Structure−Activity Relationships at Monoamine Transporters and Muscarinic Receptors for *N*-Substituted-3α-(3′-chloro-, 4′-chloro-, and 4′,4″-dichloro-substituted-diphenyl)methoxytropanes

Amy Hauck Newman,*[,†] Michael J. Robarge,[†,§] Ileana M. Howard,[†] Sharine L. Wittkopp,[†] Clifford George,[‡] Theresa Kopajtic,[#] Sari Izenwasser,[#,||] and Jonathan L. Katz[#]

Medicinal Chemistry and Psychobiology Sections, National Institute on Drug Abuse−Intramural Research Program, Baltimore, Maryland 21224, and Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, D.C. 20375

Received September 26, 2000

The design, synthesis, and evaluation of 3α-(diphenylmethoxy)tropane (benztropine) analogues have provided potent and selective probes for the dopamine transporter. Structure−activity relationships (SARs) have been developed that contrast with those described for cocaine, despite significant structural similarity. Furthermore, behavioral evaluation of many of the benztropine analogues in animal models of cocaine abuse has suggested that these two classes of tropane-based dopamine uptake inhibitors have distinct pharmacological profiles. In general, the benztropine analogues do not demonstrate efficacious locomotor stimulation in mice, do not fully substitute for a cocaine discriminative stimulus, and are not appreciably self-administered in rhesus monkeys. These compounds are generally more potent than cocaine as dopamine uptake inhibitors in vitro, although their actions in vivo are not consistent with this action. These observations suggest that differing binding profiles at the serotonin and norepinephrine transporters as well as at muscarinic receptors might have significant impact on the pharmacological actions of these compounds. In addition, by varying the structures of the parent compounds and thereby modifying their physical properties, pharmacokinetics as well as pharmacodynamics will be directly affected. Therefore, in an attempt to systematically evaluate the impact of chemical modification on these actions, a series of *N*-substituted (H, CH_3, allyl, benzyl, propylphenyl, and butylphenyl) analogues of 3′-chloro-, 4′-chloro-, and 4,4″-dichloro-3α-(diphenylmethoxy)tropanes were synthesized. These compounds were evaluated for displacement, in rat tissue, of [^{3}H]WIN 35,428 from the dopamine transporter, [^{3}H]citalopram from the serotonin transporter, [^{3}H]nisoxetine from the norepinephrine transporter, and [^{3}H]-pirenzepine from muscarinic m_1 receptors. SARs were developed and compared to a series of *N*-substituted-3α-(bis-4′-fluorophenyl)methoxytropanes. The present SARs followed previously reported studies with the single exception of the *N*-butylphenyl substituent, which did not provide the high affinity binding in any of these three sets of analogues, as it did in the 4′,4″-difluoro series. X-ray crystallographic analyses of the three parent ligands (**1a**, **2a**, and **3a**) were compared to that of 3α-(bis-4′-fluorophenyl)methoxytropane which provided supportive evidence toward the proposal that the combination of steric bulk in both the 3-position and the *N*-substituent, in this class of compounds, is not optimal for binding at the dopamine transporter. These studies provide binding profile data that can now be used to correlate with future behavioral analyses of these compounds and may provide insight into the kind of binding profile that might be targeted as a potential treatment for cocaine abuse.

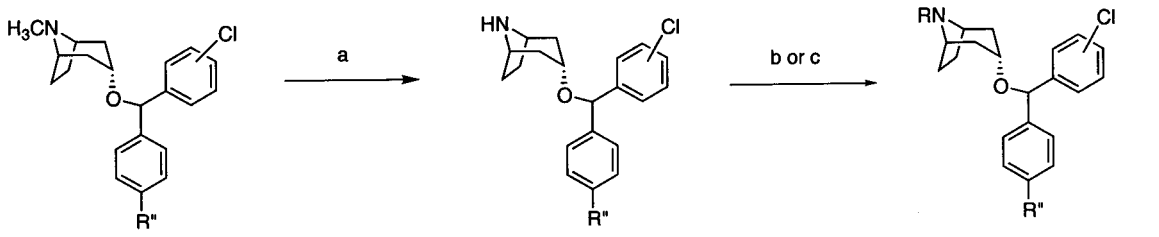
Introduction

Devising mechanistic correlates to the behavioral actions of cocaine has led researchers initially to the dopaminergic system[1−4] and more recently toward a number of different targets that may directly (serotonin system) or indirectly (excitatory or inhibitory amino acids, opioid receptor ligands) affect cocaine's actions.[5] A recent review by Carroll and colleagues has described the preclinical development of potential pharmacotherapies for cocaine abuse.[6] It has been suggested that the profile of an ideal medication would be one that has high affinity and selectivity at a targeted receptor or transporter, has minimal side effects, and would have a suitably long duration of action that would decrease the number of daily dosages required.[6] Furthermore, it has been suggested that a compound that penetrated the blood−brain barrier relatively slowly may not have the abuse liability that compounds that have a rapid central onset of action possess.[6] A review of the patent literature from 1997−2000 reflects these directions in the development of cocaine abuse medications[7] and yet highlights

* To whom correspondence should be addressed at Medicinal Chemistry Section, NIDA-IRP, 5500 Nathan Shock Dr., Baltimore, MD 21224. Tel: 410-550-1455. Fax: 410-550-1648. E-mail: anewman@intra.nida.nih.gov.
† Medicinal Chemistry Section, NIDA-IRP.
# Psychobiology Section, NIDA-IRP.
‡ Naval Research Laboratory.
§ Current address: Celgene Corp., Warren, NJ 07059.
|| Current address: Dept. of Neurology, University of Miami School of Medicine, Miami, FL 33136.

10.1021/jm000417f
Published on Web 01/12/2001

Scheme 1[a]



1a; 3'Cl, R"=H
2a; 4'Cl, R"=H
3a; 4'Cl, R"=Cl

1b; 3'Cl, R"=H
2b; 4'Cl, R"=H
3b; 4'Cl, R"=Cl

1c; R=allyl,3'Cl, R"=H
1d; R=benzyl,3'Cl, R"=H
1e; R=propylphenyl,3'Cl, R"=H
1f; R=butylphenyl,3'Cl, R"=H
2c; R=allyl, 4'Cl, R"=H
2d; R=benzyl, 4'Cl, R"=H
2e; R=propylphenyl, 4'Cl, R"=H
2f; R=butylphenyl, 4'Cl, R"=H
3c; R=allyl, 4'Cl, R"=Cl
3d; R=benzyl, 4'Cl, R"=Cl
3e; R=propylphenyl,4'Cl, R"=Cl
3f; R=butylphenyl, 4'Cl, R"=Cl

[a] (a) 1. ACE-Cl, 2. MeOH; (b) method A: RBr, DMF; (c) method B: 1. RCOOH, DCC, HOBt, 2. AlH_3.

the major advances and interest that remains focused on the dopamine transporter.[8,9]

A significant focus of our research program has been on novel dopamine transport inhibitors that have pharmacological profiles distinct from that of cocaine.[10−12] One class of agents is based on 3α-(diphenylmethoxy)-tropane (benztropine) which is a potent cholinergic antagonist, prescribed for the treatment of Parkinson's disease. Benztropine also blocks the reuptake of dopamine and has an affinity at the dopamine transporter equal to that of cocaine.[10,11] Syntheses of several series of 3-substituted,[11,13] *N*-substituted,[14−16] and 2-substituted analogues of benztropine[16,17] have revealed structure−activity relationships (SARs) at the dopamine transporter that differ significantly from that of cocaine and its analogues. CoMFA studies for these compounds have provided models for optimal binding at the dopamine transporter as well as insight into topological features of the binding site at which these compounds have been proposed to interact.[15,18] These studies have further underscored the differences in structural requirements for binding of benztropine versus cocaine analogues, at the dopamine transporter, despite their shared tropane base structure. Furthermore, many of the benztropine analogues have been evaluated in various animal models of cocaine abuse, and although, in general, they do not appear to be cocaine-like, significant variance in their behavioral profiles, when compared to one another, has been noted.[12] A goal of this research has been to identify both mechanistic and pharmacokinetic characteristics that may be useful to exploit in order to provide new leads toward potential medications for cocaine abuse. Although the design of these compounds has been targeted toward the dopamine transporter, some chemical modifications have led to significant decreases in muscarinic receptor binding and increases in binding affinities at the serotonin transporter.[14,15] As these compounds are developed as potential cocaine-abuse treatments, the entire binding profile, not just binding affinity at the dopamine transporter, will be evaluated with regard to its relevance to these compounds' behavioral actions. At this stage, although the dopamine transporter has been targeted for this therapeutic endpoint, in the absence of a successful cocaine-abuse medication, it is currently unknown whether interactions at these other sites may also have relevance and importance in the ideal pharmacotherapeutic profile.

In this study, a series of compounds were designed wherein the 3α-diphenylmethyl ether system was substituted with 3′-chloro, 4′-chloro, or 4′,4″-dichloro groups. Previous studies have shown that these small halogen substitutions would be well-tolerated at the dopamine transporter but had little effect on muscarinic receptor binding.[11,18] These substituent patterns, however, have yielded different behavioral profiles among the parent agents (**1a**, **2a**, and **3a**).[12,13,19,20] In addition, the tropane nitrogen was substituted in each series with the following substituents: CH_3 (**a** series), H (**b** series), allyl (**c** series), benzyl (**d** series), propylphenyl (**e** series), and butylphenyl (**f** series). These substituents were chosen due to their pharmacological activities (high affinity and selectivity for the dopamine transporter) in the previously reported 4′,4″-difluoro series of compounds.[14,21] In addition, we were interested in (1) determining whether the CoMFA models in the individually substituted (3 vs N) groups would apply when substitutions were combined (*N*-substituted-3-substituted) and (2) how these substitution patterns might affect binding profiles at the other monoamine transporters (serotonin and norepinephrine) and muscarinic receptors.

Results and Discussion

Chemistry. The parent compounds **1a**, **2a**, and **3a** were prepared as previously described.[11,13] In Scheme 1, *N*-demethylation using α-chloroethyl chloroformate (ACE-Cl) in 1,2-dichloroethane followed by methanolysis[14] gave the respective *N*-nor compounds **1b**, **2b**, and **3b**. The *N*-allyl analogues (**1c**, **2c**, **3c**) were prepared in anhydrous DMF with allyl bromide and anhydrous K_2CO_3, followed by purification as the HCl salts. The *N*-benzyl analogues (**1d, 2d**, **3d**) were prepared in an analogous manner using benzyl bromide as the alkylating agent. The propylphenyl (**1e**, **2e**, **3e**) and butylphenyl (**1f**, **2f**, **3f**) analogues were prepared via their respective amides. Either **1b**, **2b**, or **3b** was treated with dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) in dry DMF and triethylamine and either

Table 1. Physical Properties of Novel Compounds

compd	method	% yield	recryst solvent	mp, °C	chemical formula[a]
1b		62	MeOH/acetone	205−207	$C_{20}H_{22}NOCl\cdot HCl$
2b		54	MeOH/acetone/ether	>250	$C_{20}H_{22}NOCl\cdot HCl$
3b		59	acetone	250−252	$C_{20}H_{21}NOCl_2\cdot HCl$
1c	A	57	2-PrOH/ether	195	$C_{23}H_{26}NOCl\cdot HCl$
1d	A	70	EtOAc/ether	162−164	$C_{27}H_{28}NOCl\cdot HCl$
1e	B	58	EtOAc/ether	151−153	$C_{29}H_{32}NOCl\cdot HCl$
1f	B	55	EtOAc/ether	140−142	$C_{30}H_{34}NOCl\cdot HCl$
2c	A	67	acetone/ether	182−184	$C_{23}H_{26}NOCl\cdot HCl$
2d	A	70	acetone/ether	178−180	$C_{27}H_{28}NOCl\cdot HCl$
2e	B	78	MeOH	192−193	$C_{29}H_{32}NOCl\cdot HBr$
2f	B	60	MeOH	199−201	$C_{30}H_{34}NOCl\cdot HBr$
3c	A	45	2-PrOH/ether	197−199	$C_{23}H_{25}NOCl_2\cdot HCl$
3d	A	67	MeOH/acetone/ether	200−203	$C_{27}H_{27}NOCl_2\cdot HCl\cdot 0.25H_2O$
3e	B	73	MeOH	172−173	$C_{29}H_{31}NOCl_2\cdot HBr$
3f	B	50	2-PrOH/ether	185−187	$C_{30}H_{33}NOCl_2\cdot HCl$

[a] Anal. C, H, N ±0.4%.

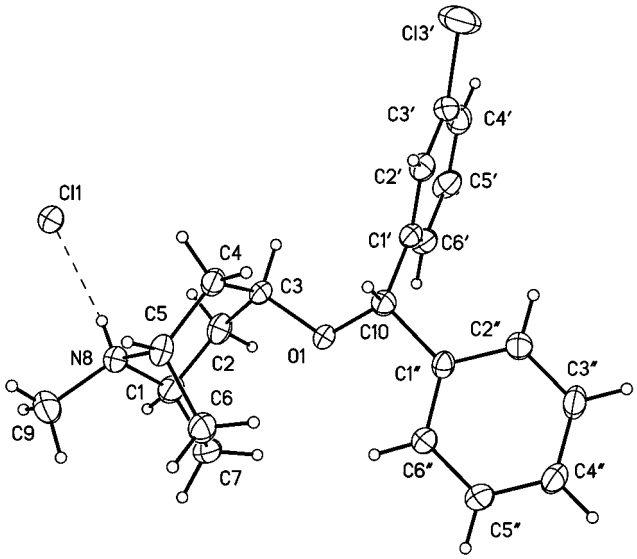


Figure 1. Molecular structure and numbering scheme for **1a** salt with displacement ellipsoids drawn at the 30% probability level. The $CHCl_3$ solvate was eliminated for clarity.

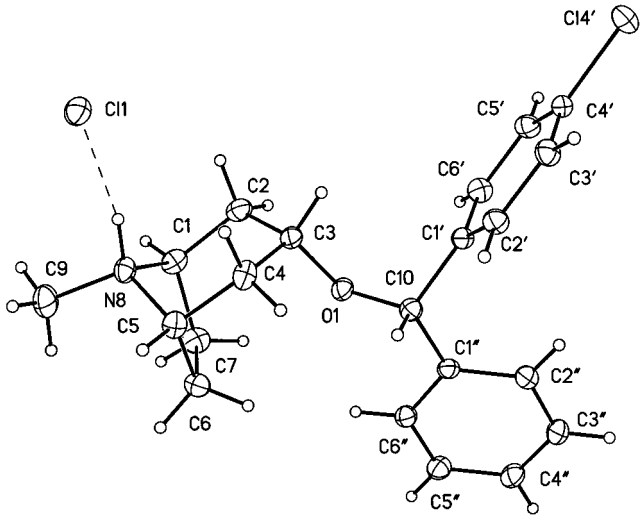


Figure 2. Molecular structure and numbering scheme for **2a** salt with displacement ellipsoids drawn at the 30% probability level.

hydrocinnamic or phenylbutyric acid to give the respective amide intermediates. Reduction of the amides to the respective amines was accomplished with AlH_3 followed by purification as the HCl or HBr salts. The physical properties and method of *N*-substitution of all final products can be seen in Table 1.

X-ray Analyses of Compounds 1a, 2a, and 3a. Compounds **1a**, **2a**, and **3a** were recrystallized as HCl salts. Compound **1a** was obtained as the $CHCl_3$ solvate and **3a** as a $CHCl_3-H_2O$ solvate in the ratio of 2 molecules of **3a** and 6 molecules of H_2O to 0.5 molecule of $CHCl_3$. The X-ray crystallographic structures for **1a**, **2a**, and **3a** are shown in Figures 1−3, respectively. As expected, the geometries of the three cations are very similar, with the 3-bis(substituted-phenyl)methoxy substituent to the piperidine rings axial. The phenyl ring orientations are defined by torsions C3−C10−O1−C1′ and C3−C10−O1−C1″ in each. These are (63.0, −174.0)°, (62.3, −174.3)°, and (77.1, −160.7 and 76.8, −160.8)° respectively in **1a**, **2a**, and the two molecules of **3a**. This geometry places the N to centroid of the phenyl ring carbons distances consistently at near 7 Å. Values for the N to (′) and (″) centroid are (6.85, 7.03), (6.86, 7.06), and (6.96, 6.96 and 6.99, 6.98) Å for **1a**, **2a**, and **3a**. The difference between the **1a** and **2a** geometries is only in their 3′- and 4′-chloro substituents. A least-squares fit of their common atoms has an average deviation of only 0.04 Å. A further comparison of **3a** to **1a** and **2a** shows differences primarily in the relative orientation of the

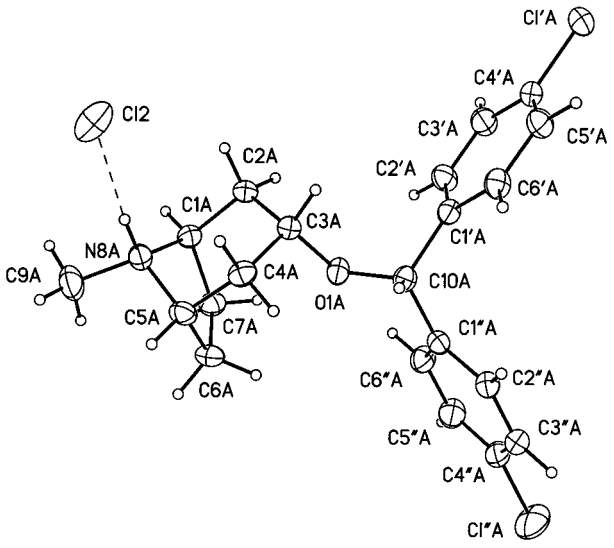
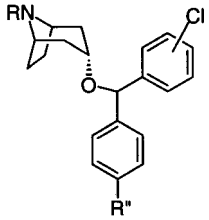


Figure 3. Molecular structure and numbering scheme for one of the two nearly identical **3a** cations with displacement ellipsoids drawn at the 30% probability level. The $CHCl_3-H_2O$ solvate was eliminated for clarity.

Table 2. Binding Results for *N*-Substituted-3-substituted-3α-(diphenylmethoxy)tropanes



				K_i, nM, ±SEM[a]			
compd	R	R′	R″	[^{3}H]WIN 35,428	[^{3}H]citalopram	[^{3}H]nisoxetine	[^{3}H]pirenzepine
1a	CH_3	3′-Cl	H	21.6 ± 1.5[b]	258 ± 19.1[d]	451 ± 62.5[d]	0.98 ± 0.01[b]
1b	H	3′-Cl	H	26.2 ± 2.1	2100 ± 285	508 ± 70.0	91.7 ± 8
1c	allyl	3′-Cl	H	33.6 ± 3.4	1200 ± 154	1230 ± 71.0	69.7 ± 7.13
1d	benzyl	3′-Cl	H	191 ± 15.3	1680 ± 235	6460 ± 882	674 ± 71.2
1e	propylphenyl	3′-Cl	H	101 ± 11.1	429 ± 53.9	1810 ± 192	337 ± 14.0
1f	butylphenyl	3′-Cl	H	153 ± 19.9	591 ± 73.3	1470 ± 76.4	564 ± 48.5
2a	CH_3	4′-Cl	H	30.0 ± 3.6[b]	5120 ± 395[d]	1470 ± 180[d]	7.90 ± 0.85
2b	H	4′-Cl	H	36.8 ± 3.3	1320 ± 194	1010 ± 116	95.5 ± 12.7
2c	allyl	4′-Cl	H	84.2 ± 7.6	2330 ± 166	4720 ± 690	127 ± 18.7
2d	benzyl	4′-Cl	H	365 ± 25.5	3530 ± 403	12990 ± 629	2560 ± 365
2e	propylphenyl	4′-Cl	H	148 ± 16.3	302 ± 15.3	10300 ± 660	397 ± 21.9
2f	butylphenyl	4′-Cl	H	53.3 ± 6.4	737 ± 38.8	2320 ± 276	1430 ± 202
3a	CH_3	4′-Cl	4″-Cl	20.0 ± 2.8[c]	1640 ± 236[d]	2980 ± 182[d]	47.9 ± 5.2
3b	H	4′-Cl	4″-Cl	61.7 ± 6.2	727 ± 41.0	6040 ± 693	649 ± 61.2
3c	allyl	4′-Cl	4″-Cl	54.6 ± 7.1	568 ± 27.2	4140 ± 438	127 ± 12.2
3d	benzyl	4′-Cl	4″-Cl	399 ± 27.9	3610 ± 214	7660 ± 1240	8630 ± 1300
3e	propylphenyl	4′-Cl	4″-Cl	158 ± 20.5	585 ± 60.1	19800 ± 3090	3050 ± 329
3f	butylphenyl	4′-Cl	4″-Cl	85.0 ± 8.5	659 ± 42.0	4950 ± 324	3730 ± 493

[a] Each K_i value represents data from at least three independent experiments, each performed in triplicate. [b] Data from ref 13. [c] Data from ref 10. [d] Data from ref 19.

phenyl rings. The dihedral angles between the phenyl ring planes are 95.1°, 90.1°, and (70.6 and 70.3)° for the 3′-chloro-, 4′-chloro-, and 4′,4″-dichloro-substituted compounds.

SARs. The binding data for all of the compounds at the dopamine, serotonin, and norepinephrine transporters, as well as at muscarinic receptors, can be seen in Table 2. Previously, we discovered that small halogens on the *meta*- or *para*-positions of one or both phenyl rings were well-tolerated at the dopamine transporter, when the tropane nitrogen was substituted with a methyl group.[10,11,13,18] Because the 4′,4″-difluoro-substituted analogue was the most potent in our first series, we chose to investigate the effect of various *N*-substituents to optimize both binding affinity and selectivity at the dopamine transporter.[14,15] The *N*-substituents that were chosen for the present study were based on those substituents that were found to have good activity at the dopamine transporter in the 4′,4″-difluoro series[14,15] and did not produce cocaine-like behavioral effects.[21]

In general, the pattern of activity at the dopamine transporter in the present series (3′-chloro, 4′-chloro, 4′,4″-dichloro) was analogous to that observed in the previous series (4′,4″-difluoro) of compounds. Although dopamine transporter and muscarinic receptor binding was reported previously, K_i values and relative selectivities at the serotonin and norepinephrine transporters were not. All three compounds (**1a**, **2a**, **3a**) demonstrated relatively low affinities for both the serotonin and norepinephrine transporters resulting in compounds with good selectivity for the dopamine transporter. This was particularly true for the *para*-substituted compounds **2a** and **3a** where selectivity ratios for DAT/SERT were 171 and 82, respectively, and those for DAT/NET were 50 and 150, respectively.

Removal of the *N*-methyl substituent (**1b**, **2b**, **3b**) did not adversely effect binding affinity at the dopamine transporter (K_i range = 26.2−61.7 nM). Likewise the *N*-allyl group (**1c**, **2c**, **3c**) was tolerated with only a small decrease in affinity (K_i range = 33.6−84.2 nM). As described previously[14] and confirmed by CoMFA,[15] a phenyl group in close proximity to the tropane nitrogen, such as a benzyl group (**1d**, **2d**, **3d**), caused a significant decrease in binding affinity (K_i range = 191−399 nM). However, extending the phenyl ring away from the tropane nitrogen by a propyl linker (**1e**, **2e**, **3e**) (K_i range = 101−158 nM) or butyl linker (**1f**, **2f**, **3f**) restored binding affinity at the dopamine transporter to values that were similar to the parent compounds (K_i = 53−153 nM). Nevertheless, in contrast to the 4′,4″-dfluoro series, the *N*-butylphenyl substituent did not result in the most potent analogues in the present series of compounds. In fact, replacing the N-CH_3 group of any of the present parent compounds either decreased or had no effect on binding affinity at the dopamine transporter.

None of the analogues in the present series binds with high affinity at the serotonin transporter, as with the 4′,4″-difluoro series of compounds, although in all three series the *N*-propylphenyl substituent (**1e**, **2e**, **3e**) resulted in the highest affinities (K_i range = 302−585 nM). Likewise, binding affinities at the norepinephrine transporter were uniformly poor (K_i > 500 nM).

Binding affinities at muscarinic receptors were decreased by 10−1000-fold when the *N*-methyl group was replaced with any substituent. The larger substituents such as butylphenyl (**1f**, **2f**, **3f**) had the most deleterious

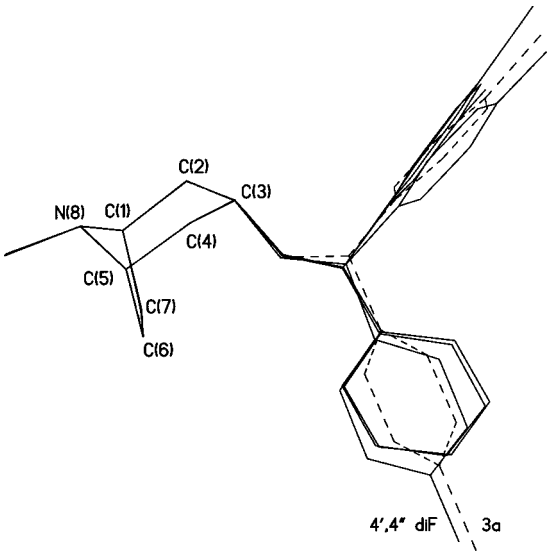


Figure 4. Overlay of **1a**, **2a**, **3a**, and 3α-(4′-bisfluorophenyl)-methoxytropane.

effect on muscarinic receptor binding (K_i = 564−3730 nM). Unfortunately, due to a concomitant decrease in binding affinity at the dopamine transporter, which was not observed in the 4′,4″-difluoro series, selectivities greater than those previously reported[14,15] were not achieved. This is likely due to the combination of increased steric bulk at both the 3-position diphenylmethyl ether and the tropane nitrogen resulting in a less than optimal binding interaction. A CoMFA model of the 3-position in the benztropine series of compounds predicted that increasing steric bulk at the *para*-position of the phenyl rings would decrease binding affinity at the dopamine transporter, with the 4′,4″-difluoro substituent being optimal.[15] However, the 3′-chloro-, 4′-chloro-, and 4′4″-dichloro substituents yielded compounds that were only 2-fold less potent than the 4′4″-difluoro analogue. Although the CoMFA model generated in the 4′4″-difluoro series predicted the *N*-butylphenyl substituent to be optimal, this did not hold true in the present series of compounds suggesting that increased steric bulk in both positions is not optimal for binding at the dopamine transporter.

One explanation may be gleaned from the X-ray analyses of the parent compounds in the present study when these structures are compared to the 4′,4″-difluoro analogue. The geometry of the 4′,4″-difluoro compound[11] has N to phenyl centroid distances of 7.05 and 6.94 Å, essentially equal to those in **1a**, **2a**, and **3a**. The N to 4′-chloro distance in **2a** is 9.45 Å. The same distances in **3a** are 9.66, 9.58, and 9.55, 9.51 Å for the 4′- and 4″-chloro atoms, respectively. These are comparable to the N−F distances of 9.37 and 9.22 Å in the 4′,4″-difluoro analogue and differ from the N−Cl distances in **2a** and **3a** by about the difference in the C−F and C−Cl bond lengths. However, when the tropane ring systems of the respective compounds are overlaid, Figure 4, the equivalent F and Cl atoms are displaced from each other by a maximum of (0.52, 0.66) and (1.16, 0.96) Å, adding to the effective steric bulk.

Summary

In summary, we have prepared a series of benztropine analogues in which the 3-position diphenylmethoxy rings were substituted with either the 3′-chloro-, 4′-chloro-, or 4′,4″-dichloro groups. For each of the parent compounds **1a**, **2a**, and **3a**, X-ray crystallographic analysis was performed in order to compare the conformations of the parent molecules. Furthermore, the N−CH_3 group of each parent molecule was removed (**1b**, **2b**, **3b**) and replaced with allyl (**1c, 2c, 3c**), benzyl (**1d, 2d, 3d**), propylphenyl (**1e, 2e, 3e**), and butylphenyl (**1f, 2f, 3f**) substituents so that a uniform comparison could be made at each transporter system and at muscarinic receptors. SARs reveal trends that were analogous to those described previously in the 4′4″-difluoro series of compounds.[14,15] However, the *N*-butylphenyl substituent, which conferred the highest affinity and selectivity for dopamine transporters in the previous series of compounds, did not provide the same profile in the present series of compounds. In fact, replacement of the N-CH_3 group in all three series of compounds either had no effect or had a negative effect on binding affinity and selectivity at the dopamine transporter.

The novel analogues in this report will provide additional tools with which to characterize the relationships between chemical structure, behavior, and binding profile. In addition, ongoing pharmacokinetic and pharmacodynamic studies with these agents may reveal structural features that can be considered and optimized toward the development of potential cocaine-abuse therapeutics.

Experimental Methods

Chemistry. All melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker (Billerica, Mass) AC-300 instrument. Samples were dissolved in an appropriate deuterated solvent ($CDCl_3$ or CD_3OD). Proton chemical shifts are reported as parts per million (δ) relative to tetramethylsilane (Me_4Si; 0.00 ppm) which was used as an internal standard. Infrared spectra were recorded as a neat film on NaCl plates with a Perkin-Elmer 1600 Series FTIR. Microanalyses were performed by Atlantic Microlab, Inc. (Norcross, GA) and agree within ±0.4% of calculated values for C, H, N. TLC solvent used was $CHCl_3$/MeOH/NH_4OH, 90:10:1, unless otherwise indicated. All chemicals and reagents were purchased from Aldrich Chemical Co. or Lancaster Synthesis, Inc. unless otherwise indicated and used without further purification.

Synthesis. Representative Method for *N*-Demethylation. Nor-3α-[(3′-chlorophenyl)methoxy]tropane Hydrochloride, 1b. *N*-Demethylation of 3α-[(3′-chlorophenyl)-methoxy]tropane (**1a**) was achieved by a modification of the method previously described.[14] The hydrochloride salt of **1a** (18.39 g, 48.8 mmol) was converted to its free base form by extracting with $CHCl_3$ (3 × 75 mL) from 20% aq NH_4OH (100 mL), drying and evaporating to an oil. Under an atmosphere of argon, the oil was dissolved in freshly distilled (over P_2O_5) 1,2-dichloroethane (150 mL). Anhydrous Na_2CO_3 (20.68 g, 195 mmol) and ACE-Cl (22.05 mL, 195 mmol) was added and allowed to stir at reflux for 3 h. The reaction was filtered and the filtrate was evaporated to the crude oil which was dissolved in MeOH (100 mL) and allowed to stir at room temperature overnight, under argon. The product precipitated from MeOH and was isolated and recrystallized in acetone/MeOH to give 9.56 g (54%) of pure **1b**: mp 205−207 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73−1.94 (m, 6H), 2.21 (d, J = 7.5 Hz, 2H), 3.37 (br s, 2H), 3.61 (br s, 1H), 5.36 (s, 1H), 7.19−7.34 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.4, 36.9, 37.2, 53.5, 70.0, 76.6, 77.0, 77.4, 80.2, 124.9, 126.8, 127.3, 127.4, 128.4, 129.5, 134.2, 142.2, 145.2; IR (neat film NaCl plate) 1064, 1185, 1601, 2594, 2885 cm^{-1}. Anal. ($C_{20}H_{22}NOCl$·HCl) C, H, N.

Representative Method for *N*-Alkylation. Method A: *N*-Benzyl-3α-[(3′-chlorophenyl)methoxy]tropane Hydrochloride, 1d. *N*-Alkylation of *N*-nor-3α-[(3′-chlorophenyl)-methoxy]tropane (**1b**) was achieved by a modification of the method previously described.[14] Compound **1b** (1.095 g, 3.0 mmol) was converted to the free base form and dissolved in dry DMF (10.0 mL). Anhydrous Na_2CO_3 (0.35 g, 6.0 mmol) and benzyl bromide (0.39 mL, 3.3 mmol) were added and the reaction mixture was allowed to stir at room temperature, under argon overnight. The reaction mixture was diluted with H_2O (100 mL) and extracted with ether (3 × 50 mL). The combined organic fraction was washed with H_2O (2 × 50 mL) and brine (1 × 50 mL) and dried (Na_2SO_4) and filtered. The volatiles were removed in vacuo and the crude oil was purified by flash column chromatography (EtOAc/hexane, 1:2). The product was converted to the HCl salt by dissolving in ether and acidifying to pH 2 with HCl saturated 2-PrOH. Crystallization from EtOAc/ether gave **1d** (0.956 g, 70%): mp 162−164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.79−2.15 (m, 8H), 3.13 (br s, 2H), 3.51 (s, 2H), 3.58 (app t, J = 4.7, 4.5 Hz, 1H), 5.36 (s, H), 7.17−7.37 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 36.3, 36.5, 56.6, 58.1, 70.0, 76.6, 77.0, 77.4, 80.1, 124.9, 126.6, 126.8, 127.3, 127.4, 128.1, 128.4, 128.5, 129.6, 134.6, 140.1, 142.4, 145.4; IR (neat film NaCl plate) 1063, 1100, 1402, 1455, 2493, 2967 cm^{-1}. Anal. ($C_{27}H_{28}ClNO$·HCl) C, H, N.

Representative Method for *N*-Alkylation. Method B: *N*-(3-Propylphenyl)-3α-[(3′-chlorophenyl)methoxy]tropane Hydrochloride, 1e. *N*-Amidation of *N*-nor-3α-[(3′-chlorophenyl)methoxy]tropane (**1b**) followed by reduction was achieved by a modification of the method previously described.[14] Compound **1b** (1.46 g, 4.0 mmol) was converted to the free base form and with triethylamine (1.23 mL, 8.8 mmol) was added to a mixture of hydrocinnamic acid (0.60 g, 4.0 mmol), dicyclohexylcarbodiimide (DCC; 0.91 g, 4.4 mmol) and 1-hydroxbenzotriazole hydrate (HOBt; 0.60 g, 4.4 mmol) in dry DMF (40 mL), at 0 °C. The reaction mixture was allowed to stir at 0 °C, under argon, for 1 h and then allowed to warm to room temperature and continued to stir for 48 h. The reaction mixture was diluted with H_2O (60 mL) and extracted from ether (3 × 75 mL). The organic fractions were combined, washed with H_2O (2 × 50 mL) and brine (1 × 50 mL), dried ($MgSO_4$), filtered and evaporated to a yellow oil. The crude product was purified by flash column chromatography (EtOAc, hexane, 2:1) to give the amide (1.71 g, 93%) as a pale yellow oil. $LiAlH_4$ was suspended in anhydrous THF (90 mL) and cooled to 0 °C. Under an atmosphere of argon, H_2SO_4 (0.73 g, 7.4 mmol) was carefully added to the suspension and allowed to stir at 0 °C for 30 min. The intermediate amide (1.71 g, 3.72 mmol) was dissolved in THF (20 mL and added dropwise to the reaction flask via an addition funnel. The reaction mixture was allowed to stir for 30 min at 0 °C and then allowed to warm to room temperature and stir for 4 h. The reaction mixture was cooled to 0 °C and THF/H_2O (2 mL, 1:1) was added dropwise followed by 15% aq NaOH (2 mL). A precipitate formed upon these additions. Ether (100 mL) was added and the mixture was filtered through Celite. The filtrate was dried ($MgSO_4$), filtered and the volatiles were removed in vacuo. The resulting crude oil was purified by flash column chromatography (EtOAc, hexane, 1:1) to give a clear oil that was acidified to pH 2 with HCl saturated MeOH. The resulting HCl salt was crystallized from EtOAc/ether to give 1.05 g (58%) pure **1e**: mp 151−153 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.77−1.94 (m, 8H), 2.09 (d, J = 7.5 Hz, 2H), 2.36 (t, J = 7.3 Hz, 2H), 2.62 (t, J = 7.6 Hz, 2H), 3.17 (br s, 2H), 3.55 (br s, 1H), 5.36 (s, 1H), 7.16−7.33 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 30.4, 33.8, 35.6, 35.8, 51.5, 58.0, 69.9, 76.6, 77.0, 77.4, 80.1, 124.9, 125.6, 126.8, 127.3, 127.4, 128.2, 128.3, 128.4, 129.5, 134.2, 142.2, 142.3, 145.3; IR (neat film NaCl plate) 1052, 1399, 1453, 1595, 2490, 2930 cm^{-1}. Anal. ($C_{29}H_{32}ClNO$·HCl) C, H, N.

Single-Crystal X-ray Diffraction Analysis of 1a, 2a, and 3a. 1a: $C_{21}H_{25}N^+OCl{\cdot}Cl^-{\cdot}CHCl_3$, FW = 497.69, monoclinic space group $P2_1/n$, a = 14.705(1), b = 9.192(1), c = 18.737(1) Å, β = 106.89(1), V = 2423.4(3) Å^3, Z = 4″ ρ_{calc} = 1.364 mg mm^{-3}, λ(Cu Kα) = 1.54178 Å, μ = 5.558 mm^{-1}, F(000) = 1032, T = 293 K.

2a: $C_{21}H_{25}N^+OCl{\cdot}Cl^-$, FW = 378.32, orthorhombic space group *Pbca*, a = 9.122(1), b = 20.334(1), c = 20.847(1) Å, V = 3866.9(4) Å^3, Z = 8, ρ_{calc} = 1.300 mg mm^{-3}, λ(Cu Kα) = 1.54178 Å, μ = 3.075 mm^{-1}, F(000) = 1600, T = 293 K.

The following parameters are common to **1** and **2** and where different they are indicated by enclosure in brackets [ ] for **2a**. A clear colorless 0.38 × 0.30 × 0.09 [0.40 × 0.36 × 012] mm crystal was used for data collection on an automated Bruker P4 diffractometer equipped with an incident beam monochromator. Lattice parameters were determined from 30 [32] centered reflections within 10 < 2θ < 55° [11 < 2θ < 60°]. The data collection range had a $\{(\sin\theta)/\lambda\}_{max}$ = 0.55. Three standards, monitored after every 97 reflections, exhibited random variations with deviations up to ±2.6 [1.9]% during the data collection. A set of 4000 [2747] reflections was collected in the $\theta/2\theta$ scan mode, and ω scan rate (a function of count rate) varied from 7.5 to 30.0°/min. There were 3318 [2648] unique reflections. Corrections were applied for Lorentz, polarization, and absorption effects. The structure was solved with SHELXTL[22] and refined with the aid of the SHELX97 system of programs. The full-matrix least-squares refinement on F^2 varied 325 [229] parameters: atom coordinates and anisotropic thermal parameters for all non-H atoms. H atoms were included using a riding model [coordinate shifts of C applied to attached H atoms, C−H distances set to 0.96−0.93 Å, H angles idealized, U_{iso}(H) were set to 1.2−1.5 U_{eq}(C)]. Final residuals were $R1$ = 0.067 [0.041] for the 2388 [2197] observed data with $F_o > 4\sigma(F_o)$ and 0.091 [0.052] for all data. Final difference Fourier excursions of 0.47 and −0.46 [0.19 and −0.21] eÅ^{-3}. In **1a** the chloroform solvate is disordered over three positions with occupancies of 45, 34 and 21%.

3a: $2(C_{21}H_{24}N^+OCl_2{\cdot}Cl^-){\cdot}6(H_2O){\cdot}1/2(CHCl_3)$, FW = 993.30, monoclinic space group *C2/c*, a = 38.198(2), b = 11.476(1), c = 22.301(1) Å, β = 90.94(1), γ = 9774.3(10) Å^3, Z = 8, ρ_{calc} = 1.350 mg mm^{-3}, λ(Cu Kα) = 1.54178 Å, μ = 4.374 mm^{-1}, F(000) = 4168, T = 293 K.

A clear colorless 0.56 × 0.20 × 0.06 mm crystal was used for data collection with an automated Bruker SMART[23] 1K CCD detector on a Platform goniometer. The Rigaku rotating Cu anode source was equipped with an incident beam Gobel mirrors. Lattice parameters were determined using SAINT[23] from 260 centered reflections within 12 < 2θ < 73°. The data collection range had a $(\sin\theta)/\lambda$ = 0.58. A set of 17808 reflections was collected in the ω scan mode. There were 6695 unique reflections. Corrections were applied for Lorentz, polarization, and absorption effects. The structure was solved with SHELX-TL[22] and refined with the aid of the SHELX97 system of programs. The full-matrix least-squares refinement on F^2 used 19 restraints and varied 592 parameters: atom coordinates and anisotropic thermal parameters for all non-H atoms. H atoms were included using a riding model [coordinate shifts of C applied to attached H atoms, C−H distances set to 0.96−0.93 Å, H angles idealized, U_{iso}(H) were set to 1.2−1.5 U_{eq}(C). Final residuals were $R1$ = 0.077 for the 5522 observed data with $F_o > 4\sigma(F_o)$ and 0.088 for all data. Final difference Fourier excursions of 0.65 and −0.94 eÅ^{-3}. In **3a**, two of the three chlorine ion sites are disordered and share equal occupancy with waters.

Tables of coordinates, bond distances and angles, and anisotropic thermal parameters have been deposited with the Crystallographic Data Centre, Cambridge CB2 1EW, England.

Pharmacology. Dopamine Transporter Binding Assay. Male Sprague−Dawley rats (200−250 g; Taconic, Germantown, NY) were decapitated and their brains removed to an ice-cooled dish for dissection of the caudate putamen. The tissue was homogenized in 30 volumes ice-cold modified Krebs-HEPES buffer (15 mM HEPES, 127 mM NaCl, 5 mM KCl, 1.2 mM $MgSO_4$, 2.5 mM $CaCl_2$, 1.3 mM NaH_2PO_4, 10 mM D-glucose, pH adjusted to 7.4) using a Brinkman polytron and centrifuged at 20000*g* for 10 min at 4 °C. The resulting pellet was then washed two more times by resuspension in ice-cold buffer and centrifugation at 20000*g* for 10 min at 4 °C. Fresh

homogenates were used in all experiments. Binding assays were conducted in modified Krebs-HEPES buffer on ice. The total volume in each tube was 0.5 mL and the final concentration of membrane after all additions was 0.5% (w/v) corresponding to 200−300 μg of protein/sample. Triplicate samples of membrane suspension were preincubated for 5 min in the presence or absence of the compound being tested. [^{3}H]WIN 35,428 (2β-carbomethoxy-3β-(4-fluorophenyl)tropane 1,5-naphthalenedisulfonate, specific activity 82.4 Ci/mmol, final concentration 1.5 nM; from New England Nuclear, Boston, MA) was added and the incubation was continued for 1 h on ice. The incubation was terminated by the addition of 3 mL of ice-cold buffer and rapid filtration through Whatman GF/B glass fiber filter paper (presoaked in 0.1% BSA in water to reduce nonspecific binding) using a Brandel cell harvester (Gaithersburg, MD). The filters were washed with three additional 3 mL washes and transferred to scintillation vials. Absolute ethanol (0.5 mL) and Beckman Ready Value scintillation cocktail (2.75 mL) were added to the vials which were counted the next day at an efficiency of about 36%. Under these assay conditions, an average experiment yielded approximately 6000 dpm total binding per sample and approximately 250 dpm nonspecific binding, defined as binding in the presence of 100 μM cocaine. Each compound was tested with concentrations ranging from 0.01 nM to 100 μM for competition against binding of [^{3}H]WIN 35,428, in three independent experiments, each performed in triplicate.

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

Saturation and displacement data were analyzed by the use of the nonlinear least-squares curve-fitting computer program LIGAND.[24] Data from replicate experiments were modeled together to produce a set of parameter estimates and the associated standard errors of these estimates. In each case, the model reported fit significantly better than all others according to the F test at $p < 0.05$. The K_i values reported are the dissociation constants derived for the unlabeled ligands.

Serotonin Transporter Binding Assay. Brains from male Sprague−Dawley rats weighing 200−225 g (Taconic Labs) were removed, midbrain dissected and rapidly frozen. Membranes were prepared by homogenizing tissues in 20 volumes (w/v) of 50 mM Tris containing 120 mM NaCl and 5 mM KCl (pH 7.4 at 25 °C) using a Brinkman polytron (setting 6 for 20 s) and centrifuged at 50000g for 10 min at 4 °C. The resulting pellet was resuspended in buffer, recentrifuged and resuspended in buffer to a concentration of 15 mg/mL. Ligand binding experiments were conducted in assay tubes containing 0.5 mL buffer for 60 min at room temperature. Each tube contained 1.4 nM [^{3}H]citalopram (NEN) and 1.5 mg midbrain tissue (original wet weight). Nonspecific binding was determined using 10 μM fluoxetine. Incubations were terminated by rapid filtration through Whatman GF/B filters, presoaked in 0.3% polyethylenimine, using a Brandel R48 filtering manifold (Brandel Instruments, Gaithersburg, MD). The filters were washed twice with 5 mL cold buffer and transferred to scintillation vials. Beckman Ready Safe (3.0 mL) was added and the vials were counted the next day using a Beckman 6000 liquid scintillation counter (Beckman Coulter Instruments, Fullerton, CA). Data were analyzed with GraphPad Prism software (San Diego, CA).

Norepinephrine Transporter Binding Assay. Brains from male Sprague−Dawley rats weighing 200−225 g (Taconic Labs) were removed, frontal cortex dissected and rapidly frozen. Membranes were prepared by homogenizing tissues in 20 volumes (w/v) of 50 mM Tris containing 120 mM NaCl and 5 mM KCl (pH 7.4 at 25 °C) using a Brinkman polytron (setting 6 for 20 s) and centrifuged at 50000g for 10 min at 4 °C. The resulting pellet was resuspended in buffer, recentrifuged and resuspended in buffer to a concentration of 80 mg/mL. Ligand binding experiments were conducted in assay tubes containing 0.5 mL buffer for 60 min at 0−4 °C. Each tube contained 0.5 nM [^{3}H]nisoxetine and 8 mg frontal cortex tissue (original wet weight). Nonspecific binding was determined using 1 μM desipramine. Incubations were terminated by rapid filtration through Whatman GF/B filters, presoaked in 0.05% polyethylenimine, using a Brandel R48 filtering manifold (Brandel Instruments, Gaithersburg, MD). The filters were washed twice with 5 mL cold buffer and transferred to scintillation vials. Beckman Ready Safe (3.0 mL) was added and the vials were counted using a Beckman 6000 liquid scintillation counter (Beckman Coulter Instruments, Fullerton, CA). Data were analyzed by using GraphPad Prism software (San Diego, CA).

Muscarinic m_1 Binding Assay. Whole frozen rat brains excluding cerebellum (Taconic, Germantown, NY) were thawed in ice-cold buffer (10 mM Tris-HCl, 320 mM sucrose, pH 7.4) and homogenized with a Brinkman polytron in a volume of 10 mL/g of tissue. The homogenate was centrifuged at 1000g for 10 min at 4 °C. The resulting supernatant was then centrifuged at 10000g for 20 min at 4 °C. The resulting pellet was resuspended in a volume of 5 mL/g in 10 mM Tris buffer (pH 7.4).

Assays were conducted in binding buffer (10 mM Tris-HCl, 5 mM $MgCl_2$). The total volume in each tube was 0.5 mL and the final concentration of membrane after all additions was approximately 200−300 mg of protein/sample. [^{3}H]Pirenzepine (specific activity 73.9 Ci/mmol, final concentration 3 nM; from New England Nuclear, Boston, MA) was added and the incubation was continued for 1 h at 37 °C. The incubation was terminated by the addition of 5 mL of ice-cold buffer (10 mM Tris-HCl, pH 7.4) and rapid filtration through Whatman GF/B glass fiber filter paper (presoaked in 0.5% polyethylenimine in water to reduce nonspecific binding) using a Brandel cell harvester (Gaithersburg, MD). The filters were washed with two additional 5 mL washes and transferred to scintillation vials. Absolute ethanol (0.5 mL) and Beckman Ready Value scintillation cocktail (2.75 mL) were added to the vials that were counted the next day at an efficiency of about 36%. Under these assay conditions, an average experiment yielded approximately 15000 dpm total binding per sample and approximately 900 dpm nonspecific binding, defined as binding in the presence of 10 μM QNB (quinuclidinyl benzilate). Each compound was tested with concentrations ranging from 0.01 nM to 100 μM for competition against binding of [^{3}H]pirenzepine, in at least three independent experiments, each performed in triplicate. Displacement data were analyzed with GraphPad Prism software (San Diego, CA).

Animals. Animals used in this study were maintained in facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC), and all experimentation was conducted according to the guidelines for the *Institutional Care and Use Committee of the Intramural Research Program*, National Institute on Drug Abuse, NIH, and the *Guide for Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources*, National Research Council, Department of Health, Education and Welfare, Publication (NIH) 85-23, revised 1985.

Acknowledgment. M.J.R, I.M.H., and S.L.W. were supported by National Institutes of Health Intramural Research Training Award Fellowships. Single-crystal X-ray analysis was funded in part by the Office of Naval Research and NIDA Contract DA09045.

References

(1) Wise, R. A. Addictive drugs and brain stimulation reward. *Annu. Rev. Neurosci.* **1996** *19*, 319−340.
(2) Kuhar, M. J.; Ritz, M. C.; Boja, J. W. The dopamine hypothesis of the reinforcing properties of cocaine. *Trends Neurosci.* **1991** *14*, 299−301.
(3) 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.
(4) Newman, A. H. Novel Dopamine Transporter Ligands: The State of the Art. *Med. Chem. Res.* **1998**, *8*, 1−11.

(5) Bardo, M. T. Neuropharmacological mechanisms of drug reward: beyond dopamine in the nucleus accumbens**.** *Crit. Rev. Neurobiol.* **1998** *12*, 37−67.
(6) Carroll, F. I.; Howell, L. l.; Kuhar, M. J. Pharmacotherapies for treatment of cocaine abuse: preclinical aspects. *J. Med. Chem.* **1999** *42*, 2721−2736.
(7) Newman, A. H. Novel Pharmacotherapies for Cocaine Abuse 1997−2000. *Exp. Opin. Ther. Pat.* **2000**, *10*, 1095−1122.
(8) Amara, S. G.; Sonders, M. S. Neurotransmitter transporters as molecular targets for addictive drugs. *Drug Alcohol Depend.* **1998** *51*, 87−96.
(9) Smith, M. P.; Hoepping, A.; Johnson, K. M.; Trzcinska, M.; Kozikowski, A. P. Dopaminergic agents for the treatment of cocaine abuse**.** *Drug Discuss. Today* **1999** *4*, 322−332.
(10) Newman, A. H.; Allen, A. C.; Izenwasser, S.; Katz, J. L. Novel 3α-Diphenylmethoxytropane Analogues are Potent Dopamine Uptake Inhibitors without Cocaine-like Behavioral Profiles. *J. Med. Chem.* **1994**, *37*, 2258−2261.
(11) Newman, A. H.; Kline, R. H.; Allen, A. C.; Izenwasser, S.; George, C.; Katz, J. L. Novel 4′- and 4′,4″-Substituted-3α-(Diphenylmethoxy)tropane Analogues are Potent and Selective Dopamine Uptake Inhibitors. *J. Med. Chem.* **1995**, *38*, 3933−3940.
(12) Katz, J. K.; Izenwasser, S.; Kline, R. H.; Allen, A. C.; Newman, A. H. Novel 3α-Diphenylmethoxytropane Analogues: Selective Dopamine Uptake Inhibitors with Behavioral Effects Distinct from those of Cocaine. *J. Pharmacol. Exp. Ther.* **1999**, *288*, 302−315.
(13) Kline, R. H.; Izenwasser, S.; Katz, J. L.; Newman, A. H. 3′-Chloro-3α-(diphenylmethoxy)tropane but not 4′-Chloro-3α-(diphenylmethoxy)tropane Produces a Cocaine like Behavioral Profile. *J. Med. Chem.* **1997**, *40*, 851−857.
(14) Agoston, G. E.; Wu, J. H.; Izenwasser, S.; George, C.; Katz, J.; Kline, R. H.; Newman, A. H. Novel N-Substituted 4′,4″-difluoro-3α-(diphenylmethoxy)tropane Analogues: Selective Ligands for the Dopamine Transporter. *J. Med. Chem.* **1997**, *40*, 4329−4339.
(15) Robarge, M. J.; Agoston, G. E.; Izenwasser, S.; Kopajtic, T.; George, C.; Newman, A. H. Highly Selective Chiral N-Substituted 3α-[bis(4′-fluorophenyl)methoxy]tropane Analogues for the Dopamine Transporter: Synthesis and Comparative Molecular Field Analysis. *J. Med. Chem.* **2000**, *43*, 1085−1093.
(16) Meltzer, P. C.; Liang, A. Y.; Madras, B. K. 2-Carbomethoxy-3-(diarylmethoxy)-1αH,5αH-tropane analogues: Synthesis and inhibition of Binding at the Dopamine Transporter and Comparison with Piperazines of the GBR series. *J. Med. Chem.* **1996**, *39*, 371−379.
(17) 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*, 2001−2110.
(18) Newman, A. H.; Robarge, M.; Izenwasser, S. Kline, R. H. A Comparative Molecular Field Analysis (CoMFA) Study of Novel Ring-Substituted 3α-(Diphenylmethoxy)tropane Analogues at the Dopamine Transporter. *J. Med. Chem.* **1999**, *42*, 3502−3509.
(19) Katz, J. L.; Agoston, G. E.; Alling, K. L.; Kline, R. H.; Forster, M. J.; Woolverton, W. L.; Izenwasser, S.; Kopajtic, T. A.; Newman, A. H. Dopamine Transporter Binding without Cocaine-like Behavioral Effects: Synthesis and Evaluation of Benztropine Analogues Alone and in Combination with Cocaine. *Psychopharmacology* **2001**, in press.
(20) Woolverton, W. L.; Hecht, G. S.; Agoston, G. E.; Newman, A. H.; Katz, J. L. Further Studies of the Reinforcing Effects of Benztropine Analogues in Rhesus Monkeys. *Psychopharmacology* **2001**, in press.
(21) Katz, J. L.; Wu, J. H.; Izenwasser, S.; Newman, A. H. N-Substituted-4′,4″-difluoro-3α-(diphenylmethoxy)tropane analogues: Behavioral Effects. 58th Annual Scientific Meeting of the College on Problems of Drug Dependence, San Juan, Puerto Rico, June 1996.
(22) Sheldrick, G. M. *SHELXTL*, version 5.1; Bruker Analytical X-ray Instruments: Madison, WI, 1997.
(23) *SMART and SAINT, Data Collection and Reduction Software for the SMART system;* Bruker-AXS: Madison, WI, 1995.
(24) Munson, P. J.; Rodbard, D. Ligand: A Versatile Approach for Characterization of Ligand-Binding Systems. *Anal. Biochem.* **1980**, *107*, 220−239.

JM000417F