Synthesis and Biological Evaluation of Tropane-like 1-{2-[Bis(4-fluorophenyl)methoxy]ethyl}-4-(3-phenylpropyl)piperazine (GBR 12909) Analogues

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We have prepared azabicyclo[3.2.1] derivatives (C-3-substituted tropanes) that bind with high affinity to the dopamine transporter and inhibit dopamine reuptake. Within the series, 3-{2-[bis-(4-fluorophenyl)methoxy]ethylidene}-8-methyl-8-azabicyclo[3.2.1]octane (**8**) was found to have the highest affinity and selectivity for the dopamine transporter. These azabicyclo[3.2.1] (bridged piperidine) series of compounds differ from the well-known benztropines by a 2-carbon spacer between C-3 and a diarylmethoxy moiety. Interestingly, these new compounds demonstrated a much lower affinity for the muscarinic-1 site, at least a 100-fold decrease compared to benztropine. Replacing *N*-methyl with *N*-phenylpropyl in two of the compounds resulted in a 3−10-fold increase in binding affinity for the dopamine transporter. However, those compounds lost selectivity for the dopamine transporter over the serotonin transporter. Replacement of the ether oxygen in the diarylmethoxy moiety with a nitrogen atom gave relatively inactive amines, indicating the important role which is played by the ether oxygen in transporter binding. Reduction of the C-3 double bond in **8** gave 3α-substituted tropanes, as shown by X-ray crystallographic analyses of **11**, **12**, and **19**. The 3α-substituted tropanes had lower affinity and less selectivity than the comparable unsaturated ligands.

Introduction

The widespread abuse of cocaine (**1**) has played a major role in transmitting acquired immune deficiency syndrome and hepatitis.[1−4] This abuse is, obviously, detrimental to public health and public safety, and that has stimulated our efforts to study the mechanism of the action of cocaine on the central nervous system (CNS) and its behavioral consequences and to attempt to develop effective medications for the treatment of cocaine abuse.[5,6]

It has been hypothesized that the interaction of cocaine with the dopamine transporter (DAT) blocks reuptake of dopamine into presynaptic neurons, resulting in an increase of dopamine in the synapse.[7−11] This elevation of extracellular dopamine (ECDA) is believed to be the cause of cocaine's euphoric and reinforcing effects, leading us to attempt to develop compounds with high affinity and selectivity for the dopamine transporter. Our assumption is that an agent with high affinity, a slow dissociation rate, and low intrinsic activity at the cocaine binding site should behave as a noncompetitive inhibitor, thereby suppressing the effect of cocaine-mediated elevation of the extracellular dopamine level.[12]

Previous SAR studies have resulted in the identification of a number of structurally diverse dopamine transporter ligands. Among these are the cocaine analogue series (**2**),[11,13] the benztropine series (**3**),[14−16] and the GBR series of compounds (**4**).[17−19] We have focused our efforts on the SAR study of GBR analogues because of their promising neurochemical and pharmacological profiles. The *N*,*N*′-disubstituted piperazines, 1-[2-(diphenylmethoxy)ethyl]-4-(3-phenylpropyl)piperazine (GBR 12935) and 1-{2-[bis(4-fluorophenyl)methoxy]-ethyl}-4-(3-phenylpropyl)piperazine (GBR 12909) (**4a** and **4b**, Chart 1), were among the first agents characterized as selective and potent dopamine uptake inhibitors.[20,21] Behavioral studies in animal models have demonstrated that administration of **4b** decreases cocaine-maintained responding in rhesus monkeys without affecting normal food intake.[22,23] Recently, Glowa et al. carried out a behavioral study with rhesus monkeys administered an extended-action formulation of **4b**.[6] Their preliminary data showed that a single treatment with the decanoate ester of the benzylic hydroxyl in **4b** (**4c**, Chart 1) resulted in a sustained and selective suppression of cocaine self-administration for almost 30 days without affecting food-seeking behavior.

An extensive SAR study on **4a** and **4b** has been carried out since their identification as selective and potent dopamine uptake inhibitors.[20,21] A series of bridged piperazine GBR derivatives, where the pipera-

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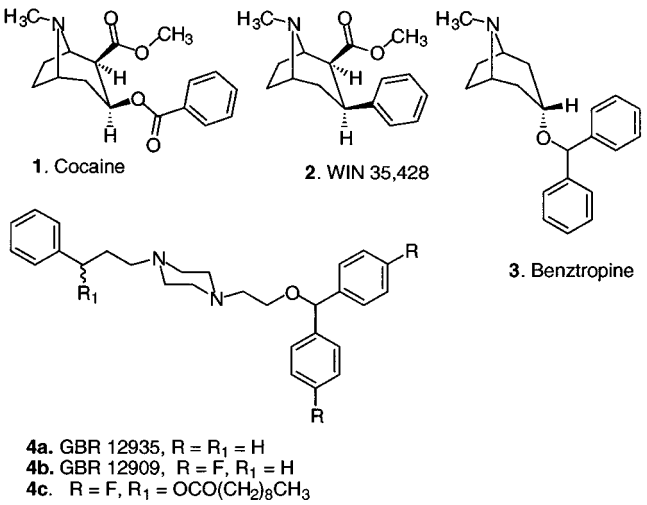
Chart 1



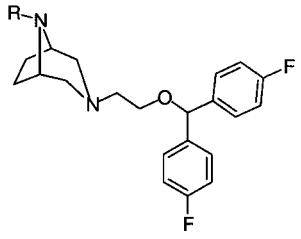
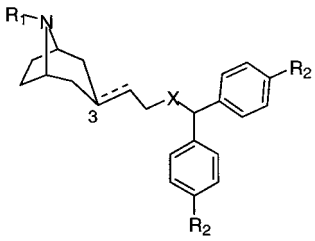
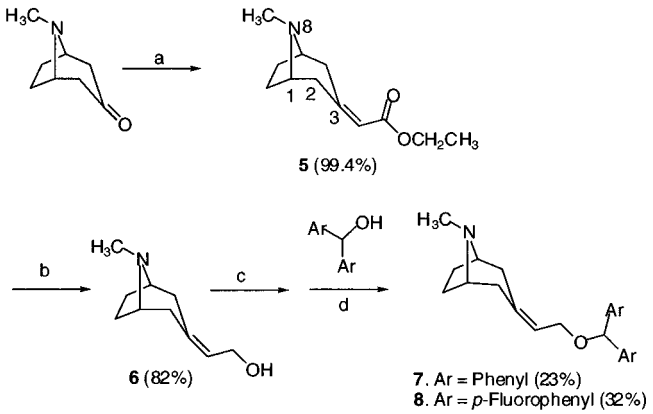


Chart 2



zine moiety in **4b** was replaced by a 3,8-diaza[3.2.1]-bicyclooctane template,[24] were among the novel structures to emerge from the study. Thus, 3-{2-[bis(4-fluorophenyl)methoxy]ethyl}-8-methyl-3,8-diazabicyclo-[3.2.1]octane (**4d**) and 3-{2-[bis(4-fluorophenyl)methoxy]-ethyl}-8-(3-phenylpropyl)-3,8-diazabicyclo[3 .2.1]octane (**4e**) (Chart 1) were designed as GBR-like diazabicyclo compounds. Dopamine transporter binding data showed that **4d** and **4e** possessed high affinity for the dopamine transporter (K_i = 8 nM for both) and high potency in dopamine uptake inhibition (K_i = 9.6 and 18.7 nM, respectively).[24] However, Dutta et al. noted that the nitrogen proximal to the diphenylmethoxyethyl chain in **4b** is not essential for maintaining high affinity and selectivity for the dopamine transporter.[25,26] Application of this finding to our bridged piperazine[24] series has given us a group of novel bridged piperidine analogues, C-3-substituted tropanes (Chart 2). Introduction of a tropane ring resulted in compounds that are structurally similar to benztropine. It is known that analogues in the benztropine series bind to the dopamine transporter with high affinity and inhibit dopamine uptake,

Scheme 1[a]



[a] a: Triethyl phosphonoacetate, NaH, THF, 0 °C to room temperature. b: 1.0 M, $LiAlH_4$, reflux. c: NaH, TsCl, THF. d: NaH, THF.

but without increasing the locomotor activity or cocaine-like subjective effects in drug discrimination models in rodents.[15,16] We now report on the synthesis and preliminary biological evaluation of a series of C-3-substituted tropane derivatives, derived from structural modification of the lead 3,8-diazabicyclo[3.2.1]octane compounds **4d** and **4e**.

Chemistry

The α,β-unsaturated ester **5** was synthesized using a Wadsworth−Horner−Emmons protocol[27] on 3-tropinone with triethyl phosphonoacetate in tetrahydrofuran (THF) in the presence of NaH. Reduction of the resulting ester **5** with 1 M $LiAlH_4$ in THF, followed by ether formation with benzhydrol or 4,4′-difluorobenzhydrol gave the unsaturated ethers **7** and **8** (Scheme 1). Synthesis of the saturated ethers **11** and **12** proceeded through a catalytic hydrogenation of the ester **5** (Scheme 2) because the double bond in compounds **6**−**8** was resistant to catalytic hydrogenation conditions. The saturated ester **9** was then reduced by 1 M $LiAlH_4$ in THF to the alcohol, followed by ether formation with benzhydrol or the substituted benzhydrol to afford **11** and **12**. *N*-Demethylation of **11** and **12** was accomplished using trichloroethyl chloroformate in refluxing toluene, followed by treatment of the resulting carbamates with Zn in HOAc at room temperature. *N*-Alkylation of the nor compounds with 1-iodo-3-phenylpropane in THF resulted in the final products **13** and **14**. Synthesis of amides **16** and **17** proceeded via amide formation between the ester **5** and amines under Weinreb conditions,[28] using trimethylaluminum as an activating agent. The double bond was reduced using catalytic hydrogenation in the presence of 10% Pd on activated carbon to afford **18** and **19**, followed by reduction of the amide function using 1.0 M AlH_3 in THF to give the final products **20** and **21**, respectively (Scheme 3). All final amine products were further purified through salt formation with organic or inorganic acids, as listed in Table 1, and recrystallization from suitable organic solvents.

Results and Discussion

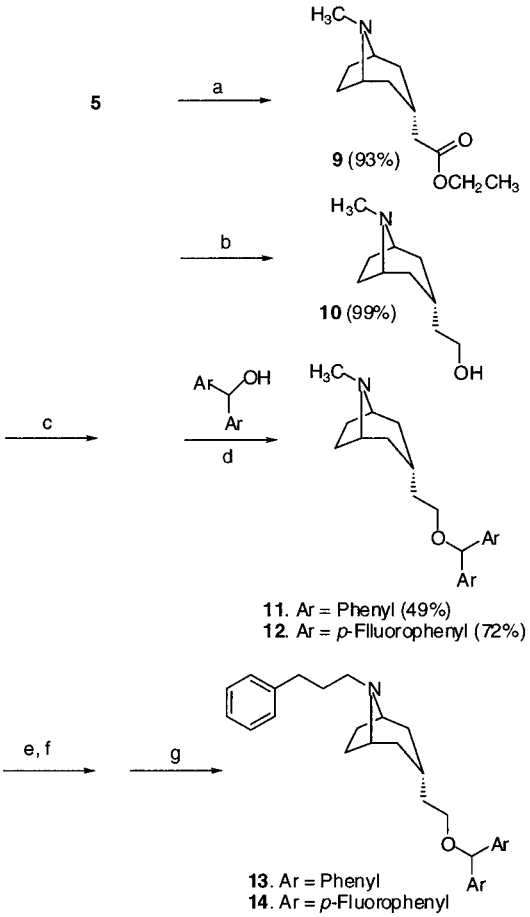
The bridged piperidine C-3-substituted analogues were evaluated for displacement of radio labeled ligand [^{125}I]RTI-55 at the dopamine and serotonin transporters,

Table 1. Physical Properties of the Ligands

no.[a]	salt	solvent	mp (°C)	CI-MS (*m/z*)	analysis[b]
5	HCl	ethyl acetate	189-90	210	$C_{12}H_{19}NO_2$·HCl
7	HCl	MeOH/acetone	240 (dec)	333	$C_{23}H_{27}NO$·HCl
8	HCl	MeOH/acetone	162-4	369	$C_{23}H_{25}NOF_2$·HCl
11	HCl	acetone	218-9	335	$C_{23}H_{29}NO$·HCl
12	fumarate	acetone	177-8	371	$C_{23}H_{27}NOF_2$·$C_4H_4O_4$
13	HCl[c]	ether	133[d]	439	$C_{31}H_{37}NO$·HCl·0.75H_2O
14	HCl[c]	ether	104[d]	475	$C_{31}H_{35}NOF_2$·HCl·1.75H_2O
16	HCl	EtOAc/*i*-PrOH	264 (dec)	346	$C_{23}H_{26}N_2O$·HCl
17	HCl	EtOAc/MeOH	226 (dec)	382	$C_{23}H_{24}N_2OF_2$·HCl
18	HCl	acetone/MeOH	300 (dec)	348	$C_{23}H_{28}N_2O$·HCl
19	HCl	acetone/MeOH	276-8	384	$C_{23}H_{26}N_2OF_2$·HCl
20	HCl	acetone/MeOH	311 (dec)	334	$C_{23}H_{30}N_2$·2HCl
21	HCl	acetone/EtOH	277 (dec)	370	$C_{23}H_{28}N_2F_2$·2HCl

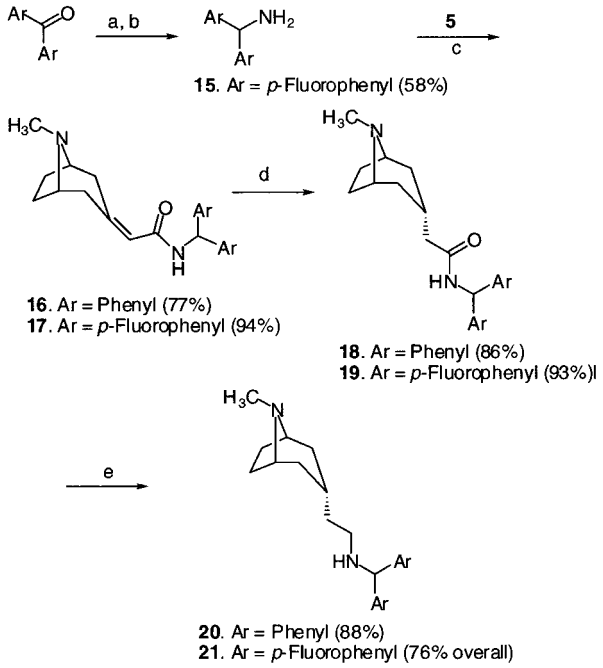
[a] The ^{1}H NMR data for the free base of these compounds are shown in the Experimental Section. [b] Elemental compositions (%) were found to be within ±0.4% of the theoretical values of C, H, and N. [c] HCl salt was triturated from ether. [d] Softens.

Scheme 2[a]



[a] a: H_2, 10% Pd on carbon, MeOH. b: 1.0 M $LiAlH_4$, reflux. c: NaH, THF. d: NaH, TsCl, THF. e: 2,2,2-Trichloroethyl chloroformate, K_2CO_3, toluene, reflux. f: Zn, HOAc, room temperature. g: 1-Iodo-3-phenylpropane, K_2CO_3, THF, reflux.

Scheme 3[a]



[a] a: NH_2OH, HCl, EtOH, reflux. b: 1.0 M $LiAlH_4$ in THF, reflux. c: 2 M $Al(CH_3)_3$ in toluene, CH_2Cl_2, reflux. d: H_2, 10% Pd on carbon, EtOH. e: 1.0 M AlH_3, THF, room temperature.

as well as inhibitory activities for dopamine and serotonin reuptake. Given the fact that benztropine is a potent muscarinic receptor ligand, we also tested the binding affinity of the bridged piperidine C-3-substituted compounds at the muscarinic-1 (M_1) receptor labeled with [^{3}H]pirenzepine. All of the tropane-like analogues with a *p*-fluoroaryl substituent (**8**, **12**, **14**, **17**, **19**, and **21**) displayed higher binding affinity at the dopamine transporter (Table 2) and were more potent in inhibition of dopamine reuptake than their corresponding nonfluorinated analogues (**7**, **11**, **13**, **16**, **18**, and **20**). This is consistent with previous studies in the GBR series where aromatic substituents that combined a large inductive effect and a small volume provided the most potent compounds for inhibition of dopamine reuptake.[20] All compounds showed higher potency at inhibition of DA uptake compared to serotonin uptake. However, the *p*-fluoro-substituted compounds generally showed greater selectivity for DA uptake when compared to the unsubstituted derivatives. An exception was the *N*-phenylpropyl analogue with a saturated C-3 side chain, **13**, which was much less selective and, like **14**, relatively promiscuous in its interaction with DAT and SERT. Compounds **13** and **14** are analogues of the much more selective, higher affinity, and potent GBR compounds **4a** and **4b**. It is interesting to note that compounds in our series followed the same trend in binding affinity at the dopamine transporter and inhibitory activity for dopamine reuptake.

3-{2-[Bis-(4-fluorophenyl)methoxy]ethylidene}-8-methyl-8-azabicyclo[3.2.1]octane exhibited the highest binding affinity (K_i = 19 nM) for the dopamine transporter and the highest activity in dopamine reuptake inhibition

Table 2. Binding Affinities for the Dopamine and Serotonin Transporters Labeled with [^{125}I]RTI-55 and the Muscarinic (M_1) Receptor Labeled with [^{3}H]Pirenzepine, and Their Potencies for DA and 5-HT Reuptake Inhibition

	binding K_i (nM ± SEM)		reuptake K_i (nM ± SEM)		5-HT/DA ratios		muscarinic K_i (nM ± SEM)
no.	DAT	SERT	[3H]DA	[3H]5-HT	binding	reuptake	M1
3	237 ± 8[a]	5150 ± 165[a]	130 ± 7	18500 ± 1400	22	147	0.59 ± 0.01[b]
4a	3.7 ± 0.2[c]	620 ± 22[c]	3.7[c]	290[c]	168	78	
4b	3.7 ± 0.4[c]	130 ± 5[c]	4.3[c]	73[c]	35	17	
7	130 ± 5	8300 ± 430	190 ± 18	8100 ± 361	64	43	94 ± 3
8	19 ± 1	3600 ± 210	35 ± 1	5000 ± 170	189	143	200 ± 18
11	280 ± 15	15 ± 2 (μM)	260 ± 13	12 ± 0.6 (μM)	54	46	56 ± 3
12	52 ± 2	4100 ± 180	80 ± 3	4100 ± 125	79	51	130 ± 7
13	28 ± 3	170 ± 11	120 ± 5	570 ± 25	6	5	78 ± 2
14	19 ± 2	79 ± 2	78 ± 4	430 ± 14	4	6	170 ± 5
16	2300 ± 80	78 ± 4 (μM)	880 ± 36	60 ± 2 (μM)	34	68	1700 ± 40
17	500 ± 12	19 ± 0.6 (μM)	240 ± 7	17 ± 0.6 (μM)	38	71	2500 ± 140
18	30 ± 2.5 (μM)	120 ± 10 (μM)	7900 ± 400	100 ± 10 (μM)	4	13	1200 ± 50
19	3400 ± 121	69 ± 8.4 (μM)	1800 ± 60	60 ± 3 (μM)	20	33	1200 ± 60
20	3800 ± 120	43 ± 2 (μM)	1100 ± 60	14 ± 0.5 (μM)	11	13	340 ± 10
21	270 ± 5	30 ± 5 (μM)	160 ± 6	7100 ± 290	111	44	630 ± 50

[a] See ref 31. [b] See ref 39. [c] See ref 36.

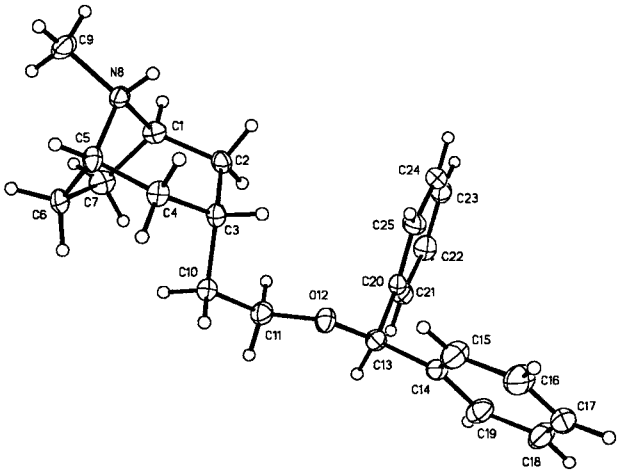


Figure 1. X-ray structure for 3-(2-benzhydryloxyethyl)-8-methyl-8-azabicyclo[3.2.1]octane (**11**), with displacement ellipsoids drawn at the 20% probability level.

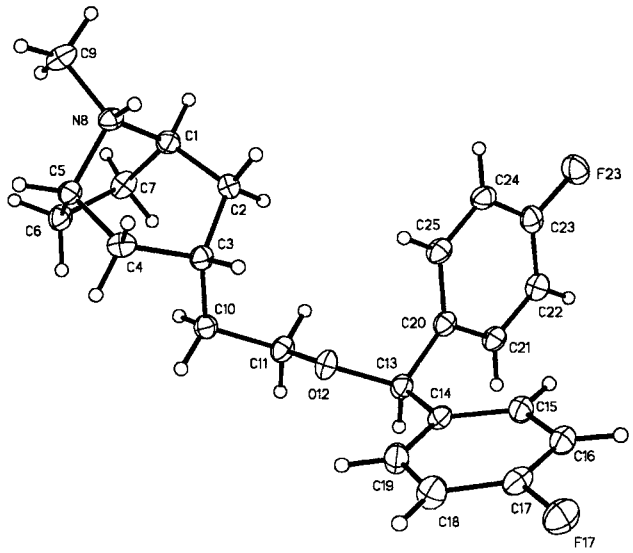


Figure 2. X-ray structure 3-{2-[bis(4-fluorophenyl)methoxy]-ethyl}-8-methyl-8-azabicyclo[3.2.1]octane (**12**), with displacement ellipsoids drawn at the 20% probability level.

(K_i = 35 nM) among all the new compounds tested in the series. This compound was also the most selective for binding at the dopamine transporter over the serotonin transporter (about 190-fold) as well as reuptake inhibition for dopamine over serotonin (about 140-fold), showing a selectivity comparable to that of **4a**. Compound **12**, with a C-3α single bond (Figure 2) rather than the double bond in **8**, exhibited about a 3-fold decrease in binding affinity at the dopamine transporter while retaining affinity at the serotonin transporter, resulting in a decrease in selectivity for the dopamine transporter site. The saturated amides **18** and **19** and unsaturated amides **16** and **17** possess low to negligible affinity for both transporters and are ineffective reuptake inhibitors.

The C-3 substituent on the tropane ring in **11**, **12**, and **19** was determined to be in the α-configuration and the piperidine ring is in, or close to, a chair conformation, using single-crystal X-ray crystallographic analyses (Figures 1−3). We presume that the C-3 substituent on the tropane ring in **13** and **14** exists in the α-configuration. We also presume that the *N*-phenylpropyl relatives (**13** and **14**) of the *N*-methyl compounds, **11** and **12**, respectively, as well as **18** and **19**−**21**, bear the α-configuration. It should be noted that both cocaine and

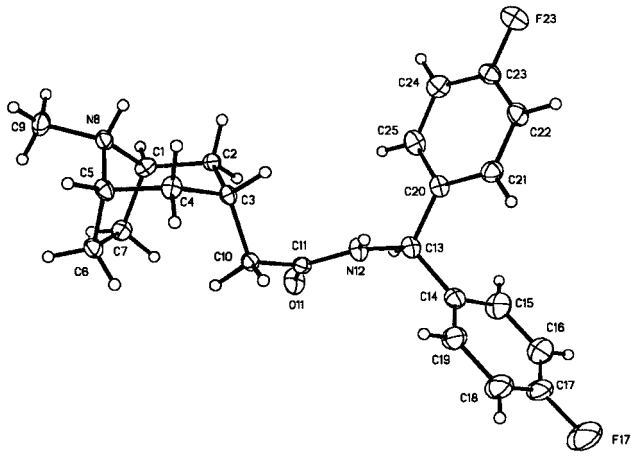


Figure 3. X-ray structure *N*-[bis(4-fluorophenyl)methyl]-2-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)acetamide (**19**), with displacement ellipsoids drawn at the 20% probability level.

8-methyl-3β-phenyl-8-azabicyclo[3.2.1]octane-2β-carboxylic acid methyl ester (WIN 35,428) have the C-3 substituent in the β-configuration whereas our com-

pounds in the benztropine series have a 3α-diarylmethoxy side chain (Chart 1). Recently, Carroll et al. have reported the preparation of a number of 3*β*-(4′-substituted phenyl)tropane-2*β*-carboxlic acid methyl esters.[13] These WIN-like compounds were noted to exist in a twist-boat conformation and were reported to be slightly less potent at the dopamine transporter, but more selective for the dopamine transporter over the serotonin transporter in comparison with the corresponding 3α-isomers.[29] Moreover, recent work by Kozikowski et al. confirmed that both the ring conformation and the stereochemistry at C-3 influence the binding affinity and selectivity of cocaine-like compounds at the dopamine transporter.[30] If this relates as well to unsaturated compounds such as **8**, then it is possible that the conformation of **8** would be closer to that of the C-3*β* series than the C-3α series, since we find that **8** has higher affinity at the dopamine transporter and better selectivity relative to the serotonin transporter than any of the C-3α compounds.

Compounds **16**−**21** result from replacement of the ether oxygen in **11** and **12** with nitrogen containing functional groups. Amides **16**−**19** and amines **20** and **21** show little affinity for the dopamine transporter. Among the compounds **16**−**21**, **21** displayed slight affinity for the dopamine transporter, 12-fold higher than the corresponding amide compound **19**. The amines **20** and **21** also showed decreased dopamine transporter binding compared with the corresponding ether analogues **7, 8**, and **12**−**14**. The oxygen atom in the diarylmethoxy moiety appears to be important in this series for the high affinity and selectivity for dopamine transporter binding. It may be informative to further derivatize the secondary amine function in the future and investigate the binding properties of those compounds.

Benztropine (**3**) possesses subnanomolar affinity at the M_1 receptor (Table 2) and has only moderate affinity for the dopamine transporter.[31] Our GBR-tropane derivatives (bridged piperidine series of compounds) differ from the benztropine series only by an ethylene spacer between the C-3 and the diarylmethoxy moiety. Interestingly, these GBR-tropane derivatives demonstrated a much lower affinity for the M_1 site, showing at least a 100-fold decrease in binding affinity compared to benztropine (Table 2). Compound **8**, the most active and selective dopamine transporter ligand of the series, exhibited a K_i value of 200 nM at the M_1 site, a >300-fold decrease in binding affinity compared with benztropine and a 30-fold lower M_1-receptor affinity than the known 4,4′-difluoro aromatic substituted benztropine.[16]

In conclusion, we have prepared a series of GBR-tropane derivatives and we have found that some of them bind with high affinity to the dopamine transporter and effectively inhibit dopamine reuptake. Within the series, **8** displayed the highest affinity and selectivity for the dopamine transporter. It should be noted that compound **8** is a racemic mixture. Considering the fact that stereoselective binding has been evident throughout the cocaine and tropane analogue series,[10,32−34] and GBR compounds were also reported to bind to the dopamine transporter in an enantioselective fashion,[35] it will be of interest to further investigate the binding properties of both of the enantiomers of **8**.

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 (Table 3). CI-MS (chemical ionization mass spectra) were performed using a Finnigan 1015 mass spectrometer. ^{1}H NMR spectra of free bases were obtained on a Varian XL-300 spectrometer in $CDCl_3$. All the chemical shifts reported are relative to a tetramethylsilane (TMS) internal reference in parts per million on the δ scale. Thin-layer chromatography (TLC) was performed on Analtech GHLF silica gel plates (250 μm) with a solvent system of 90:9:1 $CHCl_3$/MeOH/concentrated NH_4OH or as otherwise indicated. No attempt was made to optimize the reaction yields reported.

General Method A. Ester Reduction. A solution of the ester in THF (40 mmol of ester in 10 mL of THF) was added dropwise via addition funnel to a stirred solution of 1.0 M $LiAlH_4$ in THF at reflux. The molar ratio of ester to $LiAlH_4$ was approximately 1:5. The reaction mixture was heated at reflux until TLC showed the completion of the reaction. Excess $LiAlH_4$ was decomposed by slow addition of 1 wt equiv of water, 1 wt equiv of 15% aqueous NaOH solution, and 3 wt equiv of water while cooling in an ice water bath, and the obtained slurry was allowed to stir at room temperature for 1 h. The white precipitate was filtered off through Celite, and the filtrate was concentrated on a Rotavapor and then redissolved in CH_2Cl_2. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated to give the alcohol as a light beige colored oil. The product was usually pure enough for the next step.

Method B. Ether Formation. To a slurry of 1.65 equiv of NaH (60% in mineral oil, washed twice with petroleum ether) in anhydrous THF was added slowly a solution of 1.5 equiv of diarylmethyl alcohol in anhydrous THF. The mixture was allowed to stir at room temperature for 10 min before being added to a solution of 1.5 equiv of TsCl in THF. The mixture was allowed to stir at room temperature for 5 min.

To another slurry of 1.1 equiv of NaH in anhydrous THF was added slowly a solution of 1 equiv of the primary alcohol in anhydrous THF. After 10 min of stirring at room temperature, the above tosylate of diarylmethyl alcohol was added, and the mixture was allowed to stir until TLC showed the completion of the reaction. The reaction was quenched by addition of water. The layers were separated and the aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with water and brine, dried over Na_2SO_4 , and evaporated to give the product mixture, which was then purified by salt formation or by column chromatography prior to salt formation.

Method C. Catalytic Hydrogenation. A solution of the unsaturated compound in methanol or ethanol was hydrogenated in the presence of 10% Pd on activated carbon until TLC showed the completion of the reaction. The catalyst was then removed by filtration through Celite, and the filtrate was evaporated to afford the saturated product as an oil, which was usually pure enough for the next step.

Method D. 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 at room temperature. The molar ratio of amide to AlH_3 was approximately 1:5. The reaction mixture was stirred at room temperature until TLC showed the disappearance of the amide. The reaction was then quenched by slowly pouring the mixture into a 15% aqueous NaOH solution cooled 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 suitable solvent.

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

1.5 equiv of K_2CO_3 in toluene (10 mmol of *N*-methyl compound in 100 mL of solvent) was heated at reflux overnight. The solution was washed with water, extracted once with 15% aqueous citric acid solution, then washed with water and brine, dried over Na_2SO_4, and evaporated to give a light yellow colored oil. The obtained oil was then dissolved in HOAc (10 mmol of carbamate in 100 mL of 99.7% HOAc), and Zn powder was added. The suspension was vigorously stirred at room temperature until TLC showed the disappearance of the carbamate. The solvent was removed in vacuo with an equal volume of toluene, and the residue was dissolved in CH_2Cl_2. The CH_2Cl_2 solution containing a small amount of Zn powder was extracted three times with a 15% aqueous citric acid solution. The combined aqueous layer was washed once with CH_2Cl_2, basified with concentrated NH_4OH, and extracted 3 times with CH_2Cl_2. The organic extracts were combined and washed with water and brine, dried over Na_2SO_4, and evaporated to give the *N*-demethylated product as a colorless oil. The product was usually pure enough by TLC for the next step.

Method F. *N*-Alkylation. A solution of the 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 to K_2CO_3 was 1:1.5:2. THF was then evaporated, and the mixture was suspended in CH_2Cl_2. The organic suspension was washed with water and brine and dried over Na_2SO_4, and solvent was removed to give the crude product which was purified by salt formation or column chromatography prior to salt formation.

8-Methyl-8-azabicyclo[3.2.1]oct-3-ylidene)acetic Acid Ethyl Ester (5). To a slurry of 6.4 g (0.16 mole) of NaH (60% in mineral oil, washed twice with petroleum ether) in 50 mL of anhydrous THF cooled in an ice water bath was added slowly a solution of 35.8 g (0.16 mol) of triethyl phosphonoacetate in 10 mL of anhydrous THF via addition funnel. The mixture was allowed to stir at room temperature for 1 h during which time the light yellow solution gradually turned into a thick gellike mixture. A solution of 11.1 g (0.08 mol) of 3-tropinone in 20 mL of anhydrous THF was then added slowly through an addition funnel, and the reaction mixture was stirred vigorously overnight. Water was added and the layers were separated. The aqueous layer was then extracted with CH_2Cl_2. The combined organic layer was washed with water twice before being extracted with 15% aqueous citric acid solution. The aqueous extracts were combined and washed once with CH_2Cl_2, basified with concentrated NH_4OH, and then extracted with CH_2Cl_2. The organic solution was dried over Na_2SO_4 and evaporated to give 16.6 g of the α,β-unsaturated ester **5** as a light beige colored oil. CI-MS (NH_3) *m/z* 210 (MH^+); ^{1}H NMR ($CDCl_3$) δ (ppm) 1.28 (t, J = 6.9 Hz, 3H, CH_3), 1.51 (m, 2H, $H_{6,7endo}$), 1.97 (m, 3H, $H_{6,7exo}$ + H_{2ax}), 2.38 (s + m, 4H, NCH_3 + H_{4ax}), 2.69 (brd, J = 13.7 Hz, 1H, H_{2eq}), 3.25 (brs, 2H, $H_{1,5}$), 3.50 (brd, J = 15.1 Hz, 1H, H_{4eq}), 4.14 (q, J = 6.6 Hz, 2H, OCH_2), 5.69 (s, 1H, olefinic H). Anal. ($C_{12}H_{19}NO_2$•HCl) C, H, N.

2-(8-Methyl-8-azabicyclo[3.2.1]oct-3-ylidene)ethanol (6). This compound was synthesized from **5** according to general method A. CI-MS (NH_3) *m/z* 168 (MH^+); ^{1}H NMR ($CDCl_3$) δ (ppm) 1.38−1.56 (m, 2H, $H_{6,7endo}$), 1.94 (m, 3H, H_{2ax} + $H_{6,7exo}$), 2.28 (m, 2H, H_{2eq}, H_{4ax}), 2.32 (s, 3H, NCH_3), 2.57 (brd, J = 14.4 Hz, 1H, H_{4eq}), 3.18 (m, 2H, $H_{1,5}$), 4.14 (m, 2H, CH_2OH), 5.48 (t, J = 6.7 Hz, 1H, olefinic H).

3-(2-Benzhydryloxyethylidene)-8-methyl-8-azabicyclo-[3.2.1]octane (7). This compound was prepared from an ether formation between **6** and benzhydrol according to general method B. CI-MS (NH_3) *m/z* 334 (MH^+); ^{1}H NMR ($CDCl_3$) δ (ppm) 1.38−1.56 (m, 2H, $H_{6,7endo}$), 1.91 (m, 3H, $H_{6,7exo}$ + H_{2ax}), 2.15 (m, 2H, H_{2eq}, H_{4ax}), 2.32 (s, 3H, NCH_3), 2.56 (brd, J = 13.7 Hz, 1H, H_{4eq}), 3.16 (m, 2H, $H_{1,5}$), 4.00 (m, 2H, CH_2O), 5.40 (s, 1H, ArCHAr), 5.50 (t, J = 6.8 Hz, 1H, olefinic H), 7.33 (m, 10H, ArH). Anal. ($C_{23}H_{27}NO$•HCl) C, H, N.

3-{2-[Bis-(4-fluorophenyl)methoxy]ethylidene}-8-methyl-8-azabicyclo[3.2. 1]octane (8). This compound was prepared from an ether formation between **6** and 4,4′-difluorobenzhydrol according to general method B. CI-MS (NH_3) *m/z* 370 (MH^+); ^{1}H NMR ($CDCl_3$) δ (ppm) 1.44 (t, J = 8.8 Hz, 1H, H_{6endo}), 1.58 (t, J = 8.8 Hz, 1H, H_{7endo}), 1.96 (m, 3H, $H_{6,7exo}$ + H_{2ax}), 2.14 (brd, J = 14.7 Hz, 1H, H_{4ax}), 2.32 (brd, J = 14.7 Hz, 1H, H_{2eq}), 2.39 (s, 3H, NCH_3), 2.70 (brd, J = 13.7 Hz, 1H, H_{4eq}), 3.26 (m, 2H, $H_{1,5}$), 3.97 (m, 2H, CH_2O), 5.35 (s, 1H, ArCHAr), 5.51 (t, J = 6.4 Hz, 1H, olefinic H), 7.02 (t, J = 9.3 Hz, 4H, ArH), 7.28 (dd, J = 8.3 Hz, J = 2.9 Hz, 4H, ArH). Anal. ($C_{23}H_{25}NOF_2$•HCl) C, H, N.

(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)acetic Acid Ethyl Ester (9). This compound was synthesized from **5** according to general method C. CI-MS (NH_3) *m/z* 212 (MH^+); ^{1}H NMR ($CDCl_3$) δ (ppm) 1.25 (t, J = 7.1 Hz, 3H, CH_3), 1.32 (brs, 1H, H_3), 1.63 (m, 2H, $H_{6,7endo}$), 2.04−2.31 (m, 6H, $H_{2,4}$ + $H_{6,7exo}$), 2.26 (s, 3H, NCH_3), 2.46 (d, J = 8.0 Hz, 2H, CH_2CO), 3.10 (brs, 2H, $H_{1,5}$), 4.12 (q, J = 7.2 Hz, 2H, OCH_2).

2-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)ethanol (10). This compound was synthesized from **9** according to general method A. CI-MS (NH_3) *m/z* 170 (MH^+); ^{1}H NMR ($CDCl_3$) δ (ppm) 1.31 (m, 2H, $H_{6,7endo}$), 1.66 (m, 2H, $H_{6,7exo}$), 1.75 (t + m, J = 6.5 Hz, 3H), 2.00−2.18 (m, 4H, $H_{2,4}$), 2.24 (s, 3H, NCH_3), 3.09 (m, 2H, $H_{1,5}$), 3.64 (t, J = 6.6 Hz, 2H, CH_2OH).

3-(2-Benzhydryloxyethyl)-8-methyl-8-azabicyclo[3.2.1]-octane (11). This compound was prepared from an ether formation between **10** and benzhydrol according to general method B. CI-MS (NH_3) *m/z* 336 (MH^+); ^{1}H NMR ($CDCl_3$) δ (ppm) 1.34 (m, 2H, $H_{6,7endo}$), 1.65 (m, 2H, $H_{6,7exo}$), 1.83 (m, 3H), 2.01−2.15 (m, 4H, $H_{2,4}$), 2.26 (s, 3H, NCH_3), 3.08 (brs, 2H, $H_{1,5}$), 3.45 (t, J = 6.3 Hz, 2H, OCH_2), 5.31 (s, 1H, ArCHAr), 7.33 (m, 10H, ArH). Anal. ($C_{23}H_{29}NO$•HCl) C, H, N.

3-{2-[Bis-(4-fluorophenyl)methoxy]ethyl}-8-methyl-8-azabicyclo[3.2.1]octane (12). This compound was prepared from an ether formation between **10** and 4,4′-difluorobenzhydrol according to general method B. CI-MS (NH_3) *m/z* 372 (MH^+); ^{1}H NMR ($CDCl_3$) δ (ppm) 1.33 (m, 2H, $H_{6,7endo}$), 1.65 (m, 2H, $H_{6,7exo}$), 1.82 (m, 3H), 2.02−2.27 (m, 4H, $H_{2,4}$), 2.30 (s, 3H, NCH_3), 3.14 (brs, 2H, $H_{1,5}$), 3.42 (t, J = 6.3 Hz, 2H, OCH_2), 5.27 (s, 1H, ArCHAr), 7.00 (t, J = 8.8 Hz, 4H, ArH), 7.26 (dd, J = 8.4 Hz, J = 2.5 Hz, 4H, ArH). Anal. ($C_{23}H_{27}NOF_2$•$C_4H_4O_4$) C, H, N.

3-(2-Benzhydryloxyethyl)-8-(3-phenylpropyl)-8-azabicyclo[3.2.1]octane (13). This compound was synthesized from an *N*-demethylation of **11** according to general method E, followed by an *N*-alkylation with 1-iodo-3-phenylpropane according to general method F. CI-MS (NH_3) *m/z* 440 (MH^+); ^{1}H NMR ($CDCl_3$) δ (ppm) 1.28 (d, J = 13.8 Hz, 2H, $H_{6,7endo}$), 1.63 (dd, J = 13.8 Hz, J = 7.8 Hz, 2H, $H_{6,7exo}$), 1.75−2.12 (m, 9H), 2.37 (t, J = 7.3 Hz, 2H, NCH_2), 2.64 (t, J = 7.8 Hz, 2H, $ArCH_2$), 3.17 (brs, 2H, $H_{1,5}$), 3.45 (t, J = 6.3 Hz, 2H, OCH_2), 5.31 (s, 1H, ArCHAr), 7.32 (m, 15H, ArH). Anal. ($C_{31}H_{37}$-NO•HCl•0.75H_2O) C, H, N.

3-{2-[Bis-(4-fluorophenyl)methoxy]ethyl}-8-(3-phenylpropyl)-8-azabicyclo[3.2.1]octane (14). This compound was synthesized from an *N*-demethylation of **12** according to general method E, followed by an N-alkylation with 1-iodo-3-phenylpropane according to general method F. CI-MS (NH_3) *m/z* 476 (MH^+); ^{1}H NMR ($CDCl_3$) δ (ppm) 1.35 (d, J = 13.7 Hz, 2H, $H_{6,7endo}$), 1.68−2.22 (m, 11H), 2.50 (t, J = 7.8 Hz, 2H, NCH_2), 2.66 (t, J = 7.8 Hz, 2H, $ArCH_2$), 3.33 (brs, 2H, $H_{1,5}$), 3.42 (t, J = 6.4 Hz, 2H, OCH_2), 5.27 (s, 1H, ArCHAr), 7.01 (t, J = 8.8 Hz, 4H, ArH), 7.27 (m, 9H, ArH). Anal. ($C_{31}H_{35}NOF_2$•-HCl•1.75H_2O) C, H, N.

Bis(4-fluorophenyl)methylamine (15). A solution of 5.0 g (23 mmol) of 4,4′-difluorobenzophenone and 5.0 g (72 mmol) of hydroxylamine (HCl salt) in 100 mL of ethanol was heated at reflux overnight, when TLC showed only a trace amount of starting ketone left. The solvent was evaporated, and the residue was redissolved in CH_2Cl_2. The solution was washed with water and saturated aqueous $NaHCO_3$, dried over Na_2-SO_4, and evaporated to give 5.26 g (99% yield) of product as white solid. CI-MS (NH_3) *m/z* 234 (MH^+), 251 (M + 18). The crude material (5.1 g, 22 mmol) in 30 mL of THF was then added slowly to 50 mL of 1 M refluxing $LiAlH_4$ in THF. The reaction mixture turned from dark yellow to bright orange to light yellow with a precipitate while refluxing and was allowed

to stir at room temperature overnight after the addition was completed. The reaction was quenched by addition of 1.6 g of water, 1.6 g of 15% aqueous NaOH, and then 4.8 g of water and was allowed to stir at room temperature for 1 h. The white solid was filtered off through Celite, and the solvent was exchanged with CH_2Cl_2. The reaction was then worked up using an acid−base extraction with 15% aqueous citric acid solution, and 2.81 g (59% yield) of **15** was obtained as a light, beige colored liquid. CI-MS (NH_3) *m/z* 203 ($MH^+ - NH_3$), 220 (MH^+), 237 ($M + NH_4^+$); ^{1}H NMR ($CDCl_3$) δ (ppm) 5.20 (s, 1H, ArCHAr), 7.00 (t, J = 8.9 Hz, 4H, ArH), 7.32 (dd, J = 8.9 Hz, J = 3.0 Hz, 4H, ArH).

***N*-Benzhydryl-2-(8-methyl-8-azabicyclo[3.2.1]oct-3-ylidene)acetamide (16).** To a solution of 3.0 g (16.4 mmol) of aminodiphenylmethane in 30 mL of CH_2Cl_2 were added slowly 12 mL (1.5 eq.) of trimethylaluminum in toluene. The mixture was allowed to stir at room temperature for 10 min before 3.42 g (16.4 mmol) of **5** in 20 mL of CH_2Cl_2 was added, and the solution was then stirred at reflux for 48 h, when TLC showed the completion of the reaction. The reaction mixture was poured slowly into 200 mL of 15% aqueous NaOH solution after cooling to room temperature. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 several times. The combined organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated to give 5.72 g of crude product, which was further purified by salt formation with hydrochloric acid in ethanol/isopropyl alcohol to give 4.66 g (77% overall yield) of a cream colored solid. CI-MS (NH_3) *m/z* 347 (MH^+); ^{1}H NMR ($CDCl_3$) δ (ppm) 1.53 (m, 2H, $H_{6,7endo}$), 1.93 (m, 3H, H_{2ax} + $H_{6,7exo}$), 2.29 (m, 1H, H_{4ax}), 2.35 (s, 3H, NCH_3), 2.79 (d, J = 15.3 Hz, 1H, H_{2eq}), 3.22 (brs, 2H, $H_{1,5}$), 3.58 (d, J = 15.8 Hz, 1H, H_{4eq}), 5.66 (s, 1H, Olefinic H), 6.10 (d, J = 7.8 Hz, 1H, CONH), 6.26 (d, J = 7.8 Hz, 1H, ArCHAr), 7.24 (m, 10H, ArH). Anal. ($C_{23}H_{26}N_2O$•HCl) C, H, N.

***N*-[Bis(4-fluorophenyl)methyl]-2-(8-methyl-8-azabicyclo[3.2.1]oct-3-ylidene)acetamide (17).** This compound was prepared from a direct amide formation between the ester **5** with the amine **15** according to the method described above for **16**. CI-MS (NH_3) *m/z* 383 (MH^+); ^{1}H NMR ($CDCl_3$) δ (ppm) 1.53 (d, J = 10.8 Hz, 2H, $H_{6,7endo}$), 1.96 (m, 3H, H_{2ax} + $H_{6,7exo}$), 2.38 (s, 3H, NCH_3), 2.40 (d, J = 15.6 Hz, 1H, H_{4ax}), 2.76 (d, J = 14.7 Hz, 1H, H_{2eq}), 3.26 (brs, 2H, $H_{1,5}$), 3.61 (d, J = 15.6 Hz, 1H, H_{4eq}), 5.69 (s, 1H, Olefinic H), 6.20 (m, 2H, ArCHAr + CONH), 7.00 (m, 4H, ArH), 7.18 (m, 4H, ArH). Anal. ($C_{23}H_{24}N_2OF_2$•HCl) C, H, N.

***N*-Benzhydryl-2-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-acetamide (18)**. This compound was synthesized from reduction of **16** according to general method C. CI-MS (NH_3) *m/z* 349 (MH^+); ^{1}H NMR ($CDCl_3$) δ (ppm) 1.30 (d, J = 14.7 Hz, 2H, $H_{6,7endo}$), 1.59 (dd, J = 14.7 Hz, J = 7.8 Hz, 2H, $H_{6,7exo}$), 2.02−2.32 (m, 5H, $H_{2,3,4}$), 2.25 (s, 3H, NCH_3), 2.40 (d, J = 6.8 Hz, 2H, $COCH_2$), 3.09 (brs, 2H, $H_{1,5}$), 6.12 (d, J = 7.8 Hz, 1H, CONH), 6.25 (d, J = 7.8 Hz, 1H, ArCHAr), 7.20−7.35 (m, 10H, ArH). Anal. ($C_{23}H_{28}N_2O$•HCl) C, H, N.

***N*-[Bis(4-fluorophenyl)methyl]-2-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)acetamide (19).** This compound was synthesized from reduction of **17** according to general method C. CI-MS (NH_3) *m/z* 385 (MH^+); ^{1}H NMR ($CDCl_3$) δ (ppm) 1.26 (d, J = 14.8 Hz, 2H, $H_{6,7endo}$), 1.59 (m, 2H, $H_{6,7exo}$), 2.02−2.31 (m, 5H, $H_{2,3,4}$), 2.25 (s, 3H, NCH_3), 2.42 (d, J = 7.8 Hz, 2H, $COCH_2$), 3.11 (brs, 2H, $H_{1,5}$), 6.05 (d, J = 7.8 Hz, 1H, CONH), 6.21 (d, J = 7.8 Hz, 1H, ArCHAr), 7.02 (t, J = 8.3 Hz, 4H, ArH), 7.15 (dd, J = 8.8 Hz, J = 3.9, 4H, ArH). Anal. ($C_{23}H_{26}N_2OF_2$•HCl) C, H, N.

Benzhydryl[2-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-ethyl]amine (20). This compound was prepared from a reduction of the amide **18** according to general method D. CI-MS (NH_3) *m/z* 335 (MH^+); ^{1}H NMR ($CDCl_3$) δ (ppm) 1.25 (d, J = 14.7 Hz, 2H, $H_{6,7endo}$), 1.56−1.77 (m, 5H, CH_2 + H_3 + $H_{6,7exo}$), 1.97−2.12 (m, 4H, $H_{2,4}$), 2.23 (s, 3H, NCH_3), 2.56 (t, J = 7.8 Hz, 2H, NCH_2), 3.06 (brs, 2H, $H_{1,5}$), 4.79 (s, 1H, ArCHAr), 7.17−7.40 (m, 10H, ArH). Anal. ($C_{23}H_{30}N_2$•2HCl) C, H, N.

Bis-(4-fluorophenyl)methyl]-2-(8-methyl-8-azabicyclo-[3.2.1]oct-3-yl)ethyl]amine (21). This compound was prepared from a reduction of the amide **19** according to general method D. CI-MS (NH_3) *m/z* 371 (MH^+); ^{1}H NMR ($CDCl_3$) δ (ppm) 1.24 (d, J = 13.7 Hz, 2H, $H_{6,7endo}$), 1.58−1.77 (m, 5H, CH_2 + H_3 + $H_{6,7exo}$), 1.99−2.14 (m, 4H, $H_{2,4}$), 2.24 (s, 3H, NCH_3), 2.53 (t, J = 7.8 Hz, 2H, NCH_2), 3.07 (brs, 2H, $H_{1,5}$), 4.76 (s, 1H, ArCHAr), 6.98 (t, J = 8.3 Hz, 4H, ArH), 7.32 (dd, J = 8.8 Hz, J = 2.9 Hz, 4H, ArH). Anal. ($C_{23}H_{28}N_2F_2$•2HCl) C, H, N.

Biological Methods. (A) Binding Assays for the DAT and SERT. These assays followed published procedures[36,37] and used 0.01 nM [^{125}I]RTI-55[31] (sa = 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-HC1/150 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.[38] 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 2 or 5 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 of GBR 12909 (**4b**) ([^{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) of incubation at 25 °C by adding 4 mL of wash buffer (10 mM Tris-HC1, 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 $CaC1_2$, 0.83 mM $MgCl_2$, and 5 mM glucose. The tritium retained on the filters was counted, in a Taurus β counter, after an overnight extraction into ICN Cytoscint cocktail.

(B) Muscarinic-M1 Receptor Binding. Muscarinic (M_1) receptor binding was carried out using rat brain membranes as previously described.[39] P_2 membranes were prepared from male Sprague−Dawley rat brains (without cerebellum and brainstem) and stored at −80 °C. Binding assays were performed with 300 μg of membrane protein, 5 nM [^{3}H]-pirenzepine, and 5 mM $MgCl_2$ in 0.5 mL of 50 mM Tris-HCl, pH 7.4. Nonspecific binding was measured in the presence of 10 μM QNB. For competition assays, nine concentrations of test ligand (1 nM to 10 μM or 10 nM to 100 μM) were included. Following incubation for 60 min at 37 °C, membranes were filtered over glass fiber filters soaked in 0.5% polyethylenimine. Filters were rinsed three times with 5 mL of 10 mM Tris-HCl, pH 7.4, and counted in 4 mL of Cytoscint (ICN Biomedicals, Costa Mesa, CA). Competition binding data were analyzed using the nonlinear curve fitting program GraphPad Prism (GraphPad, San Diego, CA). K_i values were calculated using the Cheng-Prusoff equation[40] and are the mean ± SEM from three experiments performed in triplicate. The K_d of [^{3}H]-pirenzepine, 13.1 ± 0.5 nM (n = 2), was estimated from saturation binding analysis using the nonlinear curve fitting program LIGAND.[41]

Single-Crystal X-ray Analysis of 3-(2-Benzhydryloxyethyl)-8-methyl-8-azabicyclo[3.2.1]octane (11), 3-{2-[Bis(4-fluorophenyl)methoxy]ethyl}-8-methyl-8-azabicyclo[3.2.1]octane (12), and *N*-[Bis(4-fluorophenyl)methyl]-2-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)acetamide (19). For compounds **12** and **19**, data were collected on an automated Bruker P4 diffractometer equipped with an incident beam monochromator. For compound **11**, data were collected on an automated Bruker SMART 1K CCD diffractometer using a platform goniometer. The Rigaku rotating anode source was equipped with Gobel mirrors in the incident beam. Corrections were applied for Lorentz, polarization, and absorption effects. The structures were solved and refined with the aid of the programs in the SHELXTL-plus system of programs.[42] The full-matrix least-squares refinement on F^2 included atomic coordinates and anisotropic thermal parameters for all non-H atoms. H atoms were included using a riding model [coordinate shifts of C applied to attached H atoms, C−H distances set to 0.96−0.93 Å, H angles idealized, U_{iso}(H) were set to 1.2−1.3 U_{eq}(C). Coordinates only were refined for hydrogens on the anion in compound **12**. Atomic coordinates for all compounds have been deposited with the Cambridge Crystallographic Data Base, 12 Union Road, Cambridge CB2 1EZ, U.K. (deposit@ccdc.cam.ac.uk).

3-(2-Benzhydryloxyethyl)-8-methyl-8-azabicyclo[3.2.1]octane (11). $C_{23}H_{29}NO$•HCl, fw = 371.93, (0.05 × 0.14 × 0.40 mm^{-1}), orthorhombic space group *Pca*2(1), a = 11.382(1) Å, b = 17.748(2) Å, c = 10.121(1) Å, V = 2044.4(2) Å^3, Z = 4, ρ_{calc} = 1.21 mg mm^{-3}, λ(Cu Kα) = 1.54178 Å, μ = 1.72 mm^{-1}, F(000) = 800, T = 293 K, R_1 = 0.0364 for 1544 observed ($I > 2\sigma(I)$) reflections and 0.042 for the full set of 1703 reflections.

3-{2-[Bis(4-fluorophenyl)methoxy]ethyl}-8-methyl-8-azabicyclo[3.2.1]octane (12). $C_{23}H_{27}NOF_2$.$C_4H_4O_4$, fw = 487.5, (0.14 × 0.20 × 0.50 mm^{-1}), Monoclinic space group $P2_1/n$, a = 12.361(1) Å, b = 8.216(1) Å, c = 23.862(3) Å, β = 92.51(1)°, V = 2421.1 (5) Å^3, Z = 4, ρ_{calc} = 1.338 mg mm^{-3}, λ(Cu Kα) = 1.54178 Å, μ = 0.85 mm^{-1}, F(000) = 1032, T = 293 K, R_1 = 0.050 for 2658 observed ($I > 2\sigma(I)$) reflections and 0.062 for the full set of 3320 reflections.

***N*-[Bis(4-fluorophenyl)methyl]-2-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)acetamide (19).** $C_{23}H_{26}N_2OF_2$.HCl, fw = 420.92, (0.06 × 0.10 × 0.64 mm^{-1}), orthorhombic space group *Pca*2(1), a = 11.562(1) Å, b = 19.272(2) Å, c = 9.751(1) Å, V = 2172.7 (4) Å^3, Z = 4, ρ_{calc} = 1.28 mg mm^{-3}, λ(Cu Kα) = 1.54178 Å, μ = 1.84 mm^{-1}, F(000) = 888, T = 293 K, R_1 = 0.049 for 1220 observed ($I > 2\sigma(I)$) reflections and 0.078 for the full set of 1611 reflections.

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Supporting Information Available: Tables listing crystal data and structure refinement, atomic coordinates, bond lengths and angles, anisotropic displacement parameters, hydrogen coordinates and isotropic displacement parameters of **11**, **12**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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