Synthesis and Pharmacology of Site-Specific Cocaine Abuse Treatment Agents: 2-(Aminomethyl)-3-phenylbicyclo[2.2.2]- and -[2.2.1]alkane Dopamine Uptake Inhibitors

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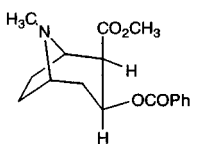
As part of a program to develop site-specific medications for cocaine abuse, a series of 2-(aminomethyl)-3-phenylbicyclo[2.2.2]- and -[2.2.1]alkane derivatives was synthesized and tested for inhibitory potency in [^{3}H]WIN 35,428 binding and [^{3}H]dopamine uptake assays using rat striatal tissue. Selected compounds were tested for their ability to substitute for cocaine in rat drug discrimination tests. Synthesis was accomplished by a series of Diels−Alder reactions, using *cis*- and *trans*-cinnamic acid derivatives (nitrile, acid, acid chloride) with cyclohexadiene and cyclopentadiene. Standard manipulations produced the aminomethyl side chain. Many of the compounds bound with high affinity (median IC_{50} = 223 nM) to the cocaine binding site as marked by [^{3}H]WIN 35,428. Potency in the binding assay was strongly enhanced by chlorine atoms in the 3- and/or 4-position on the aromatic ring and was little affected by corresponding methoxy groups. In the [2.2.2] series there was little difference in potency between *cis* and *trans* compounds or between *N*,*N*-dimethylamines and primary amines. In the [2.2.1] series the *trans exo* compounds tended to be least potent against binding, whereas the *cis exo* compounds were the most potent (4-Cl *cis exo*: IC_{50} = 7.7 nM, 27-fold more potent than 4-Cl *trans-exo*). Although the potencies of the bicyclic derivatives in the binding and uptake assays were highly correlated, some of the compounds were 5−7-fold less potent at inhibiting [^{3}H]-dopamine uptake than [^{3}H]WIN 35,428 binding (for comparison, cocaine has a lower discrimination ratio (DR) of 2.5). The DR values were higher for almost all primary amines and for the *trans*-[2.2.2] series as compared to the *cis*-[2.2.2]. Most of the compounds had Hill coefficients approaching unity, except for the [2.2.2] 3,4-dichloro derivatives, which all had n_H values of about 2.0. Two of the compounds were shown to fully substitute for cocaine in drug discrimination tests in rats, and one had a very long duration of action.

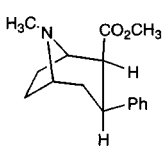
Introduction

Abuse of stimulant drugs such as cocaine, and increasingly methamphetamine, is a major continuing problem in the United States.[1,2] The focus of our work is to develop treatment agents directed toward the stimulant recognition site on the dopamine transport (DAT) complex, where the reinforcing effect of these agents is thought to be mediated.[3−5] Cocaine acts at this site by blocking the reuptake of dopamine (DA) into the presynaptic neuron, thus increasing the concentration of DA in the synapse. However, the importance of serotonergic mechanisms is increasingly being recognized.[6−8] Therapeutic drugs could act as replacement agonists, partial agonists, or antagonists. This would include drugs which would be long acting, slow onset agonists as replacement agents[9−11] or ones that could, at least in part, block the binding of cocaine, yet allow DA uptake. Our recent work in this area[12−14] supports this latter possibility and provides a summary of recent literature (also see refs 15 and 16). Taken together, these studies support the possibility that a drug could be developed which can block the cocaine binding site but have a lower potential to interfere with DA uptake.

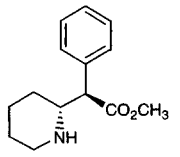
In 1978 a small series of 2-(aminomethyl)-3-phenylbicyclo[2.2.2]octane analogues were synthesized[17] and tested for biological activity.[17−20] The most potent of these compounds (**4**, LR5182) was shown to be selective for the dopamine transporter, with IC_{50} values of 3, 58, and 1700 nM for inhibition of [^{3}H]DA, [^{3}H]norepinephrine (NE), and [^{3}H]5-hydroxytryptamine (5-HT, serotonin) transport, respectively. Except for methylphenidate (**2**), GBR 12783 (**3**), and certain WIN 35,065-2 (**1**) derivatives, the potency of most uptake inhibitors at the



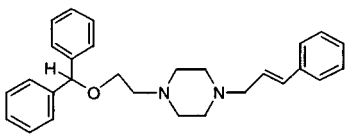
Cocaine



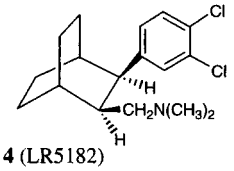
1 (WIN 35,065-2)



2 (Methylphenidate)



3 (GBR 12783)



4 (LR5182)

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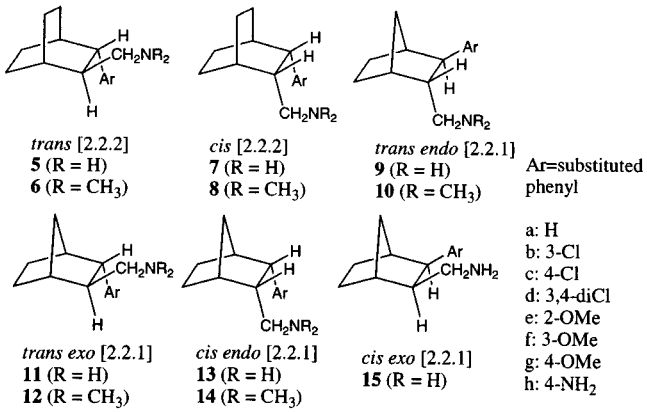
NE transporter is equal to or greater than that at the DA transporter. Lowering the relative impact on noradrenergic systems might make these drugs more useful, as it would lower sympathetic side effects and alerting/arousal functions. Whereas methylphenidate (**2**) contains a phenylethylamine subunit in a partially restricted conformation, both WIN 35,065-2 (**1**) and analogues of LR5182 (**4**) are conformationally more restricted analogues of phenylpropylamine.

The structural analogy of WIN 35,065-2 (**1**) derivatives to cocaine is obvious, but most other dopamine uptake inhibitors, such **2**−**4**, do not contain the tropane core. However, examination of molecular models suggests a high degree of analogy between the three-dimensional spatial arrangement of structural features (phenyl substituents, basic nitrogen) of these series with the structure of WIN 35,065-2 (and cocaine). Derivatives of LR5182 are of interest because they might combine the potency and selectivity of the GBR class of drugs in a molecular structure bearing more similarity to cocaine. Modification of the structure (stereochemistry, substituents on the bicyclic and phenyl rings, type of amine, etc.) of 3-(aminomethyl)-2-phenylbicycloalkanes is readily achieved through standard Diels−Alder chemistry.[17,21] This introduces the possibility of an easily synthesized rigid framework onto which myriad substituents can be placed. Thus, this framework might be used to fine-tune the activity of these compounds to provide agents ranging from cocaine agonists to antagonists.

On the basis of the above information, we initiated a program to synthesize and evaluate congeners of these bicyclic amines. The aim was to produce compounds which, because of their unique interactions with the dopamine uptake complex, would be either agonists, partial agonists, or antagonists for the reinforcing properties of cocaine. This paper describes the synthesis of both bicyclo[2,2,2]octanes and bicyclo[2,2,1]heptanes, **5**−**15**, in which the relative stereochemistry and the substitution pattern on the aromatic ring are varied. We compare their potency in the inhibition of [^{3}H]WIN 35,428 binding with their ability to inhibit [^{3}H]DA uptake. In addition, the ability of selected compounds to substitute for cocaine in a drug discrimination procedure in rats was assessed.



Results

Chemistry. Synthetic routes to bicyclo[2.2.2]octanes and bicyclo[2.2.1]heptanes are shown in Schemes 1 and 2, respectively. *trans*-Disubstituted bicycloalkanes were prepared by Diels−Alder [4+2] cycloaddition of substituted (*E*)-cinnamonitriles **18** or (*E*)-cinnamoyl chlorides **23** with 1,3-cyclodienes. Reactions of cyclic alkenes with cinnamonitriles[17] were performed in a sealed tube at 140−180 °C, whereas the more reactive cinnamoyl chlorides were treated with cyclopentadiene at reflux.[21] A convenient route to the *cis*-bicyclo[2.2.2]octane series required use of (*E*)-3-cyanopropenonitriles, **18**, Scheme 1. Knoevenagal condensation of substituted benzaldehydes **16** with cyanoacetic acid gave only (*E*)-2-cyano-3-phenylpropenoic acids which when heated with copper(I) oxide (decarboxylation)[22] gave *E*/*Z* mixtures (approximately 1:4) of 3-phenylpropenonitriles **18**. Diels−Alder reactions with 1,3-cyclohexadiene gave mixtures of *trans endo* and *trans exo* adducts **19** and the *cis endo* isomers **20** (the *cis exo* isomers were not detected in these reaction mixtures; note that in all cases the *endo*/*exo* designation relates to the substituent with the higher Cahn−Ingold−Prelog priority in relation to the larger bridge). The *cis endo* isomers were separated from the *trans* isomers by column chromatography and hydrogenated to afford *cis*-2-cyano-3-phenylbicyclo[2.2.2]-octanes **22**. The *exo*/*endo* mixtures of *trans* isomers **19** were hydrogenated to give the *trans*-disubstituted bicyclooctanes **21**. 2-Cyano-3-phenylbicyclo[2.2.2]octanes were reduced with borane−THF or Red-Al and treated with aqueous HCl to afford **5** and **7**. *N*,*N*-(Dimethylamino)methyl analogues **6** and **8** were prepared by Eschweiler−Clark methylation of the primary amines.

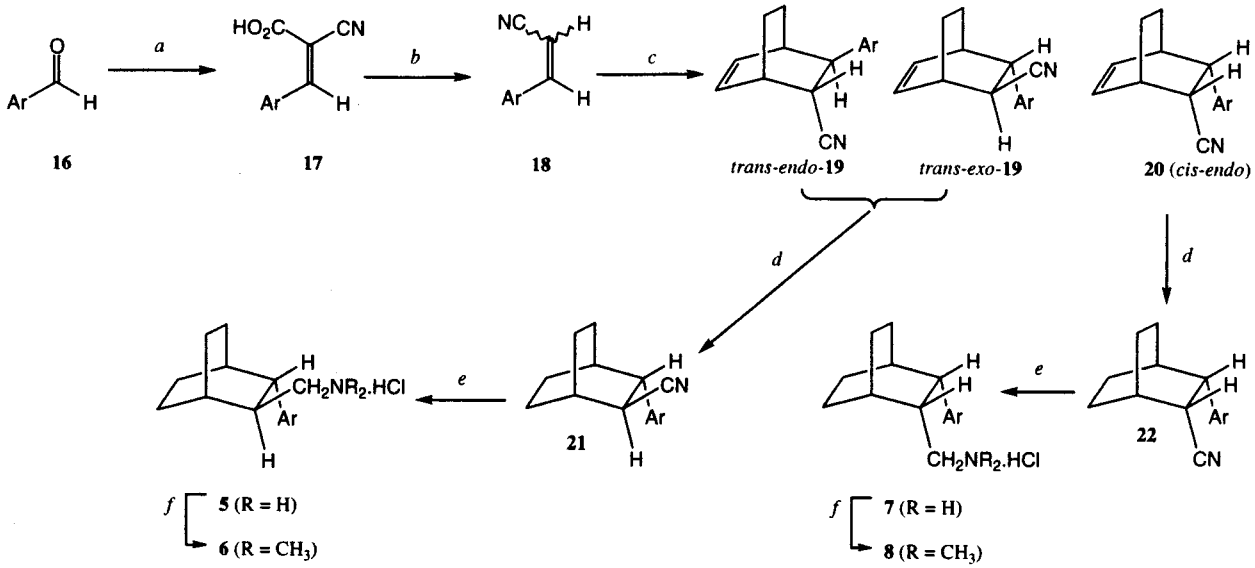
Cinnamoyl chlorides are more reactive dienophiles than corresponding acids, esters, or nitriles.[21] Diels−Alder reactions of *trans*-cinnamoyl chlorides **23** and cyclopentadiene, followed by hydrolysis, gave mixtures of *trans*-5-carboxyl-6-phenylbicyclo[2.2.1]hept-2-enes (approximately 1:1 mixture of compounds with the carboxyl group occupying the *exo* and *endo* positions) as shown in Scheme 2. The mixtures were treated with aqueous iodine, and the iodolactones **26** derived from the *endo* isomers **24** were separated from unreacted *exo* acids **25** and treated with zinc to regenerate the pure *endo* acids. Hydrogenation of the separated acids **24** and **25**, conversion to the primary amides, followed by reduction and acidification, gave hydrochloride salts **9** and **11**. Methylation gave the hydrochloride salts of the tertiary amines **10** and **12**.

The *cis endo* analogues **13** and **14** were prepared by reaction of the *E*/*Z* mixture of cinnamonitriles **18** (see above) with cyclopentadiene to form a mixture of stereoisomers (small amounts of the *cis exo* isomers were detected but were difficult to isolate). The *cis endo* isomers were isolated by column chromatography and converted to the amine hydrochlorides by the same sequence of reactions used for the bicyclo[2.2.2]octane series.

The *cis*−*trans* relationship of the substituents on the bicycloalkanes was clearly demonstrated by determination of coupling constants between protons on C2 and C3 in the ^{1}H NMR spectra. The coupling constant between protons in the *trans*-bicyclo[2.2.2]octane series is approximately 8 Hz, whereas the *cis* isomers have a 12-Hz coupling.

(*Z*)-4-Chlorocinnamic acid, **34c**, was prepared by photochemical isomerization of the commercially avail-

Scheme 1[a]



[a] Reagents: (a) $NCCH_2CO_2H$, NaOH; (b) Cu_2O, Δ; (c) cyclohexadiene, 180 °C; (d) H_2, Pd/C; (e) (i) BH_3/THF, (ii) HCl; (f) (i) $NaHCO_3$, (ii) H_2CO, HCO_2H, (iii) HCl.

able *E*-isomer **33c** in order to synthesize the *cis,exo*-bicyclo[2.2.1]heptane Diels−Alder adducts. The *Z*-isomer was easy to separate from the photostationary *E*/*Z* mixture of acids by trituration with hot water.[23] Diels−Alder reaction of the *Z*-isomer with cyclopentadiene gave a mixture of the two *cis* isomers *(cis exo,* **35c**, and *cis endo)* and two *trans* isomers (**24c** and **25c**). The crude reaction mixture contained approximately 5% of the desired *cis exo* isomer. The mixture was treated with I_2 to convert the *cis endo* and *trans endo* acids to the neutral iodolactones which were separated from the mixture of *cis exo* and *trans exo* acids. The *cis exo* acid was separated from the *trans endo* acid by column chromatography and converted, via reduction of the amide, to the *cis exo* isomer of the hydrochloride salt of *cis,exo*-2-(aminomethyl)-3-(4-chlorophenyl)bicyclo[2.2.1]-heptane, **15c**.

The unsubstituted (*Z*)-cinnamic acid, **34a**, could not be separated from the *E*-isomer by the simple trituration procedure used for the 4-chloro analogue, so another route was devised for the preparation of the unsubstituted *cis exo* ammonium chloride **15a**. The *trans endo* acid **24a** was treated with an excess of lithium diisopropylamide at −78 °C to afford the dianion, which was quenched with aqueous ammonium chloride at room temperature to afford the *trans endo* isomer **24a** and the *cis exo* isomer **35a** in a 9:1 mixture (determined by ^{1}H NMR spectroscopy). Conversion of the *trans endo* isomer to the neutral iodolactone allowed for the separation of the *cis endo* acid **35a**. Conversion of the acid via the amide to the amine hydrochloride gave the unsubstituted *cis exo* ammonium chloride **15a**.

The ^{1}H NMR spectrum of the *cis exo* isomers **15** shows a 9.5-Hz coupling constant between the protons on C2 and C3, consistent with the *cis*-stereochemistry. In addition, the spectrum is distinct from that of the *cis endo* ammonium salts **13**. The *cis exo* isomers have a coupling constant of about 1.8 Hz between the protons on C2 (and C3) and the neighboring bridgehead (the dihedral angle between these protons, calculated by MM2, is approximately 85°), whereas the *cis endo* isomers have a corresponding coupling constant of about 3.5 Hz (dihedral angle ∼50°).

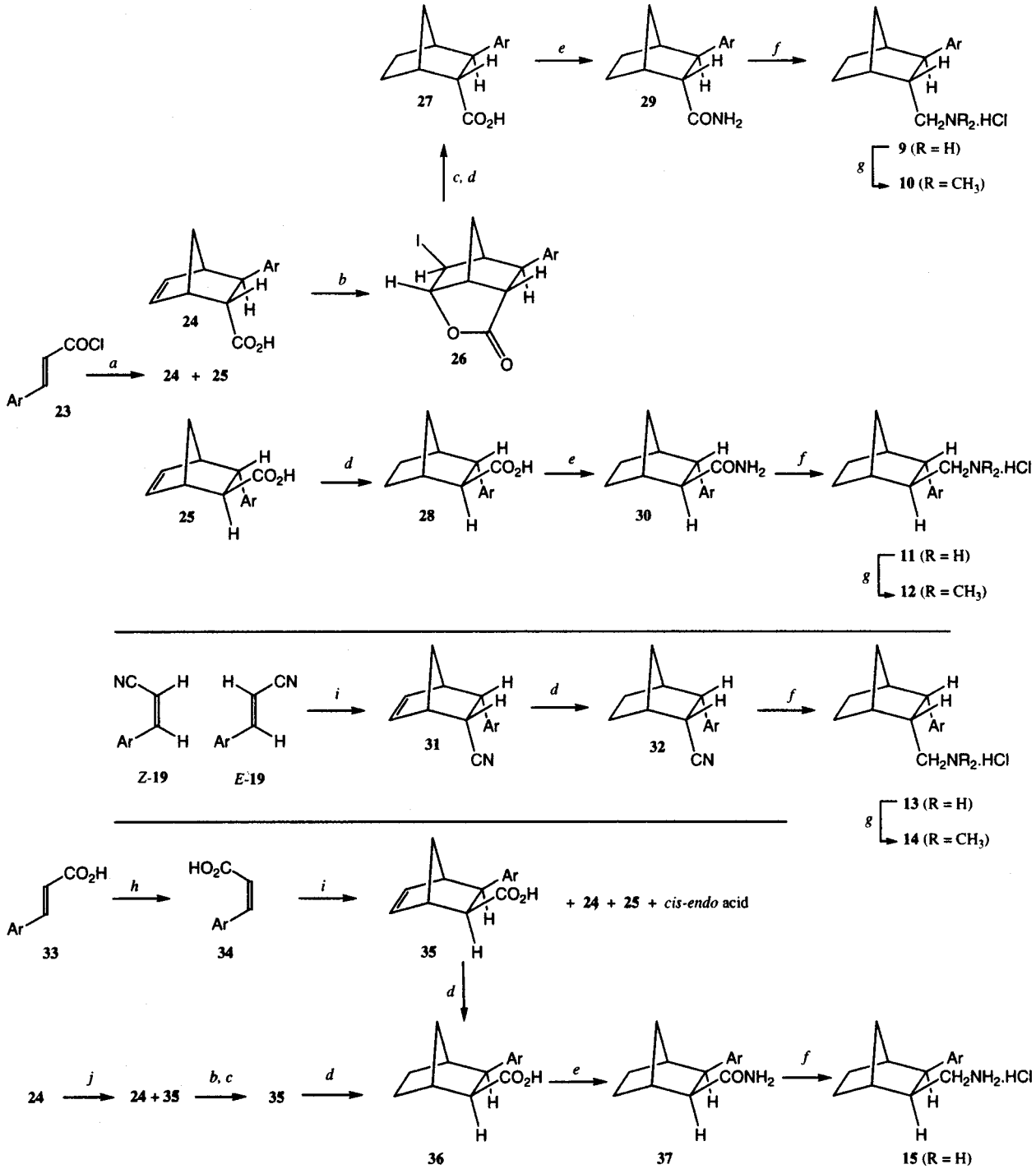
Pharmacology. All of the compounds that were synthesized in this study were tested for their ability to inhibit the binding of [^{3}H]WIN 35,428 to rat striatal tissue membrane preparations and the uptake of [^{3}H]-DA into rat striatal synaptosomes. These results are summarized in Table 1. In addition, the ability of selected members to substitute for cocaine, in rats trained to discriminate 10 mg/kg of cocaine from saline, was measured. These data are summarized in Figure 1.

[^{3}H]WIN 35,428 Binding. In terms of binding potency some trends are clear (in general the same statements can be made for uptake inhibition). As a group, all of the 3,4-dichloro compounds are more potent than the corresponding unsubstituted compounds, by a factor of 9−89-fold (average increase, 30-fold). Similarly, a 4-chloro substituent makes all the compounds more potent, by a factor of 7−21-fold (average increase, 13-fold). Substitution by chlorine in the 3-position also always increased potency, but less efficiently than in the 4-position (average increase, 5-fold). In contrast, a 4-methoxy substituent has little effect on binding potency. A small number of compounds, with methoxy groups in the 2- and 3-positions, show variable effects. In one series (*trans endo* [2.2.1]), both the 2- and 3-methoxy compounds **9e** and **9f** are much less potent (34- and 26-fold, respectively). However, the 2- and 3-methoxy *trans exo* [2.2.1] compounds **11e** and **11f** are a little different than the corresponding unsubstituted compounds.

The *trans* [2.2.2] tertiary amines **6** are all more potent (2−5-fold) than the corresponding primary amines **5**, but in most other cases (*cis* [2.2.2] *endo* and *exo* [2.2.1]) there were only small differences between amine types. Except for a few cases, amine type (primary versus tertiary) is not an important factor in determining binding potency.

In terms of *cis*−*trans* isomerism, the trends are less clear and not very dramatic. In the [2.2.2] series, all *cis*

Scheme 2[a]



[a] Reagents: (a) (i) cyclopentadiene, Δ, (ii) NaOH, H_2O, (iii) HCl; (b) I_2, KI, $NaHCO_3$; (c) Zn, AcOH; (d) H_2, Pd/C; (e) (i) $SOCl_2$, (ii) NH_4OH; (f) (i) BH_3·THF, (ii) HCl, H_2O; (g) (i) $NaHCO_3$, (ii) H_2CO, HCO_2H, (iii) HCl; (h) 254 nm, dioxane; (i) cyclopentadiene, 140 °C; (j) (i) LDA, THF, −78 °C, (ii) H_3O^+.

primary amines **7** are more potent than the corresponding *trans* primary amines **5** by factors of 1.7−5.5. The tertiary amines show no consistent difference between the *cis* and *trans* isomers. In general, the stereochemical arrangement of the phenyl ring and the aminomethyl substituent is not a large factor in influencing potency in the [2.2.2] series.

In the [2.2.1] series, in addition to *cis*−*trans* isomerism, we addressed the issue of *endo*−*exo* isomerism. With both *cis*−*trans* and *endo*−*exo* isomerism the differences are usually, but not always, fairly small. Two trends are clear: The *cis exo* compounds **15** are the most potent, and the *trans exo* **11** are the least potent. The *cis endo*, **13**, and the *trans endo*, **9**, compounds differ little in potency. Two of the most potent compounds in this study are **15c** and **7c** with IC_{50} values of 7.7 and 12.9 nM, respectively. Both of these are *cis*-4-chloro isomers.

Discrimination Ratio (DR). The discrimination ratio (DR), defined as the ratio of the IC_{50} value of a given compound against [^{3}H]DA uptake to its corresponding IC_{50} value against [^{3}H]WIN 35,428 binding,

Table 1. Inhibitory Properties of Test Compounds against [^{3}H]WIN 35,428 Binding and [^{3}H]Dopamine Uptake[a]

compd	phenyl subst X	N subst R	inhibition of [^{3}H]WIN 35,428 binding		inhibition of [^{3}H]dopamine uptake IC_{50} (nM)	discrimination ratio (DR)[b]
			IC_{50} (nM)	n_H		
			Trans [2.2.2]			
5a	H	H	1195 ± 15	1.03 ± 0.08	5930 ± 420 (3)	5.0
5b	3-Cl	H	204 ± 4.0	1.18 ± 0.04	960 ± 120	4.7
5c	4-Cl	H	71.4 ± 7.0 (3)	1.20 ± 0.04	375 ± 18	5.2
5d	3,4-Cl_2	H	37.5 ± 3.3 (3)	1.85 ± 0.31	97.5 ± 0.50	2.6
6a	H	CH_3	191 ± 19 (3)	0.99 ± 0.10	840 ± 49	4.4
6b	3-Cl	CH_3	36.8 ± 1.3	1.33 ± 0.03	186 ± 38	5.1
6d	3,4-Cl_2	CH_3	21.3 ± 0.80	2.19 ± 0.30	56.3 ± 14	2.6
6h	4-NH_2	CH_3	160 ± 28 (5)	1.21 ± 0.06	704 ± 130 (5)	4.4
			Cis [2.2.2]			
7a	H	H	270 ± 20	1.02 ± 0.03	1480 ± 80	5.5
7b	3-Cl	H	117 ± 8.0	1.25 ± 0.01	430 ± 60	3.7
7c	4-Cl	H	12.9 ± 0.60 (3)	1.21 ± 0.09	68.3 ± 0.5	5.3
7d	3,4-Cl_2	H	21.5 ± 0.50	2.29 ± 0.23	34.0 ± 5.0 (3)	1.6
7g	4-OMe	H	249 ± 36.4 (3)	1.08 ± 0.07	1500 ± 100	6.0
8a	H	CH_3	313 ± 18	1.01 ± 0.16	980 ± 20	3.1
8b	3-Cl	CH_3	86.0 ± 7.0	1.14 ± 0.07	283 ± 23	3.3
8d	3,4-Cl_2	CH_3	14.2 ± 1.6 (3)	1.58 ± 0.11	29.3 ± 1.7	2.1
8g	4-OMe	CH_3	380 ± 20	1.01 ± 0.04	1430 ± 50	3.8
			Trans Endo [2.2.1]			
9a	H	H	340 ± 32	1.05 ± 0.06	2220 ± 180 (3)	6.5
9b	3-Cl	H	149 ± 12	1.12 ± 0.12	758 ± 64 (3)	5.1
9c	4-Cl	H	46.0 ± 3.3 (3)	1.36 ± 0.10	230 ± 11 (3)	5.0
9d	3,4-Cl_2	H	11.6 ± 1.3	1.22 ± 0.03	58.0 ± 0.30	5.0
9e	2-OMe	H	11600 ± 560	1.35 ± 0.15	36600 ± 400	3.1
9f	3-OMe	H	8820 ± 1500	1.12 ± 0.08	29300 ± 400	3.3
9g	4-OMe	H	1160 ± 310	0.98 ± 0.07	5550 ± 460	4.8
10a	H	CH_3	515 ± 80	0.98 ± 0.01	1100 ± 25	2.1
			Trans Exo [2.2.1]			
11a	H	H	2900 ± 100	1.05 ± 0.09	8850 ± 950	3.1
11b	3-Cl	H	239 ± 68	1.13 ± 0.07	780 ± 120	3.3
11c	4-Cl	H	207 ± 18 (3)	1.31 ± 0.07	593 ± 34 (3)	2.9
11d	3,4-Cl_2	H	32.7 ± 5.8	1.13 ± 0.00	93.6 ± 5.2	2.9
11e	2-OMe	H	1480 ± 76	0.91 ± 0.00	7860 ± 400	5.3
11f	3-OMe	H	2010 ± 460 (4)	1.14 ± 0.05	6560 ± 150	3.3
11g	4-OMe	H	1700 ± 120	0.93 ± 0.05	7120 ± 980	4.2
12a	H	CH_3	2510 ± 110	1.01 ± 0.00	4330 ± 530	1.7
			Cis Endo [2.2.1]			
13a	H	H	816 ± 50 (4)	1.04 ± 0.04	3500 ± 32	4.3
13c	4-Cl	H	65.3 ± 11	1.11 ± 0.10	348 ± 10	5.3
13d	3,4-Cl_2	H	21.3 ± 3.6 (3)	1.25 ± 0.09	98.7 ± 2.3	4.6
13g	4-OMe	H	495 ± 140	0.99 ± 0.10	2260 ± 240	4.6
14a	H	CH_3	2140 ± 160	0.89 ± 0.02	2750 ± 370	1.3
			Cis Exo [2.2.1]			
15a	H	H	251 ± 11	1.06 ± 0.01	875 ± 41	3.5
15c	4-Cl	H	7.70 ± 0.60	1.16 ± 0.13	34.9 ± 1.5	4.5
			Tropanes			
	(−)-cocaine		160 ± 15 (3)	1.03 ± 0.01	404 ± 26	2.5
	WIN 35,428		20.4 ± 1.7 (5)	1.07 ± 0.05	51.3 ± 0.30	2.5

[a] Values are expressed as the mean ± standard error of the mean; $N = 2$ except where shown (N). [b] Discrimination ratio = (IC_{50} against [^{3}H]dopamine uptake):(IC_{50} against [^{3}H]WIN 35,428 binding).

is an empirical measure utilized in our laboratories to predict whether a test compound will behave as a cocaine agonist or antagonist.[11] In this model, a compound which is equipotent as an inhibitor of [^{3}H]-dopamine uptake and [^{3}H]WIN 35,428 binding would have a DR of 1 and would be expected to resemble cocaine in its pharmacological properties. On the other hand, a compound which could inhibit the binding of cocaine to the reuptake complex (measured with [^{3}H]-WIN 35,428), but have little or no effect on DA uptake, would have a high DR (see discussion) and would be expected to act as a cocaine antagonist. Probably due to differences in the conditions under which the two assays are run, cocaine itself has a DR value of 2.5 (instead of 1) using our methodology. The test compounds (**5**−**15**) exhibited low DR values ranging from 1.3 to 6.5. The 3,4-dichloro-substituted compounds have DR values which are 0−71% lower (average 40%) than the corresponding unsubstituted analogues. No clear trends are evident for 3- or 4-chloro or 2-, 3-, or 4-methoxy compounds. In most cases *trans* compounds show a higher DR than the corresponding *cis* isomers (average of 37% higher). Also, the primary amines have higher DR values than the corresponding tertiary amines (increasing by an average of 25%). The *exo* bicylo[2.2.1] compounds (**11**, **12**, **15**) have lower DR values than either the corresponding *endo* [2.2.1] (**9**, **10**, **13**, **14**; 26% lower) or the [2.2.2] (**5**−**8**; 32% lower).

Drug Discrimination. Compounds **8d** and **9a** were tested in the drug discrimination procedure (see Figure

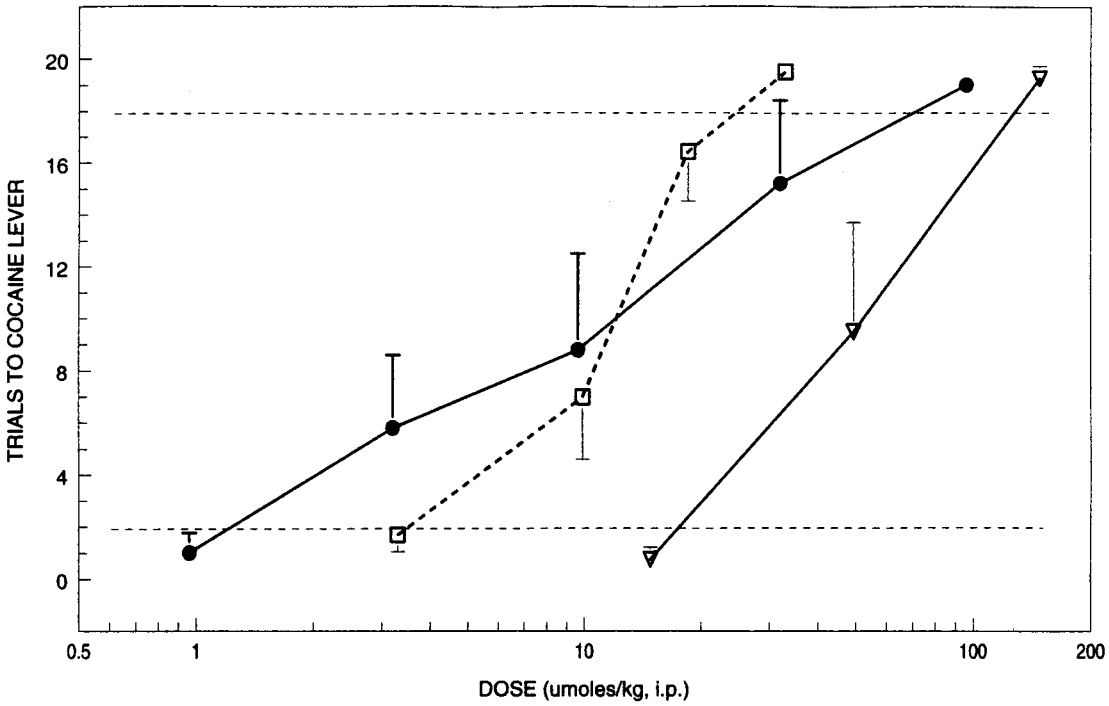


Figure 1. Dose−response curves for the discriminative stimulus effects of **8d** (●) (n = 5), **9a** (▽) (n=4), and cocaine (□) (n = 10) in rats trained on 33 μmol/kg (10 mg/kg) cocaine. Rats (n rats at each dose level) were injected with the test compound 30 min before testing for generalization to cocaine (see Experimental Section for details).

1). Both compounds **8d** and **9a** were as efficacious as cocaine but were less potent (ED_{50} values of 9.2 μmol/kg (3.2 mg/kg) and 41 μmol/kg (9.7 mg/kg), respectively) than might be predicted based on their potency in vitro. The ED_{50} for cocaine is 8.9 μmol/kg (3.0 mg/kg). To compare behavioral potencies relative to potency in vitro, the ratio of IC_{50} for inhibition of ^{3}[H]WIN 35,426 binding (nM) to ED_{50} (μmol/kg) in drug discrimination was calculated. Compounds with high ratios are very potent behaviorally at a given binding potency. For compounds **8d** and **9a** the ratios are 1.6 and 8.4, respectively. This compares to cocaine with a ratio of 18 (160/8.9). Although neither of these compounds appeared to cause unusual overt behavioral effects, several incidents should be noted. Compound **8d** might have a long duration of action as judged by the fact that animals receiving the highest dose (30 mg/kg) were still largely selecting the cocaine-appropriate lever the next day in a training session with saline (data not shown). One of the four rats given the highest dose of **9a** was observed to undergo a convulsion and was found dead in his cage the following morning.

Hill Coefficients. Except for the 3,4-dichloro-substituted bicyclo[2.2.2] compounds, all of the compounds in this study had n_H values close to unity, ranging from 0.89 to 1.36 (average = 1.11 ± 0.02; Table 1). The 3,4-dichloro-substituted bicyclo[2.2.2] compounds **5d**, **6d**, **7d**, and **8d** had Hill coefficients of approximately 2, ranging from 1.58 to 2.29 (average = 1.97 ± 0.16 (SEM)). The increase in n_H did not appear to be a function only of dichloro substitution, however, as the 3,4-dichloro substituted bicyclo[2.2.1] compounds **9d**, **11d**, and **13d** had an average n_H of 1.20 ± 0.04, which was significantly lower than the values obtained for the 3,4-dichloro bicyclo[2.2.2] group (p < 0.01, 2-tailed t-test).

Discussion

Structure−Activity Relationships. The inhibitory potency of the compounds in this series against [^{3}H]WIN 35,428 binding ranged from an IC_{50} of 7.7 nM for **15c** to 11.6 μM for **9e**. In the [^{3}H]dopamine uptake assay, IC_{50}'s of 29.3 nM (**8d**) to 36.6 μM (**9e**) were obtained. As the data in Table 1 indicate, the inhibitory potencies of the compounds in the two assays were highly correlated (R^2 = 0.978 for a log−log plot of the IC_{50} values for the two assays). Despite this excellent correlation, the potencies of the compounds did not always covary to the same degree in both assays; thus, DR values of 1.3 (**14a**) to 6.5 (**9a**) were obtained. Although assay conditions can make a huge difference,[24,25] high DRs should theoretically identify potential cocaine antagonists, because they can detect compounds which are proportionally better at displacing cocaine binding rather than blocking dopamine uptake. The highest DR values obtained for this series of compounds, however, apparently showed insufficient separation in inhibitory potency between the two functions for antagonist activity to emerge. Thus, compound **9a** (DR = 6.5) acted as an agonist in the drug discrimination assay, substituting fully for cocaine. Theoretically,[26] a DR of 36 is the value obtained when 80% of the [^{3}H]WIN 35,428 binding sites and 10% of substrate sites are occupied (the IC_{50} values were used as an approximation of the K_i and K_D in these calculations). If 90% of the [^{3}H]WIN 35,428 binding sites are occupied, a DR of 81 is required to only have 10% of the dopamine uptake inhibited. Thus, it is likely that large values of the DR are required before antagonism could be observed. Despite this, there are indications (see Results, Discrimination Ratio) that the DR values are related to some structural features of these analogues; these may be useful in future investigations aimed at the development of cocaine antagonists.

To provide some rationale for the variation in biological screening data of the bicyclic (2-aminomethyl)-3-phenyl analogues **5**−**15**, we have considered their structural homology with WIN 35,065-2 and drawn analogy with the SAR of substituted analogues of methylphenidate recently synthesized in our laboratories.[12,27] WIN 35,065-2 and the bicyclic compounds synthesized here are conformationally restricted analogues of 3-phenylpropylamine. Compounds **5**−**15** lack the methyl ester functionality of WIN 35,065-2 and possess additional conformational flexibility around the C2−exocyclic methylene bond. In addition to the effects of substituents on the phenyl ring, analysis of the SAR should also explain the effect of *cis*−*trans* and *endo*−*exo* stereochemistry on uptake and binding. It must be noted that all of the compounds synthesized in this study (**5**−**15**) are *racemic* and have not been resolved into the individual enantiomers. The earlier work on the bicyclo[2.2.2] series[17,20] indicated that there was little difference in the inhibition of either DA, NE, or 5-HT uptake between the enantiomers (enantioselectivities of 3, 2, and 5, respectively).

In a number of studies of dopamine reuptake inhibitors (e.g., methylphenidates,[12] tropanes,[28] and others[29]) the distance between the N and C4 (or the centroid) of the phenyl ring is often correlated with potency, with the suggestion that this is a gauge of the fit of this portion of the molecule into the binding site. The N−C4 distance in WIN 35,065-2 is approximately 7.0 Å (determined by MM2[30]). Recent data on WIN analogues in which this distance is extended[31] indicate that even longer distances (ca. 9 Å) may be optimal. In the bicyclic structures **5**−**15**, this distance varies depending on the conformation about the C2−exocyclic methylene bond. However, in the more potent *cis exo* series, the maximum N−C4 distance obtainable by rotation around the C2−exocyclic methylene bond is only approximately 6.1 Å, and some energy-minimized structures have considerably shorter distances. In energy-minimized conformations of the least active *trans exo* series, **11**, the N−C4 distances are generally longer than in the *cis* series; in one conformer (discussed in more detail later) this distance is about 7.0 Å. Other factors than just this distance obviously are important in determining binding potency in these series.

Analogues of WIN in which the nitrogen is replaced with oxygen and the phenyl ring is optimally substituted (e.g., 3,4-dichloro) retain relatively high potency.[32] In addition, some cocaine analogues without a basic nitrogen (e.g., 8-(trifluoromethylsulfonyl)norcocaine) retain high affinity.[33] This suggests that interaction of the nitrogen with the binding site is through hydrogen bonding rather than by ionic interactions of an ammonium cation. Recently published data have shown that in WIN analogues in which the phenyl ring is optimally substituted (e.g., 3,4-dichloro), replacement of the nitrogen with carbon[34] can lead to compounds with relatively high affinity indicating that a fit of this atom into a pocket may be all that is required. These observations indicate that the exact mode of binding of tropanes, and presumably all other DA uptake inhibitors, is far from clear.

Substituents on the phenyl ring, however, can have dramatic effects on binding, presumably by lengthening the molecule and in particular by extending the planar ring structure into a hydrophobic binding pocket. For example, 3- and 4-halogen-substituted analogues (and 3,4-dichloro analogues) of methylphenidate, WIN, and **5**−**15** have higher potencies than the unsubstituted compounds. In the case of compounds **5**−**15**, the 4-chloro compounds have greater potency than the 3-substituted analogues, in common with the effect of the position of substituents in the WIN series,[35] but different than the methylphenidate[12] series where the 3-substituted analogues are more potent. The effect of methoxy groups is inconsistent in these bicyclic compounds. In the *trans endo* series, a methoxy group in the 2-, 3-, or 4-position lowered activity (34-, 26-, and 4-fold, respectively), whereas the same substituents had no effect in the *trans exo* series. In a few other cases, a 3- or 4-methoxy group had little effect. In the methylphenidate and WIN series, methoxy groups usually have little effect, except in the 2-position[12] where all substituents tend to lower potency.

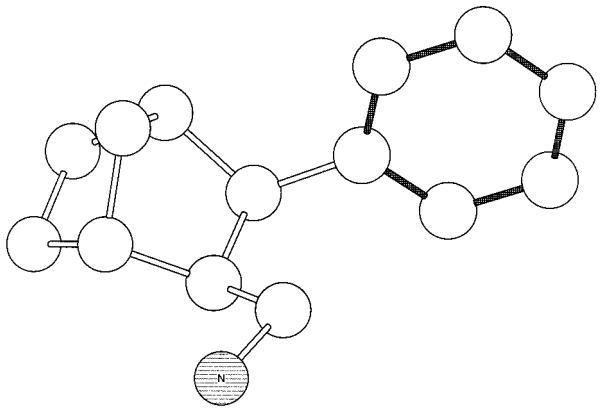


Figure 2. Energy-minimized (MM2) conformation **15** (2*S*); H atoms omitted for clarity.

In the following discussion, we have arbitrarily chosen one enantiomer (the *2S*) for both the *cis exo* series **15** and the *trans exo* series **11** to illustrate the arguments being presented. Although we also studied the other enantiomer, these results are not discussed as they do not shed any additional light on the matter. In the highly active *cis exo* series, **15**, rotation around the C3−phenyl bond is restricted by the bicyclic ring structure. Two conformations around the C2−exocyclic methylene bond lead to low-energy structures, with the minimum shown in Figure 2. In this conformation the *N*-phenyl−C4 distance, 6.1 Å, is not large enough to provide a good overlap with the structure of WIN with coplanar phenyl rings and overlap of the nitrogen atoms. The other low-energy conformations of **15** have much shorter N−C4 distances. Overlay of the carbon atoms of the phenyl rings and nitrogen atoms of **15** and WIN (rms fit of seven atoms in each structure[29]) is best achieved by tilting the molecules relative to each other, as shown in Figure 3. In this overlay most of the atoms of the unsubstituted bicyclic portion are in the area of the methyl ester of WIN 35,065-2. Studies of the SAR of the methyl ester of WIN and cocaine[36] have shown that although a β configuration is required, there is great latitude in the nature and size of groups in this position. For **15**, alternate overlays (not shown) produced similar results in terms of the way the phenyl rings overlap but differ in where the atoms of the bicyclic structure were

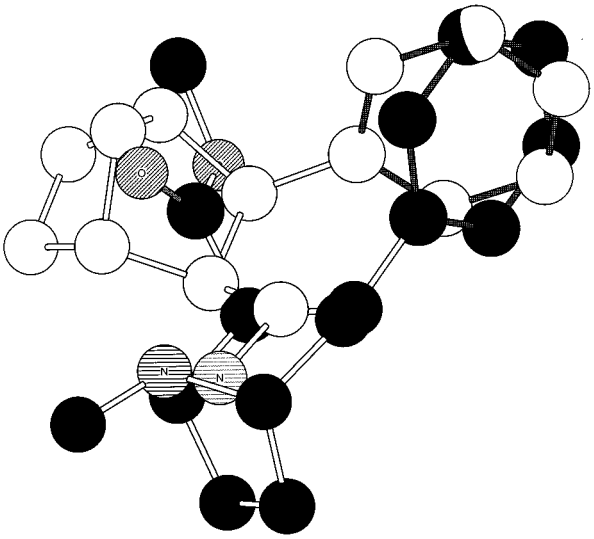


Figure 3. Overlay of **15** (2*S*) and WIN 35,065-2 (black); H atoms omitted for clarity.

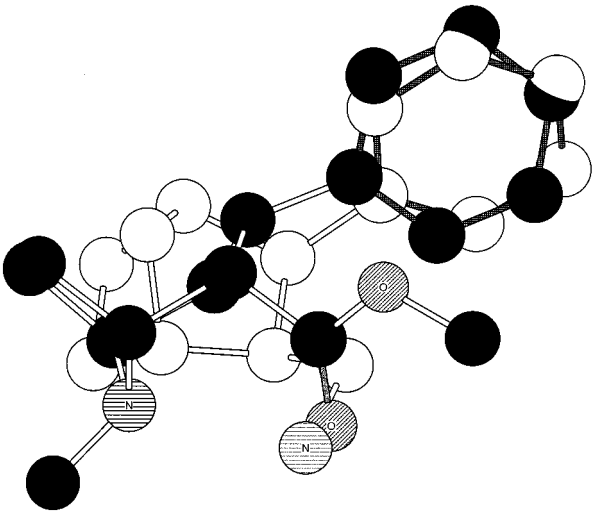


Figure 4. Overlay of **15** (2*S*) and WIN 35,065-2 (black); H atoms omitted for clarity.

placed relative to WIN 35,065-2. Until more information in available about the SAR of the bicylic amines, it is not possible to predict which overlay might be more appropriate. However, because of the relatively poor overlap of the phenyl rings, this very simple picture would not seem to predict the high potency of the *cis exo* series based on these presumed pharmacophores (nitrogen atom and phenyl).

Given the uncertainty of the mode of binding of phenyltropanes to the DAT, it is also worth considering other ways of drawing analogies to the structure of **15**. A good overlay of the phenyl rings of low-energy conformations of WIN 35,065-2 and **15** can be achieved by placement of the primary amine of **15** in the same area as the methyl ester carbonyl oxygen of WIN 35,-065-2 and is shown as Figure 4. This also provides a good overlap of the bicyclic structures of the two series.

In the energy-minimized conformations of the least active *trans exo* series **11**, the N−C4 distance is about 7.0 Å. A similar overlay to that shown in Figure 3, using this conformation of **11** and WIN 35,065-2, is shown in Figure 5. Because of the apparent better overlap of the phenyl rings in these overlays of **11** and WIN 35,065-2,

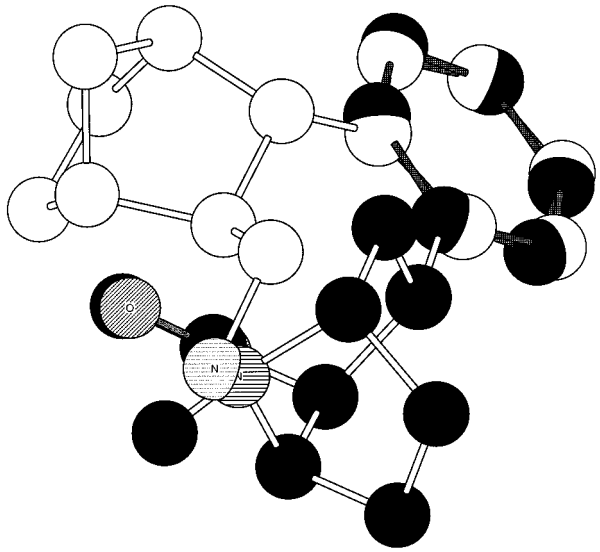


Figure 5. Overlay of **11** (2*S*) and WIN 35,065-2 (black); H atoms omitted for clarity.

it is not obvious why **11** would be less active as compared to **15**. However, it should be noted that the overlapping phenyl rings of **11** and WIN 35,065-2 assume a different orientation with respect to the bicycles.

Drug Discrimination Studies. Compounds **8d** and **9a** substituted fully for cocaine in drug discrimination studies, suggesting that they might ultimately have utility as replacement therapy for the treatment of cocaine abuse. The in vivo potency of compound **9a** could be predicted by comparison of its in vitro potency in the [^{3}H]DA uptake assay with that of cocaine (i.e., **9a** is 5-fold less potent than cocaine both as a dopamine uptake inhibitor and in the drug discrimination assay). The same correlation was not seen with **8d**; it was 14-fold more potent than cocaine as a [^{3}H]DA uptake inhibitor but equipotent as a substitute for cocaine in the drug discrimination assay. It is possible that pharmacokinetic factors dictated by the varying lipophilicity of these agents may account for the divergence between the in vivo and in vitro potency of these agents. The calculated values of log P[29] for cocaine, **9a**, and **8d** are 1.91, 2.50, and 4.20, respectively. If the more lipophilic **8d** is absorbed more slowly after ip injection or is bound to a greater extent to plasma proteins, its concentration in the brain could be relatively lower than that of a more rapidly absorbed, unbound drug. Studies of more hydrophilic analogues of bicyclic amines related to **5**−**15** are in progress.

Conclusions

Analogues of 2-(aminomethyl)-3-phenylbicycloalkanes have been prepared and tested for their binding to the DAT and their ability to inhibit DA uptake. Many of these were potent inhibitors of both binding and uptake. Several alternate explanations of the SAR of these compounds are offered in terms of known pharmacophores. In addition, two compounds were tested for their ability to substitute for cocaine in drug discrimination tests in rats. Both of these compounds did fully substitute for cocaine, proving the behavioral efficacy of this class of drugs. These, and other related analogues, may be promising candidates for development as cocaine abuse

treatment agents, due to their likely slow onset and long duration of action. Further testing of these and other related compounds is in progress.

Experimental Section

General Methods. ^{1}H NMR spectra were obtained at 300 MHz on a Varian Gemini spectrometer. Infrared spectra were obtained using KBr pellets on a Nicolet 520FT spectrometer. Melting points were determined on a Mel-Temp apparatus and are uncorrected. All starting materials were used as received from Aldrich Chemical Co. Tetrahydrofuran (THF) was dried over sodium benzophenone ketyl prior to distillation under nitrogen. Elemental analyses were obtained from Atlantic Microlabs, Atlanta, GA. Representative procedures for the synthesis of hydrochlorides of 2-(aminomethyl)-3-phenylbicycloalkanes are given below. Spectral data are presented for representative synthetic intermediates and products.

Synthesis of *cis*- and *trans*-2-(Aminomethyl)-3-phenylbicyclo[2.2.2]alkane Hydrochloride Salts 5−8. (*E*)-2-Cyano-3-phenylpropenoic Acids 17. Knoevenagal condensation of cyanoacetic acid with substituted benzaldehydes **16** was performed under basic conditions according to the method of Lapworth and Baker.[37] Cyanoacetic acid (57.7 g, 680 mol) was dissolved in a solution of Na_2CO_3 (72.0 g, 680 mol) in 500 mL H_2O with gentle warming. A solution of NaOH (3.39 g, 85.0 mol) in 250 mL H_2O was added, and the mixture was warmed to 40 °C. Benzaldehyde **16a** (60 mL, 0.54 mol) was added, with vigorous shaking. After standing for 1 h, concentrated HCl was added until the solution was strongly acidic. The mixture was shaken vigorously and allowed to stand for 1 h at room temperature. The precipitate was filtered, washed with cold water and toluene, and dried under vacuum to give (*E*)-2-cyano-3-phenylacrylic acid (**17a**) as an off-white solid (50.0 g, 53%): mp 186−188 °C (lit.[38] mp 185 °C); ^{1}H NMR (acetone-d_6) δ 8.48 (s, 1H, H−C3), 8.08−8.13 (m, 2H), 7.60−7.68 (m, 3H); IR 3104, 2841, 2210, 1690, 1604 cm^{-1}.

***(E/Z)*-3-Phenylpropenonitriles 18.** Decarboxylation of (*E*)-2-cyano-3-phenylpropenoic acids with Cu_2O was performed according to the method of Fairhurst.[22] (*E*)-2-Cyano-3-phenylacrylic acid (**17a**) (2.00 g, 11.6 mmol) was mixed with 80 mg cuprous oxide in a horizontally clamped round-bottom flask equipped with a tube leading to a cooled receiver. The solid was heated in vacuo (0.5 mmHg) with a Bunsen burner. The product (0.89 g, 60%) was collected by distillation and consisted of a mixture of *E*- and *Z*-isomers **18a** (ca. 1:5 by ^{1}H NMR analysis): IR 3071, 3032, 2971, 2219, 1628, 1481 cm^{-1}; ^{1}H NMR ($CDCl_3$) the *Z*-isomer showed characteristic absorbances at δ 7.82 (m, 2H), 7.46 (m, 3H), 7.14 (d, 12.2 Hz, 1H, H−C3), 5.46 (d, 12.2 Hz, 1H, H−C2); the *E*-isomer showed absorbances at δ 7.82 (m, 5H), 7.40 (d, 16.6 Hz, 1H, H−C3), 5.89 (d, 16.5 Hz, 1H, H−C2).

***trans,exo/endo*- and *cis,endo*-5-Cyano-6-phenylbicyclo[2.2.2]oct-2-enes 19 and 20.** A mixture of (*E*)- and (*Z*)-3-phenylpropenonitrile, **18a** (1.26 g, 12.0 mmol), 1,3-cyclohexadiene (1.40 mL, 14.9 mmol), benzene (1 mL), and a few crystals of hydroquinone was heated in a sealed tube at 180 °C for 6 days. The mixture was cooled, and the solvent was removed under reduced pressure. Chromatography (SiO_2, 30% v/v diethyl ether in hexane) afforded a mixture of the *trans exo* and *trans endo* nitriles **19a** (110 mg, 7.0%) as a colorless oil and *endo*-5-cyano-*endo*-6-phenylbicyclo[2.2.2]oct-2-ene (**20a**) (707 mg, 28.0%) as a white solid: mp 96−97 °C (lit.[39] mp 98 °C); ^{1}H NMR ($CDCl_3$) δ 7.16−7.34 (m, 5H), 6.70 (t, 7.2 Hz, 1H, H−C2), 6.48 (t, 7.2 Hz, 1H, H−C3), 3.30 (dd, 10.5 Hz, 2.7 Hz, 1H, H−C5), 3.25 (d, 10.5 Hz, 1H, H−C6), 3.06 (bs, 1H, H−C1), 2.87−2.83 (m, 1H, H−C4), 1.78−1.25 (m, 4H, H−C7,8); IR 3070, 3052, 3026, 2908, 2861, 2236, 1648 cm^{-1}.

***trans*- and *cis*-2-Cyano-3-phenylbicyclo[2.2.2]octanes 21 and 22.** Substituted bicyclo[2.2.2]oct-2-enes **19** and **20** were separately hydrogenated over 10% palladium on carbon or PtO_2 under 40 psi of H_2. A mixture of *endo*-5-cyano-*endo*-6-phenylbicyclo[2.2.2]oct-2-ene (**20a**) (90 mg, 0.43 mmol), 5.3 mg 10% Pd/C, and 1.0 mL ethyl acetate was shaken under H_2 for 1 h. The solution was filtered, and the solvent was removed under reduced pressure to give of *cis*-2-cyano-3-phenylbicyclo-[2.2.2]octane (**22a**) as a brown oil (91 mg, 99%): ^{1}H NMR ($CDCl_3$) δ 7.22−7.41(m, 5H), 3.34 (d, 11.0 Hz, 1H, H−C2), 3.24 (d, 11.0 Hz, 1H, H−C3), 2.15 (m, 4H), 1.50−1.81(m, 6H); IR 3066, 3025, 2954, 2870, 2239, 1705 cm^{-1}.

***trans*-2-Cyano-3-phenylbicyclo[2.2.2]octane (21a):** ^{1}H NMR ($CDCl_3$) δ 7.21−7.40 (m, 5H), 3.19 (d, 8.3 Hz, 1H, H−C2), 2.96 (d, 8.3 Hz, 1H, H−C3), 1.40−2.10 (m, 10H); IR 3065, 3032, 2940, 2871, 2243, 1671 cm^{-1}.

***cis*- and *trans*-2-(Aminomethyl)-3-phenylbicyclo[2.2.2]-alkane Hydrochloride Salts 5 and 7.** BH_3−THF (1.34 mL of a 1 M BH_3 solution in THF, 1.34 mmol) was added to a solution of *cis*-2-cyano-3-phenylbicyclo[2.2.2]octane (**22a**) (71 mg, 0.33 mmol) in 2 mL THF, and the mixture was heated at reflux overnight under N_2. The solution was added to 2 mL concentrated HCl, the THF was removed under reduced pressure, a few NaOH pellets were added, and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford a brown oil. Concentrated HCl was added, and the precipitate was filtered and dried to afford *cis*-2-(aminomethyl)-3-phenylbicyclo[2.2.2]octane hydrochloride (**7a**) as a white solid: mp 220 °C dec; ^{1}H NMR (D_2O) δ 7.12−7.38 (m, 5H), 3.15 (d, 11.9 Hz, 1H, H−C3), 2.64 (t, 11.9 Hz, 1H, diastereotopic H−C9), 2.42 (dd, 11.9 Hz, 4.2 Hz, 1H, diastereotopic H−C9), 2.25−2.33 (m, 1H, H−C2), 1.30−2.06 (m, 10H); IR 3447, 3033, 2934, 2868, 1604, 1499, 1453 cm^{-1}. Anal. ($C_{15}H_{22}NCl$) C, H, N, Cl.

Alternatively, the 2-cyano-3-phenylbicyclo[2.2.2]alkanes were treated with Redal (5 equiv, 65 wt % solution in toluene) in dry THF overnight at room temperature. Workup and acidification as above gave the hydrochloride salts as white solids.

***trans*-2-(Aminomethyl)-3-phenylbicyclo[2.2.2]octane hydrochloride (5a):** mp 269 °C dec; ^{1}H NMR (D_2O) δ 7.18−7.35 (m, 5H), 2.94 (dd, 9.8 Hz, 13.0 Hz, 1H, diastereotopic H−C9), 2.77 (dd, 5.7, 13.0 Hz, 1H, diastereotopic H−C9), 2.43 (d, 8.1 Hz, 1H, H−C3), 2.24 (m, 1H, H−C2), 1.20−1.66 (m, 10H); IR 3439, 3039, 2947, 2870, 1607, 1473, 1453 cm^{-1}. Anal. ($C_{15}H_{22}NCl$) C, H, N, Cl.

***cis*- and *trans*-2-(*N*,*N*-Dimethylaminomethyl)-3-phenylbicyclo[2.2.2]alkane Hydrochloride Salts 6 and 8.** The hydrochloride salt of *cis*-2-(aminomethyl)-3-phenylbicyclo-[2.2.2]octane **7a** (62.9 mg, 0.25 mmol) was dissolved in 5 mL 5% Na_2CO_3. The solution was extracted with CH_2Cl_2 (3 × 5 mL), the extacts were combined, and the solvent was removed under reduced pressure; 37% formaldehyde (1.5 mL, 20 mmol) and formic acid (0.85 mL, 20 mmol) were added to the residue, and the mixture was heated at reflux overnight; 2 N NaOH solution (15 mL) was added, and the aqueous solution was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure to give a brown oil. The residue was dissolved in 3 mL ethanol, and excess concentrated HCl was added. The solution was evaporated to dryness to give *cis*-2-(*N*,*N*-dimethylaminomethyl)-3-phenylbicyclo[2.2.2]octane hydrochloride (**8a**) as a colorless solid (16 mg, 19%): mp 218−220 °C; ^{1}H NMR (D_2O) δ 7.20−7.30 (m, 5H), 3.39 (d, 11.2 Hz, 1H, diastereotopic H−C9), 3.05 (t, 11.2 Hz, 1H, diastereotopic H−C9), 2.73 (s, 3H, NCH_3), 2.70 (s, 3H, NCH_3), 2.64 (m, 1H, H−C2), 2.57 (dd, 12.6 Hz, 4.5 Hz, 1H, H−C3), 1.60−2.00 (m, 10H); IR 3441, 3019, 2954, 2892, 2868, 1677, 1473, 1400 cm^{-1}. Anal. ($C_{17}H_{28}NCl$) C, H, N, Cl.

***trans*-2-(*N*,*N*-Dimethylaminomethyl)-3-phenylbicyclo-[2.2.2]octane hydrochloride (6a):** mp 219−228 °C dec; ^{1}H NMR (D_2O) δ 7.12−7.32 (m, 5H), 3.16 (dd, 9.3 Hz, 13.3 Hz, 1H, diastereotopic H−C9), 2.79 (dd, 4.8 Hz, 13.3 Hz, 1H, diastereotopic H−C9), 2.62 (s, 6H, $N(CH_3)_2$), 2.28−2.42 (m, 2H, H−C2,3), 1.10−1.62 (m, 10H); IR 3454, 3065, 3033, 2940, 2868, 1618, 1486, 1420 cm^{-1}. Anal. ($C_{17}H_{28}NCl$) C, H, N, Cl.

Synthesis of *trans,exo*- and *trans,endo*-2-(Aminomethyl)-3-phenylbicyclo[2.2.1]Alkane Hydrochloride Salts 9−12. *trans,exo*- and *trans,endo*-5-Carboxy-6-phenylbicyclo[2.2.1]hept-2-enes 24 and 25. A mixture of *trans*-

cinnamoyl chloride (16.0 g, 96 mmol) and freshly distilled cyclopentadiene (25.0 mL, 303 mmol) was heated at reflux for 18 h. Excess cyclopentadiene was removed under reduced pressure. The residue was dispersed in 120 mL 10% NaOH containing a small amount of detergent (Alconox), and the mixture was heated at 50 °C for 18 h. The mixture was acidified with concentrated HCl and extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were washed with saturated NaCl (2 × 50 mL) and dried over $MgSO_4$, and the solvent was evaporated to give a brown solid (16 g) containing a mixture of *exo* and *endo* Diels−Alder adducts **24a** and **25a**.

A solution of iodine (33 g, 130 mmol) and KI (66 g, 400 mmol) in 250 mL water was added dropwise to a solution containing the mixture of Diels−Alder adducts in 250 mL saturated $NaHCO_3$, and the mixture was stirred for 20 min. The precipitate was filtered and washed with 50 mL water, and the filtrate was saved to recover the exo acid **24a** (see later). The solid was washed with 40 mL 1% $Na_2S_2O_3$ and 40 mL water and dried under vacuum to afford the iodolactone **26a** as an off-white solid: mp 118−120 °C (lit.[21] mp 118.5−120 °C); ^{1}H NMR ($CDCl_3$) δ 7.13−7.40 (m, 5 H), 5.21 (d, 5.1 Hz, 1H, H−C3), 4.05 (d, 5.1 Hz, 1H, H−C2), 3.32 (s, 1H, H−C5), 3.23 (t, 4.8 Hz, 1H, H−C6), 2.87 (br s, 2H, H−C1,4), 2.30 (d, 12.0 Hz, 1H, H_a-C7), 2.11 (d, 12.0 Hz, 1H, H_b-C7); IR 3066, 3032, 2975, 2891, 1796, 1607, 1497, 1453, 1178 cm^{-1}.

A mixture of iodolactone **26a** (20.0 g, 58.8 mmol), zinc dust (40 g, 0.66 mol), and 600 mL glacial acetic acid was stirred for 18 h, and the mixture was filtered through a bed of Celite. Most of the acetic acid was removed under reduced pressure, and 2 N NaOH was added until the pH was approximately 13. The mixture was filtered, and the filtrate was washed with Et_2O (2 × 50 mL). The aqueous phase was neutralized with concentrated HCl and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford *endo*-5-carboxy-*exo*-6-phenylbicyclo[2.2.1]hept-2-ene (**24a**) as a colorless solid (7.2 g, 56% from the iodolactone): mp 113−113.5 °C (lit.[40] mp 113−114 °C); ^{1}H NMR ($CDCl_3$) δ 7.18−7.35 (m, 5H), 6.44 (dd, 5.6 Hz, 3.2 Hz, 1H, H−C3), 6.19 (dd, 5.6 Hz, 2.9 Hz, 1H, H−C2), 3.49 (s, 1H, H−C4), 3.03−3.32 (m, 3H, H−C4,5,6), 1.80 (d, 8.8 Hz, 1H, H_a-C7), 1.60 (dd, 8.8 Hz, 1.7 Hz, 1H, H_b-C7); IR 2700−3300, 3072, 3032, 2986, 2881, 1703, 1680 cm^{-1}.

The *exo* isomer **25a** was isolated from the filtrate from the iodolactonization reaction described above. The basic filtrate was acidified with concentrated HCl. The precipitate was collected by filtration and dissolved in boiling cyclohexane. The solution was cooled and filtered to remove unreacted cinnamic acid. The solvent was removed, and the residue was recrystallized from methanol−water to give *exo*-5-carboxy-*endo*-6-phenylbicyclo[2.2.1]hept-2-ene (**25a**) as colorless blades: mp 114−114.5 °C (lit.[41] mp 113−114 °C); ^{1}H NMR ($CDCl_3$) δ 7.16−7.28 (m, 5H), 6.33 (dd, 3.2 Hz, 5.6 Hz, 1H, H−C2 or 3), 6.05 (dd, 2.8 Hz, 5.6 Hz, 1H, H−C3 or 2), 3.73 (dd, 3.4 Hz, 5.2 Hz, 1H, H−C5), 3.22 (s, 2H, H−C1,4), 2.55 (dd, 1.6 Hz, 5.4 Hz,-1H,H−C6), 1.89 (d, 8.7 Hz, 1H, H_a-C7), 1.57 (d, 8.7 Hz, 1H, H_b-C7); IR 3100−3500, 3073, 3039, 2975, 2919, 1705, 1650 cm^{-1}.

***trans,endo*- and *trans,exo*-2-Carboxy-3-phenylbicyclo[2.2.1]heptanes 27 and 28.** Substituted bicyclo[2.2.1]hept-2-enes **24** and **25** were hydrogenated in quantitative yield over 10% palladium on carbon or PtO_2 under 40 psi of H_2 according to the procedure given above (for the synthesis of **21** and **22**) to afford **27** and **28**, respectively.

***endo*-2-Carboxy-*exo*-3-phenylbicyclo[2.2.1]heptane (27a):** mp 104.5−106.5 °C (lit.[21] mp 105 °C); ^{1}H NMR ($CDCl_3$) δ 11.2 (br s, 1H, COOH), 7.14−7.31 (m, 5H), 3.16 (d, 6.0 Hz, 1H, H−C2), 2.89−2.93 (m, 1H, H−C3), 2.72 (br s, 1H, H−C1), 2.49−2.51 (m, 1H, H−C4), 1.80 (d, 10.2 Hz, 1H, H−C7), 1.39−70 (m, 5H, H−C5,6,7); IR 2800−3500, 3066, 3052, 2964, 2887, 1697, 1649 cm^{-1}.

***exo*-2-Carboxy-*endo*-3-phenylbicyclo[2.2.1]heptane (28a):** mp 105−105.5 °C (lit.[23] mp 105 °C); ^{1}H NMR ($CDCl_3$) δ 8.90 (br s, 1H, CO_2H), 7.18−7.34 (m, 5H), 3.56 (dd, 3.9 Hz, 6.3 Hz, 1H, H−C2), 2.66 (d, 3.9 Hz, 1H, H−C1 or C4), 2.61 (d, 6.3 Hz, 1H, H−C3), 2.57 (br s, 1H, H−C4 or C1), 1.82 (d, 9.9 Hz, 1H, H_a-C7), 1.54 (d, 9.9 Hz, 1H, H_b-C7), 1.25−1.41 (m, 3H, H−C5,6); IR 3100−3500, 3072, 3040, 2973, 2840, 1710, 1680 cm^{-1}.

***trans,endo*- and *trans,exo*-2-Amido-3-phenylbicyclo[2.2.1]heptanes 29 and 30.** Thionyl chloride (0.57 mL, 8.2 mmol) was added dropwise to a stirred suspension of *endo*-2-carboxy-*exo*-3-phenylbicyclo[2.2.1]heptane (**27a**) (345 mg, 1.50 mmol) in 5 mL chloroform containing 0.1 mL DMF at room temperature. The solution was cooled to 0 °C and cannulated into a flask containing 15 mL concentrated NH_4OH at 0 °C. The resulting mixture was stirred at 0 °C for 10 min and at room temperature for 1 h. The mixture was extracted with chloroform (3 × 30 mL), the combined extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was recrystallized from a mixture of hexane and CH_2Cl_2 (10:1) to give *exo*-2-amido-*endo*-3-phenylbicyclo[2.2.1]-heptane (**30a**) as a colorless solid (296 mg, 92%): mp 149−150 °C (lit.[21] mp 153−154 °C); ^{1}H NMR ($CDCl_3$) δ 7.18−7.34 (m, 5H), 5.54 (br s, 1H, NH), 5.36 (br s, 1H, NH), 3.53−3.56 (m, 1H, H−C3), 2.57 (d, 3.6 Hz, 1H, H−C1), 2.48 (br s, 1H, H−C4), 2.39 (d, 6.0 Hz, 1H, H−C2), 1.89 (d, 9.9 Hz, 1H, H_a-C7), 1.59−1.71 (m, 2H), 1.41 (d, 9.9 Hz, 1H, H_b-C7), 1.28−1.36 (m, 2H); IR 3421, 3191, 3065, 3031, 2973, 2940, 1657, 1651 cm^{-1}.

***endo*-2-Amido-*exo*-3-phenylbicyclo[2.2.1]heptane (29a):** mp 141−142 °C (lit.[39] mp 138−141 °C); ^{1}H NMR ($CDCl_3$) δ 7.14−7.25 (m, 5H), 5.98 (br s, 1H, NH), 5.23 (br s, 1H, NH), 3.21 (d, 6.0 Hz, 1H, H−C2), 2.69−2.74 (m, 1H, H−C3), 2.54 (br s, 1H, H−C1), 2.50 (d, 3.9 Hz, 1H, H−C4), 1.79 (d, 9.9 Hz, 1H, H_a-C7), 1.41−1.66 (m, 5H, H−C5,6 and H_b-C7); IR 3407, 3210, 3049, 3007, 2960, 2871, 1657, 1650 cm^{-1}.

***trans,endo*- and *trans,exo*-2-(Aminomethyl)-3-phenylbicyclo[2.2.1]heptane Hydrochloride Salts 9 and 11.** *trans*-2-amido-3-phenylbicyclo[2.2.1]heptanes **29** and **30** were treated with BH_3−THF (3 equiv, 1 M BH_3 in THF) followed by aqueous acid according to the procedure given above (for the synthesis of **5** and **7**) to afford **9** and **11**.

***endo*-2-(Aminomethyl)-*exo*-3-phenylbicyclo[2.2.1]heptane hydrochloride (9a):** mp 210−211 °C; ^{1}H NMR (D_2O) δ 7.10−7.27 (m, 5H), 2.93−3.07 (m, 2H, H−C8), 2.28 (br s, 1H, H−C3), 2.11 (br s, 3H, H−C1,2,4), 1.64 (d, 10.5 Hz, 1H, H_a-C7), 1.45−1.56 (m, 1H), 1.33−1.39 (m, 2H), 1.28 (d, 10.5 Hz, 1H, H_b-C7), 1.14−1.23 (m, 1H); IR 2800−3500, 2993, 2960, 2875, 1640 cm^{-1}. Anal. ($C_{14}H_{20}NCl$) C, H, N, Cl.

***exo*-2-(Aminomethyl)-*endo*-3-phenylbicyclo[2.2.1]heptane hydrochloride (11a):** mp 218−220 °C dec; ^{1}H NMR (D_2O) δ 7.10−7.26 (m, 5H), 2.81 (dd, 9.3 Hz, 12.6 Hz, 1H, diastereotopic H−C8), 2.72 (d, 6.0 Hz, 12.6 Hz, 1H, diastereotopic H−C8), 2.64−2.67 (m, 1H, H−C3), 2.26 (br s, 1H, H−C4), 2.11 (d, 4.5 Hz, 1H, H−C2), 1.85−1.92 (m, 1H, H−C1), 1.52 (d, 9.9 Hz, 1H, H_a-C7), 1 43−1.49 (m, 1H), 1.28 (d, 9.9 Hz, 1H, H_b-C7), 1.01−1.16 (m, 3H); IR 3467, 3025, 2954, 2877, 1614, 1508, 1442 cm^{-1}. Anal. ($C_{14}H_{20}NCl$) C, H, N, Cl.

***trans,endo*- and *trans,exo*-2-(*N,N*-Dimethylaminomethyl)-3-phenylbicyclo[2.2.1]heptane Hydrochloride Salts 10 and 12.** 2-(Aminomethyl)-3-phenylbicyclo[2.2.1]-heptane hydrochlorides **9** and **11** were neutralized and treated with formaldehyde and formic acid according to the method above (for the synthesis of **6** and **8**) to afford **10** and **12**.

***endo*-2-(*N,N*-Dimethylaminomethyl)-*exo*-3-phenylbicyclo[2.2.1]heptane hydrochloride (10a):** mp 218−220 °C dec; ^{1}H NMR (D_2O) δ 7.11−7.27 (m, 5H), 3.25 (dd, 12.6 Hz, 9.9 Hz, 1H, diastereotopic H−C8), 3.09 (dd, 12.6 Hz, 4.8 Hz, 1H, diastereotopic H−C8), 2.66 (s, 6H, $N(CH_3)_2$), 2.21−2.28 (m, H−C2,3, 2H,), 2.12 (br s, 2H, H−C1,4), 1.70 (d, 10.5 Hz, 1H, H_a-C7), 1.34−1.56 (m, 3H), 1.29 (d, 10.5 Hz, 1H, H_b-C7), 1.18−1.26 (m, 1H); IR 3432, 3102, 3067, 3010, 2968, 2919, 2884, 1607, 1481, 1403 cm^{-1}. Anal. ($C_{15}H_{26}NCl$) C, H, N, Cl

***exo*-2-(*N,N*-Dimethylaminomethyl)-*endo*-3-phenylbicyclo[2.2.1]heptane hydrochloride (12a):** mp 186−187 °C dec; ^{1}H NMR (D_2O) δ 7.13−7.28 (m, 5H), 3.08 (dd, 9.3 Hz, 13.2 Hz, 1H, diastereotopic H−C8), 2.85 (dd, 6.0 Hz, 13.2 Hz, 1H, diastereotopic H−C8), 2.71 (br s, 1H, H−C3), 2.66 (s, 6H,

$N(CH_3)_2$), 2.24 (br s, 1H, H−C1), 2.09 (br s, 1H, H−C4), 1.96−2.06 (m, 1H, H−C2), 1.08−1.56 (m, 6H, H−C5,6,7); IR 3375, 3026, 2960, 2927, 2881, 2855, 1650, 1485, 1466, 1407 cm^{-1}. Anal. ($C_{16}H_{26}NCl$) C, H, N, Cl.

Synthesis of *cis,endo*-2-(Aminomethyl)-*endo*-3-phenylbicyclo[2.2.1]alkane Hydrochloride Salts 13 and 14. *endo*-5-Cyano-*endo*-6-phenylbicyclo[2.2.1]hept-2-enes 31. Diels−Alder reaction of cyclopentadiene and a mixture of (*E*)- and (*Z*)-**18** (approximately 1:4 by ^1H NMR analysis) according to the procedure given above (for the synthesis of **19** and **20**) gave a mixture of **31** and the corresponding *trans* isomers which were separated by column chromatography (SiO_2, 1/10 EtOAc/hexane).

***endo*-5-Cyano-*endo*-6-phenylbicyclo[2.2.1]hept-2-ene (31a):** ^1H NMR ($CDCl_3$) δ 7.22−7.33 (m, 5H), 6.44−6.50 (m, 2H, H−C2,3), 3.67 (dd, 3.0 Hz, 9.7 Hz, 1H, H−C6), 3.46 (dd, 3.9 Hz, 9.7 Hz, 1H, H−C5), 3.36 (br s, 1H, H−C4), 3.25 (br s, 1H, H−C1), 1.67 (dt, 1.8 Hz, 9.1 Hz, H_a-C7), 1.52 (d, 9.1 Hz, 1H, H_b-C7); IR 3065, 3033, 2973, 2875, 2243, 1661, 1491, 1438 cm^{-1}.

***endo*-2-Cyano-*endo*-3-phenylbicyclo[2.2.1]heptanes 32.** Substituted bicyclo[2.2.1]hept-2-enes **31** were hydrogenated in quantitative yield over 10% palladium on carbon or PtO_2 under 40 psi of H_2 according to the procedure given above (for the synthesis of **21** and **22**) to afford **32**.

***endo*-2-Cyano-*endo*-3-phenylbicyclo[2.2.1]heptane (32a):** ^1H NMR ($CDCl_3$) δ 7.23−7.39 (m, 5H), 3.41 (d, 13.0 Hz, 1H, H−C2), 3.30 (ddd, 2.1 Hz, 4.5 Hz, 13.0 Hz, 1H, H−C3), 2.69 (br s, 1H, H−C4), 2.57 (br s, 1H, H−C1), 1.47−1.97 (m, 6H, H−C5,6,7); IR 3065, 3033, 2970, 2888, 2243, 1652 cm^{-1}.

***endo*-2-(Aminomethyl)-*endo*-3-phenylbicyclo[2.2.1]heptane Hydrochloride Salts 13.** *endo*-2-Cyano-*endo*-3-phenylbicyclo[2.2.1]heptanes **32** were treated with BH_3−THF (3 equiv, 1 M BH_3 in THF) followed by aqueous acid according to the procedure given above (for the synthesis of **5** and **7**) to afford **13**.

***endo*-2-(Aminomethyl)-*endo*-3-phenylbicyclo[2.2.1]heptane hydrochloride (13a):** mp 259−262 °C; ^1H NMR (D_2O) δ 7.13−7.18 (m, 5H), 3.30 (dd, 3.9 Hz, 12.0 Hz, 1H, diastereotopic H−C8), 2.79−2.82 (m, 2H, diastereotopic H−C8 and H−C3), 2.36−2.46 (m, 1H, H−C2), 2.30 (br s, 2H, H−C1 and C4), 1.34−1.63 (m, 6H, H−C5, C6 and C7); IR 3441, 3033, 2947, 2871, 1611, 1482, 1426 cm^{-1}. Anal. ($C_{14}H_{20}NCl$) C, H, N, Cl.

***endo*-2-(*N,N*-Dimethylaminomethyl)-*endo*-3-phenylbicyclo[2.2.1]heptane Hydrochloride Salts 14.** *endo*-2-(Aminomethyl)-*endo*-3-phenylbicyclo[2.2.1]heptane hydrochlorides **13** were neutralized and treated with formaldehyde and formic acid according to the method provided above (for the synthesis of **6** and **8**) to afford **14**.

***endo*-2-(*N,N*-Dimethylaminomethyl)-*endo*-3-phenylbicyclo[2.2.1]heptane hydrochloride (14a):** mp 270 °C dec; ^1H NMR (D_2O) δ 7.11−7.25 (m, 5H), 3.33 (dd, 1H, 13.2 Hz, 3.3 Hz, diastereotopic H−C8), 2.96 (d, 1H, 10.8 Hz, H−C3), 2.86 (dd, 1H, 13.2 Hz, 6.0 Hz, diastereotopic H−C8), 2.63 (s, 3H, NCH_3), 2.57 (s, 3H, NCH_3), 2.30 (br s, 3H, H−C1,2,4), 1.32−1.65 (m, 6H); IR 3421, 3059, 3032, 3019, 2953, 2868,-1611, 1448, 1400 cm^{-1}. Anal. ($C_{22}H_{26}NCl$) C, H, N, Cl.

Synthesis of *cis,exo*-2-(Aminomethyl)-*exo*-3-(4-chlorophenyl)bicyclo[2.2.1]alkane Hydrochloride Salt (15c). (*Z*)-4-Chlorocinnamic Acid (34c). A solution of (*E*)-4-chlorocinnamic acid (**33c**) (8.00 g, 43.8 mmol) in 300 mL dioxane was irradiated at 254 nm in a quartz tube for 24 h. The solvent was removed under reduced pressure, and the residue was triturated with boiling water. Upon cooling, (*Z*)-4-chlorocinnamic acid (**34c**) precipitated as a colorless crystalline solid (1.1 g, 14%): mp 109−110 °C (lit.[23] mp 111 °C); ^1H NMR ($CDCl_3$) δ 7.40−7.42 (m, 4H), 6.90 (d, 12.6 Hz, 1H, H−C3), 5.96 (d, 12.6 Hz, 1H, H−C2); IR 2500−3300, 3053, 2947, 1691, 1635, 849, 765 cm^{-1}.

***exo*-5-Carboxyl-*exo*-6-(4-chlorophenyl)bicyclo[2.2.1]hept-2-ene (35c).** A mixture of (*Z*)-4-chlorocinnamic acid (**34c**) (2.6 g, 14.2 mmol) and cyclopentadiene (7 mL, 85 mmol) was heated in a sealed tube at 140 °C for 4 days. The mixture was concentrated under reduced pressure, 100 mL 10% Na_2CO_3 was added, and the solution heated at 70 °C for 3 h. The solution was cooled to room temperature and washed with CH_2Cl_2 (3 × 50 mL). The aqueous solution was acidified with concentrated HCl and extracted with CH_2Cl_2 (2 × 30 mL). The combined extracts were washed with saturated NaCl (2 × 40 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure to give a brown solid (3.1 g). Analysis of the solid by ^1H NMR showed that it consisted of a mixture of *cis endo*, *cis exo* (**35c**), *trans endo* (**27c**), and *trans exo* (**28c**) adducts in a ratio of approximately 3:1:1:1. The mixture was dissolved in 235 mL 10% $NaCO_3$, and a solution of KI_3 (prepared from 2.0 g I_2 and 4.0 g KI in 20 mL H_2O) was added until no more precipitate formed. The mixture was extracted with CH_2Cl_2 (4 × 30 mL), and the aqueous solution was acidified with concentrated HCl. The aqueous solution was extracted with CH_2Cl_2 (3 × 30 mL), the combined extracts were washed with saturated NaCl (2 × 40 mL), dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure to give an off-white solid (0.61 g). ^1H NMR showed that the solid contained a mixture of *cis exo* (**35c**) and *trans exo* (**28c**) acids (approximately 1:1). Column chromatography (SiO_2; $CHCl_3$:EtOAc, 6:1) gave the *cis exo* acid **35c** as a white solid (140 mg, 46% yield from mixture of **35c** and **28c**): mp 98−99 °C (lit.[23] mp 103 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.12−7.22 (m, 4H), 6.39 (dd, 3.3 Hz, 5.6 Hz, 1H, H−C3), 6.24 (dd, 2.7 Hz, 5.6 Hz, 1H, H−C2), 3.06−3.10 (m, 2H, H−C4 and C6), 3.00 (br s, 1H, H−C1), 2.70 (dd, 1.8 Hz, 9.5 Hz, 1H, H−C5), 2.29 (d, 9.0 Hz, 1H, H_a-C7), 1.64 (d, 9.0 Hz, 1H, H_b-C7); IR 2700−3300, 3063, 2987, 2948, 1713, 838, 730 cm^{-1}.

***exo*-2-Carboxy-*exo*-3-(4-chlorophenyl)bicyclo[2.2.1]heptane (36c).** *exo*-5-Carboxyl-*exo*-6-(4-chlorophenyl)bicyclo[2.2.1]-hept-2-ene (**35c**) (135 mg, 0.54 mmol) was hydrogenated in quantitative yield over 30 mg 10% palladium on carbon in 15 mL ethyl acetate under 40 psi of H_2 according to the procedure given above (for the synthesis of **21** and **22**) to afford *exo*-2-carboxy-*exo*-3-(4-chlorophenyl)bicyclo[2.2.1]heptane (**36c**) as an off-white solid: mp 129−130 °C; ^1H NMR ($CDCl_3$) δ 7.07−7.20 (m, 4H), 3.12 (d, 9.7 Hz, 1H, H−C3), 2.83 (d, 9.7 Hz, 1H, H−C2), 2.50 (br s, 1H, H−C1), 2.47 (br s, 1H, H−C4), 2.22 (d, 10.5 Hz, 1H, H_a-C7), 1.57−1.70 (m, 2H), 1.41 (d, 10.5 Hz, 1H, H_b-C7), 1.24−1.37 (m, 2H); IR 2700−3300, 3051, 2954, 2881, 1703, 841, 742 cm^{-1}.

***exo*-2-Amido-*exo*-3-(4-chlorophenyl)bicyclo[2.2.1]heptane (37c).** Thionyl chloride (1.0 mL, 13 mmol) was added to a solution of *exo*-2-carboxy-*exo*-3-(4-chlorophenyl)bicyclo[2.2.1]-heptane (**36c**) (120 mg, 0.48 mmol) in 10 mL $CHCl_3$ containing 0.1 mL DMF. The mixture was stirred for 30 min at room temperature, cooled to 0 °C, and added dropwise to concentrated NH_3 (15 mL). The mixture was stirred at 0 °C for 20 min and then at room temperature for 18 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The organic fractions were combined, washed with saturated NaCl (2 × 20 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure to give *exo*-2-amido-*exo*-3-(4-chlorophenyl)bicyclo[2.2.1]heptane (**37c**) as a white solid (120 mg, 100%): mp 192−194 °C; ^1H NMR ($CDCl_3$) δ 7.13−7.22 (m, 4H), 4.89 (br s, 2H, N−H), 3.07 (d, 9.5 Hz, 1H, H−C2), 2.67 (d, 9.5 Hz, 1H, H−C3), 2.58 (br s, 1H, H−C4), 2.42 (br s, 1H, H−C1), 2.35 (d, 10.5 Hz, 1H, H_a-C7), 1.63−1.68 (m, 2H), 1.44 (d, 10.5 Hz, 1H, H_b-C7), 1.23−1.38 (m, 2H); IR 3493, 3330, 3011, 2964, 2879, 1659, 1612, 830, 768 cm^{-1}.

***exo*-2-(Aminomethyl)-*exo*-3-(4-chlorophenyl)bicyclo-[2.2.1]heptane Hydrochloride Salt (15c).** *exo*-2-Amido-*exo*-3-(4-chlorophenyl)bicyclo[2.2.1]heptane (**37c**) was treated with BH_3−THF (3 equiv, 1.0 M BH_3 in THF) followed by aqueous acid according to the procedure given above (for the synthesis of **5** and **7**) to afford **15c** as a white crystalline solid (60% yield): mp 260 °C dec; ^1H NMR (D_2O) δ 7.07−7.19 (m, 4H), 2.88 (br d, 6.0 Hz, 1H, H−C8), 2.29 (br s, 1H, H−C4), 2.04−2.13 (m, 4H, H−C1,2,3,8), 1.62 (d, 10.5 Hz, 1H, H_a-C7), 1.42−1.57 (m, 2H), 1.25 (d, 10.5 Hz, 1H, H_b-C7), 1.11−1.21 (m, 2H); IR 3447, 3031, 2960, 2875, 1604, 834, 769 cm^{-1}. Anal. ($C_{14}H_{19}N_2Cl$) C, H, N, Cl.

5-*exo*-Carboxy-6-*exo*-phenylbicyclo[2.2.1]hept-2-ene (35a). A solution of 5-*endo*-carboxy-6-*exo*-phenylbicyclo[2.2.1]hept-2-ene (**24a**) (1.27 g, 5.92 mmol) in 10.0 mL dry THF was added dropwise to a solution of LDA·THF (8.0 mL of 1.5 M solution in hexane, 12.0 mmol, 2 equiv) in 10 mL dry THF at −78 °C under N_2. The mixture was warmed to room temperature and stirred for 5 h. Ice-cold saturated NH_4Cl solution was added, followed by concentrated HCl until the solution was strongly acidic. The mixture was extracted with CH_2Cl_2 (3 × 25 mL), and the combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a mixture (1.20 g) of **24a** (90% by ^{1}H NMR analysis) and 5-*exo*-carboxy-6-*exo*-phenylbicyclo[2.2.1]hept-2-ene, **35a** (10%). The solid was dissolved in 40 mL 10% Na_2CO_3, and a solution of KI_3 (2 g I_2 and 4 g KI in 20 mL H_2O) was added until no more precipitate formed. The mixture was washed with CH_2Cl_2 (3 × 30 mL), and concentrated HCl was added to the aqueous solution until it was strongly acidic. The white precipitate was filtered and dried under vacuum. Recrystallization from CH_3OH/H_2O gave 5-*exo*-carboxy-6-*exo*-phenylbicyclo-[2.2.1]hept-2-ene, **35a** (65 mg, plus 50 mg from a second crop), as colorless blades: mp 138−139 °C (lit.[42] mp 136 °C); ^{1}H NMR ($CDCl_3$) δ 7.12−7.25 (m, 5H, H−Ph), 6.38 (dd, 3.6 Hz, 5.7 Hz, 1H, H−C3), 6.22 (dd, 3.3 Hz, 5.4 Hz, 1H, H−C2), 3.11 (dd, 1.5 Hz, 9.9 Hz, H−C5), 3.02−3.04 (m, 2H, H−C1 and C4), 2.70 (dd, 1.8 Hz, 9.9 Hz, H−C6), 2.34 (d, 9.0 Hz, 1H, H−C7), 1.63 (dt, 1.5 Hz, 9.0 Hz, H−C7); IR 3098, 3065, 3026, 2980, 2736, 1776, 1705, 1492, 1427, 1262, 1203, 926, 709 cm^{-1}.

2-*exo*-Carboxy-3-*exo*-phenylbicyclo[2.2.1]heptane (36a). 5-*exo*-Carboxy-6-*exo*-phenylbicyclo[2.2.1]hept-2-ene, **35a** (60 mg, 0.28 mmol), was hydrogenated in quantitative yield over 30 mg 10% palladium on carbon in 15 mL ethyl acetate under 42 psi of H_2 according to the procedure given above (for the synthesis of **21** and **22**) to afford 2-*exo*-carboxy-3-*exo*-phenylbicyclo[2.2.1]heptane, **36a**, as a light brown oil: ^{1}H NMR ($CDCl_3$) δ 7.16−7.26 (m, 5H, H−Ph), 3.22 (d, 10.2 Hz, H−C2), 2.54−2.58 (m, 2H, H−C1 and C4), 2.90 (dd, 1.8 Hz, 10.2 Hz, H−C3), 2.54−2.58 (m, 2H, H−C1 and C4), 2.35 (dt, 1.8 Hz, 10.2 Hz, 1H, H−C7), 1.67−1.73 (m, 2H, H−C5 and C6), 1.47 (dt, 1.8H z, 10.2 Hz, H−C7), 1.30−1.41 (m, 2H, H−C5 and C6); IR 3094, 3071, 3033, 2964, 2872, 1782, 1713, 1475, 1298, 1244, 699 cm^{-1}.

2-*exo*-(Aminomethyl)-3-*exo*-phenylbicyclo[2.2.1]heptane Hydrochlorde Salt (15a). $SOCl_2$ (0.20 mL, 2.7 mmol) was added to a solution of 5-*exo*-carboxy-6-*exo*-phenylbicyclo-[2.2.1]heptane, **36a**, and 0.3 mL *N*,*N*-dimethylformamide in 10.0 mL $CHCl_3$, and the mixture was stirred under N_2 for 30 min. The mixture was cooled to 0 °C, added dropwise to ice-cold concentrated ammonium hydroxide, and stirred at 0 °C for 30 min and at room temperature for 2 h. The $CHCl_3$ layer was separated, and the aqueous solution was extracted with CH_2Cl_2 (3 × 10 mL). The organic portions were combined, washed with brine, dried over $MgSO_4$, and evaporated to give 2-*exo*-amido-3-*exo*-phenylbicyclo[2.2.1]heptane, **37a**, as a light brown solid: ^{1}H NMR ($CDCl_3$) δ 7.20−7.34 (m, 5H, H−Ph), 4.86 (br s, 1H, H−N), 3.17 (d, 9.9 Hz, H−C3), 2.75 (d, 9.9 Hz, 1H, H−C2), 2.67 (br s, 1H, H−C4), 2.52 (br s, 1H, H−C1), 2.42 (dt, 2.1 Hz, 9.9 Hz, 1H, H−C7), 1.66−1.74 (m, 2H, H−C5 and C6), 1.51 (dt, 1.8 H z, 10.2 Hz, H−C7), 1.31−1.43 (m, 2H, H−C5 and C6).

A solution of 1.0 M BH_3 in THF (1.5 mL, 1.5 mmol) was added dropwise to a solution of 2-*exo*-amido-3-*exo*-phenylbicyclo-[2.2.1]heptane, **37a**, in 10 mL THF at 0 °C. The mixture was heated at reflux for 18 h and cooled to 0 °C, and concentrated HCl was added until the solution was strongly acidic. THF was removed under reduced pressure, the mixture was washed with CH_2Cl_2 (3 × 20 mL), 20% NaOH solution was added to the aqueous solution until it was strongly basic, and the mixture was extracted with Et_2O (3 × 15 mL). The combined extracts were washed with brine, dried over $MgSO_4$ and evaporated to give 2-*exo*-(aminomethyl)-3-*exo*-phenylbicyclo-[2.2.1]heptane as a colorless oil. The oil was dissolved in 0.5 mL CH_3OH and 1 drop 12 M HCl added. The solvent was evaporated, and the resulting solid was recrystallized from CH_3OH/AcOEt to afford the hydrochlorde salt of 2-*exo*-(aminomethyl)-3-*exo*-phenylbicyclo[2.2.1]heptane, **15a**, as a white crystalline solid (35 mg, 53% yield from **35**): mp 258 °C dec; ^{1}H NMR (D_2O) δ 7.10−7.23 (m, 5H, H−Ph), 2.91 (br d, 7.2 Hz, 1H, H−C3), 2.33 (br s, 1H, H−C1), 2.06−2.11 (m, 4H, H−C8,5,4), 1.67 (d, 9.9 Hz, H−C7), 1.16−1.57 (m, 5H, H−C2,3,7); MS (EI) M^+ 201.2 (100%); IR 3425, 3061, 2937, 2892, 1606, 1506, 1463, 99, 802, 740, 730 cm^{-1}. Anal. ($C_{14}H_{20}$-NCl) C, H, N, Cl.

Pharmacology. [^{3}H]]WIN 35,428 Binding. The synthesized compounds were screened for activity in a striatal tissue preparation using a modification of the [^{3}H]WIN 35,428 binding assay described by Reith and Selmeci.[43] 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 35,428 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 P_2 suspension, 50 μL test compound, 25 μL water or amfonelic acid (to define nonspecific binding; final concentration, 10 μM), and 25 μL [^{3}H]WIN 35,428 (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 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 35,-428) were determined from dose−response curves usually containing a range of six concentrations of the test drug, with triplicate determinations made at each concentration. The IC_{50} for WIN 35,428 was 22.2 ± 4.7 nM (average ± SEM) under these conditions.

[^{3}H]Dopamine Uptake. Accumulation of [^{3}H]DA was determined as previously described.[44] Briefly, 250 μL S_1 fraction prepared as described above from striatal tissue of 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 Krebs-phosphate buffer and 100 μL 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]dopamine was terminated by the 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 35,428 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]dopamine uptake measured in duplicate samples at each concentration.

Drug Discrimination. Rats were trained to discriminate between injections of saline and 10 mg/kg of cocaine,[45] in a two-choice, discrete-trial, avoidance/escape procedure.[46] Sessions consisted of 20 trials spaced approximately 1 min apart. Rats were trained until they reliably completed at least 18 out of 20 trials on the choice lever appropriate for the injection given before the session (i.e., saline or cocaine). Pretreatment times were 30 min for all compounds. The dependent measure was the number of trials completed on the cocaine and saline appropriate choice levers, summed over the 20-trial session.

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Supporting Information Available: Analytical data for **5**−**15** as hydrochloride salts. This material is available free of charge via the Internet at http://pubs.acs.org.

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