Synthesis and Biological Evaluation of 2-Substituted 3β-Tolyltropane Derivatives at Dopamine, Serotonin, and Norepinephrine Transporters

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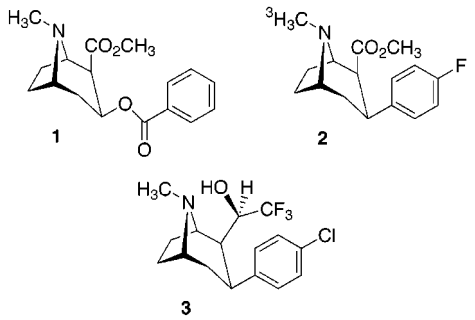
A series of eight 2-substituted 3-tolyltropane derivatives were synthesized, and the in vitro and in vivo biological activities as dopamine uptake inhibitors were determined. From the in vitro structure−activity data, it is apparent that a tolyl group in the 2-position, independent of the stereochemical attachment to the tropane ring system, provided compounds (**9**−**12**, **14**) that exhibit high-affinity binding at the dopamine transporter (DAT). Although a slight stereochemical preference in binding affinity at the DAT was observed for the 2β-(*R*)-alcohol **10** over the 2β-(*S*)-isomer **11**, no significant differences in behavioral effects were observed. Furthermore, despite a relatively low potency of **10** for the inhibition of dopamine uptake compared to its affinity for the DAT, its behavioral profile did not vary significantly from cocaine. These data indicate that a behavioral characterization of compounds is a critical feature of efforts to discover pharmacological treatments for cocaine abuse.

Introduction

Over the past decade, illicit drug use in the United States has been steadily increasing and a significant increase in cocaine (**1**) abuse, as much as 45% in some



areas of the country, has been recently reported.[1]

Despite a significant advancement in understanding the biological mechanisms of action of cocaine, a satisfactory cocaine therapeutic agent has yet to be identified.[2] The search for potential anti-cocaine medications has led to the extensive study of the structure−activity relationships (SAR) of **1** at the dopamine transporter (DAT).[3] In addition, the 2-substituted 3-aryltropanes have been studied extensively as cocaine congeners and developed as tools [e.g., [^{3}H]WIN 35 428 (**2**)] to explore the DAT. This broad class of compounds has provided tremendous insight into the nature of the dopamine transporter pharmacophore. The structural criteria for the 2-substituted 3-aryltropanes as high-affinity dopamine transporter ligands have been established for these positions, as well as for positions 6−8 of the tropane ring system.[3−23] From these studies it has been noted generally that a 4-substituted aryl group (e.g., tolyl) or a 3,4-disubstituted aryl group (e.g., 3,4-dichlorophenyl) at the 3β-position of the tropane ring affords compounds that exhibit high-affinity binding at dopamine transporters. The effects of substituents at the 2-position have also been extensively studied in terms of dopamine transporter affinity and selectivity. It is apparent from investigations at the 2-position of 3β-aryltropanes that most substituents (alkyl, vinyl, aryl, alcohol, and ester groups) with β-stereochemistry relative to the tropane ring are tolerated by the dopamine transporter and provide compounds with high affinity.

A survey of the literature revealed that relatively little structure−activity data were available for substituents at the 2β-position that possess specific stereochemistry inherent to the attached functional group. Kozikowski and co-workers reported that alcohol **3** exhibited high binding affinity at the DAT.[4] However, the DAT affinity for the epimeric alcohol was not determined. Therefore, it was of interest to study a class of DAT ligands that would further elucidate the SAR of substituents at the 2-position in terms of stereochemical effects. It was envisaged that characterization of the in vitro activity (DAT affinity, dopamine uptake inhibition) and the behavioral effects (drug discrimination, locomotor stimulation) would serve to minimally define the pharmacological activity of the compounds at the DAT and more accurately reveal the SAR of the compounds. In addition, this twofold approach would identify any inconsistencies that might arise between the in vitro SAR of a compound and its behavioral effects. Herein, we report the synthesis and biological activity of a series of 2-substituted 3β-tolytropanes.

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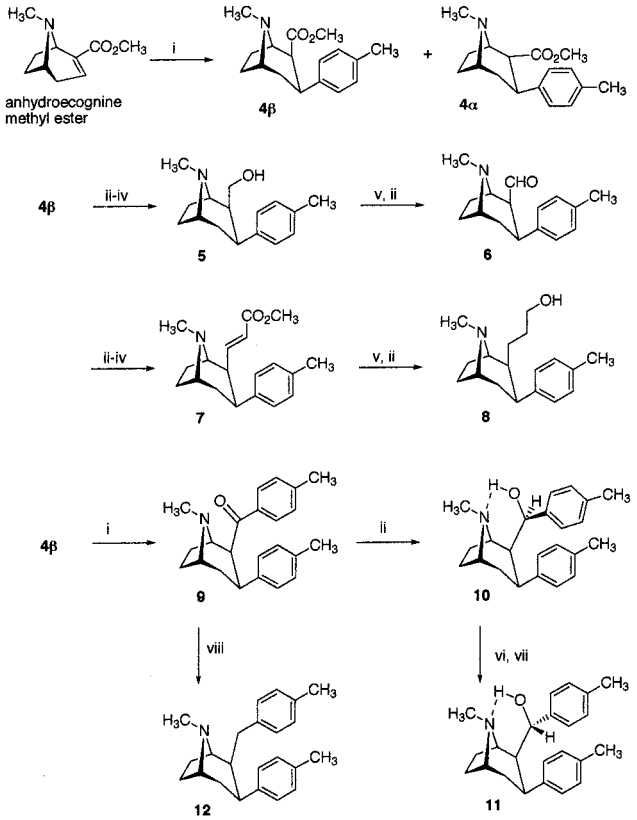
Scheme 1



Results and Discussion

Chemistry. The synthesis of the 2-substituted 3*β*-tolyltropane derivatives was completed in a straightforward fashion from anhydroecgonine methyl ester (Scheme 1).[24] The reaction of tolylmagnesium bromide with anhydroecgonine methyl ester in dichloromethane furnished the 2*β*-carbomethoxy-3*β*-tolyltropane (***4β***) stereoselectively (α/*β*, 1:5). Concomitant reduction with lithium aluminum hydride furnished the alcohol **5**. Swern oxidation of **5** afforded the aldehyde **6**, and subsequent olefination gave the vinyl ester **7** in 60% overall yield. Hydrogenation of **7** over palladium on carbon followed by reduction with lithium aluminum hydride afforded the alcohol **8** in 94% yield.

The reaction of ***4β*** with excess tolylmagnesium bromide afforded the tolyl ketone **9** in 88% yield. Reduction of **9** with lithium aluminum hydride gave the alcohol **10** in 95% yield and in >99% de. The stereoselectivity of the reduction is thought to be due to lithium chelation with the carbonyl oxygen and the bridging nitrogen atom [N(8)]. This locks the conformation of the carbonyl side chain such that delivery of hydride then can only be achieved from the less-hindered *si* face to furnish **10**. The absolute configuration of **10** was unequivocally confirmed by X-ray crystallography (Figure 1). It is evident from the X-ray structure that the hydroxyl proton is oriented toward the proximity of the lone pair of electrons on N(8), indicating the presence of an intramolecular hydrogen bond (H−N(8) distance of 1.94 Å). In addition, the aryl groups of **10** are closely aligned in parallel fashion indicative of a $\pi-\pi$ interaction. The (*R*)-stereochemistry at C(α) of **10** was readily inverted under Mitsonobu reaction conditions to provide the (*S*)-isomer **11** in 60% yield. Deoxygenation of ketone **9** was

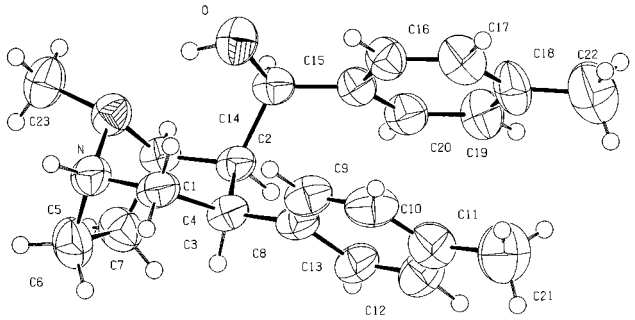
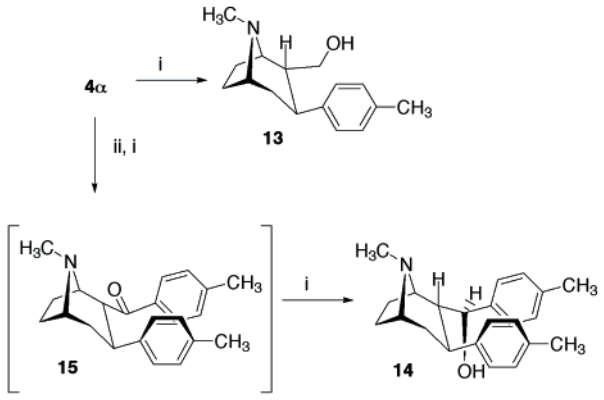
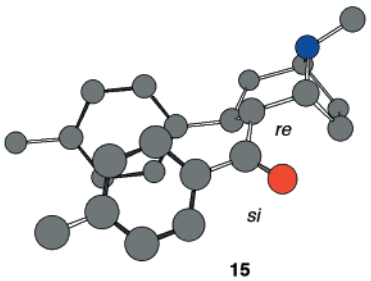


Figure 1. ORTEP diagram of 2*β*-(*R*)-hydroxymethytolyl-3*β*-tolyltropane (**10**, freebase).

Scheme 2



Reagents: i) $LiAlH_4$, Et_2O, 0 °C. ii) $CH_3C_6H_4MgBr$, CH_2Cl_2, 0 °C.



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(hydrogen atoms have been omitted for clarity)

achieved with lithium aluminum hydride/aluminum chloride to provide **12** in 78% yield.

As illustrated in Scheme 2, two 2α-substituted derivatives were prepared from **4α**. Lithium aluminum hydride reduction of **4α** gave the α-hydroxymethyl derivative **13** in 90% yield. The reaction of **4α** with tolylmagnesium bromide followed by reduction with lithium aluminum hydride gave the alcohol **14**, which was isolated as a single diastereoisomer in 90% yield. The alcohol **14** could not be crystallized to unequivocally establish the stereochemistry at C(α). The stereochemistry at C(α) of **14** was assigned empirically on the basis of the chemical reactivity of the 3*β*-tolyltropne ring system with supporting computed conformational data.[25] A conformational search was executed around the C(2)−C(α) bond in 5° increments. This revealed a preferred conformation with a dihedral angle defined by C(1)−C(2)−C(α)−O of 10° in which the tolyl groups of **15** are aligned in parallel fashion indicative of a $\pi-\pi$ interaction, thus leaving the *re* face of the carbonyl more

Table 1. cLogP Values, Dopamine, Serotonin, and Norepinephrine Transporter Binding Affinities, and Dopamine Uptake Inhibition of 2-Substituted 3β-Tolyltropanes (**7**−**14**)

compd[a]	cLogP values[b]	DAT binding [^{3}H]WIN 35 428 K_i (nM)[c]	[^{3}H]DA uptake inhibition IC_{50} (nM)[c]	SERT binding [^{3}H]citalopram K_i (nM)[c]	NET binding [^{3}H]nisoxetine K_i (nM)[c]
cocaine[d]		32 ± 5 388 ± 221	405 ± 91		
7	3.33	123 ± 9	311 ± 107		
8	3.29	136 ± 21	266 ±89		
9	4.70	17 ± 1	82 ± 26		
10	4.71	14 ± 2	144 ± 24[e]	66 ± 5	464 ± 44
11	4.71	85 ± 9	107 ± 19[e]	70 ± 9	214 ± 24
12	5.75	11 ± 2	16 ± 7[e]		271 ± 27
13	2.51	3490 ± 280	4040 ± 900	16000 ± 900	16800 ± 2000
14	4.71	25 ± 2	58 ± 18		

[a] All compounds were tested as the HCl salt. [b] See ref 29. [c] All values are the mean ± SEM of three experiments performed in triplicate. [d] The K_i and IC_{50} values are reproduced from ref 30 and were collected under identical conditions. [e] Nonlinear.

exposed than the *si* face for nucleophilic attack. This conformation is also consistent with a Felkin−Ahn model for nucleophilic attack at the carbonyl. Therefore, (*S*)-stereochemistry was confidently assigned to C(α) of alcohol **14**.

Biology. The DAT binding affinity was determined for the 2-substituted 3β-tolyltropanes **7**−**14** by their ability to displace bound [^{3}H]WIN 35 428 (**2**) from rat caudate-putamen tissue.[26] The K_i values that are reported in Table 1 are inhibition constants derived for the unlabeled ligands. The ability of these compounds to inhibit [^{3}H]dopamine uptake in chopped tissue assays was also measured.[27] In addition, the binding affinities of the 2-substituted 3β-tolyltropanes were determined at serotonin transporters (SERT) and norepinephrine transporters (NET).

In vivo characterization of the 2-substituted 3β-tolyltropanes consisted of evaluation of the compounds in two separate paradigms. First, the cocaine-like interoceptive (subjective) effects of the 2-substituted 3β-tolyltropanes **7**−**14** were examined. To this end, rats trained to discriminate between the effects of cocaine (29 μmol/kg) and those of saline injection in a two-response-key operant conditioning chamber. Each of the 2-substituted 3β-tolyltropanes was examined for its potency and efficacy in substituting for the discriminative effects of cocaine as an indication of its cocaine-like interoceptive effects. Second, selected compounds were evaluated for locomotor stimulant effects in mice. In this procedure the horizontal (locomotor/ambulatory) activity of mice after injection of a range of doses of each of the selected 2-substituted 3β-tolyltropanes was measured and compared to that obtained after injection of cocaine.

All of the 2-substituted 3β-tolyltropanes displaced [^{3}H]-WIN 35 428 from caudate-putamen membranes with relatively high affinity. The K_i values (Table 1) ranged from 11 nM (**12**) to 136 nM (**8**) among the 2β-substituted derivatives. Generally, the analogues **9**−**12** that possessed a tolyl group in the 2-position were more potent than the alkenyl ester **7** or the hydroxypropyl derivative **8**. This was consistent with previous results that suggest that lipophilic interactions at the 2-position are more important than H-bond interactions.[7,9,11,17] It is noteworthy that the (*R*)-isomer of the 2-hydroxymethyltolyl analogue **10** (K_i = 14 nM) was approximately 6-fold more potent than the (*S*)-isomer **11** (K_i = 85 nM). This result demonstrates that stereochemistry incorporated in the functional group attached to the 2-position can affect ligand affinity. Surprisingly, the (*S*)-isomer of 2α-hydroxymethyltolyl derivative **14** (K_i = 25 nM) exhibited only slightly diminished affinity relative to **10**, while an appreciably lower affinity (3490 nM) was obtained for the 2α-hydroxymethyl analogue **13**. None of the tolyltropane derivatives produced a displacement profile that better fit a two-site model than a one-site model. This is in contrast to the displacement data for **1**, which is often reported to better fit a two-site model than a single-site model.[27,28] Among the 2-substituted 3β-tolyltropanes that were tested, all appeared to have relatively high affinity for serotonin transporters with K_i values approximating those obtained at the dopamine transporter. Alternatively, the K_i values for the norepinephrine transporters among those compounds examined were generally lower than that for the other transporters (Table 1).

Each of the compounds inhibited dopamine uptake inhibition with IC_{50} values that ranged from 16 nM (**12**) to 4040 nM (**13**). There was a significant correlation (R^2 = 0.9981; $p < 0.001$) among the potencies for the inhibition of dopamine uptake and the affinities determined by displacement of [^{3}H]WIN 35 428 (Table 1). It is interesting to note that **10** had an affinity for binding to the dopamine transporter that was about 10-fold higher than its potency for the inhibition of dopamine uptake. In addition, it was unusual to find that the dopamine uptake inhibition of the 2α-analogue **14** (IC_{50} = 58 nM) was more potent than that observed for the 2β-isomers **10** (IC_{50} = 144 nM) and **11** (IC_{50} = 107 nM). It must be noted, however, that the fact that the uptake inhibition curves for the 2β-isomers **10** and **11** were not linear. Thus, although there was not a statistically significant two-component model for the inhibition of dopamine uptake, it is likely that there is more than one site involved in this function. Because of the nonlinearity of the curves, these values should be considered only as estimates of their IC_{50} values for inhibiting uptake.

As has been shown previously, there was a dose-related increase in the percentage of cocaine-appropriate responses in rats trained to discriminate cocaine (10.0 mg/kg; 29 mmol/kg) from saline (Figure 2, filled circles). Similarly, each of the 2-substituted 3β-tolyltropanes analogues also produced a level of drug-appropriate response significantly greater than that produced by saline (exceeding 20%; Figure 2, Table 2). Among the

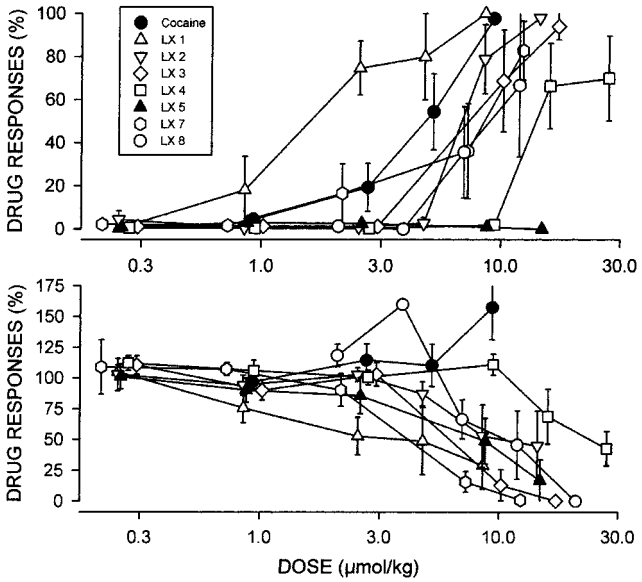

Figure 2. Effects of tolyltropane analogues in subjects trained to discriminate injections of cocaine from saline. Ordinates for top panels are the percentage of responses on the cocaine-appropriate key. Ordinates for the bottom panels are rates at which responses were emitted (as a percentage of response rate after saline administration). Abscissas represent drug dose in mmol/kg (log scale). Each point represents the effect in four to six subjects. The percentage of responses emitted on the cocaine-appropriate key was considered unreliable and not plotted if fewer than half of the subjects responded at that dose.

Table 2. Substitution of 2-Substituted 3β-Tolyltropanes in Rats Trained To Discriminate Cocaine

		drug response	
compd[a]	response rate ED_{50} (mmol/kg)	ED_{50} (mmol/kg)	% maximum effect
7	244 ((70.3−2.77) × 10^4)	54.0 (37.4−91.9)	69.9 @ 89.3 mmol/kg
8	21.5 (17.5−25.8)	23.6 (17.3−33.8)	93.9 @ 54.9 mmol/kg
9	10.9[b] (4.96−56.1)	5.06 (3.31−7.72)	100 @ 27.0 mmol/kg
10	61.6[b] ((17.1−1.22) ×10^5)	18.3 (14.6−22.3)	97.9 @45.7 mmol/kg
11	31.4 (22.0−51.4)	28.3[b] ((14.9−7.37) ×10^4)	66.7 @ 37.7 mmol/kg
12	12.0 (9.43−15.4)	23.5 (11.0−127)	82.8 @ 39.0 mmol/kg
13	20.6 (9.07−256)	NS[c]	2.96 @ 2.69 mmol/kg

[a] All compounds were tested as the HCl salt. [b] Nonsignificant effect of dose. [c] Nonsignificant linear regression.

2-substituted 3β-tolyltropanes, only **7** and **11** produced a level of substitution less than 80%, and for those two, despite a failure to achieve an average value indicating full substitution, there was a full substitution in the majority of the animals tested at the highest doses. In contrast, the 2α-hydroxymethyl 3β-tolyltropane (**13**) did not produce a level of drug-appropriate response that was greater than that obtained with saline across a range of doses from those having no effect to those that virtually eliminated response.

Selected compounds **10**, **11**, and **13** were further evaluated in locomotor stimulant assays. As has been demonstrated previously, cocaine increased ambulatory activity with a maximum of approximately 500 counts per minute during the first 30 min of the session at 59 μmol/kg (Figure 3). Both **10** and **11** increased locomotor

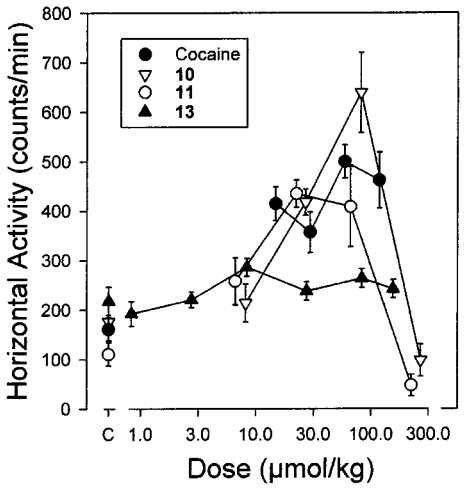

Figure 3. Dose-dependent effects of tolyltropanes on locomotor activity in mice. The ordinate represents horizontal locomotor counts after drug administration. The abscissa represents dose of drug in mmol/kg on a log scale. Each point represents the average effect determined in eight mice. The data are from the 30 min period during the first 60 min after drug administration, in which the greatest stimulant effects were observed.

activity to a level respectively exceeding and approaching that produced by cocaine. Alternatively, the 2α-derivative **13** produced only a marginal stimulation of locomotor activity, achieving significance only at the 8.3 μmol/kg dose.

For all of the 2β-substituted 3β-tolyltropanes tested in this study the behavioral effects were found to be typically cocaine-like. However, the relative potency of the behavioral effects did not correspond entirely to the relative affinities of the compounds at the DAT. Most notable were **10** and **12**, which had a lower in vivo potency than that which would be predicted on the basis of their affinity for the DAT. These findings suggest that these compounds may have characteristics (e.g., high lipophilicity) that reduced their central availability. On the basis of calculated partition coefficients (cLogP, Table 1), compound **12** is an order of magnitude more lipophilic than the oxygenated derivatives **9**−**11**.[29] However, the actual lipophilicity of **10** may be closer to that of **12** because of the intramolecular H bond between the nitrogen atom and the hydroxyl residue.

The ratio of potency for dopamine uptake inhibition to the DAT binding affinity (DUI/DAT) for **10** (10) suggested the potential for anomalous behavioral activity. Despite what was predicted on the basis of DAT affinity, alcohol **10** was among the most potent of the 2β-analogues in the drug discrimination experiments with an ED_{50} value of 18.3 mmol/kg for its full cocaine-like substitution. Moreover, **10** was the most effective of the compounds tested for stimulation of locomotor activity, and it exceeded the magnitude of the effect of cocaine. Therefore, despite a high DUI/DAT ratio, **10** exhibited typical stereoselective cocaine-like behavioral activity. The high DUI/DAT ratio may have been contributed by characteristics that limit distribution in tissue, thereby decreasing potency for inhibition of dopamine uptake without altering binding affinity, which is assayed at equilibrium. This hypothesis is consistent with the finding that **10** had a lower in vivo

potency than that which would be predicted on the basis of its affinity for the DAT.

Conclusions

From the in vitro SAR data, it is apparent that a tolyl group in the 2-position, independent of stereochemical attachment to the tropane ring system, provides compounds that exhibit high-affinity binding at the DAT. Although a slight stereochemical preference was observed for the (*R*)-alcohol **10** over the (*S*)-isomer **11** in binding affinities at DAT, no significant differences in behavioral effects were observed. Furthermore, despite a high DUI/DAT affinity ratio observed for **10**, the behavioral profile did not vary significantly from cocaine. Thus, in this case, a comparison of the DUI/DAT binding affinity ratio was not useful for identification of a cocaine antagonist. This demonstrates that characterization of the behavioral effects in addition to in vitro activity of potent DAT ligands is important for the accurate assessment of the structure−activity relationships of a compound and its potential for development as cocaine medication.

Experimental Section

All chemicals and reagents not otherwise noted were purchased from Aldrich Chemical Co. The solvents THF, ether, and 1,4-dioxane were dried by distillation from Na and benzophenone. Dichloromethane and acetonitrile were dried by distillation over P_2O_5. The spectral data for all compounds are reported for the free base. ^{1}H and ^{13}C NMR spectra were recorded on a Varian multiprobe 400 MHz spectrometer. The free base was then converted into the hydrochloride salt to give a hygroscopic solid used for microanalysis and biological testing. Microanalysis for C, H, and N were performed by Atlantic Microlabs, Inc., Norcross, GA. Melting points were recorded on a Hoover Mel-Temp apparatus and are uncorrected.

2β-Hydroxymethyl-3β-tolyltropane (5). To a stirred suspension of $LiAlH_4$ (76 mg, 2.0 mmol) in dry ether (10 mL) at 0 °C under a nitrogen atmosphere a solution of the ester **4β** (540 mg, 2.0 mmol) in dry ether (5 mL) was added dropwise via syringe. Stirring was continued overnight at room temperature. The reaction mixture was cooled to 0 °C, and an aqueous solution of NaOH (5%, 10 mL) was added dropwise. The reaction mixture was filtered, and the residue was washed with ether. The combined filtrate and washings were concentrated under reduced pressure to furnish the alcohol **5** as a colorless oil (0.45 g, 92%). $[\alpha]^{21}_D$ −66.03° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.24 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 3.74 (d, *J* = 13.0 Hz, 1H), 3.45−3.31 (m, 3H), 3.10−3.00 (m, 1H), 2.52 (m, 1H), 2.32 (s, 3H), 2.26 (s, 3H), 2.25−2.05 (m, 3H), 1.73 (d, *J* = 8.1 Hz, 2H), 1.62 (m, 1H), 1.48 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 139.6, 135.6, 129.0, 128.2, 68.5, 65.2, 62.0, 45.5, 41.2, 37.1, 36.4, 26.3, 25.2, 21.0. Anal. ($C_{16}H_{23}NO$) C, H, N.

2β-Formyl-3β-tolyltropane (6). To a solution of oxalyl chloride (1.2 mL, 2.0 M in CH_2Cl_2,) under a nitrogen atmosphere at −60 °C was added a solution of DMSO (0.31 mL, 340 mg, 4.4 mmol) in dry CH_2Cl_2 (1 mL). After 0.5 h, a solution of the alcohol **5** (490 mg, 2.0 mmol) in dry CH_2Cl_2 (3 mL) was added. Stirring was continued for 1 h at 60 °C followed by the addition of triethylamine (1.3 mL, 9.2 mmol). The reaction mixture was allowed to warm to room temperature and was diluted with water. The organic layer was separated and dried (Na_2SO_4), and the solvent was removed under reduced pressure to yield the aldehyde **6** (461 mg, 95%). The material was carried on to the olefination step without further purification.

2β-(2′Carbomethoxyethenyl)-3β-tolyltropane (7). To a stirred suspension of lithium chloride (0.10 g, 2.4 mmol) in dry acetonitrile (10 mL) at room temperature under a nitrogen atmosphere were added trimethyl phosphonoacetate (440 mg, 2.4 mmol), *N*,*N*-diisopropylethylamine (0.26 g, 2.0 mmol), and the aldehyde **6** (480 mg, 2.0 mmol). The reaction mixture was allowed to stir for 24 h. The acetonitrile was removed under reduced pressure, and the residue was diluted with water. The aqueous solution was extracted with ether (3 × 40 mL). The combined organic layers were washed with water and brine and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The product was purified by flash column chromatography (ether/triethylamine, 9:1) to afford **7** as a colorless oil (370 mg, 65%). $[\alpha]^{21}_D$ +68° (*c* 1, MeOH, HCl salt); ^{1}H NMR ($CDCl_3$) δ 7.60 (m, 4H), 6.68−6.57 (m, 1H), 5.42 (d, *J* = 16.0 Hz, 1H), 3.56 (s, 3H), 3.28 (m, 1H), 3.08 (s, 2H), 2.42 (m, 1H), 2.24 (s, 3H), 2.20 (s, 3H), 2.18−2.05 (m, 3H), 1.78−1.67 (m, 2H), 1.59 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 166.6, 150.7, 139.1, 135.4, 128.8, 127.6, 121.3, 67.5, 62.2, 50.9, 50.5, 42.0, 36.4, 26.5, 25.1, 20.9. Anal. ($C_{19}H_{25}NO$·HCl) C, H, N.

2β-(3-Hydroxypropyl)-3β-tolyltropane (8). A solution of unsaturated ester **7** (560 mg, 2.0 mmol) in dry methanol (20 mL) was hydrogenated (1 atm) over 10% palladium on carbon (50 mg). The reaction mixture was stirred at room temperature overnight and then was filtered through a pad of Celite. The solvent was removed under reduced pressure to afford the saturated ester as a colorless oil. The oil was dissolved in dry ether and was added via syringe to a stirred suspension of $LiAlH_4$ (76 mg, 2.0 mmol) in dry ether (10 mL) at 0 °C under a nitrogen atmosphere. Stirring was continued overnight at room temperature. The reaction mixture was cooled to 0 °C, and an aqueous solution of NaOH (5%, 10 mL) was added dropwise. The reaction mixture was filtered, and the residue was washed with ether (5 × 50 mL). The combined filtrate and washings were concentrated under reduced pressure to furnish an oil. The oil was purified by column chromatography (SiO_2, $CHCl_3$/CH_3OH, 95:5) to furnish **8** (510 mg, 94%). Mp 205−206 °C (HCl salt); $[\alpha]^{21}_D$ +33.7° (*c* 1, CH_3OH, HCl salt); ^{1}H NMR ($CDCl_3$) δ 7.29 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 4.08−3.90 (m, 2H), 3.39 (m, 1H), 3.17(m,1H), 2.83 (s, 3H), 2.29 (s, 3H), 2.26−2.05 (s, 2H), 2.01 (m, 2H), 1.90 (m, 2H), 1.26−1.12 (m, 4H), 1.14 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 138.5, 136.4, 129.4, 128.1, 66.6, 64.2, 61.5, 46.1, 43.3, 40.3, 39.5, 29.4, 26.3, 24.9, 26.3, 24.9, 21.1, 20.4. Anal. ($C_{18}H_{27}NO$·HCl·2.5H_2O) C, H, N.

2β-Tolylcarbonyl-3β-tolyltropane (9). A solution of **4β** (7.0 g, 26 mmol) in freshly distilled ether (50 mL) was added dropwise via syringe to a stirred solution of tolylmagnesium bromide (1 M, 50 mL) in dry ether (600 mL) at −40 °C under a nitrogen atmosphere. The mixture was stirred at −40 °C for 2.5 h. The reaction mixture was then cooled to −78 °C and quenched with a solution of TFA (11.4 g, 100 mmol) in dry ether (40 mL) over 5 min. The mixture was allowed to warm to 0 °C and was diluted with water (150 mL). The aqueous phase was acidified with HCl (concentrated) to pH 1, and the ether layer was separated. The aqueous layer was made basic with NH_4OH (concentrated) at 0 °C and was extracted with ether (4 × 100 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure to provide the crude product as a yellow oil. The crude product was purified by flash column chromatography (SiO_2, ether/Et_3N, 9:1) to give the ketone **9** as colorless crystals (4.8 g, 56%), mp 186−187 °C. Ketone **9** was homogeneous by TLC (R_f 0.85, SiO_2, ether/Et_3N, 9.5:0.5). $[\alpha]^{21}_D$ +27.94° (*c* 1, CH_3OH, HCl salt); ^{1}H NMR ($CDCl_3$) δ 7.73 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 7.7 Hz, 4H), 7.00 (d, *J* = 8.1 Hz, 2H), 3.88 (m, 1H), 3.46 (m, 1H), 3.39 (m, 1H), 3.12−3.06 (m, 1H), 2.82 (m, 1H), 2.35 (s, 3H), 2.22 (s, 3H), 2.08 (s, 3H), 1.86 (m, 2H), 1.80−1.60 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 198.4, 142.8, 140.3, 134.9, 129.1, 128.6, 128.1. 127.2, 65.0, 62.4, 53.8, 42.1, 34.3, 33.9, 26.5, 25.3, 21.5, 20.9. Anal. ($C_{23}H_{27}NO$) C, H, N.

2β-(*R*)-(Hydroxymethyltolyl)-3β-tolyltropane (10). To a stirred suspension of $LiAlH_4$ (76 mg, 2.0 mmol) in dry ether at 0 °C under a nitrogen atmosphere was added a solution of ketone **9** (670 mg, 2.0 mmol) in dry ether dropwise via syringe. Stirring was continued overnight at room temperature. The reaction mixture was then cooled to 0 °C, and an aqueous solution of NaOH was added dropwise. The reaction mixture was filtered, and the residue was washed with ether. The

solvent was removed under reduced pressure, which afforded the alcohol **10** as a white solid (640 mg, 95%). The alcohol was homogeneous by TLC (R_f 0.3, SiO_2, ether/Et_3N, 9:1). Mp 135−136 °C; $[\alpha]^{21}_D$ +55.56° (*c* 1, MeOH, HCl salt); ^{1}H NMR ($CDCl_3$) δ 7.00−7.27 (m, 8H), 4.43 (d, J = 7.0 Hz, 1H), 3.12 (m, 1H), 2.92 (m, 1H), 2.70−2.50 (m, 2H), 2.30 (s, 6H), 2.12 (s, 3H), 1.80−1.98 (m, 2H), 1.72−1.43 (m, 3H), 1.45−1.20 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 141.7, 139.3, 136.7, 136.0, 130.0, 128.6, 127.8, 126.5, 62.6, 61.8, 52.5, 46.0, 42.6, 40.4, 39.8, 25.8, 22.8, 21.0, 20.9, 11.2. Anal. ($C_{23}H_{29}NO$) C, H, N.

2β-(*S*)-Hydroxymethyltolyl-3β-tolyltropane (11). (a) To a solution of **10** (500 mg, 1.50 mmol), triphenylphosphine (920 mg, 3.5 mmol), and benzoic acid (460 mg, 3.7 mmol) in dry THF (20 mL) was added diethyl azodicarboxylate (592 mg, 3.4 mmol) dropwise. The reaction mixture was stirred overnight at room temperature. The solution was then concentrated, and the residue was purified by column chromatography (petroleum ether/triethylamine, 9:1) to afford the benzoate ester (410 mg, 62%).

(b) To a solution of the benzoate ester (130 mg, 0.3 mmol) in dry MeOH (20 mL) was added $NaOCH_3$ (400 mg, 7.4 mmol). The reaction mixture was refluxed for 24 h. The mixture was allowed to cool to room temperature and diluted with water (20 mL), and the pH was adjusted to pH 10 with concentrated NH_4OH. The mixture was extracted with ether (4 × 30 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a yellow oil. The crude product was purified by flash column chromatography (SiO_2, petroleum ether/EtOAc/triethylamine, 8.5:0.5:1) to furnish the alcohol **11** as a colorless oil (95 mg, 94%). $[\alpha]^{21}_D$ +28.74° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.00−7.30 (m, 8H), 4.44 (br, 1H), 3.10−3.20 (m, 1H), 2.88 (m, 1H), 2.45−2.38 (m, 2H), 2.36 (s. 6H), 2.29 (s, 3H), 1.97−2.10 (m, 1H), 1.97−1.80 (m, 2H), 1.80−1.60 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 141.8, 140.0, 135.5, 134.0, 129.3, 129.0, 127.5, 125.4, 76.6, 64.0, 60.3, 52.6, 39.8, 38.9, 35.2, 29.6, 26.3, 20.9. Anal. ($C_{23}H_{29}NO\cdot0.5H_2O$) C, H, N.

2β-(*p*-Methylphenylmethyl)-3β-tolyltropane (12). In a dry 50 mL round-bottomed flask was placed ketone **9** (340 mg, 1.0 mmol), $AlCl_3$ (470 mg, 3.5 mmol), and 1,4-dioxane (15 mL). The solution was stirred for 10 min under a nitrogen atmosphere followed by the addition of $LiAlH_4$ (2.5 mL, 2.5 mmol). The reaction mixture was refluxed overnight. The 1,4-dioxane was removed under reduced pressure, and a solution of NaOH (5%) was added dropwise to the residue. The aqueous solution was extracted with ether (3 × 20 mL). The combined extracts were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude product was purified by coluumn chromatography (SiO_2, petroleum ether/triethylamine, 9.5:0.5) to provide **12** as white crystals (190 mg, 60%). Mp 175−177 °C; ^{1}H NMR ($CDCl_3$) δ 7.13 (s, 4H), 6.97 (d, J = 7.9 Hz, 4H), 3.28 (br, 1H), 3.12 (m, 1H), 2.83 (m, 1H), 2.75 (t, J = 12.5 Hz, 2H), 2.33 (s, 3H), 2.28 (s, 3H), 2.23 (m, 1H), 2.20 (s, 3H), 2.02 (m, 2H), 1.82 (m, 1H), 1.67−1.59 (m, 2H), 1.32 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 140.6, 133.2, 135.2, 134.5, 129.2, 128.9, 128.6, 127.6, 63.2, 62.2, 49.1, 41.7, 36.0, 33.6, 32.6, 26.4, 25.0, 20.9. Anal. ($C_{23}H_{29}N\cdot0.33H_2O$) C, H, N.

2α-Hydroxymethyl-3β-tolyltropane (13). To a stirred suspension of $LiAlH_4$ (76 mg, 2.0 mmol) in dry ether at 0 °C under a nitrogen atmosphere was added a solution of 2α-carbomethoxy-3β-phenyltropane (**4α**) (540 mg, 2.0 mmol) in dry ether dropwise via syringe. Stirring was continued overnight at room temperature. The reaction mixture was cooled to 0 °C, and an aqueous solution of NaOH (5%, 10 mL) was added dropwise. The reaction mixture was filtered, and the residue was washed with ether. The combined filtrate and washings were concentrated under reduced pressure, which afforded alcohol **13** as a white solid (470 mg, 95%). The alcohol was homogeneous by TLC (R_f 0.3, SiO_2, petroleum ether/triethylamine, 9:1). Mp 200−202 °C; ^{1}H NMR ($CDCl_3$) δ 7.08−7.17 (d, J = 7.9, 4H), 3.44 (m, 1H), 3.41−3.33 (m, 1H), 3.30−3.20 (m, 2H), 2.37 (s, 3H), 2.32 (s, 3H), 2.35−2.20 (m, 2H), 2.05−2.16 (m, 1H), 1.88−2.04 (m, 2H), 1.74−1.84 (m, 1H), 1.56−1.64 (m, 2H), 1.38−1.45 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 140.9, 135.9, 129.3, 127.7, 63.2, 62.8, 61.9, 48.6, 40.9, 40.8, 37.9, 25.9, 21.7, 21.0; $[\alpha]^{21}_D$ +22.63° (*c* 1, $CHCl_3$). Anal. ($C_{26}H_{23}NO$) C, H, N.

2α-(*S*)-(Hydroxymethyltolyl)-3β-tolyltropane (14). A solution of **4α** (540 mg, 2.0 mmol) in freshly distilled ether (5 mL) was added dropwise via syringe to a stirred solution of tolylmagnesium bromide (1 M, 4.0 mL) in dry ether (6 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred at 0 °C for 2.5 h. The mixture was allowed to warm to room temperature and was diluted with water (15 mL). The aqueous phase was acidified with HCl (concentrated) to pH 1, and the ether layer was separated. The aqueous layer was made basic with NH_4OH (concentrated) at 0 °C and was extracted with ether (4 ×100 mL). The organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure to provide the crude ketone **15** as a yellow oil. The crude product was purified by flash column chromatography (SiO_2, ether/triethylamine, 9:1) to give the ketone **15** as a colorless oil (560 mg, 85%). Ketone **15** was homogeneous by TLC (R_f 0.75, SiO_2, ether/triethylamine, 9.5:0.5). ^{1}H NMR ($CDCl_3$) δ 7.63 (d, J = 8.0 Hz, 2H), 7.19 (m, 4H), 7.01 (d, J = 8.1 Hz, 2H), 3.88 (m, 1H), 3.46 (m, 1H), 3.39 (m,1H), 3.06−3.12 (m, 1H), 2.82 (m, 1H), 2.31 (s, 3H), 2.20 (s, 3H), 2.08 (s, 3H), 1.86 (m, 2H), 1.60−1.80 (m, 3H).

To a stirred suspension of $LiAlH_4$ (76 mg, 2.0 mmol) in dry Et_2O at 0 °C under a nitrogen atmosphere was added a solution of **15** (670 mg, 2.0 mmol) in dry ether dropwise via syringe. Stirring was continued overnight at room temperature. The reaction mixture was cooled to 0 °C, and an aqueous solution of NaOH (5%, 10 mL) was added dropwise. The mixture was then filtered, and the residue was washed with ether. The combined filtrate and washings were concentrated to provide the alcohol **14** as a white solid (640 mg, 95%). The alcohol was homogeneous by TLC (R_f 0.3, SiO_2, petroleum ether/triethylamine, 9:1). Mp 135−136 °C; $[\alpha]^{21}_D$ +26.34° (*c* 1, MeOH, HCl salt); ^{1}H NMR ($CDCl_3$) δ 6.65−6.85 (m, 8H), 5.06 (br, 1H), 3.12 (m, 1H), 2.92 (m, 1H), 2.50−2.70 (m, 2H), 2.30 (s, 6H), 2.12 (s, 3H), 1.80−1.98 (m, 2H), 1.43−1.72 (m, 3H), 1.25−1.40 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 141.7, 139.3, 136.7, 136.0, 130.0, 128.6, 127.8, 126.5, 62.6, 61.8, 52.5, 46.0 42.6, 40.4, 39.8, 25.8, 22.8, 21.0, 20.9, 11.2. Anal. ($C_{23}H_{27}NO$) C, H, N.

[^{3}H]WIN 35 428 Binding Assay. Male Sprague−Dawley rats (200−250 g, Taconic, Germantown, NY) were decapitated, and their brains were removed and placed in an ice-cooled dish for dissection of the caudate-putamen. The tissue was homogenized in 30 volumes of ice-cold modified Krebs HEPES buffer (15 mM HEPES, 127 mM NaCl, 5 mM KCl, 1.2 mM $MgSO_4$, 2.5 mM $CaCl_2$, 1.3 mM NaH_2PO_4, 10 mM glucose, pH adjusted to 7.4) using a Teflon/glass homogenizer and centrifuged at 20 000*g* for 10 min at 4 °C. The resulting pellet was then washed two more times by resuspension in ice-cold buffer and centrifugation at 20 000*g* for 10 min at 4 °C. Fresh homogenates were used in all experiments. Binding assays were conducted in modified Krebs HEPES buffer on ice, essentially as previously described.[27] The total volume in each tube was 0.5 mL, and the final concentration of membrane after all additions was approximately 0.3% (w/v) corresponding to 150−300 μg of protein per sample. Increasing concentrations of the drug being tested were added to triplicate samples of membrane suspension. Five minutes later, [^{3}H]WIN 35 428 (final concentration of 1.5 nM) was added and the incubation was continued for 1 h on ice. The incubation was terminated by the addition of 3 mL of ice-cold buffer and rapid filtration through Whatman GF/B glass fiber filter paper (presoaked in 0.1% BSA in water to reduce nonspecific binding) using a Brandel cell harvester (Gaithersburg, MD). After filtration, the filters were washed with three additional 3 mL washes and transferred to scintillation vials. Absolute ethanol (0.5 mL) and Beckman Ready Value scintillation cocktail (2.75 mL) were added to the vials, which were counted the next day at an efficiency of about 36%. Under these assay conditions, an average experiment yielded approximately 6000 dpm total binding per sample and approximately 250 dpm nonspecific

binding. Nonspecific binding was defined as binding in the presence of 100 μM cocaine. K_i values were derived from 14 point competition assays using increasing concentrations of unlabeled compounds (0.05 nM to 100 μM) against 1.5 nM [^{3}H]-WIN 35 428. Displacement data were analyzed by the use of the nonlinear least-squares curve-fitting computer program LIGAND.[31]

[^{3}H]Dopamine Uptake Inhibition Studies. Rats were sacrificed by decapitation, and their brains were removed and placed in an ice-cooled dish for dissection of the caudate-putamen. [^{3}H]Dopamine uptake was measured in a chopped tissue preparation as described previously.[26] Briefly, the tissue was chopped into 225 μm slices on a McIllwain tissue slicer with two successive cuts at an angle of 90°. The strips of tissue were suspended in oxygenated modified Krebs HEPES buffer (see above), which was pregassed with 95% O_2/5% CO_2 and warmed to 37 °C. After being rinsed, aliquots of tissue slice suspensions were incubated in buffer in glass test tubes at 37 °C to which either the drug being tested or no drug was added, as appropriate. After a 5 min incubation period in the presence of drug, [^{3}H]dopamine (final concentration of 15 nM) was added to each tube. After 5 min the incubation was terminated by the addition of 2 mL of ice-cold buffer to each tube and filtration under reduced pressure over glass fiber filters (presoaked in 0.1% polyethylenimine in water). The filters were rinsed and placed in scintillation vials to which 1 mL of methanol and 2 mL of 0.2 M HCl were added to extract the accumulated [^{3}H]dopamine. Radioactivity was determined by liquid scintillation spectrometry at an efficiency of approximately 30%. The reported values represent specific uptake from which nonspecific binding to filters was subtracted. Data were analyzed using standard analysis of variance and linear regression techniques.[32] If there was a significant deviation ($p < 0.05$) from linearity, the concentration-effect curve was resolved, if possible, into two linear components, which were analyzed independently. IC_{50} values were calculated only on curve components that exhibited a significant linear regression ($p < 0.05$).

[^{3}H]Citalopram Binding Assay. Brains from male Sprague−Dawley rats weighing 200−225 g (Taconic Labs) were removed, and the midbrain was dissected and rapidly frozen. Membranes were prepared by homogenizing tissues in 20 volumes (w/v) of 50 mM Tris containing 120 mM NaCl and 5 mM KCl (pH 7.4 at 25 °C), using a Brinkman Polytron (setting 6 for 20 s) and centrifuged at 50 000*g* for 10 min at 4 °C. The resulting pellet was resuspended in buffer, recentrifuged, and resuspended in buffer to a concentration of 15 mg/mL. Ligand binding experiments were conducted in assay tubes containing 0.5 mL of buffer for 60 min at room temperature. Each tube contained 1.4 nM [^{3}H]citalopram (NEN) and 1.5 mg of midbrain tissue (original wet weight). Nonspecific binding was determined using 10 mM fluoxetine. Incubations were terminated by rapid filtration through Whatman GF/B filters, presoaked in 0.3% polyethylenimine, using a Brandel R48 filtering manifold (Brandel Instruments, Gaithersburg, Maryland). The filters were washed twice with 5 mL of cold buffer and transferred to scintillation vials. Beckman Ready Safe (3.0 mL) was added, and the vials were counted the next day using a Beckman 6000 liquid scintillation counter (Beckman Coulter Instruments, Fullerton, California). Data were analyzed with GraphPad Prism software (San Diego, California).

[^{3}H]Nisoxetine Binding Assay. The frontal cortex of male Sprague−Dawley rats was removed and frozen. Membranes were prepared by homogenizing tissues in 50 mM Tris (120 mM NaCl, 5 mM KCl; pH 7.4 at 25 °C) and centrifuging (50 000*g*) for 10 min at 4 °C. The resulting pellet was then washed and centrifuged two more times. The final pellet was resuspended to a concentration of 80 mg/mL (original wet weight). Assays were conducted in the above Tris buffer. Volume totaled 0.5 mL with tissue concentration of 8 mg/tube. [^{3}H]Nisoxetine (specific activity of 80 Ci/mmol; final concentration of 0.5 nM; New England Nuclear, Boston, MA) was added, and the incubation continued for 1 h on ice. Incubations were terminated by rapid filtration through Whatman GF/B filters, presoaked in 0.05% polyethylenimine (PEI). Nonspecific binding was defined using 1 μM desipramine. For these assays, an initial screen was conducted to assess displacement of nisoxetine at a concentration of 1 μM of the unknown compound. If there was greater than 50% displacement of nisoxetine, a K_i value was determined in subsequent studies.

Cocaine Discrimination Studies. Sessions were conducted daily, 5 days per week. Five minutes before sessions, ip injections were given and the subjects were placed in experimental chambers. The chambers contained two response levers: a device for delivering food pellets and stimulus lights. Session start was indicated by illumination of the lights. Subjects were trained to press the response levers, with responses on one lever reinforced with food presentation after a presession injection of cocaine and responses on the other lever reinforced after an injection of saline. Over the course of several sessions the number of responses required for each food pellet was gradually increased to 20. "Cocaine" and "saline" sessions alternated in a sequence of double alternations. Sessions ended after 20 food presentations or 15 min, whichever occurred first. Test sessions began once performances met a criterion for stability (greater than 85% correct responses prior to the first food presentation and throughout the entire session). Test sessions were identical to training sessions with the exception that 20 or 30 consecutive responses on either lever were reinforced.

Locomotor Activity Studies. Subjects were experimentally naive group-housed male Swiss Webster mice approximately 14 weeks old. They were studied in 40 cm^3 clear acrylic chambers, which counted ambulatory activity with photoelectric detectors placed 2.56 cm apart along the walls. One activity count was registered each instance in which the subject crossed a beam. Multiple interruptions of the same beam (e.g., grooming, head bobbing) were not counted. Mice were injected and placed in the apparatus for 60 min. Each dose was studied in six mice.

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Supporting Information Available: X-ray crystallographic data for **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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