Development of Long-Acting Dopamine Transporter Ligands as Potential Cocaine-Abuse Therapeutic Agents: Chiral Hydroxyl-Containing Derivatives of 1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine and 1-[2-(Diphenylmethoxy)ethyl]-4-(3-phenylpropyl)piperazine

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In our search for long-acting agents for the treatment of cocaine abuse, a series of optically pure hydroxylated derivatives of 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)-piperazine (**1**) and 1-[2-(diphenylmethoxy)ethyl]-4-(3-phenylpropyl)piperazine (**2**) (GBR 12909 and GBR 12935, respectively) were synthesized and evaluated in vitro and in vivo. The enantiomers of the 2-hydroxylated analogues displayed substantial enantioselectivity. The *S* enantiomers displayed higher dopamine transporter (DAT) affinity and the *R* enantiomers were found to interact at the serotonin transporter (SERT) with higher affinity. The two-carbon spacer between the hydroxyl group and the piperazine ring was essential for enantioselectivity, and the length of the alkyl chain between the phenyl group and the piperazine ring influenced binding affinity and selectivity for the DAT and SERT. Phenylethyl analogues had a higher binding affinity for the SERT and a weaker affinity and selectivity for the DAT than the corresponding phenylpropyl analogues. Thus, (*S*)-(+)-1-[4-[2-[bis(4-fluorophenyl)methoxy]ethyl]-piperazinyl]-3-phenylpropan-2-ol (**6**) displayed the highest affinity to the DAT, and (*S*)-(+)-1-[4-[2-(diphenylmethoxy)ethyl]piperazinyl]-3-phenylpropan-2-ol (**8**) had the highest selectivity. The latter (**8**) is one of the most DAT selective ligands known. In accord with the in vitro data, **6** showed greater potency than **7** in elevating extracellular dopamine levels in a microdialysis assay and in inhibiting cocaine-maintained responding in rhesus monkeys.

Introduction

Cocaine is a widely abused drug,[1−6] causing public health and societal problems; it plays a major role in the rapid spread of the HIV virus[7,8] and drug-resistant tuberculosis.[9] Unlike the several opioid-dependent treatment agonists that are available (e.g., methadone, levo-α-acetylmethadol, and buprenorphine), there are, as yet, no effective therapeutic agents that can lessen the abuse of cocaine.

In the central nervous system, cocaine blocks the reuptake of several neurotransmitters, such as dopamine (DA), serotonin (5-HT), and norepinephrine (NE), by interacting with dopamine transporter (DAT), serotonin transporter (SERT), and norepinephrine transporter sites, respectively. Over the past decade, numerous studies have indicated that the reinforcing properties of cocaine are largely mediated by the binding of cocaine to the DAT and the subsequent blockade of DA reuptake into presynaptic terminals resulting in increased neurotransmission in the mesolimbic dopaminergic system.[10−12] On the basis of these observations, a number of studies have been aimed at the discovery and development of potent and selective DA reuptake inhibitors.[13] These inhibitors may reduce the effects of cocaine and therefore are potential treatment agents for cocaine abuse.

A variety of structural classes of DAT ligands have been used as templates for the design and synthesis of potential cocaine abuse therapeutic agents, including cocaine analogues,[14] tropanes,[15] benztropines,[16,17] mazindol,[18,19] and disubstituted piperazines.[20−22] Research in this laboratory has focused on the development of novel analogues of the disubstituted piperazines GBR 12909 (1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine, **1**) and GBR 12935 (1-[2-(diphenylmethoxy)ethyl]-4-(3-phenylpropyl)piperazine, **2**; Chart 1).[23] Compound **1**, a potent and selective DAT inhibitor agent, can suppress the reinforcing and euphorigenic effects of cocaine, but it has a relatively short duration of action (ca. 6 h). The repeated administration of **1** has been shown to decrease cocaine-maintained responding in rhesus monkeys for almost 2 weeks, without the development of tolerance and without affecting similar responding maintained by food.[24] Using **1** as a cocaine abuse therapeutic agent, however, would require compliance with repeated administration. To obviate that

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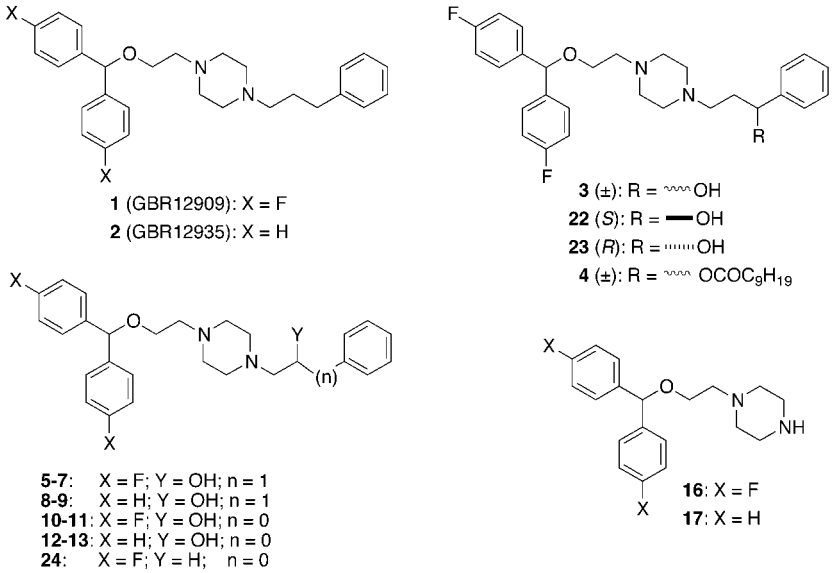
Chart 1



necessity, we have synthesized compounds containing an aliphatic alcohol that, on conversion to a long-chain ester and subsequent formulation in an oily vehicle, provided a prodrug with a relatively long half-life. This approach has been used[25] for potential cocaine-abuse therapeutic agents and has, as well, been successfully employed in the treatment of neuroleptic disorders.[26]

Lewis et al.[25] found that a racemic *N*-3-hydroxyl-3-phenyl analogue of **1** (**3**) (Chart 1) exhibited a pharmacological profile[25] similar to that of **1**. When formulated as a depot preparation (**4**), a single injection decreased cocaine-maintained responding in monkeys more than 80% within several days of the injection while food-maintained responding was unaffected. This selective effect lasted for nearly a month.[27]

With these promising results in mind, we synthesized other hydroxylated analogues (**5**−**15**) and phenethyl analogue **24**, and now, we report their binding affinities for DAT and SERT (Table 1) in comparison with **1**−**3**,[25] **22**,[25] and **23**[25] (the enantiomers of **3**; Chart 1). Compounds **6**−**13** are optically active. These, if amenable for use in a depot preparation, could eliminate problems attributable to side effects that might occur with a racemate. We further examined the most promising compounds **6** and **7** by in vivo microdialysis assays and in the inhibition of cocaine self-administration in rhesus monkeys, in comparison with **1**.

Chemistry

The monosubstituted piperazines, 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]piperazine (**16**) and 1-[2-(diphenylmethoxy)ethyl]piperazine (**17**) were synthesized in two steps according to the literature,[23] with modification. The racemic 2-hydroxylated **1** analogue, **5**, was prepared in high yield (Table 2) by heating (2,3-epoxypropyl)-benzene with **16** in *N*,*N*-dimethylformamide (DMF; Scheme 1). Initially, **5** was successfully transformed to its MTPA ester,[28] but the effort to separate the diastereomers failed. Thus, we decided to directly synthesize the optically pure hydroxyl-containing derivatives using chiral synthons.

Table 1. Binding Affinities ($K_i \pm$ SD)[a] at the DAT and SERT and K_i Ratios of Hydroxylated Analogues of **1** and **2**

	binding affinity, K_i (nM)		
no.	DAT	SERT	SERT/DAT ratio
1	3.7 ± 0.4	130 ± 5	35
2	3.7 ± 0.3	620 ± 13	168
3 (±)	2.1 ± 0.05	120 ± 7	57
5 (±)	2.3 ± 0.08	120 ± 4	52
6 (*S*)	0.75 ± 0.03	230 ± 7	307
7 (*R*)	12 ± 0.3	160 ± 4	13
8 (*S*)	2.3 ± 0.07	2160 ± 80	939
9 (*R*)	25 ± 0.7	1800 ± 90	72
10 (*S*)	11 ± 1	77 ± 2	7
11 (*R*)	26 ± 0.9	13 ± 1	0.5
12 (*S*)	30 ± 2	1400 ± 34	47
13 (*R*)	170 ± 20	330 ± 23	2
14 (±)	48 ± 3	2500 ± 50	52
15 (±)	120 ± 7	3800 ± 95	32
22 (*S*)	4.4 ± 0.5	135 ± 5	31
23 (*R*)	3.0 ± 0.3	85 ± 3	28
24	8.0 ± 0.4	36 ± 2	5

[a] The K_i values of the test ligands were determined in the above assays as described in the Biological Methods.

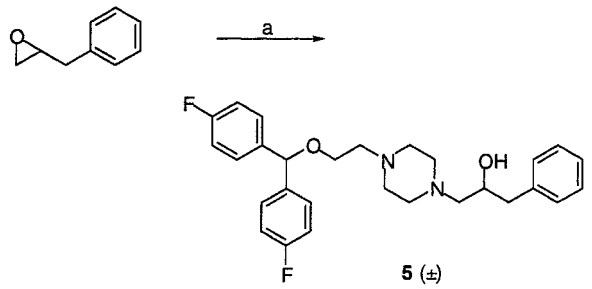
(*S*)-(+)-1-Chloro-3-phenylpropan-2-ol (**18**) and (*R*)-(−)-1-chloro-3-phenylpropan-2-ol[29] (**19**) were prepared via regioselective epoxide ring-opening by phenyllithium, using BF_3−OEt_2 as the activator, at −78 °C in tetrahydrofuran (THF). Piperazines **16** and **17** were alkylated with **18** or **19** at 60 °C in DMF, using diisopropylethylamine (DIPEA) and NaI, to afford the desired products **6** or **7** and **8** or **9**, respectively (Scheme 2). The enantiomeric excess (ee) values of chiral compounds **6**−**9** were determined by F^{19}-NMR (nuclear magnetic resonance) spectra of the corresponding MTPA esters, and all of them were above 99%.

N-Alkylation of **16** and **17** with (*S*)-(+)-2-chloro-1-phenylethanol (**20**) or (*R*)-(−)-2-chloro-1-phenylethanol (**21**), using the same reaction conditions as above (DIPEA and NaI in DMF at 60 °C), afforded **10** and **12** and **11** and **13**, respectively, in modest yields (Scheme 3). However, a significant amount of isomeric byproducts **14** or **15** were produced and isolated in this

Table 2. Physical Properties

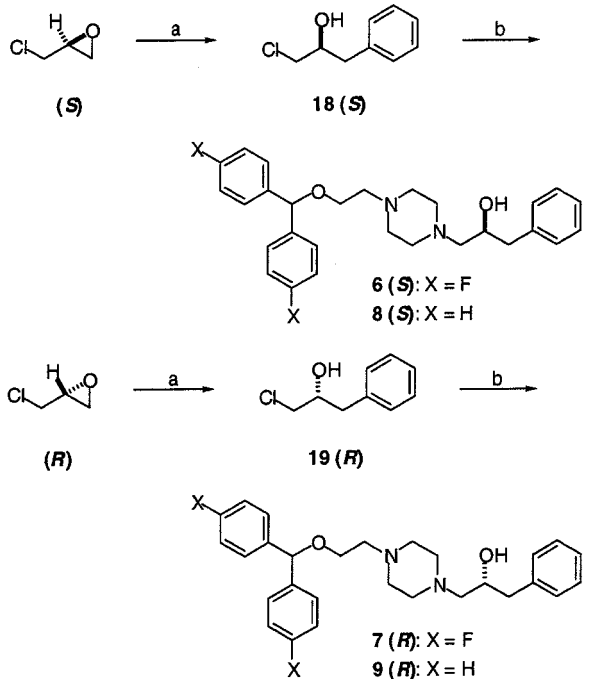
cmpd	empirical formula	mp (°C)	$[\alpha]_D^{20}$ (deg) (solvent)	yield (%)
5 (±)	$C_{28}H_{32}F_2N_2O_2{\cdot}2C_4H_4O_4$	171−172		95
6 (*S*)	$C_{28}H_{32}F_2N_2O_2{\cdot}2C_4H_4O_4$	171−172	+6.5 (CH_3OH)	79
7 (*R*)	$C_{28}H_{32}F_2N_2O_2{\cdot}2C_4H_4O_4$	168−169	−6.2 (CH_3OH)	83
8 (*S*)	$C_{28}H_{34}N_2O_2{\cdot}2C_4H_4O_4$	174−175	+8.1 (CH_3OH)	80
9 (*R*)	$C_{28}H_{34}N_2O_2{\cdot}2C_4H_4O_4$	173.5−174.5	−7.0 (CH_3OH)	78
10 (*S*)	$C_{27}H_{30}F_2N_2O_2{\cdot}2C_4H_4O_4$	182−183	+12.9 (DMF)	44
11 (*R*)	$C_{27}H_{30}F_2N_2O_2{\cdot}2C_4H_4O_4$	182−183	−11.8 (DMF)	44
12 (*S*)	$C_{27}H_{32}N_2O_2{\cdot}2C_4H_4O_4$	181−182	+12.9 (DMF)	33
13 (*R*)	$C_{27}H_{32}N_2O_2{\cdot}2C_4H_4O_4$	184−185	−13.1 (DMF)	33
14 (±)	$C_{27}H_{30}F_2N_2O_2{\cdot}2C_4H_4O_4$	145−146		38 (from **20**), 30 (from **21**)
15 (±)	$C_{27}H_{32}N_2O_2{\cdot}2C_4H_4O_4$	147−149		16 (from **20**), 27 (from **21**)
24	$C_{27}H_{30}F_2N_2O{\cdot}2C_4H_4O_4$	192−193		95

Scheme 1[a]



[a] Reagents and conditions: **16**, DMF, 60 °C.

Scheme 2[a]



[a] Reagents and conditions: (a) PhLi, $BF_3{-}OEt_2$, THF, −78 °C. (b) **16** or **17**, *N*,*N*-diisopropylethylamine, NaI, DMF, 60 °C.

coupling reaction. The ee values of the desired products **10**−**13** were determined by chiral high-performance liquid chromatography (HPLC), and all were higher than 98%. Interestingly, when the crude compounds **14** and **15** were analyzed using the same HPLC conditions, only slight ee (10−20%) was found, due to the substantial racemization that occurred in the reaction. Recrystallization of the maleate salts of **14** and **15** provided pure, optically inactive, racemates. A possible mechanism for the racemization (Chart 2) involves an intermediate **I**, readily formed by a fast iodide−chloride ion-exchange reaction. Base-catalyzed elimination could afford intermediate **II**. Nucleophilic epoxide ring-opening at the less-hindered position could give chiral product **III**, whereas nucleophilic epoxide ring-opening at the benzylic position by the iodide ion, followed by an S_N2 reaction, would be likely to produce chiral product **V**. Although most of the hydrogen chloride (or iodide) in situ was neutralized by DIPEA, a trace amount of free acid (protons) would be enough to catalyze epoxide ring-opening at the benzylic position to form the intermediate **VI**. The addition of the nucleophile to intermediate **VI** could produce a racemate (**V** + **VII**). If this mechanism pertains, **III** should possess a high ee value, but the isomeric products **V** and **VII** could only exist as enantiomeric mixtures with a low ee value.

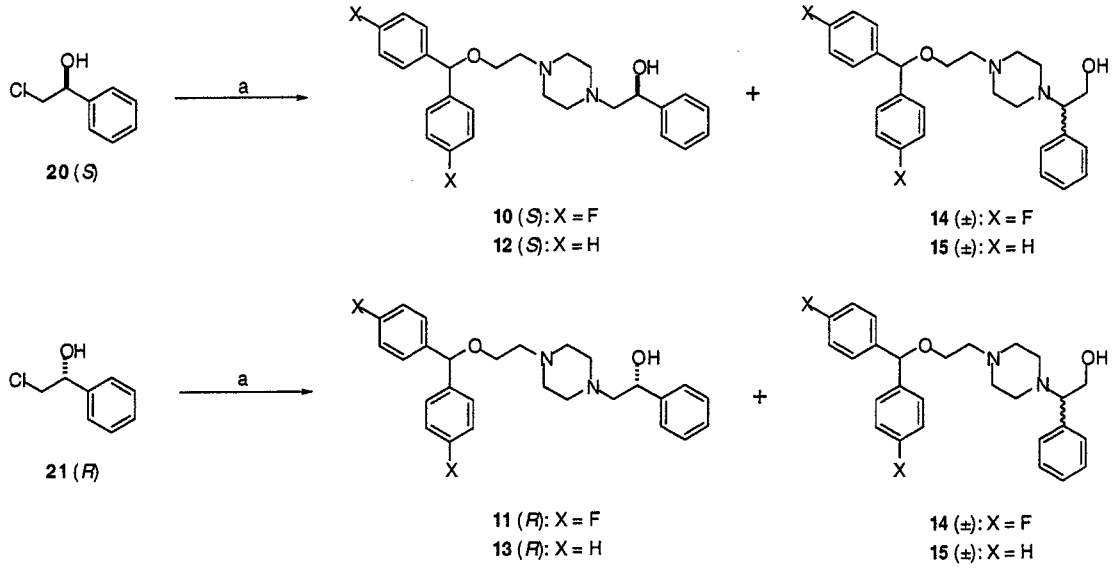
Pharmacology

In previous papers, we determined both the DA and the 5-HT transporter binding K_i values and the K_i values of test agents for the inhibition of [^{3}H]DA and [^{3}H]5-HT reuptake. One reason for doing so was to identify agents with high binding affinity and low potency in the functional assay. Such agents might, for example, act as cocaine antagonists without inhibiting [^{3}H]DA uptake. However, our experience demonstrated that compounds with high uptake binding ratios actually have ratio values of about 1 when the binding assay is conducted under uptake conditions.[30,31] In light of these data, we no longer determine reuptake K_i values.

In a recent study,[25] the benzylic hydroxyl analogues, **3**, **22**, and **23**, were found to be similar to **1** in binding affinities for the DAT and SERT (Table 1). Furthermore, there was no significant difference between the pharmacological profiles of the two enantiomers **22** and **23** and the racemate **3**, both in vitro and in vivo. In this study, the racemic 2-hydroxylated analogue **5** also displayed about the same DAT and SERT binding affinities as those of **1**, **3**, **22**, and **23** (Table 1). However, an evaluation of enantiomers **6** and **7** in our novel series of chiral hydroxylated analogues of **1** showed a quite different structure−activity relationship (SAR).

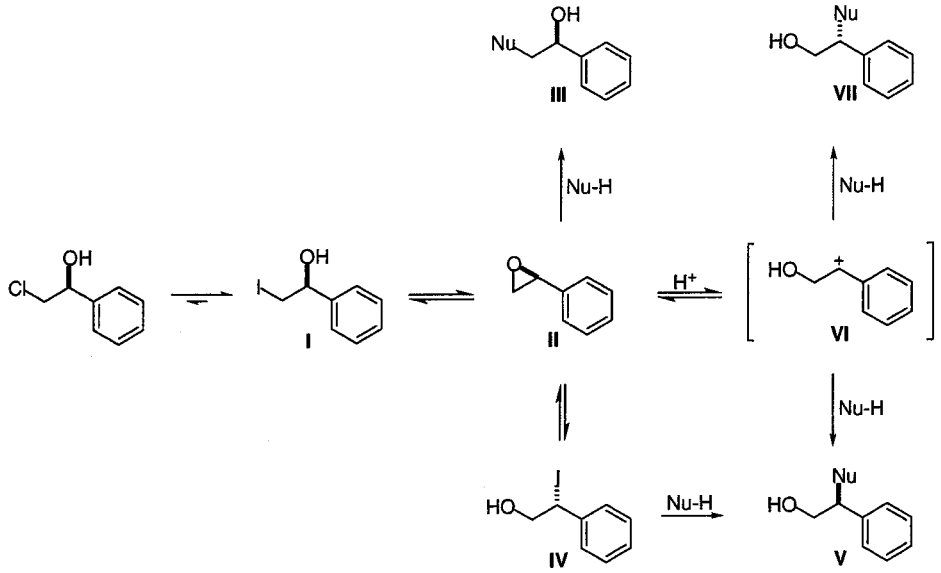
In contrast to the benzylic-hydroxylated analogues **22**[25] and **23**,[25] the 2-hydroxylated enantiomers **6** and **7** showed significant enantioselectivity in binding affinity (DAT and SERT). Analogue **6** had a subnanomolar binding affinity to DAT (K_i = 0.75 nM) and a higher affinity than **1** and enantiomer **7** (5- and 16-fold, respectively). The enantiomer **7** was more potent in

Scheme 3[a]



[a] Reagents and conditions: **16** or **17**, *N*,*N*-diisopropylethylamine, NaI, DMF, 60 °C.

Chart 2



SERT binding than **6**. Analogue **6** is much more selective than **1** and **7** in DAT binding.

We have noted that bis-4-fluorophenyl analogues (e.g., **1**) generally displayed higher affinity, but less selectivity, to the DAT than the comparable diphenyl analogues (e.g., **2**).[30] To see whether this pattern of affinity and selectivity was also true with the chiral hydroxylated derivatives, we introduced a 2-hydroxyl substituent in **2** to afford **8** and **9**. The *S* isomer **8** displayed a higher affinity and selectivity for the DAT, while the *R* isomer **9** showed a slightly higher affinity for the SERT. These diphenyl ligands, **8** and **9**, had a little less affinity for DAT and much less affinity for SERT than the corresponding bis-4-fluorophenyl analogues **6** and **7**; thus, they were considerably more selective in binding to the DAT. Analogue **8** is one of the most selective ligands known in binding to the DAT.

When we examined the structural differences between the benzylic hydroxyl ligands[25] **3**, **22**, and **23** (Chart 1) and the 2-hydroxyl ligands **6** and **7**, the distances between three functional groups (i.e., the phenyl group, the hydroxyl substituent, and the nitrogen atom (N_1) in the piperazine ring) appeared to be most significant. In ligands **3**, **22**, and **23**, the hydroxyl group is separated from the phenyl group and N_1 by one- and three-carbon atoms, respectively, whereas in ligands **6** and **7** the hydroxyl group is separated from both the phenyl group and the N_1 by two-carbon atoms. To further evaluate some of the factors that might be responsible for this dramatic change in the SAR, we evaluated the pharmacological properties of additional derivatives. We replaced the phenylpropyl group in **1** and **6**−**9** with a phenylethyl group to afford the analogues **10**−**13** and **24**.[23] The DAT and SERT binding affinities of **24**[23] have not been previously published. In these compounds, the hydroxyl group is separated from the phenyl group by a one-carbon unit (as in **3**, **22**, and **23**) and separated from N_1 by a two-carbon unit (as in **5**−**7**).

Phenethyl analogue **24** showed a slightly decreased DAT binding affinity, a substantially increased SERT

binding affinity, and therefore a much lower selectivity for DAT binding vs SERT binding than the parent compound **1**. All of the 2-hydroxyl substituted phenylethyl analogues, **10**−**13**, were less potent in binding to the DAT and more potent in SERT binding as compared to the corresponding phenylpropyl analogues (**6**−**9**). As a result, they all demonstrated lower selectivity for DAT binding vs SERT binding. Furthermore, these phenylethyl ligands also displayed the same enantioselectivity as their corresponding phenylpropyl analogues: (i) the *S* isomer is more potent and selective in DAT binding affinity than the *R* isomer; (ii) the *R* isomer has a higher affinity for SERT than the *S* isomer. Thus, a 2-hydroxyl substituent is an important structural element for enantioselective binding to the DAT and SERT.

The presence of a 2*R*-hydroxyl group, a bis-4-fluorophenyl substituent, and a phenylethyl, instead of a phenylpropyl chain, appear to be factors that induce an increase in the SERT binding affinity. Thus, **11**, which contains all three of these factors, was found to be the only SERT selective ligand in this hydroxylated analogue series. Ligands **14** and **15**, which are racemic 1-phenyl substituted isomers of **10**−**13**, showed interesting binding profiles. They retained the DAT binding affinity of the 2-phenyl substituted isomers (i.e., **10**−**13**), but the binding affinity to the SERT decreased significantly. However, these binding data were determined using racemic samples; the possibility that the two enantiomers possess substantially different selectivities could not be ruled out.

Microdialysis

To evaluate the DA reuptake inhibition properties of **6** and **7** in vivo, extracellular dopamine (ECDA) levels were determined in rat nucleus accumbens using a microdialysis assay in conscious, freely moving animals.[32] Baseline dialysate DA levels were 1.73 pg/5 μL sample (1.89 nM) and did not differ across treatment groups (total $n = 36$ rats). After various doses of **6** were administered, a 2−5-fold increase in the ECDA levels was observed, similar to that found with **1** (Figure 1). In accord with in vitro data, enantiomer **7** showed lower potency than enantiomer **6** and **1**. The ECDA level increased 2-fold above baseline after a 3 mg/kg dose of **7** was administered, whereas a 1 mg/kg dose of **6** or **1** produced the same effect. Furthermore, because **6** and **1** showed similar pharmacological profiles (i.e., slow onset, long-acting, and low efficacy on DAT reuptake inhibition) and since the enantiomer might avoid the side effects sometimes seen in racemates, **6** may be a potential cocaine abuse therapeutic agent with low abuse liability, which increases DA neurotransmission to prevent withdrawal.

Behavioral Effects

The two enantiomers **6** and **7** and the reference compound **1** were also tested for behavioral effects that influenced food- and cocaine-maintained responding in rhesus monkeys. These compounds all decreased cocaine-maintained responding to a greater extent than food-maintained responding, and none of them significantly increased responding during the fixed interval (FI) components. The effects of different doses of **1**, **6**, and **7** relative to the effects of vehicle pretreatment on cocaine-maintained responding are shown in Figure 2. Each drug dose dependently decreased cocaine-maintained responding to a different extent. Among these ligands, **6** was the most potent, whereas **7** was the least effective in this behavioral test. Reference compound **1** displayed an intermediate potency between those of the enantiomers **6** and **7** in this in vivo model.

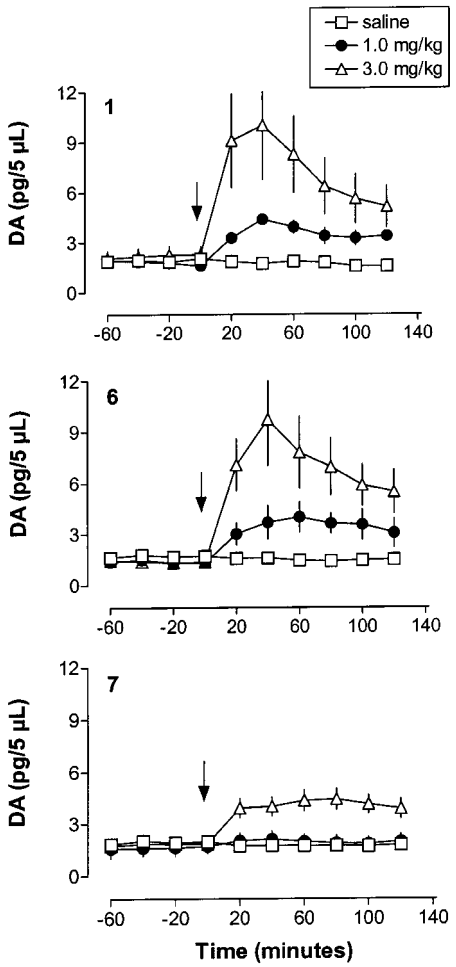


Figure 1. Effects of compound **1** and its hydroxylated enantiomers (**6** and **7**) on extracellular DA levels in rat nucleus accumbens. Rats received single iv doses of the drug or saline vehicle at time zero. Dialysate samples were collected at 20 min intervals and assayed for DA using HPLC-EC. Data are pg/5 μL sample expressed as the mean ± SEM for $N = 4$−5 rats/group.

The greater potency of **6** in the behavioral assay and the in vivo enantioselectivity of **6** and **7** were consistent with their affinities for the DAT and their different potencies in increasing the ECDA level. These results are in accord with the idea that high affinity ligands for DAT effectively reduce cocaine-maintained responding.

Conclusions

The 2-hydroxylated analogues showed a quite different SAR from the benzylic hydroxylated analogues. The enantiomers of 2-hydroxyl substituted ligands displayed substantial enantioselectivity in their binding affinity to the DAT and SERT and in inhibiting the reuptake of DA and 5-HT. The *S* enantiomers were more potent

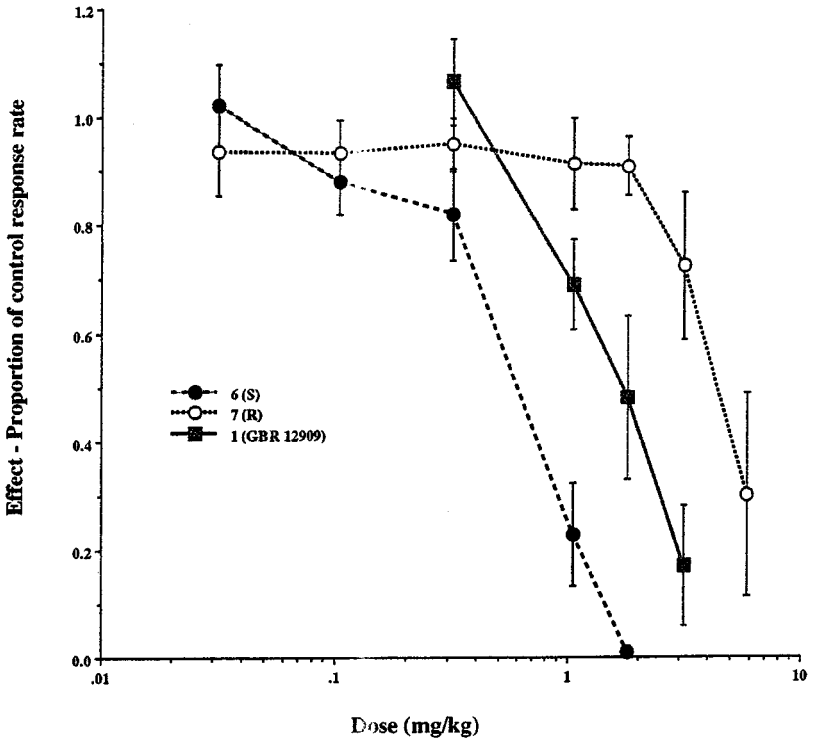


Figure 2. Behavioral effect of **6**, **7**, and **1** at various dose levels, relative to vehicle pretreatment, on cocaine-maintained responding in rhesus monkeys.

and selective in DAT binding affinity than the corresponding *R* enantiomers; the latter were more potent in SERT binding.

The bis-4-fluorophenyl analogues displayed greater affinity in binding to the DAT, while the diphenyl analogues were more selective for binding to the DAT. The length of the alkyl chain between the phenyl group and the N_1 on the piperazine ring significantly influenced DAT and SERT binding affinity and binding selectivity for the DAT vs SERT. The *N*-phenylethyl ligands were more potent for binding to the SERT and less potent for binding to the DAT and, thus, had lower DAT selectivity than the corresponding *N*-phenylpropyl analogues. The two-carbon atom distance between the hydroxyl group and the N_1 appears to be essential for enantioselectivity, whereas the distance between the phenyl group and the N_1 had little or no effect on the enantioselectivity of the *R* and *S* enantiomers.

Analogue **6** displayed the highest affinity, and **8** possessed the highest selectivity for binding to the DAT. They are among the most potent and selective ligands that have been found in these assays. As noted, they also displayed substantial enantioselectivity in the microdialysis assay and in behavioral experiments, and **6** always showed greater potency than **7**. These data exemplify the importance of synthesizing and studying the pharmacological activities of chiral compounds. Compound **5**, the racemic relative of **6**, showed only a little higher affinity and was not much more selective for DAT than **1** (Table 1).

The high affinity and selectivity for DAT binding and the promising results from in vivo biological data indicate that **6** and **8** are potential candidates for the development of cocaine abuse therapeutic agents. Furthermore, because they bear a hydroxyl substituent, **6** and **8** may be converted to oil soluble prodrugs by esterification and then formulated as extended release dosage forms.

Experimental Section

Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA, and were within ±0.4% for the elements indicated. Except where noted, all of the mass spectra (chemical ionization) were obtained using a Finnigan 1015 mass spectrometer. High-resolution mass spectroscopy measurements (HRMS) were obtained using a V. G. Micro Mass 7070F mass spectrometer. Optical rotations were obtained using a Perkin-Elmer 341 polarimeter and are reported at the sodium D-line (589 nm), unless otherwise noted. ^{1}H NMR spectra of the free bases were recorded in $CDCl_3$ using a Varian XL-300 spectrometer. ^{19}F NMR spectra were utilized in determination of ee in chiral compounds and were determined at 282 MHz in $CDCl_3$ using a Varian XL-300 spectrometer. Chemical shifts are expressed in parts per million (ppm) on the δ scale relative to a tetramethylsilane (TMS) internal standard. Thin-layer chromatography (TLC) was performed on 250 μm Analtech GHLF silica gel plates and visualized under UV light (254 nm), upon treatment with iodine vapor or upon heating after treatment with 5% phosphomolybdic acid in ethanol. Flash column chromatography was performed with Fluka 40-63 μm silica gel 60. No attempt was made to optimize yields. The (*S*)-(+)-2-chloro-1-phenylethanol and (*R*)-(−)-2-chloro-1-phenylethanol were purchased from the Aldrich Chemical Co., Milwaukee, WI.

General Procedures for the Determination of ee of Hydroxyl-Containing Derivatives: Mosher Ester Analysis. The Mosher ester derivatives of the hydroxylated analogues of **1** and **2** were prepared according to the literature method[28] with modification. To a solution of the alcohol (20 mg) and triethylamine (0.2 mL) in CH_2Cl_2 (3 mL) were added DMAP (20 mg) and (*R*)-(−)-MTPA-Cl (30 μL). The reaction mixture was stirred at room temperature and monitored by TLC, ensuring complete reaction before quenching with 3-(dimethylamino)propylamine (0.2 mL). After the solution was stirred for another 15 min, silica gel was added and the solvent

was evaporated. The residue was loaded onto a short column of silica gel and eluted with 50−100% EtOAc in *n*-hexane to afford the Mosher ester as a pale yellow solid. The diastereomeric excess was then determined by ^{19}F or ^{1}H NMR.

Chiral HPLC Analysis. The free base of the sample was dissolved in 1% 2-propanol (IPA) in *n*-hexane. Then, the sample solution (10 μL) was eluted using 1−10% IPA in *n*-hexane as mobile phase on the CHIRALCEL OD column (250 mm × 4 mm, DAICEL). The ee values were calculated based on the UV absorption (254 nM) areas of the two enantiomers.

General Procedure for the Conversion of the Free Bases to the Corresponding Bis-maleate Salts. Maleic acid (6.6 mmol) was added to a boiling solution of the free base (3 mmol) in MeOH (30−40 mL). After the solution was cooled to room temperature, a white crystalline solid formed and precipitated. The crystals were collected by filtration and washed with cold MeOH. The product was dried in a vacuum oven (1 mm Hg, 45−50 °C, 12 h) to afford the desired bis-maleate salts. The salts were further purified by recrystallization with MeOH if necessary.

(±)-1-[4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]piperazinyl]-3-phenylpropan-2-ol (5). A solution of **16** (4.63 g, 13.9 mmol) and (2,3-epoxypropyl)benzene (1.87 g, 13.9 mmol) in DMF (30 mL) was heated at 60 °C for 48 h. The reaction mixture was quenched with water and extracted with ether, and then, the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and evaporated. The residue was chromatographed (silica gel, 5% MeOH in CH_2Cl_2) to afford **5** (6.17 g, 95%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22−7.32 (m, 9H), 6.97−7.03 (m, 4H), 5.32 (s, 1H), 3.87−3.96 (m, 1H), 3.55 (t, J = 5.9 Hz, 2H), 2.81 (dd, J = 13.7, 6.8 Hz, 1H), 2.31−2.70 (m, 14H). MS: *m/z* 467 (MH$^+$). Anal. **5**·2 maleate ($C_{28}H_{32}F_2N_2O_2{\cdot}2C_4H_4O_4$) C, H, N.

General Procedure for the Synthesis of 2-Hydroxylated Analogues of 1 and 2. (*S*)-(+)-1-[4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]piperazinyl]-3-phenylpropan-2-ol (6). A mixture of **16** (4.00 g, 12.0 mmol), **18** (3.00 g, 17.6 mmol), NaI (3.60 g, 24.0 mmol), and *N*-ethyldiisopropylamine (6.30 mL, 36.0 mmol) in DMF (25 mL) was stirred at 65 °C under argon for 48 h. The reaction was quenched with water, and then, the resulting mixture was extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and evaporated. The oily residue was chromatographed (silica gel, 4% MeOH in CH_2Cl_2) to afford **6** (4.45 g, 79%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22−7.32 (m, 9H), 6.97−7.03 (m, 4H), 5.32 (s, 1H), 3.87−3.96 (m, 1H), 3.55 (t, J = 5.9 Hz, 2H), 2.81 (dd, J = 13.7, 6.8 Hz, 1H), 2.31−2.70 (m, 14H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.8, 160.5, 138.3, 137.8, 129.3, 128.5, 128.4, 126.3, 115.4, 115.1, 82.4, 67.1, 66.7, 63.3, 57.6, 53.6, 53.0, 41.2. MS: *m/z* 467 (MH$^+$). Anal. **6**·2 maleate ($C_{28}H_{32}F_2N_2O_2{\cdot}2C_4H_4O_4$) C, H, N.

(*R*)-(−)-1-[4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]piperazinyl]-3-phenylpropan-2-ol (7). Compound **7** was synthesized using **16** and **19** according to the general procedure and yielded an oil. MS: *m/z* 467 (MH$^+$). Anal. **7**·2 maleate ($C_{28}H_{32}F_2N_2O_2{\cdot}2C_4H_4O_4$) C, H, N.

(*S*)-(+)-1-[4-[2-(Diphenylmethoxy)ethyl]piperazinyl]-3-phenylpropan-2-ol (8). Compound **8** was synthesized using **17** and **18** according to the general procedure and yielded a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22−7.35 (m, 15H), 5.36 (s, 1H), 3.87−3.96 (m, 1H), 3.58 (t, J = 5.9 Hz, 2H), 2.27−2.85 (m, 15H). MS: *m/z* 431 (MH$^+$). Anal. **8**·2 maleate ($C_{28}H_{34}N_2O_2{\cdot}2C_4H_4O_4$) C, H, N.

(*R*)-(−)-1-[4-[2-(Diphenylmethoxy)ethyl]piperazinyl]-3-phenylpropan-2-ol (9). Compound **9** was synthesized using **17** and **19** according to the general procedure and yielded a colorless oil. MS: *m/z* 431 (MH$^+$). Anal. **9**·2 maleate ($C_{28}H_{34}N_2O_2{\cdot}2C_4H_4O_4$) C, H, N.

(*S*)-(+)-2-[4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]piperazinyl]-1-phenylethan-1-ol (10) and (±)-2-[4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]piperazinyl]-2-phenylethan-1-ol (14). Compounds **10** and **14** were synthesized using **16** and (*S*)-2-chloro-1-phenylethanol according to the general procedure and yielded colorless oils. **10**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27−7.39 (m, 9H), 6.99−7.04 (m, 4H), 5.35 (s, 1H), 4.73 (dd, J = 9.7, 4.9 Hz, 1H), 3.57 (t, J = 5.9 Hz, 2H), 2.43−2.78 (m, 13H). MS: *m/z* 453 (MH$^+$). Anal. **10**·2 maleate ($C_{27}H_{30}F_2N_2O_2{\cdot}2C_4H_4O_4$) C, H, N. **14**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17−7.36 (m, 9H), 6.95−7.04 (m, 4H), 5.28 (s, 1H), 3.93−4.00 (m, 1H), 3.63−3.70 (m, 2H), 3.50 (t, J = 5.9 Hz, 2H), 2.62 (t, J = 5.9 Hz, 2H), 2.39−2.58 (m, 9H). MS (CI): *m/z* 453 (MH$^+$). Anal. **14**·2 maleate ($C_{27}H_{30}F_2N_2O_2{\cdot}2C_4H_4O_4$) C, H, N.

(*R*)-(−)-2-[4-[2-[Bis(4-fluorophenyl)methoxy]ethyl]piperazinyl]-1-phenylethan-1-ol (11) and 14. Compounds **11** and **14** were obtained using **16** and (*R*)-2-chloro-1-phenylethanol according to the general procedure and yielded colorless oils. **11**: MS: *m/z* 453 (MH$^+$). Anal. **11**·2 maleate ($C_{27}H_{30}F_2N_2O_2{\cdot}2C_4H_4O_4$) C, H, N.

(*S*)-(+)-2-[4-[2-(Diphenylmethoxy)ethyl]piperazinyl]-1-phenylethan-1-ol (12) and (±)-2-[4-[2-(Diphenylmethoxy)ethyl]piperazinyl]-2-phenylethan-1-ol (15). Compounds **12** and **15** were synthesized using **17** and (*S*)-2-chloro-1-phenylethanol according to the general procedure and yielded colorless oils. **12**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24−7.38 (m, 15H), 5.38 (s, 1H), 4.72 (dd, J = 10.3, 4.4 Hz, 1H), 3.61 (t, J = 5.9 Hz, 2H), 2.42−2.75 (m, 13H). MS: *m/z* 417 (MH$^+$). Anal. **12**·2 maleate ($C_{27}H_{32}N_2O_2{\cdot}2C_4H_4O_4$) C, H, N. **15**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16−7.33 (m, 15H), 5.32 (s, 1H), 3.91−3.99 (m, 1H), 3.61−3.70 (m, 2H), 3.54 (t, J = 5.9 Hz, 2H), 2.63 (t, J = 5.9 Hz, 2H), 2.46−2.59 (m, 8H), 2.37 (broad s, 1H). MS: *m/z* 417 (MH$^+$). Anal. **15**·2 maleate ($C_{27}H_{32}N_2O_2{\cdot}2C_4H_4O_4$) C, H, N.

(*R*)-(−)-2-[4-[2-(Diphenylmethoxy)ethyl]piperazinyl]-1-phenylethan-1-ol (13) and 15. Compounds **13** and **15** were prepared using **17** and (*R*)-2-chloro-1-phenylethanol according to the general procedure and yielded colorless oils. **13**: MS: *m/z* 417 (MH$^+$). Anal. **13**·2 maleate ($C_{27}H_{32}N_2O_2{\cdot}2C_4H_4O_4$) C, H, N.

(*S*)-1-Chloro-3-phenylpropan-2-ol (18). To a solution of $BF_3{\cdot}OEt_2$ (22.8 mL, 180 mmol) in THF (140 mL) at −78 °C was added dropwise phenyllithium (1.8 M in cyclohexanes−ether, 100 mL, 180 mmol), followed by a solution of (*S*)-(+)-epichlorohydrin (97% ee, 4.7 mL, 60 mmol) in THF (20 mL). After the solution was stirred for 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (100 mL), allowed to warm to room temperature, and evaporated under reduced pressure. The aqueous residue was extracted with ether (200 mL × 2), and then, the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and evaporated. The crude product was purified by flash column chromatography (silica gel, 15% EtOAc in *n*-hexane) to afford **18** (7.96 g, 78%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21−7.34 (m, 5H), 4.02 (m, 1H), 3.58 (dd, J = 11.2, 3.9 Hz, 1H), 3.47 (dd, J = 11.2, 5.8 Hz, 1H), 2.86 (d, J = 6.6 Hz, 2H), 2.40 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.1, 129.4, 128.7, 126.8, 72.1, 49.0, 40.4. HRMS *m/z* calcd for $C_9H_{11}ClO^+$, 170.0498; found, 170.0494. 188 (M + NH_4^+); $[\alpha]^{20}_D$ +3.6° (c = 0.56, $CHCl_3$).

(*R*)-1-Chloro-3-phenylpropan-2-ol (19).[29] Compound **19** was synthesized from (*R*)-(−)-epichlorohydrin as described above to afford **19** in 72% yield as a colorless oil: $[\alpha]^{20}_D$ −3.7° (c = 0.52, $CHCl_3$).

1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(2-phenylethyl)piperazine (24). Compound **24** was synthesized and converted to a dimaleate salt. It was previously prepared as the dihydrochloride salt, mp 207−8 °C.[23] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20−7.30 (m, 9H), 6.98−7.04 (m, 4H), 5.34 (s, 1H), 3.58 (t, J = 5.9 Hz, 2H), 2.79−2.84 (m, 2H), 2.69 (t, J = 5.9 Hz, 2H), 2.50−2.64 (m, 10H). MS: *m/z* 437 (MH$^+$). Anal. **24**·2 maleate ($C_{27}H_{30}F_2N_2O{\cdot}2C_4H_4O_4$) C, H, N.

Biological Methods: Binding Assay. Binding assays for the DAT and SERT followed published procedures[33] and used 0.01 nM [^{125}I]RTI-55[34] (s.a. = 2200 Ci/mmol). Briefly, 12 mm × 75 mm polystyrene test tubes were prefilled with 100 μL of drugs, 100 μL of radioligand ([^{125}I]RTI-55), and 50 μL of a "blocker" or buffer. Drugs and blockers were made up in 55.2 mM sodium phosphate buffer, pH 7.4 (BB), containing 1 mg/

mL bovine serum albumin (BB/BSA). Radioligands were made up in a protease inhibitor cocktail containing 1 mg/mL BSA [BB containing chymostatin (25 μg/mL), leupeptin (25 μg/mL), ethylenediaminetetraacetic acid (100 μM), and EGTA (100 μM)]. The samples were incubated in triplicate for 18−24 h at 4 °C (equilibrium) in a final volume of 1 mL. Brandel cell harvesters were used to filter the samples over Whatman GF/B filters, which were presoaked in wash buffer (ice-cold 10 mM Tris-HCl/150 mM NaCl, pH 7.4) containing 2% poly(ethylenimine).

Microdialysis Assay. Male Sprague−Dawley rats (300−450 g) were obtained from Charles River Laboratories (Wilmington, MA). The animal housing facilities were fully accredited by the American Association of the Accreditation of Laboratory Animal Care, and all experiments were performed according to the guidelines delineated by the Institutional Animal Care and Use Committee of the National Institute on Drug Abuse (NIDA), Intramural Research Program (IRP).

Surgical implantation of indwelling jugular catheters and intra-accumbens guide cannulae was carried out as previously described.[32] Rats were housed individually after surgery and were allowed at least 1 week to recover. On the evening prior to testing, extension tubes were connected to the catheters, and microdialysis probes (2 mm × 0.5 mm exchange surface, CMA/12, CMA/Microdialysis) were inserted into the nucleus accumbens via the guide cannulae. The next morning, dialysate samples were collected at 20 min intervals and immediately assayed for DA using microbore HPLC-EC as described elsewhere.[35] Once three baseline samples were obtained, various doses of **6**, **7**, **1**, or a saline vehicle were administered via the jugular catheter. Dialysate samples were collected every 20 min for 2 h postinjecton. Drug solutions were prepared immediately before use, and doses are expressed as the salt. Data were evaluated by one-way (acute drug treatment) analysis of variance with repeated measures.

Behavioral Methods. Three individually housed, adult male rhesus monkeys (*Macaca mulatta*), weighing between 7.8 and 9.2 kg, served as subjects in these studies. Each monkey was maintained at about 90% of its free-feeding weight to allow the use of food-maintained responding as a control performance. These monkeys had been previously equipped with a chronically indwelling catheter/port system.[36] Experimental sessions were conducted 5 days a week in separate sound- and light-attenuating chambers, in a manner similar to previous reports.[24,27] Lever-pressing was maintained by a multiple chained FI 10 min FR 30 (food) chained FI 10 min FR 30 (cocaine) schedule. The completion of the FI chain component produced the second component of the chain schedule and availability of food or cocaine under an FR schedule. In the FR component, a maximum of 10 reinforcers could be delivered. Each (FI and FR) component of the multiple schedule included a 60 s limited hold (LH) period: in the FI, if no responses occurred within 60 s after 10 min, the stimuli were extinguished and the FR component was started; in the FR component, the availability of that reinforcer was canceled and the ratio requirements and the LH period were reset. Each session was composed of four repetitions of the following sequence: FI 10 min, FR 30 (food), FI 10 min, FI 30 (cocaine). Green lights were illuminated during the food-availability periods, and red lights were illuminated during the cocaine-availability periods. The unit dose of cocaine used as a reinforcer was 5.6 μg/kg/injection throughout the experiment.

The effects of 4−5 doses of compounds **6** and **7** or vehicle (a mixture of distilled water and saline) were examined for five consecutive sessions for each drug. For each drug, the effects of the vehicle were assessed first, and then, an ascending series of doses were tested. The range of doses was chosen to include a dose large enough to decrease responding substantially. The order of drug testing was mixed among the animals, except **1** was always tested last. Doses of each drug or vehicle were infused intravenously over about 15 min starting 30 min prior to the session onset. The dependent measures collected were the average response rates in the food and cocaine components of each session. For each subject, data from the last three sessions for each dose of pretreatment drug or vehicle phase were averaged and represented a stable effect.

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