Synthesis and Monoamine Transporter Binding of 2-(Diarylmethoxymethyl)-3β-aryltropane Derivatives

Lifen Xu,[†] Santosh S. Kulkarni,[§] Sari Izenwasser,[‡] Jonathan L. Katz,[§] Theresa Kopajtic,[§] Stacey A. Lomenzo,[†] Amy Hauck Newman,[§] and Mark L. Trudell*,[†]

Department of Chemistry, University of New Orleans, New Orleans, Louisiana 70148, Department of Psychiatry and Behavioral Sciences, University of Miami School of Medicine, Miami, Florida 33136, and Medications Discovery Research Branch, National Institute on Drug Abuse, Intramural Research Program, 5500 Nathan Shock Drive, Baltimore, Maryland 21224

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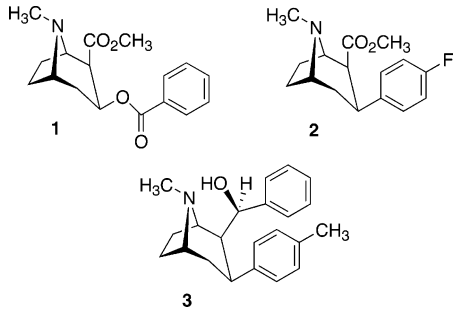
3β-Aryltropane analogues wherein the 2-position was substituted with various diarylmethoxyalkyl groups were synthesized and evaluated for binding at the dopamine transporter (DAT), serotonin transporter (SERT), norepinephrine transporter (NET), and muscarinic (M_1) receptors. The 2β-analogues **9a**−**i** generally demonstrated high to moderate binding affinities (K_i = 34−112 nM) at the DAT with good selectivity over SERT, NET, and M_1 receptors. Alternatively, the 2α-isomers **10a**−**i** were 10-fold less potent at the DAT with poor selectivity over SERT. These SAR studies provide further evidence for the varied binding requirements of structurally diverse tropane-based ligands and support future studies to elucidate DAT binding requirements in relation to cocaine-like behavioral endpoints.

Introduction

Cocaine (**1**) is a powerful psychostimulant and drug of abuse that inhibits dopamine reuptake by binding to the dopamine transporter (DAT). The 2-substituted 3-aryltropanes [e.g., [^{3}H]WIN 35,428 (**2**)] have been studied extensively as cocaine congeners and developed as tools to explore the DAT.[1−23] This broad class of compounds has provided significant insight into the nature of the DAT pharmacophore and the pharmacological actions associated with cocaine abuse. It has been well established for the 2-substituted 3-aryltropanes that β-stereochemistry at the 2-position and a 4-substituted or 3,4-disubstituted aryl group (e.g., tolyl, 4-chlorophenyl, or 3,4-dichlorophenyl, respectively) at the 3β-position of the tropane ring affords compounds that exhibit high-affinity binding at the DAT. However, a variety of functional groups and substituents (alkyl, vinyl, aryl, alcohol, and ester groups) are well tolerated at the 2-position with little variation in pharmacological activity. Recently we reported on the DAT binding affinity and dopamine uptake inhibition of a series of novel 2-substituted 3β-tolyltropane derivatives.[23] The 2β-(*R*)-(hydroxymethyltolyl)-3β-tolyltropane (**3**) exhibited an unexpectedly high dopamine uptake inhibition (DUI)/DAT affinity ratio (10:1), suggesting that this compound was not as potent in inhibiting dopamine uptake as its DAT binding affinity may have predicted. Nevertheless, the behavioral profile of **3** did not vary significantly from cocaine, and thus, further investigation of the effects of alkylaryl substituents at the 2-position seemed warranted.



In another class of DAT inhibitors, the diarylmethoxy moiety when attached to the tropane ring system has produced benztropine analogues with unique pharmacological profiles (e.g., 3′-chlorobenztropine and difluoropine).[24−27] In addition, the diarylmethoxy group has been established as an important structural feature of the DAT selective ligand GBR 12909 and related GBR/tropane hybrid analogues.[28−33] Therefore, it was of interest to investigate the effects of the diarylmethoxy group at the 2-position for a series of 3β-aryltropanes. Herein, we describe the synthesis, DAT, serotonin (SERT), norepinephrine transporter (NET), and muscarinic M_1 receptor binding affinities for a series of 2-(diarylmethoxyalkyl)-3β-aryltropanes. In addition, CoMFA studies were performed in an attempt to correlate chemical structures and DAT binding activity.

Results and Discussion

Chemistry. The syntheses of the 2-substituted 3β-aryltropane derivatives were completed in a straightforward fashion from anhydroecgonine methyl ester (**4**) (Scheme 1).[34] The reaction of an arylmagnesium bromide with anhydroecgonine methyl ester in dichloromethane furnished a mixture of 2β-carbomethoxy-3β-aryltropane (**5**) and 2α-carbomethoxy-3β-aryltropane

* To whom correspondence should be addressed. Phone: (504)-280-7337. Fax: (504) 280-6860. E-mail: mtrudell@uno.edu.
[†] University of New Orleans.
[§] National Institute on Drug Abuse, Intramural Research Program.
[‡] University of Miami School of Medicine.

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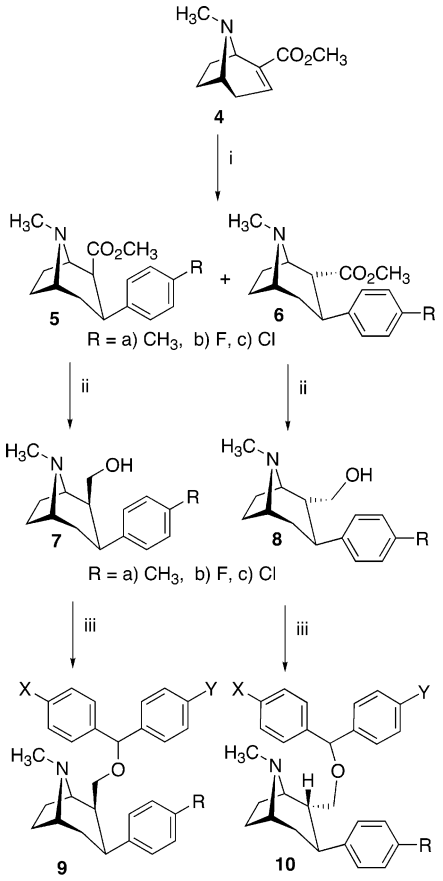
Scheme 1[a]



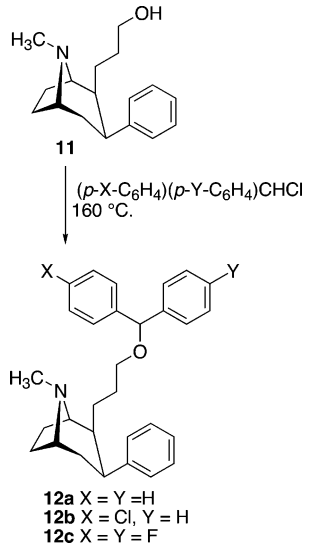
[a] Reagents: (i) *p*-R-C_6H_4MgBr, CH_2Cl_2, −78 °C, then TFA; (ii) $LiAlH_4$, Et_2O; (iii) (*p*-X-C_6H_4)(*p*-Y-C_6H_4)CHCl, 160 °C.

(**6**).[34] Separation of the isomers by flash column chromatography and independent reduction of each isomer with lithium aluminum hydride furnished the alcohols **7** and **8**, respectively, in excellent yield (>90%). The alcohols **7** and **8** were then converted into the diarylmethoxymethyl-3β-aryltropanes **9** and **10** using a modified melt procedure with the corresponding benzhydryl chloride. The 2β-isomers **9** were obtained in yields ranging from 50% to 86%, while the 2α-isomers **10** were furnished in yields ranging from 32% to 66%. The stereochemistry of the 2β-derivatives **7a** (R = CH_3), **9g**, and **9i** was unequivocally established by X-ray crystallography.[35]

The 2β-three-carbon-chain homologues **12a**−**c** were synthesized from the alcohol **11**[16] (Scheme 2). The diarylmethoxy group was attached in a fashion similar to that described above to afford the 2β-three-carbon-chain homologues **12a**−**c** in good yields (66−85%).

Biology. DAT binding affinities were determined for the 2-substituted 3β-aryltropanes **9**, **10**, and **12** by their ability to displace bound [^{3}H]WIN 35,428 (**2**) from rat caudate-putamen tissue.[36] The K_i values that are reported in Table 1 are inhibition constants derived for the unlabeled ligands. The binding affinities of the 2-substituted 3β-aryltropanes were also determined at SERT by inhibition of [^{3}H]citalopram and at NET by inhibition of [^{3}H]nisoxetine in assays previously described.[23] In addition, because of the structural similarity of **9**, **10**, and **12** to benztropine, muscarinic receptor (M_1) binding affinities were also determined using a [^{3}H]pirenzepine binding assay.[27]

Scheme 2



All of the 2-substituted 3β-aryltropanes displaced [^{3}H]WIN 35,428 from caudate putamen membranes with relatively high affinity (K_i) ranging from 34 nM (**9a**) to 112 nM (**9e**). In general, the 2β-isomers (**9**) were 10-fold more potent than the corresponding 2α-isomers (**10**) at DAT. Among the 2β-isomers (**9**), the selectivity (SERT/DAT) for DAT was significant and ranged from 6.1 (**9f**) to 2.5 (**9i**). However, there was less difference between the DAT and the SERT affinities for the 2α-isomers (**10**). The 2α-isomers (**10**) generally exhibited, if any, only a slight preference for the DAT (SERT/DAT from 0.8 to 2.8). The 2β-[(4-chlorophenyl)phenylmethoxymethyl]-3β-(4-chlorophenyl)tropane (**9f**) was the most selective analogue of the series (SERT/DAT = 6.1), though its DAT binding affinity (K_i = 76 nM) was 2-fold lower than the most potent analogue (**9a**), which had a more modest selectivity (SERT/DAT = 3.6). All of the 2-substituted 3β-aryltropanes (**9** and **10**) exhibited low binding affinities at NET (≥684 nM) and muscarinic (M_1) receptors (>9 μM).

The substituents (CH_3, F, Cl) on the 3β-aryl ring had little effect; however, the stereochemistry at the 2-position had a profound effect on DAT affinity. Similar to most 2-substituted 3β-aryltropanes, the 2β-isomers (**9**) were significantly more potent at the DAT than the corresponding 2α-isomers (**10**). Despite the bulky diarylmethoxy group of **9**, the binding affinities at DAT were not significantly affected. This further demonstrates the ability of the DAT to tolerate a wide variety of functionality and steric bulk at the 2β-position.[16,23] The particular substituents on the diarylmethoxy moiety appeared to have only a subtle effect on DAT affinity for the 2β-isomers (**9**). It is noteworthy that the diphenylmethoxy derivatives (**9a**, **9b**, and **9c**) were always slightly more potent than the bis(4-fluorophenyl)-methoxy derivatives (**9g**, **9h**, and **9i**). This is consistent with the SAR of the diarylmethoxy moiety of GBR-related compounds. However, the high SERT/DAT selectivity often observed for GBR-related compounds was not observed for any of the 2β-isomers **9**.

The three-carbon-chain homologues **12a**−**c** exhibited a slightly different pharmacological profile than the corresponding congeners (**9**). The unsubstituted homologue **12a** and the (4-chlorophenyl)phenylmethoxy ho-

Table 1. Dopamine, Serotonin, Norepinephrine Transporter, and Muscarinic Receptor Binding Affinities of 2-(Diarylmethoxymethyl)-3β-aryltropanes and 2β-[3-(Diarylmethoxy)propyl]-3β-aryltropanes

compd[a]	R	X	Y	[^{3}H]WIN 35,428 (DAT) K_i (nM)[b]	[^{3}H]citalopram (SERT) K_i (nM)[b]	[^{3}H]nisoxetine (NET) K_i (nM)[b]	[^{3}H]pirenzepine (M1) K_i (nM)[b]
9a	CH_3	H	H	34 ± 2	121 ± 19	684 ± 100	10600 ± 1100
9b	F	H	H	49 ± 12			
9c	Cl	H	H	52 ± 2.1	147 ± 8	1190 ± 72	11000 ± 1290
9d	CH_3	Cl	H	80 ± 9	443 ± 60	4400 ± 238	31600 ± 4300
9e	F	Cl	H	112 ± 11			
9f	Cl	Cl	H	76 ± 7	462 ± 36	2056 ± 236	39900 ± 5050
9g	CH_3	F	F	62 ± 7	233 ± 24	1830 ± 177	15500 ± 1400
9h	F	F	F	63 ± 13			
9i	Cl	F	F	99 ± 18	245 ± 16	2890 ± 222	16300 ± 1300
10a	CH_3	H	H	455 ± 36	530 ± 72	2609 ± 195	12600 ± 1790
10c	Cl	H	H	478 ± 72	408 ± 16	3998 ± 256	11500 ± 1720
10d	CH_3	Cl	H	937 ± 84	1001 ± 109	22500 ± 2831	18200 ± 2600
10f	Cl	Cl	H	553 ± 106	1293 ± 40	5600 ± 183	9600 ± 600
10g	CH_3	F	F	690 ± 76	786 ± 67	16000 ± 637	9700 ± 900
10i	Cl	F	F	250 ± 40	724 ± 100	52300 ± 13600	9930 ± 1090
12a	H	H	H	139 ± 15	61 ± 9	207 ± 30	7970 ± 631
12b	H	Cl	H	261 ± 19	45 ± 3		24600 ± 2930
12c	H	F	F	60 ± 7			

[a] All compounds were tested as the HCl salt. [b] All values are the mean ± SEM of three experiments performed in triplicate.

mologue **12b** exhibited high affinity for SERT (K_i = 61 and 45 nM, respectively). In addition, **12a** and **12b** each exhibited a greater affinity for the SERT than DAT (DAT/SERT = 2.3 and 5.8, respectively). Moreover, the unsubstituted derivative **12a** exhibited a significantly greater affinity for the NET (K_i = 207 nM) than all of the other compounds tested in this study. In addition, **12a** and **12c** exhibited the opposite trends in DAT binding affinities compared to the homologues **9a** and **9g** in that the 4,4-di-F-substituted **12c** displayed higher affinity for the DAT than the unsubstituted **12a**. The homologues **12a** and **12b**, however, exhibited low affinity at muscarinic (M_1) sites with binding affinities similar to those of series **9** and **10**.

Molecular Modeling

To further investigate structural requirements for optimal DAT binding and directly compare 3D structures of these analogues, a molecular modeling study was undertaken. In the absence of protein structural information of the DAT, the nature of binding interactions must be inferred from indirect methods. The three-dimensional quantitative structure−activity relationship (3D QSAR) method, comparative molecular field analysis (CoMFA), provides a tool in which the contributions of the binding interactions can be inferred via 3D contour graphs. The 3-substituted tropane analogues provide a unique set of DAT inhibitors in which several SAR and 3D-QSAR studies have already been reported.[2−4,10,14,37]

In this study, the SAR of the 2-(diarylmethoxy)-substituted tropanes was compared with other 2-, 3-, and 6-substituted tropane-based DAT inhibitors. These compounds contain structural features of several classes of DAT inhibitors, namely, the benztropines, GBR series, and 3-aryltropanes and, as such, provide a unique opportunity to identify structural features required for high-affinity DAT binding. Hence, a data set of compounds previously reported from our laboratory[16,38,39] was used to derive a molecular model. This model was used to further characterize structural requirements of 2-substituted tropanes for binding with DAT.

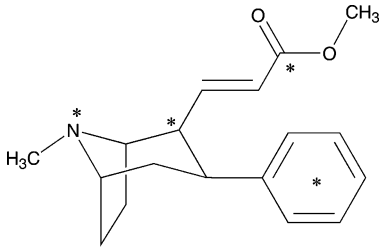


Figure 1. Atoms/centroid selection of the template molecule **14** used for alignments in model A.

The alignment of the compounds using four superimposing elements (Figure 1) gave model A, which provided a PLS model having an r^2_{cv} value of 0.798 with a standard error of prediction (SEP) of 0.517, using five components. The non-cross-validated PLS analysis provided a conventional correlation coefficient of 0.970 with a significant F value of 224.840. This CoMFA model showed a strong correlation between the steric descriptors because their global contribution (57.2) was more than that for the electrostatic descriptors (42.8). This suggests that hydrophobic groups on the molecules could improve binding to DAT.

Figure 2 shows the CoMFA contour maps for model A. The large green contours were found to surround the 2-position substituent, suggesting that large substituents in this region are well-tolerated, and many studies have shown the existence of a large binding pocket in this region. The existence of blue and red contours in the vicinity of the 2-position indicates the role of electrostatic interaction in this region. As such, ligands having ester groups or the equivalent may form hydrogen bonds in this region.[5] Therefore, the 2-position substituent may bind in a cavity that is lined with residues capable of forming hydrogen bonds but also has a large hydrophobic binding pocket.

Conclusions

3β-Aryltropane analogues wherein the 2-position was substituted with various (diarylmethoxy) substituents were synthesized and evaluated for binding at the DAT, SERT, NET, and muscarinic M1 receptors. The 2β-analogues **9a**−**i** generally demonstrated high-affinity

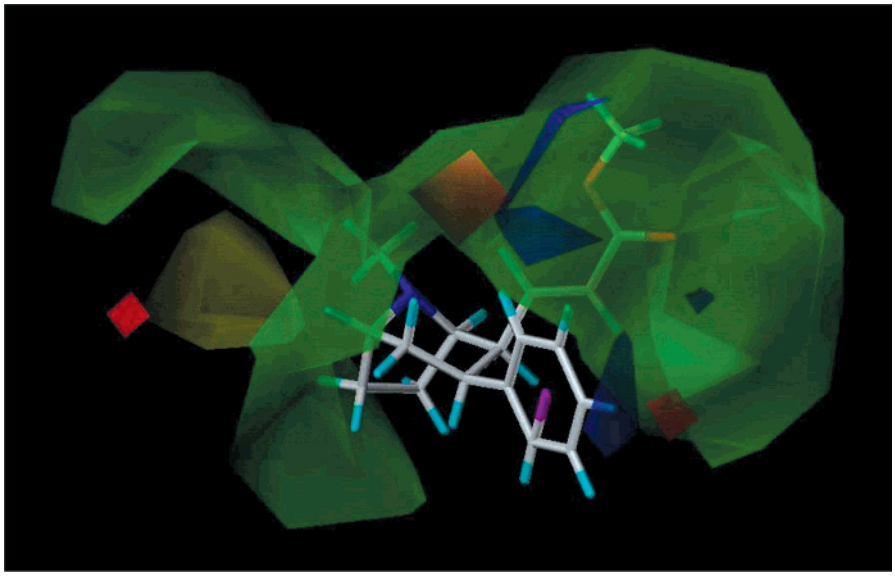


Figure 2. CoMFA steric and electrostatic STDEV*COEFF contour plots from the analysis of model A. The sterically favored (contribution, 80%) and unfavored (contribution, 20%) plots are shown as green and yellow contours, respectively. The electrostatic plots of positive (contribution, 80%) and negative (contribution, 20%) charge favoring areas are shown as blue and red contours, respectively.

binding at DAT with good selectivity over the SERT, NET, and M_1 receptors. Alternatively, the 2α-isomers **10a**−**i** were 10-fold less potent at DAT with poor selectivity over SERT. The 2-(diarylmethoxyalkyl)-3*β*-aryltropanes **9** and **10** exhibited SAR at DAT, SERT, NET, and M1 that is consistent with the SAR of the broad class of 2-substituted 3*β*-aryltropanes. A CoMFA-based 3D-QSAR model was derived and provided further insight into the structural requirements of 2-substituted tropanes for binding with DAT.

It is widely accepted that the DAT protein exists as 12 transmembrane-spanning helices, and presumably the inhibitor binding regions are located within or across these transmembrane regions. Structure−activity relationships derived from different classes of DAT ligands, as well as photoaffinity label studies, support the existence of multiple binding regions or orientations of the DAT.[37] Subtle changes in the structures of these molecules have resulted in distinct binding profiles, which may ultimately influence in vivo behavioral activity.[40] This flexibility in binding interaction might explain the consistently high-affinity binding profiles for this structurally diverse family of compounds. Nevertheless, it remains to be seen what compounds provide in vitro and in vivo profiles that will aid in the design of cocaine abuse medications. To that end, the dopamine uptake inhibition, locomotor stimulant activities, and discriminative stimulus effects of these compounds are currently under investigation and will be reported in due course.

Experimental Section

All chemicals and reagents not otherwise noted were purchased from Aldrich Chemical Co. Ether was dried by distillation from Na/benzophenone ketyl. The spectral data for all compounds are reported for the free base. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Multiprobe 400 MHz spectrometer. The free base was then converted into the hydrochloride salt to give a hygroscopic solid or solid foam used for microanalysis and biological testing. Microanalysis for C, H, and N were performed by Atlantic Microlabs Inc, Norcross, GA. Melting points were recorded on a Hoover Mel-Temp apparatus and are uncorrected.

Method A. Reduction of 2-Carbomethoxy-3*β*-aryltropanes. To a stirred suspension of $LiAlH_4$ (76 mg, 2.0 mmol) in dry Et_2O (25 mL) at 0 °C under a nitrogen atmosphere was added dropwise a solution of 2-carbomethoxy-3*β*-aryltropane (**5** or **6**) (2.0 mmol) in dry Et_2O (5 mL). Stirring was continued overnight at room temperature. The reaction mixture was cooled to 0 °C, and an aqueous solution of NaOH (5%, 10 mL) was added dropwise. The solids were filtered and washed with ether. The combined filtrate and washings were then washed with brine and the organic portion was separated, dried over Na_2SO_4, and concentrated under reduced pressure to furnish the alcohol (**7** or **8**). The alcohol was usually of sufficient purity that chromatography was unnecessary for subsequent transformations. An analytically pure sample of the alcohol could be obtained by elution of the crude material through a short silica gel column (petroleum ether: Et_3N, 9:1).

2*β*-Hydroxymethyl-3*β*-tolyltropane (7a):[23] general method A; colorless oil (450 mg, 92%).

2*β*-Hydroxymethyl-3*β*-(4-fluorophenyl)tropane (7b): general method A; colorless oil (450 mg, 87%); mp 73−74 °C [lit.,[18] 75−78 °C].

2*β*-Hydroxymethyl-3*β*-(4-chlorophenyl)tropane (7c): general method A; colorless oil (500 mg, 91%); mp 190−192 °C [lit.,[12] 189 °C].

2α-Hydroxymethyl-3*β*-tolyltropane (8a):[23] general method A; colorless oil (460 mg, 95%).

2α-Hydroxymethyl-3*β*-(4-chlorophenyl)tropane (8c): general method A; white solid (470 mg, 85%); mp 202−206 °C; ^{1}H NMR ($CDCl_3$) δ 7.24 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 3.48 (s, 1H), 3.43 (m, 1H), 3.33−3.22 (m, 3H), 2.36 (s, 3H), 2.35−2.27 (m, 1H), 2.24−2.19 (m, 1H), 2.15−2.07 (m, 1H), 1.94−1.91 (m, 1H), 1.89−1.86 (m, 1H), 1.80−1.75 (m, 1H), 1.61−1.55 (m 2H); $[\alpha]^{22}_D$ +24.2° (*c* 1, $CHCl_3$). Anal. ($C_{16}H_{20}NOCl$) C, H, N.

General Method B. 2-(Diphenylmethoxyalkyl)-3*β*-aryltropane. Bromodiphenylmethane (300 mg, 1.2 mmol) was added dropwise to a melt of the 2-substituted-3*β*-aryltropane alcohol (1.0 mmol) at 160 °C (oil bath) over 3 min. Evolution of HBr gas over 30 min resulted in a brown oil that solidified into a glass upon cooling. The crude product was dissolved in Et_2O (30 mL) and was transferred to a separatory funnel. The aqueous phase was made acidic (pH 2) with concentrated HCl, and the Et_2O layer was separated. The aqueous layer was made basic with concentrated NH_4OH and was extracted with

Et_2O (4 × 30 mL). The dried ethereal solution (Na_2SO_4) was evaporated under reduced pressure to give a yellow oil. The residue was purified by column chromatography (SiO_2; petroleum ether/triethlamine, 9.5:0.5) to furnish the corresponding 2-diarylmethoxyalkyl-3β-aryltropane derivatives.

General Method C. 2-[(4-Chlorophenyl)phenylmethoxyalkyl]-3β-aryltropane Derivatives. The chloro(4-chlorophenyl)phenylmethane (280 mg, 1.2 mmol) was added dropwise to a melt of the 2-hydroxyalkyl-3β-aryltropane (1.0 mmol) at 180 °C (oil bath) over 30 min. Evolution of HCl gas over 30 min resulted in a brown oil that solidified into a glass upon cooling. The residue was dissolved in Et_2O (30 mL) and transferred to a separatory funnel. The aqueous phase was made acidic (pH 2) with concentrated HCl, and the Et_2O layer was separated. The aqueous layer was then made basic with concentrated NH_4OH and was extracted with Et_2O (4 × 30 mL). The dried ethereal solution (Na_2SO_4) was evaporated under reduced pressure to give a yellow oil. The residue was purified by column chromatography (SiO_2; petroleum ether/triethylamine, 9.5:0.5) to furnish the corresponding 2-[(4-chlorophenyl)phenylmethoxyalkyl]-3β-aryltropane derivatives.

General Method D. 2-[Bis(4-fluorophenyl)methoxyalkyl]-3β-aryltropane Derivatives. Chlorobis(4-fluorophenyl)methane (360 mg, 1.5 mmol) was added dropwise to a melt of the 2-hydroxyalkyl-3β-aryltropane (1.0 mmol) at 180 °C (oil bath) over 1 h. Evolution of HCl gas over 30 min resulted in a brown oil that solidified into a glass upon cooling. The crude product was dissolved in Et_2O (30 mL) and transferred to a separatory funnel. The aqueous phase was made acidic (pH 2) with concentrated HCl, and the Et_2O layer was separated. The aqueous layer was made basic with concentrated NH_4OH and was extracted with Et_2O (4 × 30 mL). The dried ethereal solution (Na_2SO_4) was evaporated to give a yellow oil. The residue was purified by column chromatography (SiO_2; petroleum ether/triethylamine, 9.5:0.5) to furnish the corresponding 2-[bis(4-fluorophenyl)methoxyalkyl]-3β-aryltropane derivatives.

2β-Diphenylmethoxymethyl-3β-tolyltropane (9a): general method B; white solid (290 mg, 70%); mp 103−105 °C (free base); $[\alpha]^{21}_D$ −121° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.34−6.96 (m, 14H), 5.11 (s, 1H), 3.74 (t, *J* = 9.0 Hz, 1H), 3.50 (d, *J* = 4.4 Hz, 1H), 3.22 (m, 1H), 3.45−2.92 (m, 2H), 2.25 (s, 3H), 2.22 (s, 3H), 2.22−1.94 (m, 4H), 2.75−1.40 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 142.6, 139.3, 135.1, 128.7, 128.0, 127.2, 126.7, 126.5, 83.3, 67.5, 63.8, 61.9, 46.8, 41.6, 34.1, 25.9, 24.6, 20.8. Anal. ($C_{29}H_{33}NO\cdot HCl\cdot H_2O$) C, H, N.

2β-Diphenylmethoxymethyl-3β-(4-fluorophenyl)tropane (9b): general method B; white solid (310 mg, 75%); mp 81−83 °C (free base); $[\alpha]^{21}_D$ −72.2° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.24−6.84 (m, 14H), 5.07 (s, 1H), 3.68 (t, *J* = 9.0 Hz, 1H), 3.44 (d, *J* = 5.0 Hz, 1H), 3.16 (m, 1H), 3.20 (m, 1H), 2.91 (m, 1H), 2.19 (s, 3H), 2.15−1.91 (m, 4H), 1.59 (m, 2H), 1.43 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 159.4, 142.6, 138.4, 128.1, 128.0, 127.1, 127.0, 126.9, 126.8, 126.6, 114.9, 114.6, 83.5, 67.7, 63.9, 61.8, 47.1, 41.8, 34.3, 34.0, 26.0, 24.8. Anal. ($C_{28}H_{30}NOF\cdot HCl\cdot 2H_2O$) C, H, N.

2β-(Diphenylmethoxymethyl)-3β-(4-chlorophenyl)tropane (9c): general method B; white solid (350 mg, 80%); mp 99−101 °C (free base); $[\alpha]^{21}_D$ −7.45° (*c* 1, $CHCl_3$); ^{1}HNMR ($CDCl_3$) δ 7.29−6.96 (m, 14H), 5.06 (s, 1H), 3.67 (t, *J* = 8.7 Hz, 1H), 3.42 (d, *J* = 4.6 Hz, 1H), 3.13 (br s, 1H), 3.05−2.90 (m, 2H), 2.17 (s, 3H), 2.20−1.85 (m, 4H), 1.57 (m, 2H), 1.42 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 142.6, 141.4, 131.4, 128.8, 128.2, 128.1, 126.8, 126.6, 83.5, 67.7, 64.0, 61.7, 47.0, 41.9, 34.2, 34.0, 26.1, 24.8. Anal. ($C_{28}H_{30}NOCl\cdot HCl\cdot H_2O$) C, H, N.

2β-[(4-Chlorophenyl)phenylmethoxymethyl]-3β-tolyltropane (9d): general method C; colorless oil (220 mg, 50%); $[\alpha]^{21}_D$ −81.5° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.24−6.92 (m, 13H), 5.05 (s, 1H), 3.69 (t, *J* = 6.3 Hz, 1H), 3.45 (br s, 1H), 3.21 (br s, 1H), 3.10−2.90 (m, 2H), 2.26, (s, 3H), 2.21 (s, 3H), 2.20−1.95 (m, 4H), 1.76−1.42 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 142.2, 141.3, 135.2, 132.7, 132.6, 128.8, 128.2, 128.0, 127.3, 127.0, 126.9, 126.5, 82.7, 67.9, 63.9, 61.9, 46.9, 41.8, 34.2, 26.0, 24.8, 20.8. Anal. ($C_{29}H_{32}NOCl\cdot HCl\cdot H_2O$) C, H, N.

2β-(4-Chlorophenylphenylmethoxymethyl)-3β-(4-fluorophenyl)tropane (9e): general method C; colorless oil (270 mg, 60%); $[\alpha]^{21}_D$ −1.39° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.44−6.80 (m, 13H), 5.04, (s, 1H), 3.66 (t, *J* = 8.6 Hz, 1H), 3.43, (m, 1H), 3.18 (m, 1H), 3.02 (m, 1H), 2.91 (m, 1H), 2.19 (s, 3H), 2.20−1.90 (m, 4H), 1.63 (m, 2H), 1.49 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 159.7, 142.1, 141.2, 138.4, 132.7, 128.2, 128.0, 127.2, 126.6, 114.9, 114.6, 82.8, 67.8, 64.0, 61.7, 47.0, 41.8, 34.2, 34.0, 26.0, 24.7. Anal. ($C_{28}H_{29}NOFCl\cdot HCl\cdot 2H_2O$) C, H, N.

2β-[(4-Chlorophenyl)phenylmethoxy]methyl]-3β-(4-chlorophenyl)tropane (9f): general method C; colorless oil (300 mg, 64%); $[\alpha]^{21}_D$ −137° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.30−6.93 (m, 13H), 5.05 (d, *J* = 6.1 Hz, 1H), 3.66 (t, *J* = 8.6 Hz, 1H), 3.44 (m, 1H), 3.23 (br s, 1H), 3.05 (m, Hz, 1H), 2.94 (m, 1H), 2.22 (s, 3H), 2.16−1.95 (m, 4H), 1.65 (m, 2H), 1.49 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 141.8, 141.1, 140.9, 132.6, 131.4, 128.6, 128.1, 128.0, 127.8, 126.6, 126.4, 82.7, 67.8, 64.1, 63.9, 61.6, 46.8, 41.7, 34.0, 25.9, 24.6. Anal. ($C_{28}H_{29}NOCl_2\cdot HCl\cdot 0.5H_2O$) C, H, N.

2β-[Bis(4-fluorophenyl)methoxymethyl]-3β-tolyltropane (9g): general method D; colorless oil (190 mg,43%); mp 93−95 °C (HCl salt); ^{1}H NMR ($CDCl_3$) δ 7.33−6.96 (m, 12H), 5.01 (s, 1H), 3.66 (t, *J* = 8.5 Hz, 1H), 3.40 (d, *J* = 4.8 Hz, 1H), 3.21 (br s, 1H), 3.08−2.93 (m, 2H), 2.26 (s, 3H), 2.19 (s, 3H), 2.20−1.94 (m, 4H), 1.75−1.40 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 163.3, 160.1, 139.6, 138.3, 134.9, 128.6, 128.3, 129.0, 127.1, 114.9, 114.6, 114.4, 81.8, 67.7, 63.9, 61.7, 47.0, 41.7, 34.1, 25.9, 24.7, 20.6. Anal. ($C_{29}H_{31}NOF_2\cdot HCl$) C, H, N.

2β-[Bis(4-fluorophenyl)methoxymethyl]-3β-(4-fluorophenyl)tropane (9h): general method D; colorless oil (230 mg, 50%); ^{1}H NMR ($CDCl_3$) δ 7.20−6.85 (m, 12H), 5.04 (s, 1H), 3.64 (t, *J* = 8.6 Hz, 1H), 3.41 (d, *J* = 4.8 Hz, 1H), 3.22 (m, 1H), 3.07 (m, 1H), 2.91 (m, 1H), 2.22 (s, 3H), 2.15−1.90 (m, 4H), 1.65 (t, *J* = 11.6 Hz, 2H), 1.51 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 163.6, 162.7, 160.3, 138.2, 128.7, 128.4, 128.3, 128.1, 115.1, 114.9, 114.8, 114.7, 82.1, 67.8, 64.1, 61.8, 47.1, 41.9, 34.3, 34.1, 26.0, 24.8. Anal. ($C_{28}H_{28}NOF_3\cdot HCl$) C, H, N.

2β-[Bis(4-fluorophenyl)methoxymethyl]-3β-(4-chlorophenyl)tropane (9i): general method D; colorless oil **(** 270 mg, 58%); mp 125−127 °C (HCl salt); ^{1}H NMR ($CDCl_3$) δ 7.17−6.81 (m, 12H), 5.00 (s, 1H), 3.62 (t, *J* = 8.1 Hz, 1H), 3.36 (m, 1H), 3.15 (br s, 1H), 3.01 (m, 1H), 2.92 (q, *J* = 4.3 Hz, 1H), 2.17 (s, 3H), 2.15−1.86 (m, 4H), 1.59 (m, 2H), 1.44 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 163.5, 160.2, 141.4, 138.1, 131.4, 128.7, 128.2, 128.1, 115.1, 114.9, 114.8, 114.6, 82.1, 67.9, 64.2, 61.6, 47.0, 41.8, 34.2, 34.0, 26.0, 24.7. Anal. ($C_{28}H_{28}NOClF_2\cdot HCl$) C, H, N.

2α-(Diphenylmethoxymethyl)-3β-4-tolyltropane (10a): general method B; colorless oil (270 mg, 65%); $[\alpha]^{21}_D$ +4.84° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.26−6.99 (m, 14H), 5.06 (s, 1H), 3.49 (d, *J* = 7.3 Hz, 1H), 3.20−3.04 (m, 2H), 2.35 (m, 2H), 2.34 (s, 3H), 2.26 (s, 3H), 2.10−1.94 (m, 2H), 1.84 (m, 2H), 1.68 (m, 1H), 1.52 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 142.4, 142.2, 140.9, 135.4, 128.4, 128.0, 127.4, 126.4, 83.2, 69.0, 63.3, 61.7, 45.8, 40.9, 37.5, 25.8, 21.7, 20.8. Anal. ($C_{29}H_{33}NO\cdot HCl\cdot H_2O$) C, H, N.

2α-(Diphenylmethoxy)methyl-3β-(4-chlorophenyl)tropane (10c): general method C; colorless oil (290 mg, 66%); $[\alpha]^{21}_D$ −27.95° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.60−6.90 (m, 14H), 5.09 (s, 1H), 3.68 (t, *J* = 8.6 Hz, 1H), 3.46 (br s, 1H), 3.20 (br s, 1H), 3.10−2.90 (m, 2H), 2.22 (s, 3H), 2.15−1.90 (m, 4H), 1.64 (t, *J* = 11.2 Hz, 2H), 1.48 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 142.6, 135.2, 131.4, 130.7, 128.8, 128.4, 128.0, 127.4, 127.3, 127.0, 126.9, 83.5, 67.8, 64.1, 61.8, 47.0, 41.9, 34.3, 26.1 24.9, 21.0. Anal. ($C_{28}H_{30}NOCl\cdot HCl\cdot H_2O$) C, H, N.

2α-[(4-Chlorophenyl)phenylmethoxymethyl]-3β-tolyltropane (10d): general method C; colorless oil (200 mg, 45%); $[\alpha]^{21}_D$ +29.1° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.45−6.95 (m, 13H), 5.53 (s, 1H), 3.46 (m, 1H), 3.20 (m, 1H), 3.07 (d, *J* = 6.6 Hz, 2H), 2.37 (s, 3H), 2.30 (s, 3H), 2.15−1.98 (m, 2H), 1.97−1.76 (m, 2H), 1.75−1.46 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 141.8, 140.8, 135.6, 133.0, 132.7, 129.0, 128.3, 128.2, 127.5, 127.2, 126.8, 126.4, 82.6, 69.0, 63.4, 61.8, 45.8, 40.8, 37.5, 25.8, 21.8, 20.9. Anal. ($C_{29}H_{32}NOCl\cdot HCl\cdot 2H_2O$) C, H, N.

2α-[(4-Chlorophenyl)phenylmethoxymethyl]-3β-(4-chlorophenyl)tropane (10f): general method C; colorless oil (220 mg, 48%); $[\alpha]^{21}_D$ +46.9° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.27−7.08 (m, 13H), 5.06 (s, 1H), 3.45 (d, *J* = 6.5 Hz, 1H), 3.22 (m, 1H), 3.07 (d, *J* = 5.0 Hz, 2H), 3.83 (br s, 1H), 2.38 (s, 3H), 2.05 (m, 2H), 2.00−1.63 (m, 3H), 1.58 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 142.6, 141.8, 140.9, 132.9, 131.7, 129.1, 128.5, 128.4, 128.3, 127.6, 126.8, 126.5, 82.7, 69.2, 63.5, 61.7, 46.1, 41.0, 40.9, 37.7, 25.8, 21.9. Anal. ($C_{28}H_{29}NOCl_2$·HCl·H_2O) C, H, N.

2α-[Bis(4-fluorophenyl)methoxy]methyl]-3β-tolyltropane (10g): general method D; colorless oil (140 mg, 32%); mp 170−172 °C (HCl salt); ^{1}H NMR ($CDCl_3$) δ 7.22−6.87 (m, 12H), 5.03 (s, 1H), 3.43 (d, *J* = 5.1 Hz, 1H), 3.18 (br s, 1H), 3.05 (d, *J* = 6.0 Hz, 2H), 2.36 (s, 3H), 2.28 (s, 3H), 2.15−1.96 (m, 2H), 1.94−1.78 (m, 2H), 1.72−1.47 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 163.3, 159.9, 140.7, 137.9, 137.5, 135.2, 128.7, 128.2, 127.8, 127.2, 114.8, 114.5, 81.5, 68.7, 63.1, 61.4, 45.9, 40.5, 37.4, 25.5, 21.5, 20.5. Anal. ($C_{29}H_{31}NOF_2$·HCl) C, H, N.

2α-[Bis(4-fluorophenyl)methoxymehyl]-3β-(4-chlorophenyl)tropane (10i): general method D; colorless oil (160 mg, 35%); ^{1}H NMR ($CDCl_3$) δ 7.30−6.92 (m, 12H), 5.29 (s, 1H), 3.78−3.62 (m, 2H), 3.16 (br s, 1H), 2.70 (m, 1H), 2.30 (s, 3H), 2.06, (br s, 4H), 1.94 (t, *J* = 13.1, Hz, 1H), 1.55 (m, 1H), 1.36 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 163.7, 160.5, 140.8, 137.7, 130.6, 128.5, 128.4, 128.3, 128.2, 128.1, 115.4, 115.1, 83.4, 73.2, 70.0, 64.7, 62.1, 48.7, 46.1, 42.1, 25.2, 20.6. Anal. ($C_{28}H_{28}NOClF_2$·HCl) C, H, N.

2β-[3-(Diphenylmethoxy)propyl]-3β-phenyltropane (12a): general method B; colorless oil (370 mg, 86%); $[\alpha]^{21}_D$ −117° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.32−7.10 (m, 15H), 5.16 (s, 1H), 3.35−3.10 (m, 4H), 3.04 (m, 1H), 2.18 (s, 3H), 2.14−2.06 (m, 2H), 2.10−1.90 (m, 1H), 1.62−1.53 (m, 4H), 1.53−1.40 (m, 2H), 1.34−1.18 (m, 1H), 0.97−0.80 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 143.4, 142.3, 128.0, 127.9, 127.6, 127.0, 126.7, 125.5, 83.2, 69.1, 64.3, 61.8, 45.9, 41.9, 36.2, 33.3, 27.7, 26.2, 24.6, 23.2. Anal. ($C_{20}H_{35}NO$·HCl·H_2O) C, H, N.

2β-[3-(4-Chlorophenylphenylmethoxy)propyl]-3β-phenyltropane (12b): general method B; colorless oil (300 mg, 66%); $[\alpha]^{21}_D$ −64.0° (*c* 1 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.35−7.04 (m, 14H), 5.11 (s, 1H), 3.35−3.00 (m, 6H), 2.18 (s, 3H), 2.12 (m, 1H), 1.99 (m, 1H), 1.70−1.40 (m, 6H), 1.30−1.15 (m, 1H), 0.86 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 143.5, 142.0, 141.2, 132.8, 128.3, 128.2, 128.1, 128.0, 127.8, 127.4, 126.8, 125.7, 82.6, 69.3, 64.5, 66.0, 46.0, 42.1, 36.3, 33.4, 27.8, 26.4, 24.8, 23.4. Anal. ($C_{30}H_{34}NOCl$·HCl·$2H_2O$) C, H, N.

2β-[3-{Bis(4-fluorophenyl)methoxy}propyl]-3β-phenyltropane (12c): general method D; colorless oil (330 mg, 71%); mp 54−56 °C (HCl salt); ^{1}H NMR ($CDCl_3$) δ 7.28−6.90 (m, 13H), 5.13 (s, 1H), 3.30−3.06 (m, 5H), 2.21 (s, 3H), 2.20−2.10 (m, 2H), 2.10−1.95 (m, 1H), 1.70−1.55 (m, 4H), 1.55−1.40 (m, 2H), 1.25 (m, 1H), 0.89 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 163.5, 160.2, 143.5, 138.0, 128.4, 128.3, 127.9, 127.6, 125.6, 115.1, 114.8, 81.8, 69.1, 64.4, 61.9, 46.0, 42.0, 36.2, 33.3, 27.7, 26.3, 24.7, 23.3. Anal. ($C_{30}H_{33}NOF_2$·HCl) C, H, N.

Molecular Modeling Methods. The 3D-QSAR studies were performed using CoMFA method with SYBYL 6.7 running on Silicon Graphics Octane workstation. The X-ray crystal structural data of compounds **16**, **30**, and **37** (see Supporting Information) were used to build the closest structure. The nitrogen of the tropane ring was considered as a neutral atom. The structures were assigned semiempirical AM1 charges and energy-minimized to the local minima. The conformations of the compounds were explored by systematic conformational searching of all nonterminal rotatable bonds for 360° with an increment of 15°. The low-energy conformers were extracted and minimized by conjugate gradient minimization. The compounds were superimposed by selecting the atoms/centroid shown in Figure 1. The compounds containing a diarylmethoxy substituent at the 2-position were used as a validation set. The standard steric and electrostatic CoMFA interaction fields were calculated by default parameters. The statistical analyses of the descriptors were performed by a partial least-squares (PLS) algorithm leave one out (LOO) cross-validation method. The optimum number of components was chosen on the basis of criterioa where at least a 5% increase in r^2_{cv} value was observed with addition of each component and the point where use of additional components did not show a 5% increase in r^2_{cv} the previous components were considered optimum. The CoMFA contour graphs were derived automatically. The training set consisted of 41 compounds in which 18 compounds were 2-substituted 3-phenyltropanes (Table 2) and 23 compounds were 6-substituted 3-benzyltropanes (Table 3).

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Supporting Information Available: Tables 2 and 3 listing the activities and structures of aryl- and benzyltropanes. This material is available free of charge via the Internet at http://pubs.acs.org.

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