Synthesis and Pharmacology of Site-Specific Cocaine Abuse Treatment Agents: 2-Substituted-6-amino-5-phenylbicyclo[2.2.2]octanes

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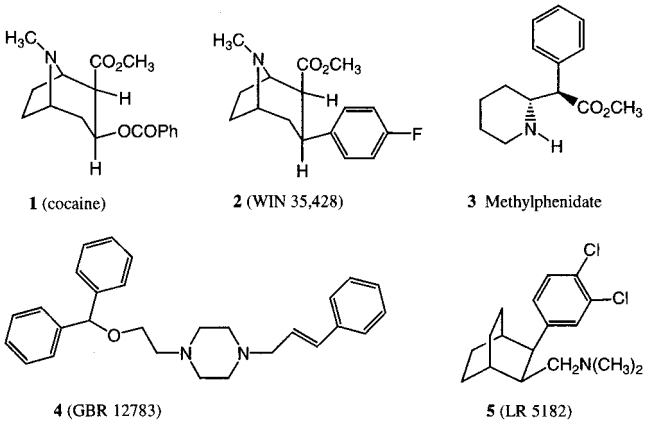
A series of 2-substituted-6-amino-5-phenylbicyclo[2.2.2]octanes was synthesized and tested for inhibitor potency in [^{3}H]WIN 35,428 (WIN) binding at the dopamine (DA) transporter and [^{3}H]DA uptake assays. To demonstrate transporter selectivity for the compounds, inhibitor potency was also tested using [^{3}H]nisoxetine and [^{3}H]paroxetine binding assays for the norepinephrine (NE) and serotonin (5-HT) transporters, respectively. Synthesis was accomplished by bisannulation of the enamine derived from phenylacetaldehyde and dimethylamine with 2-cyclohexenone to give a mixture of *endo*- and *exo*-*trans*-6-amino-5-phenylbicyclo[2.2.2]-octan-2-ones. The separated ketones were reduced to the four diastereomeric alcohols which were converted to acetyl and benzoyl esters. The ketones, alcohols, and acetyl esters generally have low affinity for the three transporters and do not effectively inhibit the uptake of [^{3}H]DA. In all cases, the benzoates show significantly greater inhibition of WIN binding compared to the corresponding ketones, alcohols, or acetate esters. One compound, (1*R*/*S*,4*R*/*S*)-6*R*/*S*-(*N*,*N*-dimethylamino)-5*R*/*S*-phenylbicyclo[2.2.2]oct-2*S*/*R*-yl benzoate, is almost as potent as cocaine in binding to the DA transporter (IC_{50} = 270 nM versus 159 nM for cocaine). The C-2 epimer, (1*R*/*S*,4*R*/*S*)-6*R*/*S*-(*N*,*N*-dimethylamino)-5*R*/*S*-phenylbicyclo[2.2.2]oct-2*R*/*S*-yl benzoate, was selective and potent in binding to the 5-HT transporter (IC_{50} = 53 nM versus 1050 nM for cocaine) as compared to the DA transporter (IC_{50} = 358 nM). A preliminary molecular modeling study of the benzoyl esters indicates that their relative potencies in the WIN binding assay are not correlated to the nitrogen to benzoate phenyl (centroid) distance or to the deviation of the nitrogen from the plane defined by the benzoate ring.

Introduction

A natural component of coca leaves (*Erythroxylum coca*), (−)-cocaine, **1**, is a psychostimulant and powerful reinforcer.[1,2] It has become one of the most prevalent and problematic drugs of abuse, and considerable effort has been expended in the study of its mechanism of action. It is now widely accepted that (−)-cocaine binds to specific recognition sites associated with monoamine transporters[3,4] in the mammalian brain. Its primary mechanism of action has been ascribed to its ability to inhibit the dopamine (DA) transporter for the reuptake of DA[5−7] into the presynaptic neuron, thus increasing the concentration of DA in the synapse.

Several approaches to the development of effective treatment agents for cocaine abuse have been proposed. One approach is to identify agonists (or partial agonists) which can serve as cocaine substitutes, the pharmacological equivalent of methadone in the treatment of opiate abuse.[8] Such a substance would elicit some of the same effects in the user as cocaine itself but, perhaps, not cause the same degree of euphoria. The most promising drug of this type might be a long-acting, slow-onset agonist. An alternative approach would be to make use of an antagonist, a substance which blocks the binding of cocaine yet still allows DA reuptake. However, no drugs of this type are currently known. The structures of known potent DA reuptake inhibitors provide guidance in the design of potential treatment agents. For example, WIN 35,428 (**2**, WIN) and GBR 12783 (**4**) are phenylpropylamines, whereas methylphenidate (**3**) is a phenylethylamine. To develop further leads to agonists, partial agonists, and antagonists of cocaine, we have undertaken a program of study of rigid bicyclic, non-tropane amines upon which a myriad of substituents can be placed in various regio- and stereochemical arrangements. These are used to probe structure−activity relationships for DA binding and reuptake, along with binding at the serotonin (5-HT) and norepinephrine (NE) transporters. An approach[9] that appeared attractive was based on a series of 2-aminomethyl-3-phenylbicyclo[2.2.2]octane analogues which were



1 (cocaine) **2** (WIN 35,428) **3** Methylphenidate

4 (GBR 12783) **5** (LR 5182)

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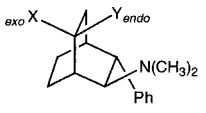
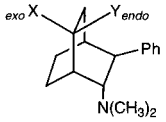
initially synthesized[10] and tested for biological activity[10−13] in the late 1970s. The most potent of these compounds, LR 5182 (**5**), was shown to be selective for the DA transporter, with K_i values of 3, 58, and 1700 nM for inhibition of [^{3}H]DA, [^{3}H]NE, and [^{3}H]5-HT, respectively.[11] Despite a lack of the tropane core, LR 5182 has a reasonable degree of structural analogy with cocaine, including the three-dimensional spatial arrangement of the basic nitrogen and phenyl ring.

In contrast to our previous work[9] on variants of **5**, the study described here involves synthesis of rigid bicyclic amines **6**−**19** which: (i) lack the exocyclic methylene group present in **5** and (ii) incorporate an oxygen functionality (ketone, alcohol, or ester) on the bicyclic framework. Incorporation of the oxygen functionality provides the opportunity to enhance the water solubility of agents by increasing the hydrophilicity of the hydrocarbon face of **5** and provides for additional structural diversity. Bicyclic amines **6**−**19** were studied for their effect on the DA transporter by measuring inhibition of [^{3}H]WIN binding and [^{3}H]DA uptake. To demonstrate transporter selectivity of the compounds, data for the NE and 5-HT transporters are also reported by measuring the displacement of [^{3}H]nisoxetine and [^{3}H]paroxetine binding, respectively.



endo amine



exo amine

	X	Y
6	=O	
7	OH	H
8	H	OH
9	$OCOCH_3$	H
10	H	$OCOCH_3$
11	OCOPh	H
12	H	OCOPh

	X	Y
13	=O	
14	OH	H
15	H	OH
16	$OCOCH_3$	H
17	H	$OCOCH_3$
18	OCOPh	H
19	H	OCOPh

Results and Discussion

Chemistry. Enamine **20**, which was prepared by condensation of phenylacetaldehyde with dimethylamine,[14] underwent reaction with cyclohexenone[15] to give a mixture of substituted bicyclo[2.2.2]octan-2-ones, **6** and **13**, as shown in Scheme 1. The isomeric ketones were formed in approximately a 1:1 ratio and were separated by flash chromatography on silica gel. It has been previously shown[15] that similar bisannulation procedures yield mixtures of *endo* and *exo* isomers in some cases and only the *endo* isomer in other cases. Single-crystal X-ray crystallography showed that the less polar (thin-layer chromatography: silica gel/EtOAc, R_f = 0.38) ketone was **6**, which has the *N*,*N*-dimethylamino substituent in the *endo* position (i.e., the amine is *syn* to the carbonyl) and the *trans* relationship between the phenyl and amino substituents.

We speculate that the mechanism of this reaction would involve an initial Michael addition of the enamine **20** to 2-cyclohexenone to form enolate **A**, as shown in Figure 1. This enolate would be in equilibrium with the regioisomeric enolate **B** which could ring close from the conformations shown in which the phenyl and iminium groups are approximately *anti* to each other. This would lead to only *trans* isomers, and in the case illustrated here, the *S*/*S* and *R*/*S* diastereomers would form the *exo* and *endo* isomers, respectively. Apparently the initial Michael addition leads to equal amounts of the *R*/*S* (*S*/*R*) and *S*/*S* (*R*/*R*) diastereomers, since we observe equal amounts of the *exo* and *endo* isomers.

Reduction of the *endo* amino ketone **6** with $NaBH_4$ in absolute EtOH gave exclusively **8** with the hydroxyl group in the *endo* position presumably due to shielding of one face of the carbonyl carbon of **6** by the *N*,*N*-dimethylamino group. The structure of **8** was confirmed by single-crystal X-ray crystallography. Treatment of **6** with borane−THF at −78 °C led exclusively to the diastereomeric *exo* alcohol **7** in which hydride has been introduced to the *most* sterically hindered face of the ketone. This observation is consistent with the complexation of the electron-rich amine and electron-deficient borane prior to hydride transfer to the carbonyl. ^{1}H NMR spectroscopy clearly differentiates **7** and **8** by observation of chemical shifts for the carbinol methine at 4.4 and 4.0 ppm, respectively.

Reduction of the *exo* amino ketone **13** with $NaBH_4$ gave a mixture of diastereomeric alcohols, **14** and **15** (1:1 ratio), which were separated by triturating the mixture with EtOAc. Single-crystal X-ray crystallography showed that the EtOAc-insoluble material is alcohol **15**, which confirms that it is an *exo* amine and shows that the hydroxyl substituent is in the *endo* position. The EtOAc-soluble fraction contained the diastereomer with the hydroxyl in the *exo* position (i.e., **14**). The carbinol proton of alcohols **14** and **15** coincide in the ^{1}H NMR spectrum (δ 4.1). Alcohols **7**, **8**, **14**, and **15** were converted to acetyl and benzoyl esters, **9**−**12** and **16**−**19**, by treatment with the appropriate acid chlorides in benzene containing triethylamine.

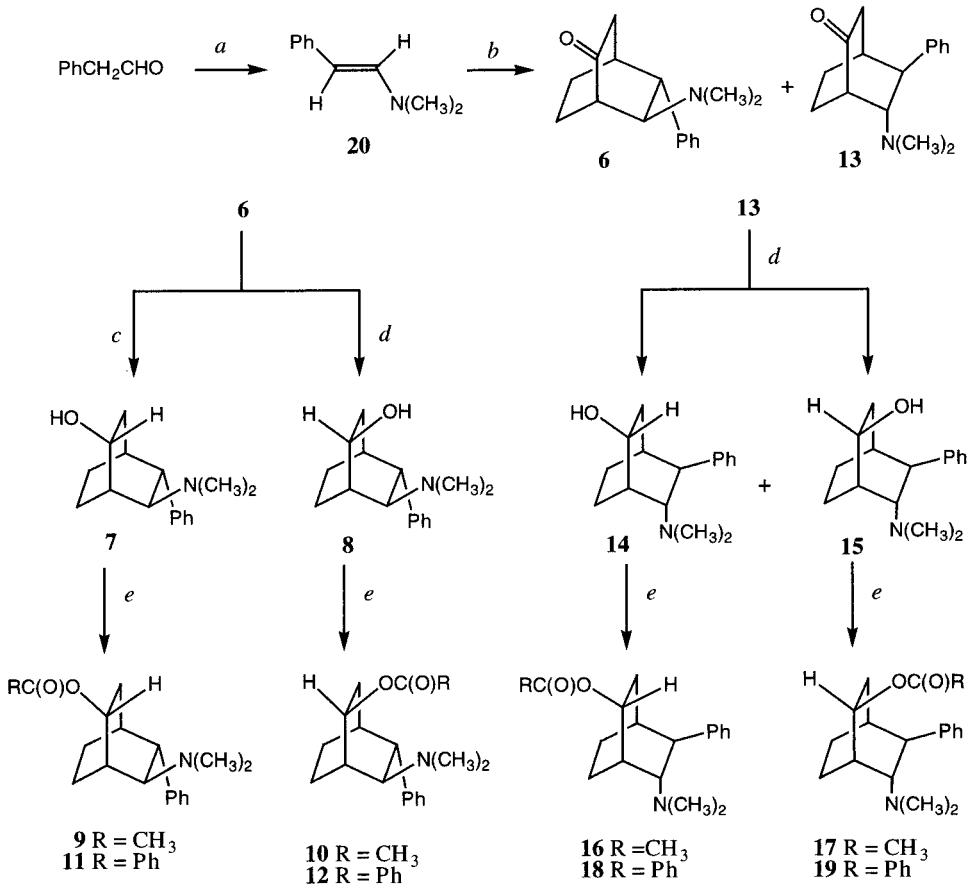
Pharmacology. The IC_{50} values for the inhibition of ligand binding to the DA,[16] 5-HT, and NE[17] transporters and the inhibition of [^{3}H]DA uptake[18] into synaptosomes were determined according to established protocols and are shown in Table 1. Binding to the DA transporter was measured using [^{3}H]WIN 35,428 (WIN), to the 5-HT transporter using [^{3}H]paroxetine (PAR), and to the NE transporter using [^{3}H]nisoxetine (NIS).

Inhibition of WIN Binding. In all cases, the *endo* amines are more potent than the corresponding *exo* amines by 3−8-fold. In addition, in all cases, the benzoate esters are more potent than the corresponding alcohols (3−8-fold). The alcohols have little difference in potency as compared to the corresponding ketones, which are somewhat more potent than the corresponding acetates (1.5−4-fold). The most potent compound is *endo* amine *endo* benzoyl ester **12** (IC_{50} = 0.270 μM) which is comparable to (−)-cocaine (IC_{50} = 0.159 μM). For all of the synthesized compounds, the stereochemistry at the 2-position has little effect on the potency.

Inhibition of [^{3}H]DA Uptake. Similar conclusions to those discussed about WIN binding can be reached when considering the inhibition of DA uptake.

Inhibition of PAR Binding. Generally, but not in all cases, the *endo* amines are more potent than the corresponding *exo* amines (2−14-fold more potent in four cases, 6−8-fold less potent in two cases). Somewhat similar trends in potency are observed for the 5-HT transporter as for the DA transporter for the different derivatives. In all cases, the benzoate esters are more potent than the corresponding alcohols (2-, 16-, 50-, and

Scheme 1[a]



[a] Reagents and conditions: (a) $(CH_3)_2NH$, Et_2O, $CaCl_2$; (b) cyclohexenone, benzene, Δ; (c) BH_3−THF, THF, −78 °C; (d) $NaBH_4$, EtOH, Δ; (e) RC(O)Cl, Et_3N, benzene.

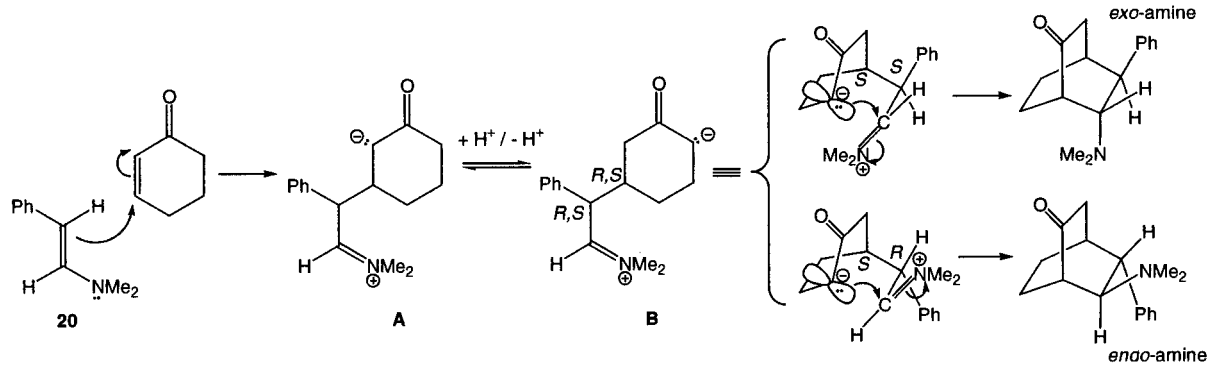


Figure 1. Possible mechanism of the bisannulation reaction.

160-fold). The alcohols are generally slightly more potent than the corresponding ketones, which are not uniformly more potent than the corresponding acetates (in one case 6-fold more potent, in three cases 3−13-fold less potent). For PAR binding at the 5-HT transporter, the stereochemistry of the 2-position has a large influence on activity. In all cases the *exo* isomers are more potent than the corresponding *endo* isomers (3−210-fold) with the *endo* amine *exo* benzoate **11** being 210-fold more potent than the *endo* benzoate isomer **12**. However, in the *exo* amine series, there is only a 2.5-fold decrease in potency when the benzoate function is moved from the *exo* to the *endo* position (**18** versus **19**). As in the case of the benzoate esters in the *endo* amine series, there is also a significant effect of the stereochemistry at C-2 for the acetate esters in the *endo* series. Changing the stereochemistry of the acetyl group from *exo* (**9**) to *endo* (**10**) reduces the potency 71-fold. Overall, the most effective compound at inhibiting PAR binding at the 5-HT transporter is **11** (IC_{50} = 0.053 μM).

Inhibition of NIS Binding. In all cases, the *endo* amines are more potent than or equipotent to the corresponding *exo* amines. The compound most potent for the NE transporter is the *endo* amine *exo* benzoate **11** (IC_{50} = 0.225 μM). The order of potency of the compounds in inhibiting the binding of NIS at the NE transporter generally, but not always, follows the pattern benzoyl > ketone > alcohol > acetate. Somewhat surprisingly, the *endo* amine *exo* acetate **9** was the second most potent compound (IC_{50} = 0.535 μM). As with the 5-HT transporter, the stereochemistry of the 2-position has a much greater effect on activity in the

Table 1. Binding and Uptake Data for 2-Substituted-6-amino-5-phenylbicyclo[2.2.2]octanes and Reference Compounds

compd[a]	IC_{50} (μM) DA [^{3}H]WIN[b]	NE [^{3}H]NIS[c]	5-HT [^{3}H]PAR[c]	[^{3}H]DA uptake[d]	IC_{50} NE/DA	IC_{50} 5-HT/DA
(−)-cocaine	0.160 ± 0.015	3.30 ± 0.29	1.05 ± 0.089	0.404 ± 0.026	21	6.6
WIN 35,428	0.0204 ± 0.0017	0.835 ± 0.045	0.809 ± 0.059	0.0513 ± 0.00030	41	40
methylphenidate	0.083 ± 0.0079	0.989 ± 0.054	224 ± 19	0.024 ± 0.019	12	2700
LR 5182[9]	0.0142 ± 0.0016	0.0960 ± 0.003	0.261 ± 0.016	0.0293 ± 0.0017	6.8	18
6	4.01 ± 0.40	4.12 ± 0.29	31.4 ± 7.6	9.14 ± 0.63	1.0	7.8
7	1.77 ± 0.13	1.51 ± 0.21	8.38 ± 1.1	4.45 ± 0.12	0.85	4.7
8	2.04 ± 0.24	7.23 ± 0.71	21.8 ± 2.75	2.81 ± 0.270	3.5	11
9	5.33 ± 0.36	0.535 ± 0.025	2.45 ± 0.18	4.93 ± 0.63	0.10	0.46
10	12.2 ± 0.69	55.4 ± 11.9	176 ± 5.5	25.8 ± 3.00	4.5	14
11	0.358 ± 0.067	0.225 ± 0.044	0.053 ± 0.012	0.372 ± 0.061	0.65	0.15
12	0.270 ± 0.029	1.47 ± 0.017	11.1 ± 1.39	0.687 ± 0.015	5.4	41
13	10.3 ± 0.40	10.6 ± 1.6	61.2 ± 17	24.7 ± 0.45	1.0	5.9
14	7.04 ± 0.29	7.73 ± 0.80	12.3 ± 2.5	10.9 ± 2.3	1.1	1.7
15	9.92 ± 0.94	34.4 ± 4.7	>100	23.0 ± 1.6	3.5	>10
16	13.6 ± 1.43	10.4 ± 3.6	4.77 ± 0.12	16.3 ± 0.16	0.76	0.35
17	45.6 ± 6.24	46.8 ± 2.6	22.8 ± 0.51	~75[e]	1.0	0.50
18	2.20 ± 0.31	7.38 ± 0.66	0.760 ± 0.081	4.84 ± 0.064	3.4	0.35
19	2.27 ± 0.066	4.19 ± 0.74	1.88 ± 0.039	8.24 ± 0.33	1.8	0.83

[a] Compounds tested as the HCl salts. [b] All values are the mean of two experiments performed in triplicate. [c] All values are the mean of three experiments performed in triplicate. [d] All values are the mean of two experiments performed in duplicate. [e] 55.3 ± 0.7% inhibition at 75 μM.

endo amine series than in the *exo* series. For example, changing the stereochemistry of the acetyl and benzoyl substituents from *exo* (**9** and **11**) to *endo* (**10** and **12**) decreases the potency by 100- and 7-fold, respectively. Similar comparisons in the *endo* series show much smaller (or no) decreases in potency: *exo* (**16** and **18**) to *endo* (**17** and **19**) result in 4.5- and 0.6-fold potency reductions, respectively.

Transporter Selectivity. Selectivity of compounds **6**−**19** for the three transporters was calculated by comparing the ratio of IC_{50} values, NIS/WIN for NE/DA selectivity and PAR/WIN for 5-HT/DA selectivity, as shown in Table 1. The compound that shows the highest selectivity for the DA transporter was *endo* amine *endo* benzoate **12**, which is 41 times more potent for the DA transporter than for the 5-HT transporter and 5 times more potent for the DA transporter than for the NE transporter. Interestingly, *endo* amine *exo* benzoate **11** is most active and selective for the 5-HT transporter, being 7-fold selective compared to the DA transporter and 4-fold selective compared to the NE transporter.

General Considerations. Since the benzoate esters were generally the most potent derivatives, it was hypothesized that the benzoate ester phenyl ring was important in the binding interactions of these compounds. To test if the distance and orientation of the benzoate phenyl ring from the nitrogen atom are important parameters in the pharmacophore of these compounds, energy-minimized (MM2)[19] conformational searches were computed to obtain the global minima. Different conformations about the two C−Ph and two C−O bonds were manually searched. The distances between the nitrogen and the centroid of the benzoate phenyl ring (N−Ph_C) and between the nitrogen and the plane of the phenyl ring[20] (N−Ph_P) were calculated and are shown in Table 2 (also see Figure 2). In its energy-minimized (MM2)[19] conformation, the highly potent DA uptake inhibitor WIN, **2**, has a N−Ph_C distance of 5.57 Å with the nitrogen only slightly out of the plane defined by the phenyl ring (0.07 Å). Examination of the interaction of the test compounds with the DA transporter revealed that the most active of the benzoyl esters (**12**, IC_{50} = 0.270 μM) has a N−Ph_C distance of 5.43 Å with the nitrogen further out of the plane of the phenyl ring (0.74 Å). One of the less active of the benzoate esters (**18**, IC_{50} = 2.20 μM) has a larger N−Ph_C distance (8.64 Å) and a considerably larger deviation of the nitrogen from the plane of the phenyl ring (1.1 Å). However, the other less active benzoate ester (**19**, IC_{50} = 2.27 μM) has a much shorter N−Ph_C distance (7.19 Å) and smaller out of plane distance (0.35 Å). This is comparible to the more active **11** (IC_{50} = 0.358 μM, N−Ph_C = 7.68 Å, N−Ph_p = 0.43 Å). These data alone do not show how either the *orientation* of the benzoate phenyl ring with respect to the nitrogen or the *distance* between the two is of significance in determining the potency of these agents in inhibiting binding to the DA transporter.

Table 2. Interatomic Distances and Relative Distribution of Atoms in Space

	distances (Å) N−Ph_c[a]	N−Ph_{fa}[b]	N−Ph_p[c]
WIN	5.57	8.30	0.07
PAR	6.91	10.81	1.4
11	7.68	10.18	0.43
12	5.43	8.15	0.74
18	8.64	11.01	1.1
19	7.19	9.61	0.35

[a] Ph_c = centroid of benzoate phenyl ring. [b] Ph_{fa} = furthest atom on benzoate phenyl ring. [c] Ph_p = benzoate phenyl plane.

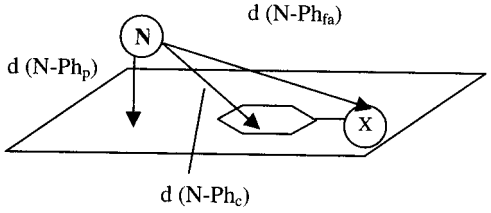


Figure 2. Definitions of distances used in the description of models

In contrast, the 5-HT transporter seems to be able to accommodate a larger N−Ph_C distance. Although the N−Ph_c distance has been correlated to potency before,[21,22] such an analysis did not take the phenyl substituents into account. Thus, we also tabulate the distance between the nitrogen and the furthest atom

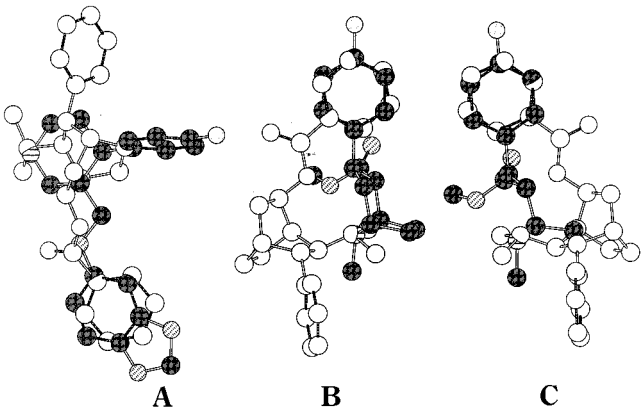


Figure 3. A. Overlay of PAR (shaded) and 6*R* enantiomer **11** (white). B. Overlay of WIN (shaded) and 6*R* enantiomer of **12** (white). C. Overlay of WIN (shaded) and 6*S* enantiomer of **12** (white).

($N-Ph_{fa}$) on the ring in Table 2 (also see Figure 2). The compound most effective at inhibiting PAR binding at the 5-HT transporter, **11** (IC_{50} = 0.052 μM), has an $N-Ph_{fa}$ distance (10.18 Å) comparable to that of PAR (10.81 Å). In contrast the least active benzoate, **12** (IC_{50} = 11.1 μM), has a much shorter $N-Ph_{fa}$ distance (8.15 Å). Figure 3A shows an overlay of PAR and the 6*R* enantiomer of benzoate ester **11** and illustrates the good overlap of the phenyl groups and nitrogen atoms.

Figure 3 also shows an overlay of WIN and the 6*R* enantiomer of benzoate ester **12** (B) and the 6*S* enantiomer of **12** (C). Substituents on the two-carbon bridge often dramatically decrease the potency of of tropane-based compounds.[23] Comparison of these two overlays demonstrates that the enantiomer shown in Figure 3C has atoms in the region of the two-carbon bridge of the tropane whereas that shown in Figure 3B does not; this might provide future direction in targeting the development of potent DA uptake inhibitors.

Due to the many possible low-energy conformations of NIS, it is difficult to comment on the distances that are optimal for effective binding.

Conclusions

A series of *trans*-6-(*N*,*N*-dimethylamino)-5-phenylbicyclo[2.2.2]octanes was prepared by a bisannulation procedure with a variety of substituents at the 2-position. Interestingly, the ketone **6** could be stereospecifically reduced to either alcohol **7** or **8** with diborane or sodium borohydride, respectively. The ketones (**6**, **13**), alcohols (**7**, **8**, **14**, **15**), acetates (**9**, **10**, **16**, **17**), and benzoates (**18** and **19**) usually have moderate to low affinity for the DA, 5-HT, and NE transporters and do not effectively inhibit the uptake of [^{3}H]DA, relative to cocaine. The benzoate ester **12** is the most potent derivative for inhibiting radioligand binding to the DA transporter, while benzoate **11** is quite potent and somewhat selective for inhibiting the 5-HT transporter. In these benzoate esters (**11** and **12**) the ester phenyl ring (and not the phenyl at C-5) might be binding to the "aromatic ring binding region" in the various transporters. Future work will test the importance of the benzoate ester phenyl ring by removal of the phenyl at C-5. In addition, the enantiomers of **12** will be prepared to determine which is most active; this will provide further input into a model for the development of potent and selective inhibitors of the monoamine transporters.

Experimental Section

General Methods. Melting points were determined on a Mel-Temp apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on a Varian Gemini spectrometer at 300 and 75 MHz, respectively. IR spectra were obtained using KBr pellets on a Nicolet 520FT spectrometer. All starting materials were used as received from Aldrich Chemical Co. Tetrahydrofuran (THF) was dried over sodium benzophenone ketyl prior to distillation under nitrogen. Benzene was dried over 4 Å molecular sieves. Free bases were dissolved in minimum amount of MeOH and were converted to HCl salts by the addition of 1.5 equiv of concentrated HCl. MeOH was added and the HCl was removed under reduced pressure. The resulting solid was recrystallized from MeOH/EtOAc. Elemental analyses were obtained from Atlantic Microlabs, Atlanta, GA.

***E*-2-(*N*,*N*-Dimethylamino)-1-phenylethene (20).** A mixture of dimethylamine (2.76 mL, 41.7 mmol), Et_2O (34 mL), phenylacetaldehyde (1.95 mL, 6.60 mmol), and $CaCl_2$ pellets (3.75 g) was stirred at room temperature for 64 h. The mixture was filtered and concentrated under reduced pressure to give **20** (2.25 g, 91.8%) as a dark yellow viscous oil. Distillation gave 1.65 g (73.3%) of **20** as a yellow liquid: bp 165−168 °C at 0.5 mmHg (lit.[14] bp 100−102 °C/0.5 mmHg); ^{1}H NMR ($CDCl_3$) δ 2.82 (s, 6H, CH_3), 5.22 (d, J = 13 Hz, 1H, C*H*=CHN), 6.84 (dd, J = 13 Hz, J = 2.1 Hz, 1H, CH=C*H*N), 7.00−7.25 (m, 5H, Ar).

(1*R*/*S*,4*R*/*S*)-6-(*N*,*N*-Dimethylamino)-5-phenylbicyclo-[2.2.2]octan-2-ones 6 and 13. A solution of **20** (1.5 g, 10 mmol) and 2-cyclohexenone (1.54 mL, 15.9 mmol) in benzene was heated at reflux for 48 h. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL) and the solution was extracted with 6 M aqueous HCl (3 × 10 mL). The aqueous extracts were combined, made basic with NaOH pellets, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$ and filtered and the solvent was removed under reduced pressure to afford a viscous brown oil. Purification by flash column chromatography (silica gel; eluted sequentially with 2:1 hexane:EtOAc, 1:1 hexane:EtOAc, and EtOAc) gave **6** as an off-white solid (0.19 g, 25%) and further elution (1:1 EtOAc:MeOH then MeOH) gave **13** as a viscous brown oil (0.15 g, 20%).

(1*R*/*S*,4*R*/*S*)-6*R*/*S*-(*N*,*N*-Dimethylamino)-5*R*/*S*-phenylbicyclo[2.2.2]octan-2-one (6): ^{1}H NMR ($CDCl_3$) δ 1.04−1.28 (m, 1H), 1.46−62 (m, 1H), 1.74−1.79 (m, 2H), 1.99−2.01 (m, 7H, $N(CH_3)_2$), 2.16 (dd, J = 19 Hz, J = 3, 1H), 2.37 (dd, J = 19 Hz, J = 3 Hz, 1H), 2.64−2.69 (m, 2H, C-5), 2.88 (br s, 1H, C-6), 7.12−7.30 (m, 5H, aromatic); ^{13}C NMR ($CDCl_3$) δ 12.7, 16.3, 30.9, 37.7, 39.7, 40.2, 44.9, 62.8 (aliphatic); 120.9, 122.4, 123.1, 138.5 (aryl); 209.7 (C=O).

6-HCl: 97% yield; mp 203−204 °C; ^{1}H NMR (D_2O) δ 1.25−1.34 (m, 1H), 1.52−1.62 (m, 1H), 1.81−1.92 (m, 1H), 1.95−2.05 (m, 1H), 2.10 (q, J = 3.0 Hz, 1H), 2.45 (d, J = 2.7 Hz, 1H), 2.49 (t, J = 2.7 Hz, 1H), 2.56 (s, 6H, $N(CH_3)_2$), 2.84 (q, J = 2.7 Hz, 1H, C-5), 3.12 (d, J = 7.2 Hz, 1H, C-6), 4.07 (dt, J = 7.2 Hz, J = 1.8 Hz, 1H, C-2), 7.18−7.29 (m, 5H, Ar); IR 2657−2591, 1729 cm^{-1}. Anal. ($C_{16}H_{22}ONCl\cdot1.2H_2O$) C, H, N, Cl.

(1*R*/*S*,4*R*/*S*)-6*S*/*R*-(*N*,*N*-Dimethylamino)-5*S*/*R*-phenylbicyclo[2.2.2]octan-2-one (13): ^{1}H NMR ($CDCl_3$) δ 1.45−1.60 (m, 2H), 1.75 (s, 1H), 1.82−1.88 (m, 1H), 1.92−1.97 (m, 7H, $N(CH_3)_2$), 2.04−2.18 (m, 2H), 2.48 (br s, 1H), 2.61 (br s, 1H, C-5), 2.78 (br s, 1H, C-6), 6.98−7.21 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$) δ 10.1, 20.6, 31.2, 33.1, 38.7, 41.6, 45.3, 59.6 (aliphatic); 120.9, 122.5, 123.2, 139.0 (aryl); 210.8 (C=O).

13-HCl: 74% yield; mp 184−186 °C; ^{1}H NMR (D_2O) δ 1.64−1.77 (m, 2H), 1.88−1.91 (m, 2H), 2.10−2.25 (m, 2H), 2.50−2.77 (m, 6H, $N(CH_3)_2$), 2.95 (br s, 1H), 3.11−3.15 (m, 1H), 3.17 (dd, J = 4.8 Hz, J = 3.3 Hz, 1H, C-5) 3.88−3.98 (m, 1H, C-6), 7.15−7.33 (m, 5H, Ar); IR 2664−2460, 1729, 1130 cm^{-1}. Anal. ($C_{16}H_{22}ONCl\cdot1.52H_2O$) C, H, N, Cl.

(1*R*/*S*,4*R*/*S*)-6*R*/*S*-(*N*,*N*-Dimethylamino)-5*R*/*S*-phenylbicyclo[2.2.2]octan-2*R*/*S*-ol (7). BH_3−THF (8 mL) was slowly added to a solution of **6** (2.26 g, 9.92 mmol) dissolved in THF (20 mL) at −78 °C and stirred under nitrogen for 20 h. Aqueous 6 M HCl (10 mL) was added to the mixture and THF was removed under reduced pressure. The resulting solution was made basic with NaOH pellets and extracted with CH_2Cl_2 (4 × 10 mL). The organic extracts were combined, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure to afford **7** as a white solid (2.27 g, 100% yield): ^{1}H NMR ($CDCl_3$) δ 1.25−1.35 (m, 1H), 1.40−1.50 (m, 3H), 1.61 (d, J = 2.7 Hz, 1H), 2.12−2.21 (m, 8H, $N(CH_3)_2$), 2.34−2.43 (m, 1H), 2.62 (br s, 1H, C-5), 2.69 (br s, 1H, C-6), 4.42 (d, J = 9.9 Hz, 1H, C-2), 7.10−7.35 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$) δ 12.5, 13.5, 29.6, 29.6, 33.5, 38.8, 45.2, 58.5, 62.8 (aliphatic); 120.6, 122.6, 123.0, 139.8 (aryl).

7-HCl: 84% yield; mp 296−297 °C; ^{1}H NMR (D_2O) δ 1.10−1.37 (m, 4H), 1.51−1.56 (m, 1H), 1.91−1.95 (m, 1H), 2.12−2.22 (m, 2H), 2.56 (br s, 6H, $N(CH_3)_2$), 2.73−2.76 (m, 1H, C-5), 3.67 (dd, J = 15.5 Hz, J = 6.6 Hz, C-6), 4.02 (br s, 1H, C-2), 7.09−7.35 (m, 5H, Ar); IR 3381, 2703, 2479, 1077 cm^{-1}. Anal. ($C_{16}H_{24}ONCl$) C, H, N, Cl.

(1*R*/*S*,4*R*/*S*)-6*R*/*S*-(*N*,*N*-Dimethylamino)-5*R*/*S*-phenylbicyclo[2.2.2]octan-2*S*/*R*-ol (8). To a solution of **6** (1.49 g, 6.12 mmol) in absolute EtOH (50 mL) was added slowly $NaBH_4$ (0.464 g, 12.3 mmol) and the mixture was heated at reflux under nitrogen for 3 h. The resulting solution was poured onto ice, EtOH was removed under reduced pressure, and the aqueous solution was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried over $MgSO_4$, and filtered and the solvent was removed under reduced pressure to afford **8** as a white solid (1.50 g, 100% yield): ^{1}H NMR ($CDCl_3$) δ 0.91−0.95 (m, 1H), 1.31−1.56 (m, 5H), 1.75 (dd, J = 14.4 Hz, J = 1.6 Hz, 1H), 1.91−2.00 (m, 1H), 2.05−2.07 (m, 6H, $N(CH_3)_2$), 2.43 (d, J = 1.2 Hz, 1H), 2.65 (dd, J = 6.5 Hz, J = 1.6 Hz, 1H, C-5), 2.99 (d, J = 6.5 Hz, 1H, C-6), 3.92−3.96 (m, 1H, C-2), 7.05−7.25 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$) δ 12.3, 16.6, 25.7, 28.9, 35.7, 38.4, 44.1, 62.4, 64.0 (aliphatic); 120.6, 122.6, 123.0, 140.1 (aryl).

8-HCl: 87% yield; mp 245−247 °C; ^{1}H NMR (D_2O) δ 0.98−1.02 (m, 1H), 1.26−1.28 (m, 1H), 1.49−1.60 (m, 1H), 1.63 (s, 3H), 1.97−2.06 (m, 1H), 2.40 (br s, 4H), 2.50 (br s, 1H), 2.83 (s, 2H), 3.10 (d, J = 6.9 Hz, 1H, C-5), 3.65 (d, J = 6.9, 1H, C-6), 4.07 (d, J = 9.3 Hz, 1H, C-2), 7.21−7.35 (m, 5H, Ar); IR 3335−3295, 1150, 1031 cm^{-1}. Anal. ($C_{16}H_{24}ONCl\cdot 0.07H_2O$) C, H, N, Cl.

6-(*N*,*N*-Dimethylamino)-5-phenylbicyclo[2.2.2]octan-2-ols 14 and 15. Treatment of **13** according to the procedure for the synthesis of **8** afforded a mixture of **14** and **15** which was triturated with EtOAc (10 mL) and filtered to give **14** as a white solid (1.26 g, 57%). The solvent was removed from the filtrate to afford **15** as a white solid (0.95 g, 43%).

(1*R*/*S*,4*R*/*S*)-6*S*/*R*-(*N*,*N*-Dimethylamino)-5*S*/*R*-phenylbicyclo[2.2.2]-octan-2*R*/*S*-ol (14): ^{1}H NMR ($CDCl_3$) δ 1.09 (d, J = 14.1 Hz, 1H), 1.56 (d, J = 2.1 Hz, 1H), 1.64−1.95 (m, 5H), 2.10 (m, 7H, $N(CH_3)_2$), 2.31 (d, J = 3.6 Hz, 1H, C-5), 2.70 (d, J = 4.8 Hz, 1H, C-6), 3.6 (br s, 1H, OH), 4.01 (dd, J = 3.3 Hz, J = 6.6 Hz, 1H, C-2), 7.10−7.30 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$) δ 6.9, 21.7, 26.0, 28.9, 30.2, 39.1, 45.5, 62.1, 63.3 (aliphatic); 120.5, 122.5, 123.0, 140.3 (aryl).

14-HCl: 86% yield; mp 250−251 °C; ^{1}H NMR (D_2O) δ 0.93 (br d, J = 14.7 Hz, 1H), 1.32−1.37 (m, 1H), 1.55−1.60 (m, 3H), 1.73−1.76 (m, 3H), 2.19 (br s, 1H), 2.57−2.79 (m, 6H, $N(CH_3)_2$), 3.51 (d, J = 4.5 Hz, 1H, C-6), 4.00 (d, J = 9.9 Hz, 1H, C-2), 7.01−7.25 (m, 5H, Ar); IR 3368−3328, 2683, 1170, 1097 cm^{-1}. Anal. ($C_{16}H_{24}ONCl$) C, H, N, Cl.

(1*R*/*S*,4*R*/*S*)-6*S*/*R*-(*N*,*N*-Dimethylamino)-5*S*/*R*-phenylbicyclo[2.2.2]octan-2*S*/*R*-ol (15): ^{1}H NMR ($CDCl_3$) δ 1.32−1.41 (m, 3H), 1.45−1.52 (m, 3H), 1.60−1.80 (m, 3H), 1.95−2.02 (m, 2H), 2.11 (m, 7H, $N(CH_3)_2$), 2.67 (d, J = 5.9 Hz, 1H, C-5), 2.92 (d, J = 5.9 Hz, 1H, C-6), 4.06−4.08 (m, 1H, C-2), 7.18−7.30 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$) δ 11.9, 20.7, 25.3, 29.8, 30.1, 38.9, 46.4, 55.8, 63.8 (aliphatic); 120.3, 122.9, 123.2, 140.5 (aryl).

15-HCl: 78% yield; mp 225−226 °C; ^{1}H NMR (D_2O) δ 1.20−1.25 (m, 1H), 1.43−1.61 (m, 6H), 2.25 (br s, 1H, C-1), 2.62 (br s, 6H, $N(CH_3)_2$), 2.82 (d, J = 6.0 Hz, 1H, C-5), 3.89 (d, J = 6.0 Hz, 1H, C-6), 4.06−4.20 (m, 1H, C-2), 7.21 (m, 5H, Ar); IR 3473−3361, 2710, 1110, 1045 cm^{-1}. Anal. ($C_{16}H_{24}ONCl\cdot 0.20H_2O$) C, H, N, Cl.

6-(*N*,*N*-Dimethylamino)-5-phenylbicyclo[2.2.2]octan-2-yl Acetates and Benzoates 9−12 and 16−19. The conversion of **14** to **16** is illustrated. Acetyl chloride (40.0 μL, 0.567 mmol) and Et_3N (91.0 μL, 0.654 mmol) were added to a solution of **14** (0.107 g, 0.436 mmol) in benzene (6 mL). The solution was stirred under nitrogen at room temperature for 24 h. The mixture was washed with water (1 × 10 mL) and 5% aqueous Na_2CO_3 (3 × 10 mL). The organic layer was dried over $MgSO_4$ and filtered and the solvent was removed under reduced pressure to afford **16** as a white solid (0.120 g, 96% yield).

(1*R*/*S*,4*R*/*S*)-6*S*/*R*-(*N*,*N*-Dimethylamino)-5*S*/*R*-phenylbicyclo[2.2.2]oct-2*R*/*S*-yl acetate (16): 73% yield; ^{1}H NMR ($CDCl_3$) δ 1.13 (dd, J = 14.7 Hz, J = 1.2 Hz, 1H), 1.58−1.69 (m, 5H), 1.96−2.02 (m, 1H), 2.05 (s, 3H, CH_3), 2.10 (s, 6H, $N(CH_3)_2$), 2.22−2.26 (m, 1H), 2.42−2.44 (m, 1H, C-5), 2.75 (d, J = 5.1 Hz, 1H, C-6), 4.98 (dt, J = 9.9 Hz, J = 3.3 Hz, 1H, C-2), 7.10−7.20 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$) δ 7.4, 15.8, 21.3, 23.2, 26.7, 28.5, 38.6, 45.3, 61.1, 66.4 (aliphatic); 120.7, 122.5, 123.1, 139.8 (aryl); 165.5 (C═O).

16-HCl: 71% yield; mp 250−251 °C; ^{1}H NMR (D_2O) δ 1.10−1.14 (m, 1H), 1.30−1.45 (m, 1H), 1.50−1.68 (m, 3H), 1.79−1.87 (m, 2H), 1.93 (br s, 3H, CH_3), 2.39 (br s, 1H, C-1), 2.59 (br s, 6H, $N(CH_3)_2$), 2.80−2.84 (m, 1H, C-5), 3.60−3.68 (m, 1H, C-6), 4.83−4.92 (m, 1H, C-2), 7.15−7.28 (m, 5H, Ar); IR 2670−2591, 1729, 1262, 1038 cm^{-1}. Anal. ($C_{18}H_{26}O_2NCl\cdot 0.75H_2O$) C, H, N, Cl.

(1*R*/*S*,4*R*/*S*)-6*R*/*S*-(*N*,*N*-Dimethylamino)-5*R*/*S*-phenylbicyclo[2.2.2]oct-2*R*/*S*-yl acetate (9): 100% yield; ^{1}H NMR ($CDCl_3$) δ 1.22−1.49 (m, 3H), 1.54 (dt, J = 14.4 Hz, J = 3.0 Hz, 1H), 1.63 (dd, J = 3.0 Hz, J = 2.7 Hz, 1H), 1.91−2.03 (m, 1H), 2.05 (s, 3H, CH_3), 2,13 (m, 6H, $N(CH_3)_2$), 2.32 (m, 2H, C-1 and C-4), 2.44 (dd, J = 4.8 Hz, J = 2.7 Hz, 1H, C-5), 2.70 (br s, 1H, C-6), 5.27 (dt, J = 10.2 Hz, J = 3.0 Hz, C-2), 7.15−7.39 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$) δ 13.0, 13.2, 15.9, 26.2, 28.9, 30.2, 38.9, 45.8, 62.3, 63.3 (aliphatic); 120.6, 122.6, 122.9, 139.9 (aryl); 165.7 (C═O).

9-HCl: 74% yield; mp 197−199 °C; ^{1}H NMR (D_2O) δ 1.21−1.65 (m, 7H), 1.90 (br s, 1H), 1.97 (s, 3H, CH_3), 2.18−2.26 (m, 1H), 2.46−2.85 (m, 6H, $N(CH_3)_2$), 3.74 (dd, J = 15 Hz, J = 3.9 Hz, 1H, C-6), 4.95 (m, 1H, C-2), 7.18−7.40 (m, 5H, Ar); IR 2670−2591, 1729, 1262, 1038 cm^{-1}. Anal. ($C_{18}H_{26}O_2NCl\cdot 0.30H_2O$) C, H, N, Cl.

(1*R*/*S*,4*R*/*S*)-6*R*/*S*-(*N*,*N*-Dimethylamino)-5*R*/*S*-phenylbicyclo[2.2.2]oct-2*S*/*R*-yl acetate (10): 74% yield; ^{1}H NMR ($CDCl_3$) δ 1.10−1.14 (m, 1H), 1.39−1.42 (m, 1H), 1.58−1.68 (m, 3H), 1.79 (dt, J = 13.8 Hz, J = 4.8 Hz, J = 2.7 Hz, 1H), 2.07 (s, 3H, CH_3), 2.1 (s, 6H, $N(CH_3)_2$), 2.17−2.28 (m, 1H), 2.41−2.45 (m, 1H), 2.51 (d, J = 4.8 Hz, 1H, C-5), 3.02 (br s, 1H, C-6), 4.94−4.97 (m, 1H, C-2), 7.10−7.35 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$) δ 12.3, 15.9, 18.6, 25.6, 28.3, 30.6, 39.0, 46.2, 63.0, 66.3 (aliphatic); 120.7, 122.4, 123.4, 123.0, 139.8 (aryl); 166.0 (C═O).

10-HCl: 95% yield; mp 252−253 °C; ^{1}H NMR (D_2O) δ 0.80−1.10 (m, 1H), 1.08−1.38 (m, 1H), 1.56−1.67 (m, 4H), 2.00 (s, 3H, CH_3), 2.17−2.25 (m, 1H, C-4), 2.58−2.62 (m, 7H, $N(CH_3)_2$ and C-1), 3.01 (d, J = 6.0 Hz, 1H, C-5), 3.67 (d, J = 6.0 Hz, 1H, C-6), 4.94 (br d, J = 10 Hz, 1H, C-2), 7.19−7.40 (m, 5H, Ar); IR 1749, 1249, 1038 cm^{-1}. Anal. ($C_{18}H_{26}O_2NCl$) C, H, N, Cl.

(1*R*/*S*,4*R*/*S*)-6*S*/*R*-(*N*,*N*-Dimethylamino)-5*S*/*R*-phenylbicyclo[2.2.2]oct-2*S*/*R*-yl acetate (17): 92% yield; ^{1}H NMR ($CDCl_3$) δ 1.32−1.49 (m, 3H), 1.59 (br s, 1H), 1.68−1.78 (m, 2H), 1.90−1.99 (m, 1H), 2.04 (m, 6H, $N(CH_3)_2$), 2.12 (s, 3H, CH_3), 2.20 (d, J = 2.7 Hz, 1, C-1), 2.66 (br s, J = 5.6 Hz, 1H, C-5), 2.73 (br d, J = 5.7 Hz, 1H, C-6), 4.95 (dt, J = 10.2 Hz, J = 3.6 Hz, C-2), 7.15−7.28 (m, 5H, Ar); ^{13}C ($CDCl_3$) δ 11.4, 15.9, 20.5, 22.7, 26.7, 29.4, 38.8, 45.9, 56.2, 66.7 (aliphatic); 120.5, 122.9, 122.9, 140.1 (aryl); 165.3 (C═O).

17-HCl: 80% yield; mp 118−120 °C; ^{1}H NMR (D_2O) δ 1.26−1.32 (m, 1H), 1.48−1.77 (m, 6H), 2.04 (s, 3H, CH_3), 2.41 (br s, 1H, C-5), 2.60 (br s, 6H, $N(CH_3)_2$), 2.85 (d, J = 6 Hz, 1H, C-6), 4.90 (dt, J = 9.9 Hz, J = 3.9 Hz, 1H, C-2), 7.15−7.28 (m, 5H, Ar); IR 1755, 1262, 1038 cm^{-1}. Anal. ($C_{18}H_{26}O_2NCl\cdot2.5H_2O$) C, H, N, Cl.

(1*R*/*S*,4*R*/*S*)-6*R*/*S*-(*N*,*N*-Dimethylamino)-5*R*/*S*-phenylbicyclo[2.2.2]oct-2*R*/*S*-yl benzoate (11): 90% yield; ^{1}H NMR ($CDCl_3$) δ 1.33−1.56 (m, 3H), 1.72 (br s, 1H), 1.77−1.78 (m, 1H), 2.06−2.17 (m, 1H), 2.21−2.22 (m, 6H, $N(CH_3)_2$), 2.42−2.46 (m, 1H), 2.51−2.53 (m, 2H, C-5 and C-1), 2.79 (br s, 1H, C-6), 5.54 (br d, J = 9.9 Hz, 1H, C-2), 7.19−8.22 (m, 10H, Ar); ^{13}C ($CDCl_3$) δ 13.2, 13.3, 26.4, 28.9, 30.4, 38.9, 45.8, 62.4, 64.0 (aliphatic); 120.6, 122.7, 123.0, 123.6, 124.1, 125.2, 125.5, 127.4, 129.2, 139.8 (aryl); 161.1 (C═O).

11-HCl: 82% yield; mp 261−262 °C; ^{1}H NMR (D_2O) δ 1.29−1.41 (m, 2H), 1.45−1.61 (m, 1H), 1.73 (br s, 1H), 1.75−1.77 (m, 1H), 2.04−2.18 (m, 1H), 2.28−2.38 (m, 1H), 2.45−2.58 (m, 2H), 2.62 (br s, 1H), 2.83−2.95 (m, 4H), 3.18 (br s, 1H, C-5), 3.78−3.85 (m, 1H, C-6), 5.19−5.24 (m, 1H, C-2), 7.19−8.01 (m, 10H, Ar); IR 2677−2473, 1722, 1275, 1117 cm^{-1}. Anal. ($C_{23}H_{28}O_2NCl\cdot0.33H_2$) C, H, N, Cl.

(1*R*/*S*,4*R*/*S*)-6*R*/*S*-(*N*,*N*-Dimethylamino)-5*R*/*S*-phenylbicyclo[2.2.2]oct-2*S*/*R*-yl benzoate (12): 94% yield; ^{1}H NMR ($CDCl_3$) δ 1.15 (br s, 1H), 1.38−1.57 (m, 1H), 1.60−1.79 (m, 3H), 1.90 (br s, 1H, C-4), 2.10 (br s, 6H, $N(CH_3)_2$), 2.22−2.41 (m, 1H), 2.50 (br s, 2H, C-5 and C-1), 3.09 (br s, 1H, C-6), 5.20 (br s, 1H, C-2), 7.10−7.58 (m, 8H, Ar), 8.1 (s, 2H, Ar); ^{13}C NMR ($CDCl_3$) δ 12.4, 18.6, 25.9, 28.5, 31.3, 39.4, 46.6, 63.0, 67.0; 120.6, 122.6, 122.9, 123.0, 124.5, 125.7, 127.3, 140.1 (aryl); 161.6 (C═O).

12-HCl: 75% yield; mp 260−261 °C; ^{1}H NMR (D_2O) δ 1.05−1.20 (m, 1H), 1.21−1.39 (m, 1H), 1.72 (br s, 4H), 2.35−2.44 (m, 1H), 2.49 (s, 3H, NCH_3), 2.73 (br s, 1H, C-1), 2.97 (s, 3H, NCH_3), 3.10 (br s, 1H, C-5), 3.79 (br d, 1H, J = 5.4 Hz, C-6), 5.08−5.20 (m, 1H, C-2), 7.19−7.81 (m, 10H, Ar); IR 1722, 1277, 1113 cm^{-1}. Anal. ($C_{23}H_{28}O_2NCl\cdot0.66H_2O$) C, H, N, Cl.

(1*R*/*S*,4*R*/*S*)-6*S*/*R*-(*N*,*N*-Dimethylamino)-5*S*/*R*-phenylbicyclo[2.2.2]oct-2*R*/*S*-yl benzoate (18): 98% yield; ^{1}H NMR ($CDCl_3$) δ 1.25−1.39 (m, 1H), 1.67 (br s, 1H), 1.75−1.87 (m, 4H), 2.16−2.21 (m, 7H, $N(CH_3)_2$ and C-4), 2.41 (br s, 1H, C-1), 2.50 (dd, J = 5.4 Hz, J = 3.3 Hz, 1H, C-5), 2.80 (br s, 1H, C-6), 5.27 (dt, J = 9.9 Hz, J = 3.3 Hz, 1H, C-2), 7.19−8.20 (m, 10H, Ar); ^{13}C NMR ($CDCl_3$) δ 7.7, 21.5, 23.4, 27.0, 28.6, 39.0, 45.5, 61.0, 67.1 (aliphatic); 120.7, 122.6, 123.0, 123.1, 123.5, 124.2, 125.2, 127.6, 129.2, 140.0 (aryl); 160.9.

18-HCl: 85% yield; mp 273−275 °C; ^{1}H NMR (D_2O) δ 1.28−1.33 (m, 1H), 1.48−1.55 (m, 1H), 1.69−1.73 (m, 3H), 1.91−2.01 (m, 2H), 2.55−2.59 (m, 4H), 2.79 (s, 3H), 2.92 (d, J = 5.7 Hz, 1H, C-5), 3.73 (d, J = 5.7 Hz, 1H, C-6), 5.18 (m, 1H, C-2), 7.19−7.98 (m, 10H, Ar); IR 1722, 1275, 1123 cm^{-1}. Anal. ($C_{23}H_{28}O_2NCl\cdot0.33H_2O$) C, H, N, Cl.

(1*R*/*S*,4*R*/*S*)-6*S*/*R*-(*N*,*N*-Dimethylamino)-5*S*/*R*-phenylbicyclo[2.2.2]oct-2*S*/*R*-yl benzoate (19): 91% yield; ^{1}H NMR ($CDCl_3$) δ 1.54−1.62 (m, 2H), 1.66−1.72 (m, 2H), 1.80−1.94 (m, 2H), 2.02−2.14 (m, 7H, $N(CH_3)_2$ and C-1), 2.43 (t, J = 2.4 Hz, 1H), 2.79 (d, J = 6.15 Hz, 1H, C-5), 2.94 (d, J = 6.15 Hz, 1H, C-6), 5.22−5.29 (m, 1H, C-2), 7.25−8.19 (m, 10H, Ar); ^{13}C NMR ($CDCl_3$) δ 11.5, 20.6, 22.9, 27.0, 29.6, 38.9, 45.8, 56.7, 67.5 (aliphatic); 120.6, 122.9, 123.0, 123.2, 124.2, 125.4, 127.7, 140.1 (aryl); 160.8 (C═O).

19-HCl: 91% yield; mp 163−165 °C; ^{1}H NMR (D_2O) δ 1.36−1.42 (m, 1H), 1.53−1.70 (m, 5H), 1.77−1.90 (m, 1H), 2.50 (br s, 3H, NCH_3), 2.76 (br s, 3H, NCH_3), 2.91 (br s, 1H, C-5), 3.91−4.00 (m, 1H, C-6), 5.05−5.18 (m, 1H, C-2), 7.15−7.97 (m, 10H, Ar); IR 1729, 1281, 1117 cm^{-1}. Anal. ($C_{23}H_{28}O_2NCl\cdot0.66H_2O$) C, H, N, Cl.

Pharmacology. [^{3}H]]WIN Binding. The synthesized compounds were screened for activity in a striatal tissue preparation using a modification of the [^{3}H]WIN binding assay described by Reith and Selmeci.[16] Male Sprague−Dawley rats (Harlan Sprague−Dawley, Indianapolis, IN) weighing 150−300 g were anesthetized using CO_2 gas and sacrificed by decapitation. (Preliminary experiments demonstrated no difference in the K_D or B_{max} of [^{3}H]WIN binding in unanesthetized rats versus anesthetized rats; data not shown.) Their brains were quickly removed and placed in ice-cold 0.32 M sucrose. The striatal tissue was removed and homogenized in 20 volumes of 0.32 M sucrose, using 10 up/down strokes of a motorized Potter-Elvejhm homogenizer. The supernatant obtained after centrifugation for 10 min at 0 °C (S_1 fraction) was removed and centrifuged for 20 min at 20000*g* and 0 °C to obtain the P_2 fraction, which was then resuspended in 50 volumes (original wet weight) of ice-cold 25 mM sodium phosphate buffer (pH 7.7) using a Tekmar tissuemizer. Samples containing 750 μL phosphate buffer, 150 μL of the P_2 suspension, 50 μL of the test compound, 25 μL of water or amfonelic acid (to define nonspecific binding; final concentration, 10 μM) and 25 μL of [^{3}H]WIN (final concentration, 2 nM) were incubated for 2 h at 0 °C. The incubation was terminated by vacuum filtration through Whatman GF/B filters presoaked with 0.05% (w/v) poly(ethylenimine), mounted in Millipore filtration manifolds. A 5-mL aliquot of assay buffer was added to the sample immediately before filtering it, and a second 5-mL aliquot of assay buffer was used to wash the filter. The filters were transferred to scintillation vials, shaken vigorously in the presence of 8 mL of Beckman Ready-Safe scintillation fluid for 30 min, and counted in a liquid scintillation counter.

IC_{50} values (that concentration of test compound required to inhibit 50% of the control specific binding of [^{3}H]WIN) were determined from dose−response curves usually containing a range of seven concentrations of the test drug, with triplicate determinations made at each concentration. The IC_{50} for WIN was 22.2 ± 4.7 nM (average ± SEM) under these conditions.

[^{3}H]DA Uptake. Accumulation of [^{3}H]DA was determined as previously described.[18] Briefly, 250 μL of an S_1 fraction prepared as described above from striatal tissue of CO_2-anesthetized rats was diluted 4-fold with a modified Krebs-phosphate buffer (120 mM NaCl, 4.9 mM KCl, 1.2 mM $MgSO_4$, 11 mM glucose, 0.16 mM Na_2EDTA, 1.1 mM ascorbic acid, 0.01 mM pargyline, and 15.5 mM Na_2PO_4, equilibrated with 95% O_2−5% CO_2, and adjusted to pH 7.4 with NaOH) and preincubated with 1100 μL of Krebs-phosphate buffer and 100 μL of vehicle or drug for 10 min at 37 °C. A solution of [^{3}H]DA hydrochloride (50 μL; DuPont/NEN, Boston, MA, or Amersham Corp., Arlington Heights, IL) which had been previously diluted with sufficient unlabeled DA-HCl to bring the specific activity to approximately 5 Ci/mmol was added to give a final concentration of DA of about 30 nM. The samples were exposed to the [^{3}H]DA for exactly 2.0 min. Nonspecific dopamine transport was determined by following the same protocol at 0 °C. Accumulation of [^{3}H]DA was terminated by rapid addition of 5 mL of the chilled Krebs-phosphate buffer to each sample, followed by filtration through a Whatman GF/C filter under vacuum, after which the filter was washed with an additional 5-mL aliquot of buffer. The filters were extracted, and the trapped radioactivity was quantified as described for the [^{3}H]WIN binding assay.

The IC_{50} values were determined from dose−response curves usually containing a range of five concentrations of test drug, with [^{3}H]DA uptake measured in duplicate samples at each concentration.

[^{3}H]PAR[17] and [^{3}H]NIS[24,25] Binding. Brains from male Sprague−Dawley rats weighing 200−250 g (Harlan Labs, Indianapolis, IN) were removed, dissected, and rapidly frozen. Ligand binding experiments for the serotonin transporter were conducted in assay tubes containing 4 mL of buffer (50 mM Tris, 120 mM NaCl, 0.5 mM KCl, pH 7.4 at 25 °C) for 90 min at room temperature. Each assay tube contained 0.2 nM [^{3}H]PAR and 1.5 mg of hindbrain tissue (original wet weight). Nonspecific binding of [^{3}H]PAR was defined by 1 μM citalopram. Ligand binding experiments for the norepinephrine transporter were conducted in Tris buffer (50 mM Tris, 120 mM NaCl, 0.5 mM KCl, pH 7.4 at 4 °C) at a total volume of 0.5 mL for 60 min. Each assay tube contained 0.5 nM [^{3}H]NIS and 8 mg of frontal cerebral cortex. Nonspecific binding of [^{3}H]NIS was defined using 1 μM desipramine. Incubations were terminated by filtration with two 5-mL washes of ice-cold

buffer through GF/B filters that were previously soaked in 0.05% poly(ethylenimine). Results were analyzed using the Equilibrium Binding Data Analysis software (EBDA, Biosoft).

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