH_4OH) prior to salt formation if necessary.

Method D: *N*-Alkylation. A solution of amine, alkyl iodide, and K_2CO_3 in THF was heated at reflux overnight, when TLC showed the completion of the reaction. The molar ratio of amine to alkyl iodide and K_2CO_3 was about 1:1.5:2. THF was then evaporated, and the mixture was dissolved in CH_2Cl_2, washed with water and brine, and dried over Na_2SO_4. The solution was evaporated to give the desired crude product, which was purified by salt formation or column chromatography prior to salt formation.

8-Methyl-3,8-diazabicyclo[3.2.1]octane (5). Prepared according to the literature method with some modification.[47−49] A solution of 20.0 g (82 mmol) of 3-benzyl-8-methyl-3,8-diaza-[3.2.1]bicyclooctane-2,4-dione in 60 mL of anhydrous THF was added to 200 mL of 0.5 M freshly prepared AlH_3 in THF while cooling in an ice water bath. The mixture was allowed to stir at 0 °C until TLC showed the disappearance of imide. The reaction was quenched by pouring the mixture into 300 mL of ice cold 15% aqueous NaOH solution. The layers were separated and the aqueous phase was extracted with ethyl acetate several times. The combined organic layer was washed with water once, brine once and dried over Na_2SO_4. Evaporation of the solution gave 11.5 g of 3-benzyl-8-methyl-3,8-diazabicyclo-[3.2.1]octane as a yellow oil in 65% yield: CI-MS 217 (M + 1).

To a solution of 3.8 g of 3-benzyl-8-methyl-3,8-diazabicyclo-[3.2.1]octane in 100 mL of ethanol was added 1.9 g of 10% Pd/C under Ar, and the mixture was hydrogenated on a Parr reduction apparatus. The catalyst was filtered off through Celite after TLC showed the completion of the reaction, and the product in EtOH was converted to its HCl salt by treatment with 20 mL of 4 M HCl in methanol. White crystals were collected after vacuum filtration (1.9 g, 54% overall yield, reduction and salt formation).

3-{2-[Bis(4-fluorophenyl)methoxy]ethyl}-8-methyl-3,8-diazabicyclo[3.2.1]octane (7). To a suspension of 0.79 g (4.0 mmol) of **5** (HCl salt) and 0.80 g of triethylamine in 20 mL of toluene were added 2.24 g (2 equiv) of 2-[bis(4-fluorophenyl)-methoxy]ethyl chloride and 1 g of K_2CO_3. The mixture was heated at reflux for 2 days, when TLC showed only a small amount of starting piperazine **5**. The reaction solution was washed with water, then extracted with 15% aqueous citric acid solution until TLC showed no product present in the organic layer. The extracts were combined and basified with concentrated NH_4OH to pH 9. The cloudy solution was then extracted with CH_2Cl_2 three times. The organic layer was washed with water, brine, dried over Na_2SO_4, and evaporated to give 0.40 g of product as a light brown colored oil, which was converted to its oxalic acid salt in acetone to give 0.50 g of light yellow colored solid: CI-MS (NH_3) *m/z* 373 (M + 1); ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 4H, ArH), 7.01 (t, J = 8.8 Hz, 4H, ArH), 5.34 (s, 1H, ArCHAr), 3.49 (t, J = 5.9 Hz, 2H, OCH_2),

3.06 (brs, 2H, NCH), 2.60 (t, J = 5.8 Hz, 4H, NCH_2), 2.38 (d, J = 10.5 Hz, 2H, NCH_2), 2.27 (s, 3H, NCH_3), 1.76−1.92 (m, 4H).

3-[2-(Diphenylmethoxy)ethyl]-8-methyl-3,8-diazabicyclo[3.2.1]octane (6). Synthesized by *N*-alkylation of **5** with 2-[diphenylmethoxy]ethyl chloride according to the method described above for **7**. The obtained product was further purified by preparing its HBr salt in ethanol resulting an off-white colored solid that was collected after vacuum filtration: CI-MS (NH_3) m/z 337 (M + 1); ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 10H, ArH), 5.38 (s, 1H, ArCHAr), 3.54 (t, J = 5.9 Hz, 2H, OCH_2), 3.14 (brs, 2H, NCH), 2.65 (m, 4H, NCH_2), 2.54 (d, J = 10.8 Hz, 2H, NCH_2), 2.34 (s, 3H, NCH_3), 1.87 (m, 4H).

3-{2-[Bis(4-fluorophenyl)methoxy]ethyl}-3,8-diazabicyclo[3.2.1]octane (9). Prepared from *N*-demethylation of **7** according to method A: CI-MS (NH_3) m/z 359 (M + 1); ^{1}H NMR ($CDCl_3$) δ 7.28 (dd, J = 8.6 Hz, J = 3.0 Hz, 4H, ArH), 7.01 (t, J = 8.7 Hz, 4H, ArH), 5.34 (s, 1H, ArCHAr), 3.50 (t, J = 5.9 Hz, 2H, OCH_2), 3.42 (brs, 2H, NCH) 2.67 (dd, J = 11.0 Hz, J = 1.6 Hz, 2H, NCH_2), 2.59 (t, J = 5.9 Hz, 2H, NCH_2), 2.26 (d, J = 10.8 Hz, 2H, NCH_2), 1.69−1.89 (m, 4H).

3-[2-(Diphenylmethoxy)ethyl]-8-(3-phenylpropyl)-3,8-diaza[3.2.1]bicyclooctane (10). *N*-Demethylation of **6** according to method A afforded 3-[2-(diphenylmethoxy)ethyl]-3,8-diazabicyclo[3.2.1]octane **(8)** in 77% yield. To a solution of 300 mg (0.93 mmol) of **8** in 10 mL of CH_2Cl_2 was added 160 μL of hydrocinnamoyl chloride, and the mixture was allowed to stir at room temperature for 0.5 h, when TLC showed the completion of the reaction. The reaction mixture was washed with 10% aqueous NaOH, water, brine, dried over Na_2SO_4, and evaporated to give a product mixture as a light yellow oil. The oil was purified on a preparative TLC plate with 100:10:1 $CHCl_3$/MeOH/concentrated NH_4OH to give 339 mg of the amide in 80% yield: CI-MS(NH_3) m/z 455 (M + 1). This amide then underwent an alane reduction according to method C to give the desired compound **10**: CI-MS (NH_3) m/z 441 (M + 1); ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 15H, ArH), 5.39 (s, 1H, ArCHAr), 3.53 (t, J = 5.9 Hz, 2H, OCH_2), 3.12 (brs, 2H, NCH), 2.62 (m, 6H, NCH_2 + $ArCH_2$), 2.35 (m, 4H, NCH_2), 1.78 (m, 6H).

3-{2-[Bis-(4-fluorophenyl)methoxy]ethyl}-8-(3-phenylpropyl)-3,8-diazabicyclo[3.2.1]octane (11). Synthesized according to the same procedure as **10**: CI-MS (NH_3) m/z 477 (M + 1); ^{1}H NMR ($CDCl_3$) δ 7.15−7.29 (m, 9H, ArH), 7.00 (t, J = 8.7 Hz, 4H, ArH), 5.34 (s, 1H, ArCHAr), 3.48 (t, J = 5.9 Hz, 2H, OCH_2), 3.18 (brs, 2H, NCH) 2.61 (m, 6H, NCH_2 + $ArCH_2$), 2.40 (m, 4H, NCH_2), 1.78 (m, 6H).

(3-{2-[Bis(4-fluorophenyl)methoxy]ethyl}-3,8-diazabicyclo[3.2.1]oct-8-yl)(1*H*-indol-2-yl)methanone (12). Synthesized from acylation of **9** with indole-2-carboxylic acid according to method B: mp 56 °C; CI-MS (NH_3) m/z 502 (M + 1); ^{1}H NMR ($CDCl_3$) δ 7.66 (d, J = 7.8 Hz, 1H, ArH), 7.44 (d, J = 7.8 Hz, 1H, ArH), 7.29 (m, 6H, ArH), 7.15 (t, J = 6.9 Hz, 1H, ArH) 7.01 (t, J = 8.7 Hz, 4H, ArH), 6.81 (s, 1H, ArH), 5.33 (s, 1H, ArCHAr), 4.86 (brs, 2H, NCH), 3.55 (t, J = 5.9 Hz, 2H, OCH_2), 2.84 (brs, 2H, NCH_2) 2.70 (t, J = 5.9 Hz, 2H, NCH_2), 2.59 (bs, 2H, NCH_2), 2.00 (m, 4H).

1-(3-{2-[Bis(4-fluorophenyl)methoxy]ethyl}-3,8-diazabicyclo[3.2.1]oct-8-yl)-3-furan-2-ylpropenone (13). Synthesized from acylation of **9** with 2-furylacrylic acid according to method B. The compound was purified by column chromatography using 100:1 $CHCl_3$:MeOH and was obtained as a light yellow oil: CI-MS (NH_3) m/z 479 (M + 1); ^{1}H NMR ($CDCl_3$) δ 7.46 (d, J = 14.7 Hz, 1H, olefinic H), 7.27 (m, 5H, ArH), 7.01 (t, J = 9.2 Hz, 4H, ArH) 6.66 (d, J = 15.6 Hz, 1H, olefinic H), 6.55 (1H, ArH), 6.47 (m, 1H, ArH), 5.31 (s, 1H, ArCHAr), 4.73 (d, J = 6.0 Hz, 1H, NCH), 4.34 (brs,1H, NCH), 3.51 (t, J = 5.9 Hz, 2H, OCH_2), 2.76 (m, 2H, NCH_2) 2.65 (t, J = 5.4 Hz, 2H, NCH_2), 2.43 (m, 2H, NCH_2), 1.91 (m, 4H).

1-(3-{2-[Bis(4-fluorophenyl)methoxy]ethyl}-3,8-diazabicyclo[3.2.1]oct-8-yl)-3-thiophen-2-ylpropenone (14). Synthesized from acylation of **9** with 3-(2-thienyl)acrylic acid according to method B. The compound was purified by column chromatography using 100:1 $CHCl_3$:MeOH and was obtained as a colorless oil: CI-MS (NH_3) m/z 495 (M + 1); ^{1}H NMR ($CDCl_3$) δ 7.84 (d, J = 14.7 Hz, 1H, olefinic H), 7.27 (m, 6H, ArH), 7.01 (m, 4H, ArH) 6.55 (d, J = 14.7 Hz, 2H, ArH + olefinic H), 5.31 (s, 1H, ArCHAr), 4.73 (d, J = 5.1 Hz, 1H, NCH), 4.30 (brs, 1H, NCH), 3.51 (t, J = 5.4 Hz, 2H, OCH_2), 2.75 (m, 2H, NCH_2) 2.65 (t, J = 5.9 Hz, 2H, NCH_2), 2.44 (m, 2H, NCH_2), 1.91 (m, 4H).

1-(3-{2-[Bis(4-fluorophenyl)methoxy]ethyl}-3,8-diazabicyclo[3.2.1]oct-8-yl)-3-pyridin-3-ylpropenone (15). Synthesized from **9** with *trans*-3-(3-pyridyl)acrylic acid according to method B. The compound was purified by column chromatography using 30:1 CH_2Cl_2:MeOH and was obtained as a yellow oil: CI-MS(NH_3) m/z 490 (M + 1); ^{1}H NMR ($CDCl_3$) δ 8.77 (s, 1H, ArH), 8.58 (d, J = 4.0 Hz, 1H, ArH), 7.83 (dt, J = 7.8 Hz, J = 1.9 Hz, 1H, ArH), 7.77 (d, J = 15.6 Hz, 1H, olefinic H), 7.27 (m, 5H, ArH), 7.01 (m, 4H, ArH), 6.89 (d, J = 15.6 Hz, 1H, olefinic H), 5.31 (s, 1H, ArCHAr), 4.75 (d, J = 5.9 Hz, 1H, NCH), 4.32 (brs, 1H, NCH), 3.51 (t, J = 5.9 Hz, 2H, OCH_2), 2.79 (m, 2H, NCH_2) 2.65 (t, J = 5.9 Hz, 2H, NCH_2), 2.44 (m, 2H, NCH_2), 1.94 (m, 4H).

3-{2-[Bis(4-fluorophenyl)methoxy]ethyl}-8-(1*H*-indol-2-ylmethyl)-3,8-diazabicyclo[3.2.1]octane (16). Synthesized from **12** according to method C: CI-MS(NH_3) m/z 488 (M + 1); ^{1}H NMR ($CDCl_3$) δ 7.54 (d, J = 7.8 Hz, 1H, ArH), 7.37 (d, J = 7.8 Hz, 1H, ArH), 7.27 (dd, J = 8.7 Hz, J = 3.0 Hz, 4H, ArH), 7.16 (t, J = 7.4 Hz, 1H, ArH), 7.10 (t, J = 7.4 Hz, 1H, ArH), 7.01 (t, J = 8.9 Hz, 4H, ArH), 6.30 (s, 1H, ArH), 5.34 (s, 1H, ArCHAr), 3.67 (s, 2H, $ArCH_2N$), 3.50 (t, J = 5.9 Hz, 2H, OCH_2), 3.11 (bs, 2H, NCH) 2.62 (t, J = 5.9 Hz, 2H, NCH_2), 2.61 (s, 2H, NCH_2), 2.38 (m, 2H, NCH_2), 1.83 (m, 4H).

3-{2-[Bis(4-fluorophenyl)methoxy]ethyl}-8-(3-furan-2-ylallyl)-3,8-diazabicyclo[3.2.1]octane (17). Synthesized from **13** according to method C: CI-MS (NH_3) m/z 465 (M + 1); ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 5H, ArH + olefinic H), 7.01 (t, J = 8.9 Hz, 4H, ArH), 6.21−6.37 (m, 4H, ArH + olefinic H), 5.35 (s, 1H, ArCHAr), 3.50 (t, J = 5.9 Hz, 2H, OCH_2), 3.21 (brs, 2H, NCH), 3.13 (d, J = 6.0 Hz, 2H, NCH_2), 2.62 (m, 4H, NCH_2), 2.42 (m, 2H, NCH_2), 1.83 (m, 4H).

3-{2-[Bis(4-fluorophenyl)methoxy]ethyl}-8-(3-thiophen-2-ylallyl)-3,8-diazabicyclo[3.2.1]octane (18). Synthesized from **14** according to method C: CI-MS (NH_3) m/z 481 (M + 1); ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 5H, ArH), 7.14 (m, 1H, ArH), 7.01 (m, 5H, ArH) 6.63 (d, J = 15.6 Hz, 1H, olefinic H), 6.15 (dt, J = 15.6 Hz, J = 6.8 Hz, 1H, olefinic H), 5.35 (s, 1H, ArCHAr), 3.50 (t, J = 5.9 Hz, 2H, OCH_2), 3.21 (brs, 2H, NCH), 3.11 (d, J = 6.8 Hz, 2H, NCH_2), 2.62 (m, 4H, NCH_2), 2.41 (t, J = 10.7 Hz, 2H, NCH_2), 1.83 (m, 4H).

3-{2-[Bis(4-fluorophenyl)methoxy]ethyl}-8-(3-pyridin-3-ylallyl)-3,8-diazabicyclo[3.2.1]octane (19). Synthesized from **15** according to method C: CI-MS (NH_3) m/z 476 (M + 1); ^{1}H NMR ($CDCl_3$) δ 8.58 (d, J = 2.0 Hz, 1H, ArH), 8.47 (d, J = 4.9 Hz, 1H, ArH), 7.73 (d, J = 7.8 Hz, 1H, ArH), 7.27 (m, 5H, ArH), 7.01 (t, J = 8.8 Hz, 4H, ArH) 6.48 (m, 2H, olefinic H), 5.34 (s, 1H, ArCHAr), 3.50 (t, J = 5.9 Hz, 2H, OCH_2), 3.22 (m, 4H, NCH_2), 2.64 (m, 4H, NCH_2), 2.47 (m, 2H, NCH_2), 1.87 (m, 4H).

2-[Bis(4-fluorophenyl)methoxy]ethyl Iodide (20). Sodium iodide (4.5 g,1.5 equiv) was added to a solution of 5.65 g (20 mmol) 2-[bis(4-fluorophenyl)methoxy]ethyl chloride in 50 mL of acetone, and the reaction mixture was heated at reflux overnight. The yellow solution with white precipitate was evaporated and suspended in dry chloroform. The solution was filtered through Celite and the filtrate was then evaporated to give 7.36 g of **20** as a brown colored oil in 94% yield: ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 4H, ArH), 7.02 (t, J = 8.7 Hz, 4H, ArH), 5.39 (s, 1H, ArCHAr), 3.69 (t, J = 6.6 Hz, 2H, OCH_2), 3.30 (t, J = 6.7 Hz, 2H, ICH_2).

***(1S,4S)*-2-[2-(Diphenylmethoxy)ethyl]-5-methyl-2,5-diazabicyclo[2.2.1]heptane (23).** Alkylation of (1*S*,4*S*)-*N*-*t*-Boc-2,5-diazabicyclo[2.2.1]heptane with 2-(diphenylmethoxy)-ethyl iodide was carried out according to method D and gave (1*S*,4*S*)-2-[2-(diphenylmethoxy)ethyl]-5-*t*-Boc-2,5-diazabicyclo-[2.2.1]heptane **(21)** in 98% yield: CI-MS (NH_3) m/z 409 (M + 1). A solution of 1.00 g (2.5 mmol) of **21** in 10 mL of anhydrous THF was then added slowly via an addition funnel to a

refluxing solution of 1.0 M $LiAlH_4$ in THF, and the solution was allowed to reflux for another 2 h, when TLC showed the completion of the reaction. After the mixture was allowed to cool to room temperature, the reaction was quenched by addition of 40 mL brine and 5 g of sodium potassium tartrate. The layers were separated and the aqueous layer was extracted with chloroform. The combined organic layer was washed with water, brine, dried over Na_2SO_4, and evaporated to give 0.70 g of **23** as a light yellow colored oil in 90% yield. The compound was purified via salt formation with oxalic acid in ethanol to give 0.90 g of first crop as a white solid: CI-MS (NH_3) *m*/*z* 323 (M + 1); ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 10H, ArH), 5.37 (s, 1H, ArCHAr), 3.55 (t, J = 6.3 Hz, 2H, OCH_2), 3.35 (brs, 1H, NCH), 3.17 (bs, 1H, NCH), 2.82 (m, 6H, NCH_2), 2.38 (s, 3H, NCH_3), 1.71 (m, 2H).

(1*S*,4*S*)-3-{2-[Bis(4-fluorophenyl)methoxy]ethyl]-5-methyl-2,5-diazabicyclo[2.2.1]heptane (24). Alkylation of (1*S*,4*S*)-*N*-*t*-Boc-2,5-diazabicyclo[2.2.1]heptane with 2-(bis(4-fluororphenyl)methoxy)ethyl iodide according to method D gave 3-[2-[bis(4-fluorophenyl)methoxy]ethyl]-8-(1*S*,4*S*)-*N*-*t*-Boc-2,5-diazabicyclo[2.2.1]heptane **(22)** in 91% yield: CI-MS(NH_3) *m*/*z* 445 (M + 1). LAH reduction on **22** was then carried out according to the same procedure used for **23** to afford **24** as a light yellow oil in 95% yield. The oil was purified via salt formation with oxalic acid in ethanol to give the first crop as a white solid in 90% yield: CI-MS (NH_3) *m*/*z* 359 (M + 1); ^{1}H NMR ($CDCl_3$) δ 7.27 (dd, J = 8.8 Hz, J = 3.0 Hz, 4H, ArH), 7.03 (t, J = 8.8 Hz, 4H, ArH), 5.33 (s, 1H, ArCHAr), 3.51 (t, J = 5.9 Hz, 2H, OCH_2), 3.33 (brs, 1H, NCH), 3.17 (bs, 1H, NCH), 2.55−2.85 (m, 6H, NCH_2), 2.37 (s, 3H, NCH_3), 1.70 (dd, J = 9.7 Hz, J = 6.9 Hz, 2H).

(1*S*,4*S*)-2-[2-(Diphenylmethoxy)ethyl]-5-(3-phenylpropyl)-2,5-diazabicyclo[2.2.1]heptane (25). (1*S*,4*S*)-2-[2-(Diphenylmethoxy)ethyl]-5-*N*-*t*-Boc-2,5-diazabicyclo[2.2.1]heptane **(21)** was deprotected in 88% aqueous formic acid solution at room temperature. After TLC showed the completion of the reaction, the solution was extracted with CH_2Cl_2. The combined organic layer was washed with water, brine, dried over Na_2SO_4, and evaporated to give a light brown oil. The oil was directly carried on to the *N*-alkylation step with 1-iodo-3-phenylpropane without purification according to method D. The crude product **25** was purified by salt formation with oxalic acid in methanol to give the first crop as white solid: CI-MS (NH_3) *m*/*z* 427 (M + 1); ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 15H, ArH), 5.37 (s, 1H, ArCHAr), 3.55 (t, J = 6.3 Hz, 2H, OCH_2), 3.35 (s, 1H, NCH), 3.29 (s, 1H, NCH), 2.49−2.87 (m, 10H, NCH_2 + $ArCH_2$), 1.77 (tt, J = 7.8 Hz, 2H), 1.70 (s, 2H).

(1*S*,4*S*)-2-{2-[Bis(4-fluorophenyl)methoxy]ethyl}-5-(3-phenylpropyl)-2,5-diazabicyclo[2.2.1]heptane (26). Synthesized from (1*S*,4*S*)-{2-[bis(4-fluorophenyl)methoxy]ethyl}-5-*N*-*t*-Boc-2,5-diazabicyclo[2.2.1]heptane **(22)** according to the procedure for **25**: CI-MS (NH_3) *m*/*z* 463 (M + 1); ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 9H, ArH), 7.01 (t, J = 8.8 Hz, 4H, ArH), 5.33 (s, 1H, ArCHAr), 3.50 (t, J = 5.9 Hz, 2H, OCH_2), 3.31 (brs, 1H, NCH), 3.27 (bs, 1H, NCH), 2.43−2.87 (m, 10H, NCH_2 + $ArCH_2$), 1.77 (tt, J = 7.8 Hz, 2H), 1.68 (s, 2H).

(±)-3-[2-(Diphenylmethoxy)ethyl]-9-methyl-3,9-diazabicyclo[4.2.1]nonane (28). Synthesized by *N*-alkylation of (±)-9-methyl-3,9-diazabicyclo[4.2.1]nonane **(27)**[51] with 2-(diphenylmethoxy)ethyl iodide according to method D: CI-MS (NH_3) *m*/*z* 351 (M + 1); ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 10H, ArH), 5.37 (s, 1H, ArCHAr), 3.52 (t, J = 5.9 Hz, 2H, OCH_2), 3.21 (t, J = 7.8 Hz, 1H, NCH), 3.09 (d, J = 8.8 Hz, 1H, NCH), 2.73 (t, J = 5.9 Hz, 2H, NCH_2), 2.59 (m, 4H, NCH_2), 2.42 (s, 3H, NCH_3), 1.38−2.17 (m, 6H).

(±)-3-{2-[Bis(4-fluorophenyl)methoxy]ethyl}-9-methyl-3,9-diazabicyclo[4.2.1]nonane (29). Synthesized by *N*-alkylation of 9-methyl-3,9-diazabicyclo[4.2.1]nonane **(27)** with 2-[bis(4-fluorophenyl)methoxy]ethyl iodide according to method D: CI-MS (NH_3) *m*/*z* 387 (M + 1); ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 4H, ArH), 7.01 (t, J = 8.8 Hz, 4H, ArH), 5.33 (s, 1H, ArCHAr), 3.48 (t, J = 5.9 Hz, 2H, OCH_2), 3.21 (t, J = 7.5 Hz, 1H, NCH), 3.10 (m, 1H, NCH), 2.77 (t, J = 5.9 Hz, 2H, NCH_2), 2.59 (m, 4H, NCH_2), 2.42 (s, 3H, NCH_3), 1.80−2.20 (m, 4H), 1.61 (m, 2H).

(±)-3-[2-(Diphenylmethoxy)ethyl]-3,9-diazabicyclo[4.2.1]-nonane (30). Synthesized from 3-[2-(diphenylmethoxy)ethyl]-3,9-diazabicyclo[4.2.1]nonane **(28)** according to method A: CI-MS (NH_3) *m*/*z* 337 (M + 1); ^{1}H NMR ($CDCl_3$) δ 7.31 (m, 10H, ArH), 5.36 (s, 1H, ArCHAr), 3.68 (t, J = 7.3 Hz, 1H, NCH), 3.53 (t, J = 5.9 Hz, 3H, NCH + OCH_2), 2.77 (t, J = 5.9 Hz, 2H, NCH_2), 2.66 (dd, J = 7.8 Hz, J = 2.9 Hz, 2H, NCH_2), 2.59 (brs, 2H, NCH_2), 1.67 (m, 6H).

(±)-3-{2-[Bis(4-fluorophenyl)methoxy]ethyl}-3,9-diazabicyclo[4.2.1]nonane (31). Synthesized from 3-{2-[bis-(4-fluorophenyl)methoxy]ethyl}-9-methyl-3,9-diazabicyclo[4.2.1]-nonane **(29)** according to method A: CI-MS (NH_3) *m*/*z* 373 (M + 1); ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 4H, ArH), 7.01 (t, J = 8.8 Hz, 4H, ArH), 5.33 (s, 1H, ArCHAr), 3.66 (t, J = 7.3 Hz, 1H, NCH), 3.54 (d, J = 7.8 Hz, 1H, NCH), 3.49 (t, J = 5.9 Hz, 2H, OCH_2), 2.75 (t, J = 5.9 Hz, 2H, NCH_2), 2.63 (m, 2H, NCH_2), 2.56 (d, J = 2.9 Hz, 2H, NCH_2), 1.65 (m, 6H).

(±)-3-[2-(Diphenylmethoxy)ethyl]-9-(3-phenylpropyl)-3,9-diazabicyclo[4.2.1]nonane (32). Prepared from 3-[2-(diphenylmethoxy)ethyl]-9-methyl-3,9-diazabicyclo[4.2.1]-nonane **(30)** according to method D: CI-MS (NH_3) *m*/*z* 455 (M + 1); ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 15H, ArH), 5.37 (s, 1H, ArCHAr), 3.51 (t, J = 5.9 Hz, 2H, OCH_2), 3.32 (t, J = 7.5 Hz, 1H, NCH), 3.22 (d, J = 7.5 Hz, 1H, NCH), 2.73 (t, J = 6.5 Hz, 2H, NCH_2), 2.63 (m, 8H, NCH_2 + $ArCH_2$), 1.43−2.06 (m, 8H).

(±)-3-{2-[Bis(4-fluorophenyl)methoxy]ethyl}-9-(3-phenylpropyl)-3,9-diazabicyclo[4.2.1]nonane (33). Prepared by *N*-demethylation of 3-{2-[bis(4-fluorophenyl)methoxy]-ethyl}-9-methyl-3,9-diazabicyclo[4.2.1]nonane **(29)** according to method A, followed by an *N*-alkylation according to method D: CI-MS (NH_3) *m*/*z* 490 (M + 1); ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 9H, ArH), 7.01 (t, J = 8.8 Hz, 4H, ArH), 5.33 (s, 1H, ArCHAr), 3.47 (t, J = 5.9 Hz, 2H, OCH_2), 3.34 (t, J = 7.3 Hz, 1H, NCH), 3.23 (d, J = 7.8 Hz, 1H, NCH), 2.72 (t, J = 5.9 Hz, 2H, NCH_2), 2.63 (m, 8H, NCH_2 + $ArCH_2$), 1.40−2.08 (m, 8H).

Biological Methods. Binding assays for the DAT and SERT followed published procedures[46] and used 0.01 nM [^{125}I]-RTI-55 (s.a. = 2200 Ci/mmol). Briefly, 12 × 75 mm polystyrene test tubes were prefilled with 100 μL of drug, 100 μL of radioligand ([^{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% poly(ethylenimine).

The [^{3}H]DA and [^{3}H]5-HT uptake assays also proceeded according to published procedures.[46] Briefly, synaptosomes were prepared by homogenization of rat caudate (for [^{3}H]DA reuptake) or whole rat brain minus cerebellum (for [^{3}H]5-HT 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 prefilled with 750 μL of [^{3}H]DA or [^{3}H]5-HT (final concentration of 5 nM and 2 nM, 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 **3** ([^{3}H]DA) and 10 μM fluoxetine ([^{3}H]5-HT). The incubations were terminated after 20 min ([^{3}H]DA) or 30 min ([^{3}H]5-HT) 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.

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