Oxygenated Analogues of 1-[2-(Diphenylmethoxy)ethyl]- and 1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazines (GBR 12935 and GBR 12909) as Potential Extended-Action Cocaine-Abuse Therapeutic Agents

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An investigation into the preparation of potential extended-release cocaine-abuse therapeutic agents afforded a series of compounds related to 1-[2-(diphenylmethoxy)ethyl]-4-(3-phenylpropyl)piperazine **(1a)** and 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine **(1b)** (GBR 12935 and GBR 12909, respectively), which were designed, synthesized, and evaluated for their ability to bind to the dopamine transporter (DAT) and to inhibit the uptake of [^{3}H]-labeled dopamine (DA). The addition of hydroxy and methoxy substituents to the benzene ring on the phenylpropyl moiety of **1a**−**1d** resulted in a series of potent and selective ligands for the DAT (analogues **5**−**28**). The hydroxyl groups were included to incorporate a medium-chain carboxylic acid ester into the molecules, to form oil-soluble prodrugs, amenable to "depot" injection techniques. The introduction of an oxygen-containing functionality to the propyl side chain provided ketones **29** and **30**, which demonstrated greatly reduced affinity for the DAT and decreased potency in inhibiting the uptake of [^{3}H]DA, and benzylic alcohols **31**−**36**, which were highly potent and selective at binding to the DAT and inhibiting [^{3}H]DA uptake. The enantiomers of **32** (**34** and **36**) were practically identical in biological testing. Compounds **1b**, **32**, **34**, and **36** all demonstrated the ability to decrease cocaine-maintained responding in monkeys without affecting behaviors maintained by food, with **34** and **36** equipotent to each other and both more potent in behavioral tests than the parent compound **1b**. Intramuscular injections of compound **41** (the decanoate ester of racemate **32**) eliminated cocaine-maintained behavior for about a month following one single injection, without affecting food-maintained behavior. The identification of analogues **32**, **34**, and **36**, thus, provides three potential candidates for esterification and formulation as extended-release cocaine-abuse therapeutic agents.

Introduction

Cocaine is one of the most widely abused drugs today.[1−7] In addition to affecting the lives of those who abuse it, it has also had enormous effects on public health worldwide, through the increased spread of infectious diseases[8] (e.g. HIV-1, hepatitis B and C, and drug-resistant tuberculosis[9]), which are transmitted via behavioral practices commonly associated with cocaine abuse. Furthermore, cocaine abusers show an increased incidence of cerebrovascular accident (stroke), myocardial infarction (heart attack), and pulmonary diseases (e.g. pneumonia).[10] Additionally, there is evidence that cocaine abuse plays a part in decreased performance in several neuropsychological (NP) parameters, including attention and concentration, learning and verbal memory, reaction time, visuo-spatial skills, calculating ability, and abstracting ability. These NP decrements seem to last beyond the period of actual cocaine use, in that several NP functions are measurably impaired, after up to 3 months of abstinence from cocaine.[10] Although the estimated potential worldwide production of cocaine declined slightly in 1997, U.S. cocaine abuse seems to have stabilized at a high level from data on price, availability, cocaine-related emergency room episodes, and other indicators. The extent of this abuse is reflected by U.S. Federal seizures of about 100 metric tons of cocaine during 1997, while the abuse of crack cocaine remained high and stable and continued to spread to smaller cities and towns.[11]

Numerous studies have indicated that the reinforcing effects of cocaine are largely mediated by the mesolimbic dopaminergic system according to the dopamine (DA)

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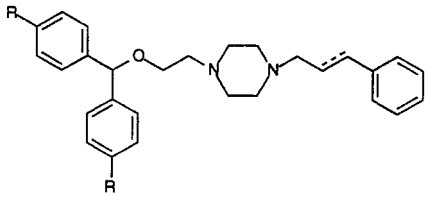
hypothesis of reinforcement.[12] According to this hypothesis, cocaine interacts with a site on the dopamine transporter protein (DAT),[13] lowering DA reuptake into dopaminergic neurons, resulting in increased synaptic DA levels. The resultant elevated synaptic DA levels interact with DA receptors on postsynaptic neurons and result in a variety of clinically observable effects, including reinforcement and locomotor stimulation.[14] Based on these observations, a great deal of emphasis has been directed toward the development of selective and potent DA reuptake inhibitors as putative therapeutic agents for the treatment of cocaine abuse.[15]

However, as reviewed in detail elsewhere,[16] the ability of the DA hypothesis to explain the acute euphoric effects of cocaine in humans is unclear. For example, schizophrenic patients who are on therapeutic doses of antipsychotic medication abuse cocaine and experience cocaine-induced euphoria.[17] Controlled studies in humans also fail to support the DA hypothesis.[18]

Recent studies showed that DAT knockout mice self-administer cocaine[19] and demonstrate cocaine-conditioned place preference,[20] indicating that in the absence of the DAT, cocaine can still establish rewarding effects. Although these data suggest that the DAT is not critical for mediating cocaine reward, the data do not rule out a role for mesolimbic DA as a mediator of cocaine reward. Since DA is a substrate of the norepinephrine (NE) transporter,[21] DA could be accumulated by NE nerves. This has been shown to occur in both the medial frontal cortex[22] and nucleus accumbens, but not in the striatum of rats,[23] which lacks noradrenergic innervation.[24] The inability of cocaine to elevate extracellular DA in the striatum of DAT knockout mice is consistent with the lack of NE transporters in this brain region.[18] Thus, in the absence of the DAT, it is reasonable to assume that some of the extracellular DA in the nucleus accumbens would be accumulated by NE nerves. Since cocaine is a potent inhibitor of the NE transporter,[25] administration of cocaine would block DA accumulation and increase extracellular DA, triggering the cocaine reward. Viewed collectively, these data indicate the need to further test the clinical relevance of the DA hypothesis of cocaine reward. One approach to testing the DA hypothesis is to develop appropriate pharmacological tools such as high-affinity slowly dissociating DAT ligands with low intrinsic activity.[14,26] The DA hypothesis predicts that such an agent would have efficacy in treating cocaine addiction. The present study focuses on developing potential medications for testing the DA hypothesis as opposed to evaluating the clinical relevance of the hypothesis. The medications required for testing the DA hypothesis must have high selectivity for the DAT, and thus there is a need to determine their K_i values at the serotonin transporter protein (SERT) and their serotonin (5-HT) reuptake inhibition.

A variety of structural classes of DA uptake blockers (which bind to the DAT with varying affinities) have been used as templates for the synthesis of potential cocaine-abuse treatment agents, including cocaine analogues,[27] tropanes,[28] benztropines,[29] mazindol,[30] and disubstituted piperazines.[31] Research in this laboratory has focused on the development of novel analogues of the disubstituted piperazines GBR 12935 [1-[2-(diphenylmethoxy)ethyl]-4-(3-phenylpropyl)piperazine **(1a)**] and

Chart 1. Parent Compounds GBR 12935, 12909, 12783, and 13069 (Analogues **1a**−**1d**)



1a R=H, bond = single; GBR 12935
1b R=F, bond = single; GBR 12909
1c R=H, bond = double; GBR 12783
1d R=F, bond = double; GBR 13069

GBR 12909 [1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine **(1b)**] (Chart 1).[32] Tritiated piperazine **1a** is commonly used as a standard radioligand for binding studies involving the DAT,[33] and **1b** has been shown to decrease cocaine-maintained responding in rhesus monkeys without affecting similar responding maintained by food.[34] We have previously demonstrated that modifications in the piperazine ring of **1b** can lead to greatly enhanced affinity and selectivity in binding to the DAT and in the ability to inhibit the uptake of radiolabeled DA.[35] Additionally, modifications in the 3-phenylpropyl moiety of **1a** or **1b** have resulted in another series of potent and selective ligands for the DAT.[36]

The scope of our research and that of others on the development of potential cocaine treatment medications has focused in large part on the development of DAT-selective ligands, which exhibit enhanced selectivity and/or potency for binding to the DAT and for inhibiting the uptake of DA.[37] However, the development of potent and selective DAT ligands suitable for the treatment of cocaine abuse alone is insufficient for a successful drug-abuse treatment agenda. Such an agenda requires strict patient compliance to suppress the extremely potent reinforcing and euphorigenic effects of cocaine. Thus, we have examined methodology designed to address the potential future problem of patient noncompliance and relapse to cocaine abuse.

One approach that has successfully been employed in the treatment of neuroleptic disorders is the use of controlled-release dosage forms of therapeutic agents.[38] The duration of action of a parenterally administered pharmaceutical can be increased by changing the solvent to a nonaqueous medium, such as a fixed oil of vegetable origin (e.g. castor, cottonseed, olive, peanut, or sesame oil), which serves to reduce the release rate into the plasma.[39] The half-life can be increased yet again by the preparation of an oil-soluble prodrug; this can be accomplished by the conversion of an aliphatic alcohol to an ester, using a medium-chain alkanoic acid (e.g. hexanoic, heptanoic, decanoic, cyclopentylpropionic, or phenylpropionic acid).[40] The esterified alcohol is then formulated in an oily vehicle and administered by intramuscular injection, forming a "depot" of the prodrug. The esterified prodrug then diffuses to the surface of the oil droplet, partitions into the aqueous (plasma) phase, and is hydrolyzed to the parent compound, presumably at the interface.[41] This "depot" approach has been used successfully for formulating phenothiazines in the treatment of schizophrenic patients, effecting a much longer duration of clinical action for these antip-

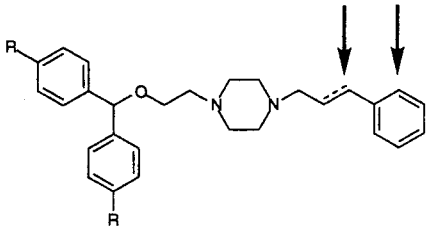


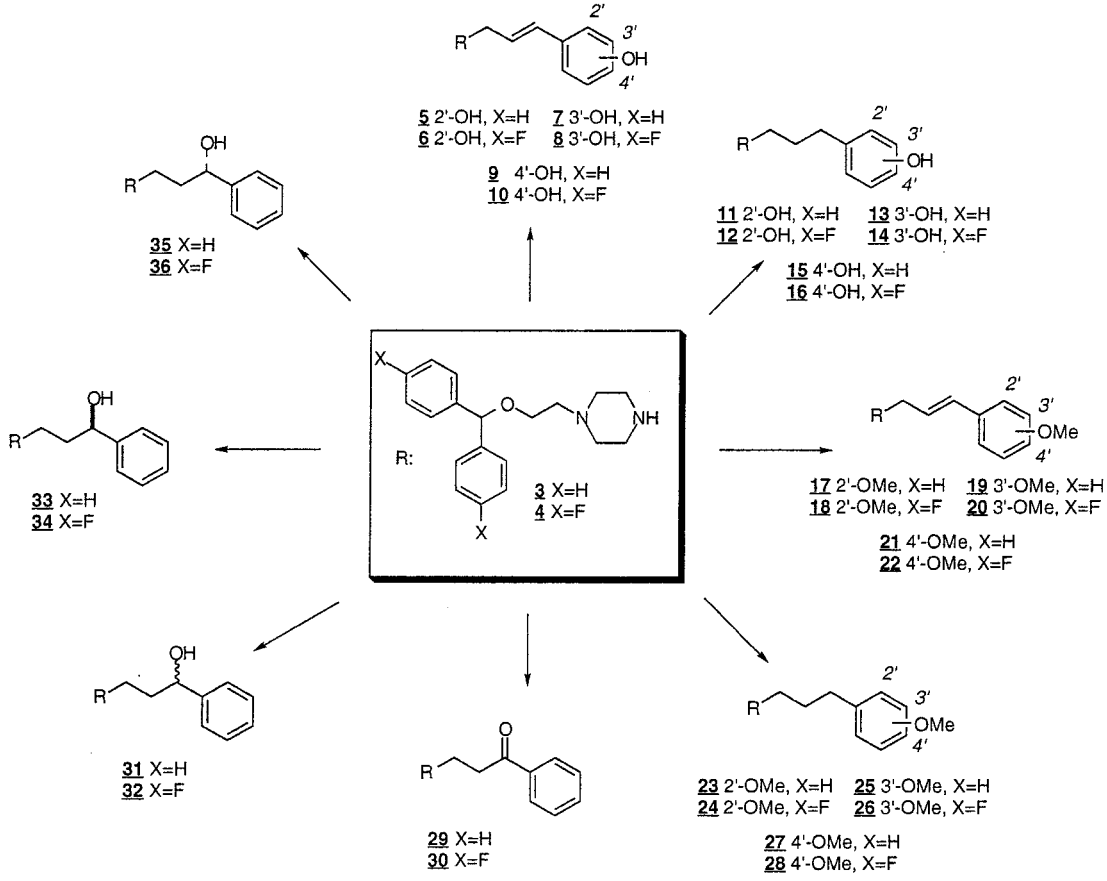
Figure 1. Potential sites for the incorporation of the hydroxyl group.

sychotic drugs and allowing discharge of patients from institutional settings. This methodology has also been used for antipsychotics (haloperidol, fluphenazine, clophenthixol), sex hormones (testosterone, estradiol), and other steroids (nandrolone, methylprednisolone).[42]

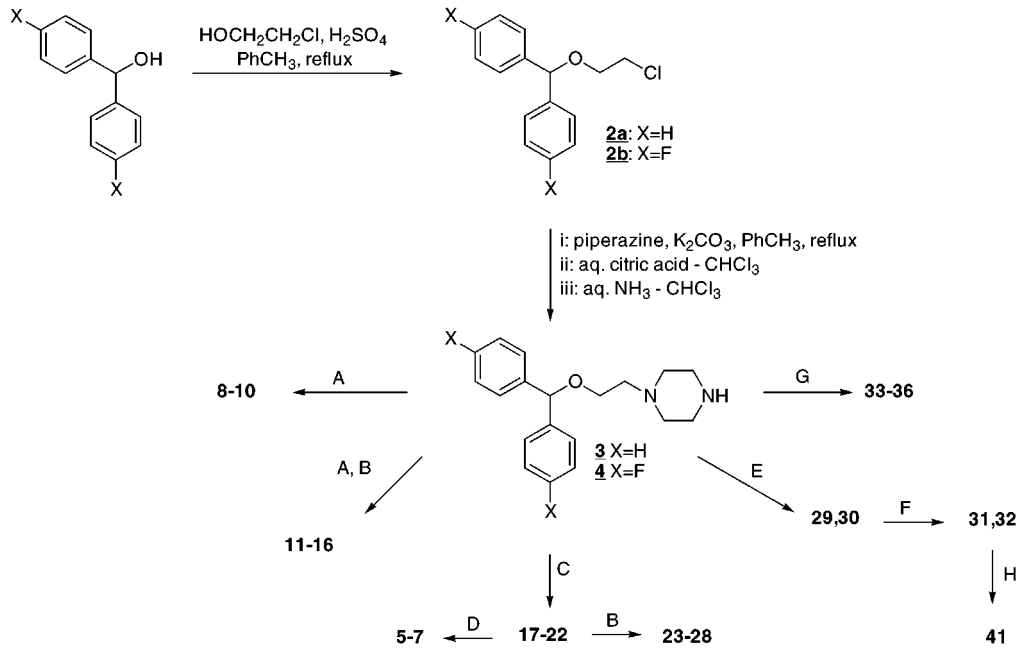
We sought to apply this approach toward the development of extended-action formulations of **1a** and **1b** analogues. Previous work in this laboratory had determined that **1b** eliminated cocaine-maintained responding without affecting similar behavior maintained by food and could maintain these effects for at least 12 days via repeated administration without developing tolerance.[34] Furthermore, when administration of **1b** was discontinued, cocaine-maintained responding reverted to the previously established (predrug) levels. Resumption of administration of **1b** again abolished cocaine-maintained responding, without affecting food-maintained responding.[34] Since none of the parent compounds **1a**−**1d** contained a hydroxyl group to serve as the "anchor" for the ester functionality, we designed a series of analogues of compounds **1a**−**1d**, in which a hydroxyl group was connected at various sites on the phenylpropyl moiety (Figure 1). A series of phenolic derivatives of **1a**−**1d** (**5**−**16**, Chart 2) were synthesized, along with their methoxy congeners (**17**−**28**, Chart 2). The corresponding methoxy-bearing analogues were utilized as synthetic precursors to several of the hydroxy analogues and were also subjected to biological evaluation (DAT and SERT binding; DA and 5-HT uptake inhibition), to compare the biological activity of the methoxy analogues with that for their phenolic congeners. In addition, the aliphatic benzylic hydroxy analogues **31**−**36** were synthesized. The racemates (**31**, **32**) were synthesized initially, followed by the *R*- and *S*-enantiomers (**33**−**36**).

Based on biological evaluation in DAT and SERT binding, along with DA and 5-HT uptake inhibition, the most promising hydroxylated analogues (**16** and **32**, Chart 2) were then administered to rhesus monkeys in drug self-administration studies, to assess behavioral activity. The racemic benzylic alcohol **32** was chosen for formulation as a decanoate ester (**41**, Scheme 1), based on its behavioral profile in monkeys (decrease in drug-maintained performance, without a concurrent decrease in food-maintained responding). When a single injection of a sufficient dose of the decanoate ester formulation **41** was given to monkeys responding under schedules of food and cocaine self-administration, cocaine-maintained responding decreased more than 80% within several days of the injection while food-maintained responding was unaffected. This selective effect on cocaine-maintained responding lasted almost 30 days pursuant to a single injection, and was followed by a return to control levels of responding.[43] These results

Chart 2. Analogues **5**−**36**, Along with the Common Intermediates **3** and **4**

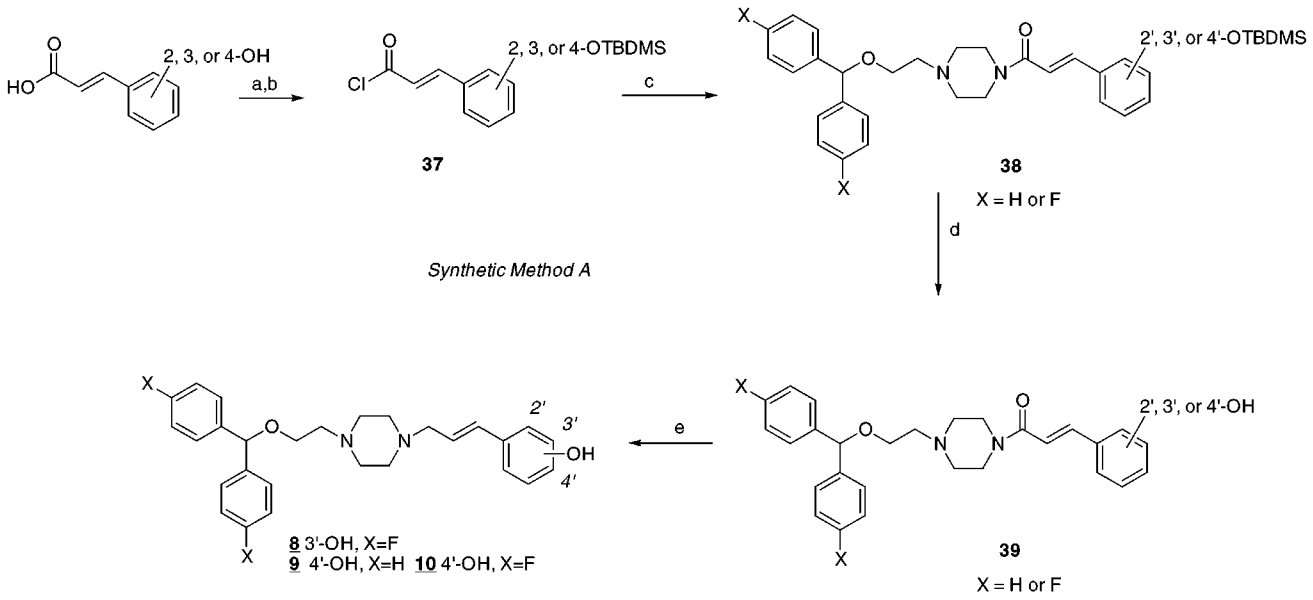


Scheme 1[a]



[a] Synthetic methods A−H: (A) (a) 2′-, 3′-, or 4′-TBDMS-protected hydroxycinnamoyl chloride, $CHCl_3$−aq $NaHCO_3$; (b) TBAF, THF, rt; (c) aluminum hydride, THF. (B) H_2, 10% Pdm-C, MeOH. (C) (a) 2′-, 3′-, or 4′-Methoxycinnamic acid, DCC, CH_2Cl_2; (b) aluminum hydride, THF. (D) L-Selectride, THF. (E) 3-Chloropropiophenone, acetone. (F) LAH, THF. (G) (*R*)-(+)- or (*S*)-(−)-3-Chloro-1-phenyl-1-propanol, NaI, K_2CO_3, 80 °C. (H) $C_9H_{19}COCl$, $CHCl_3$.

Scheme 2[a]



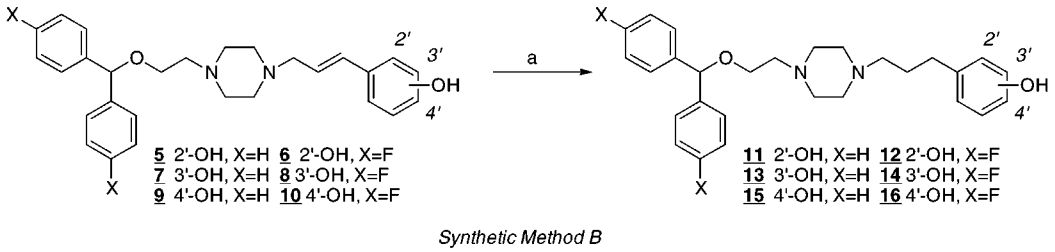
[a] (a) TBDMSCl, imidazole, DMF; (b) oxalyl chloride, DMF (cat.), CH_2Cl_2; (c) **3** or **4**, aq $NaHCO_3$−$CHCl_3$; (d) TBAF, THF; (e) AlH_3, THF.

suggest that a similar formulation, if proven safe for human use, should be tested as a potential medication for cocaine abuse. In addition, the *R*- and *S*-enantiomers of analogue **16** (**34** and **36**) were administered to test subjects (monkeys), to compare their efficacy as potential cocaine-abuse treatment agents (with comparison to the racemic compound **16**). Herein, we report the binding affinities of analogues **5**−**36** to the DAT and SERT, along with the ability to inhibit the reuptake of DA and 5-HT. In addition, behavioral (cocaine and food self-administration) studies are reported for analogues **15**, **16**, **32**, and the enantiomers of **32** (**34** and **36**) to allow comparison with previously published data on **41** (the decanoate ester of alcohol **32**).[43]

Chemistry

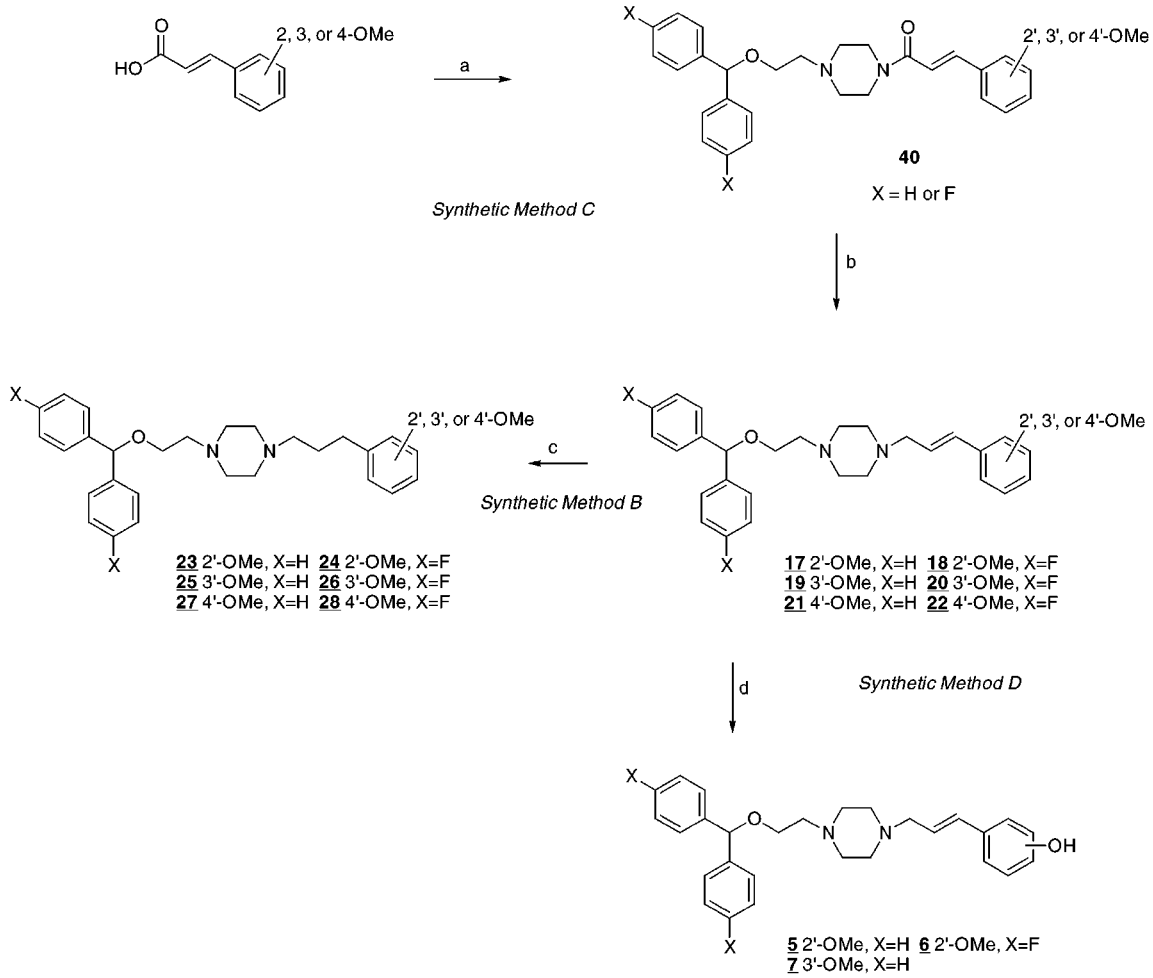
The monosubstituted piperazines 1-[2-(diphenylmethoxy)ethyl]piperazine **(3)** and 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]piperazine **(4)** were synthesized as previously described[32] by a two-step sequence: conversion of either benzhydrol or 4,4′-difluorobenzhydrol to the diarylmethoxyethyl chloride, followed by reaction with an excess of piperazine, affording the key intermediates **3** and **4** in ca. 70% yield (Scheme 1). The alkyl

Scheme 3[a]



[a] (a) H_2, Pd−C, MeOH.

Scheme 4[a]



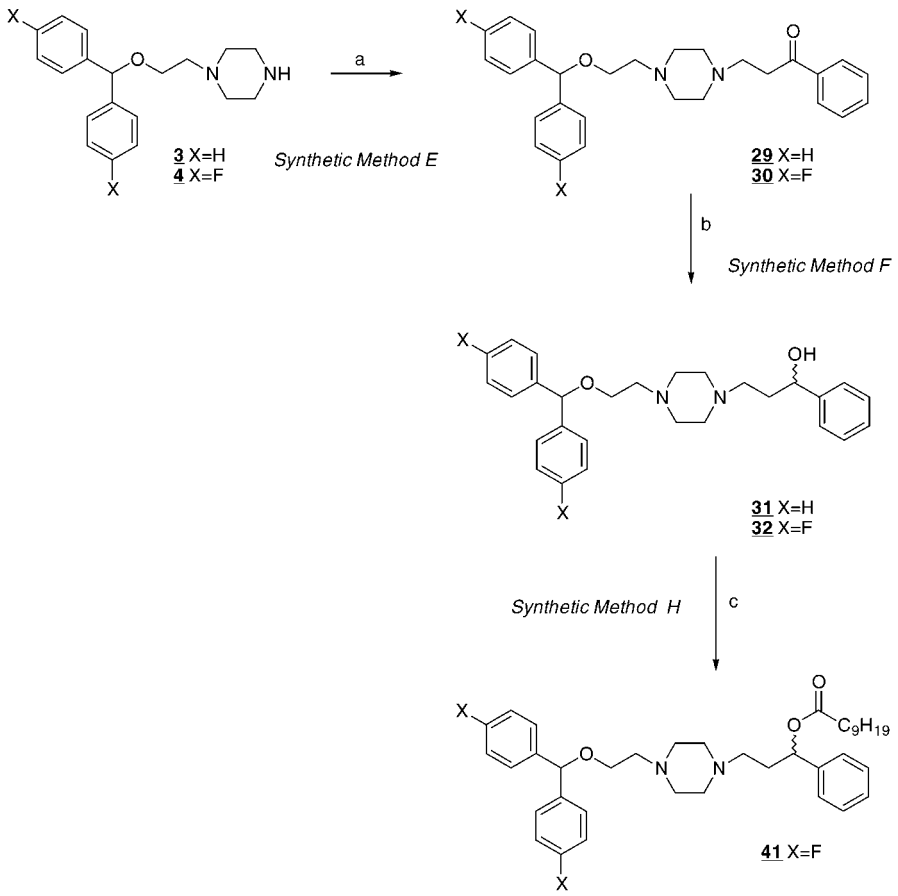
[a] (a) **3** or **4**, DCC, CH_2Cl_2; (b) AlH_3, THF; (c) H_2, Pd−C, MeOH; (d) L-Selectride, THF.

chlorides were purified by distillation in vacuo, and the monosubstituted piperazines **3** and **4** were purified by partition between aqueous citric acid and chloroform.[44]

Analogues **8**−**10** were prepared by coupling either **3** or **4** with 3′- or 4′-*tert*-butyldimethylsiloxycinnamoyl chloride **(37)**, employing Schotten−Baumann conditions, affording amides **38** (method A, Scheme 2). The required acid chlorides **37** were prepared by a two-step process: diprotection of the appropriate hydroxycinnamic acid with *tert*-butyldimethylsilyl chloride (TBDMS chloride), followed by selective conversion of the silyl ester to the acid chloride by treatment with oxalyl chloride in the presence of dimethylformamide (DMF).[45] The silyl protecting groups were removed by treatment with tetrabutylammonium fluoride (TBAF), and the resultant phenolic amides **39** were reduced with aluminum hydride[46] in THF, affording the unsaturated analogues **8**−**10**.

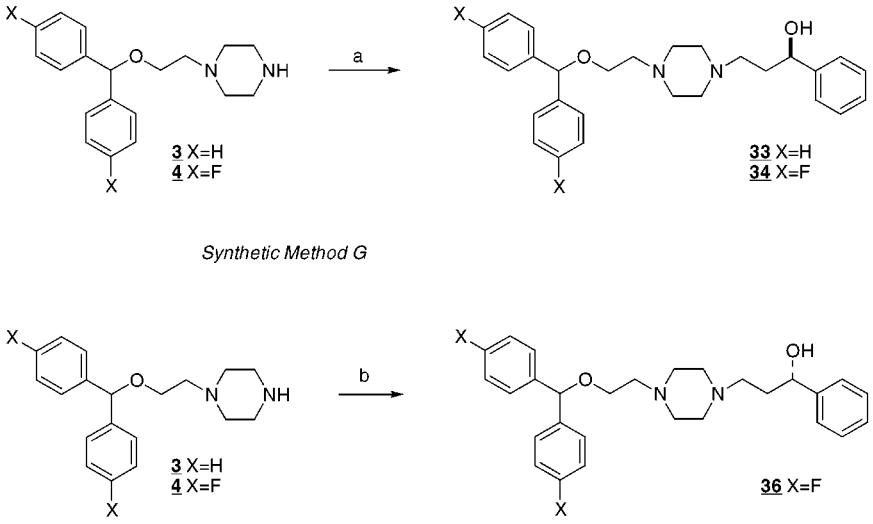
Analogues **5** and **6** (see Scheme 4), however, were unavailable by this method, as the presence of the *o*-hydroxy group on the phenyl ring of the 1-phenylpropenyl moiety caused the hydride reduction step to give a mixture of the desired product and the product resulting from the reduction of the olefinic bond, which were not separable by chromatography or crystallization. The saturated analogues **11**−**16** were prepared by catalytic reduction of the double bond in compounds **5**−**10** by hydrogenation over palladium-on-carbon (Pd−C) (method B, Scheme 3). The unsaturated methoxy-containing analogues (anisoles **17**−**22**) were synthesized by coupling the monosubstituted piperazines **3** and **4** with either 2′-, 3′-, or 4′-methoxycinnamic acid, using

Scheme 5[a]



[a] (a) 3-Chloropropiophenone, acetone; (b) LAH, THF; (c) $C_9H_{19}COCl$, $CHCl_3$.

Scheme 6[a]



[a] (a) (*R*)-(+)-3-Chloro-1-phenyl-1-propanol, NaI, K_2CO_3, DMF, 70 °C; (b) (*S*)-(−)-3-chloro-1-phenyl-1-propanol, NaI, K_2CO_3, DMF, 70 °C.

dicyclohexylcarbodiimide (DCC), affording the methoxyamides **40** and subsequently reducing the amide functionality by treatment with aluminum hydride, affording the amines **17**−**22** (method C, Scheme 4). Analogues **5** and **6** were prepared by treating the unsaturated methoxy analogues **17** and **18** with L-Selectride, resulting in *O*-demethylation[47] without reduction of the double bond (method D, Scheme 4). Analogue **7** was also prepared from the corresponding unsaturated methoxy analogue **19**, using this same method. Analogues **23**−**28** were synthesized via catalytic reduction of **17**−**22** over Pd−C (method B, Scheme 4).

The ketones **29** and **30** were synthesized by treatment of piperazines **3** and **4** with 3-chloropropiophenone (method E, Scheme 5). Lithium aluminum hydride (LAH) reduction of **29** and **30** afforded the racemic benzylic alcohols **31** and **32** (method F, Scheme 5).

Table 1. Physical Properties of the Final Amines (Ligands **5**−**36**)

compd	salt[a]	mp (°C)	crystn solvent	% yield[b]	synth method
5	2 maleate	168−169	2-PrOH−EtOH	74	D
6	2 maleate	175−176	2-PrOH−EtOH	79	D
7	2 maleate	168−169	2-PrOH−EtOH	68	D
8	2 maleate	158−159	MeOH	41	A
9	2 maleate	156−158	MeOH	36	A
10	2 maleate	150−153	MeOH	32	A
11	2 maleate	162−164	MeOH	82	B
12	2 maleate	166−167	MeOH	77	B
13	2 maleate	155−157	MeOH	86	B
14	2 maleate	159−160	MeOH	80	B
15	2 maleate	164−166	MeOH	76	B
16	2 maleate	177−178	MeOH	79	B
17	2 maleate	176−178	MeOH	69	C
18	2 maleate	173−174	MeOH	63	C
19	2 maleate	183−185	MeOH	55	C
20	2 maleate	188−190	MeOH	44	C
21	2 maleate	194−196	MeOH	64	C
22	2 maleate	195−198	MeOH	47	C
23	2 maleate	181−182	MeOH	81	B
24	2 maleate	182−183	MeOH	84	B
25	2 maleate	175−176	2-PrOH−EtOH	52	B
26	2 maleate	170−171	MeOH	34	B
27	2 maleate	192−194	MeOH	56	B
28	2 maleate	188−190	MeOH	62	B
29	2 maleate	171−174	MeOH	65	E
30	2 maleate	165−166	MeOH	64	E
31	2 maleate	169−170	MeOH	88	F
32	2 HCl	216−218	2-PrOH	93	F
33	2 maleate	170−171	MeOH	39	G
34	2 maleate	175−176	MeOH	58	G
36	2 maleate	175−176	MeOH	59	G

[a] The CI mass spectra of all the final amines and precursor amides contained the predicted (M + 1) peaks. All compounds gave CHN analysis within ±0.4 of calculated values. [b] The yields for compounds **5**−**7**, **11**−**16**, and **23**−**28** are for the final synthetic step; the yields for compounds **8**−**10**, **17**−**22**, and **29**−**36** are for the steps from the intermediate **3** or **4**.

Analogues **33** and **34** were synthesized by alkylating piperazines **3** and **4** with *R*-(+)-3-chloro-1-phenyl-1-propanol, and analogue **36** was prepared from *S*-(−)-3-chloro-1-phenyl-1-propanol (method G, Scheme 6).[48] The decanoate ester **41** was prepared by treating alcohol **32** with a slight molar excess of decanoyl chloride, as previously described (method H, Scheme 5).[43] This oily "prodrug" was purified by conversion to the bis-maleate salt in a concentrated methanolic solution, followed by careful conversion back to the free base, to eliminate ester hydrolysis.

Results and Discussion

The binding data shown in Table 2 indicate that the addition of a hydroxy or methoxy substituent to the phenyl ring of the propylphenyl (or propenylphenyl) moiety of compounds **1a**−**1d** resulted in a novel series of disubstituted piperazines (**5**−**28**) with generally high affinity and selectivity for the DAT and a high degree of potency and selectivity for the inhibition of DA uptake versus SERT binding and 5-HT uptake inhibition.

As previously observed in this laboratory, the bis-fluoro analogues (even-numbered compounds from **6** to **28**) generally displayed greater affinity in binding to the DAT and were more potent at inhibiting the uptake of DA, while the des-fluoro analogues (odd numbered compounds from **5** to **27**) were usually more selective for binding to the DAT and for inhibiting the uptake of DA.[35,36] This trend seems to be due, in part, to a decreased affinity for the SERT among the des-fluoro analogues. Among the phenolic analogues **5**−**10** (containing an unsaturated side chain), the *ortho*- and *meta*-substituted compounds **5**−**8** showed greater affinity for the DAT than the *para*-substituted compounds **9** and **10**. A similar relationship was seen among analogues **17**−**22**, which contain a methoxy-substituted cinnamyl side chain, in that the *ortho*- and *meta*-substituted analogues **17**−**20** displayed a greater affinity for the DAT than the *para*-substituted analogues **21** and **22**. Among the analogues with a saturated (propyl) side chain (**11**−**16** and **23**−**28**), the *meta*-substituted (**13**, **14**, **25**, **26**) and *para*-substituted (**15**, **16**, **27**, **28**) analogues displayed a greater affinity for the DAT than the *ortho*-substituted (**11**, **12**, **23**, **24**) analogues in these series. There was no significant difference in either DAT affinity/selectivity or DA uptake inhibition potency/selectivity between the hydroxy-substituted analogues and the corresponding methoxy-substituted congeners. Table 2 also displays the binding and uptake inhibition data for the propyl-chain-substituted analogues **29**−**36**. The two benzylic ketones **29** and **30** displayed greatly decreased affinity for the DAT and were less potent in the ability to inhibit the uptake of DA, when compared with the parent compounds **1a**−**1d**, and when compared with compounds **5**−**28** with one exception. (Analogue **12** displayed DAT binding affinity, which was practically identical to that for **30**.) When ketones **29** and **30** were reduced to the racemic benzylic alcohols **31** and **32**, the DAT binding affinity and the ability to inhibit DA uptake were both restored to values quite similar to those for the parent compounds **1a**−**1d**. On the basis of the preliminary behavioral results in rhesus monkeys for the decanoate ester **41** of racemic alcohol **32**,[43] we decided to synthesize and test the two enantiomers of **32**. The *R*- and *S*-benzylic carbinols (**34** and **36**, respectively) were found to be practically identical, in terms of DAT affinity and DA uptake inhibition, to their racemic congener **32**. In the des-fluoro series, the racemic benzylic alcohol **31** was found to have practically identical biological properties (in vitro and ex vivo biological test results) to the *R*-enantiomer **33**. The *S*-enantiomer **35** was not prepared, based on the comparison of the biological results for **32**, **34**, and **36**,

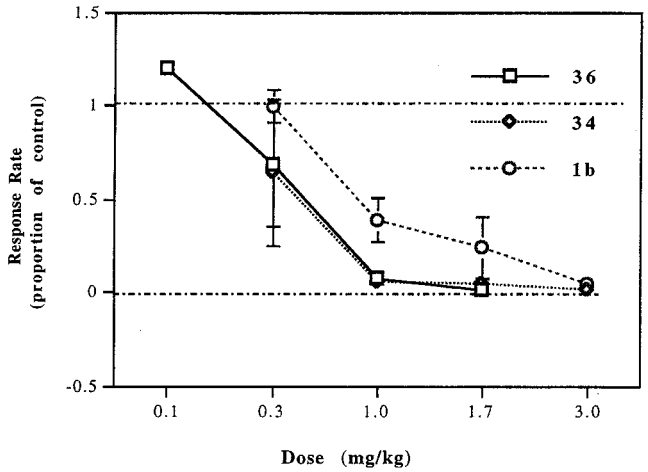


Figure 2. Dose−response curves are shown for **1b** and for **34** and **36** (the enantiomers of **32**), with cocaine-maintained responding shown on the horizontal axis. The baseline (unmedicated, control) response is 1.

Table 2. Binding Affinities at the DAT and SERT Labeled with [^{125}I]RTI-55 and DA and 5-HT Reuptake Inhibition of Analogues **5**−**36** (IC_{50} ± SD, NM)[a]

	binding		reuptake		5-HT/DA ratios	
ligand	DAT	SERT	[^{3}H]DA	[^{3}H]5-HT	binding	uptake
1a	3.7 ± 0.3	623 ± 13	3.7 ± 0.4	298 ± 29	168	80.5
1b	3.7 ± 0.4	126 ± 5	7.3 ± 0.2	73 ± 2	34.1	10.0
1d	0.9 ± 0.1	135 ± 7	11 ± 0.6	576 ± 32	158	52.4
5	2.90 ± 0.14	203 ± 16	7 ± 0.2	1580 ± 85	70.0	225
6	0.92 ± 0.05	27 ± 1.2	7 ± 0.63	397 ± 18	29.3	56.7
7	2.3 ± 0.22	180 ± 5	9 ± 0.6	866 ± 72	78.3	96.2
8	4.2 ± 0.1	47 ± 2	9.7 ± 0.3	226 ± 14	11.2	23.3
9	22.8 ± 2.5	448 ± 24	43 ± 0.8	1430 ± 116	19.6	33.1
10	13.7 ± 0.6	68 ± 3	20 ± 1.5	391 ± 37	5.0	19.6
11	24.8 ± 0.84	869 ± 53	6.8 ± 0.3	1090 ± 40	35.0	161
12	41 ± 1.5	174 ± 5	15 ± 0.6	297 ± 15	4.2	19.8
13	9.9 ± 0.3	449 ± 10	8.7 ± 0.2	881 ± 27	45.4	101
14	5.7 ± 0.3	74 ± 3	5.7 ± 0.12	113 ± 7.6	13.0	19.8
15	15 ± 0.8	894 ± 56	17.4 ± 0.5	872 ± 31	59.6	50.1
16	11.6 ± 0.3	72.2 ± 2.4	11.4 ± 0.3	258 ± 10	6.2	22.6
17	7.1 ± 0.4	339 ± 15	5.6 ± 0.28	1180 ± 93	47.7	211
18	2.69 ± 0.1	157 ± 7	7.4 ± 0.4	499 ± 17	58.4	67.4
19	4.9 ± 0.3	461 ± 10	5.1 ± 0.4	1690 ± 109	94.0	331
20	2.5 ± 0.3	112 ± 4.4	6.7 ± 1.0	473 ± 17	44.8	70.6
21	28.7 ± 3.6	701 ± 25	37 ± 1.3	1920 ± 159	24.4	51.8
22	15.1 ± 0.9	90 ± 3.4	9.8 ± 1.4	392 ± 17	6.0	40.0
23	28 ± 0.9	232 ± 7	6.5 ± 0.25	494 ± 17	8	76.0
24	19 ± 0.7	191 ± 7	8.7 ± 0.33	342 ± 13	10.1	39.3
25	2.5 ± 0.005	101 ± 2	4 ± 0.35	1180 ± 44	40.4	295
26	3.8 ± 0.1	100 ± 3.5	6.5 ± 0.6	265 ± 13	26.3	40.8
27	12.4 ± 1.0	550 ± 19	7.4 ± 1.2	982 ± 52	44.4	133
28	4.87 ± 0.35	96 ± 4	9.4 ± 0.16	219 ± 7	19.7	23.3
29	208 ± 4	1310 ± 34	329 ± 13	2990 ± 135	6.3	9.0
30	47.8 ± 1.7	215 ± 6.14	41.6 ± 1.9	452 ± 17	4.5	10.9
31	6.09 ± 0.2	700 ± 51	7.03 ± 0.24	1480 ± 45	114	211
32	2.14 ± 0.05	117 ± 7	5.57 ± 0.13	69 ± 17	54.7	12.4
33	8.4 ± 0.4	939 ± 27	5.4 ± 0.10	1090 ± 77	112	202
34	3 ± 28	85 ± 3	3.5 ± 0.16	101 ± 3	28.3	28.8
36	4.4 ± 0.45	135 ± 5	3.6 ± 0.16	178 ± 7	30.7	49.4

[a] The IC_{50} values of the test agents were determined in the above assays as described in Biological Methods (see Experimental Section).

coupled with a comparison of the biological data for **31** and **33**. Attempts to evaluate the DAT binding affinity of the decanoate ester **41** gave K_i values of 18.2 ± 0.9 nM (bis-maleate salt) and 1.73 ± 0.06 nM (free base). While the results of these studies indicate that the ester **41** does potently inhibit DAT binding, it is not possible to distinguish between inhibition produced by **41** and **32**, as the parent alcohol **32** may be produced by the action of membrane-associated esterases or by hydrolysis by the aqueous buffer utilized in the assay. The unexpectedly high DAT affinity is presumably due to the hydrolysis of the ester during the performance of the assay. Since the alcohol **32** has demonstrated a high affinity for the DAT and is a potent inhibitor of DA uptake, even a relatively small percent amount of hydrolysis would lead to a biological result quite similar to that for the alcohol itself. Studies are ongoing, involving the preparation and biological testing of a nonhydrolyzable isostere of the decanoate ester **41**, to estimate the DAT binding and DA uptake inhibition potency of the ester prodrug **41**.

Compound **1b** and the enantiomers **34** and **36** were studied for behavioral effects on modulation of food- and cocaine-maintained responding in rhesus monkeys. These drugs all decreased cocaine-maintained responding to a greater extent than food-maintained responding, and none of these analogues significantly increased responding during the fixed interval (FI) components. Figure 2 shows the effects of different doses of **1b** and enantiomers **34** and **36**, relative to the effects of vehicle pretreatment (i.e. the horizontal line at $y = 1$ indicates no effect relative to that of vehicle), on cocaine-maintained responding. Each drug dose-dependently decreased cocaine-maintained responding, with the highest doses tested decreasing cocaine-maintained responding almost completely. Enantiomers **34** and **36** were approximately equipotent, and both were more potent than **1b** in this behavioral test.

These results show that enantiomers **34** and **36** not only retained the ability to selectively decrease cocaine-maintained responding much in the same way that **1b** had been shown to affect these behaviors previously,[49] but also both compounds were more potent than **1b**. The lack of difference in potency between **34** and **36** was consistent with their similar abilities in inhibiting DA reuptake and in their similar affinities for the DAT and supports the notion that this could be the primary mechanism by which they reduce cocaine-maintained responding. However, additional studies examining factors such as the possibility that their enhanced in vivo potency may be the result of bioavailability are warranted.

In summary, compounds with an oxygen-containing substituent on the benzene ring of the phenylpropyl or phenylpropenyl moiety generally displayed potent and selective binding to the DAT, with respect to the SERT, as did compounds containing a hydroxyl group at the benzylic position of the phenylpropyl moiety. There were small differences in potency and affinity among the phenols and anisoles, based on the isomeric position of

the hydroxy or methoxy group. Among the benzylic alcohols, there seemed to be little difference in biological activity in DAT and SERT binding and DA and 5-HT uptake inhibition between the racemates, the *R*-enantiomers, and the *S*-enantiomers with the same aromatic substitution patterns. The results indicate that the use of the racemic compound **32** for further in vivo investigations in live animals is warranted. Ketones **29** and **30** showed reduced DAT affinity and also displayed a greatly decreased ability to inhibit DA uptake, relative to the corresponding benzylic alcohols **31** and **32**. The SERT affinity and the ability to inhibit 5-HT uptake were affected to a much smaller extent. In rhesus monkey behavioral studies, the bis-fluoro *para*-phenolic analogue **16** decreased both cocaine- and food-maintained responding equally. The des-fluoro *para*-phenolic analogue **15** displayed some behavioral selectivity, in that cocaine-maintained responding was decreased to a significantly greater extent than food-maintained responding. The racemic benzylic alcohol **32** exhibited the greatest promise among the preliminary analogues, regarding separation of cocaine- and food-maintained response. On the basis of the behavioral activity comparisons of **15**, **16**, and **32**, analogue **32** was converted to the decanoate ester **41** and formulated as a "depot" that was then administered to monkeys via intramuscular injection, affording 24 days of activity pursuant to a single injection.[43] Further studies now in progress of **41** in multiple animals appear to be promising and will be reported in due course.[50] Compounds **34** and **36**, which decreased cocaine-maintained responding with high degrees of potency and selectivity over food-maintained responding, have not yet been converted to the corresponding decanoate esters. Studies are ongoing at this time to evaluate the behavioral effects of the decanoate ester **41** and hopefully detect blood levels of the putative active compound **32**, and these will be reported in a future communication.

Conclusions

The addition of hydroxyl or methoxyl substituents to the phenyl ring of the phenylpropyl moiety of **1a** and **1b** analogues resulted in retention of DAT affinity and DA uptake inhibition potency for the new compounds. Likewise, addition of a benzylic hydroxyl group to the phenylpropyl side chain resulted in retention of DAT binding affinity and selectivity (when compared with SERT binding affinity) and DA uptake inhibition potency. The stereochemistry at the benzylic position did not affect the biological activity to any significant extent. This finding suggested that the use of racemic compound **32** for esterification and formulation as a "depot" injection was warranted. Among the two potential candidates for esterification and formulation as a "depot" injection, the phenolic compound **16** inhibited both food- and cocaine-maintained responding almost equally, and the benzylic compound **32** selectively decreased cocaine-maintained responding with respect to those behaviors maintained by food. All available data (binding, neurotransmitter uptake, and primate behavior) for compounds **32**, **34**, and **36** (the optically pure enantiomers of **32**) suggest that these analogues are promising candidates for esterification and formulation as potential extended-release dosage forms. The identification of analogues **32**, **34**, and **36** provides the choice of three potential cocaine-abuse therapeutic agents, all amenable to conversion to an oil-soluble "prodrug" which should (as in the case of compound **41**) provide the desired pharmaceutical effect for a greatly extended time period following a single injection. This choice of alternative drug substances affords the possibility of singling out the specific molecular entity possessing the optimal therapeutic and toxicological properties within the defined set consisting of compounds **32**, **34**, and **36**.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA, and were within ±0.4% for the elements indicated. Chemical ionization mass spectra (CIMS) were obtained using a Finnegan 1015 mass spectrometer. Electron ionization mass spectra (EIMS) 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). ^{1}H NMR spectra were recorded on the free bases in $CDCl_3$ or $CDCl_3$ plus D_2O using a Varian XL-300 spectrometer. ^{19}F NMR spectra were utilized in determination of enantiomeric excess in chiral compounds and were determined at 282 MHz in $CDCl_3$. Chemical shifts are expressed in parts per million (ppm) on the δ scale relative to a TMS internal standard. Thin-layer chromatography (TLC) was performed on 250-μm Analtech GHLF silica gel plates. No attempt was made to optimize the yields reported.

1-[2-(Diphenylmethoxy)ethyl]piperazine (3) was synthesized from **2a** by a modification of the method described by van der Zee.[32] To a stirred solution of **2b** (159 g, 663 mmol) in 1.2 L of toluene were added piperazine (357 g, 4.11 mol, 6.4 equiv) and anhydrous K_2CO_3 (180 g, 1.3 mol, 99+%; ACS Reagent, granular). The reagents were rinsed into the reaction vessel with an additional 100 mL of toluene, and the reaction was run at reflux for 12 h and then cooled to room temperature. The organic mixture was washed with water (4 × 500 mL) and brine, dried over Na_2SO_4, and concentrated to ca. 190 g of a yellow oil. The crude monosubstituted piperazine was dissolved in ca. 2 L of chloroform and divided into four 500-mL portions. Each portion was extracted with 10% aq citric acid (500 + 250 + 100 mL), and the organic layer was discarded. The acidic aqueous portions were combined, and made alkaline with concentrated NH_4OH solution, and extracted into $CHCl_3$. The organic solutions from the four initial portions of the crude piperazine were combined, dried over Na_2SO_4, and concentrated to 168 g of a pale yellow oil, which was dissolved in 2.5 L of MeOH, heated to boiling, and treated with 169 g of maleic acid (1.45 mol, 2.2 equiv, based on the amount of the starting material **2b**). The bis-maleate salt crystallized upon cooling, was collected by filtration, and was washed with MeOH and Et_2O, affording 224 g (424 mmol, 64% yield) of snow-white crystals: mp 168−169 °C (lit.[32] mp 169−170 °C).

1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]piperazine (4) was synthesized from **2b** in an analogous procedure to that used for **3**. The yield was 69% of snow-white crystals: mp 157−159 °C (lit.[32] mp 158−159 °C).

Synthetic Method A. i. To a stirred solution of 2-, 3-, or 4-hydroxycinnamic acid (ca. 10 g, 60 mmol) in dimethylformamide (DMF; 80 mL) were added *tert*-butyldimethylsilyl chloride (TBDMSCl; 140 mmol) and imidazole (260 mmol). The mixture was stirred for 12−24 h at room temperature, poured into water, and extracted into ether (3 × 100 mL). The ethereal solution was dried ($MgSO_4$) and concentrated at reduced pressure, affording the ester ether, which was not purified further (reaction product analyzed by TLC, MS, NMR).

ii. The bis-silyl-protected hydroxycinnamic acid (ca. 12 g, 30 mmol of the ester ether) was dissolved in 100 mL of dry dichloromethane, cooled to ca. 0 °C with a water−ice bath, and treated with oxalyl chloride (1.2 equiv of a 2.0 M solution in dichloromethane) and DMF (4−5 drops). The reaction was stirred at 0 °C for 1 h and at room temperature for 1 h and

concentrated, affording the TBDMS ether-protected hydroxycinnamoyl chloride as a pale yellow oil. This intermediate, being relatively unstable, was then used directly without further purification.

iii. Monosubstituted piperazine **3** or **4** (ca. 3 g, 10 mmol) was dissolved in a biphasic mixture of chloroform and saturated solution of sodium bicarbonate and treated with the appropriate TBDMS-protected hydroxycinnamoyl chloride (crude, ca. 15 mmol, 1.5 equiv, dissolved in 10−15 mL of dry ethanol−free chloroform). After 10 min, brine was added to the reaction, the layers were separated, and the organic portion was dried (Na_2SO_4) and concentrated to a yellow oil. The crude TBDMS-protected phenolic amide was dissolved in tetrahydrofuran (THF; 40 mL) and treated with tetrabutylammonium fluoride (TBAF; trihydrate, ca. 20 mmol, 2 equiv). The THF solution was stirred for 20 min and poured into 40 mL of brine, and the layers were separated. The solvent was removed under reduced pressure; the residue was taken up in chloroform, washed with brine, dried (Na_2SO_4), and concentrated to a yellow oily solid, which was purified either by chromatography (chloroform−methanol, 20:1) or by precipitation from ethyl acetate.

iv. To a stirred 1 M solution of alane (AlH_3) in THF (ca. 3 mL, 3 mmol, 9 mequiv) was added a solution of the deprotected product from step iii (2−3 mmol, in 20 mL of THF). The reaction was stirred at room temperature for 15−30 min and poured into 100 mL of dilute aqueous sodium hydroxide. The crude product was extracted into chloroform (3 × 50 mL); the organic portions were combined, washed with brine, dried (Na_2SO_4), and concentrated at reduced pressure. The α,β-unsaturated phenolic analogue was purified by conversion to the bis-maleate salt, followed by recrystallization from methanol.

1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-[1-(3′-hydroxyphenyl)propenyl]piperazine (8) was synthesized from **4** according to synthetic method A (Scheme 2): ^{1}H NMR ($CDCl_3$) δ 2.58 (m, 8H), 2.68 (t, J = 5.9 Hz, 2H), 3.14 (d, J = 6.8 Hz, 2H), 3.56 (t, J = 5.9 Hz, 2H), 5.32 (s, 1H), 6.17−6.27 (m, 1H), 6.44 (d, J = 15.6 Hz, 1H), 6.67−6.71 (m, 1H), 6.80 (s, 1H), 6.89 (d, J = 7.8 Hz, 1H), 6.96−7.02 (m, 4H), 7.16 (t, J = 7.8 Hz, 1H), 7.24−7.29 (m, 4H); MS (CI-NH_3) m/z 465 (MH+). Anal. **8**·2 maleate ($C_{28}H_{30}N_2F_2O_2$·$2C_4H_4O_4$) C, H, N.

1-[2-(Diphenylmethoxy)ethyl]-4-[1-(4′-hydroxyphenyl)propenyl]piperazine (9) was synthesized from **3** according to synthetic method A (Scheme 2): ^{1}H NMR ($CDCl_3$) δ 2.65 (m, 8H), 2.72 (t, J = 5.7 Hz, 2H), 3.17 (d, J = 6.6 Hz, 2H), 3.61 (t, J = 6.0 Hz, 2H), 5.37 (s, 1H), 5.96−6.08 (m, 1H), 6.42 (d, J = 15.6 Hz, 1H), 6.71 (d, J = 8.7 Hz, 2H), 7.12 (d, J = 8.7 Hz, 1H), 7.22−7.35 (m, 11H); MS (CI-NH_3) m/z 429 (MH+). Anal. **9**·2 maleate ($C_{28}H_{32}N_2O_2$·$2C_4H_4O_4$·$0.5CH_3OH$) C, H, N.

1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-[1-(4′-hydroxyphenyl)propenyl]piperazine (10) was synthesized from **4** according to synthetic method A (Scheme 2): ^{1}H NMR ($CDCl_3$) δ 2.57 (m, 8H), 2.68 (t, J = 6.0 Hz, 2H), 3.14 (d, J = 6.6 Hz, 2H), 3.57 (t, J = 6.0 Hz, 2H), 5.33 (s, 1H), 6.08−6.18 (m, 1H), 6.47 (d, J = 16.2 Hz, 1H), 6.73 (d, J = 8.7 Hz, 2H), 6.97−7.04 (m, 4H), 7.25−7.28 (m, 4H), 7.31 (d, J = 8.7 Hz, 2H); MS (CI-NH_3) m/z 465 (MH+). Anal. **10**·2 maleate ($C_{28}H_{30}N_2F_2O_2$·$2C_4H_4O_4$·CH_3OH) C, H, N.

Synthetic Method B. A solution of the hydroxyphenylpropenylpiperazine (analogues containing an unsaturated cinnamoyl side chain, **5**−**10** and **17**−**22**, 1−3 mmol, in ca. 50 mL of methanol) was added to a Parr bottle, treated with ca. 10−20 wt % of 10% Pd−C catalyst, and hydrogenated at 45−50 psi for 2−4 h. The reaction was stopped and filtered through a bed of Celite, the filter cake was washed with more methanol, and the organic solutions were combined and concentrated to an oily residue. The crude product was taken up in chloroform, washed with aqueous ammonia and brine, dried (Na_2SO_4), concentrated at reduced pressure, and purified by conversion to the bis-maleate salt and recrystallization from methanol.

1-[2-(Diphenylmethoxy)ethyl]-4-[3-(2′-hydroxyphenyl)propyl]piperazine (11) was synthesized from **5** according to synthetic method B (Scheme 3): ^{1}H NMR ($CDCl_3$) δ 1.87 (m, 2H), 2.28 (t, J = 6.3 Hz, 2H), 2.67 (m, 8H), 2.73 (t, J = 6.0 Hz, 2H), 3.62 (t, J = 5.9 Hz, 2H), 5.38 (s, 1H), 6.80−6.89 (m, 4H), 7.05−7.14 (m, 3H), 7.22−7.29 (m, 4H), 7.32−7.36 (m, 4H); MS (CI-NH_3) m/z 431 (MH+). Anal. **11**·2 maleate ($C_{28}H_{34}N_2O_2$·$2C_4H_4O_4$·CH_3OH) C, H, N.

1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-[3-(2′-hydroxyphenyl)propyl]piperazine (12) was synthesized from **6** according to synthetic method B (Scheme 2): ^{1}H NMR ($CDCl_3$) δ 1.78−1.82 (m, 2H), 2.34−2.37 (m, 2H), 2.51−2.59, (m, 10H), 2.67 (t, J = 6.0 Hz, 2H), 3.54−3.58 (m, 2H), 5.32 (s, 1H), 6.62 (d, J = 6.8 Hz, 1H), 6.97−7.03 (m, 4H), 7.09−7.14 (m, 1H), 7.24−7.29 (m, 5H); MS (CI-NH_3) m/z 467 (MH+). Anal. **12**·2 maleate ($C_{28}H_{32}N_2F_2O_2$·$2C_4H_4O_4$) C, H, N.

1-[2-(Diphenylmethoxy)ethyl]-4-[3-(3′-hydroxyphenyl)propyl]piperazine (13) was synthesized from **7** according to synthetic method B (Scheme 3): ^{1}H NMR ($CDCl_3$) δ 1.74−1.84 (m, 2H), 2.36 (t, J = 7.8 Hz, 2H), 2.49−2.57, (m, 8H), 2.68 (t, J = 5.9 Hz, 2H), 3.59 (t, J = 5.9 Hz, 2H), 5.36 (s, 1H), 6.60 (s, 1H), 6.61 (d, J = 7.5 Hz, 1H), 6.70 (d, J = 7.5 Hz, 1H), 7.08−7.35 (m, 11H); MS (CI-NH_3) m/z 431 (MH+). Anal. **13**·2 maleate ($C_{28}H_{34}N_2O_2$·$2C_4H_4O_4$) C, H, N.

1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-[3-(3′-hydroxyphenyl)propyl]piperazine (14) was synthesized from **8** according to synthetic method B (Scheme 3): ^{1}H NMR ($CDCl_3$) δ 1.77−1.82 (m, 2H), 2.34−2.37 (m, 2H), 2.51−2.59, (m, 10H), 2.67 (t, J = 5.9 Hz, 2H), 3.54−3.58 (m, 2H), 5.32 (s, 1H), 6.62 (d, J = 6.8 Hz, 1H), 6.97−7.03 (m, 4H), 7.09−7.14 (m, 1H), 7.24−7.29 (m, 5H); MS (CI-NH_3) m/z 467 (MH+). Anal. **14**·2 maleate ($C_{28}H_{32}N_2F_2O_2$·$2C_4H_4O_4$) C, H, N.

1-[2-(Diphenylmethoxy)ethyl]-4-[3-(4′-hydroxyphenyl)propyl]piperazine (15) was synthesized from **9** according to synthetic method B (Scheme 3): ^{1}H NMR ($CDCl_3$) δ 1.78−1.89 (m, 2H), 2.51 (t, J = 7.5 Hz, 2H), 2.67, (m, 8H), 2.64 (t, J = 5.9 Hz, 2H), 3.60 (t, J = 6.0 Hz, 2H), 5.35 (s, 1H), 6.65 (d, J = 8.7 Hz, 2H), 6.96 (d, J = 8.7 Hz, 2H), 7.23−7.32 (m, 10H); MS (CI-NH_3) m/z 431 (MH+). Anal. **15**·2 maleate ($C_{28}H_{34}N_2O_2$·$2C_4H_4O_4$($1CH_3OH$) C, H, N.

1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-[3-(3′-hydroxyphenyl)propyl]piperazine (16) was synthesized from **10** according to synthetic method B (Scheme 3): ^{1}H NMR ($CDCl_3$) δ 1.81−1.87 (m, 2H), 2.48−2.45 (m, 4H), 2.66−2.73, (m, 10H), 3.55 (t, J = 5.4 Hz, 2H), 5.30 (s, 1H), 6.61 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 8.4 Hz, 2H), 6.90−7.01 (m, 4H), 7.22−7.27 (m, 4H); MS (CI-NH_3) m/z 467 (MH+). Anal. **16**·2 maleate ($C_{28}H_{32}N_2F_2O_2$·$2C_4H_4O_4$) C, H, N.

Synthetic Method C. i. To a stirred solution of 2-, 3-, or 4-methoxycinnamic acid (ca. 10 g, 55 mmol) in dichloromethane (30 mL) was added dicyclohexylcarbodiimide (DCC; 80 mmol, in 20 mL of dichloromethane). The mixture was stirred until a copious white precipitate formed (5−10 min) and was then treated with a solution of **3** or **4** (25 mmol, in 30 mL of dichloromethane). The reaction was stirred until TLC analysis showed no further starting material (**3** or **4**), at which time the mixture was filtered through a bed of Celite and concentrated at reduced pressure. The crude amide was purified by chromatography (EtOAc to elute dicyclohexylcarbonylurea, DCU, generated in the reaction; followed by chloroform−methanol, 20:1, to elute the amide).

ii. The amide from step i was dissolved in 20 mL of THF and treated with alane (ca. 2 equiv of a 1 M solution in THF) for 15−30 min. The reaction mixture was worked up and purified as in synthetic method A (bis-maleate salt, from methanol).

1-[2-(Diphenylmethoxy)ethyl]-4-[1-(2′-methoxyphenyl)propenyl]piperazine (17) was synthesized from **3** according to synthetic method C (Scheme 4): ^{1}H NMR ($CDCl_3$) δ 2.58 (m, 8H), 2.70 (t, J = 6.1 Hz, 2H), 3.19 (d, J = 6.7 Hz, 2H), 3.61 (t, J = 6.1 Hz, 2H), 3.84 (s, 3H), 5.37 (s, 1H), 6.29 (dt, J = 16.0, 6.8 Hz, 1H), 6.82−6.94 (m, 3H), 7.19−7.36 (m, complex, 11H), 7.44 (dd, J = 7.6, 1.8 Hz, 1H); MS (CI-NH_3) m/z 443 (MH+). Anal. **17**·2 maleate ($C_{29}H_{34}N_2O_2$·$2C_4H_4O_4$) C, H, N.

1-[2-[Bis(4-fluorophenylmethoxy)ethyl]-4-[1-(2′-methoxyphenyl)propenyl]piperazine (18) was synthesized from **4** according to synthetic method C (Scheme 4): ^{1}H NMR ($CDCl_3$) δ 2.56 (m, 8H), 2.88 (t, J =

6.7 Hz, 2H), 3.56 (t, J = 6.1 Hz, 2H), 3.84 (s, 3H), 5.34 (s, 1H), 6.26−6.34 (m, 1H), 6.82−6.88 (m, 3H), 6.92−7.04 (m, 3H), 7.19−7.30 (m, 6H), 7.44 (d, J = 5.9 Hz, 1H); MS (CI-NH_3) m/z 479 (MH+). Anal. **18**·2 maleate ($C_{29}H_{32}N_2F_2O_2 \cdot 2C_4H_4O_4$) C, H, N.

1-[2-(Diphenylmethoxy)ethyl]-4-[1-(3′-methoxyphenyl)-propenyl]piperazine (19) was synthesized from **3** according to synthetic method C (Scheme 4): ^{1}H NMR ($CDCl_3$) δ 2.57 (m, 8H), 2.70 (t, J = 6.0 Hz, 2H), 3.15 (d, J = 6.6 Hz, 2H), 3.60 (t, J = 6.0 Hz, 2H), 3.81 (s, 3H), 5.37 (s, 1H), 6.24−6.32 (m, 1H), 6.49 (d, J = 16.5 Hz, 1H), 6.78−6.81 (m, 1H), 6.92−6.98 (m, 2H), 7.20−7.35 (m, 6H); MS (CI-NH_3) m/z 443 (MH+). Anal. **19**·2 maleate ($C_{29}H_{34}N_2O_2 \cdot 2C_4H_4O_4$) C, H, N.

1-[2-[Bis(4-fluorophenylmethoxy)ethyl]-4-[1-(3′-methoxyphenyl)propenyl]piperazine (20) was synthesized from **4** according to synthetic method C (Scheme 4): ^{1}H NMR ($CDCl_3$) δ 2.56 (m, 8H), 2.68 (t, J = 5.7 Hz, 2H), 3.15 (d, J = 6.0 Hz, 2H), 3.57 (t, J = 6.0 Hz, 2H), 3.81 (s, 3H), 5.34 (s, 1H), 6.22−6.31 (m, 1H), 6.49 (d, J = 15.3 Hz, 1H), 6.78−6.81 (m, 1H), 6.92−7.04 (m, 5H), 7.20−7.30 (m, 6H); MS (CI-NH_3) m/z 479 (MH+). Anal. **20**·2 maleate ($C_{29}H_{32}N_2F_2O_2 \cdot 2C_4H_4O_4$) C, H, N.

1-[2-(Diphenylmethoxy)ethyl]-4-[1-(4′-methoxyphenyl)-propenyl]piperazine (21) was synthesized from **3** according to synthetic method C (Scheme 4): ^{1}H NMR ($CDCl_3$) δ 2.59 (m, 8H), 2.71 (t, J = 6.0 Hz, 2H), 3.15 (d, J = 6.6 Hz, 2H), 3.61 (t, J = 6.0 Hz, 2H), 3.81 (s, 3H), 5.37 (s, 1H), 6.08−6.18 (m, 1H), 6.47 (d, J = 15.3 Hz, 1H), 6.84 (d, J = 8.7 Hz, 2H), 7.21−7.36 (m, complex, 12H); MS (CI-NH_3) m/z 443 (MH+). Anal. **21**·2 maleate ($C_{29}H_{34}N_2O_2 \cdot 2C_4H_4O_4$) C, H, N.

1-[2-[Bis(4-fluorophenylmethoxy)ethyl]-4-[1-(4′-methoxyphenyl)propenyl]piperazine (22) was synthesized from **4** according to synthetic method C (Scheme 4): ^{1}H NMR ($CDCl_3$) δ 2.57 (m, 8H), 2.68 (t, J = 6.0 Hz, 2H), 3.14 (d, J = 6.6 Hz, 2H), 3.57 (t, J = 6.0 Hz, 2H), 3.81 (s, 3H), 5.33 (s, 1H), 6.08−6.18 (m, 1H), 6.47 (d, J = 16.2 Hz, 1H), 6.86 (d, J = 8.7 Hz, 2H), 6.97−7.04 (m, 4H), 7.25−7.28 (m, 4H), 7.31 (d, J = 8.7 Hz, 2H); MS (CI-NH_3) m/z 479 (MH+). Anal. **22**·2 maleate ($C_{29}H_{32}N_2F_2O_2 \cdot 2C_4H_4O_4$) C, H, N.

1-[2-(Diphenylmethoxy)ethyl]-4-[3-(2′-methoxyphenyl)-propyl]piperazine (23) was synthesized from **17** according to synthetic method B (Scheme 4): ^{1}H NMR ($CDCl_3$) δ 1.69−1.83 (m, 4H), 2.39 (t, J = 7.8 Hz, 2H), 2.49−2.64 (m, 8H), 2.66−2.71 (m, 2H), 3.60 (t, J = 5.9 Hz, 2H), 3.81 (s, 3H), 5.37 (s, 1H), 6.82−6.90 (m, 2H), 7.12−7.35 (m, complex, 12H); MS (CI-NH_3) m/z 445 (MH+). Anal. **23**·2 maleate ($C_{29}H_{36}N_2O_2 \cdot 2C_4H_4O_4$) C, H, N.

1-[2-[Bis(4-fluorophenylmethoxy)ethyl]-4-[3-(2′-methoxyphenyl)propyl]piperazine (24) was synthesized from **18** according to synthetic method B (Scheme 4): ^{1}H NMR ($CDCl_3$) δ 1.69−1.78 (m, 2H), 2.29 (t, J = 7.5 Hz, 2H), 2.44−2.55 (m, 8H), 2.61 (t, J = 6.0 Hz, 2H), 3.53 (t, J = 6.0 Hz, 2H), 3.72 (s, 3H), 5.30 (s, 1H), 6.65−6.72 (m, 3H), 7.09−7.30 (m, complex, 11H); MS (CI-NH_3) m/z 481 (MH+). Anal. **24**·2 maleate ($C_{29}H_{34}N_2F_2O_2 \cdot 2C_4H_4O_4$) C, H, N.

1-[2-(Diphenylmethoxy)ethyl]-4-[3-(3′-methoxyphenyl)-propyl]piperazine (25) was synthesized from **19** according to synthetic method B (Scheme 4): ^{1}H NMR ($CDCl_3$) δ 1.79−1.85 (m, 4H), 2.38 (t, J = 7.8 Hz, 2H), 2.49−2.64 (m, 8H), 2.66−2.71 (m, 2H), 3.60 (t, J = 5.9 Hz, 2H), 3.79 (s, 3H), 5.37 (s, 1H), 6.74−6.79 (m, 4H), 7.19−7.35 (m, complex, 10H); MS (CI-NH_3) m/z 445 (MH+). Anal. **23**·2 maleate ($C_{29}H_{36}N_2O_2 \cdot 2C_4H_4O_4$) C, H, N.

1-[2-[Bis(4-fluorophenylmethoxy)ethyl]-4-[3-(3′-methoxyphenyl)propyl]piperazine (26) was synthesized from **20** according to synthetic method B (Scheme 4): ^{1}H NMR ($CDCl_3$) δ 1.77−1.86 (m, 2H), 2.37 (t, J = 7.8 Hz, 2H), 2.48−2.55 (m, 8H), 2.66 (t, J = 6.0 Hz, 2H), 3.56 (t, J = 6.0 Hz, 2H), 3.79 (s, 3H), 5.33 (s, 1H), 6.72−6.78 (m, 3H), 6.97−7.04 (m, 4H), 7.16−7.29 (m, 5H); MS (CI-NH_3) m/z 481 (MH+). Anal. **26**·2 maleate ($C_{29}H_{34}N_2F_2O_2 \cdot 2C_4H_4O_4$) C, H, N.

1-[2-(Diphenylmethoxy)ethyl]-4-[3-(4′-methoxyphenyl)-propyl]piperazine (27) was synthesized from **21** according to synthetic method B (Scheme 4): ^{1}H NMR ($CDCl_3$) δ 1.73−1.81 (m, 2H), 2.36 (t, J = 7.8 Hz, 2H), 2.48−2.55 (m, 8H), 2.57 (t, J = 7.5 Hz, 2H), 3.56 (t, J = 6.0 Hz, 2H), 3.79 (s, 3H), 5.33 (s, 1H), 6.81−6.83 (d, J = 7.8 Hz, 3H), 7.08−7.11 (d, J = 8.1 Hz, 2H), 7.16−7.35 (m, 10H); MS (CI-NH_3) m/z 445 (MH+). Anal. **27**·2 maleate ($C_{29}H_{36}N_2O_2 \cdot 2C_4H_4O_4$) C, H, N.

1-[2-[Bis(4-fluorophenylmethoxy)ethyl]-4-[3-(4′-methoxyphenyl)propyl]piperazine (28) was synthesized from **22** according to synthetic method B (Scheme 4): ^{1}H NMR ($CDCl_3$) δ 1.73−1.81 (m, 2H), 2.36 (t, J = 7.8 Hz, 2H), 2.48−2.55 (m, 8H), 2.57 (t, J = 7.5 Hz, 2H), 3.56 (t, J = 6.0 Hz, 2H), 3.79 (s, 3H), 5.33 (s, 1H), 6.81−6.83 (d, J = 7.8 Hz, 3H), 6.97−7.04 (m, 4H), 7.08−7.11 (d, J = 8.1 Hz, 2H), 7.16−7.29 (m, 5H); MS (CI-NH_3) m/z 481 (MH+). Anal. **28**·2 maleate ($C_{29}H_{34}N_2F_2O_2 \cdot 2C_4H_4O_4$) C, H, N.

Synthetic Method D. A 1 M solution of L-Selectride in THF (15 mL) was added to the methyl ether (3−5 mmol, product from synthetic method C). The reaction mixture was heated at reflux for 18−24 h and then cooled to room temperature. Water was added, and the layers were separated. The aqueous portion was extracted with chloroform, and the organic portions were combined, washed (water, brine), dried (Na_2SO_4), and concentrated, affording a bright yellow oil. The phenolic analogues were purified by silica gel column chromatography (chloroform−methanol, 20:1), followed by conversion to the bis-maleate salt and recrystallization from 2-propanol−ethanol.

1-[2-(Diphenylmethoxy)ethyl]-4-[1-(2′-hydroxyphenyl)-propenyl]piperazine (5) was synthesized from **17** according to synthetic method D: ^{1}H NMR ($CDCl_3$) δ 2.60 (m, 8H), 2.70 (t, J = 5.8 Hz, 2H), 3.18 (d, J = 6.8 Hz, 2H), 3.60 (t, J = 5.8 Hz, 2H), 5.35 (s, 1H), 6.35 (m, 1H), 6.73−6.88 (m, 2H), 6.86 (m, 1H), 7.08 (m, 1H), 7.20−7.34 (complex m, 11H); MS (CI-NH_3) m/z 429 (MH+). Anal. **5**·2 maleate ($C_{28}H_{32}N_2O_2 \cdot 2C_4H_4O_4$) C, H, N.

1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-[1-(2′-hydroxyphenyl)propenyl]piperazine (6) was synthesized from **18** according to synthetic method D (Scheme 4): ^{1}H NMR ($CDCl_3$) δ 2.60 (m, 8H), 2.69 (t, J = 5.9 Hz, 2H), 3.19 (d, J = 6.8 Hz, 2H), 3.57 (t, J = 5.9 Hz, 2H), 5.32 (s, 1H), 6.27−6.37 (m, 1H), 6.74−6.80 (m, 2H), 6.87 (m, 1H), 6.97−7.04 (m, 4H), 7.10 (m, 1H), 7.24−7.29 (m, 4H), 7.35 (m, 1H); MS (CI-NH_3) m/z 465 (MH+). Anal. **6**·2 maleate ($C_{28}H_{30}N_2F_2O_2 \cdot 2C_4H_4O_4$) C, H, N.

1-[2-(Diphenylmethoxy)ethyl]-4-[1-(2′-hydroxyphenyl)-propenyl]piperazine (7) was synthesized from **19** according to synthetic method D (Scheme 4): ^{1}H NMR ($CDCl_3$) δ 2.59 (m, 8H), 2.70 (t, J = 5.8 Hz, 2H), 3.15 (d, J = 6.8 Hz, 2H), 3.60 (t, J = 5.8 Hz, 2H), 5.36 (s, 1H), 6.16−6.26 (m, 1H), 6.41−6.47 (m, 1H), 6.60 (m, 1H), 6.68−6.71 (m, 1H), 6.79 (bs, 1H), 6.87−6.90 (m, 1H), 7.20−7.34 (complex m, 11H); MS (CI-NH_3) m/z 429 (MH+). Anal. **7**·2 maleate ($C_{28}H_{32}N_2O_2 \cdot 2C_4H_4O_4 \cdot 0.25H_2O$) C, H, N.

Synthetic Method E. To a stirred solution of 3-chloropropiophenone (100 g, 581 mmol) in 1.0 L of acetone was added piperazine **3** or **4** (ca. 400 mmol, in 800 mL of acetone). The reaction was stirred at room temperature for 12−18 h (overhead mechanical stirrer) and concentrated at reduced pressure. The resultant residue was partitioned between 1 L of chloroform and 500 mL of dilute aqueous ammonia. The layers were separated; the organic portion was washed with brine, dried (Na_2SO_4), and concentrated to a yellow oil. The crude ketone was purified by conversion to the bis-maleate salt and recrystallization from methanol.

1-[2-(Diphenylmethoxy)ethyl]-4-(3-oxo-3-phenylpropyl)-piperazine (29) was synthesized from **3** according to synthetic method E (Scheme 5): ^{1}H NMR ($CDCl_3$) δ 2.63 (m, 8H), 2.73 (t, J = 6.0 Hz, 2H), 2.90 (t, J = 7.5 Hz, 2H), 3.23 (t, J = 7.5 Hz, 2H), 3.62 (t, J = 6.3 Hz, 2H), 5.37 (s, 1H), 6.97−7.03 (m, 4H), 7.25−7.29 (m, 4H), 7.43−7.49 (m, 2H), 7.53−7.59 (m, 1H), 7.95 (d, J = 7.8 Hz, 1H); MS (CI-NH_3) m/z 429 (MH+). Anal. **29**·2 maleate ($C_{28}H_{32}N_2O_2 \cdot 2C_4H_4O_4$) C, H, N.

1-[2-[Bis(4-fluorophenylmethoxy)ethyl]-4-(3-oxo-3-phenylpropyl)piperazine (30)[51] was synthesized from **4** according to synthetic method E (Scheme 5)T **30**·2 maleate, mp 165−166 °C,(lit.[32] mp 165−166 °C); ^{1}H NMR ($CDCl_3$) δ 2.55 (m, 8H),

2.67 (t, J = 6.0 Hz, 2H), 2.84 (t, J = 7.5 Hz, 2H), 3.18 (t, J = 7.5 Hz, 2H), 3.56 (t, J = 6.3 Hz, 2H), 5.33 (s, 1H), 7.24−7.33 (m, 10H), 7.43−7.49 (m, 2H), 7.53−7.59 (m, 1H), 7.95 (d, J = 7.8 Hz, 1H); MS (CI-NH_3) m/z 465 (MH+). Anal. **30**·2 maleate ($C_{28}H_{30}N_2F_2O_2$·$2C_4H_4O_4$) C, H, N.

Synthetic Method F. Lithium aluminum hydride (ca. 3 g, 95% powder, 80 mmol) was added carefully to 200 mL of dry THF at room temperature. The flask was cooled with a water−ice bath, and the ketone (100 mmol, in 200 mL of THF) was added via an addition funnel over 30−40 min. The reaction was stirred for an additional 30 min and quenched using the basic workup.[52] The precipitated aluminum salts were removed by filtration of the quenched reaction mixture through a pad of Celite. The cake was washed three times with portions of THF and the organic portions were combined and concentrated at reduced pressure. The alcohol was purified by conversion to either the bis-maleate salt (see synthetic methods A, B, C) or the bis-HCl salt (recrystallized from 2-propanol).

(±)-1-[2-(Diphenylmethoxy)ethyl]-4-(3-hydroxy-3-phenylpropyl)piperazine (31) was synthesized from **29** according to synthetic method F (Scheme 5): ^{1}H NMR ($CDCl_3$) δ 1.84−1.88 (m, 2H), 2.59 (m, complex, 10H), 2.71 (t, J = 5.9 Hz, 2H), 3.60 (t, J = 6.0 Hz, 2H), 4.93 (t, J = 6.6 Hz, 1H), 5.37 (s, 1H), 7.25−7.39 (m, complex, 15H); MS (CI-NH_3) m/z 431 (M^+). Anal. **31**·2 maleate ($C_{28}H_{34}N_2O_2$·$2C_4H_4O_4$) C, H, N.

(±)-1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-hydroxy-3-phenylpropyl)piperazine (32)[43] was synthesized from **30** according to synthetic method F (Scheme 5): **32**·2HCl, mp 216−218 °C (lit.[43] mp 216−218 °C); ^{1}H NMR ($CDCl_3$) δ 1.84−1.88 (m, 2H), 2.59 (m, complex, 10H), 2.68 (t, J = 5.7 Hz, 2H), 3.57 (t, J = 6.0 Hz, 2H), 4.93 (t, J = 6.6 Hz, 1H), 5.34 (s, 1H), 6.98−7.04 (m, 4H), 7.25−7.39 (m, complex, 9H); MS (CI-NH_3) m/z 467 (M^+). Anal. **32**·2HCl ($C_{28}H_{32}N_2F_2O_2$·2HCl) C, H, N.

Synthetic Method G. *R*-(+)- or *S*-(−)-3-Chloro-1-phenyl-1-propanol (10 mmol; Aldrich, 99% ee/gc) was added to a stirred solution of **3** or **4** (7 mmol, in 30 mL of DMF). Potassium carbonate (20−25 mmol) was added, followed by sodium iodide (11 mmol). The reaction was stirred at 70−80 °C for 18−24 h, cooled to room temperature, and poured into 200 mL of water. The resultant creamy suspension was extracted into ether (3 × 100 mL) and the organic portions were combined, washed with brine, dried ($MgSO_4$), and concentrated. The product was purified by conversion to the bis-maleate salt and recrystallization from methanol.

***(R)*-(+)-1-[2-(Diphenylmethoxy)ethyl]-4-(3-hydroxy-3-phenylpropyl)piperazine (33)** was synthesized from **3** according to synthetic method G (Scheme 6): ^{1}H NMR ($CDCl_3$) δ 1.84−1.88 (m, 2H), 2.59 (m, complex, 10H), 2.71 (t, J = 5.9 Hz, 2H), 3.60 (t, J = 6.0 Hz, 2H), 4.93 (t, J = 6.6 Hz, 1H), 5.37 (s, 1H), 7.25−7.39 (m, complex, 15H); MS (CI-NH_3) m/z 431 (M^+); $[\alpha]_D^{20}$ = +10.0° (c 0.86, DMF). Anal. **33**·2 maleate ($C_{28}H_{34}N_2O_2$·$2C_4H_4O_4$) C, H, N.

***(R)*−(+)-1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-hydroxy-3-phenylpropyl)piperazine (34)** was synthesized from **4** according to synthetic method G (Scheme 6): ^{1}H NMR ($CDCl_3$) δ 1.84−1.88 (m, 2H), 2.59 (m, complex, 10H), 2.68 (t, J = 5.7 Hz, 2H), 3.57 (t, J = 6.0 Hz, 2H), 4.93 (t, J = 6.6 Hz, 1H), 5.34 (s, 1H), 6.98−7.04 (m, 4H), 7.25−7.39 (m, complex, 9H); MS (CI-NH_3) m/z 467 (M^+); $[\alpha]_D^{20}$ = +12.5 (c 1.59, MeOH). Anal. **34**·2 maleate ($C_{28}H_{32}N_2F_2O_2$·$2C_4H_4O_4$) C, H, N.

***(S)*-(−)-1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-hydroxy-3-phenylpropyl)piperazine (36)** was synthesized from 4 according to synthetic method G (Scheme 6): ^{1}H NMR ($CDCl_3$) δ 1.84−1.88 (m, 2H), 2.59 (m, complex, 10H), 2.68 (t, J = 5.7 Hz, 2H), 3.57 (t, J = 6.0 Hz, 2H), 4.93 (t, J = 6.6 Hz, 1H), 5.34 (s, 1H), 6.98−7.04 (m, 4H), 7.25−7.39 (m, complex, 9H); MS (CI-NH_3) m/z 467 (M^+); $[\alpha]_D^{20}$ = −12.4° (c 1.60, MeOH). Anal. **36**·2 maleate ($C_{28}H_{32}N_2F_2O_2$·$2C_4H_4O_4$) C, H, N.

The optical purity of compounds **34** and **36** was determined by ^{19}F and ^{1}H NMR spectral analysis of the Mosher esters of these compounds. To a stirred solution of **34** or **36** (15 mg), triethylamine (0.2 mL), and 4-(dimethylamino)pyridine (DMAP; 20 mg) in CH_2Cl_2 (3 mL) was added (*R*)−(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl; 30 μL; Fluka ChiraSelect Reagent, 99% [99+% ee/GLC]). After reaction completion (TLC analysis), 3-(dimethylamino)propylamine (0.2 mL) was added, and the mixture stirred for an additional 15 min. Silica gel was added and the solvent removed at reduced pressure. The residue was loaded onto a short silica gel column and eluted with 50−100% ethyl acetate/*n*-hexane to afford the purified Mosher ester. The diastereomeric ratio was determined by spectral comparison of the optically active compound (ester of **34** or **36**) with the product derived from the racemic compound (**32**).

(±)-1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-hydroxy-3-phenylpropyl)piperazine decanoate (41)[43,51] was synthesized according to synthetic method H, Scheme 5). To a stirred solution of 96.5 g of **32** (207 mmol) in 800 mL of pentene-stabilized, ethanol-free $CHCl_3$ was added decanoyl chloride (70 mL, 330 mmol) over 20−30 min. The reaction was stirred for 12 h at room temperature and then concentrated in vacuo. The crude decanoyl ester **41** was converted to the bis-maleate salt in portions. A 24-g portion of crude **41** (39 mmol) was dissolved in 75 mL of MeOH, and the solution was heated to boiling and treated with 11.7 g of maleic acid (100 mmol, 2.5 equiv). The salt crystallized and was collected on a filter. The snow-white crystalline product was washed twice with petroleum ether and air-dried, affording 29.4 g of **41**·2 maleate (34 mmol, 87% from the free base): mp 152−154 °C (lit.[43] mp 154−155 °C). Several batches of the bis-maleate salt (102 g, 120 mmol) were combined and partitioned between 500 mL of $CHCl_3$ and 500 mL of dilute aq $NaHCO_3$. The aqueous portion was discarded, and the organic fraction was washed with water and brine, dried over Na_2SO_4, concentrated at reduced pressure, and dried in vacuo (0.1 mmHg) to constant weight, affording 67 g of **41** (free base), as an almost colorless, viscous oil (108 mmol, 90% from the bis-maleate salt): ^{1}H NMR ($CDCl_3$) δ 0.87 (3H, t, J = 6.7 Hz), 1.24 (12H, bs), 1.60 (2H, t, J = 6.9 Hz), 1.87−1.95 (1H, m), 2.03−2.18 (1H, m), 2.31 (2H, t, J = 7.5 Hz), 2.43 (4H, m), 2.53 (4H, m), 2.66 (2H, t, J = 6.0 Hz), 3.55 (2H, t, J = 6.0 Hz), 5.33 (1H, s), 5.81 (1H, t, J = 6.9 Hz), 7.00 (4H, m), 7.24−7.34 (9H, m, ar); MS (CI-NH_3) m/z 621 (M^+). Anal. **41**·2 maleate ($C_{38}H_{50}N_2F_2O_3$·$2C_4H_4O_4$·$1CH_3OH$) C, H, N.

(±)-1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-hydroxy-3-phenylpropyl)piperazine Decanoate (41) (50% solution in sesame oil).[43,51] The purified free base **41** (67 g) was dissolved in 400 mL of Et_2O and combined with 67 g of sesame oil (Sigma Catalog No. S-7131), and the resultant solution was stirred for 1 h, concentrated on the rotovap, and dried in vacuo (0.1 mmHg) for 16 h, at which time constant mass was reached (134.1 g, calculated as a 49.9% w/w solution in sesame oil).

Biological Methods. Binding assays for the DAT and SERT followed published procedures[36] and used 0.01 nM [^{125}I]RTI-55[53] (s.a. = 2200 Ci/mmol). Briefly, 12- × 75-mm polystyrene test tubes were prefilled with 100 μL of drug, 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), EDTA (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).

The [^{3}H]DA and [^{3}H]5-HT uptake assays also proceeded according to published procedures.[54] Briefly, synaptosomes were prepared by homogenization of rat caudate (for [^{3}H]DA reuptake) or whole rat brain minus cerebellum (for [^{3}H]5-HT reuptake) in ice-cold 10% sucrose, using a Potter-Elvehjem homogenizer. After a 1000*g* centrifugation for 10 min at 4 °C, the supernatants were retained on ice. The uptake assays were initiated by the addition of 100 μL of synaptosomes to 12- ×

75-mm polystyrene test tubes prefilled with 750 μL of [^{3}H]-ligand (5 nM final concentration) in a Krebs-phosphate buffer (pH 7.4), which contained ascorbic acid (1 mg/mL) and pargyline (50 μM) (buffer), 100 μL of test drugs made up in buffer, and 50 μL of buffer. The nonspecific uptake of each [^{3}H]ligand was measured by incubations in the presence of 1 μM **1a** ([^{3}H]-DA) and 10 μM fluoxetine ([^{3}H]5-HT). The incubations were terminated after 20 min ([^{3}H]DA) or 30 min ([^{3}H]5-HT) of incubation at 25 °C by adding 4 mL of wash buffer (10 mM Tris-HCl, pH 7.4, containing 0.9% NaCl at 25 °C) followed by rapid filtration over Whatman GF/B filters and one additional wash cycle. The Krebs-phosphate buffer contained 154.5 mM NaCl, 2.9 mM KCl, 1.1 mM $CaCl_2$, 0.83 mM $MgCl_2$, and 5 mM glucose. The tritium retained on the filters was counted, in a Taurus beta counter, after an overnight extraction into ICN Cytoscint cocktail.

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.[49] Experimental sessions were conducted 5 days a week in separate sound- and light-attenuating chambers, in a manner similar to previous reports.[34,43] Lever pressing was maintained by a multiple chained fixed-interval (FI) 10-min FR 30 (food) chained FI 10-min FR 30 (cocaine) schedule. Completion of the FI chain component produced the second component of the chain schedule, 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 **34**, **36**, and **1b** 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 **1b** was always tested last. Doses of each drug or vehicle were infused intravenously over about 15 min starting 30 min prior to 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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References

(1) Johanson, C.-E.; Fischman, M. W. The Pharmacology of Cocaine Related to its Abuse. *Pharmacol. Rev*. **1989**, *41*, 3−52.
(2) Benowitz, N. L. Clinical Pharmacology and Toxicology of Cocaine. *Pharmacol. Toxicol*. **1993**, *72*, 3−12.
(3) Das, G. Cocaine Abuse in North America: A Milestone in History. *J. Clin. Pharmacol*. **1993**, *33*, 296−310.
(4) Musto, D. F. Opium, Cocaine, and Marijuana in American History. *Sci. Am*. **1991**, *265*, 40−47.
(5) Warner, E. A. Cocaine Abuse. *Ann. Intern. Med*. **1993**, *119*, 226−235.
(6) Tims, F. M.; Leukfeld, C. G. Treatment of Cocaine Abusers: Issues and Perspectives. In *Cocaine Treatment: Research and Clinical Perspectives*; Tims, F. M., Leukfeld, C. G., Eds.; U.S. Department of Health and Human Services: Washington, DC, 1993; pp 1−14.
(7) White, P. T. Coca − An Ancient Herb Turns Deadly. *Natl. Geographic* **1989**, *175*, 3−47.
(8) (a) McCoy, C. B.; Inciardi, J. A. *Sex Drugs, and the Continuing Spread of AIDS*; Roxbury Publishing Co.: Los Angeles, CA, 1995. (b) Hser, Y.-I.; Chih-Ping, C.; Hoffman, V.; Anglin, M. D. Cocaine Use and High-Risk Sexual behavior Among STD Clinic Patients. *Sex. Transm. Dis*. **1999**, *26*, 82−86. (c) McCoy, C. B.; Metsch, L. R.; Inciardi, J. A.; Anwyl, R. S.; Wingerd, J.; Bletzer, K. Sex, Drugs, and the Spread of HIV/AIDS in Belle Glade, Florida. *Med. Anthrop. Quart*. **1996**, *10*, 83−93.
(9) Mitscher, L. A.; Baker, W. Tuberculosis: A Search for Novel Therapy Starting with Natural Products. *Med. Res. Rev*. **1998**, *18*, 363−374.
(10) For an excellent review, see: Goodkin, K.; Shapshak, P.; Metsch, L. R.; McCoy, C. B.; Crandall, K. A.; Kumar, M.; Fujimura, R. K.; McCoy, V.; Zhang, B. T.; Reyblat, S.; Xin, K.-Q.; Kumar, A. M. Cocaine Abuse and HIV-1 Infections: Epidemiology and Neuropathogenesis. *J. Immunol*. **1998**, *83*, 88−101 and references therein. See also: Bolla, K. I.; Rothman, R.; Cadet, J. L. Dose-related Neurobehavioral Effects of Chronic Cocaine Use. *J. Neuropsych. Clin. Neurosci*. **1999**, *11*, 361−369.
(11) The National Narcotic Intelligence Consumers Committee (NNICC) Report, 1997. *The Supply of Illicit Drugs to the United States*; Drug Enforcement Administration Publication DEA-98036, November 1998.
(12) (a) Wise, R. A. Catecholamine Theories of Reward. A Critical Review. *Brain Res*. **1978**, *152*, 215−247. (b) Kuhar, M. J. Molecular Pharmacology of Cocaine: A Dopamine Hypothesis and its Implications. In *Cocaine: Scientific and Social Dimensions*; Bock, G. R., Whelan, J., Eds.; John Wiley & Sons: New York, 1992; pp 81−95.
(13) (a) Kuhar, M. J.; Ritz, M. C.; Boja, J. W. The Dopamine Hypothesis of the Reinforcing Properties of Cocaine. *Trends Neurosci*. **1991**, *14*, 299−302. (b) Ritz, M. C.; Lamb, R. J.; Goldberg, S. R.; Kuhar, M. J. Cocaine Receptors on Dopamine Transporters are Related to Self-Administration of Cocaine. *Science* **1987**, *237*, 1219−1223.
(14) Rothman, R. B.; Mele, A.; Reid, A. A.; Akunne, H.; Greig, N.; Thurkauf, A.; Rice, K. C.; Pert, A. Tight Binding Dopamine Inhibitors as Cocaine Antagonists. A Strategy for Drug Development. *FEBS Lett*. **1989**, *257*, 341−344.
(15) Rothman, R. B. High Affinity Dopamine Reuptake Inhibitors as Potential Cocaine Antagonists: A Strategy for Drug Development. *Life Sci*. **1990**, *46*, PL217−PL221.
(16) Rothman, R. B.; Glowa, J. R. A Review of the Effects of Dopaminergic Agents on Humans, Animals and Drug Seeking Behavior, and its Implications for Medication Development: Focus on GBR 12909. *Mol. Neurobiol*. **1995**, *11*, 1−19.
(17) Ohuoha, D. C.; Maxwell, J. A.; Thomson, L. E.; Cadet, J. L.; Rothman, R. B. Effect of Dopamine Receptor Antagonists on Cocaine Subjective Effects: a Naturalistic Case Study. *J. Subst. Abuse Treat*. **1997**, *14*, 249−258.
(18) For a review, see: Villemagne, V.; Rothman, R. B.; Yokoi, F.; Rice, K. C.; Matecka, D.; Clough, D. J.; Dannals, R. F.; Wong, D. F. Doses of GBR 12909 Which Suppress Cocaine Self-Administration in Non-Human Primates Substantially Occupy DA Transporters as Measured by [^{11}C]WIN 35,428 PET Scans. *Synapse* **1999**, *32*, 44−50.
(19) Rocha, B. A.; Fumagalli, F.; Gainetdinov, R. R.; Jones, S. R.; Ator, R.; Giros, B.; Miller, G. W.; Caron, M. G. Cocaine Self-Administration in Dopamine-Transporter Knockout Mice. *Nature Neurosci*. **1998**, *1*, 132−137.
(20) Sora, I.; Wichems, C.; Takahashi, N.; Li, X. F.; Zeng, Z.; Revay, R.; Lesch, K. P.; Murphy, D. L.; Uhl, G. R. Cocaine Reward Models: Conditioned Place Preference can be Established in Dopamine- and in Serotonin-Transporter Knockout Mice. *Proc. Natl. Acad. Sci. U.S.A*. **1998**, *95*, 7699−7704.
(21) Chen, N.; Trowbridge, C. G.; Justice, J. B., Jr. Voltammetric Studies on Mechanisms of Dopamine Efflux in the Presence of Substrates and Cocaine from Cells Expressing Human Norepinephrine Transporter. *J. Neurochem*. **1998**, *71*, 653−665.
(22) Tanda, G.; Pontieri, F. E.; Frau, R.; Di Chiara, G. Contribution of Blockade of the Noradrenaline Carrier to the Increase of Extracellular Dopamine in the Rat Prefrontal Cortex by Amphetamine and Cocaine. *Eur. J. Neurosci*. **1997**, *9*, 2077−2085.
(23) Yamamoto, B. K.; Novotney, S. Regulation of Extracellular Dopamine by the Norepinephrine Transporter. *J. Neurochem*. **1998**, *71*, 274−280.
(24) Kelly, J. P. In *Principles of Neural Science, 2nd ed*.; Kandel, E. R., Schwartz, J. H., Eds.; Elsvier: New York; 1985; pp 537−561.

(25) Koe, B. K. Molecular Geometry of Inhibitors of the Uptake of Catecholamines and Serotonin in Synaptosomal Preparations of Rat Brain. *J. Pharmacol. Exp. Ther.* **1976**, *199*, 649−661.
(26) Rothman, R. B.; Greig, N.; Kim, A.; de Costa, B. R.; Rice, K. C.; Carroll, F. I.; Pert, A. Cocaine and GBR 12909 Produce Equivalent Motoric Responses at Different Occupancy of the Dopamine Transporter. *Pharmacol. Biochem. Behav.* **1992**, *43*, 1135−1142.
(27) Carroll, F. I.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Cocaine Receptor: Biochemical Characterization and Structure−Activity Relationship Studies of Cocaine Analogues at the Dopamine Transporter. *J. Med. Chem.* **1992**, *35*, 969−981.
(28) Madras, B. K.; Spealman, R. D.; Fahey, M. A.; Neumeyer, J. L.; Saha, J. K.; Milius, R. A. Cocaine Receptors Labeled by [^{3}H]2β-carbomethoxy-3β-(fluorophenyl)tropane. *Mol. Pharmacol.* **1989**, *36*, 518−524.
(29) (a) Meltzer, P. C.; Liang, A. Y.; Madras, B. K. The Discovery of an Unusually Selective and Novel Cocaine Analog: Difluoropine. Synthesis and Inhibition of Binding at Cocaine Recognition Sites. *J. Med. Chem.* **1994**, *37*, 2001−2010. (b) Newman, A. H.; Alen, A. C.; Izenwasser, S.; Katz, J. L. Novel 3α-(Diphenylmethoxy)-tropane Analogues: Potent Dopamine Uptake Inhibitors Without Cocaine-like Behavioral Profiles. *J. Med. Chem.* **1994**, *37*, 2258−2261.
(30) (a) Aeberli, P.; Eden, P.; Gogerty, J. H.; Houlihan, W. J.; Penberthy, C. 5-Aryl-2,3-dihydro-5*H*-imidazo[*2,1-a*]isoindol-5-ols. A Novel Class of Anorectic Agents. *J. Med. Chem.* **1975**, *18*, 177−182. (b) Berger, P.; Gawin, F.; Koster, T. R. Treatment of Cocaine Abuse with Mazindol. *Lancet* **1989**, *1*, 283.
(31) (a) Anderson, P. H. Biochemical and Pharmacological Characterization of [^{3}H]GBR 12935 Binding in vitro to Rat Striatal Membrane; Labeling of the Dopamine Uptake Complex. *J. Neurochem.* **1987**, *48*, 1887−1896. (b) Berger, P.; Janowsky, A.; Vocci, F.; Skolnick, P.; Schweri, M. M.; Paul, S. M. [^{3}H]GBR 12935: A Specific High Affinity Ligand for Labeling the Dopamine Transporter Complex. *Eur. J. Pharmacol.* **1985**, *107*, 289−290. (c) Bonnet, J.-J.; Protais, P.; Chagraoui, A.; Costentin, J. High Affinity [^{3}H]GBR 12783 Binding to a Specific Site Associated with the Neuronal Dopamine Uptake Complex in the Central Nervous System. *Eur. J. Pharmacol.* **1986**, *126*, 211−222.
(32) (a) van der Zee, P.; Koger, H. S.; Gootjes, J.; Hespe, W. Aryl 1,4-Dialk(en)ylpiperazines as Selective and Very Potent Inhibitors of Dopamine Uptake. *Eur. J. Med. Chem.* **1980**, *15*, 363−370. (b) Piperazine Derivatives, and Pharmaceutical Compositions Containing Them. Netherlands Patent 8202636A, Jan 16, 1984; *Chem. Abstr.* **1984**, *100*, 191909. (c) Gootjes, J. European Patent 0 099 148 B1, Feb 17, 1988. (d) Gootjes, J. U.S. Patent 4,476,129, Oct 9, 1984.
(33) (a) Vignon, J.; Pinet, V.; Cerruti, C.; Kamenka, J.-M.; Chicheportiche, R. [^{3}H]*N*-[1-(2-Benzo(*b*)thiophenyl)cyclohexyl]piperidine ([^{3}H]BTCP): A New Phencyclidine Analogue Selective for the Dopamine Uptake Complex. *Eur. J. Pharmacol.* **1988**, *148*, 427−436. (b) Schweri, M. M.; Skolnick, P.; Rafferty, M. F.; Rice, K. C.; Janowsky, A. J.; Paul, S. M. [^{3}H]Threo-(±)-methylphenidate Binding to 3,4-Dihydroxyphenylethylamine uptake Sites in Corpus Striatum: Correlation to the Stimulant Properties of Ritalinic Acid Esters. *J. Neurochem.* **1985**, *45*, 1062−1070.
(34) Glowa, J. R.; Wojnicki, F. H. E.; Matecka, D.; Rice, K. C.; Rothman, R. B. Effects of Dopamine Reuptake Inhibitors on Food- and Cocaine-Maintained Responding: II. Comparisons With Other Drugs and Repeated Administrations. *Exp. Clin. Psychopharmacol.* **1995**, *3*, 232−239.
(35) Matecka, D.; Rothman, R. B.; Radesca, L.; de Costa, B. R.; Dersch, C. M.; Partilla, J. S.; Pert, A.; Glowa, J. R.; Wojnicki, F. H. E.; Rice, K. C. Development of Novel, Potent, and Selective Dopamine Reuptake Inhibitors through Alteration of the Piperazine Ring of 1-[2-(Diphenylmethoxy)ethyl]- and 1-[2-[Bis-(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazines (GBR 12935 and GBR 12909). *J. Med. Chem.* **1996**, *39*, 4704−4716.
(36) Matecka, D.; Lewis, D.; Rothman, R. B.; Dersch, C. M.; Wojnicki, F. H. E.; Glowa, J. R.; DeVries, A. C.; Pert, A.; Rice, K. C. Heteroaromatic Analogues of 1-[2-(Diphenylmethoxy)ethyl]- and 1-[2-[Bis-(4-fluorophenyl)methoxy] ethyl]-4-(3-phenylpropyl)piperazines (GBR 12935 and GBR 12909) as High-Affinity Dopamine Reuptake Inhibitors. *J. Med. Chem.* **1997**, *40*, 705−716.
(37) Zhang, Y. The Identification of GBR 12909 as a Potential Therapeutic Agent for Cocaine Abuse. *Med. Chem. Res.* **1998**, *8*, 66−76.
(38) Longer, M. A.; Robinson, J. R. Sustained-Release Delivery Systems. In *Remington's Pharmaceutical Sciences*, 18th ed.; Gennaro, A. R., Editor-in-Chief; Mack Publishing Co.: Easton, PA, 1990; pp 1676−1693.
(39) Krowczynski, L. *Extended-Release Dosage Forms*; CRC Press: Boca Raton, FL, 1987; pp 59−95.
(40) (a) Florence, A. T.; Vezin, W. R. Prolongation of the Action of Intramuscular Formulations of Phenothiazines. In *Optimization of Drug Delivery (Alfred Benzon Symposium 17)*; Bundgaard, H., Bagger Hansen, A., Kofod, H., Eds.; Munksgaard Publishing Co.: Copenhagen, Denmark, 1981; pp 93−111. (b) Dreyfuss, J.; Ross, J. J.; Shaw, J. M.; Miller, I.; Schreiber, E. C. Release and Elimination of ^{14}C−Fluphenazine Enanthate and Decanoate Esters Administered in Sesame Oil to Dogs. *J. Pharm. Sci.* **1976**, *65*, 502−507.
(41) Krowczynski, L. *Extended-Release Dosage Forms*; CRC Press: Boca Raton, FL, 1987; pp 1−19.
(42) *Physician's Desk Reference*, 53rd ed.; Medical Economics: Oradell, NJ, 1999; pp 865, 2121, 2190, 2397, 2472, 3131.
(43) Glowa, J. R.; Fantegrossi, W. E.; Lewis, D. B.; Matecka, D.; Rice, K. C.; Rothman, R. B. Sustained Decrease in Cocaine-Maintained Responding in Rhesus Monkeys with 1-[2-[Bis-(4-fluorophenyl)methoxy]-ethyl]-4-(3-hydroxy-3-phenylpropyl)piperazinyl Decanoate, a Long-Acting Ester Derivative of GBR 12909. *J. Med. Chem.* **1996**, *39*, 4689−4691.
(44) The alkylation step gave a mixture of the desired monosubstituted piperazine **3** or **4** (major) and the bis-1,4-dialkylated byproduct (minor), along with unreacted piperazine. The piperazine could be removed by repeated washing with water, and the remaining mixture could be purified by partition between 10% aqueous citric acid and chloroform (or dichloromethane), the desired product (**3** or **4**) remaining in the citric acid (aqueous) layer and the bis-alkylated byproduct remaining in the organic layer.
(45) Wissner, A.; Grudzinskas, C. V. Reaction of *tert*-Butyldimethylsilyl Esters with Oxalyl Chloride-Dimethylformamide: Preparation of Carboxylic Acid Chlorides under Neutral Conditions. *J. Org. Chem.* **1978**, *43*, 3972−3974.
(46) Yoon, N. M.; Brown, H. C. Selective Reductions. XII. Exploration in Some Representative Applications of Aluminum Hydride for Selective Reductions. *J. Am. Chem. Soc.* **1968**, *90*, 2927−2938.
(47) (a) Coop, A.; Lewis, J. W.; Rice, K. C. Direct and Simple O-Demethylation of Thebaine to Oripavine. *J. Org. Chem.* **1996**, *61*, 6774. (b) Majetich, G.; Zhang, Y.; Wheless, K. Hydride-promoted Demethylation of Methyl Phenyl Ethers. *Tetrahedron Lett.* **1994**, *35*, 8727−8730. (c) Coop, A.; Janetka, J. W.; Lewis, J. W.; Rice, K. C. L-Selectride as a General Reagent for the O-Demethylation and N-Decarbomethoxylation of Opium Alkaloids and Derivatives. *J. Org. Chem.* **1998**, *63*, 4392−4396.
(48) Robertson, D. W.; Krushinski, J. H.; Fuller, R. W.; Leander, J. D. Absolute Configurations and Pharmaceutical Activities of the Optical Isomers for Fluoxetine, a Selective Serotonin-Uptake Inhibitor. *J. Med. Chem.* **1988**, *31*, 1412−1417.
(49) Wojnicki, F. H. E.; Bacher, J. B.; Glowa, J. R. Use of Subcutaneous Vascular Access Ports in Rhesus Monkeys. *Lab. Anim. Sci.* **1994**, *44*, 491−494.
(50) Stafford, D.; Rice, K. C.; Glowa, J. R. GBR 12909 Decanoate Produces Long-lasting Decreases in Cocaine-Reinforced Progressive Ratio Responding. *Abstracts of 61st Annual Meeting, College on Problems of Drug Dependence*; Acapulco, Mexico, **1999**; in press.
(51) A preliminary procedure for the synthesis of this compound was described in the Supporting Information for ref 43.
(52) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; John Wiley and Sons: New York; Vol 1, p 584.
(53) Rothman, R. B.; Cadet, J. L.; Akunne, H. C.; Silverthorn, M. L.; Baumann, M. H.; Carroll, F. I.; Rice, K. C.; de Costa, B. R.; Partilla, J. S.; Wang, J.-B.; Uhl, G. U.; Glowa, J. R.; Dersch, C. M. Studies of the Biogenic Amine Transporters. IV. Demonstration of a Multiplicity of Binding Sites in Rat Caudate Membranes for the Cocaine Analogue [^{125}I]RTI-55. *J. Pharmacol. Exp. Ther.* **1994**, *270*, 296−309.
(54) Rothman, R. B.; Lewis, B.; Dersch, C. M.; Xu, X.; Radesca, L.; de Costa, B. R.; Rice, K. C.; Kilburn, R. B.; Akunne, H. C.; Pert, A. Identification of a GBR 12935 Homolog, LR 1111, Which is over 4,000-fold Selective for the Dopamine Transporter, Relative to Serotonin and Norepinephrine Transporters. *Synapse* **1993**, *14*, 34−39.

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