Novel N-Substituted 3α-[Bis(4′-fluorophenyl)methoxy]tropane Analogues: Selective Ligands for the Dopamine Transporter

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A series of N-substituted 3α-[bis(4′-fluorophenyl)methoxy]tropane analogues has been prepared that function as dopamine uptake inhibitors. The *N*-methylated analogue of this series had a significantly higher affinity for the dopamine transporter than the parent compound, *N*-methyl-3α-(diphenylmethoxy)tropane (benztropine, Cogentin). Yet like the parent compound, it retained high affinity for muscarinic receptors. A series of N-substituted compounds were prepared from nor-3α-[bis(4′-fluorophenyl)methoxy]tropane via acylation followed by hydride reduction of the amide or by direct alkylation. All compounds containing a basic tropane nitrogen displaced [^{3}H]WIN 35,428 at the dopamine transporter (K_i range = 8.5−634 nM) and blocked dopamine uptake (IC_{50} range = 10−371 nM) in rat caudate putamen, whereas ligands with a nonbasic nitrogen were virtually inactive. None of the compounds demonstrated high binding affinity at norepinephrine or serotonin transporters. Importantly, a separation of binding affinities for the dopamine transporter versus muscarinic m_1 receptors was achieved by substitution of the *N*-methyl group with other *N*-alkyl or arylalkyl substituents (eg. *n*-butyl, allyl, benzyl, 3-phenylpropyl, etc.). Additionally, the most potent and selective analogue in this series at the dopamine transporter, *N*-(4″-phenyl-*n*-butyl)-3α-[bis(4′-fluorophenyl)methoxy]-tropane analogue failed to substitute for cocaine in rats trained to discriminate cocaine from saline. Potentially, new leads toward the development of a pharmacotherapeutic for cocaine abuse and other disorders affecting the dopamine transporter may be discovered.

Introduction

The cocaine recognition site on the dopamine transporter has been the target for numerous compounds with structural diversity. The majority of these compounds have been based on cocaine or structural analogues of WIN 35,428.[1] These ligands have been developed as probes to further elucidate the role of the dopamine transporter in neurological disorders including Parkinsonism, schizophrenia, and drug abuse. Cocaine (**1**, Figure 1), a prototypic dopamine uptake inhibitor, is a potent psychomotor stimulant and drug of abuse. Despite its nonselective binding profile among monoamine transporters, its mechanism of reinforcing action appears to be related to the blockade of dopamine reuptake into presynaptic terminals.[2]

Until recently, all of the dopamine uptake inhibitors that have been evaluated behaviorally in animal models of psychomotor stimulant action demonstrated a cocaine-like behavioral profile. However, we recently reported[3] a series of 3α-(diphenylmethoxy)tropane analogues (**2**) that were potent inhibitors of dopamine uptake but did not produce cocaine-like efficacious locomotor stimulation or cocaine-like subjective effects.[4] Chemical modification at the 3-position of the tropane ring, and in particular the aromatic ring substituents, yielded an interesting series of compounds that bound with a range of affinities (K_i range = 11.8−2000 nM) to the dopamine transporter. Additionally, the K_i values for binding were well correlated to their potency for blocking dopamine uptake.[3b] Structure−activity relationships for this series of compounds revealed a striking divergence from cocaine and related tropane analogues.[3,5] In combination with the lack of psychomotor stimulant effects of several of these compounds, a binding domain on the dopamine transporter, not identical with that of cocaine, was proposed to exist that may provide a pharmacological target for a cocaine abuse medical treatment.[3,5]

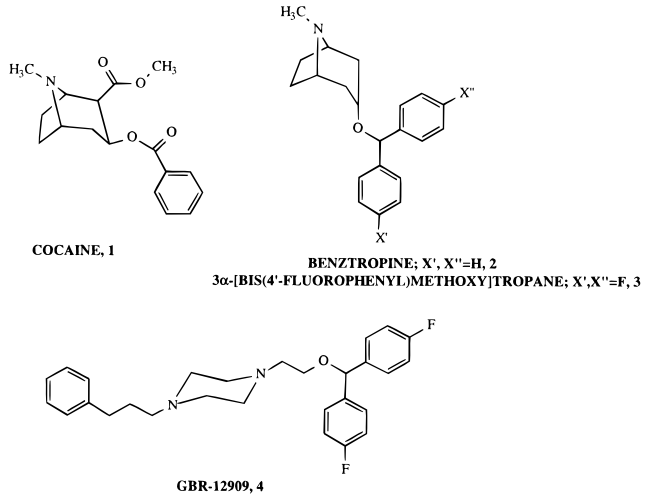

Figure 1.

The most potent compound in the initial series of 3-substituted tropane analogues was 3α-[bis(4′-fluorophenyl)methoxy]tropane (**3**). This compound bound to the dopamine transporter with a K_i value of 11.8 nM and potently blocked dopamine uptake (IC_{50} = 71 nM).[3b] Additionally, compound **3** only partially substituted for cocaine in rats trained to discriminate cocaine from saline, at doses that were far higher than would be

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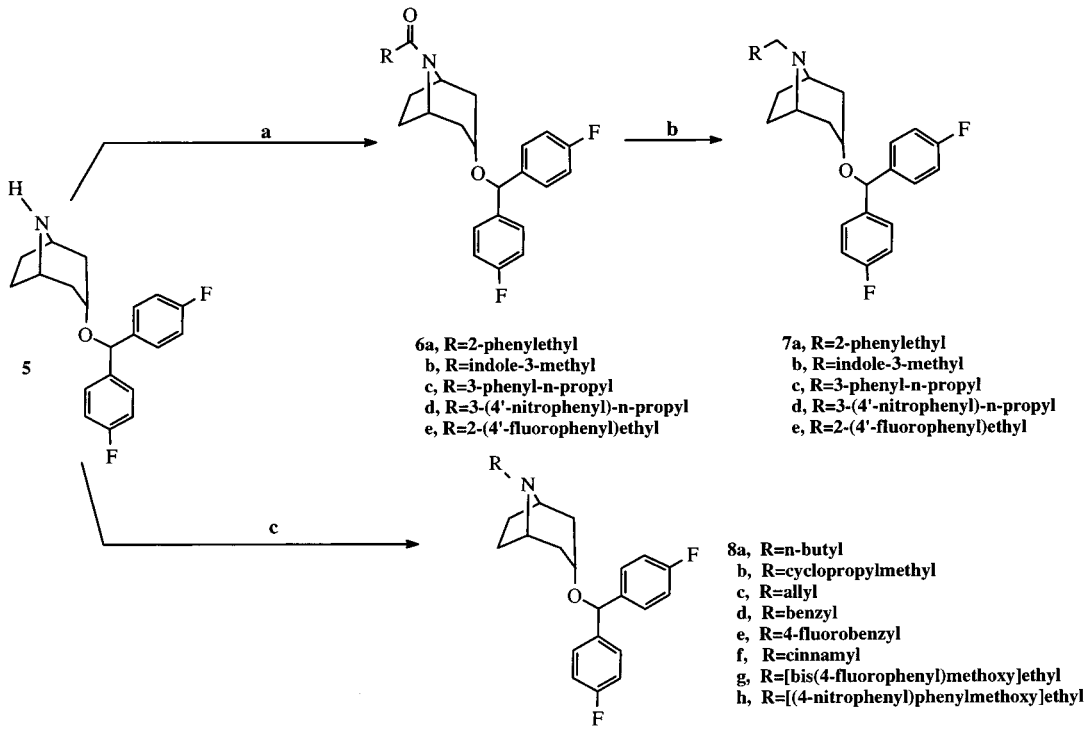
Scheme 1[a]



[a] (a) RCOOH, DCC, 1-hydroxybenzotriazole hydrate, Et_3N, DMF; (b) AlH_3, THF; (c) RBr, K_2CO_3, DMF.

predicted based on its high affinity for the dopamine transporter.[6] In addition, this compound demonstrated excellent selectivity over the serotonin and norepinephrine transporters (200- and 700-fold, respectively). Despite the selectivity for the dopamine transporter over the other monoamine transporters, substitution on the aromatic rings of the 3-position did not significantly decrease binding affinity at muscarinic receptors.[3b]

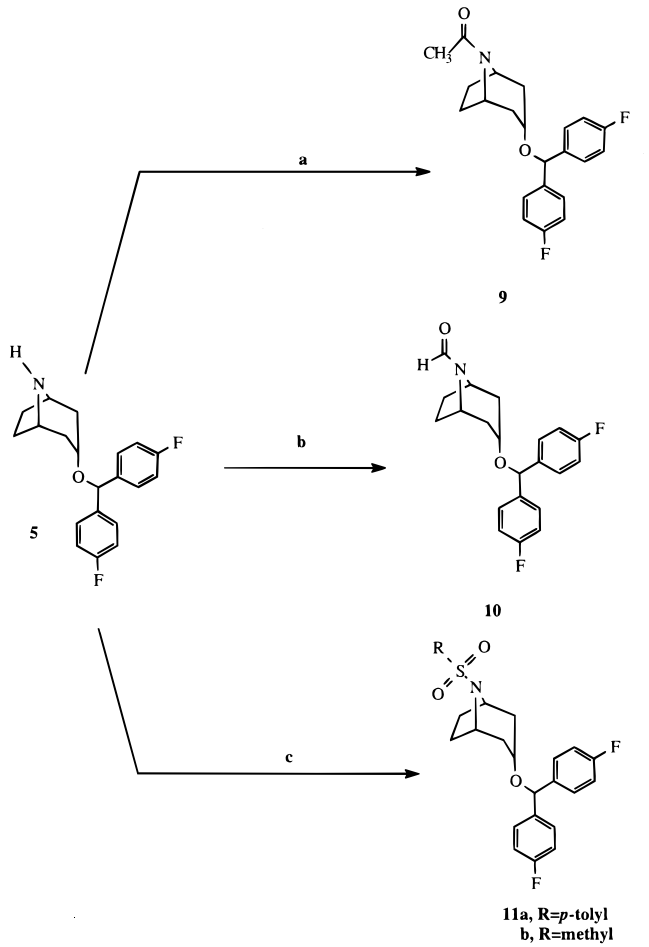
The bis(4′-fluorophenyl)methoxy moiety is seen in another series of potent dopamine uptake inhibitors, e.g. 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine (GBR 12,909, **4**). Matecka et al.[7] and Dutta et al.[8] recently reported an extensive structure−activity relationship for a series of heteroaromatic and piperazine-modified GBR 12,909 analogues. In addition to the diphenylmethyl ether moiety, 3α-[bis(4′-fluorophenyl)methoxy]tropane also resembles the GBR series since the tropane ring can be considered a conformationally rigid congener of the GBR 12,909 piperazine ring.[9] Recently, Meltzer et al. described a series of N-substituted 2-carbomethoxy-3-(diarylmethoxy)tropane analogues and compared them to other tropane and piperazine GBR 12,909-like dopamine transporter ligands. The structure−activity relationships reported for this series of compounds showed that they are more GBR-like rather than cocaine-like despite the presence of a tropane moiety.[10] Notably, GBR 12,909 has not been reported to have high affinity for muscarinic receptors. Since the other terminal nitrogen of the piperazine ring is substituted with a 3-phenyl-*n*-propyl group, it was envisioned that perhaps substituting the *N*-methyl group of GBR 12,909-like 3α-[bis(4′-fluorophenyl)-methoxy]tropane with alkyl or arylalkyl substituents may result in a compound that retains high affinity for the dopamine transporter but has decreased muscarinic receptor binding affinity. Therefore, a series of N-substituted 3α-[bis(4′-fluorophenyl)methoxy]tropane analogues were prepared to further develop the structure−activity relationships and compare them with other structurally similar analogues at the dopamine transporter. In addition, this study addresses whether diverse substitutions at the tropane nitrogen of 3α-[bis-(4′-fluorophenyl)methoxy]tropane will provide selective ligands for the dopamine transporter as compared to muscarinic m_1 sites.

Chemistry

N-Substituted 3α-[bis(4′-fluorophenyl)methoxy]tropane analogues were prepared by the following methods. Nor-3α-[bis(4′-fluorophenyl)methoxy]tropane (**5**) was prepared by demethylation of compound **3**.[11] Several analogues, **7a**−**e**, were prepared using an amidation method with DCC and 1-hydroxybenzotriazole hydrate (HOBt) to yield amide **6**, which gave amine **7** upon reduction with allane (Scheme 1). Alternatively, nor-3α-[bis(4′-fluorophenyl)methoxy]tropane (**5**) could be alkylated directly with the appropriate alkyl bromide in DMF with potassium carbonate (Scheme 1, **8a**−**h**).[12] The acetamide analogue **9**, (Scheme 2) was prepared by nor-3α-[bis(4′-fluorophenyl)methoxy]tropane (**5**) coupling with acetyl chloride in chloroform and aqueous bicarbonate under Schotten−Bauman conditions. Formamide analogue **10** (Scheme 2) preparation was accomplished with ethyl formate and formic acid. Sulfonamide analogues **11a**,**b** were synthesized by coupling **5** and the appropriate sulfonyl chloride in triethylamine (Scheme 2).[13] Finally, the quaternary iodide analogue **12** was prepared by stirring **5** with excess methyl iodide in ethanol.

Quaternary analogue **12** structure was elucidated by X-ray crystallography as shown in Figure 2. The bond distances and angles for the cation for **12** are at expected values. The 3α-bis(4′-fluorophenyl)methoxy substituent is axial to the chair-shaped piperidine ring with the

Scheme 2[a]



[a] (a) Acetyl chloride, $NaHCO_3$(aq), $CHCl_3$; (b) CH_3CH_2OCHO, HCOOH; (c) RSO_2Cl, Et_3N, −10 °C.

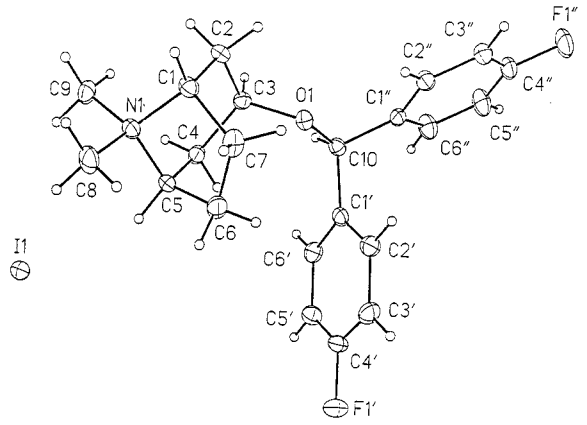


Figure 2. Thermal ellipsoid plot drawn from experimental coordinates for **12**.

phenyl groups orientation defined by torsions C3−O1−C10−C1′ = −104.9° and C3−O1−C10−C1″ = 132.4° as anticlinal. This places the centroid of the phenyl rings to N atom distances at 5.96 Å for the C1′ thru C6′ centriod and 7.54 Å for the C1″ thru C6″ centroid. The dihedral angle between the phenyl rings is 79.1°. The arrangement of **12** is similar to the previously reported X-ray structure of parent compound **3**.[3b]

Results and Discussion

All compounds were tested for their displacement of [^{3}H]WIN 35,428 from the dopamine transporter in rat caudate putamen. The compounds that demonstrated moderate to high binding affinity (K_i < 108 nM) to the dopamine transporter were further tested for binding to serotonin and norepinephrine transporters, muscarinic m_1 sites, and for inhibition of dopamine uptake (Tables 1 and 2).

In general, a large variety of N-substitutions providing tertiary amines, including alkyl (e.g. *n*-butyl **8a**, allyl **8c**, and methyl **3**) aromatic (phenylalkyl **7a**,**c**,**d**,**e**, **8d**,**e**, indole-3-ethyl **7b**, and cinnamyl **8f**), are tolerated at the dopamine transporter binding site. None of the compounds tested had high affinity for the norepinephrine and serotonin transporters (Table 2). All compounds tested inhibited dopamine uptake (Table 1), and their potencies (IC_{50} values) significantly correlated with binding to the dopamine transporter (r^2 = 0.452, p = 0.006).

Ligands containing a nonbasic nitrogen (amides **9, 10** and sulfonamides **11a,b**) did not effectively bind to the dopamine transporter. This finding is in contrast to recent reports by Kozikowski[13] and Madras[14] which convey a nonbasic tropane nitrogen or non-nitrogen bridge does not have a detrimental effect on dopamine transporter affinity. However, our findings are in agreement with prior studies by Abraham et al. concluding a basic nitrogen is needed for high ligand affinity to the dopamine transporter.[15] One possible explanation for a basic nitrogen requirement in this series is that the bioactive form of tropane may be protonated and interacts with the dopamine transporter through an ionic attraction. In support of this notion, the methiodide analogue **12** demonstrated only a 10-fold decrease in binding affinity as compared to the parent ligand **3**. The modest decrease in binding affinity might be explained by the addition of the steric bulk of the additional methyl moiety. Recently, Meltzer et al. reported on a series of oxytropane analogues of WIN 35,428 that demonstrated high-affinity binding at the dopamine transporter and supported the notion that a basic tropane nitrogen was not necessary.[16] However, when the nitrogen in the tropane ring of the difluoropine series was replaced with oxygen, a significant decrease in binding resulted, supporting the findings in our study. Future molecular modeling studies will address the issues of sterics and charge of this ligand and its parent compound.

Aromatic substituents and their distance from the tropane nitrogen can have a significant effect on dopamine transporter binding affinity. For example, as distance increases between the phenyl ring and tropane nitrogen (benzyl **8d**, 3-phenyl-*n*-propyl **7a**, and 4-phenyl-*n*-butyl **7c**), a 10-fold increase in binding affinity to the dopamine transporter (K_i = 82.2 nM to K_i = 8.51 nM) is observed (Figure 3). Methods for obtaining centroid distances are described in the Experimental Section. Inhibition of dopamine uptake also follows an analogous trend (IC_{50} range = 285 to 39 nM). The most potent and selective dopamine transporter ligand in this series was the *N*-(4-phenyl-*n*-butyl) analogue **7c**. Also of note, phenyl ring substitution of the tropane nitrogen does not appear to have a large effect on dopamine transporter binding affinity as evidenced by a comparison of ligands **7c** and **7d**, **7a** and **7e**. Bulky N-substituted aromatic substituents (**7b, 8h**) retain high binding affinity to the dopamine transporter as well.

Table 1. N-Substituted 3α-[Bis(4′-fluorophenyl)methoxy]tropanes Binding to the Dopamine Transporter and Inhibition of Dopamine Uptake

compd no.	R substitution	DAT, K_i, nM (% error)[a]	[^{3}H]DAU[a]
7c	4″-phenyl-*n*-butyl	8.51 (14)	39
5	H	11.2 (11)	9.7
3	methyl	11.8 (11)[b]	71[b]
7d	4″-(4‴-nitrophenyl)-*n*-butyl	20.2 (11)	650
8a	*n*-butyl	24.6 (8)	370[c]
8c	allyl	29.9 (10)	14
8b	cyclopropylmethyl	32.4 (9)	180
7a	3″-phenyl-*n*-propyl	41.9 (11)	230
7b	indole-3″-ethyl	44.6 (11)	1200
8h	2′-{[(4″-nitrophenyl)phenyl]methoxy}ethyl	57.0 (17)	NT[e]
7e	3″-(4‴-fluorophenyl)-*n*-propyl	60.7 (12)	NT[e]
8d	benzyl	82.2 (15)	290
8f	cinnamyl	86.4 (12)	180
8e	4″-fluorobenzyl	95.6 (10)	200
12	dimethyl quaternary	108 (12)	130
8g	2″-[bis(4‴-fluorophenyl)methoxy]ethyl	634 (23)	NT[e]
10	formyl	2020 (13)	5400
9	acetyl	2340 (5)	4600
11b	methylsulfonyl	18%[d]	NT[e]
11a	*p*-tolylsulfonyl	0%[d]	NT[e]

[a] Each K_i value represents data from at least three independent experiments, each performed in triplicate. [b] Data from ref 4. [c] The curve is significantly different from linearity; the IC_{50} value is only an estimate. [d] Percent inhibition at 10 μM. [e] NT = not tested.

Table 2. N-Substituted 3-[Bis(4′-fluorophenyl)methoxy]tropane Binding to Norepinephrine and Serotonin Transporters and Muscarinic m_1 Sites

compd no.	R substitution	NET, K_i, nM[a]	5-HTT, K_i, nM[a]	m_1, K_i, nM (% error)
7c	4″-phenyl-*n*-butyl	NT[e]	NT[e]	483 (8)
5	H	>8000	2100	156 (6)
3	methyl	>8500[b]	2440[b]	9.00 (10)
8a	*n*-butyl	1330	1730	251 (5)
8c	allyl	5920	1450	126 (6)
8b	cyclopropylmethyl	4790	1190	136 (8)
7a	3″-phenyl-*n*-propyl	3520	375	136 (9)
8d	benzyl	2080	74%[b]	773 (7)
8f	cinnamyl	577	1490	238 (9)
8e	4″-fluorobenzyl	60%[b]	NT[e]	611 (7)
12	dimethyl quaternary	38%[c]	79%[c]	29.1 (12)
10	formyl	29.4%[c]	1.6%[c]	12,300 (12)
9	acetyl	8.5%[c]	1.3%[c]	NT[e]

[a] Data provided by NOVASCREEN and should be considered preliminary. [b] Data from ref 4. [c] Percent inhibition at 10 μM. [e] NT = not tested.

Thus several members in this series of N-substituted tropanes have comparable binding profiles for the dopamine, serotonin, and norepinephrine transporters as well as for inhibition of dopamine uptake compared to the parent ligand **3**. However, by substituting other moieties for the methyl group, muscarinic affinity can be significantly decreased while generally retaining the other binding characteristics of **3**. For example, norligand **5** has a 17-fold lower affinity for the muscarinic m_1 site compared to **3**. Additionally, replacement of the methyl group for other alkyl groups such as cyclopropyl methyl (**8b**), allyl (**8c**), or *n*-butyl (**8a**) lowers m_1 binding affinity by 14-, 15-, and 28-fold, respectively. Indeed, the most potent and selective ligand in this series was the *N*-(4-phenyl-*n*-butyl) analogue (**7c**) which had approximately the same affinity for the dopamine transporter but was 54-fold lower affinity for the muscarinic m_1 sites compared to the parent ligand **3**. This compound was selected for in vivo evaluation.

Cocaine, as has been demonstrated previously, increased ambulatory activity to greater than 5000 counts per 10 min at a dose of 20 mg/kg, with a higher dose producing less stimulation. The maximal activity of cocaine occurred in the first 30 min after injection. In contrast, over the first 30 min following injection, **7c** did not significantly increase locomotor activity to values greater than obtained after vehicle injection (Figure 4). In subjects trained to discriminate 10.0 mg/kg cocaine from vehicle, there was a dose-related increase in the percentage of responses emitted on the cocaine-appropriate response key as cocaine dose was increased from 1.0 to 10.0 mg/kg (Figure 5, circles). In contrast, no dose of **7c** produced a level of drug-appropriate responding that exceeded 10%. This lack of appreciable cocaine-like discriminative stimulus effects was obtained across a range of doses from those having no effect on response rates to those decreasing rates to approximately 31% of control (saline) values. Together these behavioral results indicate that **7c** retained a novel behavioral spectrum of action compared to that of other dopamine uptake inhibitors. Further, these results suggest that N-substitution in general, while potentially decreasing affinity at muscarinic receptors, does not render these compounds more similar to cocaine with regard to their behavioral effects.

Summary and Conclusions

A series of novel N-substituted 3α-[bis(4′-fluorophenyl)methoxy]tropane ligands have been synthesized and tested for binding to the dopamine, norepinephrine, and serotonin transporters, muscarinic m_1 sites, and inhibition of dopamine uptake. Further, the most potent and selective compound in this series, **7c**, was evaluated for cocaine-like behavioral effects. The structure−activity relationships in this series demonstrate that the 3α-(diphenylmethoxy)tropanes can tolerate a wide range of N-substitutions and remain potent and selective dopamine transporter ligands. This series of compounds also suggests that a basic tropane nitrogen is required for high affinity at the dopamine transporter. Importantly, a separation in the binding affinities of the dopamine transporter versus muscarinic m_1 sites was achieved by making alkyl and arylalkyl substitutions at the tropane nitrogen.

Molecular modeling studies using conformational molecular field analysis (CoMFA) are being conducted

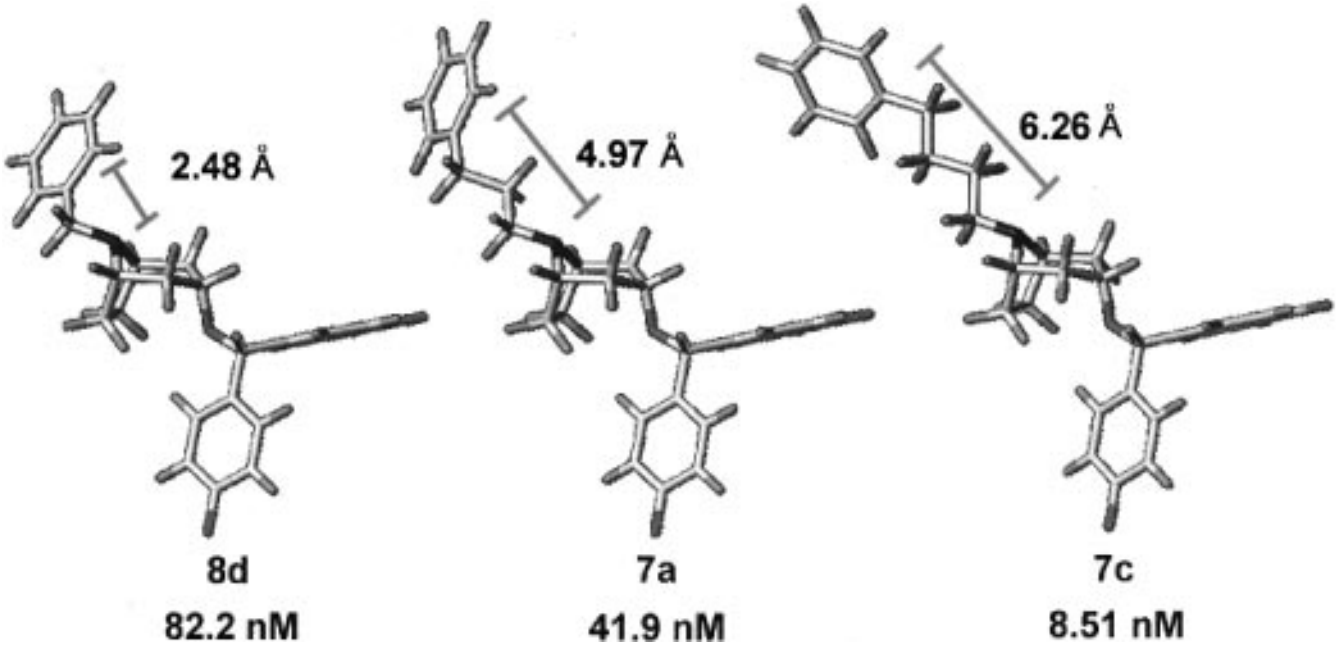


Figure 3. Dopamine transporter binding affinities (K_i, nM) related to the distance between the phenyl ring (C_1) of N-substitutent and the tropane nitrogen of ligands **8d**, **7a**, and **7c**.

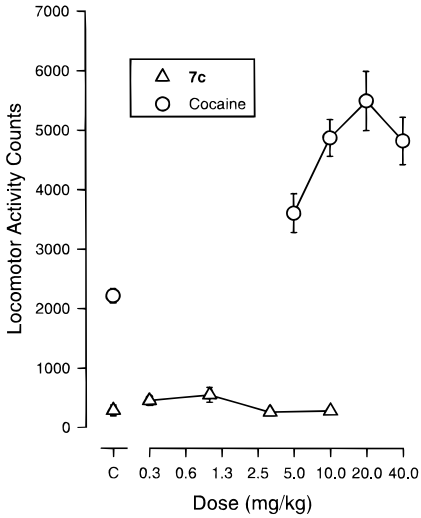


Figure 4. Dose-dependent effects of **7c** and cocaine on locomotor activity in mice. Ordinates: horizontal activity counts per 10 min. Abscissae: dose of drug in mg/kg, log scale. Unfilled points above C represent the effects of saline or propylene glycol vehicle controls. Each point represents the average effect determined in eight mice, with error bars representing ±1 SEM. For those points that have no error bars the symbol encompassed the error. The data are from the first 30-min period after drug administration, in which the greatest stimulant effects were obtained.

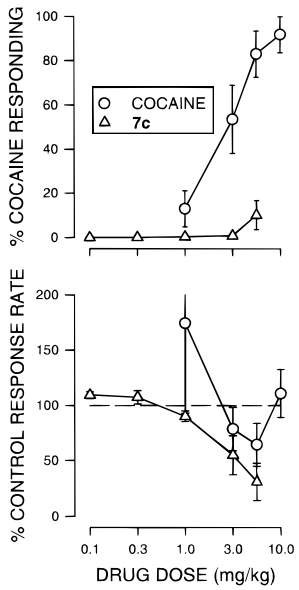


Figure 5. Effects of **7c** and cocaine in rats trained to discriminate injections of cocaine from saline. Ordinates: percentage of responses on the cocaine-appropriate lever. Abscissae: drug dose in mg/kg (log scale). Top panel: percentage of responses emitted on the lever on which rats were trained to respond after injections of cocaine. Bottom panel: rates at which responses were emitted as a percentage of response rate after saline administration. Each point represents the effect in three to six rats. Each point represents the average effect determined in three to six rats, with error bars representing ±1 SEM. For those points that have no error bars the symbol encompassed the error.

to design more potent and selective dopamine transporter ligands and to provide insight into the 3α-[bis-(4′-fluorophenyl)methoxy]tropane−dopamine transporter binding domain. Currently, several of the N-substituted analogues are being evaluated behaviorally in animal models of psychomotor stimulant abuse. These compounds may ultimately yield new leads toward the development of a therapeutic for cocaine abuse/addiction.

Experimental Section

All melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a Bruker (Billerica, Mass) AC-300 instrument. Samples were dissolved in an appropriate deuterated solvent ($CDCl_3$ or CD_3OD). Proton chemical shifts are reported as parts per million (δ) relative to tetramethylsilane (Me_4Si; 0.00 ppm) which was used as an internal standard. Mass spectra were recorded on a Hewlett-Packard (Palo Alto, CA) 5971A mass selective ion detector in the electron-impact mode with sample introduction via a HP-5890 series II, gas chromatograph fitted with an HP-1 (cross-linked methyl silicone gum) 25 m × 0.2 mm i.d., 50 μm film thickness. Ultrapure grade helium was used as the carrier gas at a flow rate of 1.2 mL/min. The injection port and transfer line

temperatures were 250 and 280 °C, respectively. The initial oven temperature was 100 °C, held for 3.0 min, programmed to 295 °C at 15.0 °C/min, and maintained at 295 °C for 10.0 min. Infrared spectra were recorded in KBr with a Perkin-Elmer 1600 Series FTIR. Microanalyses were performed by Atlantic Microlab, Inc. (Norcross, GA) and agree within ±0.4% of calculated values. TLC solvent used was $CHCl_3$/MeOH/NH_4-OH; 90:10:1, unless otherwise indicated. All chemicals and reagents were purchased from Aldrich Chemical Co. or Lancaster Synthesis, Inc. unless otherwise indicated and used without further purification.

Synthesis. Nor-3α-[bis(4′-fluorophenyl)methoxy]tropane Hydrochloride (5). The hydrochloride salt of compound **3**[3] (10.9 g, 28.7 mmol) was converted to its free base form by extracting with $CHCl_3$ (3 × 50 mL) from 20% aqueous NH_4OH (100 mL), drying, and evaporating to an oil, which solidified upon drying. Under an atmosphere of argon, the crystalline free base was dissolved in 1,2-dichloroethane (100 mL, freshly distilled over P_2O_5). Anhydrous K_2CO_3 (15.9 g, 115 mmol) and 1-chloroethyl chloroformate (ACE-Cl, 16.5 g, 115 mmol) were added to the reaction mixture, and it was warmed and allowed to stir at reflux for 5 h. The mixture was allowed to cool to room temperature, ACE-Cl (5.0 g, 35 mmol) was added, and the reaction mixture was stirred at reflux for 3 h. The reaction mixture was allowed to cool to room temperature, filtered, and washed with methylene chloride; the excess solvent was removed in vacuo. The residue was dissolved in MeOH (60 mL) and allowed to stir overnight at room temperature under an atmosphere of argon. (Note: if the reaction mixture was allowed to stir at reflux, varying amounts of nortropine were detected/isolated from the reaction mixture. After just 2 h of reflux, complete conversion of product to the undesired cleavage product was obtained. This cleavage did not appear to occur at ambient temperature). The product crystallized from methanol and was isolated to give 4.3 g of white crystalline product, as the HCl salt (41%). A second crop crystallized from acetone to give **5** (total 6.9 g, 21 mmol, 66%): mp 279 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72−1.92 (m, 6H, H-2,4$_{ax,eq}$ and H-6,7$_{exo}$), 2.17−2.23 (m, 2H, H-6,7$_{endo}$), 3.47 (br s, 2H, H-1,5), 3.60 (br s, 1H, H-3$_{eq}$), 5.38 (s, 1H, H-CHAr$_2$), 6.97−7.03 (m, 4H, H-ArH), 7.23−7.29 (m, 4H, H-ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3, 35.6, 53.3, 69.1, 79.6, 115.0, 115.3, 128.1, 128.2, 138.2, 160.3, 163.6; EIMS *m*/*z* 329 (M^+). Anal. ($C_{20}H_{22}NOF_2Cl$) C, H, N.

***N*-(3-Phenylpropyl)-3α-[bis(4′-fluorophenyl)methoxy]tropane Hydrochloride (7a).** Compound **5** (370 mg, 1.0 mmol) and triethylamine (0.3 mL, 2.2 mmol) were added to a mixture of hydrocinnamic acid (150 mg, 1.0 mmol), dicyclohexylcarbodiimide (DCC, 250 mg, 1.2 mmol), and 1-hydroxybenzotriazole hydrate (HOBT, 180 mg, 1.3 mmol) in 10 mL of dry DMF. The reaction mixture was allowed to stir for 1 h at 0 °C, under an atmosphere of argon. The reaction mixture was then allowed to warm to room temperature and to stir for 48 h. After completion of the reaction (assessed by TLC), 15 mL of H_2O was added. The reaction mixture was basified by adding a few drops of concentrated NH_4OH to pH 9. The organic products were extracted with ether (3 × 30 mL), and the combined ether fractions were washed with H_2O (2 × 25 mL), dried, filtered, and evaporated to an orange oil. A 0.4 g (10 mmol) portion of $LiAlH_4$ in 20 mL of anhydrous THF was treated carefully with 0.5 g of 98% sulfuric acid in 1 mL of anhydrous THF at 0 °C under an atmosphere of argon. After 15 min of stirring at room temperature, a solution of the intermediate amide in 5 mL of anhydrous THF was added dropwise to the reaction mixture, under argon. After 2 h of stirring at room temperature, the reaction mixture was hydrolyzed by slowly adding 1.6 mL of a 1:1 mixture of THF and H_2O at 0 °C. After 5 min of stirring at room temperature, the gelatinous product was dissolved in 30 mL of ether, and 2 mL of 15% NaOH was carefully added. After 20 min of stirring at room temperature, a white precipitate was observed and separated by suction filtration. The organic filtrate was dried and evaporated to yield 330 mg (74%) of the crude product as a light brown oil. The oil was dissolved in a minimal volume of ether and acidified to pH 2 with a saturated solution of HCl/2-PrOH. Recrystallization in 2-PrOH/ether yielded **7a** (220 mg, 0.5 mmol, 46% from **5**): mp 170−171 °C; ^{1}H NMR ($CDCl_3$) δ 1.73−2.09 (m, 8H, H-2, 4, 6,7$_{exo}$, H-CH$_2$), 2.03−2.08 (m, 2H, H-6,7$_{endo}$), 2.34 (t, J = 8 Hz, 2H, H-CH$_2$Ar), 2.63 (t, J = 8 Hz, 2H, N-CH$_3$), 3.16 (br s, 2H, H-1,5), 3.50−3.55 (m, 1H, H-3$_{eq}$), 5.36 (s, 1H, H-CAr$_2$), 6.98 (m, 4H, H-Ar), 7.14−7.30 (m, 9H, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.0, 30.5, 33.0, 35.6, 52.0, 57.9, 69.0, 79.0, 114.9, 115.2, 125.6, 128.2, 128.2, 128.3, 138.0, 143.0, 160.0, 163.0. Anal. ($C_{29}H_{32}NOF_2Cl$) C, H, N.

***N*-(Indole-3″-ethyl)-3α-[bis(4′-fluorophenyl)methoxy]tropane Hydrochloride (7b).** **7b** was prepared as in **7a** from **5** (660 mg, 2.0 mmol) and indole-3-acetic acid (390 mg, 2.2 mmol). After coupling and reduction, the crude amine was converted to the HCl salt with a saturated solution of HCl/2-PrOH. The product was dried under vacuum and recrystallized from hot ethyl actetate to yield **7b** (330 mg, 0.60 mmol, 36% from **5**): mp > 230 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.81−2.02 (m, 6H, H-2,4$_{ax,eq}$ and H-6,7$_{exo}$), 2.10−2.12 (m, 2H, H-6,7$_{endo}$), 2.65−2.71 (m, 2H, H-CH$_2$), 2.92−2.97 (m, 2H, H-NCH$_2$), 3.32 (br s, 2H, H-1,5), 3.57 (t, J = 5 Hz, 1H, H-3$_{eq}$), 5.38 (s, 1H, H-CHAr$_2$), 6.97−7.36 (m, 12H, H-Ar), 7.60 (d, J = 7.6 Hz, 1H, H-indole); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.5, 26.2, 35.5, 52.9, 58.4, 69.5, 79.5, 111.1, 115.1, 115.4, 118.7, 119.2, 121.4, 121.9, 127.4, 128.3, 128.4, 136.1, 138.6, 160.4, 163.6. Anal. ($C_{30}H_{31}N_2OF_2Cl\cdot{}^1/_4H_2O$) C, H, N.

***N*-(4″-Phenyl-*n*-butyl)-3α-[bis(4′-fluorophenyl)methoxy]tropane Hydrobromide (7c).** **7c** was prepared as in **7a** from **5** (1.30 g, 4.0 mmol) and 4-phenylbutyric acid (730 mg, 4.4 mmol). The crude amine product was converted to the HBr salt with a saturated solution HBr/methanol and crystallized using methanol to give **7c** (1.4 g, 2.6 mmol, 63% from **5**). **6c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.93−2.05 (m, 8H, H-2,4$_{ax,eq}$, H-6,7$_{exo}$, and H-CH$_2$), 2.19−2.40 (m, 2H, H-6,7$_{endo}$), 2.70 (app t, J = 7.8, 7.3 Hz, 2H, H-CH$_2$Ar), 3.68 (br t, 1H, H-3$_{eq}$), 4.05−4.08, 4.69−4.71 (m, total 2H, H-1,5), 5.42 (s, 1H, H-CHAr$_2$), 7.01−7.07 (m, 4H, H-Ar), 7.20−7.24 (m, 4H, H-Ar), 7.29−7.34 (m, 5H, H-Ar). **7c**: mp 204−205 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61 (br s, 4H, H-CH$_2$), 1.80−2.00 (m, 6H, H-2,4$_{ax,eq}$ and H-6,7$_{exo}$), 2.00−2.10 (m, 2H, H-6,7$_{endo}$), 2.35−2.45 (m, 2H, H-CH$_2$Ar), 2.62 (m, 2H, H-NCH$_2$), 3.20−3.30 (m, 2H, H-1,5), 3.57 (br s, 1H, H-3), 5.40 (s, 1H, H-CHAr$_2$), 6.96−7.02 (m, 4H, H-Ar), 7.15−7.26 (m, 9H, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7, 26.9, 29.1, 35.1, 35.6, 51.8, 58.3, 68.9, 79.8, 115.2, 115.5, 125.6, 128.3, 128.4, 128.4, 138.2, 142.1, 160.5, 163.7. Anal. ($C_{30}H_{34}NOF_2Br$) C, H, N.

***N*-[4″-(4‴-Nitrophenyl)butyl]-3α-[bis(4′-fluorophenyl)-methoxy]tropane Hydrobromide (7d).** **7d** was prepared as in **7b** from **5** (2.5 g, 7.6 mmol) and 4-(4-nitrophenyl)butyric acid (1.9 g, 9.1 mmol). The crude amine product was converted to the HBr salt with a saturated solution of HBr/methanol and crystallized using methanol and diethyl ether to give **7d** (3.0 g, 5.1 mmol, 67%). **6d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90−2.10 (m, 8H, H-2,4$_{ax,eq}$, H-6,7$_{exo}$, and H-CH$_2$), 2.20−2.41 (m, 4H, H-6,7$_{endo}$ and H-CH$_2$ α to amide carbonyl), 2.81 (app dd, J = 9, 6.6, 6.4 Hz, 2H, H-CH$_2$Ar), 3.69 (br s, 1H, H-3), 4.11, 4.70 (br s, total 2H, H-1,5), 5.42 (s, 1H, H-CHAr$_2$), 7.01−7.07 (m, 4H, H-Ar), 7.28−7.33 (m, 4H, H-Ar), 7.38 (d, J = 8.6 Hz, 2H, H-Ar), 8.18 (d, J = 8.6 Hz, 2H, H-Ar). **7d**: mp 111−115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50−1.70 (m, 2H, H-CH$_2$), 1.72−1.85 (m, 6H, H-2,4$_{ax,eq}$ and H-6,7$_{exo}$), 2.05−2.18 (m, 2H, H-6,7$_{endo}$), 2.32−2.45 (m, 2H, H-CH$_2$Ar), 2.73 (t, J = 7.7 Hz, 2H, H-NCH$_2$), 3.13−3.28 (m, 2H, H-1,5), 3.25−3.61 (m, 1H, H-3$_{eq}$), 5.36 (s, 1H, H-CHAr$_2$), 7.00−7.06 (m, 4H, H-Ar), 7.28−7.36 (m, 6H, H-Ar), 8.17 (d, J = 8.6 Hz, 2H, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.0, 27.0, 28.8, 35.6, 35.7, 51.8, 58.1, 69.0, 79.3, 114.9, 115.2, 123.5, 128.2, 128.3, 129.0, 137.0, 146.0, 151.0, 161.0, 163.0. Anal. ($C_{30}H_{33}N_2O_3F_2Br\cdot{}^1/_4H_2O$) C, H, N.

***N*-[3″-(4‴-Fluorophenyl)propyl]-3α-[bis(4′-fluorophenyl)methoxy]tropane Hydrobromide (7e).** **7e** was prepared as in **7a** using **5** (830 mg, 2.5 mmol) and 3-(4′-fluorophenyl)propionic acid. The crude amine was converted to the HBr salt with a saturated solution of HBr/methanol and crystallized using methanol and diethyl ether to give **7e** (750 mg, 1.4 mmol, 54%). **6e**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.81−1.95 (m, 6H, H-2,4$_{ax,eq}$ and H-6,7$_{endo}$), 2.19−2.24 (m, 2H, H-CH$_2$ α to amide carbonyl), 2.97 (app q, J = 7.9, 7.0, 6.5 Hz, 2H, H-CH$_2$Ar), 3.62 (br s, 1H, H-3$_{eq}$), 4.06, 4.70 (s, total 2H, H-1,5),

5.40 (s, 1H, H-CHAr$_2$), 6.95−7.06 (m, 6H, H-Ar), 7.17−7.22 (m, 2H, H-Ar), 7.27−7.31 (m, 4H, H-Ar). **7e**: mp 183−185 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 1.80−1.92 (m, 8H, H-2,4$_{ax,eq}$, H-6,7$_{exo}$ and H-CH$_2$), 2.11−2.14 (m, 2H, H-6,7$_{endo}$), 2.39 (br t, 2H, H-NCH$_2$), 2.64 (t, J = 7.6 Hz, H-CH$_2$Ar), 3.22 (br s, 2H, H-1,5), 3.58 (br s, 1H, H-3$_{eq}$), 5.40 (s, 1H, H-CHAr$_2$), 6.96−7.06 (m, 6H, H-Ar), 7.14−7.19 (m, 2H, H-Ar), 7.28−7.32 (m, 4H, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.6, 32.5, 51.0, 58.8, 58.9, 68.8, 79.6, 114.8, 115.0, 115.1, 115.3, 128.1, 128.2, 129.5, 129.5, 137.0, 138.2, 159.8, 160.4, 163.0, 163.7. Anal. ($C_{29}H_{31}NOF_3Br$) C, H, N.

The starting material, **3-(4′-fluorophenyl)propionic acid**, was prepared by dissolving 4-fluorocinnamyl carboxylic acid (450 mg, 2.7 mmol) in ethanol (100 mL) in a 250 mL Parr pressure bottle with Pd on carbon (10%, 20 mg). The vessel was pressurized to 30 psi and agitated for 18 h. The mixture was filtered through a Celite pad, and solvent was removed in vacuo. 3-(4′-Fluorophenyl)propionic acid (490 mg, 2.9 mmol) was obtained and used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.70 (app t, J = 7.8, 7.6 Hz, 2H, H-CH$_2$ α to carbonyl), 2.98 (t, J = 7.6 Hz, 2H, H-CH$_2$Ar), 6.98−7.06 (m, 2H, H-Ar), 7.19−7.23 (m, 2H, H-Ar); IR (NaCl plate, neat) 1701 (CO stretch), 2800−3400 (aromatic, aliphatic C−H and O−H stretch) cm^{-1}.

***N*-Allyl-3α-[bis(4′-fluorophenyl)methoxy]tropane Hydrochloride (8c).** Compound **5** (370 mg, 1.0 mmol) was converted to its free base form by extracting with $CHCl_3$ (3 × 10 mL) from 20% NH_4OH (20 mL), drying, evaporating, and dissolving in 3.0 mL of dry DMF. Anhydrous K_2CO_3 (280 mg, 2.0 mmol) and allyl bromide (100 mL, 1.1 mmol) were added, and the reaction mixture was allowed to stir at room temperature for 1 h. Inorganics were removed by suction filtration, the filter pad was washed with ether, and the filtrate was poured into a separatory funnel. Extraction from H_2O (10 mL) with ether (3 × 10 mL) was followed by washing the combined organic portions with H_2O (1 × 10 mL) and drying. Evaporation of the volatiles resulted in 350 mg of crude product (95%) as a clear oil. The crude free base was dissolved in a minimal volume of anhydrous ether and acidified to pH 2 with a saturated solution of HCl/2-PrOH. Evaporation of the solvent and recrystallization in ether gave **8c** (300 mg, 0.8 mmol, 76% from **5**): mp 190 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73−1.87 (m, 6H, H-2,4$_{ax,eq}$ and H-6,7$_{exo}$), 1.97−2.05 (m, 2H, H-6,7$_{endo}$), 2.90 (d, J = 6.4 Hz, 2H, H-allylic), 3.11 (br t, 2H, H-1,5), 5.00−5.10 (m, 2H, H-terminal vinyl), 5.29 (s, 1H, H-CHAr$_2$), 5.75−5.88 (m, 1H, H-vinyl), 6.88−6.95 (m, 4H, H-Ar), 7.18−7.23 (m, 4H, H-Ar); EIMS m/z 369 (M$^+$). Anal. ($C_{23}H_{26}NOF_2Cl$) C, H, N.

***N*-Butyl-3α-[bis(4′-fluorophenyl)methoxy]tropane Hydrochloride (8a).** Compound **8a** was synthesized according to the procedure described for compound **8c**, from **5** (1.8 g, 5.5 mmol) and 1-bromobutane (0.90 g, 6.6 mmol). The reaction was allowed to stir at room temperature overnight, under an atmosphere of argon. After extractive workup, evaporation of the solvent resulted in 1.9 g of crude product (88%). The crude free base was dissolved in a minimal volume of ether and acidified to pH 2 with a saturated solution of HCl/2-PrOH to give **8a** (1.9 g, 4.4 mmol, 81%): mp 180−180.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 3H, H-CH$_3$), 1.24−1.36 (m, 2H, H-CH$_2$), 1.39−1.49 (m, 2H, H-CH$_2$) 1.76−1.96 (m, 6H, H-2,4$_{ax,eq}$ and H-6,7$_{exo}$), 2.03−2.10 (m, 2H, H-6,7$_{endo}$), 2.28−2.33 (m, 2H, H-NCH$_2$), 3.17 (br t, 2H, H-1,5), 3.54 (t, J = 5.0 Hz, 1H, H-3$_{eq}$), 3.56 (s, 1H, H-CHAr$_2$), 6.95−7.03 (m, 4H, H-Ar), 7.24−7.30 (m, 4H, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0, 20.8, 26.1, 30.9, 35.6, 57.8, 70.0, 79.0, 114.9, 115.2, 128.2, 128.3, 138.0, 160.0, 163.0; EIMS m/z 385 (M$^+$). Anal. ($C_{24}H_{30}NOF_2Cl\cdot{}^1/_2H_2O$) C, H, N.

***N*-(Cyclopropylmethyl)-3α-[bis(4′-fluorophenyl)methoxy]tropane Hydrochloride (8b).** Compound **8b** was synthesized according to the procedure described for compound **8c**, from **5** (660 mg, 2.0 mmol), using bromomethyl cyclopropane (300 mg, 2.2 mmol, 0.22 mL). The reaction was allowed to stir for an additional hour at room temperature under an atmosphere of argon. After extractive workup, evaporation of the solvent resulted in 650 mg of crude product (85%). The crude free base was dissolved in a minimal volume of ether and acidified to pH 2 with a saturated solution of HCl/2-PrOH. The crystalline product was isolated and recrystallized in 2-PrOH/ether to give **8b** (570 mg, 1.4 mmol, 68%): mp 212−213 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.076 (app q, J = 4.9, 5.4 Hz, 2H, H-CH$_2$), 0.45−0.51 (m, 2H, H-CH$_2$), 0.81−0.94 (m, 1H, H-CH), 1.78−1.98 (m, 6H, H-2,4$_{ax,eq}$ and H-6,7$_{exo}$), 2.03−2.40 (m, 2H, H-6,7$_{endo}$), 2.23 (d, J = 6.4 Hz, 2H, H-NCH$_2$), 3.31−3.34 (m, 2H, H-1,5), 3.54 (t, J = 5.0 Hz, 1H, H-3), 5.36 (s, 1H, H-CHAr$_2$), 6.96−7.02 (m, 4H, H-Ar), 7.25−7.30 (m, 4H, H-Ar); EIMS m/z 383 (M$^+$). Anal. ($C_{24}H_{28}NOF_2Cl$) C, H, N.

***N*-Benzyl-3α-[bis(4′-fluorophenyl)methoxy]tropane Fumarate (8d).** Compound **8d** was synthesized according to the procedure described for compound **8c**, from **5** (660 mg, 2.0 mmol), and benzyl bromide (380 mg, 2.2 mmol, 0.26 mL). After extractive workup, evaporation of the solvent resulted in 750 mg of crude product (90%) as a clear oil. A portion of the crude free base (0.9 mmol) was dissolved in a minimal volume of 2-PrOH and added to a solution of fumaric acid (110 mg, 0.9 mmol) in 2-PrOH. Recrystallization in ethyl acetate gave **8d** (360 mg, 0.7 mmol, 33%): mp 194−195 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78−2.15 (m, 8H, H-2,4$_{ax,eq}$ and H-6,7$_{exo,\ endo}$), 3.13 (br s, 2H, H-1,5), 3.52 (s, 2H, H-CH$_2$Ar), 3.56 (t, J = 5.05 Hz, 1H, H-3), 5.36 (s, 1H, CHAr$_2$), 6.95−7.03 (m, 4H, H-Ar), 7.20−7.37 (m, 9H, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 36.3, 56.3, 58.0, 69.7, 79.0, 114.9, 115.2, 126.5, 128.0, 128.2, 128.3, 128.4, 138.0, 140.0, 160.0, 163.0; EIMS m/z 419 (M$^+$). Anal. ($C_{31}H_{31}NO_5F_2$) C, H, N.

***N*-(4″-Fluorobenzyl)-3a-[bis(4′-fluorophenyl)methoxy]tropane Fumarate (8e).** Compound **8e** was prepared according to the procedure described for compound **8c**, from **5** (660 mg, 2.0 mmol), using 4-fluorobenzyl chloride (320 mg, 2.2 mmol, 0.3 mL). Evaporation of the solvent resulted in 520 mg of crude product (60%) as a clear oil. The crude free base was dissolved in a minimal volume of 2-PrOH and added to a solution of fumaric acid (140 mg, 1.2 mmol) in 2-PrOH. Recrystallization from 2-PrOH yielded **8e** (600 mg, 1.1 mmol, 54%): mp 201 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.79−1.98 (m, 6H, H-2,4$_{ax,eq}$ and H-6,7$_{exo}$), 2.08−2.12 (m, 2H, H-6,7$_{endo}$), 3.10 (br t, 2H, H-1,5), 3.46 (s, 2H, CH$_2$Ar), 3.56 (t, J = 5.0 Hz, 1H, H-3), 5.37 (s, 1H, H-CHAr$_2$), 6.95−7.03 (m, 6H, H-Ar), 7.25−7.34 (m, 6H, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.5, 35.1, 54.4, 58.4, 68.9, 79.8, 115.2, 115.4, 115.5, 115.7, 128.2, 128.4, 131.4, 131.2, 136.0, 138.1, 160.4, 160.2, 163.7, 164.2, 172.6; EIMS m/z 437 (M$^+$). Anal. ($C_{31}H_{30}NO_5F_3$) C, H, N.

***N*-Cinnamyl-3α-[bis(4′-fluorophenyl)methoxy]tropane Hydrochloride (8f).** Compound **8f** was synthesized according to the procedure described for compound **8c**, from **5** (330 mg, 1.0 mmol), and cinnamyl bromide (220 mg, 1.1 mmol, 0.16 mL). After extractive workup, evaporation of the solvent resulted in 380 mg of crude product (85%). The crude free base was dissolved in a minimal volume of ether and acidified to pH 2 with a saturated solution of HCl/2-PrOH. The solvents were removed in vacuo, and the product was crystallized from ether followed by recrystallization from 2-PrOH to give **8f** (320 mg, 0.7 mmol, 66%): mp 219 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.74−1.87 (m, 6H, H-2,4$_{ax,eq}$ and H-6,7$_{exo}$), 2.01−2.05 (m, 2H, H-6,7$_{endo}$), 3.07 (d, J = 6.3 Hz, 2H, H-CH$_2$), 3.15 (br t, 2H, H-1,5), 3.50 (t, J = 5 Hz, 1H, H-3$_{eq}$), 5.29 (s, 1H, H-CHAr$_2$), 6.23 (dt, J = 15.8, 6.5 Hz, 1H, H-vinyl), 6.40 (d, J = 15.8 Hz, 1H, H-vinyl), 6.89−6.95 (m, 4H, H-Ar), 7.12−7.32 (m, 9H, H-Ar); IR (KBr) 1501 (ROR), 1602 (aromatic), 2800−3000 (aliphatic C−H stretch) cm^{-1}. Anal. ($C_{29}H_{30}NOF_2Cl$) C, H, N.

***N*-[2″-[Bis(4‴-fluorophenyl)methoxy]ethyl]-3α-[bis(4′-fluorophenyl)methoxy]tropane Hydrobromide (8g). 8g** was prepared as in compound **8c** from **5** (340 mg, 1.0 mmol) and 1-bromo-2-[bis(4′-fluorophenyl)methoxy]ethane (670 mg, 2.1 mmol). The crude product (590 mg) was purified via flash chromatography (3:1 hexanes/ethyl acetate (trace triethylamine), SiO_2, obtain 280 mg, 48%) and converted to the HBr salt with a saturated solution HBr/methanol. The salt was crystallized using methanol and diethyl ether to give **8c** (240 mg, 0.4 mmol, 35%): mp 200−202 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.8−2.0 (m, 6H, H-2,4$_{ax,eq}$ and H-6,7$_{exo}$), 2.10−2.15 (m, 2H, H-6,7$_{endo}$), 2.63−2.67 (m, 2H, H-NCH$_2$), 3.22−3.26 (m, 2H, H-1,5), 3.53−3.58 (m, 3H, H-3$_{eq}$ and H-CH$_2$), 5.39 (s, 2H,

H-CHAr$_2$), 7.00−7.07 (m, 8H, H-Ar), 7.28−7.33 (m, 8H, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2, 35.6, 51.9, 58.8, 68.0, 69.0, 79.2, 82.4, 114.9, 115.0, 115.2, 115.3, 128.1, 128.3, 128.3, 128.5, 137.0, 138.0, 160.3, 160.4, 163.6, 163.7. Anal. ($C_{35}H_{34}NO_2F_4Br$) C, H, N.

***N*-[2″-[(4‴-Nitrophenyl)phenylmethoxy]ethyl]-3α-[bis(4′-fluorophenyl)methoxy]tropane Hydrobromide (8h).** **8h** was prepared as in **8c** from **5** (290 mg, 2.5 mmol) and 1-bromo-2-[(4′-nitrophenyl)phenyl]ethane (1.04 g, 3.09 mmol). The crude product was converted to the HBr salt with a saturated solution of HBr/methanol and crystallized in methanol to give **8h** (850 mg, 1.3 mmol, 63%): mp 129−133 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.76−1.89 (m, 6H, H-2,4$_{ax,eq}$ and H-6,7$_{exo}$), 2.09 (d, J = 7.1 Hz, H-6,7$_{endo,major}$) and 2.18 (d, J = 7.4 Hz, H-6,7$_{endo,minor}$), 2.64 (t, J = 6.2 Hz, 2H, H-NCH$_2$), 3.20 (br s, 2H, H-1,5), 3.48−3.57 (m, 3H, H-3$_{eq}$ and H-CH$_2$), 5.36 (s, 1H, H-CHAr(Ar-NO$_2$)), 5.46 (s, 1H, H-CHAr$_2$), 6.96−7.02 (m, 4H, H-Ar), 7.25−7.33, (m, 9H, H-Ar), 7.52 (d, J =9 Hz, 2H, H-Ar), 8.16 (d, J = 8.7 Hz, 2H, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2 (major) and 29.0 (minor), 51.9, 54.0, 58.9, 69.0, 69.3, 79.2, 82.9, 115.0, 115.2, 123.5, 126.9, 127.3, 128.0, 128.1, 128.3, 128.6, 138.0, 141.0, 147.0, 149.0, 160.0, 163.0. Anal. ($C_{35}H_{35}N_2O_4F_2Br\cdot{}^3/_4H_2O$) C, H, N.

***N*-Acetyl-3α-[bis(4′-fluorophenyl)methoxy]tropane (9).** Compound **5** (1.3 g, 3.4 mmol) was converted to the free base form as described for compound **3** and dissolved in 50 mL of methylene chloride. An aqueous solution of $NaHCO_3$ (1.0 g in 14 mL of H_2O) was added followed by a solution of acetyl chloride (400 mg, 5.1 mmol) in methylene chloride (4 mL), at 0 °C. The biphasic reaction mixture was allowed to warm to room temperature and stir for 3 h. The reaction mixture was then poured into a separatory funnel, the organic layer was removed, and the aqueous layer was washed with $CHCl_3$ (2 × 20 mL). The combined organic fraction was dried and evaporated to an oil. Purification using flash column chromatography (EtOAc) gave compound **9** as a pure clear oil (640 mg, 1.7 mmol, 51%). **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.82−2.03 (m, 9H, H-2,4$_{ax,eq}$, H-6,7$_{exo}$ and H-COCH$_3$), 2.15−2.30 (m, 2H, H-6,7$_{endo}$), 3.66 (app br t, J = 4.41, 3.68 Hz, 1H, H-3$_{eq}$), 4.07−4.09, 4.64−4.66 (m, total 2H, H-1,5), 5.39 (s, 1H, H-CHAr$_2$), 6.98−7.03 (m, 4H, H-Ar), 7.25−7.30 (m, 4H, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 27.2 and 28.7, 35.1 and 37.1, 50.4 and 54.5, 69.7, 79.8, 115.1, 115.1, 115.4, 128.0, 128.2, 128.2, 128.3, 133.0, 160.0, 163.0, 166.0; IR (neat) 1631 cm^{-1}; EIMS m/z 371 (M$^+$). Anal. ($C_{22}H_{23}NO_2F_2$) C, H, N.

***N*-Formyl-3α-[bis(4′-fluorophenyl)methoxy]tropane (10).** Compound **3** (740 mg, 2.0 mmol) was converted to the free base as described for compound **5** and dissolved in ethyl formate (9 mL, 111 mmol, freshly distilled over P_2O_5). Formic acid (6 mL, 100%, Fluka) was added, and the reaction mixture was allowed to stir, under an atmosphere of argon, overnight. Removal of volatiles, in vacuo, followed by purification through a short silica gel column with ethyl acetate resulted in 400 mg (56%) of the product as a white solid which recrystallized from ethyl acetate/hexane to give **10** as shiny white crystals (300 mg, 0.8 mmol, 42%), mp 117−118 °C. **10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83−2.10 (m, 6H, H-2,4$_{ax,eq}$ and H-6,7$_{exo}$), 2.22−2.30 (m, 2H, H-6,7$_{endo}$), 3.67−3.72 (m, 1H, H-5), 4.00−4.07 (m, 1H, H-1), 4.55−4.62 (m, 1H, H-3), 5.40 (s, 1H, H-CHAr$_2$), 7.02−7.10 (m, 4H, H-Ar, 7.25−7.30 (m, 4H, H-Ar), 8.10 (s, 1H, H-CHO); EIMS m/z 357 (M$^+$). Anal. ($C_{21}H_{21}NO_2F_2$) C, H, N.

***N*-(Methylsulfonyl)-3α-[bis(4′-fluorophenyl)methoxy]tropane (11b).** Compound **2** (790 mg, 2.4 mmol) was converted to the free base form as described for **5** and dissolved in anhydrous triethylamine (18 mL), cooled to −10 °C, and stirred for 20 min. Methanesulfonyl chloride (300 mg, 2.6 mmol) was added dropwise, and the mixture was stirred for 1 h at −10 °C and then 14 h at room temperature, after which, another 1.1 equiv of methanesulfonyl chloride was added to the mixture and stirred for an additional 3 h. A white solid formed during the course of the reaction that over time turned to a brown gum. Triethylamine was removed under vacuum, and the resulting residue was purified via flash chromatography (SiO_2, methylene chloride) to give **11b** as a white powder (300 mg, 0.7 mmol, 31%): mp 109−112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02−2.06 (m, 6H, H-2,4$_{ax,eq}$ and H-6,7$_{exo}$), 2.31 (app q, J = 7.4, 6.5, 6.4 Hz, 2H, H-6,7$_{endo}$) 2.91 (s, 3H, H-CH$_3$), 3.68−3.70 (m, 1H, H-3$_{eq}$), 4.25−4.27 (m, 2H, H-1,5), 5.43 (s, 1H, H-CHAr$_2$), 7.0−7.08 (m, 4H, H-Ar), 7.28, 7.33 (m, 4H, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.7, 37.3, 40.1, 55.8, 60.1, 79.7, 115.1, 115.4, 128.1, 128.2, 137.0, 160.0, 163.0. Anal. ($C_{21}H_{23}NO_3SF_2$) C, H, N.

***N*-(*p*-Tolylsulfonyl)-3α-[bis(4′-fluorophenyl)methoxy]tropane (11a).** **11a** was prepared as in **11b** from **2** (370 mg, 1.1 mmol) and *p*-toluenesulfonyl chloride (220 mg, 1.1 mmol) except the reaction was only stirred for 1 h. After purification via column chromatography, **11a** was obtained as a white powder (400 mg, 0.8 mmol, 74%): mp 165−168 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48−1.54 (m, 2H, H-6,7$_{endo}$), 1.96−2.07 (m, 6H, H-2,4$_{ax,eq}$ and H-6,7$_{exo}$), 2.45 (s, 3H, H-CH$_3$Ar), 3.66 (br s, 1H, H-3$_{eq}$), 4.25 (br s, 2H, H-1,5), 5.37 (s, 1H, H-CHAr$_2$), 6.98−7.04 (m, 4H, H-Ar), 7.23−7.30 (m, 6H, H−Ar), 7.77 (d, J = 8.2 Hz, 2H, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 28.1, 37.5, 55.9, 68.0, 79.0, 115.1, 115.3, 127.2, 128.0, 128.2, 129.4, 137.0, 138.0, 143.0, 160.0, 161.0, 163.0. Anal. ($C_{27}H_{27}NO_3SF_2$) C, H, N.

***N*-Methyl-3α-[bis(4′-fluorophenyl)methoxy]tropane Methiodide (12).** Compound **5** (760 mg, 2.0 mmol) was converted to the free base as described for **3** and was dissolved in 10 mL of absolute ethanol. Under an atmosphere of argon, iodomethane (2.0 mL, 32 mmol, passed through a small column of anhydrous potassium carbonate) was added, and the reaction mixture was allowed to stir at reflux for 1 h. The reaction mixture was allowed to cool and stir overnight at room temperature. The resulting crystalline product was isolated by filtration and washed with ethyl ether to give **12** as white crystals (720 mg, 1.8 mmol, 91%): mp 248 °C; ^{1}H NMR (300 MHz, $CDCl_3$/CD_3OD (1 mL/1 drop)) δ 2.11 (s, 2H, H-6,7$_{endo}$), 2.16 (s, 2H, H-6,7$_{exo}$), 2.33−2.39 (m, 2H, H-2,4), 2.46−2.49 (m, 2H, H-2,4), 3.25 (s, 3H, H-NCH$_3$), 3.30 (s, 3H, H-NCH$_3$), 3.78 (t, J = 5.9 Hz, 1H, H-3$_{eq}$), 4.11 (br s, 2H, H-1,5), 5.45 (s, 1H, H-CHAr$_2$), 7.00−7.06 (m, 4H, H-Ar), 7.24−7.32 (m, 4H, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$/CD_3OD (1 mL/1 drop)) δ 25.1, 32.2, 44.6, 51.0, 64.5, 67.9, 80.2, 115.3, 115.6, 128.1, 128.2, 137.0, 160.0, 163.0. Anal. ($C_{22}H_{26}NOF_2I$) C, H, N.

Molecular Modeling Methods. Molecular modeling studies were performed using the SYBYL[17] software package (Tripos, version 6.3, R4000) installed on a Silicon Graphics IRIS Indigo XZ workstation running IRIX 5.3. The chemical structures were drawn using the SKETCH option. Optimized geometries and partial charges were obtained using the AM1[18] model Hamiltonian as implemented in the MOPAC[19] program (version 6.0) using the PRECISE convergence criteria. Centroids were defined perpendicular to the surface of the aromatic rings contained in the N-substituents. The distance from the bridge N to the centroid dummy atom was measured using the MEASURE DISTANCE command.

Single-Crystal X-ray Analysis of 12. A clear rectangular 0.18 × 0.18 × 0.44 mm crystal recrystallized from EtOH, $C_{22}H_{26}OF_2N^{\bullet+}I^-$, FW = 485.34, was selected for data collection. Data were collected on a computer controlled diffractometer with an incident beam graphite monochromator (Siemens P4 with Cu Kα radiation, l = 1.541 78 Å, T = 295 K). A least-squares refinement using 28 centered reflections within 14 < 2q < 60° gave the monoclinic $P2_1/c$ cell, a = 16.755(2) Å, b = 10.660(1) Å, c = 12.958(1) Å, with V = 2151.7(4) Å^3, Z = 4, and d_{calc} = 1.498 g/cm^3. A total of 3283 reflections were measured in the q/2q mode to 2q_{max} = 116.5°, of which there were 3014 independent reflections. Corrections were applied for Lorentz and polarization effects. A face indexed numerical absorption correction was applied, m = 11.93 mm^{-1}, and max and min transmissions were 0.74 and 0.28, respectively. The structure was solved by direct methods with the aid of the program SHELXTL.[20] The full-matrix least-squares refinement on F_o^2 varied 245 parameters including the coordinates and anisotropic thermal parameters for all non-hydrogen atoms. H atoms were included using a riding model [coordinate shifts of C applied to attached H atoms, C−H distances set to 0.96 Å, H angles idealized, U_{iso}(H) were set to 1.2 U_{eq}(C) or, if methyl, 1.5 U_{eq}(C)]. The final R values for the 2396 observed reflections with F_o > 4sF_o were R1 = 0.041, and wR2

= 0.11 for all data.[21] The final difference Fourier excursions were 0.70 and −0.68 e Å^{-3}.

Pharmacology. Dopamine Transporter Binding Assay. Male Sprague−Dawley rats (200−250 g, Taconic, Germantown, NY) were decapitated and their brains removed to an ice-cooled dish for dissection of the caudate putamen. The tissue was homogenized in 30 volumes 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 D-glucose, pH adjusted to 7.4) using a Brinkman polytron and centrifuged at 20000*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 20000*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. The total volume in each tube was 0.5 mL, and the final concentration of membrane after all additions was 0.5% (w/v), corresponding to 200−300 mg of protein/sample. Triplicate samples of membrane suspension were preincubated for 5 min in the presence or absence of the compound being tested. [^{3}H]WIN 35,428 [2-β-carbomethoxy-3-β-(4-fluorophenyl)tropane−1,5-naphthalenedisulfonate; specific activity 82.4 Ci/mmol, from New England Nuclear, Boston, MA, final concentration 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). 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, defined as binding in the presence of 100 μM cocaine. Each compound was tested with concentrations ranging from 0.01 nM to 100 μM for competition against binding of [^{3}H]WIN 35,-428, in three independent experiments, each performed in triplicate.

In both saturation and competition experiments, two components of [^{3}H]WIN 35,428 binding were apparent. Analysis of the data utilizing the LIGAND program revealed a high affinity component with a K_D of 7 ± 5 nM and a B_{max} of 445 ± 338 fmol/mg of protein and a low-affinity component with a K_D of 126 ± 115 nM and a B_{max} of 1995 ± 559 fmol/mg of protein.

Saturation and displacement data were analyzed by the use of the nonlinear least squares curve-fitting computer program LIGAND.[22] Data from replicate experiments were modeled together to produce a set of parameter estimates and the associated standard errors of these estimates. In each case, the model reported fit significantly better than all others according to the F test at $p < 0.05$. The K_i values reported are the dissociation constants derived for the unlabeled ligands.

[^{3}H]Dopamine Uptake Assay. Rats were sacrificed by decapitation and their brains removed to an ice-cooled dish for dissection of the caudate putamen. [^{3}H]Dopamine uptake was measured in a chopped tissue preparation as described previously.[23] 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 rinsing, 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 15 nM, specific activity 50 Ci/mmol, from Amersham Corp, Arlington Heights, IL) 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. Uptake data were analyzed using standard analysis of variance and linear regression techniques. IC_{50} values were calculated using the linear portion of the concentration−response curve (linear regression $p < 0.05$).

Muscarinic m_1 Binding Assay. Whole frozen rat brains excluding cerebellum (Taconic, Germantown, NY) were thawed in ice-cold buffer (10 mM Tris-HCl, 320 mM sucrose, pH 7.4) and homogenized with a Brinkman polytron in a volume of 10 mL/g of tissue. The homogenate was centrifuged at 1000*g* for 10 min at 4 °C. The resulting supernatant was then centrifuged at 10000*g* for 20 min at 4 °C. The resulting pellet was resuspended in a volume of 1.53 mL/g in 10 mM Tris buffer (pH 7.4).

Assays were conducted in binding buffer (10 mM Tris-HCl, 5 mM $MgCl_2$). The total volume in each tube was 0.5 mL, and the final concentration of membrane after all additions was approximately 200−300 mg of protein/sample. Triplicate samples of membrane suspension were preincubated for 5 min in the presence or absence of the compound being tested. [^{3}H]-Pirenzepine (specific activity 73.9 Ci/mmol, from New England Nuclear, Boston, MA, final concentration 3 nM) was added, and the incubation was continued for 1 h at 37 °C. The incubation was terminated by the addition of 5 mL of ice-cold buffer (10 mM Tris-HCl, pH 7.4) and rapid filtration through Whatman GF/B glass fiber filter paper (presoaked in 0.5% polyethylenimine in water to reduce nonspecific binding) using a Brandel Cell Harvester (Gaithersburg, MD). The filters were washed with two additional 5 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 15000 dpm total binding per sample and approximately 900 dpm nonspecific binding, defined as binding in the presence of 10 μM QNB (quinuclidinyl benzilate). Each compound was tested with concentrations ranging from 0.01 nM to 100 μM for competition against binding of [^{3}H]pirenzepine, in at least three independent experiments, each performed in triplicate.

Serotonin (5-HTT) and norepinephrine transporter (NET binding data were provided by NOVASCREEN, Hanover, MD). The radiolabeled ligands used and the methods were from the following published procedures: 5-HTT, [^{3}H]citalopram (specific activity 70−87 Ci/mmol, final ligand concentration 0.7 nM);[24] NET, [^{3}H]desmethylimipramine (specific activity 40−70 Ci/mmol, final ligand concentration 3.0 nM).[25]

Locomotor Activity. Ambulatory activity of male Swiss Webster mice (Taconic Farms) were studied in 40 cm^3 clear acrylic chambers. The acrylic chambers were placed inside monitors (Omnitech Electronics, Columbus, OH) that were equipped with light sensitive detectors, spaced 2.5 cm apart along two perpendicular walls. Mounted on the opposing walls were infrared light sources that were directed at the detectors. One count of horizontal activity was registered each time the subject interrupted a single beam. Mice were injected with cocaine or **7c** and immediately placed in the apparatus for 60 min, with horizontal activity counts collected each 10 min. Intraperitoneal (ip) injections were administered in volumes of 1 mL/100 g. Each dose was studied in eight mice, and mice were used only once. Vehicle was saline (cocaine) or 50% propylene glycol (**7c**).

The data from the 60-min observation period were analyzed and those from the 30-min period in which maximal stimulation of activity was observed were selected for presentation. Each dose−effect curve was analyzed using standard analysis of variance (ANOVA) and post-hoc testing to determine significance of effects at individual doses.

Cocaine Discrimination. Male Sprague−Dawley rats (Charles River, Wilmington, MA) weighing 310−385 g were individually housed with free access to water under a 12 h

light/dark cycle (lights on 07.00 h). The rats had not been tested previously. All testing was between 14 and 15.00 h. Rats were fed 15 g standard lab chow daily at least 30 min after testing.

Rats were tested in two-lever operant-conditioning chambers (modified Med Associates, model ENV 007, St. Albans, VT) housed within light- and sound-attenuating enclosures with white noise present throughout testing. Ambient illumination was by a lamp in the top center of the front panel. Levers were set 17 cm apart, with a pair of red lamps above the left lever and a pair of white lamps above the right. A force of 0.4 N through 1 mm was required to register a lever press; reinforced presses activated an audible click and dispensed one 45 mg pellet (BioServe, Frenchtown, NJ) into the centrally located food tray.

Rats were initially trained to press both levers under a fixed-ratio 20-response schedule of food reinforcement. Following ip cocaine injection, responses on only one lever were reinforced; following saline, responses on the other lever were reinforced. The assignment of cocaine- and saline-appropriate levers was counterbalanced across rats. Immediately after injection, rats were placed inside the experimental chambers and a 5 min time-out period was initiated, during which all lamps were extinguished and responding was not reinforced. All lamps were then illuminated and responses on the appropriate lever were reinforced. Responses on the inappropriate lever reset the FR 20 response requirement on the appropriate lever. Each food presentation was followed by a 20 s time-out period during which all lamps were off, and responding had no scheduled consequences. Sessions ended after 20 food presentations or 15 min, whichever occurred first. Training sessions for which cocaine (C) and saline (S) injections were administered were ordered in an SCCS sequence, with test sessions conducted after consecutive SC or CS training sessions.

Test sessions were conducted if the subject attained criterion performance on both of the immediately preceding saline and cocaine training sessions. The criteria were at least 85% appropriate responding overall, and during the first FR of the session. Test sessions were identical with training sessions, with the exception that 20 consecutive responses on either lever were reinforced. Before test sessions, different doses of cocaine or doses of **7c** were administered. Vehicles were the same as those used in assessing effects on locomotor activity.

On-line experimental control and data collection were by PC MS-DOS computers operating Med Associates software (Med Associates, St. Albans, VT). For each rat, the overall response rate and the percentage of responses occurring on the cocaine-appropriate lever were calculated. The mean values were calculated for each measure at each drug dose tested. Data from any rat which failed to respond at a rate exceeding 0.02 responses per second was not included in the calculation of mean cocaine-appropriate responding at that dose. If less than three rats met the response rate requirement, no mean value was calculated for percentage of cocaine-appropriate responding at that dose.

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Supporting Information Available: X-ray unit cell, torsion angle list, crystal data, refinement parameters, atomic coordinates and isotropic displacement parameters, bond angles and lengths, anistropic displacement parameters, and hydrogen coordinates and isotropic displacement parameters for **12** (7 pages). Ordering information is given on any current masthead page.

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