Synthesis, Ligand Binding, and Quantitative Structure−Activity Relationship Study of 3*β*-(4′-Substituted phenyl)-2*β*-heterocyclic Tropanes: Evidence for an Electrostatic Interaction at the 2*β*-Position

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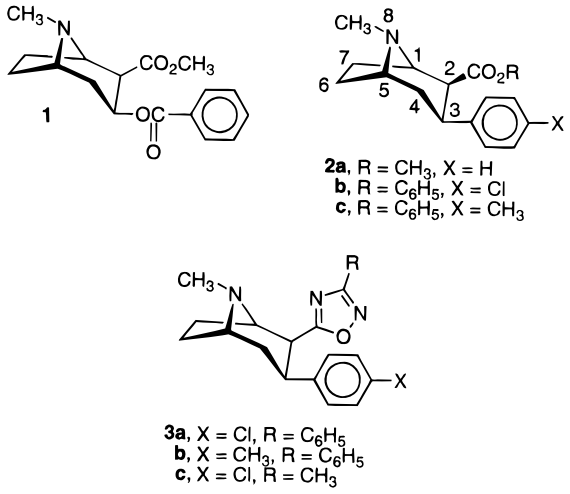
A set of 3*β*-(4′-substituted phenyl)-2*β*-heterocyclic tropanes was designed, synthesized, and characterized. We discovered that these compounds can function as bioisosteric replacements for the corresponding WIN 35,065-2 analogs which possess a 2*β*-carbomethoxy group. Several of the compounds showed high affinity and selectivity for the dopamine transporter (DAT) relative to the serotonin and norepinephrine transporters. From the structure−activity relationship study, the 3*β*-(4′-chlorophenyl)-2*β*-(3′-phenylisoxazol-5-yl)tropane (**5d**) emerged as the most potent and selective compound. The binding data for 2*β*-heterocyclic tropanes were found to show a high correlation with molecular electrostatic potential (MEP) minima near one of the heteroatoms in the 2*β*-substituents. In contrast, low correlations were found for other MEP minima near the 2*β*-substituent as well as for calculated log *P* or substituent volume. These quantitative structure−activity relationship studies are consistent with an electrostatic contribution to the binding potency of these WIN 35,065-2 analogs at the DAT.

Cocaine (**1**), which inhibits the presynaptic uptake of dopamine (DA), serotonin (5-HT), and norepinephrine (NE) in brain, is one of the most reinforcing and addictive compounds ever studied.[1−3] Interest in cocaine and dopamine transporter (DAT) research was greatly stimulated by reports that a binding site on the DAT might be the site responsible for the reinforcing properties of cocaine.[4,5] Thus, the behaviors associated with cocaine addiction are believed to result from the inhibition of DA uptake by the binding of cocaine to specific recognition site(s) located on the DAT of mesolimbocorticol neurons which potentiate dopaminergic neurotransmission leading to reinforcement.

In order to gain information about the pharmacophore for this binding site, we have examined the effects of variation in the structure of 3*β*-phenyl-2*β*-carbomethoxytropane (WIN 35,065-2, **2a**) on the inhibition of radioligand binding of the DAT. The pharmacophore features identified to be present in **2a** analogs which are both potent and selective for the dopamine transporter relative to the 5-HT and NE transporters were a tropane ring with (a) an N atom at the 8-position, (b) a small to medium size group possessing at least one heteroatom on the 2*β*-position, and (c) a 4′-substituted or 3′,4′-disubstituted phenyl ring in the 3*β*-position.

In previous reports we described the synthesis and biochemical evaluation of several 3*β*-(4′-substituted phenyl)-2*β*-(3′-substituted-1′,2′,4′-oxadiazol-5′-yl)tropanes **3**. These compounds were found to be excellent bioisosteres for 3*β*-(4′-substituted phenyl)tropane-2*β*-carboxylic acid esters such as **2b,c**.[6−8] The primary objective of the present study was to replace the metabolically labile 2*β*-ester group by other stable bioisosteric heterocyclic groups. The inhibition of [^{3}H]-WIN 35,428, [^{3}H]paroxetine, and [^{3}H]nisoxetine binding at the DA, 5-HT, and NE transporters was used as an indication of the target compound's ability to inhibit uptake of these neurotransmitters. The study demonstrates that high affinity at the cocaine binding site on the DAT can be obtained by replacing the 2*β*-carbomethoxy group of **2a** with several different heterocyclic bioequivalents and that the 2*β*-isoxazole group provides high potency and DAT selectivity. A part of this study was described in a preliminary communication.[9]



Structure−activity relationship (SAR) studies directed toward defining the pharmacophore for the cocaine binding site on the DAT have been the subject of many reports in the last 6 years.[10] These studies have largely been qualitative in nature and are still in a speculative stage. Despite the existence of common features, significant differences in binding may exist even between compounds which are structurally very similar. In previous reports, we have applied quantita-

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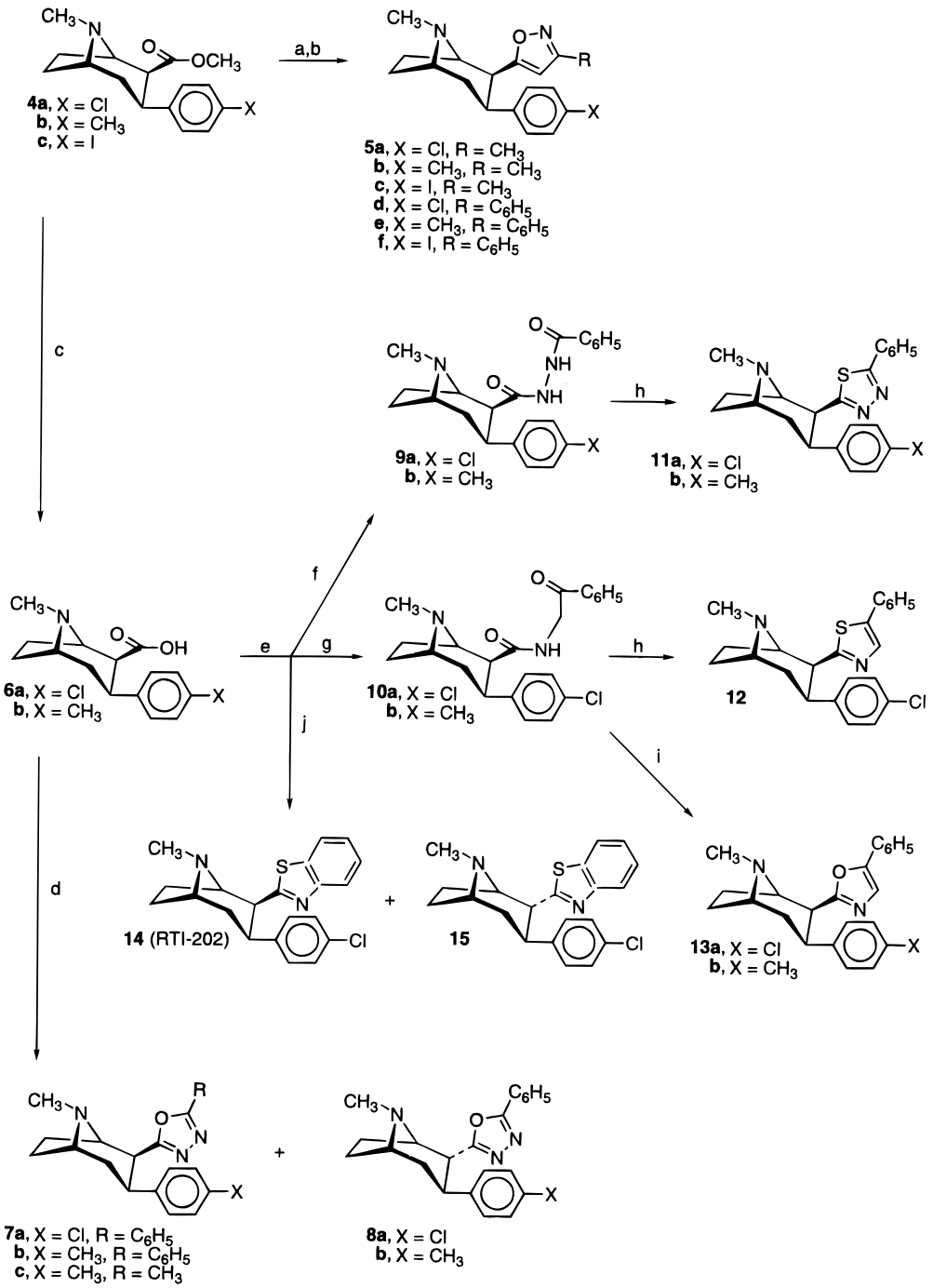
Scheme 1[a]



[a] Reagents: (a) $CH_3C(=NOH)R$, nC_4H_9Li, THF, 0 °C; (b) H_2SO_4, THF; (c) H_2O; (d) $POCl_3$, $RCONHNH_2$; (e) $(COCl)_2$, CH_2Cl_2; (f) $C_6H_5CONHNH_2$; (g) $C_6H_5COCH_2NH_2$; (h) $(4\text{-}CH_3OC_6H_4P(O)\text{-}S\text{-})_2$, toluene; (i) $POCl_3$; (j) 2-aminothiophenol, CH_2Cl_2.

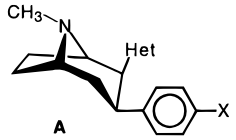
tive structure−activity relationship (QSAR) studies to gain information about the 3β-aryl group of the WIN 35,065-2 class of compounds.[11,12] In this work we now apply QSAR studies to learn about the effects of the 2β-substituent on binding potency.

Chemistry

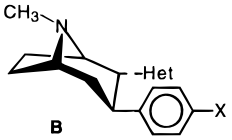
The syntheses of the 2-heterocyclic analogs of 3β-phenyl-2β-carbomethoxytropanes **5a**−**f**, **7a**−**c**, **11a,b**, **12**, **13a**−**b**, and **14** are outlined in Scheme 1. A solution of the appropriate 3β-(4′-substituted phenyl)tropane-2β-carboxylic acid methyl esters **4a**−**c**[8,11,12] was added to the dilithium salt of the oxime of acetone, or of acetophenone, in tetrahydrofuran at 0 °C, and the reaction mixture was warmed to 25 °C. After 18 h at 25 °C, the reaction mixture was added to a tetrahydrofuran solution containing sulfuric acid and was refluxed for 1 h to give the 3β-(4′-substituted phenyl)-2β-(3′-substituted isoxazol-5′-yl)tropanes **5a**−**f**.[13] The 3β-(4′-substituted phenyl)-2β-(5′-substituted 1′,3′,4′-oxadiazol-2′-yl)tropanes **7a**−**c** were obtained by refluxing the 3β-(4′-chloro- or 4′-methylphenyl)tropane-2β-carboxylic acid **6a,b**[8] with *N*-acetyl or *N*-benzoyl hydrazide in phosphorus oxychloride.[14] In the case of **7a,b**, a small amount of the 2α-isomers **8a,b** was obtained.

Acids **6a**,**b** were treated with oxalyl chloride, and the resultant acid chlorides were condensed with *N*-benzoyl

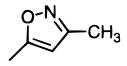
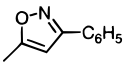
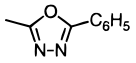
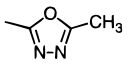
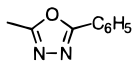
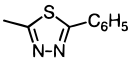
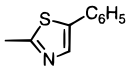
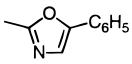
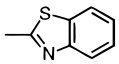
Table 1. Chemical Shift and Vicinal Coupling Constants for the C-2 and C-3 Protons of the 3β-Substituted-2-heterocyclic Tropanes[a]



A



B

Cmpd	Structure	Het	X	Chemical Shift[b] C2-H	Chemical Shift[b] C3-H	Coupling Constants[c] $J_{2,3}$
5a	A		Cl	4.25	3.73	6.0
b	A		CH_3	4.10	3.65	6.0
c	A		I	4.22	4.0	5.8
d	A		Cl	4.23	3.75	5.7
e	A		CH_3	4.24	3.20	5.7
f	A		I	4.32	3.27	5.9
7a	A		Cl	4.31	3.83	6.1
b	A		CH_3	4.35	3.86	6.0
c	A		CH_3	4.26	3.72	6.1
8a	B		Cl	3.63	3.85	12.2
b	B		CH_3	3.70	3.35	11.9
11a	A		Cl	3.73	3.30	5.9
b	A		CH_3	3.76	3.30	5.9
12	A		Cl	3.76	3.30	5.9
13a	A		Cl	4.25	3.72	6.1
b	A		CH_3	3.56	3.35	6.0
14	A		Cl	3.65	3.33	6.1
15	B		Cl	3.86	3.41	11.7
18a	A		Cl	3.97	3.33	6.1
b	A		CH_3	3.75	3.36	6.1

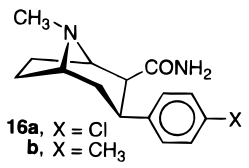
[a] Spectra were carried out on the free bases of the compounds at 500 mHz. [b] In parts per million downfield from TMS. [c] *J* values are in Hz.

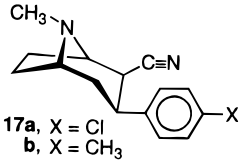
hydrazide and 2-aminoacetophenone to give the hydrazides **9a,b** or the amides **10a,b**, respectively. Cyclization of **9a,b** and **10a** with Lawesson's reagent[15] gave the 3β-(4′-substituted phenyl)-2β-(5′-phenyl-1′,3′,4′-thiadiazol-2′-yl)tropanes **11a,b** and the 3β-(4′-chlorophenyl)-2β-(5′-phenylthiazol-2′-yl)tropane (**12**), respectively. Cyclodehydration of **10a**,**b** with phosphorus oxychloride afforded the 3β-(substituted phenyl)-2β-(5′-phenyloxazol-2′-yl)tropanes **13a,b**. Condensation of the acid chloride from **6a** with 2-aminothiophenol gave 3β-(4′-chlorophenyl)-2β-(benzothiozol-2-yl)tropane (**14**). An attempt to convert **6a** directly to **14** using refluxing phosphorus oxychloride gave mainly the α-isomer **15**.

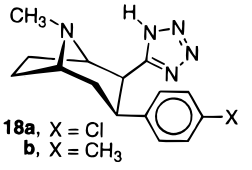
The synthesis of the 3β-(substituted phenyl)tropane-2β-tetrazoles **18a,b** is shown in Scheme 2. Dehydration of 3β-(4′-substituted phenyl)tropane-2β-carboxamides **16a,b**[8] with trifluoroacetic anhydride and pyridine in tetrahydrofuran gave the 2β-nitriles **17a,b**. Subjection of the nitriles **17a,b** to a cycloaddition reaction using trimethylsilyl azide[13] afforded the tetrazoles **18a,b**.

The structural assignment for the 3β-(substituted phenyl)-2-heterocyclic tropanes was based largely on the methods of synthesis and elemental and ^{1}H NMR analysis. The vicinal couplings $J_{2eq,3ax} = 5.67-6.13$ Hz and $J_{2ax,3ax} = 11.73-12.19$ Hz for the 2β- and 2α-heterocyclic, respectively, are in accord with the stereochemical assignments (Table 1).

Scheme 2[a]

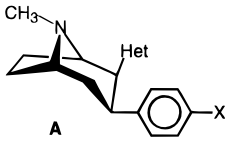




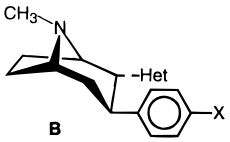


[a] Reagents: (a) $(CF_3CO)_2O$, pyridine, THF; (b) $(CH_3)_3SiN_3$.

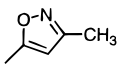
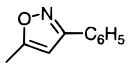
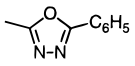
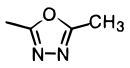
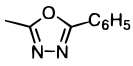
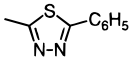
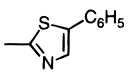
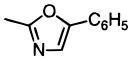
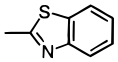
Table 2. Comparison of Transporter Binding Potencies for 3β-(Substituted phenyl)-2β-heterocyclic Tropanes



A



B

				IC$_{50}$ (nM)[a]				
Cmpd	Structure	Het	X	DA [^{3}H]WIN 35,428	NE [^{3}H]nisoxetine	5-HT [^{3}H]paroxetine	NE/DA Ratio[b]	5-HT/DA Ratio[b]
3a[c]	A		Cl	1.62 ± 0.02	245 ± 13	195 ± 4.8	151	120
b[c]	A		CH$_3$	2.33 ± 0.26	60 ± 2	1070 ± 125	26	460
c[c]	A		Cl	4.05 ± 0.57	363 ± 36	2580 ± 799	90	637
5a	A		Cl	0.59 ± 0.04	181 ± 12	572 ± 58	307	970
b	A		CH$_3$	0.93 ± 0.09	254 ± 31	3820 ± 346	273	4107
c	A		I	0.73 ± 0.04	67.9 ± 5.25	36.4 ± 5.0	93	498
d	A		Cl	1.28 ± 0.18	504 ± 29	2420 ± 136	393	1891
e	A		CH$_3$	1.58 ± 0.02	398 ± 18	5110 ± 187	251	3234
f	A		I	2.57 ± 0.14	868 ± 95	100 ± 9.0	337	39
7a	A		Cl	12.6 ± 1.03	929 ± 88	3300 ± 196	73	262
b	A		CH$_3$	47.5 ± 4.76	1310 ± 37	23,300 ± 822	28	491
c	A		CH$_3$	4.45 ± 0.12	253 ± 19	4890 ± 155	57	1099
8a	B		Cl	1100 ± 96	286,000 ± 23,000	19,200 ± 1780	260	18
b	B		CH$_3$	523 ± 48	48,700 ± 324	65,000 ± 817	93	124
11a	A		Cl	15.3 ± 2.43	4140 ± 466	18,400 ± 1510	271	1203
b	A		CH$_3$	35.9 ± 3.4	24,300 ± 3820	51,500 ± 4510	677	1432
12	A		Cl	5.71 ± 0.36	8560 ± 824	10,300 ± 76	1500	1804
13a	A		Cl	19.7 ± 1.98	496 ± 42	1120 ± 107	25	57
b	A		CH$_3$	35.4 ± 1.74	677 ± 68	1700 ± 167	19	48
14	A		Cl	1.37 ± 0.14	403 ± 30	1120 ± 120	294	818
15	B		Cl	188 ± 5	59,500 ± 5,740	5,210 ± 488	317	28
18a	A		Cl	911 ± 6.1	17,400 ± 2050	5460 ± 64	19	6
b	A		CH$_3$	1560 ± 196	32,500 ± 2080	43,600 ± 5420	21	28

[a] Data are mean ± standard error of three or four experiments performed in triplicate. [b] Ratios of IC$_{50}$ values. [c] The IC$_{50}$ values are from ref 7. Cocaine has IC$_{50}$ values of 89, 3300, and 1050 nM at the DA, NE, and 5-HT transporters (ref 8).

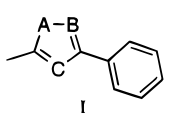
Biological Evaluation

Competitive radioligand binding assays were used to determine the affinities of target compounds. DA, 5-HT, and NE transporter binding studies were performed as previously described[7] using [^{3}H]WIN 35,428, [^{3}H]paroxetine, and [^{3}H]nisoxetine in striatum, frontal cortex, and midbrain from rats, respectively. The ratios of IC$_{50}$ values 5-HT/DA and NE/DA were used as a measure of the in vitro selectivity of the compounds for the DAT relative to the 5-HT and NE transporters. This method of estimating selectivity has been described in previous reports.[8] Ratios above 300 have been shown to correlate with selectivity of DA uptake relative to 5-HT and NE uptake. The results of the binding studies are summarized in Tables 2 and 3.

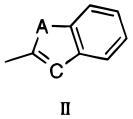
Selected compounds were evaluated for their ability to inhibit [^{3}H]DA uptake in rat striatal synaptosomes.[8] The K_i values, calculated using the Cheng and Prusoff equation,[16] are listed in Table 4. A correlation of the [^{3}H]DA uptake data with the [^{3}H]WIN 35,428 binding data gave the following statistical values: $n = 6$, $s = 0.21$, $F = 24$, $r^2 = 0.89$.

Molecular Modeling

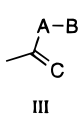
We have studied the relationship between the electrostatic (molecular electrostatic potential), hydrophobic (calculated log P), and steric (substituent volume) properties of the 2β-heterocyclic moiety of several 3β-(4′-chlorophenyl)tropane analogs and their binding affinities at the DAT. In order to make these calculations feasible, simplified models of each compound were formed by replacing the common 3β-(4′-chlorophenyl)tropane with a methyl group (see model structures I−III). Details



I

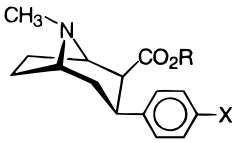


II



III

Table 3. Comparison of Transporter Binding Potencies for WIN 35,065-2 Ester and Acid Analogs



			IC50 (nM)[a]			ratio[a]	
compd	R	X	DA [3H]WIN 35,428	NE [3H]nisoxetine	5-HT [3H]paroxetine	NE/DA	5-HT/DA
4a[b]	CH_3	Cl	1.12 ± 0.1	37 ± 2.1	44.5 ± 1.34	33	40
4b[b]	CH_3	CH_3	1.71 ± 0.31	60 ± 0.53	240 ± 27	35	140
2a[b]	C_6H_5	Cl	1.98 ± 0.05	2950 ± 220	2300 ± 176	1490	1162
2b[b]	C_6H_5	CH_3	3.26 ± 0.06	5800 ± 373	24 500 ± 1500	1779	7515
6a	H	Cl	2070 ± 21	>200 000	59 500 ± 4900	>96	29

[a] See footnotes a and b from Table 2. [b] The IC_{50} values are taken from refs 8 and 10.

Table 4. Inhibition of Dopamine Transport by WIN 35,065-2 Analogs

compd	DA uptake[a] K_i (nM)[b]
2a[c]	5.25 ± 0.76
3a	0.59 ± 0.05
5d	2.08 ± 0.27
7a	18.7 ± 1.2
13a	19 ± 1.6

[a] Inhibition of [3H]dopamine. [b] Calculated using the Cheng and Prusoff equation (ref 16); the K_m value for dopamine uptake was 105 nM (ref 18). The data ± standard error represent the mean of three or four independent experiments, each performed in triplicate. [c] Data taken from ref 8.

of the calculations are presented in the Experimental Section. All three molecular descriptors were obtained for 12 model compounds: methyl- and phenyl-substituted oxazoles (models of **13a**), isoxazoles (**5a**,**d**), oxadiazoles (**3a**, **7a**), thiazoles (**12**), thiadiazoles (**11a**), tetrazoles (**18a**), benzothiazoles (**14a**), phenyl and methyl esters (**2b**, **4a**), and carboxylic acids (**6a**). Substituents with acidic protons were modeled as the anionic conjugate bases. The local minimum (V_{min}) of the molecular electrostatic potential (MEP) of the 2β-substituent models was determined in the vicinity of the heteroatoms labeled A−C in model structures I−III. QSAR analysis was then performed using the DAT binding affinities of the corresponding 2β-heterocyclic-(4′-chlorophenyl)tropanes as the reference values.

Results and Discussion

Bioisosteric replacement of ligands containing a carbomethoxy group by structurally related heterocyclic moieties possessing properties similar to those of the carbomethoxy group has led to compounds potent and selective for certain receptors.[17] In a previous report, we showed that an analog of **2a** in which the 2β-carbomethoxy group had been replaced by a 1,2,4-oxadiazole ring was recognized by the cocaine binding site on the DAT.[6,7] This finding, combined with the recent interest in the SAR of the 2β-position of analogs of **2a**, prompted us to study other 2β-heterocyclic ring groups.[8,18−23] In the present study, we have synthesized analogs possessing seven different 2β-heterocyclic groups. Analysis of their affinities at the DAT shows that when the substituent on the heterocycle is a phenyl group, the order of DA binding potencies for the bioisosteric heterocycles is 1,2-isoxazole > 1,2,4-oxadiazole > 1,3-thiazole > 1,3,5-oxadiazole > 1,3,5-thiadiazole > 1,3-oxazole. When the substituent is a methyl, the rank order of binding potencies is 1,2-isoxazole > 1,2,4-oxadiazole ≅ 1,3,5-oxadiazole. It is particularly interesting to note that the 1,2-isoxazoles (**5a**−**e**) have the highest affinity for the DAT and that the isomeric 1,3-oxazoles (**13a,b**) showed markedly lower affinity for the DAT than **5d,e**. In addition, the bioisosteric 2β-1,2,4-oxadiazole analogs **3a,b** bind to the DAT with affinities equal to, or better than, those of the parent esters, whereas the isomeric 1,3,4-oxadiazole analogs **7a,b** have much lower affinities for the DAT. Since these markedly different DAT affinities for isomeric compounds are not likely due to steric or hydrophobic properties, these results suggested that the differences were due to other factors.

One of the more interesting features of the SAR of WIN 35,065-2 analogs for the DAT is the number of different types of 2β-substituents that provide good affinity.[10] Almost any group at C-2 of a 3β-phenyltropane will provide a compound with affinity exceeding that of cocaine. In contrast, the analog **6a**, which has a 2β-carboxy group, has very low affinity for the DAT. We also found that **18a**, the bioisosteric 2β-tetrazole analog of the acid **6a**, had very low affinity for the DAT, suggesting that groups possessing negative charge are not well accommodated at the DAT. The second 2β-tetrazole studied, **18b**, also had low affinity at the DAT, as expected. A computational analysis of all the 2β-heterocyclic analogs along with the parent esters and acids was conducted to gain information on the binding requirements of 2β-substituents of the DAT. To investigate the possibility that electrostatic properties may be important in determining the relative potencies of the 2β-heterocyclic analogs and their parent compounds, a series of semiempirical quantum mechanics calculations using Spartan[24] were performed. Semiempirical methods have been demonstrated to reproduce MEP values adequate for QSAR studies, especially if relative minima are used rather than absolute values.[25−27] (When considered necessary to verify the accuracy of the semiempirical calculations, some values were recalculated at a higher level of theory using STO-3G and 6-31G* *ab initio* calculations. In agreement with the published reports, the AM1 values were found to be satisfactory.) The resulting relative local minima of the MEP adjacent to heteroatoms A−C are listed in Table 5. A good correlation between the relative MEP minima adjacent to heteroatom A [ΔV_{min}(A)] and the IC_{50} values

Table 5. Relative MEP Minima (ΔV_{min}, kcal/mol), Calculated log *P* (Clog*P*), and Substituent Volume (VOL, Å^3)

substituent model	ΔV_{min} A	B	C	Clog*P*	VOL
2b	223	226	198	1.49	116
3a	244	152	197	1.83	122.5
4a	217	226	192	0.18	66.7
5a	239	144	290	0.66	86.1
5d	240	144	290	2.49	134.8
6a	0	226	0	-0.17	42.9
7a	194	131	247	0.89	124.8
11a	193	133	290	1.93	134.4
12	180	226	290	3.08	140.9
13a	181	226	241	2.19	132
14a	290	226	187	2.58	119.3
18a	62	0	63	-0.18	59.6

Table 6. Actual and Calculated $-\log(IC_{50})$ Values

compd	actual	calcd
2b	−0.3	−0.47
3a	−0.21	−0.19
4a	−0.05	−0.55
5a	0.23	−0.25
5d	−0.11	−0.24
6a	−3.32	−3.47
7a	−1.1	−0.86
11a	−1.18	−0.87
12	−0.76	−1.05
13a	−1.29	−1.03
14a	−0.14	0.43
18a	−2.96	−2.64

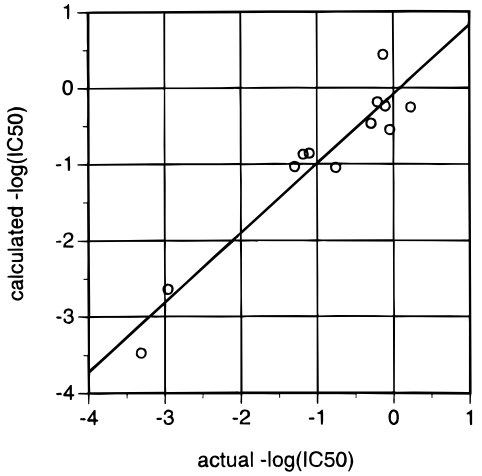


Figure 1. Calculated vs experimental $-\log(IC_{50})$ values for inhibition of [^{3}H]WIN 35,428 binding to the dopamine transporter for 12 2β-heterocyclic analogs.

for inhibition of radioligand binding at the DAT [expressed as $-\log(IC_{50})$] was obtained from a least-squares linear regression analysis. The resulting QSAR equation is:

$$-\log(IC_{50}) = 0.014V_{min}(A) - 3.47$$

$$r^2 = 0.91,\ n = 12,\ F = 101,\ s = 0.36$$

The actual and calculated $-\log(IC_{50})$ values (based on the QSAR equation shown above) are listed in Table 6 and plotted in Figure 1. As reported in a preliminary publication,[28] the sign of the coefficient for the MEP minimum is not consistent with the formation of a hydrogen bond at this site on the ligand. Increasingly negative V_{min} adjacent to nucleophilic atoms has been shown to correlate strongly with the ability to form increasingly strong hydrogen bonds.[29,30] This provides a convenient physicochemical rationale for several QSAR studies[13,28,31,32] that have observed that increasingly negative V_{min} in the vicinity of hydrogen bond acceptor atoms correlates with increases in receptor binding affinities. In contrast to these QSAR studies reported for ligands bearing similar heterocyclic substituents, increased binding affinity at the DAT correlates with decreasing negative potentials. This suggests a different type of electrostatic interaction mediating binding at the DAT for the 5-membered ring heterocyclic, ester, and carboxylic acid analogs modeled in this study. No comparable correlation between binding affinity and MEP minima at position B or C was found. Furthermore, neither the calculated log *P* (Clog*P*) nor the substituent volume (VOL) of the 2β-substituents contributes to satisfactory binding affinity correlations.

Considering that a combination of electrostatic, steric, and hydrophobic factors may be of importance for potent DAT affinity, the high correlation of binding potency with only the MEP at position A is noteworthy. Also noteworthy is the fact that this electrostatic correlation is observed for a diverse set of compounds spanning several structural types. Although considering other factors such as the conformational arrangement of the 2β-substituent may provide a useful refinement of the model, such factors were not necessary to obtain a good statistical correlation.

In the construction of a pharmacophore for the 2β-substituent, it was assumed that all of the 2β-heterocyclic analogs and their parent esters or carboxylic acids interact with the DAT in a similar fashion. Apparently, heteroatom A in the general model structures I−III is the essential pharmacophoric contact point for this entire series of compounds.

Since 2β-substituents not possessing a heteroatom (and therefore an associated negative MEP minimum) have been reported to possess high affinity for the DAT,[10] other structural parameters must be considered in order to formulate a pharmacophore that will encompass these analogs. Although no useful correlation with hydrophobic or steric effects was observed for the 2β-heterocyclic analogs studied here, it is possible that relatively weaker steric or hydrophobic effects that also contribute to binding may become evident for analogs with nonpolar 2β-substituents.

Reports from some laboratories have shown that there are differences between the cocaine binding site(s) on the DAT and the site(s) for DA uptake.[10] These results suggest that some compound(s) might inhibit radioligand binding without inhibiting the translocation of DA. The high correlation (r^2 = 0.89) between [^{3}H]WIN 35,428 binding and [^{3}H]DA uptake for selected compounds from this study suggests that these compounds do not show significant differences between binding and uptake.

In summary, a series of analogs of 3β-phenyl-2β-carbomethoxytropane (**2a**) with eight different types of heterocyclic rings in the 2-position of the tropane ring were prepared and evaluated for inhibition of radioligand binding at the DA, 5-HT, and NE transporters. Several of the compounds showed potent binding at the DAT combined with low affinities for the 5-HT and NE

transporters. 3β-(4′-Chlorophenyl)-2β-(3′-phenylisoxazol-5-yl)tropane (**5d**) with an IC_{50} value at the DAT of 1.28 nM combined with NE/DA and 5-HT/DA ratios of 393 and 889, respectively, emerged as a potent and selective compound for the DAT.

The binding data for 2β-heterocyclic tropanes were found to correlate significantly with the molecular electrostatic potential of one of the heteroatoms in the 2β-substituents. In contrast, low correlations were found for MEP of other atoms in the 2β-substituents as well as for Clog*P* or substituent volume. These QSAR studies are consistent with a predominantly electrostatic interaction of these analogs.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary tube apparatus. All optical rotations were determined at the sodium D line using a Rudolph Research Autopol III polarimeter (1 dm cell). NMR spectra were recorded on a Bruker WM-250 or AM-500 spectrometer using tetramethylsilane as internal standard. Flash chromatography was carried out using the solvent indicated. Visualization was accomplished under UV or in an iodine chamber. Since all the compounds described were prepared starting from natural cocaine, they are all optically active and have the absolute configuration of natural cocaine. Microanalyses were carried out by Atlantic Microlab, Inc. Cocaine was provided by the National Institute on Drug Abuse. [^{3}H]-3β-(*p*-Fluorophenyl)-tropane-2β-carboxylic acid methyl ester ([^{3}H]WIN 35,428) and [^{3}H]paroxetine were purchased from DuPont-New England Nuclear (Boston, MA). [^{3}H]Nisoxetine was purchased from American Radiolabeled Chemicals, Inc. (St. Louis, MO). When anhydrous conditions were required, solvents were distilled and dried by standard techniques immediately prior to use. All air and moisture sensitive reactions were conducted under a prepurified nitrogen atmosphere in flame-dried glassware previously dried at 150 °C. Anhydrous solvents were transferred using conventional syringe or steel cannula techniques under an inert atmosphere.

3β-(4′-Chlorophenyl)-2β-(3′-methylisoxazol-5′-yl)tropane (5a) Hydrochloride. A solution of *n*-butyllithium in hexane (5.9 mL, 2.5 M, 14.6 mmol) was added to a stirred solution of acetone oxime (0.55 g, 7.3 mmol) in dry tetrahydrofuran (15 mL) at 0 °C under nitrogen. After 1 h, a solution of 1.65 g (5.62 mmol) of 3β-(4′-chlorophenyl)-2β-carbomethoxytropane (**4a**) in 10 mL of dry THF was added dropwise with stirring at 0 °C. The solution was allowed to warm to room temperature over 18 h. The mixture was poured into a stirred solution of concentrated sulfuric acid (3.2 g) in THF (15 mL) and water (4 mL) and heated under reflux for 1 h. The cooled solution was made basic using saturated aqueous K_2CO_3 (10 mL) and extracted with methylene chloride (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo to give 1.8 g of crude **5a**. Purification by flash column chromatography [10% $CHCl_3$/CH_3OH/concentrated NH_4OH (40:9:1) in CH_2Cl_2] gave 0.74 g (46%) of pure isoxazole **5a** which was further purified by crystallization from methylene chloride/hexane: mp 154−156 °C; ^{1}H NMR (**(**$CDCl_3$) δ 1.71 (m, 3H), 2.10 (m, 3H), 2.18 (s, 3H), 2.24 (s, 3H), 3.20 (m, 2H), 3.32 (m, 2H), 6.18 (s, 1H), 6.9 (d, J = 8 Hz, 2H), 7.14 (d, J = 8 Hz, 2H); IR (CCl_4) 2950, 1590, 1490, 1420, 1350, 1020, 910 cm^{-1}. Anal. ($C_{18}H_{21}N_2OCl$) C, H, N.

The free base was converted to the hydrochloride salt: mp >235 °C dec; $[\alpha]_D$ −102.89° (*c* 0.46, MeOH); ^{1}H NMR (CD_3OD) δ 2.04 (s, 3H), 2.19 (m, 1H), 2.30 (m, 1H), 2.48 (m, 2H), 2.60 (m, 1H), 2.70 (m, 1H), 2.90 (s, 3H), 3.68 (m, 1H), 3.81 (m, 1H), 4.04 (m, 1H), 4.15 (m, 1H), 5.55 (s, 1H), 7.04 (d, J = 8 Hz, 2H), 7.14 (d, J = 8 Hz, 2H). Anal. ($C_{18}H_{22}Cl_2N_2O$) C, H, N.

3β-(4′-Methylphenyl)-2β-(3′-methylisoxazol-5′-yl)tropane (5b) Hydrochloride. A 1.09 g (4 mmol) sample of 3β-(4′-methylphenyl)-2β-carbomethoxytropane (**4b**) was converted to **5b** by a procedure analogous to that described for **5a**. Purification by flash column chromatography (15% CMA in methylene chloride) gave 0.73 g (62%) of pure isoxazole **5b**: ^{1}H NMR ($CDCl_3$) δ 1.73 (m, 3H), 2.11 (m, 3H), 2.17 (s, 3H), 2.23 (s, 3H), 2.25 (s, 3H), 3.20 (m, 2H), 3.32 (m, 2H), 6.13 (s, 1H), 6.97 (m, 4H); IR (CCl_4) 2935, 2785, 1590, 1510, 1460, 1421, 1350, 1125, 1010, 910 cm^{-1}.

The free base was converted to the hydrochloride salt: mp 277 °C; $[\alpha]_D$ −107.28° (*c* 0.71, MeOH); ^{1}H NMR (CD_3OD) δ 2.01 (s, 3H), 2.24 (s, 3H), 2.32 (m, 2H), 2.42 (m, 4H), 2.81 (s, 3H), 3.61 (m, 1H), 3.78 (m, 1H), 4.03 (m, 1H), 4.15 (m, 1H), 5.45 (s, 1H), 6.96 (m, 4H). Anal. ($C_{19}H_{25}ClN_2O$) C, H, N.

3β-(4′-Iodophenyl)-2β-(3′-methylisoxazol-5′-yl)tropane (4c) Hydrochloride. A 0.73 g (1.9 mmol) sample of 3β-(4′-iodophenyl)-2β-carbomethoxytropane (**4c**) was converted to **5c** by a procedure analogous to that described for **5a**. Purification by flash column chromatography [5% $CHCl_3$/CH_3OH/concentrated NH_4OH (40:9:1) in CH_2Cl_2] gave 0.37 g (49%) of pure isoxazole **5c**: ^{1}H NMR ($CDCl_3$) δ 1.71 (m, 3H), 2.12 (m, 3H), 2.18 (s, 3H), 2.24 (s, 3H), 3.17 (m, 2H), 3.33 (m, 2H), 6.18 (s, 1H), 6.74 (m, 2H), 7.49 (m, 2H); IR ($CHCl_3$) 2940, 1600, 1485, 1450, 1420, 1355 cm^{-1}.

The free base was converted to the hydrochloride salt: mp >235 °C dec; $[\alpha]_D$ −94.57° (*c* 0.39, MeOH); ^{1}H NMR (CD_3OD) δ 2.11 (s, 3H), 2.50 (m, 6H), 2.89 (s, 3H), 3.70 (m, 1H), 3.90 (m, 1H), 4.14 (m, 1H), 4.22 (m, 1H), 5.66 (s, 1H), 6.96 (m, 2H), 7.56 (m, 2H). Anal. ($C_{18}H_{22}ClIN_2O\cdot0.25H_2O$) C, H, N.

3β-(4′-Chlorophenyl)-2β-(3′-phenylisoxazol-5′-yl)tropane (5d) Hydrochloride. A 1.18 g (4 mmol) sample of 3β-(4′-chlorophenyl)-2β-carbomethoxytropane (**4a**) was converted to **5d** by a procedure analogous to that described for **5a** but using acetophenone oxime in place of acetone oxime. Purification by flash column chromatography [20% ether/triethylamine (9:1) in hexane] gave 0.75 g (50%) of pure isoxazole **5d** which was further purified by crystallization from ether/petroleum ether: ^{1}H NMR ($CDCl_3$) δ 1.74 (m, 3H), 2.22 (m, 3H), 2.27 (s, 3H), 3.24 (m, 2H), 3.36 (m, 2H), 6.80 (s, 1H), 6.94 (m, 2H), 7.12 (m, 2H), 7.40 (m, 3H), 7.76 (m, 2H); IR ($CHCl_3$) 2940, 1600, 1590, 1490, 1450, 1405, 1350 cm^{-1}.

The free base was converted to the hydrochloride salt: mp 287 °C; $[\alpha]_D$ −97.5° (*c* 0.28, MeOH); ^{1}H NMR (CD_3OD) δ 2.35 (m, 6H), 2.84 (s, 3H), 3.73 (m, 1H), 4.09 (m, 1H), 4.21 (m, 1H), 6.12 (s, 1H), 7.14 (m, 4H), 7.34 (m, 3H), 7.57 (m, 2H). Anal. ($C_{23}H_{24}Cl_2N_2O\cdot0.25H_2O$) C, H, N.

3β-(4′-Methylphenyl)-2β-(3′-phenylisoxazol-5′-yl)tropane (5e) Hydrochloride. A 1.09 g (4 mmol) sample of 3β-(4′-methylphenyl)-2β-carbomethoxytropane (**4b**) was converted to **5e** by a procedure analogous to that described for **5d**. Purification by flash column chromatography [25% ether/triethylamine (9:1) in hexane] gave 1.1 g (77%) of pure isoxazole **5e** which was further purified by crystallization from methylene chloride/hexane: ^{1}H NMR ($CDCl_3$) δ 1.76 (m, 3H), 2.23 (m, 3H), 2.24 (s, 3H), 2.27 (s, 3H), 3.23 (m, 2H), 3.36 (m, 2H), 6.74 (s, 1H), 6.93 (m, 4H), 7.41 (m, 3H), 7.76 (m, 2H); IR (CCl_4) 2935, 1590, 1455, 1410, 1215 cm^{-1}

The free base was converted to the hydrochloride salt: mp 270 °C dec; $[\alpha]_D$ −102.22° (*c* 0.68, MeOH); ^{1}H NMR (CD_3OD) δ 2.08 (m, 1H), 2.15 (s, 3H), 2.45 (m, 5H), 2.84 (s, 3H), 3.68 (m, 1H), 3.88 (m, 1H), 4.07 (m, 1H), 4.22 (m, 1H), 5.97 (s, 1H), 7.0 (m, 4H), 7.33 (m, 3H), 7.54 (m, 2H). Anal. ($C_{24}H_{27}ClN_2O$) C, H, N.

3β-(4′-Iodophenyl)-2β-(3′-phenylisoxazol-5′-yl)tropane (5f) Hydrochloride. A 0.73 g (1.9 mmol) sample of 3β-(4′-iodophenyl)-2β-carbomethoxytropane (**4c**) was converted to **5f** by a procedure analogous to that described for **5d**. Purification by flash column chromatography [20% ether/triethylamine (9:1) in hexane] gave 0.5 g (56%) of pure isoxazole **5f** which was further purified by crystallization from methylene chloride/hexane: ^{1}H NMR ($CDCl_3$) δ 1.72 (m, 3H), 2.15 (m, 2H), 2.28 (s, 3H), 3.22 (m, 2H), 3.35 (m, 2H), 6.74 (m, 2H), 6.79 (s, 1H), 7.44 (m, 5H), 7.75 (m, 2H); IR ($CHCl_3$) 2940, 1580, 1480, 1475, 1450, 1400, 1355, 1005 cm^{-1}.

The free base was converted to the hydrochloride salt: mp >267 °C dec; $[\alpha]_D$ −91.11° (*c* 0.43, MeOH); ^{1}H NMR (CD_3OD) δ 2.54 (m, 6H), 2.92 (s, 3H), 3.79 (m, 1H), 4.05 (m, 1H), 4.19

(m, 1H), 4.33 (m, 1H), 6.18 (s, 1H), 7.02 (m, 2H), 7.43 (m, 3H), 7.63 (m, 4H). Anal. ($C_{23}H_{24}ClIN_2O\cdot0.5H_2O$) C, H, N.

3β-(4′-Chlorophenyl)-2β-(5′-phenyl-1′,3′,4′-oxadiazol-2′-yl)tropane (7a) Hydrochloride. To a solution of 0.59 g (2 mmol) of 3β-(4′-chlorophenyl)tropane-2β-carboxylic acid (**6a**) in 2 mL of $POCl_3$ was added 0.31 g (2.2 mmol) of *N*-benzoyl hydrazide. The reaction mixture was refluxed under a nitrogen atmosphere for 2 h, cooled, poured into ice, and rendered basic to pH 7−8 using concentrated NH_4OH. To the ice-cold aqueous layer was added 10 mL of brine, and the mixture was extracted with methylene chloride (3 × 10 mL). The organic layers were combined, dried ($NaSO_4$), and filtered, and the solvent was removed in vacuo to give 0.9 g of residue. Purification by flash column chromatography [50% ether/triethylamine (9:1) in hexane] gave 0.33 g (42%) of **7a** which was recrystallized from ether/petroleum ether: $[\alpha]_D$ −106.25° (*c* 0.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.81 (m, 3H), 2.18 (s, 3H), 2.26 (m, 2H), 2.66 (m, 1H), 3.33 (m, 2H), 3.51 (m, 2H), 7.16 (m, 4) 7.45 (m, 3H), 7.86 (m, 2H); IR ($CHCl_3$) 2950, 1550, 1490, 1450, 1340, 1090 cm^{-1}.

The free base was converted to the hydrochloride salt: mp 160−162 °C; $[\alpha]_D$ +84.59° (*c* 0.36, CH_3OH); ^{1}H NMR (CD_3OD) δ 2.08 (m, 1H), 2.57 (m, 5H), 3.0 (s, 3H), 4.01 (m, 2H), 4.15 (m, 1H), 4.39 (m, 1H), 7.24 (m, 4H), 7.52 (m, 5H). Anal. ($C_{22}H_{23}Cl_2N_3O\cdot0.75H_2O$) C, H, N.

Further elution gave as a second fraction 0.1 g (13%) of white solid which was characterized as 3β-(4′-chlorophenyl)-2α-(5′-phenyl-1′,3′,4′-oxadiazol-2′-yl)tropane (**8a**): mp 168−170 °C; $[\alpha]_D$ +33.06° (*c* 0.18, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.76 (m, 3H), 2.06 (s, 3H), 2.45 (s, 3H), 3.36 (m, 2H), 3.51 (m, 1H), 3.65 (m, 1H), 7.21 (m, 4H), 7.47 (m, 3H), 7.91 (m, 2H). Anal. ($C_{22}H_{22}ClN_3O$) C, H, N.

3β-(4′-Methylphenyl)-2β-(5′-phenyl-1′,3′,4′-oxadiazol-2′-yl)tropane (7b) Hydrochloride. A 0.65 g (2.5 mmol) sample of 3β-(4′-methylphenyl)tropane-2β-carboxylic acid (**6b**) was converted to **7b** by a procedure analogous to that described for **7a**. Purification by flash column chromatography [50% ether/triethylamine (9:1) in hexane] gave 0.36 g (40%) of **7b**: $[\alpha]_D$ −163.92° (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 1.83 δ (m, 3H), 2.18 (s, 3H), 2.21 (s, 3H), 2.3 (m, 2H), 2.67 (m, 1H), 3.33 (m, 1H), 3.41 (m, 1H), 3.53 (m, 1H), 3.61 (m, 1H), 7.0 (m, 2H), 7.13 (m, 2H), 7.44 (m, 3H), 7.86 (m, 2H); IR ($CHCl_3$) 2990, 1545, 1505, 1440, 1350 cm^{-1}.

The free base was converted to the hydrochloride salt: mp 175−178 °C; $[\alpha]_D$ +97.22° (*c* 0.25, CH_3OH); ^{1}H NMR (CD_3OD) δ 2.05 (m, 1H), 2.21 (s, 3H), 2.51 (m, 5H), 2.99 (s, 3H), 3.86 (m, 1H), 3.95 (m, 1H), 4.14 (m, 1H), 4.35 (m, 1H), 7.02 (m, 4) 7.53 (m, 5H). Anal. ($C_{23}H_{26}ClN_3O\cdot0.75H_2O$) C, H, N.

Further elution gave as a second fraction 0.18 g (20%) of solid which was characterized as 3β-(4′-methylphenyl)-2α-(5′-phenyl-1′,3′,4′-oxadiazol-2-yl)tropane (**8b**) and recrystallized from ether/petroleum ether: mp 126−128 °C; $[\alpha]_D$ +40.73° (*c* 0.28, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.77 (m, 2H), 2.0 (m, 4H), 2.25 (s, 3H), 2.47 (s, 3H), 3.33 (m, 2H), 3.51 (m, 1H), 3.69 (d of d, J = 2.6, 12 Hz, 1H), 6.91 (m, 2) 7.03 (m, 2H), 7.45 (m, 2H), 7.45 (m, 3H), 7.89 (m, 2H); IR ($CHCl_3$) 3020, 1540, 1510, 1415, 1250, 1215 cm^{-1}. Anal. ($C_{23}H_{25}N_3O$) C, H, N.

3β-(4′-Methylphenyl)-2β-(5′-methyl-1′,3′,4′-oxadiazol-2′-yl)tropane (7c) Hydrochloride. A 0.65 g (2.5 mmol) sample of **6b** was converted to **6c** by a procedure analogous to that described for **6a** but using 0.21 g (2.75 mmol) of *N*-acetyl hydrazide in place of the *N*-benzyl hydrochloride. Purification by flash column chromatography [75% ether/triethylamine (9:1) in hexane] gave 0.29 g (39%) of **7c**: $[\alpha]_D$ −108.47° (*c* 0.14, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.75 (m, 3H), 2.18 (s, 3H), 2.22 (s, 3H), 2.25 (m, 2H), 2.35 (s, 3H), 2.56 (m, 1H), 3.24 (m, 1H), 3.4 (m, 2H), 3.47 (m, 1H), 7.0 (m, 4H); ^{13}C NMR ($CDCl_3$) 11.06, 20.9, 25.08, 26.32, 34.11, 34.6, 41.83, 45.73, 61.97, 66.21, 127.11, 128.85, 135.85, 138.19, 162.5, 167.44; IR ($CHCl_3$) 2950, 1590, 1510, 1450, 1350, 1215 cm^{-1}.

The free base was converted to the hydrochloride salt: mp 146 °C dec; $[\alpha]_D$ −43.05° (*c* 0.15, CH_3OH); ^{1}H NMR (CD_3OD) δ 1.99 (m, 1H), 2.23 (s, 3H), 2.27 (s, 3H), 2.47 (m, 5H), 2.94 (s, 3H), 3.72 (m, 1H), 3.79 (m, 1H), 4.10 (m, 1H), 4.23 (m, 1H), 7.05 (m, 4H). Anal. ($C_{18}H_{24}ClN_3O\cdot0.5H_2O$) C, H, N.

3β-(4′-Chlorophenyl)-2β-(5′-phenyl-1′,3′,4′-thiadiazol-2′-yl)tropane (11a) Hydrochloride. To a solution of the acid chloride of **6a** [prepared from 0.59 g (2 mmol) of 3β-(4′-chlorophenyl)tropane-2β-carboxylic acid as previously described][8] in CH_2Cl_2 was added benzoyl hydrazide. The mixture was stirred at room temperature overnight and basified with concentrated NH_4OH, the organic layer separated, and the aqueous layer extracted with of $CHCl_3$ (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo to give crude product. Purification by recrystallization from ethyl acetate/ether gave 0.52 g (66%) of pure 3β-(4′-chlorophenyl)-2β-carboxytropane-*N*′-benzoylhydrazide (**9a**): ^{1}H NMR ($CDCl_3$) δ 1.76 (m, 3H), 2.24 (m, 2H), 2.41 (s, 3H), 2.51 (m, 1H), 2.68 (m, 1H), 3.18 (m, 1H), 3.44 (m, 2H), 7.22 (m, 4H), 7.46 (m, 3H), 7.78 (m, 2H), 9.02 (br s, 1H), 12.97 (br s, 1H); IR ($CHCl_3$) 3385, 3035, 3000, 1620, 1570, 1485, 1450, 1215 cm^{-1}.

A solution of 0.4 g (1 mmol) of **9a** and 0.8 g (2 mmol) of Lawesson's reagent in 10 mL of toluene was refluxed for 4 h under nitrogen. The reaction mixture was cooled and solvent removed in vacuo to give a yellow residue. To the residue was added 3 g of silica gel and 10 mL of methylene chloride, the resulting slurry was mixed, and the solvent was removed in vacuo. The crude compound impregnated on silica gel was loaded on a column and purified by flash column chromatography [50% ether/triethylamine (9:1) in hexane] to give 0.23 g (58%) of **11a** which was further purified by recrystallization from ether: ^{1}H NMR ($CDCl_3$) δ 1.75 (m, 3H), 2.20 (m, 3H), 2.32 (s, 3H), 3.30 (m, 3H), 3.78 (m, 1H), 6.86 (m, 2H), 7.08 (m, 2H), 7.43 (m, 3H), 7.97 (m, 2H); ^{13}C NMR 25.55, 25.88, 34.60, 36.09, 41.55, 49.73, 61.48, 65.33, 127.59, 128.28, 128.78, 128.88, 130.37, 130.88, 132.19, 139.27, 168.29, 169.56; IR (CCl_4) 2940, 1490, 1460, 1340, 1245, 1100, 1010 cm^{-1}

The free base was converted to the hydrochloride salt: mp 165−170 °C; $[\alpha]_D$ −42.81° (*c* 0.16, MeOH); ^{1}H NMR (CD_3OD) δ 2.06 (m, 1H), 2.53 (m, 5H), 2.97 (s, 3H), 3.92 (m, 1H), 4.17 (m, 2H), 4.39 (m, 1H), 7.11 (m, 2H), 7.26 (m, 2H), 7.51 (m, 3H), 7.79 (m, 2H). Anal. ($C_{22}H_{23}Cl_2N_3S\cdot0.75H_2O$) C, H, N.

3β-(4′-Methylphenyl)-2β-(5′-phenyl-1′,3′,4′-thiadiazol-2′-yl)tropane (11b) Hydrochloride. A 0.65 g (2.5 mmol) sample of 3β-(4′-methylphenyl)tropane-2β-carboxylic acid (**6b**) was converted to **11b** as described for **11a**. Purification by flash column chromatography [50% $CHCl_3$/CH_3OH/concentrated NH_4OH (40:9:1) in CH_2Cl_2] gave 0.48 g (51%) of pure 3β-(4′-methylphenyl)-2β-carboxytropane-*N*′-benzoylhydrazide (**9b**) which was further purified by recrystallization from ether/petroleum ether: ^{1}H NMR ($CDCl_3$) δ 1.75 (m, 3H), 2.20 (m, 2H), 2.27 (s, 3H), 2.42 (s, 3H), 2.51 (m, 1H), 2.67 (m, 1H), 3.18 (m, 1H), 3.47 (m, 2H), 7.11 (m, 4H), 7.48 (m, 3H), 7.81 (m, 2H), 9.06 (br s, 1H), 13.09 (br s, 1H); IR ($CHCl_3$) 3385, 3045, 1625, 1570, 1460, 1420, 1100 cm^{-1}.

Reaction of 0.29 g (0.75 mmol) of 3β-(4′-methylphenyl)-2β-carboxytropane-*N*′-benzoylhydrazide (**9b**) as described for **9a** gave after workup and purification by flash chromatography [40% ether/triethylamine (9:1) in hexane] 0.16 g (58%) of pure **11b**: ^{1}H NMR ($CDCl_3$) δ 1.70 (m, 1H), 1.88 (m, 2H), 2.20 (s, 3H), 2.23 (m, 2H), 2.21 (s, 3H), 2.38 (m, 1H), 3.21 (m, 1H), 3.32 (m, 1H), 3.39 (m, 1H), 3.78 (m, 1H), 6.81 (m, 2H), 6.92 (m, 2H), 7.43 (m, 3H), 7.97 (m, 2H); ^{13}C NMR 20.98, 25.65, 25.95, 34.79, 36.25, 41.65, 50.05, 61.68, 65.49, 127.32, 127.65, 128.89, 128.95, 130.29, 131.11, 135.94, 137.68, 168.83, 169.45; IR (CCl_4) 2935, 1510, 1450, 1250, 1120, 1100, 1060 cm^{-1}.

The free base was converted to the hydrochloride salt: mp 180−185 °C; $[\alpha]_D$ −33.5° (*c* 0.2, MeOH); ^{1}H NMR (CD_3OD) δ 1.95 (m, 1H), 2.17 (s, 3H), 2.41 (m, 5H), 2.89 (s, 3H), 3.76 (m, 1H), 4.05 (m, 2H), 4.30 (m, 1H), 4.22 (m, 1H), 6.89 (m, 2H), 6.99 (m, 2H), 7.39 (m, 3H), 7.67 (m, 2H). Anal. ($C_{23}H_{26}ClN_3S\cdot H_2O$) C, H, N.

3β-(4′-Chlorophenyl)-2β-(5′-phenylthiazol-2′-yl)tropane (12) Hydrochloride. A 0.73 g (0.0025 mol) sample of **6a** was converted to 3β-(4′-chlorophenyl)tropane-2β-*N*-phenacylcarboxamide (**10a**) by a procedure analogous to that described for the synthesis of **9a** except 2-aminoacetophenone was used in place of benzoyl hydrazide. Purification by flash column chromatography [15% $CHCl_3$/CH_3OH/concentrated NH_4OH (40:9:1) in CH_2Cl_2] gave 0.8 g (81%) of **10a**: ^{1}H NMR

($CDCl_3$) δ 1.71 (m, 3H), 2.19 (m, 2H), 2.39 (s, 3H), 2.46 (m, 1H), 2.58 (m, 1H), 3.13 (m, 1H), 3.43 (m, 2H), 4.74 (m, 2H), 7.13 (m, 4H), 7.49 (m, 2H), 7.59 (m, 1H), 7.96 (m, 2H), 10.57 (br s, 1H); IR ($CHCl_3$) 3135, 3010, 2930, 1695, 1650, 1590, 1530, 1485, 1450, 1355, 1220 cm^{-1}.

A solution of 0.74 g (0.001 86 mol) of **10a** and 1.51 g (0.007 45 mol) of Lawesson's reagent in 18 mL of toluene was refluxed under N_2 for 5 h. The reaction mixture was cooled and solvent removed in vacuo to give crude residue. To the residue were added 3 g of silica gel and 10 mL of methylene chloride, the resulting slurry was mixed properly, and the solvent was removed in vacuo. The crude compound impregnated on silica gel was loaded on a column and purified by flash column chromatography [40% ether/triethylamine (9:1) in hexane] to give 0.21 g (30%) of **12**: ^1H NMR ($CDCl_3$) δ 1.61 (m, 1H), 1.82 (m, 2H), 2.22 (m, 2H), 2.34 (s, 3H), 2.39 (m, 1H), 3.28 (m, 2H), 3.39 (m, 1H), 3.49 (m, 1H), 6.8 (m, 2H), 7.07 (m, 2H), 7.32 (m, 3H), 7.57 (m, 2H), 7.60 (s, 1H); ^{13}C NMR (CD_3OD) 25.51, 25.99, 35.01, 36.92, 41.72, 52.97, 61.58, 65.70, 126.45, 127.60, 128.13, 128.89, 129.05, 131.91, 132.43, 136.11, 139.91, 140.27, 168.97; IR ($CHCl_3$) 2945, 1590, 1485, 1445, 1350, 1125, 1090 cm^{-1}.

The free base was converted into the hydrochloride salt: mp 228−230 °C; $[\alpha]_D$ +27.43° (*c* 0.11, CH_3OH); ^1H NMR (CD_3OD) δ 1.99 (m, 1H), 2.51 (m, 5H), 2.93 (s, 3H), 3.79 (m, 2H), 4.15 (m, 1H), 4.28 (m, 1H), 7.02 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 8.5 Hz, 2H), 7.39 (m, 5H), 8.06 (s, 1H). Anal. ($C_{23}H_{24}ClN_2S \cdot H_2O$) C, H, N.

3β-(4′-Chlorophenyl)-2β-(5′-phenyloxazol-2′-yl)tropane (13a) Tartrate. A solution of 0.725 g (0.001 83 mol) of **10a** (prepared as described for the synthesis of **12**) in 6 mL of $POCl_3$ was heated at 125 °C under nitrogen for 2 h. The reaction mixture was cooled, poured into ice, and rendered basic to pH 7−8 using concentrated NH_4OH. To the ice-cold aqueous layer was added 10 mL of brine, and the mixture was extracted with methylene chloride (3 × 10 mL). The organic layers were combined, dried ($NaSO_4$), and filtered, and the solvent was removed in vacuo to give 0.63 g of **13a**. Purification by flash column chromatography [40% ether/triethylamine (9:1) in hexane] gave 0.34 g (49%) of **13a** which was further purified by recrystallization from ether/petroleum ether: $[\alpha]_D$ −70.37° (*c* 0.19, $CHCl_3$); ^1H NMR ($CDCl_3$) 1.79 (m, 3H), 2.22 (s, 3H), 2.27 (m, 2H), 2.66 (m, 1H), 3.27 (m, 1H), 3.40 (m, 2H), 3.53 (m, 1H), 7.11 (s, 1H), 7.16 (s, 4H), 7.31 (m, 5H); IR ($CHCl_3$) 2950, 1540, 1490, 1445, 1350, 1120, 1090 cm^{-1}.

The free base was converted to the tartrate salt: mp 126 °C dec; $[\alpha]_D$ +101.43° (*c* 0.21, CH_3OH); ^1H NMR (CD_3OD) 2.14 (m, 1H), 2.54 (m, 5H), 2.96 (s, 3H), 3.75 (m, 2H), 4.12 (m, 1H), 4.25 (m, 1H), 4.41 (s, 2H), 7.05 (m, 2H), 7.29 (m, 7H), 7.45 (s, 1H), 7.43 (s, 1H). Anal. ($C_{27}H_{29}ClN_2O_7 \cdot 0.75H_2O$) C, H, N.

3β-(4′-Methylphenyl)-2β-(5′-phenyloxazol-2′-yl)tropane (13b) Tartrate. A 0.52 g (0.02 mol) sample of 3β-(4′-methylphenyl)tropane-2β-carboxylic acid (**6b**) was converted to 0.54 g (72%) of pure 3β-(4′-methylphenyl)tropane-2β-*N*-phenacylcarboxamide (**10b**) by a procedure analogous to that described for **10a**: ^1H NMR ($CDCl_3$) δ 1.73 (m, 3H), 2.14 (m, 2H), 2.26 (s, 3H), 2.40 (s, 3H), 2.47 (m, 1H), 2.59 (m, 1H), 3.14 (m, 1H), 3.42 (m, 2H), 4.74 (m, 2H), 7.05 (m, 4H), 7.48 (m, 2H), 7.59 (m, 2H), 7.97 (m, 2H), 10.62 (br s, 1H); IR ($CHCl_3$) 3155, 3005, 2930, 1690, 1650, 1520, 1450, 1355, 1215 cm^{-1}.

Cyclization of 0.5 g (1.33 mmol) of **10b** as described above for the synthesis of **13a** after workup and purification by flash column chromatography [40% ether/triethylamine (9:1)] gave 0.19 g (42%) of **13b**: ^1H NMR ($CDCl_3$) 1.8 (m, 3H), 2.18 (m, 2H), 2.21 (s, 3H), 2.22 (s, 3H), 2.67 (m, 1H), 3.28 (m, 1H), 3.42 (m, 2H), 3.53 (m, 1H), 6.98 (m, 2H), 7.11 (m, 3H), 7.30 (m, 5H).

The free base was converted to the tartrate salt: mp 175−181 °C; $[\alpha]_D$ −104.04° (*c* 0.6, CH_3OH); ^1H NMR (CD_3OD) 1.99 (m, 1H), 2.19 (s, 3H), 2.54 (m, 5H), 2.95 (s, 3H), 3.74 (m, 2H), 4.13 (m, 1H), 4.26 (m, 1H), 4.4 (s, 2H), 6.91 (m, 2H), 7.0 (m, 2H), 7.25 (m, 2H), 7.33 (m, 3H), 7.43 (s, 1H). Anal. ($C_{28}H_{32}N_2O_7 \cdot 1H_2O$) C, H, N.

3β-(4′-Chlorophenyl)-2β-(benzothiazol-2′-yl)tropane (14) Hydrochloride. To a solution of **6a** acid chloride [prepared from 0.59 g (2 mmol) of 3β-(4′-chlorophenyl)tropane-2β-carboxylic acid (**6a**) as previously described][8] in 10 mL of CH_2Cl_2 under a nitrogen atmosphere was added 0.45 mL (0.0042 mol) of 2-aminothiophenol. After 16 h, the reaction mixture was concentrated. The residue was basified (3 N NaOH) and then extracted with CH_2Cl_2. Concentrates of the dried (Na_2SO_4) extract gave 0.94 g. Purification of the product by flash column chromatography [50% $CHCl_3$/CH_3OH/concentrated NH_4OH (40:9:1) in CH_2Cl_2] gave 0.3 g (41%) of **14** which was further purified by recrystallization from ether/hexane: $[\alpha]_D$ −233.89° (*c* 0.09, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.65 (m, 1H), 1.87 (m, 2H), 2.24 (m, 2H), 2.34 (s, 3H), 2.41 (m, 1H), 3.28 (m, 2H), 3.40 (m, 1H), 3.62 (m, 1H), 6.8 (m, 2H), 6.81 (m, 2H), 7.29 (m, 2H), 7.70 (m, 1H), 7.84 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.58, 26.07, 35.40, 36.95, 41.56, 53.09, 61.57, 65.47, 120.95, 122.42, 124.11, 125.20, 128.05, 129.03, 131.87, 136.72, 139.91, 151.33, 171.11; IR ($CHCl_3$) 2940, 2795, 1495, 1445, 1305, 1130, 1105, 1015, 907 cm^{-1}.

The free base was converted to the hydrochloride salt: mp 140−150 °C dec; $[\alpha]_D$ −172.49° (*c* 0.28, MeOH); ^1H NMR (CD_3OD) δ 2.02 (m, 1H), 2.43 (m, 4H), 2.89 (m, 1H), 2.98 (s, 3H), 3.90 (m, 2H), 4.23 (m, 1H), 4.34 (m, 1H), 7.02 (m, 2H), 7.13 (m, 2H), 7.45 (m, 2H), 7.81 (m, 1H), 8.16 (m, 1H). Anal. ($C_{21}H_{22}Cl_2N_2S \cdot 0.75H_2O$) C, H, N.

In a separate run, 0.59 g (0.002 mol) of **6a** and 1.1 equiv of 2-aminothiophenol in 5 mL of $POCl_3$ were refluxed under N_2 for 30 min. The reaction mixture was cooled, poured into ice, and basified to pH 7−8 using concentrated NH_4OH. To the aqueous layer was added 10 mL of brine, and the mixture was extracted with methylene chloride (3 × 10 mL). The combined organic layers were dried ($NaSO_4$), and filtered, and the solvent was removed in vacuo to give 0.77 g of residue. Purification of this residue by flash column chromatography [50% ether/triethylamine 9:1)] in hexane gave as a first fraction 0.08 g (11%) of **14**. Further elution gave 0.42 g (57%) of 3β-(4′-chlorophenyl)-2α-(benzothiazol-2′-yl)tropane (**15**): mp 127−129 °C; $[\alpha]_D$ +114.65° (*c* 0.19, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.86 (m, 4H), 2.17 (m, 2H), 2.46 (s, 3H), 3.32 (m, 1H), 3.45 (m, 1H), 3.56 (m, 1H), 3.88 (m, 1H), 7.14 (m, 2H), 7.26 (m, 3H), 7.39 (m, 1H), 7.73 (m, 1H), 7.94 (m, 1H). Anal. ($C_{21}H_{21}ClN_2S$) C, H, N.

3β-(4′-Chlorophenyl)tropane-2β-nitrile (17a). To a solution of 0.95 g (0.0035 mol) of 3β-(4′-chlorophenyl)tropane-2β-carboxamide (**16a**)[8] in 20 mL of dry tetrahydrofuran was added 0.56 mL (7 mmol) of pyridine. To the resulting solution at room temperature was added dropwise with stirring under nitrogen 0.35 mL (4.2 mmol) of trifluoroacetic anhydride. The reaction mixture was stirred at room temperature for 30 min and the reaction quenched with 10 mL of water. The solvent was removed in vacuo, and the residue was dissolved in 10 mL of saturated aqueous K_2CO_3 and extracted with $CHCl_3$ (3 × 10 mL). The organic layers were combined and washed with 20 mL of brine, dried ($NaSO_4$), and filtered, and the solvent was removed in vacuo to give 0.26 g of product. Purification by flash column chromatography (10% CMA in methylene chloride) gave 0.68 g (77%) of **17a** which was recrystallized from methylene chloride and hexane: mp 167−173 °C; $[\alpha]_D$ −73.33° (*c* 0.48, MeOH); ^1H NMR ($CDCl_3$) δ 1.70 (m, 3H), 2.22 (m, 3H), 2.35 (s, 3H), 2.80 (m, 1H), 3.04 (m, 1H), 3.34 (m, 1H), 3.43 (m, 1H), 7.26 (m, 4H); IR ($CHCl_3$) 3700, 2950, 2225, 1490, 1470, 1090, 900 cm^{-1}. Anal. ($C_{15}H_{18}Cl_2N_2 \cdot 0.75H_2O$) C, H, N.

3β-(4′-Methylphenyl)tropane-2β-nitrile (17b) Hydrochloride. Reaction of 0.26 g (0.001 mol) of 3β-(4′-methylphenyl)tropane-2β-carboxamide as described for **17a** gave after workup and purification 0.16 g (67%) of **17b**: ^1H NMR ($CDCl_3$) δ 1.68 (m, 3H), 2.18 (m, 3H), 2.32 (s, 3H), 2.35 (s, 1H), 2.82 (m, 1H), 3.02 (m, 1H), 3.36 (m, 1H), 3.43 (m, 1H), 7.18 (m, 4H); IR ($CHCl_3$) 3675, 3000, 2950, 2200, 1600, 1510, 1450, 1350, 1220, 1100 cm^{-1}.

The product was converted to the HCl salt: mp 270 °C (dec.); $[\alpha]_D$ −76.4° (*c* 0.5, MeOH); ^1H NMR (CD_3OD) δ 2.08−2.58 (m, 9H), 2.92 (s, 3H), 3.54 (m, 1H), 3.69 (br s, 1H), 4.12 (br s, 1H), 4.29 (m, 1H), 7.21 (m, 4H). Anal. ($C_{16}H_{21}ClN_2$) C, H, N.

3β-(4′-Chlorophenyl)-2β-tetrazolyltropane (18a). To a solution of 130 mg (0.5 mmol) of **17a** in 5 mL of dry

tetrahydrofuran was added 0.28 mL (5 mmol) of azidotrimethylsilane, and the mixture was placed in a PTFE-lined autoclave. The solution was heated to 150 °C for 24 h in an oil bath, cooled, and transferred to a flask using MeOH, and the solvent was removed in vacuo to give a brownish residue. Purification by flash column chromatography (20−50% CMA in methylene chloride) gave 0.05 g (33%) of **18a**: mp 296−300 °C; $[\alpha]_D$ −124.94° (*c* 0.39, MeOH); ^{1}H NMR ($CDCl_3$ + 1 drop of CD_3OD) δ 1.73 (m, 1H), 2.44−2.02 (m, 4H), 2.6 (m, 1H), 2.68 (s, 3H), 3.33 (m, 1H), 3.65 (m, 1H), 3.73 (m, 1H), 3.97 (m, 1H), 6.68 (d, J = 8 Hz, 2H), 7.07 (d, J = 8 Hz, 2H). Anal. ($C_{15}H_{18}ClN_5 \cdot 0.75H_2O$) C, H, N.

3β-(4′-Methylphenyl)-2β-tetrazolyltropane (18b) Hydrochloride. Reaction of 0.12 g (0.5 mmol) of **17b** as described above for **17a** gave after workup and purification by flash column chromatography [$CHCl_3/CH_3OH$/concentrated NH_4OH (40:9:1)] 0.14 g (88%) of **18b**: ^{1}H NMR ($CDCl_3$ + 1 drop of CD_3OD) δ 1.8 (m, 1H), 2.14 (s, 3H), 2.35 (m, 5H), 2.71 (s, 3H), 3.36 (m, 1H), 3.75 (m, 2H), 4.02 (m, 1H), 6.48 (d, J = 8 Hz, 2H), 6.82 (d, J = 8 Hz, 2H).

The free base was converted to the HCl salt: mp 212 °C dec; $[\alpha]_D$ −110.97° (*c* 0.16, MeOH); ^{1}H NMR (CD_3OD) δ 2.01 (m, 1H), 2.27 (s, 3H), 2.69 (m, 5H), 2.97 (s, 3H), 3.81 (m, 2H), 4.18 (m, 2H), 5.5 (s, 1H), 6.76 (d, J = 8 Hz, 2H), 7.02 (d, J = 8 Hz, 2H). Anal. ($C_{16}H_{21}ClN_5 \cdot 0.75H_2O$) C, H, N.

Binding Assays. Inhibition of 0.5 nM [^{3}H]WIN 35,428, 0.5 nM [^{3}H]nisoxetine, and 0.2 nM [^{3}H]paroxetine binding was carried out as described previously.[7]

[^{3}H]Neurotransmitter Uptake Assay. [^{3}H]Dopamine uptake into rat striatal synaptosomes was carried out as preiously described.[8]

Molecular Modeling. Structures for the model compounds were built on a Silicon Graphics 4D/310 VGX workstation using standard bond lengths and angles in the SYBYL (version 6.03) software package.[33] Geometry optimization was carried out using the semiempirical AM1 method in the MOPAC (version 6.0) software package.

Model structures of the 2β-substituents of compounds **5a**,**d**, **6a**, **7a**, **11a**, **12**, **13a**, **14a**, **18a**, **2b**, **3a**, and **4a** were constructed with methyl groups replacing the constant 2β-(4′-chlorophenyl)tropane moiety using the SYBYL modeling package running on Silicon Graphics 4D/310 VGX and Indigo^2 workstations. Geometry optimizations were first performed using the SYBYL MAXIMIN force field followed by further geometry optimization with Spartan semiempirical quantum mechanics calculations based on the AM1 Hamiltonian. MEPs were then obtained by Spartan electrostatic potential calculations ("elpot" at medium resolution). Relative V_{min} values adjacent to heteroatoms A−C were then calculated by substracting the most negative value in each case from the remaining V_{min}. Substituent volumes were calculated using the SYBYL VOLUME command. Calculated log *P* values were obtained by generating SMILES strings using ChemDraw Pro for input into the Macintosh version of Clog*P*. Statistical analysis was performed using the JMP[34] statistics package.

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