Synthesis and Pharmacology of Site Specific Cocaine Abuse Treatment Agents: 8-Substituted Isotropane (3-Azabicyclo[3.2.1]octane) Dopamine Uptake Inhibitors

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A series of 8-substituted-3-azabicyclo[3.2.1]octanes (isotropanes) were synthesized and tested for inhibitor potency using [³H]WIN 35,428 binding at the dopamine (DA) transporter, [³H]-citalopram binding at the serotonin (5-HT) transporter, and [³H]DA uptake assays. The synthesis started with a Mannich condensation of cyclopentanone, benzylamine, and fomaldehyde to afford *N*-benzyl-3-azabicyclo[3.2.1]octan-8-one (**6**). The 8-phenyl group was introduced by Grignard addition to ketone **6** or nucleophilic displacement via a triflate of the corresponding alcohol **7a**. The 8β-phenyl-8α-alcohols from Grignard addition generally have low affinity for the two transporters and do not effectively inhibit the uptake of [³H]DA. The 8β-phenyl compound (**14**) without the hydroxyl group at C-8 was much more potent (22-fold) for [³H]WIN 35,428 binding inhibition than the corresponding 8β-phenyl-8α-hydroxy compound (**7a**). The 8α-phenyl compound **8a** was almost as potent as cocaine in binding to the DA transporter (IC$_{50}$ = 234 nM vs 159 nM for cocaine), whereas the C-8 epimer, compound **14**, was somewhat less potent (IC$_{50}$ = 785 nM). The lower potency of **14** (β-orientation of 8-phenyl group) as compared to **8a** (α-orientation) was unexpected, based on modeling studies comparing the new compounds to WIN 35,065-2, an analogue of cocaine. The benzhydryl ethers at C-8 (**17**), analogous to the benztropines, had better selectivity than the corresponding phenyl compounds, **8a** and **14**, for the DA transporter as compared to the 5-HT transporter. The isotropane and benzisotropine analogues seem to bind in a manner that is more similar to that of the benztropine compounds **5** rather than those of cocaine and WIN 35,065-2.

Introduction

Cocaine (**1**) abuse and addiction continues to be a problem that plagues our society.[1] Once a person tries cocaine, an individual sometimes cannot predict or control the extent to which he or she will continue to use the drug.[2] According to *Monitoring the Future National Survey Results on Drug Use, 1975−2001*,[3] in 1998, the proportion of teenagers who have used cocaine at least once in their lifetime increased slightly in the early 1990s, although it is still lower than its peak in 1985.

Despite a large amount of research in this area,[4] there are currently no safe and effective pharmacotherapies available to help habitual users of cocaine who want to stop their usage of the drug. Its reinforcing and stimulant properties are, in part, a consequence of its propensity to inhibit monoamine transport systems, in particular the dopamine transporter (DAT).[5] This inhibition results in an increase in synaptic dopamine levels, which then leads to overstimulation of postsynaptic dopamine receptors. However, the importance of serotoneric mechanisms is being increasingly recognized.[6]

The work described here is part of an ongoing project[7] aimed at the development of drugs that are targeted at the DAT to treat cocaine abuse. The goal is to synthesize agents that will fall along a continuum ranging from full agonist to full antagonist at the cocaine binding sites. Those compounds that prove to be full agonists will be developed as a substitution therapy for cocaine abusers, analogous to the use of methadone[8] (a long-acting and orally effective opiod agonist) for the treatment of heroin addiction. To be effective in this application, these agents will need to have a slow onset and long duration of action. At the opposite end of the continuum are agents that might be able to inhibit the binding of cocaine to the transporter yet not interfere with DA transport. While this is theoretically possible, to our knowledge, no such compounds have yet been identified. Work in this area (see Figure 1) has focused on the tropane ring system (8-azabicyclo[3.2.1]octane). For example, WIN 35,065-2 (**2**), in which the β-benzoate ester of cocaine is replaced by β-phenyl, results in a more potent compound.[9] Although the nitrogen atom and phenyl group are commonly regarded as important elements of the pharmacophore, there are some examples of bicyclo[3.2.1]octanes without nitrogen, compounds **3**, which show potent binding to the DAT when the phenyl ring is 3,4-dichloro-substituted.[10] This may mean that in part, the complete three-dimensional topology of the ligand may be more important for binding to the biological macromolecule than the individual pharmacophore elements. Interestingly, piperidine analogues[11] such as **4**, which lack cocaine's two carbon bridge, are much less potent than WIN 35,065-2
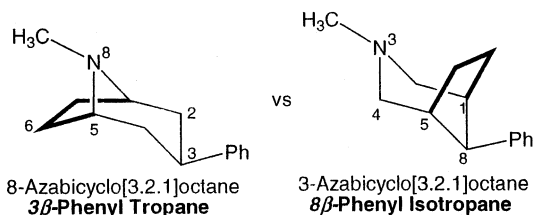
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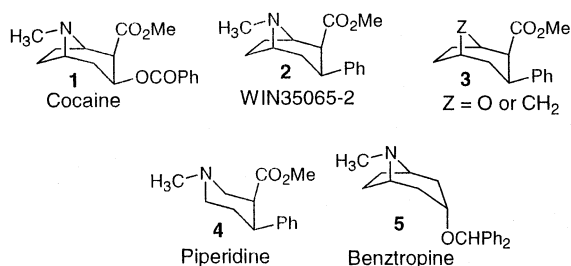
Figure 1. Dopamine uptake inhibitors.

Figure 2. Design of isotropane.

(33-fold). That means that the [3.2.1]bridge structure is important for potent binding at the DAT.

Benztropine (**5**), 3α-diphenylmethoxytropane,[12] is a dopamine uptake inhibitor, equipotent to cocaine, that inhibits cocaine-induced central nervous system (CNS) stimulant activity in animal modes. Generally, 4-β-substituted isomers are more potent than the corresponding 4-α-substituted compounds for the inhibition of WIN binding in the tropane series. However, all benztropine derivatives have shown reversed potency; that is, the α-isomers are more potent than the β-isomers.

We report here a series of novel tropane analogues, which we have named "isotropane", 3-azabicyclo[3.2.1]-octane. Tropane and isotropane are structurally different only in the locations of the two carbon bridge as shown in Figure 2. In the isotropanes, the two carbon bridge in part takes the place of the methyl ester of cocaine. These analogues, which do not have an ester group, have a significantly different topology as compared to compounds that have been previously synthesized.

Results and Discussion

Chemistry. *N*-Benzyl-3-azabicyclo[3.2.1]octan-8-one (**6**) was prepared by a Mannich condensation of cyclopentanone, benzylamine, and formaldehyde (Scheme 1).[13] In our hands, the *N*-methyl analogue of **6** could not be isolated when methylamine was used instead of benzylamine in the Mannich condensation.[14] Addition of Grignard reagents such as phenylmagesium bromide to the ketone **6** introduced the aromatic group at C-8. Nucleophilic reagents are reported[14] to approach with only β-directional preference for this compound. This afforded only the α-alcohols such as **7a**,**b**; single-crystal X-ray crystallography of **7a** supported the structural assignments and the preferential β-approach of phenylmagnesium bromide (Figure 3).

Ionic reduction of the hydroxyl group of **7a**,**b** failed under a variety of conditions, such as NaI/CH$_3$CN/TMSI, NaBH$_4$/CF$_3$CO$_2$H, and ZnI$_2$/NaBH$_4$. However, reduction under free radical conditions[15] was successful to afford benzylamines **8a**,**b**. In this procedure, the hydroxyl group was converted to an *S*-methyl xanthate and

reduced by treatment with Bu$_3$SnH and a catalytic amount of AIBN. Reduction of the *S*-methyl xanthate group also occurred only from the β-face to afford α-phenyl compounds **8a**,**b**. Selective reduction of the xanthate of **7b**, without the reduction of the aromatic chlorine, occurred when 1 equiv of Bu$_3$SnH was used.

The stereochemistry of these products, **8a**,**b**, was determined as the α-orientation in part by ^{1}H NMR spectroscopy. The nuclear Overhauser enhancement spectroscopy (NOESY) spectrum of **8a** showed an interaction between the benzylic proton at C-8 and the bridge protons at C-6 and C-7 and no interaction between the aromatic protons of the phenyl ring at C-8 and the bridge protons at C-6 and C-7. In addition, there was an interaction between the protons at C-2 and C-4 and the aromatic protons of the phenyl ring at C-8. The structure of **8a** was further confirmed by single-crystal X-ray crystallography (Figure 3).

Debenzylation of **8a** with hydrogen and Pd afforded **9a**. Chloroethyl chloroformate[16] was used for debenzylation of **8b** to obtain **9b** and avoid the hydrogenolysis of the aromatic chlorine. Reductive alkylation of amines **9a**,**b** with formaldehyde afforded the *N*-methylamines, **10a**,**b** (Scheme 1).

Our approach to the synthesis of the β-phenyl isomer **14** was envisioned to be by a nucleophilic substitution reaction using a good α-oriented leaving group at the C-8 position, based on the preference for β-approach of reagents (Scheme 2). As expected, the NaBH$_4$ reduction of ketone **6** afforded only the α-alcohol **13a**, which was converted to the triflate using triflic anhydride. When the crude triflate was treated with phenyllithium at −78 °C, thin-layer chromatography and ^{1}H NMR analysis did not show any recognizable major product. In addition, the 8β-bromo compound **15** was obtained as the only major product when the triflate was treated with PhMgBr at −78, 0, or 25 °C. However, the β-phenyl isomer **14** could be obtained in low yield when a mixture of PhMgBr and CuBr·Me$_2$S was added to the triflate of α-alcohol in hexamethylphosphoramide (HMPA) solvent at 90 °C. This procedure also gave a low yield of the deoxygenated product **16**.

The stereochemistry at C-8 of the product **14** was determined by ^{1}H NMR spectroscopy. The benzylic proton at C-8 of β-isomer **14** was a broadened singlet, while that of the α-isomer **8a** was a clear triplet. The coupling constants between H−C8 and the adjacent protons on C1 and C5 can be explained by the dihedral angles between these protons in **14** and **8**. Using the global minimized structure of **8a** and **14** as calculated by MM2,[17] the calculated dihedral angle between the protons at C-8 and the protons at C-1 and C-5 is 55° in **8a** while it is 80° in **14**. According to Karplus's equation,[18] the vicinal coupling constant would be expected to be between 2.5 and 4.5 Hz when the dihedral angle is 55° and between 0.0 and 0.2 Hz when the dihedral angle is 80°. The proton NMR of **8a** shows a triplet (*J* = 4.2 Hz) at 3.00 ppm while **14** shows a singlet at 2.74 ppm. Therefore, **8a** and **14** could be assigned as the α- and β-stereoisomers, respectively.

The benzisotropine analogues, 8-diphenylmethoxy-isotropanes **17a**,**b**, were synthesized to compare their pharmacophores with benztropine (**5**). To get the β-alcohol **13b**, reactions of α-triflate of **13a** were investi-

Scheme 1[a]
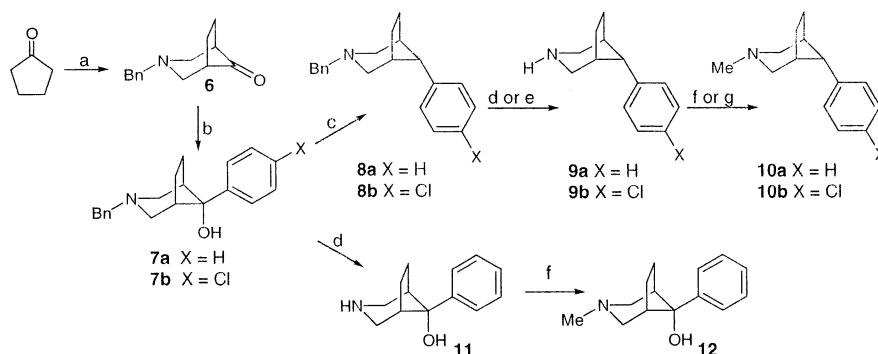
[a] Reagents and conditions: (a) Benzylamine/37% HCHO. (b) Grignard reagent/THF. (c) (i) NaH/imidazole/THF, CS$_2$, MeI; (ii) Bu$_3$SnH/AIBN/benzene. (d) H$_2$, Pd/C. (e) Chloroethyl chloroformate/dichloroethane. (f) (CH$_2$O)$_n$, NaBH$_4$, molecular sieve. (g) 37% HCHO/HCO$_2$H.
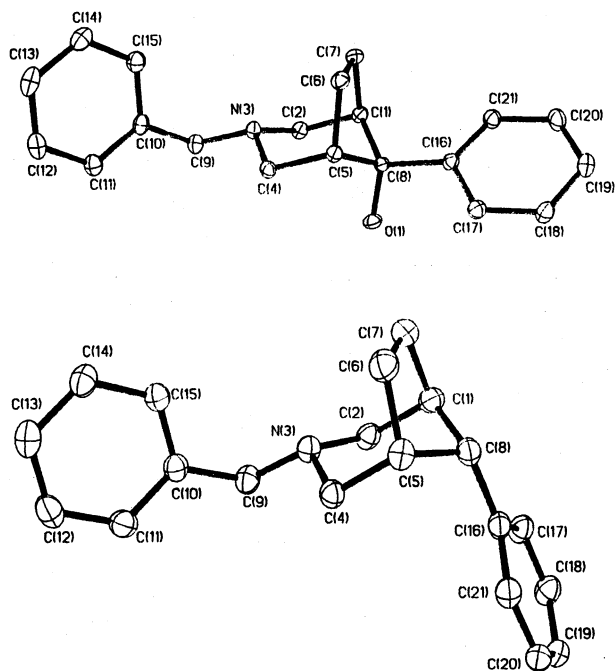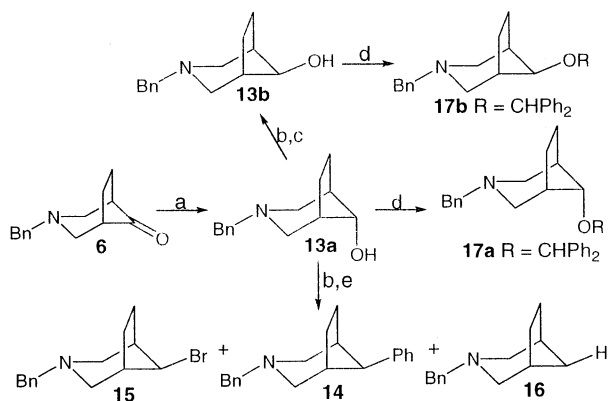

Figure 3. ORTEP of **7a** (up) and **8a** (down).

Scheme 2[a]

[a] Reagents and conditions: (a) NaBH$_4$. (b) Tf$_2$O, pyridine. (c) TsOH·H$_2$O/water/DMSO/benzene. (d) Benzhydrol/TsOH·H$_2$O/benzene. (e) PhMgBr, CuBr·Me$_2$S, HMPA, 90 °C.
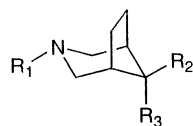
gated. With aqueous NaOH or KOH solutions, only the α-alcohol **13a** was obtained, presumably by hydrolysis. However, **13b** could be obtained by reaction under acidic conditions. The best conditions (60% yield) to obtain the

β-alcohol **13b** involve heating to reflux a mixture of the triflate of **13a**, 1.5 equiv of *p*-toluenesulfonic acid in cosolvents of water, benzene, and dimethyl sulfoxide (DMSO) (1:10:4). The ^{1}H NMR splitting patterns of the protons at C-8 in these isomers **13a,b** are very similar to compounds **8a** and **14** allowing their stereochemistry to be assigned. The β-isomer **13b** shows a singlet while the α-isomer **13a** is triplet ($J = 4.8$ Hz). Using the method developed by Meltzer et al.,[19] the coupling between isotropan-8-ols **13a** or **b** and benzhydrol afforded ethers **17a,b** in good yields, respectively (Scheme 2).

Pharmacology. The compounds were tested for their ability to inhibit the binding of [^{3}H]WIN 35,428 to the cocaine binding site on the DAT in synaptosomal membrane preparations from rat striatal tissue,[7a] [^{3}H]-DA uptake into rat striatal synaptosomes,[7a,20] and [^{3}H]-citalopram binding to the 5-HTT in synaptosomal membrane preparations from rat cortical tissue.[21] The results are summarized in Table 1.

Inhibition of [^{3}H]WIN 35,428 Binding. Substituents such as methyl or benzyl on the *N*-atom of isotropanes have little effect on binding potencies. For example (*N*-substituent, IC$_{50}$), compounds **8a** (*N*-benzyl; 234 nM), **10a** (*N*-methyl; 360 nM), and **9a** (*N*-hydrogen; 258 nM) show similar potencies. The same trend has been reported for many tropane compounds, for example, WIN 35,065-2 (*N*-methyl; 23.0 nM) and WIN 35,-981 (*N*-hydrogen; 30.8 nM).[22]

The aromatic group at C-3 in tropanes such as WIN 35,065-2 is regarded as a critical pharmacophore for the recognition site. Binding affinities for the DAT are also highly dependent upon substituents on the phenyl ring.[4,23] Likewise, a phenyl group at C-8 in isotropanes greatly increases their potency. For example, **8a** (C-8α-phenyl) is 104-fold more potent than compound **16** without a phenyl group. This effect is greatly diminished, however, when the other substituent at C-8 is a hydroxyl group (compare **13a** and **7a**). The orientation of the phenyl group at C-8 has a significant effect on potency. Compound **8a** (α-orientation) is more potent than the corresponding β-epimer (**14**) by 3.4-fold. The same trend is also observed for the benzhydryl ethers (benzisotropines); for example, **17a** (α-orientation; IC$_{50}$ = 363 nM) is slightly more potent than **17b** (β-orientation; IC$_{50}$ = 536 nM). These results contrast to phenyltropanes such as WIN 35,065-2 and its C-3 epimer,

Table 1. Binding and Uptake Data for 3-Azabicyclo[3.2.1]octane Isotropane Derivatives and Reference Compound (Value ± SEM)[a]

no.	R_1	R_2	R_3	DAT [3H]WIN 35,428	DAT [3H]DA	5-HTT [3H]CIT	% inhibition [3H]CIT at 10 μM	selectivity 5-HHT/DAT [3H]CIT/[3H]WIN 35,428
1		cocaine		160 ± 15	404 ± 26	389		2.43
7a	Bn	Ph	OH	17500 ± 4800	$27\,100 \pm 560$	3060 ± 450		0.17
7b	Bn	4-ClPh	OH	1510 ± 260	2630 ± 79	997 ± 110		0.66
8a	Bn	H	Ph	234 ± 10	309 ± 5.5	3460 ± 640		14.8
8b	Bn	H	4-ClPh	95.5 ± 20	601 ± 13	402 ± 13		4.2
9a	H	H	Ph	258 ± 70	893 ± 6	4000 ± 850		16
9b	H	H	4-ClPh	81.5 ± 2.5	478 ± 59	363 ± 3.0		4.4
10a	CH_3	H	Ph	360 ± 43	1040 ± 110	1850 ± 310		5.1
10b	CH_3	H	4-ClPh	273 ± 59	926 ± 88	220 ± 24		0.81
11	H	Ph	OH	9830 ± 420	8480 ± 370	~10 000	46.2 ± 2.8	~1.0
12	CH_3	Ph	OH	$10\,100 \pm 710$	9770 ± 440	>10 000	27.8 ± 2.6	>1.0
13a	Bn	H	OH	$22\,100 \pm 1000$	$45\,000 \pm 8600$	>10 000	23.8 ± 4.8	>0.45
14	Bn	Ph	H	785 ± 67	4450 ± 480	3880 ± 440		4.9
15	Bn	Br	H	4630 ± 830	8640 ± 900	>10 000	30.4 ± 9.5	>2.2
16	Bn	H	H	$24\,300 \pm 660$	$35\,700 \pm 3800$	>10 000	24.4 ± 4.2	>0.41
17a	Bn	H	$OCHPh_2$	363 ± 37	735 ± 78	~10 000	61.0 ± 4.6	~27
17b	Bn	$OCHPh_2$	H	536 ± 61	1980 ± 220	>10 000	29.8 ± 0.5	>18

[a] Abbreviations: Bn, benzyl; Ph, phenyl; CIT, citalopram. [b] Compounds tested as HCl salts.

which have IC$_{50}$ values of 101 (α-orientation) and 23 nM (β-orientation), repectively.[23a] However, benztropines show the same trend as isotropanes; that is, α-benztropine (K_i = 118 nM) is 7.2-fold more potent than β-benzisotropine.[12]

A 4-chloro substituent on the phenyl ring of **8b** and **9b** increases the potency about 3-fold as compared to the corresponding unsubstituted phenyl derivatives **8a** and **9a**. The most potent compound in this study is the 4-chlorophenyl-substituted derivative, **9b** (IC$_{50}$ = 81.5 nM), which is 2-fold more potent than (−)-cocaine. Interestingly, the *N*-Me derivative (**10a**) showed little or no increase in potency upon 4-chloro substitution of the phenyl ring (**10b**). In contrast, the 4-chloro substitution of the phenyl group of the tropane WIN 35,065-2 was reported to elicit a 20-fold increase in inhibitory potency at the stimulant binding site.[9,23] The compound with an 8α-hydroxyl group (**7a**) has a much lower affinity (22-fold) as compared to the corresponding compound (**14**) without the hydroxyl group.

The Hill coefficients (n_H) for most of the compounds in the binding assay were close to unity (data not shown here). The two compounds with the highest n_H values were **17a,b** with values of 1.66 ± 0.16 and 1.38 ± 0.08, respectively. These compounds required the maximal amount of DMSO tolerated by the assay to solubilize them. It is possible, therefore, that these higher n_H values associated with these compounds were artifacts resulting from their extreme hydrophobicity.

Inhibition of [3H]DA Uptake. Similar conclusions to those discussed about [3H]WIN 35,428 binding can be reached when considering the inhibition of [3H]DA uptake since there is a high correlation between them. The correlation is not perfect, and a term called the "discrimination ratio" (DR) is utilized by us to detect any marked departure from linearity that occurs between these two measures.[7a,24] The DR value is defined as a ratio of the IC$_{50}$ for a given compound against [3H]-DA uptake to its corresponding IC$_{50}$ against [3H]WIN

35, 428 binding. Compounds with high DR values ($\geq$36) have theoretical promise as cocaine antagonists[7a] because they should be able to prevent cocaine from binding at a dose that does not affect DA uptake. The range of values obtained for the present series was 1.3 (**8a**) to 6.3 (**8b**), suggesting that the compounds in this series will likely be more agonist- than antagonist-like. Compounds **8a,b** are unique in that this pair represents the only instance in which a chemical modification (4-Cl substitution of the α-phenyl group) caused a concomitant increase in potency against binding and a decrease in potency against uptake. In all other cases, the direction of the change in potency is the same in both assays but to differing degrees.

The usefulness of the DR has been questioned because it has been shown to vary greatly depending on assay conditions.[25] Data collected under our closely controlled experimental conditions as part of a previous study of another series of compounds revealed an unexpected correlation between the DR values and the slopes of dose−response curves measuring their generalization to cocaine,[21a] suggesting that even if this parameter proves unsatisfactory as a predictor of antagonist efficacy, it may have other useful applications.

Inhibition of [3H]Citalopram Binding. These compounds generally showed low potency against [3H]-citalopram binding at the 5-HTT with IC$_{50}$ values ranging from 220 (**10b**) to well over 10 000 nM. As with [3H]WIN 35,428 binding, phenyl substitution increased potency; for example, the phenyl-containing compounds **8a** (α-phenyl; 3460 nM) and **14** (β-phenyl; 3880 nM) were more potent than the desphenyl compound **16**, whose IC$_{50}$ was well over 10 000 nM. Unlike the [3H]-WIN 35,428 binding results, however, there is no orientation effect of the phenyl group at C-8 between isomers **8a** and **14**. A slight preference for the α-orientation is retained for the benzhydryl ethers (**17a** vs **17b**), however, despite the fact that their affinity for the [3H]-citalopram binding site is markedly reduced.

Whereas the hydroxyl group at C-8 greatly reduces the potency for [³H]WIN 35,428 binding inhibition, it does not change the potency for [³H]citalopram inhibition. For example, α-oriented hydroxy compound **7a** (3060 nM) and the corresponding compound without hydroxyl group **14** (3880 nM) show similar potencies, as do **13a** and **16**. The chlorine substituent (**8b**, **9b**, and **10b**) on the phenyl ring at C-8 increases the potencies from 8.4- to 11.0-fold when they are compared to the corresponding unsubstituted compounds (**8a**, **9a**, and **10a**). These increases in potency are somewhat larger than that for [³H]WIN 35,428 binding inhibition (about 3-fold increase for these compounds). As with [³H]WIN 35,428 binding, the substituents on the *N*-atom, benzyl (**8b**; 402 nM), hydrogen (**9b**; 363 nM), or methyl (**10b**; 220 nM), do not show a significant effect on the potencies. The *N*-methylisotropanes, **10a** and **b**, show small increases in potency as compared to the corresponding norisotropane compounds, **9a**,**b**. In comparison, norcocaine and WIN 35,981 (*N*-hydrogen) have been reported to be 8.3- and 12.6-fold more potent, respectively, than cocaine and WIN 35,065-2 (*N*-methyl).[4,23b]

Transporter Selectivity. Selectivity of all of the compounds screened for the two transporters was calculated by comparing the ratio of IC$_{50}$ values for [³H]-citalopram to [³H]WIN 35,428 (5-HTT/DAT) as shown in Table 1. The compound that shows the highest selectivity (ratio ~27) for the DA transporter is α-benzisotropine **17a**. Thus, none of the compounds studied were highly selective.

Generally, the selectivity for the DAT against 5-HTT is decreased in these derivatives when chlorine is substituted on the phenyl ring at C-8. For example, compounds **8a**, **9a**, and **10a**, which have an unsubstituted phenyl ring at C-8, are 15-, 16-, and 5.1-fold selective, respectively, for the DA transporter. However, the corresponding compounds **8b**, **9b**, and **10b**, which have a 4-chlorophenyl ring at C-8, are only 4.2-, 4.4-, and 0.8-fold selective, respectively, for the DAT.

General Consideration. [³H]WIN 35,428 binding data for tropane compounds, such as WIN 35,065-2, show that β-orientation of the phenyl group at C-3 is more potent (5-fold) than for the α-orientation.[4,20] As shown in Figure 4A,B, the isotropane *N*-methyl-3-aza-8β-phenylbicyclo[3.2.1]octane (β-orientation of a phenyl group) is more closely superimposed topologically with WIN 35,065-2 (Figure 4A) than *N*-methyl-3-aza-8α-phenylbicyclo[3.2.1]octane **10a** (α-orientation) when the N atom and phenyl group of each structure are overlaid, respectively.[17] This leads to the expectation that the 8β-phenylisotropane would be a more potent inhibitor of [³H]WIN 35,428 binding at the DAT. However, the α-orientation **8a** (234 nM) is more potent by 3.4-fold than the β-isomer **14** (785 nM). This trend is similar to that of the benztropines[12] (**5**), which show that the α-orientation is 7-fold more potent. This may imply that the isotropane analogues bind in a manner that is more similar to that of benztropine compounds **5** rather than those of cocaine and WIN 35,065-2.

When chlorine is substituted at the 4-position of the phenyl ring of WIN 35,065-2, the potency for the inhibition of WIN binding is increased by 20-fold. This 4-chlorine substitution effect on the phenyl ring is reduced for benztropine analogues, which show a 4- and

(A)

(B)
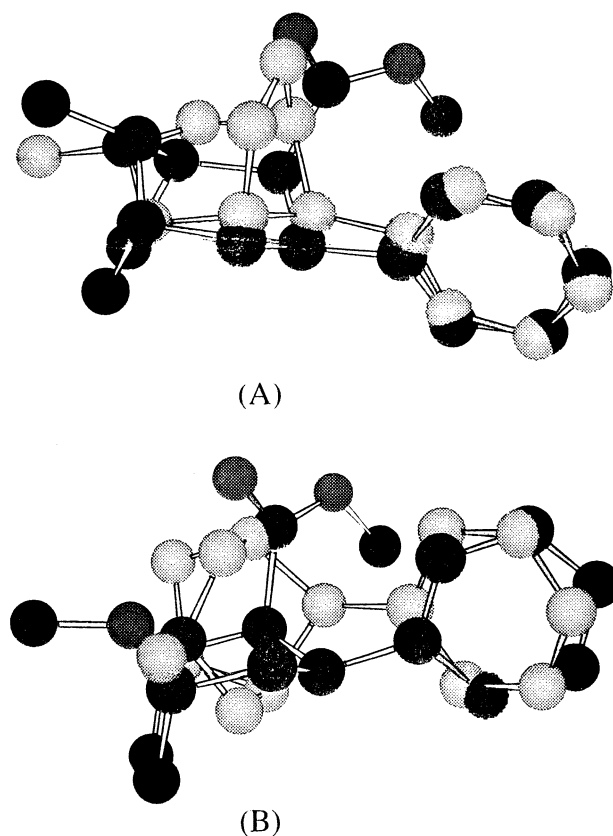
Figure 4. (A) Overlay of WIN 35,065-2 (dark) and *N*-methyl-8β-phenyl-3-azabicyclo[3.2.1]octane (gray). (B) Overlay of WIN 35,065-2 (dark) and **10a** (gray).

6-fold increase, respectively, for mono- and dichloro substitution. Interestingly, 4-chlorophenyl derivatives of isotropanes C-8 (**8b**, **9b**, and **10b**) also show a small increase in potency (less than 3-fold) when they are compared, respectively, to the corresponding unsubstituted compounds (**8a**, **9a**, and **10a**). Again, this implies that the isotropane analogues may be more similar in binding characteristics to the benztropines than to the tropane analogues.

The fact that the isotropanes resemble the benztropines more than the tropanes in biochemical activity could have far-reaching implications for the development of pharmacotherapies for the treatment of cocaine abuse. Several benztropines have been found to be potent inhibitors of both [³H]WIN 35,428 binding and DA uptake, yet have behavioral profiles that indicate diminished psychomotor stimulant effects and self-administration potential relative to cocaine.[26]

Conclusions

Derivatives of a novel structure, 8-phenyl-3-azabicyclo[3.2.1]octane, which we have named isotropane, were designed and synthesized as dopamine uptake inhibitors, which might be used as lead compounds for the development of treatment agents for cocaine abuse. The isomers at C-8 of the isotropane structure were synthesized selectively, and these derivatives were tested for their binding to the DAT and 5-HTT and their ability to inhibit [³H]DA uptake. Several alternate explanations of the structure−activity relationships of these compounds are offered in terms of known pharmacophores. Compound **8b** shows a relatively high affinity (IC$_{50}$ =

95.5 nM) for the [^{3}H]WIN 35,428 binding site and has little selectivity (4.2-fold) for the DAT over the 5-HTT. The benzisotropine derivative (**17a**) shows better selectivity (27-fold) but somewhat less potency (IC$_{50}$ = 363 nM). The isotropane analogues seem to bind in a manner that is more similar to that of benztropines rather than those of cocaine and WIN 35,065-2. Further testing and synthesis of these and other related compounds are in progress.

Experimental Section

General Methods. Starting materials were purchased from Aldrich Chemical Co. and used without further purification. Tetrahydrofuran (THF) was dried over sodium benzophenon ketyl prior to distillation under argon. Benzene was dried over sodium before it was used. Compound **6** was synthesized according to the literature.[13] Flash chromatography was run using 230−400 mesh silica gel. Melting points were determined on a Mel-Temp apparatus and are uncorrected. ^{1}H (300 or 500 MHz), ^{13}C (75 or 100 MHz) NMR, and COSY/NOESY spectra were obtained on either a Varian Gemini-300 or a Bruker DSX-500 spectrometer. High-resolution mass spectra (electron impact (EI) or fast atom bombardment (FAB)) were recorded on a VG Analytical 70-SE mass spectrometer equipped with a 11-250J data system. Elemental analyses were obtained from Atlantic Microlabs, Atlanta, GA. Free bases were dissolved in CH$_2$Cl$_2$ and converted to HCl salts by the addition of 1 M HCl (1.5 equiv) in diethyl ether. An excess amount of HCl was removed under reduced pressure, and the solid was recrystallized from MeOH/EtOAc/diethyl ether/CH$_2$Cl$_2$.

***N*-Benzyl-3-azabicyclo[3.2.1]-8β-phenyloctan-8α-ol (7a).** A 1 M solution of phenylmagnesium bromide (6.3 mL) was added to a solution of **6** (900 mg, 4.18 mmol) in THF (20 mL) at 0 °C. After it was stirred for 2 h, the mixture was quenched with water and extracted with petroleum ether. The organic layer was dried over MgSO$_4$, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with 1:6 EtOAc:hexane to afford a white solid, **7a** (1.04 g, 85%); mp 90−91 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.49 (d, *J* = 8.4 Hz, 2H), 7.38−7.22 (m, 8H), 3.60 (s, 2H) 2.87 (d, *J* = 10.5 Hz, 2H), 2.62 (dd, *J* = 3.3, 10.5 Hz, 2H), 2.41 (s, 2H), 1.79 (d, *J* = 7.8 Hz, 2H), 1.58 (br. s, 1H), 1.40 (m, 2H). HRMS (EI) calcd for C$_{20}$H$_{23}$NO *m/z*, 293.1780; found, 293.1779.

(7a)−HCl. mp 239−241 °C. ^{1}H NMR (D$_2$O, 300 MHz): δ 7.54−7.32 (m, 10H), 4.26 (s, 2H), 3.63 (d, *J* = 12.0 Hz, 2H), 3.23 (d, *J* = 12.0 Hz, 2H), 2.72 (s, 2H), 1.57 (s, 4H). Anal. (C$_{20}$H$_{24}$NOCl): C, H, N, Cl.

***N*-Benzyl-3-azabicyclo[3.2.1]-8β-(4-chloro)-phenyloctan-8α-ol (7b).** Using a similar procedure as that used to prepare **7a**, a white solid (mp 118−119 °C) was obtained with 86% yield. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.42 (d, *J* = 8.7 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.43−7.22 (m, 5H), 3.59 (s, 2H), 2.85 (d, *J* = 10.8 Hz, 2H), 2.61 (dd, *J* = 3.6, 10.8 Hz, 2H), 2.36 (d, *J* = 1.5 Hz, 2H), 1.80 (d, *J* = 7.5 Hz, 2H), 1.54 (s, 1H), 1.37 (m, 2H). HRMS (EI) calcd for C$_{20}$H$_{22}$NOCl *m/z*, 327.1390; found, 327.1379.

(7b)−HCl. mp 238−241 °C. ^{1}H NMR (D$_2$O, 300 MHz): δ 7.42 (d, *J* = 4.2 Hz, 2H), 7.35 (d, *J* = 4.8 Hz, 2H), 7.46−7.31 (m, 5H), 4.26 (s, 2H), 3.62 (d, *J* = 12.0 Hz, 2H), 3.23 (d, *J* = 11.1 Hz, 2H), 2.67 (s, 2H), 1.57 (br s, 4H). Anal. (C$_{20}$H$_{23}$NOCl$_2$): C, H, N, Cl.

***N*-Benzyl-3-azabicyclo[3.2.1]-8α-phenyloctane (8a).** A mixture of alcohol **7a** (406 mg, 1.38 mmol), 60% NaH in mineral oil (166 mg, 4.16 mmol), and a catalytic amount of imidazole (7 mg) in THF (6 mL) was refluxed overnight under argon, and carbondisulfide (2 mL) was added to the mixture. After 1 h, methyl iodide (1 mL) was added and refluxed for 1 h. The mixture was cooled, quenched with water, and extracted with petroleum ether. The organic layer was dried over MgSO$_4$, filtered, and concentrated. The residue was purified by silica gel chromatography eluting 1:30 EtOAc:hexane to afford yellow solid (468 mg, 89%). *S*-Methyl xanthate formation was confirmed by ^{1}H NMR (δ 2.42, singlet, S−CH$_3$). A solution of

S-methyl xanthate (468 mg, 1.22 mmol), Bu$_3$SnH (495 μL, 1.83 mmol), and AIBN (61 mg) in benzene (10 mL) was degassed with argon at room temperature and refluxed for 12 h. After it was cooled and concentrated, the residue was recrystallized from hexane to afford colorless crystals of **8a** (276 mg, 82%); mp 108−109 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.34−7.24 (m, 8H), 7.21−7.14 (m, 2H), 3.28 (s, 2H), 3.00 (t, *J* = 4.2 Hz, 1H), 2.63 (br s, 2H), 2.45−2.36 (m, 4H), 2.02−1.95 (m, 2H), 1.83−1.79 (m, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 140.7, 139.9, 129.4, 128.5, 128.3, 128.0, 126.5, 125.2, 62.3, 53.5, 47.4, 36.7, 29.2. HRMS (EI) calcd for C$_{20}$H$_{23}$N *m/z*, 277.1830; found, 277.1814.

(8a)−HCl. mp 168−169 °C. ^{1}H NMR (D$_2$O, 300 MHz): δ 7.26−7.12 (m, 10H), 3.88 (s, 2H), 3.00 (br s, 5H), 2.81 (s, 2H), 1.99−1.96 (m, 2H), 1.70 (d, *J* = 8.7 Hz, 2H). Anal. (C$_{20}$H$_{24}$NCl·0.3H$_2$O): C, H, N, Cl.

***N*-Benzyl-3-azabicyclo[3.2.1]-8α-(4-chloro)phenyloctane (8b).** Compound **8b** was made using a similar procedure as that used to prepare **8a** except that 1 equiv of Bu$_3$SnH was employed, and the colorless crystals of **12b** (mp 134−135 °C) were obtained with 76% yield. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.34−7.22 (m, 9H), 3.32 (s, 2H), 2.99 (t, *J* = 4.0 Hz, 1H), 2.63 (br s, 2H), 2.45 (dd, *J* = 3.8, 10.9 Hz, 2H), 2.37 (d, *J* = 10.8 Hz, 2H), 2.03 (m, 2H), 1.86 (m, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 139.8, 139.3, 130.9, 130.7, 128.5, 128.4, 128.0, 126.6, 62.3, 53.4, 46.9, 36.8, 29.2. HRMS (EI) calcd for C$_{20}$H$_{22}$NCl *m/z*, 311.1441; found, 311.1435.

(8b)−HCl. mp 189−190 °C. ^{1}H NMR (D$_2$O, 500 MHz): δ 7.38 (t, *J* = 7.4 Hz, 1H), 7.28 (t, *J* = 7.7 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 7.6 Hz, 2H), 7.11 (d, *J* = 8.2 Hz, 2H), 3.98 (s, 2H), 3.06 (m, 5H), 2.86 (br s, 2H), 2.07 (m, 2H), 1.80 (d, *J* = 8.7 Hz, 2H). Anal. (C$_{20}$H$_{23}$NCl$_2$·1.7H$_2$O): C, H, N, Cl.

3-Azabicyclo[3.2.1]-8α-phenyloctane (9a). A mixture of **8a** (250 mg, 0.903 mmol) and Pd/C (10%, 40 mg) in AcOH/EtOAc (2:5) was shaken overnight under hydrogen atmosphere at 40 psi. The mixture was filtered on Celite and concentrated under reduced pressure. The residue was mixed with water, treated with K$_2$CO$_3$ (pH 10), and extracted with CH$_2$Cl$_2$ to afford **9a** (154 mg, 91%). ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.33−7.27 (m, 4H), 7.19−7.14 (m, 1H), 3.10 (s, 1H), 3.08 (d, *J* = 12.0 Hz, 2H), 2.56 (br s, 2H), 2.43 (dd, *J* = 3.0, 12.6 Hz, 2H), 1.96 (m, 2H), 1.91 (m, 1H), 1.84 (m, 2H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 140.4, 129.2, 128.4, 125.3, 47.7, 46.2, 36.9, 28.3. HRMS (EI) calcd for C$_{13}$H$_{17}$N *m/z*, 187.1361; found, 187.1354.

(9a)−HCl. mp 291−294 °C. ^{1}H NMR (D$_2$O, 300 MHz): δ 7.38 (t, *J* = 6.9 Hz, 2H), 7.22 (d, *J* = 6.9 Hz, 2H), 7.14 (t, *J* = 7.2 Hz, 1H), 3.06 (br s, 2H), 3.02 (s, 1H), 2.85 (br s, 1H), 2.79 (m, 3H), 2.01 (m, 2H), 1.70 (d, *J* = 8.4 Hz, 2H). Anal. (C$_{13}$H$_{18}$NCl·0.2H$_2$O): C, H, N, Cl.

3-Azabicyclo[3.2.1]-8α-(4-chloro)phenyloctane·HCl (9b·HCl). A mixture of **8b** (84 mg, 0.270 mmol) in dichloroethane (3 mL) and chloroethyl chloroformate (31 μL, 0.287 mmol) was cooled to 0 °C. After 10 min, the solution was refluxed overnight and then concentrated. The residue was dissolved in methanol (3 mL) and heated for 1 h at 50 °C. After it was cooled, the mixture was concentrated and recrystallized to give **9b** (55 mg, 79%); mp 272−273 °C. ^{1}H NMR (D$_2$O, 300 MHz): δ 7.32 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 3.07 (d, *J* = 12.6 Hz, 2H), 3.05 (m, 1H), 2.88 (dd, *J* = 2.7, 12.6 Hz, 2H), 2.79 (br s, 2H), 2.05 (m, 2H), 1.74 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (D$_3$O, 100 MHz): δ 136.3, 131.2, 130.1, 128.7, 44.6, 43.7, 33.5, 25.7. HRMS (CI) calcd for C$_{13}$H$_{17}$NCl *m/z*, 222.1050; found, 222.1037 (M + 1). Anal. (C$_{13}$H$_{17}$NCl$_2$): C, H, N, Cl.

***N*-Methyl-3-azabicyclo[3.2.1]-8α-phenyloctane (10a).** To a solution of **9a** (330 mg, 1.76 mmol) in methanol (3 mL) was added paraformaldehyde (265 mg, 8.82 mmol), the molecular sieves (5 Å, 500 mg), and NaBH$_4$ (201 mg, 5.31 mmol), and it was stirred for 3 days. The mixture was filtered on Celite and concentrated to give compound **10a** (324 mg, 92%). ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.34−7.24 (m, 4H), 7.18−7.13 (m, 1H), 3.00 (t, *J* = 3.6 Hz, 1H), 2.66 (br s, 2H), 2.46 (dd, *J* = 3.6, 11.1 Hz, 2H), 2.35 (d, *J* = 10.5 Hz, 2H), 2.07 (s, 3H), 1.95−1.85 (m, 4H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 140.6, 129.3, 128.3, 125.2,

56.0, 47.1, 46.0, 36.5, 29.1. HRMS (EI) calcd for $C_{14}H_{19}N$ *m/z*, 201.1518; found, 201.1502.

(10a)−HCl. mp 244−246 °C. ^{1}H NMR (D_2O, 300 MHz): δ 7.38−7.20 (m, 5H), 3.15−3.00 (m, 5H), 2.90 (br s, 2H), 2.48 (s, 3H), 2.08 (m, 2H), 1.78 (d, *J* = 8.7 Hz, 2H). Anal. ($C_{14}H_{20}NCl$· 0.1H_2O): C, H, N, Cl.

***N*-Methyl-3-azabicyclo[3.2.1]-8α-(4-chloro)phenyloctane (10b).** Compound **9b** (148 mg, 0.668 mmol) was dissolved in 2 mL of 37% HCHO and 1 mL of formic acid at room temperature, and the mixture was refluxed overnight. After it was cooled, the mixture was concentrated, and the residue was dissolved in water and treated with K_2CO_3. The mixture was extracted with CH_2Cl_2 (three times) to afford a crystalline **10b** (128 mg, 81%); mp 74−75 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.28 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 2.92 (t, *J* = 3.9 Hz, 1H), 2.60 (br s, 2H), 2.43 (dd, *J* = 3.3, 11.4 Hz, 2H), 2.27 (d, *J* = 11.1 Hz, 2H), 2.05 (s, 3H), 1.92−1.83 (m, 4H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 139.1, 130.9, 130.7, 128.5, 55.8, 46.4, 45.9, 36.6, 29.1. HRMS (EI) calcd for $C_{14}H_{18}NCl$ *m/z*, 235.1125; found, 235.1129.

(10b)−HCl. mp 282−284 °C. ^{1}H NMR (D_2O, 300 MHz): δ 7.29 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 3.06 (dd, *J* = 2.7, 13.2 Hz, 2H), 2.99 (br s, 1H), 2.92 (d, *J* = 12.6 Hz, 2H), 2.79 (br s, 2H), 2.42 (s, 3H), 2.01 (m, 2H), 1.70 (d, *J* = 12.0 Hz, 2H). Anal. ($C_{14}H_{19}NCl_2$·0.2H_2O): C, H, N, Cl.

***N*-Benzyl-3-azabicyclo[3.2.1]-8β-phenyloctane (14).** To a solution of **6** (1.27 g, 5.91 mmol) in CH$_3$OH (15 mL) was added NaBH$_4$ (300 mg, 7.93 mmol) at 0 °C. After 2 h, the mixture was quenched with water and extracted with CH$_3$Cl to afford *N*-benzyl-3-azabicyclo[3.2.1]octan-8α-ol **13a** (1.2 g, 95%). ^{1}H NMR (D_2O, 300 MHz): δ 7.37−7.23 (m, 5H), 3.97 (t, *J* = 4.8 Hz, 1H), 3.52 (s, 2H), 2.60 (d, *J* = 10.2 Hz, 2H), 2.45 (dd, *J* = 3.3, 11.1 Hz, 2H), 1.96 (br s, 1H), 1.82 (m, 2H), 1.65 (m, 2H).

Compound **13a** (90 mg, 0.41 mmol) was treated with Tf$_2$O (150 μL, 0.892 mmol) and pyridine (300 μL, 3.71 mmol) in CH$_2$-Cl$_2$ (3 mL) for 30 min at 0 °C. The mixture was poured into saturated NaHCO$_3$ solution and extracted with CH$_2$Cl$_2$. The organic layer was concentrated after drying, and the residue was dissolved in HMPA (1.5 mL). To the solution was added a mixture of phenylmagnesium bromide (1 M, 1.5 mL) and CuBr·Me$_2$S (5 mol %) under argon at 90 °C. After 2 h, the mixture was quenched with water and extracted with diethyl ether. The combined organic layer was dried over MgSO$_4$, concentrated, and purified by flash column chromatography with 1:20 EtOAc:hexane to afford *N*-benzyl-3-azabicyclo[3.2.1]-8β-bromooctane **15** (40 mg, 35%) and the mixture of **14** and *N*-benzyl-3-azabicyclo[3.2.1]octane **16** (37 mg). This mixture was once more purified by flash column chromatography with 1:15:15 diethyl ether:petroleum ether:CH$_2$Cl$_2$ to afford **14** (9.1 mg, 8%) and **16** (26.4 mg, 32%).

***N*-Benzyl-3-azabicyclo[3.2.1]-8β-phenyloctane (14).** mp 70−71 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.35−7.14 (m, 10H), 3.53 (s, 2H), 2.83 (dd, *J* = 3.0, 9.9 Hz, 2H), 2.74 (s, 1H), 2.48 (br s, 2H), 2.28 (d, *J* = 10.2 Hz, 2H), 1.74 (d, *J* = 7.5 Hz, 2H), 1.57 (m, 2H). HRMS (EI) calcd for $C_{20}H_{23}N$ *m/z*, 277.1830; found, 277.1834.

(14)−HCl. mp 214−215 °C. ^{1}H NMR (D_2O, 300 MHz): δ 7.38 (s, 5H), 7.30−7.14 (m, 5H), 4.20 (s, 2H), 3.34 (dd, *J* = 3.3, 12.9 Hz, 2H), 3.22 (d, *J* = 12.6 Hz, 2H), 2.97 (s, 1H), 2.72 (br s, 2H), 1.67 (m, 2H), 1.54 (m, 2H). Anal. ($C_{20}H_{24}NCl$·0.3H_2O): C, H, N, Cl.

***N*-Benzyl-3-azabicyclo[3.2.1]-8β-bromooctane (15).** ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.28 (m, 5H), 4.14 (s, 1H), 3.43 (s, 2H), 2.71 (ddd, *J* = 1.2, 4.2, 9.9 Hz, 2H), 3.36 (m, 2H), 2.19 (d, *J* = 10.8 Hz, 2H), 2.04 (m, 2H), 1.81 (d, *J* = 9.0 Hz, 2H). MS (CI) calcd for $C_{14}H_{18}NBr$ *m/z*, 279; found, 280.1 (M + 1).

(15)−HCl. mp 218−219 °C. ^{1}H NMR (D_2O, 300 MHz): δ 7.35 (m, 5H), 4.27 (s, 1H), 4.13 (s, 2H), 3.26 (dd, *J* = 3.0, 13.2 Hz, 2H), 3.16 (d, *J* = 12.6 Hz, 2H), 2.51 (br s, 2H), 2.15 (m, 2H), 1.62 (d, *J* = 8.7 Hz, 2H). Anal. ($C_{14}H_{19}NBrCl$): C, H, N, Br, Cl.

***N*-Benzyl-3-azabicyclo[3.2.1]octane (16).** ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.31−7.06 (m, 5H), 3.46 (s, 2H), 2.62 (d, *J* = 9.3

Hz, 2H), 2.06 (m, 4H) 1.74 (d, *J* = 6.6 Hz, 2H), 1.56 (m, 2H), 1.44 (m, 1H), 1.34 (d, *J* = 11.1 Hz, 1H). HRMS (EI) calcd for $C_{14}H_{19}N$ *m/z*, 201.1517; found, 201.1520.

(16)−HCl. mp 215−216 °C. ^{1}H NMR (D_2O, 300 MHz): δ 7.62 (m, 2H), 7.43 (m, 3H), 4.17 (d, *J* = 4.5 Hz, 2H), 3.21 (d, *J* = 11.1, 2H), 3.75 (t, *J* = 10.8 Hz, 2H), 2.48 (dd, *J* = 2.1, 9.3 Hz, 2H), 2.39 (br s, 2H), 1.82 (m, 2H), 1.58 (m, 2H), 1.39 (d, *J* = 11.7 Hz, 1H). Anal. ($C_{14}H_{20}NCl$): C, H, N, Cl.

3-Azabicyclo[3.2.1]-8β-phenyloctan-8α-ol (11). Using a similar procedure with the synthesis of **9a**, compound **7a** was hydrogenated in acetic acid to afford a white solid **11** (91%); mp 209−211 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.49 (d, *J* = 6.9 Hz, 2H), 7.39−7.26 (m, 3H), 3.54 (d, *J* = 12.6 Hz, 2H), 2.63 (dd, *J* = 2.7, 12.6 Hz, 2H), 2.37 (br s, 2H), 1.83 (br s, 2H), 1.60−1.50 (m, 4H).

(11)−HCl. mp >320 °C. ^{1}H NMR (D_2O, 300 MHz): δ 7.41 (m, 2H), 7.32−7.23 (m, 3H), 3.63 (d, *J* = 12.3 Hz, 2H), 3.10 (d, *J* = 12.0 Hz, 2H), 2.70 (br s, 2H), 1.59 (br s, 4H). Anal. ($C_{13}H_{18}$-NOCl·0.05H_2O): C, H, N, Cl.

***N*-Methyl-3-azabicyclo[3.2.1]-8β-phenyloctan-8α-ol (12).** Using a similar procedure with the synthesis of **10a**, compound **11a** was treated to afford **12** (99%). ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.44 (d, *J* = 7.2 Hz, 2H), 7.35−7.22 (m, 3H), 2.78 (d, *J* = 10.5 Hz, 2H), 2.56 (d, *J* = 10.5 Hz, 2H), 2.36 (s, 2H), 2.26 (s, 3H), 2.30−1.90 (br s, 1H), 1.66 (d, *J* = 7.8 Hz, 2H), 1.37 (m, 2H). HRMS (self-CI) calcd for $C_{14}H_{20}NO$ *m/z*, 218.1545; found, 218.1526 (M + 1).

(12)−HCl. mp >300 °C. ^{1}H NMR (D_2O, 300 MHz): δ 7.41 (m, 2H), 7.39−7.30 (m, 3H), 3.59 (d, *J* = 12.6 Hz, 2H), 3.31 (d, *J* = 12.3 Hz, 2H), 2.79 (s, 3H), 2.73 (s, 2H), 1.60 (s, 4H). Anal. ($C_{14}H_{20}NOCl$·0.25H_2O): C, H, N, Cl.

***N*-Benzyl-3-azabicyclo[3.2.1]-octan-8β-ol (13b).** Compound **13a** (90 mg, 0.41 mmol) was treated with Tf$_2$O (150 μL, 0.892 mmol) and pyridine (300 μL, 3.71 mmol) in the CH$_2$Cl$_2$ (3 mL) for 30 min at 0 °C. The mixture was poured into saturated NaHCO$_3$ solution and extracted with CH$_2$Cl$_2$. After it was dried with anhydrous MgSO$_4$, the organic layer was concentrated to give the triflate as a quantitative yield. Without further purification, it was refluxed with 1.5 equiv of *p*-TsOH·H$_2$O in a mixture of water (1 mL), DMSO (4 mL), and benzene (10 mL) under reflux for 3 days. After it was quenched with saturated K$_2$CO$_3$, the mixture was extracted with CH$_2$-Cl$_2$ and the organic layer was concentrated to give the crude product, which was purified by flash column chromatography with 1:2 ethyl acetate:hexane to afford the β-isomer **13b** (54 mg, 60%); mp 103−104 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.35−7.20 (m, 5H), 3.75 (s, 1H, C-8), 3.45 (s, 2H), 2.65 (ddd, *J* = 1.5, 4.8, 9.6 Hz, 2H), 2.11 (d, *J* = 10.8 Hz, 2H), 2.05 (br. s, 2H), 1.82−1.72 (m, 4H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 139.5, 128.6, 128.1, 126.7, 81.0, 61.5, 58.2, 41.1, 26.1. MS (CI) for $C_{14}H_{20}NO$ *m/z*, 218.3 (M + 1).

***N*-Benzyl-8β-diphenylmethoxy-3-azabicyclo[3.2.1]-octane (17b).** A mixture of 8β-alcohol **13b** (75 mg, 0.346 mmol), benzhydrol (127 mg, 0.691 mmol), *p*-toluenesulfonic acid monohydrate (131 mg, 0.691 mmol), and benzene (20 mL) was heated at reflux for 6 h. Benzhydrol (127 mg, 0.691 mmol) and *p*-toluenesulfonic acid monohydrate (65 mg, 0.346 mmol) were added, and the reaction mixture was further refluxed overnight. Benzene was removed, and the residue was dissolved in water, basified with K$_2$CO$_3$, and extracted with CH$_2$Cl$_2$. The extract was concentrated after drying with anhydrous MgSO$_4$, and the residue was chromatographed over silica gel (1:30 ethyl acetate:hexane) to afford **17b** (109 mg, 82%). ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.31−7.20 (m, 15H), 5.45 (s, 1H), 3.47 (s, 1H), 3.41 (s, 2H), 2.64 (dd, *J* = 4.2, 11.1 Hz, 2H), 2.23 (br. s, 2H), 1.99 (d, *J* = 10.8 Hz, 2H), 1.87 (m, 2H), 1.73 (m, 2H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 142.9, 139.5, 128.6, 128.2, 127.1, 126.7, 85.8, 79.5, 61.5, 58.3, 39.5, 26.8. HRMS (EI) calcd for $C_{27}H_{29}NO$ *m/z*, 383.2249; found, 383.2252 (M$^+$).

(17b)−HCl. mp >172.5−174 °C. ^{1}H NMR (D_2O, 300 MHz): δ 7.33−7.20 (m, 15H), 5.55 (s, 1H), 4.05 (s, 2H), 3.71 (s, 1H), 3.20 (d, *J* = 10 Hz, 2H), 2.90 (d, *J* = 13.2 Hz, 2H), 2.44 (br s, 2H), 1.92 (m, 2H), 1.55 (m, 2H). Anal. ($C_{27}H_{30}NOCl$·0.06HCl): C, H, N, Cl.

***N*-Benzyl-8α-diphenylmethoxy-3-azabicyclo[3.2.1]-octane (17a).** Using a similar coupling procedure to prepare ether **17b**, compound **13a** was coupled with benzhydrol to afford **17a** (79%). ¹H NMR (CDCl₃, 300 MHz): δ 7.41−7.20 (m, 15H), 5.45 (s, 1H), 3.56 (t, *J* = 4.5 Hz, 1H), 3.54 (s, 2H), 2.77 (d, *J* = 10.2 Hz, 2H), 2.41 (dd, *J* = 3.3, 10.2 Hz, 2H), 2.03 (br. s, 2H), 1.77 (m, 2H), 1.56 (m, 2H).

(17a)−HCl. mp >172.5−174 °C. ¹H NMR (D₂O, 300 MHz): δ 7.37−6.96 (m, 15H), 5.35 (s, 1H), 4.07 (s, 2H), 3.55 (t, *J* = 4.8 Hz, 1H), 3.31 (d, *J* = 12.0 Hz, 2H), 2.93 (dd, *J* = 2.7, 12.6 Hz, 2H), 2.09 (br s, 2H), 1.64−1.48 (m, 4H). Anal. (C₂₇H₃₀NOCl· 0.14H₂O): C, H, N, Cl.

Pharmacology. [³H]WIN 35,428 Binding. The synthesized compounds were screened for activity in a striatal synaptosomal membrane preparation by a previously described method.[7a,20]

[³H]DA Uptake. Accumulation of [³H]DA was determined as previously described.[20]

[³H]Citalopram Binding to the Transporter. The method used here was as described previously.[21] Briefly, a P₂ fraction prepared as described above from selected rat cortical tissue was homogenized in 16 volumes of ic-cold assay buffer (25 mM sodium phosphate buffer, pH 7.7, at 0 °C). Binding was initiated by addition of 150 μL of the P₂ suspension to samples containing 750 μL of assay buffer, 50 μL of the test compound, 25 μL of water or clomipramine (to define nonspecific binding; final concentration, 1 μM), and 25 μL of [³H]CIT (final concentration, 2 nM). Test compounds were dissolved in water, dilute DMSO, or dilute methanol, with the concentration of organic solvent in any assay tube limited to 0.3 vol %. Usually, a range of seven drug concentrations was used to generate the dose−response curve; triplicate samples were run at each concentration. The samples were incubated for 3 h at 0 °C. The reaction was terminated by addition of 5 mL of ice-cold assay buffer to the assay tubes, followed by rapid filtration through glass microfiber filter strips (presoaked in 0.05% polyethyleneimine) under reduced pressure using a Brandel 30 port cell harvester (Brandel Inc., Gaithersburg, MD). Assay tubes were washed with an additional 5 mL aliquot of ice-cold assay buffer. The filters were extracted and counted for radioactivity as described above. After correction of the data for displacement of filter binding by clomipramine and/or the test drug, IC₅₀ values and Hill coefficients were determined as described above. The dose−response curves usually contained a range of seven concentrations of the test drug, with triplicate determinations made at each concentration.

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