Structure−Activity Relationships at Monoamine Transporters for a Series of N-Substituted 3α-(Bis[4-fluorophenyl]methoxy)tropanes: Comparative Molecular Field Analysis, Synthesis, and Pharmacological Evaluation

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The development of structure−activity relationships (SAR) with divergent classes of monoamine transporter ligands and comparison of their effects in animal models of cocaine abuse have provided insight into the complex relationship among structure, binding profiles, and behavioral activity. Many 3α-(diphenylmethoxy)tropane (benztropine) analogues are potent dopamine uptake inhibitors but exhibit behavioral profiles that differ from those of cocaine and other compounds in this class. One of the most potent and dopamine transporter (DAT) selective N-substituted benztropine analogues (*N*-(4-phenyl-*n*-butyl)-3α-(bis[4-fluorophenyl]methoxy)-tropane, **1c**) is devoid of cocaine-like behaviors in rodent models but is also highly lipophilic (cLogD = 5.01), which compromises its water solubility and may adversely affect its pharmacokinetic properties. To further explore the SAR in this series and ultimately to design dopamine uptake inhibitors with favorable lipophilicities for drug development, a comparative molecular field analysis (CoMFA) was performed on a set of benztropine analogues previously synthesized in our laboratory. The CoMFA field analysis on the statistically significant (r^2_{cv} = 0.632; r^2_{ncv} = 0.917) models provided valuable insight into the structural features required for optimal binding to the DAT, which was used to design a series of novel benztropine analogues with heteroatom substitutions at the tropane N-8. These compounds were evaluated for binding at DAT, serotonin (SERT) and norepinephrine (NET) transporters, and muscarinic M1 receptors in rat brain. Inhibition of [^{3}H]DA uptake in synaptosomes was also evaluated. Most of the analogues showed high DAT affinity (12−50 nM), selectivity (10- to 120-fold), potent inhibition of dopamine uptake, and lower lipophilicities as predicted by cLogD values.

Introduction

Cocaine is a potent psychomotor stimulant and drug of abuse that binds with moderate affinity to all three monoamine transporters. The primary mechanism by which cocaine exerts its reinforcing and psychomotor stimulant effects is by inhibiting dopamine reuptake through blockade of the dopamine transporter (DAT) and subsequent accumulation of dopamine in mesocorticolimbic regions of the brain.[1−4] Although roles for the other monoamine transporters, serotonin (SERT) and norepinephrine (NET), in the reinforcing actions of cocaine are under intensive investigation, the DAT remains a primary target for the development of cocaine-abuse medications.[5,6] Extensive SAR with structurally different chemical classes of DAT inhibitors and the development of photoaffinity ligands and other molecular tools have provided insight into inhibitor binding site characteristics of the DAT.[7−10] The three-dimensional quantitative structure−activity relationship (3D-QSAR) based models have also been used to understand the binding site topology around several series of tropane-based DAT inhibitors.[11−15]

In general, the 3α(bis[4-fluorophenyl]methoxy)tropanes bound to the DAT with higher affinities than cocaine but had relatively lower affinities for SERT and NET than for DAT.[16−18] Muscarinic receptor binding affinities were significantly reduced when the *N*-methyl group was replaced with substituents with greater steric bulk, resulting in selective DAT ligands.[19−21] Many of these compounds potently blocked dopamine uptake in vitro but did not produce stimulation of locomotor activity or cocaine-like discriminative stimulus effects in rodent models of cocaine abuse.[22,23] Their distinctive SAR, compared to the 3-aryltropane class of DAT inhibitors, and results of photoaffinity labeling experiments suggested that the benztropines bound to a distinctive site or sites on the DAT.[8] It has been proposed that these distinctive interactions at the protein level may contribute to the benztropine's discrepant behavioral profiles.[18,24]

In contrast, perhaps a more important consideration in drug development is the pharmacokinetic properties of the compounds that are related to their physical properties, including lipophilicity.[25] Even if these compounds have potent and selective in vitro actions, poor bioavailability or slow pharmacokinetics could significantly contribute to altering or negating in vivo actions. Recently, a pharmacokinetic and blood−brain barrier penetration study on several of these N-substituted benztropine analogues was conducted.[26] This study demonstrated that these compounds show high brain-to-plasma ratios that are comparable to cocaine. How-

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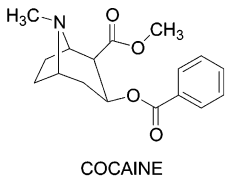
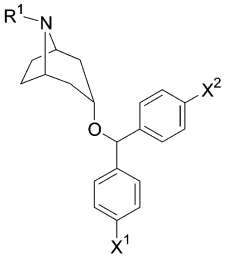


COCAINE



1a, R^1 = H, X^1 = X^2 = F
1b, R^1 = CH_3, X^1 = X^2 = F
1c, R^1 = 4-Phenyl-n-butyl, X^1 = X^2 = F
1d, R^1 = CH_3, X^1 = X^2 = Cl
1e, R^1 = H, X^1 = X^2 = Cl

Figure 1. Chemical structures of cocaine and the parent benztropine analogues.

ever, they have long durations of action and other distinctive pharmacokinetic properties, which may contribute to their lack of cocaine-like behavioral actions. Complete pharmacokinetic and behavioral characterization of *N*-(4-phenyl-*n*-butyl)-3α-[bis(4-fluorophenyl)-methoxy]tropane (**1c**, Figure 1; DAT K_i = 8.51 nM), one of the most potent and selective compounds in this series,[18,19] was hampered by its high lipophilicity (cLogD = 5.01), which limited its water solubility.[26,27] To design a series of compounds that retained the desirable binding profile of **1c** and to reduce lipophilicity, a 3D-QSAR based CoMFA model was derived from a series of 76 benztropine analogues reported earlier[16–21] to ascertain the important regions of the molecules for binding with the DAT and subsequently to identify those regions where modifications could be introduced to reduce lipophilicity without compromising DAT binding affinities. It was determined that the diphenyl ether portion of the benztropine molecule was critical for binding to the DAT and that significant modification could not be made without severely reducing activity. Conversely, a wide diversity of N-substituent modifications were considerably better tolerated and suggested that a novel series of heteroatom N-substituted 3α-(bis-[4-fluorophenyl]methoxy)tropanes could be designed to have desired pharmacological and pharmacokinetic properties. Thirteen novel N-substituted analogues were synthesized and evaluated for DAT, SERT, NET, muscarinic M1 receptor binding, and inhibition of dopamine uptake.

Molecular Modeling

A 3D-QSAR based CoMFA study was performed on a structurally diverse set of 76 benztropine analogues, using DAT binding affinities (see Supporting Information for more details). This set of ligands included modifications at the C-3 diphenylmethoxy group as well as at the N-8 position. These analogues varied in DAT affinities over about 3 log units. The test set of compounds was designed and synthesized on the basis of the SAR of the training set of compounds,[21] thus serving as a validation set for the CoMFA models.

Table 1. Summary of CoMFA Results

	alignment			
	AFI	FFI	AFII	FFII
r^2_{cv}	0.632	0.468	0.654	0.441
no. of comp	5	4	5	4
SEP	0.368	0.438	0.357	0.450
r^2_{ncv}	0.917	0.862	0.917	0.856
SEE	0.175	0.224	0.175	0.228
F	121.851	87.251	121.163	82.937
steric	52.9	60.9	49.0	55.2
electrostatic	47.1	39.1	51.0	44.8
r^2_{pred}	0.522	0.418	0.351	0.555
r^2_{bs} [a]	0.924	0.894	0.930	0.886
standard deviation[a]	0.023	0.029	0.020	0.029

[a] Bootstrapping analysis (100 samples).

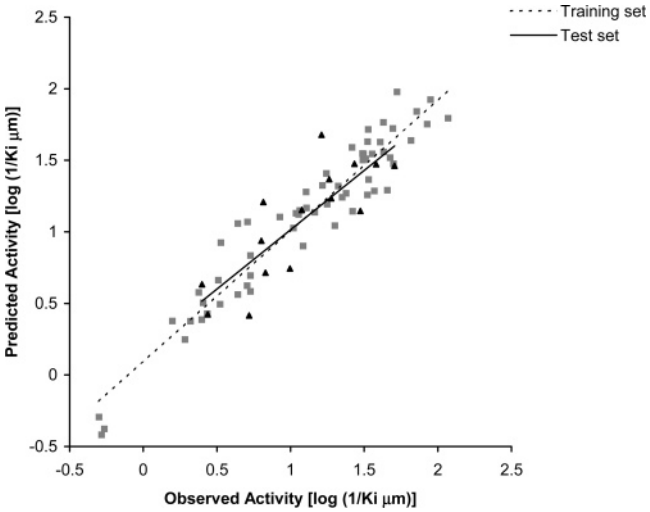


Figure 2. Plot of predicted vs observed activity of molecules from training (■) and test (▲) sets using alignment AFI.

The results of the CoMFA studies are summarized in Table 1. A rigid-body rms fitting of the non-hydrogen atoms of the tropane ring (AFI) showed a correlative and predictive model. A cross-validated r^2 of 0.632 was obtained with five components, and a non-cross-validated r^2 of 0.917 was observed with this model. The relative contributions of steric (52.9%) and electrostatic (47.1%) interactions were almost equal. A plot depicting the observed vs predicted activities of the molecules used in deriving this model is shown in Figure 2.

The test set of compounds contained variation at both the diphenylmethoxy and N-8 substitutions. The N substituent was varied in both size and shape. When the CoMFA model was used to predict activity of the test set of compounds, a predictivity measure r^2_{pred} of 0.522 was obtained. Figure 2 depicts the plot of observed vs predicted activities of the test set compounds.

Realignment of these compounds using rigid-body field fit (FFI) on the steric and electrostatic fields of the template molecule decreased the significance of the models. This alignment showed an r^2_{cv} of 0.468 with four components, and the non-cross-validated r^2 was 0.862. However, it had reduced external predictivity with r^2_{pred} of 0.418. The analysis of the CoMFA models with alignment derived from superimposing the centroids of the aromatic rings and the N-8 atom (AFII) showed a high internal consistency with r^2_{cv} of 0.654 with five components and non-cross-validated r^2 of 0.917. How-

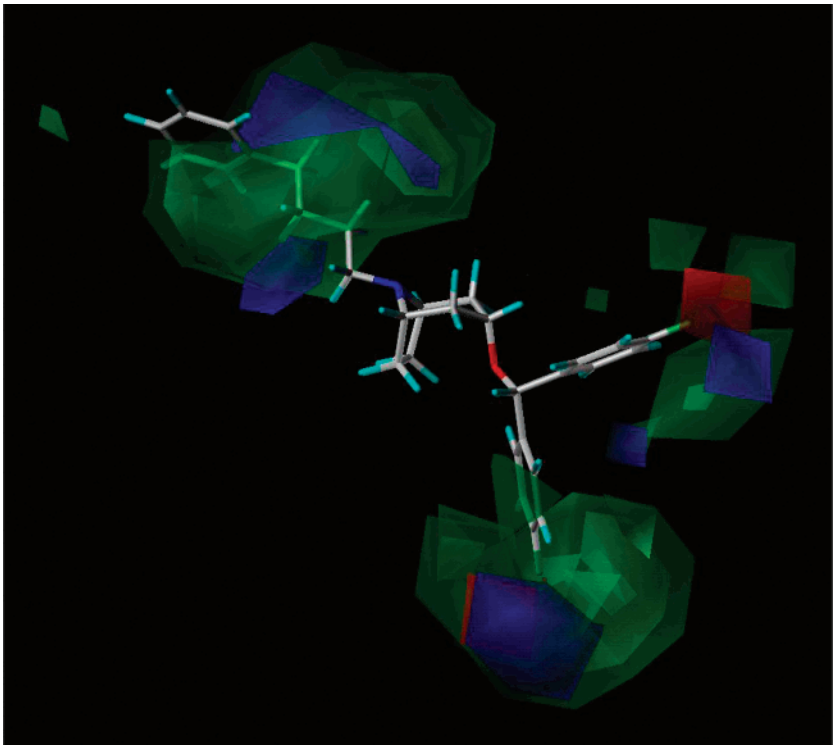


Figure 3. CoMFA SD X Coeff contour plots from analysis of alignment AFI. Sterically favored (70% contribution) and unfavored (30% contribution) regions are shown as green and yellow contours. The positive charge favoring (70% contribution) and negative charge favoring (30% contribution) regions are shown as blue and red contours, respectively. Compound **1c** is shown as a capped stick model in these regions.

ever, this model had reduced external predictivity because its r^2_{pred} was 0.351. When this alignment was used as an input for rigid-body field fit, it provided a reasonable degree of internal predictivity. There was an improvement in the predictivity of the test set compounds, r^2_{pred} of 0.555. Because the alignments in CoMFA ignore the entropic effects, it is difficult to speculate about the binding modes of these compounds based on the alignment rules.

The analysis of the CoMFA contour maps can provide more insight into the SAR of these compounds with DAT. The steric and electrostatic contour maps (Figure 3) were derived from the product of the standard deviation associated with the CoMFA column and coefficient (SD X coeff) at each lattice point. Since rigid-body rms fitting of the non-hydrogen atoms of the tropane ring (AFI) showed a correlative and predictive model, contour graphs were interpreted with this model.

The green contours represent regions of high steric tolerance, while yellow contours represent regions of unfavorable steric effects. There are many sterically favored green contours around the molecule. These green contours were dominant in the diphenylmethoxy terminus of the molecules as well as at the N-8 substituent. The large green contours in the diphenylmethoxy region indicate that increasing steric bulk in these regions will improve DAT binding affinity. The few yellow contours are buried in two large green contours, suggesting that in this region the relative orientation of the phenyl rings is important because variation in the torsion angles due to different substituents (especially at the 2′-position) in the phenyl ring decreased DAT binding affinities.[15,28] This also suggests that the diphenylmethoxy group has a significant influence on the DAT affinity.

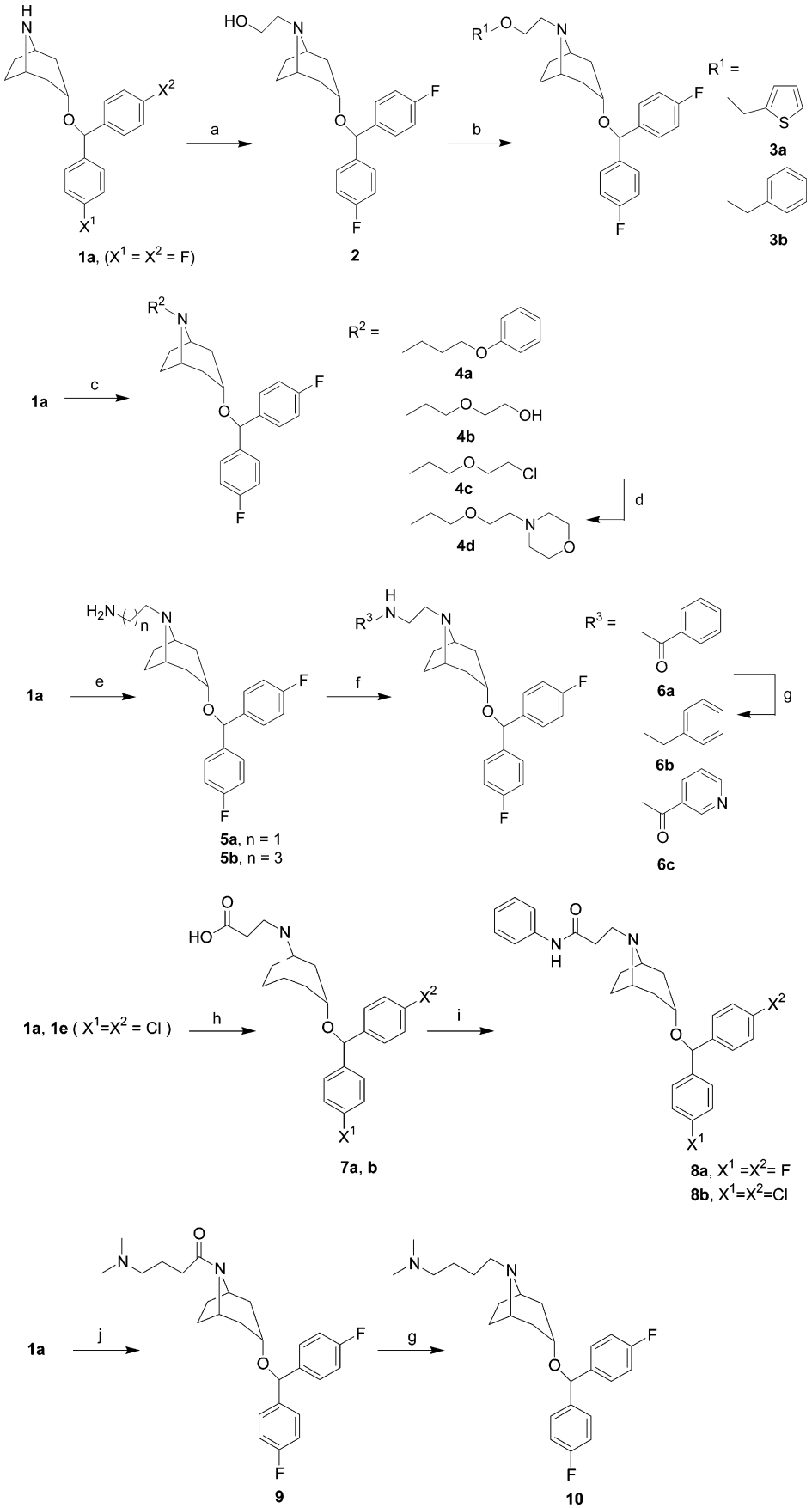
In the electrostatic contours, the blue contours describe regions where positively charged groups enhance the activity and red contours describe regions where negatively charged groups enhance activity. The electrostatic contour can be seen primarily toward the diphenylmethoxy group. The red and blue contours are seen near the para position of one of the phenyl rings. One blue contour can be seen around the N-8 substituent, but steric interactions seem to have major contribution to the activity in this position.

Previously described SAR and the CoMFA contour graphs showed the importance of different structural regions on the benztropine molecule. An appropriately substituted (i.e., 4′,4″-diF) diphenylmethoxy group is required for high-affinity DAT binding. This region of the binding site is restricted because only small halogen substitution in the para or meta positions are well tolerated. This effect is more prominent when the N-8 position is substituted with sterically bulky groups (allyl, benzyl, propylphenyl, butylphenyl).[21] Thus, it was hypothesized that the N-8 position would provide an avenue to vary the physicochemical properties of these molecules without adversely affecting DAT binding affinity. Thus, the N-8 of 3α-(bis[4-fluorophenyl]methoxy)-tropane was substituted with moieties having varied physicochemical properties.

Chemistry

In Scheme 1, compound **1a**[19] was alkylated with 2-bromoethanol to give compound **2**, which was then reacted with the appropriate arylalkyl halides to give compounds **3a** and **3b**. Direct alkylation of **1a** gave the final compounds **4a**−**c**. Compound **4d** was obtained after reacting compound **4c** with morpholine. Compounds **5a** and **5b** were synthesized after alkylation

Scheme 1[a]



[a] (a) 2-Bromoethanol, TEA, toluene; (b) R^1−x (x = Br, Cl), aqueous NaOH; (c) R^2−Br, TEA, toluene, or R^2−Cl, K_2CO_3, DMF; (d) morpholine, K_2CO_3, DMF; (e) *N*-(2-bromoalkyl)phthalimide, K_2CO_3 or $NaHCO_3$, DMF or acetonitrile; anhydrous hydrazine, EtOH; (f) R^3−Cl, aqueous $NaHCO_3$, $CHCl_3$; (g) $LiAlH_4$, THF; (h) ethyl 3-bromopropionate, K_2CO_3, DMF; 4 N NaOH, EtOH; (i) aniline, DCC, HOBt, DMF; (j) 4-(dimethylamino)butyric acid, hydrochloride, CDI, pyridine.

Table 2. Binding Data for the Novel N-Substituted Benztropines at DAT, SERT, NET, and M_1 Receptor and Inhibition of Dopamine Uptake[a]

compd	DAT	SERT	NET	M_1	DAUI[b]
1b	11.8 ± 1.3[c]	3260 ± 110[d]	610 ± 81[d]	11.6 ± 0.9[e]	13.8 ± 1.7[d]
1c	8.51 ± 1.2[f]	376 ± 52	2210 ± 240	576 ± 11[e]	39[f]
1d	20.0 ± 2.8[g]	1640 ± 240	2980 ± 180	47.9 ± 5.2	23.4 ± 3.0
3a	65.9 ± 5.0	2090 ± 220	3450 ± 440	613 ± 90	18.7 ± 2.0
3b	48.5 ± 6.7	1300 ± 75	3060 ± 346	390 ± 51	22.3 ± 2.6
4a	703 ± 100	7730 ± 740	12100 ± 1600	9280 ± 1000	227 ± 29
4b	42.6 ± 2.2	14300 ± 640	3650 ± 520	336 ± 47	48.9 ± 6.6
4d	1620 ± 31	23000 ± 2300	28100 ± 2800	15800 ± 2300	659 ± 96
5a	13.9 ± 1.7[e]	4600 ±680	1420 ± 130	1250 ± 140	26.0 ± 2.9
5b	26.0 ± 1.6	555 ± 69	NT[h]	2370 ± 170	NT[h]
6a	13.1 ± 1.5	597 ± 14	637 ± 49	556 ± 49	6.5 ± 0.5
6b	36.0 ± 2.9	1090 ± 81	1130 ± 120	1230 ± 150	8.1 ± 1.2
6c	12.6 ± 0.1	572 ± 76	652 ± 62	394 ± 16	14.2 ± 1.7
8a	27.6 ± 1.9	1490 ± 82	1420 ± 170	3280 ± 420	5.0 ± 0.1
8b	181 ± 5.6	558 ± 81	NT[h]	4140 ± 340	NT[h]
10	48 ± 5.5	499 ± 64	NT[h]	368 ± 49	NT[h]
cocaine	285 ± 27	286 ± 38	3300 ± 170	61400 ± 11000	236 ± 21

[a] All binding data are recorded in K_i ± SEM (nM); the methods used to obtain these data are described in Experimental Methods. [b] The inhibition of dopamine uptake data is recorded as IC_{50} ± SEM (nM). [c] Data from ref 16. [d] Data from ref 33. [e] Data from ref 20. [f] Data from ref 19. [g] Data from ref 21. [h] NT = not tested.

with appropriately N-substituted phthalimides followed by treatment with anhydrous hydrazine. Compound **5a** was then reacted with the respective acid chlorides under Schotten−Baumann conditions to give compounds **6a** and **6c**. Reduction of compound **6a** with lithium aluminum hydride ($LiAlH_4$) gave compound **6b**. Compounds **8a** and **8b** were synthesized from the acids **7a** and **7b**, which were obtained by alkylation of compounds **1a** and **1e**, respectively, with ethyl 3-bromopropionate followed by saponification. Amidation of **1a** with 4-(*N*-dimethylamino)butyric acid using 1,1′-carbonyldiimidazole (CDI) followed by reduction with $LiAlH_4$ gave compound **10**. All compounds were converted into HBr or oxalate salts for biological evaluation.

Structure−Activity Relationships

All compounds were tested for displacement of the respective radioligands labeling the DAT, SERT, NET, and muscarinic M1 receptors. Several compounds showed high to moderate binding affinities at the DAT (Table 2). Substitution with the amide linker (**6a**, **6c**, **8a**, and **8b**) reduced the conformational flexibility of the N substituent in the molecules but retained high affinity and selectivity for the DAT. In contrast, DAT binding affinity for the bis[4-chlorophenyl] analogue **8b** was significantly reduced (K_i = 181 nM), even compared to the reduction observed previously when the *N*-(4-phenyl)-*n*-butyl substituent replaced the *N*-methyl group on **1d**.[21]

Although the role of conformational flexibility in the N-8 binding region is not known, in the case of the GBR series of DAT inhibitors, introduction of a double bond in the N substituent improves DAT binding affinity (GBR 12909 IC_{50} = 3.7 nM, GBR13069 IC_{50} = 0.9 nM).[29] It is interesting to note that the number of rotatable bonds have been found to be an important determinant of oral bioavailability,[30] suggesting that substitution with an amide linker should have favorable effects on bioavailability. The order of amide substitution has little effect on DAT activity because compounds **6a** and **8a** are similarly active. Thus, addition of an amide group in this region of the 3α-(bis[4-fluorophenyl]methoxy)-tropane molecule successfully reduced the lipophilicity by about 1.5 log units without adversely affecting DAT binding affinity. This substitution also showed good selectivity (see Table 3) over muscarinic M1 receptor binding. For example, compound **8a** shows 119-fold DAT/M1 selectivity, which is in accordance with earlier observations where large N-8 substituents increased DAT selectivity.[19] The reduction of the amide in compound **6b** resulted in ∼3-fold reduction in the DAT binding affinity. Modification of the four-carbon-linked phenyl ring as in **1c** with a terminal ether-linked phenyl ring produced a significant reduction in DAT affinity (**4a**). However, moving the oxygen in the linking chain (**3b**) and replacing the phenyl ring with a heteroaryl group (**3a**) or OH (**4b**) improved DAT binding affinity although not to the high affinity of **1c**. Substitution of the phenyl ring with the amino group (**5b** and **10**) showed a slight reduction in activity. However, substitution with a large aliphatic group (morpholine, **4d**), which resulted in a significant reduction in lipophilicity, caused a substantial reduction in DAT binding affinity, suggesting that there is a limitation to the steric bulk at the N-8 position that can be tolerated by the DAT in this series of molecules.

Table 3. Binding Selectivities for the Novel N-Substituted Benztropines

compd	DAT/SERT	DAT/NET	DAT/M1	ClogD[a]
1b	276	52	1	2.27
1c	44	260	68	5.01
1d	82	149	2	3.36
3a	32	52	9	4.19
3b	27	63	8	4.44
4a	11	17	13	4.73
4b	336	86	8	2.01
4d	14	17	10	2.05
5a	331	102	90	1.61
5b	21		91	0.94
6a	46	49	42	3.29
6b	30	31	34	3.74
6c	45	52	31	2.62
8a	54	51	119	3.53
8b	3		23	4.62
10	10		8	1.71
cocaine	1	12	215	1.51

[a] Calculated lipophilicity at pH 7.4 from ACD/LogD Suite, release 7.00, version 7.05, Advanced Chemistry Development Inc. Toronto, Canada.

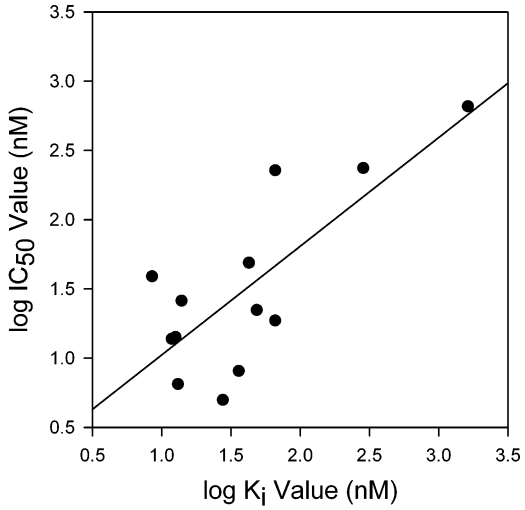


Figure 4. Correlation between DAT binding affinity and dopamine uptake inhibition for N-substituted benztropines.

All of these N-substituted analogues were tested for the inhibition of DA uptake, and these data (Figure 4) were positively correlated with DAT binding affinities ($r^2 = 0.5919$, $F_{1,11} = 15.95$, $p = 0.0021$). A significant and positive correlation is to be expected because ligand binding to the DAT is the initial event in the inhibition of DA uptake.

Although none of the N-substituted analogues showed high-affinity binding to SERT, the polar aliphatic chain (**4b**) showed particularly weak binding affinity, thus resulting in the most DAT/SERT selective compound in this series. All of the N-substituted analogues showed low binding affinities at NET, though most were less selective than **1c**.[19]

Previous studies showed that optimal binding affinity to DAT was obtained with the *N*-(4-phenyl)-*n*-butyl substituent (**1c**). This compound also showed good DAT selectivity over muscarinic M1 receptor binding.[19] Additional SAR confirmed that the four-atom spacer between the N-8 and terminal phenyl ring gave optimal DAT binding affinity.[31] The results of the present study demonstrated that substitution with polar linkers and heteroatoms on the N-8 position could retain desirable binding profiles of the previous series of compounds, with reduced lipophilicities, which may prove to be favorable for in vivo pharmacokinetic properties and behavioral activity.

Conclusions

A CoMFA model was derived using a data set of 76 previously reported 3α-(bis[4-fluorophenyl]methoxy)-tropanes. This CoMFA model showed a good correlation with steric and electrostatic descriptors. On the basis of these studies, the diphenyl ether moiety appears to be vital for binding this class of compounds to the DAT. It may be noteworthy that the diphenyl ring system has been observed in many GPCR ligands, suggesting this moiety is conferring a unique functionality or "privileged structure" for binding with the transmembrane receptor site on the DAT.[32] In contrast, the N-8 position tolerates varied substitutions, and thus, it could be varied to modulate the physicochemical properties of these compounds. As such, a novel series of N-8 substituted benztropine analogues was prepared in which the linker between the terminal binding element and the N-8 atom was varied with heteroatom substitution. Most of these compounds showed good binding affinity at DAT with excellent selectivity over SERT, NET, and muscarinic receptors. These compounds also showed potent inhibition of dopamine uptake with predicted favorable physicochemical properties. Thus, modification of the N-substituent allowed the retention of a desired in vitro profile while reducing the lipophilicity. Ongoing in vivo studies will provide additional insight into the role of physicochemical properties on the behavioral actions of the benztropine analogues and may provide new leads toward a cocaine-abuse medication.

Experimental Methods

All chemicals and reagents were purchased from Aldrich Chemical Co. or Lancaster Synthesis, Inc., unless otherwise indicated and were used without further purification. 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 Bruker (Billerica, MA) AC-300 or a Varian Mercury Plus 400 instrument. Samples were dissolved in an appropriate deuterated solvent ($CDCl_3$). Proton chemical shifts are reported as parts per million (δ ppm) relative to tetramethylsilane (Me_4Si, 0.00 ppm), which was used as an internal standard. Chemical shifts for ^{13}C NMR spectra are reported as δ relative to deuterated chloroform ($CDCl_3$, 77.0 ppm). Infrared spectra were recorded as a neat film on NaCl plates, unless otherwise indicated, with a Perkin-Elmer Spectrum RX I FT-IR system. Microanalyses were performed by Atlantic Microlab, Inc. (Norcross, GA), and the results agree within ±0.4% of the calculated values. All column chromatography was performed using silica gel (Aldrich, 230−400 mesh, 60A) and $CHCl_3$/MeOH (9:1) as eluting solvent unless otherwise indicated. The free base was converted into oxalate salts by treating the free base in acetone or ethanol with 1.1 or 2.1 equiv of oxalic acid followed by precipitation with diethyl ether. Similarly, HBr salts were prepared by treating the free base with methanolic HBr followed by precipitation with diethyl ether.

Synthesis. *N*-(2-Hydroxyethyl)-3α-[(bis(4′-fluorophenyl)methoxy]tropane (2). The HCl salt of **1a** (1.60 g, 4.38 mmol) was first converted to its free base form by extracting with $CHCl_3$ (3 × 50 mL) from 10% (w/v) aqueous sodium carbonate solution (50 mL), drying, and evaporating to an oil, which was refluxed with 2-bromoethanol (1.80 g, 14.40 mmol) and triethylamine (1.20 mL) in toluene (20 mL) for 3 h under argon gas. The solvent was evaporated under reduced pressure, and the residue obtained was extracted with $CHCl_3$ (50 mL × 2), washed with water (50 mL × 2), and passed over anhydrous Na_2SO_4. The organic layer was evaporated under reduced pressure to give the product (yield, 1.40 g, 86%), which was used for further reactions, without purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.03−2.17 (m, 4H), 2.49−2.52 (m, 2H), 2.89−2.93 (m, 2H), 3.05−3.06 (m, 2H), 3.78 (m, 1H), 3.97 (m, 2H), 4.05−4.06 (m, 2H), 5.01 (broad s, 1H), 5.39 (s, 1H), 6.99−7.04 (m, 4H), 7.22−7.27 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.17, 34.56, 55.85, 57.18, 62.67, 67.58, 80.73, 115.84, 116.13, 128.61, 128.72, 137.80, 137.84, 161.00, 164.27.

***N*-[2(Thiophen-2-ylmethoxy)ethyl]-3α-[(bis(4′fluorophenyl)methoxy]tropane Oxalate (3a).** Compound **2** (0.75 g, 2.00 mmol) was dissolved in acetone (3 mL), and 2-chloromethylthiophene (0.40 g, 3.02 mmol) [prepared from thiophene 2-methanol (5 g, 43.75 mmol) and thionyl chloride (6.25 g, 3.83 mL, 52.52 mmol) in THF (20 mL), with heating at 50 °C for 2 h, evaporation under vacuum gave an oily product, which was used without purification] was added. The reaction mixture was stirred at reflux for 20 h after addition of 50% (w/v) aqueous NaOH (12 mL). The reaction was quenched by dilution of the mixture with water (25 mL), and the mixture was extracted with $CHCl_3$ (50 mL × 2). The solvent was

evaporated under reduced pressure, and the residue was purified by column chromatography to obtain 0.07 g (7%) of free base of compound **3a**, which was converted to the oxalate salt: semisolid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78−2.12 (m, 8H), 2.61−2.65 (t, 2H), 3.27 (m, 2H), 3.53−3.56 (m, 1H), 3.62−3.66 (m, 2H), 4.69 (s, 2H), 5.35 (s, 1H), 6.94−7.02 (m, 6H), 7.24−7.29 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.53, 35.99, 52.24, 59.45, 59.48, 68.04, 69.56, 69.83, 79.85, 115.50, 115.78, 126.10, 126.65, 127.00, 128.68, 128.79, 138.97, 139.01, 141.59, 160.80, 164.10. Anal. ($C_{27}H_{29}F_2NO_2S\cdot C_2H_2O_4\cdot 0.25H_2O$) C, H, N.

***N*-(2-Benzyloxyethyl)-3α-[(bis(4′-fluorophenyl)methoxy]tropane Hydrobromide (3b).** Compound **3b** was obtained from **2** (1.00 g, 2.68 mmol) and benzyl bromide (0.48 mL, 4.04 mmol) as described for compound **3a** by refluxing for 4 h. The free base was converted into the HBr salt (yield, 0.28 g, 22%): mp 123−126 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.81−2.17 (m, 8H), 2.72 (m, 2H), 3.29 (m, 2H), 3.59 (m, 1H), 3.71 (m, 2H), 4.53 (s, 2H), 5.36 (s, 1H), 6.99−7.02 (m, 4H), 7.26−7.32 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.37, 35.78, 52.23, 59.76, 69.55, 73.57, 79.94, 115.53, 115.82, 128.01, 128.67, 128.77, 138.62, 138.87, 160.81, 164.07. Anal. ($C_{29}H_{31}F_2NO_2\cdot$HBr) C, H, N.

***N*-(3-Phenoxypropyl)-3α-[(bis(4′-fluorophenyl)methoxy]tropane Hydrobromide (4a).** The free base of compound **1a** (1.00 g, 3.04 mmol) was refluxed with 3-phenoxypropyl bromide (1.96 g, 9.10 mmol) and triethylamine (1.00 mL) in toluene (20 mL) for 4 h under an inert atmosphere. The solvent was evaporated under reduced pressure, and the residue was dissolved in $CHCl_3$ (50 mL). After repeated washing with water (50 mL × 2), the organic layer was evaporated under reduced pressure to obtain an oily product, which was purified by column chromatography as clear oil. The free base was converted to the HBr salt (yield, 0.39 g, 27%): mp 190−193 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.82−2.17 (m, 10H), 2.61 (m, 2H), 3.30 (m, 2H), 3.58 (m, 1H), 4.02−4.06 (t, 2H), 5.37 (s, 1H), 6.87−7.02 (m, 7H), 7.24−7.29 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.42, 28.55, 35.98, 49.46, 59.09, 66.38, 69.77, 79.92, 114.87, 115.53, 115.81, 121.04, 128.68, 128.79, 129.82, 138.86, 159.29, 160.81, 164.07.

***N*-(2-Ethoxyethan-2-ol)-3α-[(bis(4′-fluorophenyl)methoxy]tropane Hydrobromide (4b).** Compound **1a** (1.20 g, 3.65 mmol) was heated to 100 °C for 10 h with 2-chloroethoxyethanol (0.55 g, 4.40 mmol) and anhydrous K_2CO_3 (0.76 g, 5.50 mmol) in DMF (10 mL). The reaction was worked up by extraction with ethyl acetate (50 mL × 2) from water (25 mL). The organic layer was washed with brine (25 mL × 2) and dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography. The free base was converted to the HBr salt (yield, 0.50 g, 32%): mp 115−119 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83−2.18 (m, 10H), 2.59 (m, 2H), 3.32 (m, 2H), 3.59−3.69 (m, 6H), 5.36 (s, 1H), 6.96−7.02 (m, 4H), 7.23−7.28 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.14, 38.99, 60.23, 73.05, 80.02, 115.60, 115.86, 128.38, 128.73, 128.83, 138.66, 160.84, 162.02; IR 3369 cm^{-1}. Anal. ($C_{24}H_{29}F_2NO_3\cdot$1HBr$\cdot$1H_2O) C, H, N.

***N*-[2(2-Chloroethoxy)ethyl]-3α-[(bis(4′-fluorophenyl)-methoxy]tropane (4c).** Compound **4c** was obtained from **1a** (3.00 g, 9.10 mmol), 2-(bis-chloroethyl)ether (3.91 g, 27.30 mmol), and anhydrous K_2CO_3 (3.75 g, 27.10 mmol) in DMF (20 mL) as described for compound **4b**. The crude product was purified by column chromatography, eluting with *n*-hexane/ethyl acetate (4:1) to give a clear oil (yield, 1.00 g, 25%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84−1.95 (m, 6H), 2.15−2.19 (m, 2H), 3.59−3.65 (m, 3H), 3.69−3.76 (m, 4H), 4.23−4.26 (m, 4H), 5.38 (s, 1H), 6.96−7.04 (m, 4H), 7.24−7.29 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.21, 31.31, 43.13, 53.22, 64.14, 70.11, 70.27, 71.49, 80.23, 115.58, 115.86, 128.65, 128.76, 138.68, 138.72, 153.77, 160.84, 164.10.

***N*-[2(2-Morpholin-4-ylethoxy)ethyl]-3α-[(bis(4′fluorophenyl)methoxy]tropane Oxalate (4d).** Compound **4c** (1.00 g, 2.29 mmol) was stirred and heated with morpholine (0.20 g, 2.29 mmol) and anhydrous K_2CO_3 (0.63 g, 4.56 mmol) in DMF (10 mL) at 110 °C for 10 h. The reaction mixture was cooled to room temperature, diluted with water (25 mL), and extracted with ethyl acetate (50 mL × 2). After the organic layer was washed with water (25 mL × 2), the volatiles were evaporated under reduced pressure. The crude product was purified by column chromatography. The free base was converted into the oxalate salt (yield, 0.21 g, 19%): mp 120−122 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.88−1.94 (m, 6H), 2.17−2.19 (m, 2H), 2.47−2.50 (t, 4H), 2.55−2.58 (t, 2H), 3.59−3.66 (m, 5H), 3.69−3.72 (t, 4H), 4.20−4.23 (m, 4H), 5.38 (s, 1H), 6.97−7.03 (m, 4H), 7.24−7.29 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.23, 35.30, 53.17, 54.44, 58.60, 64.18, 67.29, 69.02, 69.90, 70.22, 80.24, 115.59, 115.88, 128.65, 128.76, 138.65, 138.69, 153.86, 160.84, 164.10. Anal. ($C_{28}H_{36}F_2N_2O_3\cdot 1.5C_2H_2O_4$) C, H, N.

***N*-(2-Aminoethyl)- 3α-[(bis(4′-fluorophenyl)methoxy]-tropane Hydrobromide (5a).**[20] Compound **1a** (3.00 g, 9.10 mmol) was reacted with *N*-(2-bromoethyl)phthalimide (2.54 g, 10 mmol) and anhydrous K_2CO_3 (1.88 g, 13.60 mmol) in DMF (20 mL) for 2 h at 80 °C. The product was isolated by diluting the reaction mixture with cold water (50 mL), extracted with ethyl acetate (50 mL × 2), dried ($MgSO_4$), and evaporated under reduced pressure to give an oily product (4.00 g, 7.96 mmol), which was dissolved in anhydrous ethanol (30 mL). Anhydrous hydrazine (0.60 mL, 19.10 mmol) was added to the reaction flask, and the mixture was allowed to stir at reflux for 2 h. The mixture was evaporated under reduced pressure, and the residue was treated with 40% (w/v) KOH solution (100 mL), extracted with $CHCl_3$ (50 mL × 2), dried over anhydrous $MgSO_4$, and evaporated under reduced pressure to obtain 2.10 g (61% from **1a**) of compound **5a**, which was converted to the HBr salt: mp >230 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78−1.91 (m, 8H), 2.04−2.11 (m, 2H), 2.36−2.40 (t, 2H), 2.69−2.73 (t, 2H), 3.12−3.13 (m, 2H), 3.51−3.54 (m, 1H), 5.36 (s, 1H), 6.96−7.03 (m, 4H), 7.25−7.29 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.67, 36.70, 41.19, 55.87, 58.96, 70.10, 79.68, 115.46, 115.74, 128.69, 128.80, 139.10, 139.12, 160.75, 164.01. Anal. ($C_{22}H_{26}F_2N_2O\cdot$2HBr) C, H, N.

***N*-(4-Amino-*n*-butyl)-3α-[(bis(4′-fluorophenyl)methoxy]-tropane Oxalate (5b).** A suspension of compound **1a** (1.62 g, 4.93 mmol), *N*-(4-bromo-*n*-butyl)phthalimide (1.46 g, 5.20 mmol), and sodium bicarbonate (2.10 g, 25 mmol) in 10 mL of anhydrous acetonitrile was heated under an atmosphere of argon at 120 °C in a sealed tube overnight. The volatiles were removed in vacuo, and the residue was purified by flash chromatography (eluant $CHCl_3/CH_3OH$, gradient from 20:1 to 10:1) to give 1.89 g (72%) of the phthalimide derivative. A solution of the intermediate phthalimide (1.74 g, 3.30 mmol) and hydrazine (0.20 mL, 6.40 mmol) in 50 mL of absolute ethanol was refluxed for 2.5 h. After this time, the ice-cold reaction mixture was filtered and solvent was removed under reduced pressure. The residue was taken up in $CHCl_3$ (10 mL) and washed with 40% (w/v) KOH solution. The organic phase was dried with Na_2SO_4 and concentrated in vacuo to give compound **5b**. The free base was converted to the oxalate salt (0.75 g, 41%, from **1a**): mp 202 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41−1.46 (m, 4H), 1.77−1.91 (m, 6H), 2.05 (d, 2H), 2.32 (t, 2H), 2.68 (t, 2H), 3.16 (s, 2H), 3.52 (t, 1H), 5.34 (s, 1H), 6.95 (m, 4H), 7.24 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 27.08, 27.22, 32.61, 36.59, 42.94, 52.74, 58.60, 70.27, 79.69, 115.25, 115.46, 128.37, 128.45, 138.71, 138.74, 160.56, 162.99; IR 3369 cm^{-1}. Anal. ($C_{24}H_{30}F_2N_2O\cdot C_2H_2O_4\cdot 1.5H_2O$) C, H, N.

***N*-(2-Benzamidoethyl)-3α-[(bis(4′-fluorophenyl)methoxy]tropane Oxalate (6a).** Compound **5a** (0.54 g, 1.45 mmol) was dissolved in $CHCl_3$ (10 mL) and stirred with 5 mL (0.73 g, 8.70 mmol) of aqueous $NaHCO_3$ solution. To this biphasic solution, benzoyl chloride (0.17 mL, 1.45 mmol) in $CHCl_3$ (2 mL) was added slowly at room temperature. The mixture was stirred vigorously for 30 min. The aqueous layer was separated, and the organic layer was washed with aqueous Na_2CO_3 solution (25 mL × 2), dried over anhydrous $MgSO_4$, and evaporated to give an oily product. Purification by column chromatography gave the free base as a foam, which was converted to the oxalate salt (yield, 0.20 g, 29%): mp 206−

208 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.91–2.01 (m, 4H), 2.27–2.30 (m, 4H), 2.83–2.86 (t, 2H), 3.48 (m, 2H), 3.62–3.70 (m, 3H), 5.36 (s, 1H), 6.96–7.04 (m, 4H), 7.23–7.27 (m, 4H), 7.32–7.49 (m, 3H), 7.85–7.88 (d, 2H), 8.10 (broad s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.10, 35.74, 37.36, 51.57, 60.19, 68.88, 80.18, 115.66, 115.94, 127.54, 128.13, 128.64, 128.75, 128.90, 129.83, 131.82, 134.51, 138.43, 138.47, 160.88, 164.14, 167.92. Anal. ($C_{29}H_{30}F_2N_2O_2 \cdot C_2H_2O_4$) C, H, N.

***N*-(2-Benzylaminoethyl)-3α-[(bis(4′-fluorophenyl)methoxy]tropane Hydrobromide (6b).** To a suspension of $LiAlH_4$ (0.32 g, 8.40 mmol) in THF (30 mL) a solution of compound **6a** (0.50 g, 1.05 mmol) in THF (10 mL) was added slowly at 0 °C under inert atmosphere. The reaction mixture was heated to reflux for 4 h. The product was carefully worked up by adding 4 mL of water to a well-cooled (0 °C) reaction mixture followed by 2.00 mL of 15% (w/v) aqueous NaOH solution. The white suspension was stirred with ethyl acetate (50 mL) and dried ($MgSO_4$). The organic layer was filtered and evaporated to obtain an oily product, which was purified by column chromatography, and the free base was converted to the HBr salt (yield, 0.19 g, 39%): mp 243–247 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.79–2.12 (m, 9H), 2.51–2.55 (m, 2H), 2.69–2.73 (t, 2H), 3.20 (m, 2H), 3.53–3.56 (m, 1H), 3.81 (s, 2H), 5.35 (s, 1H), 6.95–7.02 (m, 4H), 7.24–7.32 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.44, 36.44, 47.51, 52.24, 54.25, 59.17, 69.76, 79.80, 115.50, 115.78, 127.15, 127.33, 128.51, 128.68, 128.79, 129.10, 138.96, 140.63, 160.78, 164.04; IR 3307 cm^{-1}. Anal. ($C_{29}H_{32}F_2N_2O \cdot 2HBr$) C, H, N.

***N*-(2-Nicotinamidoethyl)-3α-[(bis(4′-fluorophenyl)methoxy]tropane Oxalate (6c).** This compound was synthesized as compound **6a** using 1.00 g (2.69 mmol) of compound **5a**, 8.00 mL of aqueous $NaHCO_3$ (1.35 g, 16.10 mmol) and 0.48 g (2.69 mmol) of nicotinoyl chloride hydrochloride in 15 mL of $CHCl_3$ by stirring at room temperature for 2 h. The free base was converted to the oxalate salt (yield, 0.28 g, 21%): mp 153–155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87–1.95 (m, 6H), 2.18–2.21 (m, 2H), 2.63–2.67 (t, 2H), 3.26 (m, 2H), 3.49–3.56 (m, 2H), 3.59 (m, 1H), 5.37 (s, 1H), 6.96–7.04 (m, 4H), 7.25–7.29 (m, 4H), 7.36–7.40 (q, 1H), 7.52 (broad s, 1H), 8.15–8.18 (dt, 1H), 8.70–8.72 (dd, 1H), 8.98 (d, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.50, 36.74, 51.28, 54.18, 59.06, 69.45, 79.95, 115.27, 115.54, 115.98, 116.27, 128.63, 128.96, 130.60, 135.57, 138.79, 148.16, 160.83, 164.09, 165.69. Anal. ($C_{28}H_{29}F_2N_3O_2 \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

3-{3α-[(Bis(4′-fluorophenyl)methoxy]tropan-8-yl}propionic Acid (7a). Compound **1a** (3.00 g, 9.10 mmol) was stirred with anhydrous K_2CO_3 (1.88 g, 13.60 mmol) in DMF (15 mL) under argon, and ethyl 3-bromopropionate (1.98 g, 10.94 mmol) was added. The reaction mixture was stirred and heated to 80 °C for 2 h. The product was isolated by extraction with ethyl acetate (50 mL × 2) after diluting the reaction mixture with 30 mL of water. The organic layer was washed with brine (50 mL × 2), dried over anhydrous $MgSO_4$, and evaporated under reduced pressure to give 2.90 g (6.75 mmol) of oily product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22–1.26 (t, 3H), 1.77–1.81 (m, 2H), 1.87–1.90 (m, 4H), 2.05–2.08 (m, 2H), 2.44–2.48 (t, 2H), 2.62–2.66 (t, 2H), 3.14 (m, 2H), 3.49–3.52 (m, 1H), 4.08–4.13 (q, 2H), 5.33 (s, 1H), 6.94–6.99 (m, 4H), 7.22–7.25 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 15.19, 27.10, 35.39, 36.72, 48.58, 59.01, 60.89, 70.14, 79.81, 115.30, 115.51, 128.39, 128.47, 138.65, 138.69, 160.63, 163.05, 172.54.

The above product was dissolved in ethanol (20 mL). A 4 N NaOH solution (5 mL) was added, and the reaction mixture was stirred for 2 h at room temperature. Evaporation of the reaction mixture under reduced pressure gave the product **7a**, which was used for the next step without further purification (yield, 2.80 g, 100% crude): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.03–2.52 (m, 8H), 2.92–2.96 (m, 2H), 3.23 (m, 2H), 3.79–3.86 (m, 2H), 4.02 (m, 1H), 5.20 (s, 1H), 6.98–7.04 (m, 4H), 7.22–7.38 (m, 4H), 9.38 (broad s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.10, 34.75, 57.28, 57.39, 78.40, 115.53, 115.88, 128.64, 128.75, 138.02, 138.07, 160.94, 164.20, 171.44; IR 1737, 3351 cm^{-1}.

***N*-[3-(*N*-Phenyl)propionamido]-3α-[(bis(4′-fluorophenyl)methoxy]tropane Oxalate (8a).** To a solution of compound **7a** (2.80 g, 6.98 mmol) in DMF (25 mL), 1.72 g (8.34 mmol) of dicyclohexylcarbodiimide and 1.13 g (8.36 mmol) of 1-hydroxybenzotriazole hydrate were added, and the mixture was stirred under inert atmosphere. Aniline (0.70 mL, 7.68 mmol) was added to the reaction mixture slowly. The reaction mixture was cooled to 0 °C, and 2.13 mL (15.3 mmol) of triethylamine was added. The mixture was then stirred at room temperature for 72 h. The mixture was diluted with water (50 mL) and extracted with $CHCl_3$ (50 mL × 2). The organic layer was washed with brine (50 mL × 2) and dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography, and the free base was converted to the oxalate salt (yield, 1.10 g, 33%): mp 188–190 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.94–2.00 (m, 6H), 2.18–2.24 (q, 2H), 2.44–2.48 (t, 2H), 2.69–2.73 (t, 2H), 3.35 (m, 2H), 3.66–3.68 (m, 1H), 5.41 (s, 1H), 6.99–7.06 (m, 4H), 7.24–7.33 (m, 7H), 7.45–7.48 (m, 2H), 11.51 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.45, 34.37, 36.92, 48.67, 58.27, 69.61, 80.00, 115.47, 115.61, 115.75, 115.89, 119.80, 123.90, 128.67, 128.78, 129.37, 138.73, 138.77, 139.22, 160.86, 164.12, 171.51. Anal. ($C_{29}H_{30}F_2N_2O_2 \cdot C_2H_2O_4 \cdot 0.25H_2O$) C, H, N.

3-{3α-[(Bis(4′-chlorophenyl)methoxy]tropan-8-yl}propionic Acid (7b). This compound was prepared from the free base of compound **1e** (5.1 g, 14.07 mmol) as described for compound **7a** (yield, 6.00 g, 92% crude): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22–1.25 (t, 3H), 1.76–1.89 (m, 6H), 2.04–2.06 (m, 2H), 2.43–2.46 (t, 2H), 2.61–2.64 (t, 2H), 3.13 (m, 2H), 3.50 (m, 1H), 4.08–4.13 (q, 2H), 5.31 (s, 1H), 7.20–7.26 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 15.19, 27.11, 35.43, 36.76, 48.62, 58.98, 60.89, 70.39, 79.84, 128.19, 128.69, 133.22, 141.14, 172.55. The saponification of the ester, similar as for **7a**, gave the acid **7b** (yield, 5.00 g, 88% crude): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80–1.89 (m, 4H), 2.01–2.11 (m, 4H), 2.34 (m, 2H), 2.71 (m, 2H), 3.36 (m, 2H), 3.49 (m, 1H), 5.28 (s, 1H), 7.15–7.24 (m, 8H), 8.39 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 26.36, 34.60, 35.59, 49.05, 59.20, 69.21, 80.09, 128.13, 128.84, 133.47, 140.54, 171.55.

***N*-[3-(*N*-Phenyl)propionamido]-3α-[(bis(4′-chlorophenyl)methoxy]tropane (8b).** This compound was prepared from compound **7b** (5.00 g, 11.52 mmol) as described for compound **8a** (yield, 2.00 g, 34%): mp 64–68 °C; oxalate salt, mp 190–192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.94–1.99 (m, 6H), 2.16–2.21 (m, 2H), 2.45–2.48 (t, 2H), 2.69–2.72 (t, 2H), 3.34 (m, 2H), 3.64–3.66 (m, 1H), 5.36 (s, 1H), 7.19–7.29 (m, 11H), 7.42–7.45 (m, 2H), 11.42 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 26.89, 34.75, 37.28, 48.99, 58.52, 69.89, 80.04, 119.55, 123.66, 128.15, 128.82, 129.07, 133.43, 138.81, 140.79, 170.84. Anal. ($C_{29}H_{30}Cl_2N_2O_2 \cdot {}^1/_3H_2O$) C, H, N.

***N*-(4-Dimethylaminobutyl)-3α-[(bis(4′-fluorophenyl)-methoxy]tropane Oxalate (10).** A solution of 4-(dimethylamino)butyric acid hydrochloride (0.42 g, 2.50 mmol) in 3 mL of anhydrous pyridine was treated with 1,1′-carbonyldiimidazole (0.41 g, 2.50 mmol), and the mixture was stirred for 1 h. After this time, a solution of compound **1a** (0.33 g, 1.00 mmol) in 5 mL of absolute $CHCl_3$ was added and the mixture was stirred overnight. After hydrolysis by addition of water (10 mL), the organic phase was dried with Na_2SO_4 and all volatiles were removed in vacuo: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77–1.97 (m, 8H), 2.14–2.39 (m, 11H), 3.64 (m, 1H), 4.10 (m, 1H), 4.16 (m, 1H), 4.64 (m, 1H), 5.38 (s, 1H), 6.94–6.99 (m, 4H), 7.23–7.27 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.07, 28.02, 29.73, 32.13, 36.03, 37.00, 38.00, 46.09, 51.16, 54.39, 59.70, 70.33, 115.31, 115.33, 115.52, 115.54, 128.17, 128.25, 128.28, 128.36, 138.10, 160.51, 160.55, 162.94, 162.97, 168.07; IR 1632.

To a solution of the crude amide in absolute THF (5 mL) was added $LiAlH_4$ (0.052 g, 1.40 mmol) at 0 °C, and the reaction mixture was strirred at room temperature for 1 h. Hydrolysis by the addition of Glauber's salt ($Na_2SO_4 \cdot 10H_2O$) and filtration, followed by recrystallization of its oxalate salt from acetone/diethyl ether, yielded **10** (yield, 0.37 g, 63%): mp 124–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (m, 2H), 1.56 (m, 2H), 1.83 (d, 2H), 1.94 (m, 2H), 2.16–2.25 (m, 4H), 2.24 (s, 6H), 2.32 (t, 2H), 2.53 (t, 2H), 3.39 (s, 2H), 3.59 (t, 1H),

5.33 (s, 1H), 6.93−6.98 (m, 4H), 7.20−7.26 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.94, 35.87, 36.54, 45.85, 52.25, 59.22, 59.79, 69.59, 79.95, 115.38, 115.56, 128.35, 128.44, 138.37, 138.40, 160.63, 163.06. Anal. ($C_{26}H_{34}F_2N_2O \cdot 1.5C_2H_2O_4 \cdot 1.25H_2O$) C, H, N.

Molecular Modeling. Molecular modeling and CoMFA studies were performed using the SYBYL 6.7 (Tripos Inc.) package running on a Silicon Graphics Octane workstation. Standard Tripos force field and MOPAC charges (AM1 Hamiltonian) were used for all energy calculations. The X-ray crystal structures of compounds **1c**, **17**, and **42** were used to build the rest of the compounds. The geometries were optimized by conjugate gradient minimization until a convergence criteria of 0.001 kcal/(mol Å) was achieved. Our data set contained a total of 76 benztropine analogues synthesized previously in the laboratory.[16−21] The compounds with an asymmetric center were modeled by following the weighting protocol described earlier.[15,20] These compounds had a range of substitutions at the 3-diarylmethoxy group as well as on the N-8. The predictive power of the molecular models was assessed by setting aside a set of compounds as a test set. The mean/standard deviation of the activity for the training and test sets were 1.12/0.57 and 1.04/0.35, respectively (see Supporting Information for structures and biological activity). These compounds were aligned using the non-hydrogen atoms of the tropane ring (alignment I, AFI) and the centroids of the diphenyl substituent with the N-8 atom (alignment II, AFII). These alignments were also used as inputs for rigid-body field fit analysis (alignment FFI and FFII). The CoMFA interaction energies were calculated using the default settings. The statistical analyses were performed using the partial least squares (PLS) method, leave one out (LOO) procedure. The optimum number of components was chosen based on the highest r^2_{cv} value and the lowest standard error of prediction. To estimate the statistical confidence limits on the analysis, PLS analysis using 100 bootstrap groups with an optimum number of components was performed. The CoMFA contour maps were derived from a product of the standard deviation associated with the CoMFA column and coefficient (SD X coeff) at each lattice point.

Biological Assays. 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 centrifuged 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 1.5 mg (original wet weight). Triplicate samples of membrane suspension were preincubated for 5 min in the presence or absence of the compound being tested. [^{3}H]WIN 35,428 (2-β-carbomethoxy-3-β-(4-fluorophenyl)tropane 1,5-naphthalene disulfonate (PerkinElmer Life Sciences, Boston, MA) at a final concentration 1.5 nM) was added, and the incubation was continued for 1 h on ice. The incubation was terminated by the addition of 3 mL of ice-cold buffer and rapid filtration through Whatman GF/B glass fiber filter paper (presoaked in 0.1% BSA in water) using a Brandel cell harvester (Brandel Instruments, Gaithersburg, MD). The filters were washed with three additional 3 mL washes and transferred to scintillation vials. Beckman Ready Value scintillation cocktail (3 mL) was added to the vials, which were counted using a Beckman 6000 liquid scintillation counter (Beckman Coulter Instruments, Fullerton, CA). Nonspecific binding was 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. The K_i values reported are the dissociation constants derived for the unlabeled ligands. Data were analyzed with either LIGAND or GraphPad Prism software (San Diego, CA).

Serotonin Transporter Binding Assay. Brains from male Sprague-Dawley rats weighing 200−225 g (Taconic Labs, Germantown, NY) were removed; the midbrain was dissected and rapidly frozen. Membranes were prepared by homogenizing tissues in 20 volumes (w/v) of 50 mM Tris containing 120 mM NaCl and 5 mM KCl (pH 7.4 at 25 °C) using a Brinkman Polytron and centrifuged at 50000*g* for 10 min at 4 °C. The resulting pellet was resuspended in buffer, recentrifuged, and resuspended in buffer to a concentration of 15 mg/mL. Ligand binding experiments were conducted in assay tubes containing 0.5 mL buffer for 60 min at room temperature. Each tube contained 1.4 nM [^{3}H]citalopram (Amersham Biosciences, Piscataway, NJ) and 1.5 mg of 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 3 mL of cold buffer and transferred to scintillation vials. Beckman Ready Value (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). Each compound was tested with concentrations ranging from 0.01 nM to 100 μM for competition against binding of [^{3}H]citalopram, in at least three independent experiments, each performed in triplicate**.** 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, Germantown, NY) were removed; the frontal cortex was dissected and rapidly frozen. Membranes were prepared by homogenizing tissues in 20 volumes (w/v) of 50 mM Tris containing 120 mM NaCl and 5 mM KCl (pH 7.4 at 25 °C) using a Brinkman Polytron and centrifuged at 50000*g* 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 of buffer for 60 min at 0−4 °C. Each tube contained 0.5 nM [^{3}H]nisoxetine (PerkinElmer Life Sciences, Boston, MA) and 8 mg of 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 3 mL of cold buffer and transferred to scintillation vials. Beckman Ready Value (3.0 mL) was added, and the vials were counted using a Beckman 6000 liquid scintillation counter (Beckman Coulter Instruments, Fullerton, CA). Each compound was tested with concentrations ranging from 0.01 nM to 100 μM for competition against binding of [^{3}H]nisoxetine, in at least three independent experiments, each performed in triplicate**.** Data were analyzed by using GraphPad Prism software (San Diego, CA).

Muscarinic M_1 Receptor Binding Assay. Whole frozen rat brains excluding cerebellum (Taconic, Germantown, NY) were thawed in ice-cold buffer (10 mM Tris-HCl, 320 mM sucrose, pH 7.4) and homogenized with a Brinkman Polytron in a volume of 10 mL/*g* of tissue. The homogenate was centrifuged at 1000*g* for 10 min at 4 °C. The resulting supernatant was then centrifuged at 10000*g* for 20 min at 4 °C. The resulting pellet was resuspended in a volume of 1 g/5 mL 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 20 mg (original wet weight). [^{3}H]pirenzepine (PerkinElmer Life Sciences, Boston, MA) at a final concentration 3 nM was added, and the incubation was continued for 1 h at 37 °C. The incubation was terminated by the addition of 3 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) using a Brandel cell harvester (Brandel Instruments, Gaithersburg, MD). The filters were washed with two additional 5 mL washes and transferred to scintillation vials. Beckman Ready Value scintillation cocktail (3 mL) was added to the vials, which were counted the next day using a Beckman liquid scintillation counter (Beckman Coulter, Fullerton, CA). Nonspecific binding was 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).

Dopamine Uptake Assay. The tissue was homogenized in ice-cold buffer (5 mM HEPES, 0.32 M sucrose) using 10 strokes with a Teflon glass homogenizer followed by centrifugation at 1000*g* for 10 min at 4 °C. The supernatant was saved and recentrifuged at 10000*g* for 20 min at 4 °C. The supernatant was then discarded, and the pellet was gently resuspended in ice-cold incubation buffer (127 mM NaCl, 5 mM KCl, 1.3 mM NaH_2PO_4, 1.2 mM $MgSO_4$, 2.5 mM $CaCl_2$, 1.498 mM HEPES acid, 10 mM D-glucose, 1.14 mM L-ascorbic acid, pH 7.4) and placed on ice for 15 min. The synaptosomal tissue preparation was incubated in buffer in glass test tubes at 37 °C to which 10 μM pargyline and either the drug being tested or no drug was added, as appropriate. After a 10 min preincubation in the presence of drug, [^{3}H]dopamine (final concentration of 0.5 nM) (Amersham Biosciences, Piscataway, NJ) was added to each tube and the incubation was carried on for 5 min. The reaction was terminated by the addition of 3 mL of ice-cold buffer to each tube and rapid filtration through Whatman GF/B glass fiber filter paper (presoaked in 0.1% polyethylenimine in water) using a Brandel cell harvester (Brandel Instruments, Gaithersburg, MD). After filtration, the filters were washed with two additional 5 mL washes and transferred into scintillation vials. Beckman Ready Value (Beckman-Coulter Instruments, Fullerton, CA) was added, and the vials were counted the next day using a Beckman 6000 liquid scintillation counter (Beckman Coulter Instruments, Fullerton, CA). The reported values represent specific uptake from which nonspecific uptake was subtracted (defined as uptake in the presence of 100 μM (−)-cocaine HCl). Data were analyzed using the nonlinear regression analysis of GraphPad Prism software (San Diego CA).

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Supporting Information Available: Structures and activities of compounds used for molecular modeling and elemental analysis results. This material is available free of charge via the Internet at http://pubs.acs.org.

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