Novel Conformationally Constrained Tropane Analogues by 6-*endo-trig* Radical Cyclization and Stille Coupling − Switch of Activity toward the Serotonin and/or Norepinephrine Transporter

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Received March 8, 2000

A novel class of tricyclic tropane analogues has been synthesized by making use of radical cyclization technology in combination with the Stille coupling reaction. As hybrids between tropanes and quinuclidines, these tropaquinuclidines represent a significant structural departure from many of the other classes of tropane ligands synthesized to date. This structure class is characterized by the boat conformation of the tropane ring and the orientation of the additional bridge (and therefore of the nitrogen lone pair) together with the unusual placement of the aromatic moiety. All compounds were tested for their ability to inhibit monoamine reuptake under identical conditions. The ability to inhibit reuptake of dopamine in comparison to cocaine is generally decreased in this series but for one compound. (1*S*,3*R*,6*S*)-(*Z*)-9-(thienylmethylene)-7-azatricyclo[4.3.1.0^{3,7}]decane-2β-carboxylic acid methyl ester **(5h)** exhibits reasonable activity at the dopamine transporter (DAT) (K_i = 268 nM) and good activity at the norepinephrine transporter (NET) (K_i = 26 nM). The potency and selectivity shown by some of these ligands for the NET, serotonine transporter (SERT), or NET/SERT is striking, particularly in view of the displacement of the aromatic ring in this series from its usual position at C-3 in the WIN analogues. Thus, (1*S*,3*R*,6*S*)-(*Z*)-9-(4-biphenylylmethylene)-7-azatricyclo[4.3.1.0^{3,7}]-decane-2β-carboxylic acid methyl ester **(5a)** is a selective inhibitor of norepinephrine reuptake (K_i = 12 nM). Its *p*-methoxy analogue **5c** is a mixed inhibitor of norepinephrine and serotonin reuptake (K_i = 187 nM at the NET and 56 nM at the SERT). The most active and selective compound we found in the present series is compound **8b** [(1*S*,3*R*,6*S*)-2-(acetoxymethyl)-(*Z*)-9-(3,4-dichlorophenylmethylene)-7-azatricyclo[4.3.1.0^{3,7}]decane]. This compound is a potent (K_i = 1.6 nM) and selective inhibitor of serotonin reuptake into rat midbrain synaptosomes. Its selectivity is about 400-fold over the NET and about 1000-fold over the DAT. The results of this study further demonstrate the possibility of tuning the selectivity of tropane analogues toward the SERT or NET binding site. The ligands disclosed herein provide additional pharmacological tools of use in attempting to correlate structure and transporter selectivity with in vivo studies of behavioral outcomes.

Introduction

Cocaine abuse remains a serious health and social problem in the United States and worldwide, with an estimated 1.5 million cocaine users in the United States alone.[1] As a consequence, it is obvious that immediate strategies are needed for the treatment of cocaine addiction to combat the destructive effects of this reinforcing drug on individuals and on society at large.

According to the dopamine theory of addiction, cocaine is believed to elicit its behavioral and pharmacological effects primarily by binding to the dopamine transporter (DAT) in the nucleus accumbens and striatum, thereby inhibiting the removal of dopamine from the synaptic cleft. In addition to the DAT, cocaine also binds with high affinity to the serotonin (SERT) and the norepinephrine transporters (NET).[2] More recent work suggests that both the SERT and the NET may also play prominent roles in cocaine addiction.[3−5] Thus, the selective transport inhibitors desipramine and fluoxetine have been shown to shift cocaine's dose−response curve to the left, demonstrating that low doses of cocaine that do not elicit cocaine-lever-appropriate responding acquire full cocaine-like properties when combined with selective inhibitors of the NET and the SERT, which when administered alone produce only partial cocaine-like responding.[6,7] Furthermore, experiments with DAT knockout mice suggest that a certain amount of redundancy in the cocaine reward circuit may exist.[8] To date, antidepressant agents such as fluoxetine or desipramine that interact selectively with biogenic amine transporters have met with limited success in clinical trials.[9,10] It may be that these agents do not possess the right profile of inhibitory activity at these transporters, or it could mean that this approach is simply without merit. Currently, there are too little data to confirm either of these hypotheses. To further study the role of the different transport systems in cocaine reward and craving, ligands exhibiting varying selectivities for one

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10.1021/jm0001121 CCC: $19.00
Published on Web 05/03/2000

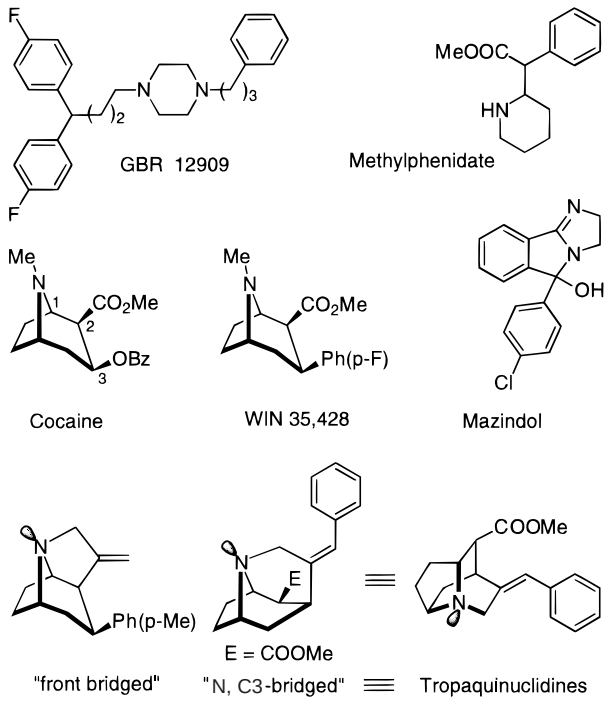


Figure 1.

or more of the monoamine transporters will be valuable. In fact, it is reasonable to suggest that drugs lacking the ability to inhibit transport at all three monoaminergic transporters would exhibit only partial cocaine-like properties, and thus possibly serve as medications. The present study was designed to provide additional tools to investigate this largely untested hypothesis.

To date numerous tropane and non-tropane derivatives have been prepared (Figure 1), both with the aim to better understand structure−activity relationships at the DAT and with the notion that the identification of ligands of improved potency and DAT selectivity may lead to "cocaine medications."[11,12] However, despite these notable efforts, ligands that have targeted solely the DAT have not at present led to a clinically useful medication. Yet important progress has been made in the synthesis of ligands that show improved selectivity in the inhibition of either dopamine or serotonin reuptake.[13] For example, we have recently shown that constraint of the nitrogen lone pair by making "front-" or "back-bridged" tropane analogues leads to compounds with selectivity for either the SERT or the DAT.[14] The NET affinity was generally not influenced by this structural change. Because of our interest in identifying ligands showing diminished DAT activity, we chose to further explore the SAR of the front-bridged tropanes. In particular, we felt that a more dramatic departure from the structure exhibited by the WIN analogues might facilitate the identification of ligands showing only partial cocaine-like effects. Thus, we chose to introduce a ring constraint between the 3-position of the tropane ring and the nitrogen atom which by necessity forces the six-membered ring of the tropane moiety into a boat conformation. These new N,C3-bridged compounds can also be viewed as tropaquinuclidines, hybrids of tropanes and quinuclidines as illustrated in Figure 1.

Moreover, this modification would allow us to maintain the ester group at the 2-position, which is known

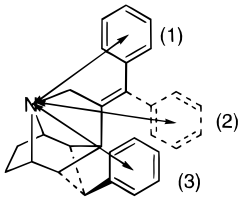
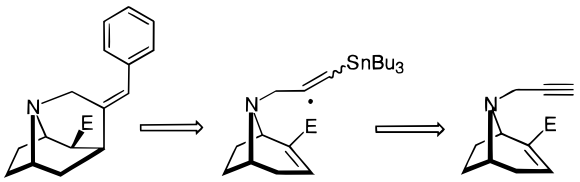


Figure 2. Schematic overlay of **5** and **6** with a WIN compound; distances between the nitrogen and centroid of the aromatic ring: (1) 5.6 Å, (2) 7.6 Å, (3) 5.6 Å.

Scheme 1



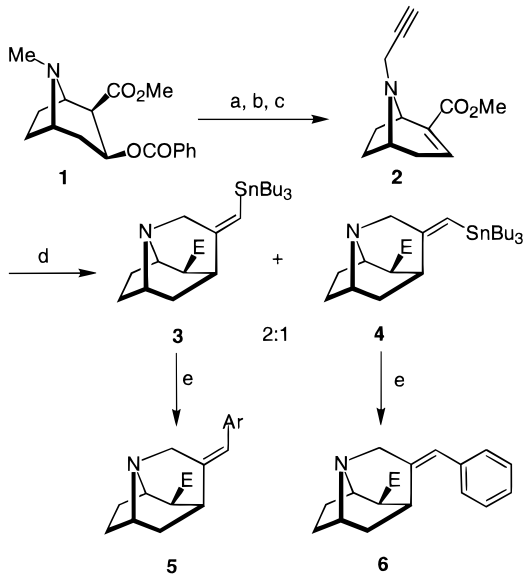
to contribute to binding at the monoamine transporters.[11] At the same time, the aromatic ring is displaced from its original 3-position to a position above the basal plane of the tropane ring without changing its approximate directionality. The distance between nitrogen and the centroid of the aromatic ring in the WIN compounds is about 5.63 Å and seems to be optimal for high binding affinity.[15] Since 3β-(phenyl)alkyltropanes[16] or 3β-carbamoyl analogues of cocaine[17,18] are in general less active than WIN compounds, we regarded it as necessary to maintain about the same interatomic distance. Essentially the same distance of about 5.64 Å is maintained by installation of a three-carbon linker between the nitrogen and the aromatic ring in the N,-C3-bridged[19] compound possessing a *Z*-configured double bond (Figure 2). For the *E*-configured compound **6** this distance is enhanced to about 7.6 Å.

Chemistry

Retrosynthetic analysis of the envisioned N,C3-bridged tropanes reveals that the installation of the new bridge could be accomplished using an intramolecular radical cyclization reaction starting from a propargyl-substituted anhydroecgonine methyl ester. This would lead to a tricyclic vinylstannane, which in turn would be a suitable substrate to introduce a phenyl substituent by means of a Stille coupling (Scheme 1).

The preparation of the bridged tropanes was accomplished using the general strategy outlined in Scheme 2. Starting from cocaine (**1**), norcocaine was prepared by *N*-demethylation with α-chloroethyl chloroformate.[20] Alkylation with propargyl bromide afforded *N*-propargylnorcocaine in 84% yield. Saponification, dehydration, and reesterification provided *N*-propargylnoranhydroecgonine methyl ester (**2**). The key step in the synthesis is a 6-*endo*-*trig* cyclization. It was envisioned that the vinyl radical, generated by addition of a stannyl radical to the triple bond, would react in an endo manner with the double bond because of the radical stabilizing effect of the ester group, thus preventing a competing 5-*exo*-*trig* cyclization.[21] The cyclization was carried out using syringe pump methodology, an excess of tributyltin hydride, and equimolar amounts of AIBN. The cyclization proceeded in good yield (73%) and with high diastereoselectivity as relates to the orientation of the ester group. Due to the bulky nature

Scheme 2[a]

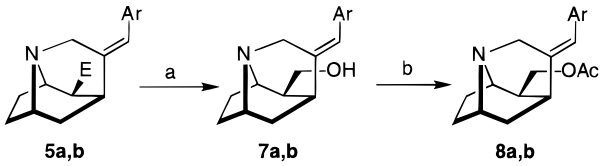


[a] Reagents and conditions: (a) $CH_3CH(Cl)OCOCl$, 1,2-dichloroethane, K_2CO_3; MeOH, 92%; (b) propargyl bromide, K_2CO_3, MeCN, 84%; (c) 2 N HCl; $POCl_3$; MeOH, −78 °C → rt, 82%; (d) AIBN, *n*-Bu_3SnH, PhH, 73%; (e) ArI, CuI, (*o*-Tol)$_3$P, $Pd_2(dba)_3$, DMF, 8−65%; **a**, Ar = Ph; **b**, Ar = 3,4-dichlorophenyl; **c**, Ar = 4-MeO−C_6H_4; **d**, Ar = 4-F-C_6H_4; **e**, Ar = 1-naphthyl; **f**, Ar = 2-furyl; **g**, Ar = 3-furyl; **h**, Ar = 2-thienyl; **i**, Ar = biphenylyl.

of the tributylstannyl residue, the cyclized radical is trapped predominantly from the endo face of the tropane ring, thus giving rise to the formation of the tricycles **3** and **4** with the ester group in a β-orientation.[22] However, two double bond isomers[23,24] (**3** and **4**) were obtained in an *Z*/*E* ratio of about 2:1, and these were easily separated by flash chromatography. No attempts were made to assign the structure of the two isomers at this stage. Next, we converted the vinylstannanes into the phenyl derivatives **5a** and **6** by means of a Stille coupling with iodobenzene.

The use of DMF as solvent, tris(dibenzylideneacetone)dipalladium(0) as palladium source, tri(*o*-tolyl)-phosphine as stabilizing ligand, and copper(I) iodide as additive, as well as a strict temperature regimen, were necessary to obtain the coupling products in acceptable yields. The two stereoisomers were analyzed by NMR methods using COSY, NOESY, and HETCOR. From the NMR studies, **5a** was assigned the *Z*-configuration and **6** the *E*-configuration (Figure 3). These assignments were also confirmed by X-ray analysis.[25] Since the Stille reaction proceeds with retention of configuration, the configurations of the starting vinylstannanes follow from those of their phenyl derivatives.[26] Compounds **7a** and **7b** were obtained in good yields by reduction of the ester group using either $LiAlH_4$ or DIBAL-H in THF. Acylation with acetic anhydride afforded the acetates **8a** and **8b** (Scheme 3).

Scheme 3[a]



[a] Reagents and conditions: (a) $LiAlH_4$ or DIBAL-H/THF; (b) pyridine, Ac_2O, DMAP; E = COOMe; **a**, Ar = Ph; **b**, Ar = 3,4-dichlorophenyl.

Results and Discussion

These novel ligands were tested for their inhibition of reuptake of NE, 5-HT, and DA at their specific transporters (Table 1).[27,28]

Compound **6** with the *E*-configured double bond is only weakly active at all three transporters, whereas compounds in the *Z*-series show high activity at the monamine transport binding sites. As is apparent, the orientation of the phenyl ring constitutes an important structural determinant of transporter activity in this ligand series.

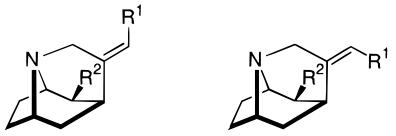
Only one compound, **5h**, shows higher activity at the DAT than cocaine. This compound was derived from **5a** by bioisosteric replacement of the phenyl ring with a thiophene ring. **5h** exhibits improved activity at the NET and, as a consequence of its significant DAT activity, acts as a combined dopamine and norepinephrine reuptake inhibitor. The remaining compounds show decreased activity at the DAT with K_i values from about 480 nM for **5a** to 10 μM for **5e**, thus confirming our previous finding that a ring constraint over the three-carbon bridge leads to compounds with reduced DAT activity.[14]

The SAR for the NET and for the SERT is not as easy to interpret. Compound **5a** lacking substitution on the phenyl ring shows potent inhibition of norepinephrine reuptake. It is also reasonably selective, as its K_i values at the SERT and DAT are 20-fold and 9-fold higher, respectively. The thiophene derivative (**5h**), already mentioned above, exhibits an improved activity at the NET and 100-fold selectivity over the SERT. The most active compound at the NET binding site is the biphenyl derivative **5i** with good selectivity over the DAT (50-fold) and SERT (50-fold). The *p*-methoxy-substituted compound **5c** as well as the two furyl analogues **5f** and **5g** still exhibit good activity for the NET. The remaining compounds exhibit a dramatic drop in activity. Apparently, the steric requirements for the hydrophobic recognition pocket for the phenyl ring at the NET are rather strict, allowing only para substitution. These findings are further supported by the decreased activity found for the 3,4-dichlorophenyl bearing analogue **5b** as well as the very poor activity shown by the naphthyl analogue **5e**. Moreover a certain electron density in the phenyl ring seems to be necessary for binding, as a fluoro substituent decreases norepinephrine reuptake activity by a factor of about 10 (**5d** vs **5a**).

To investigate the influence of the ester group on binding activity and selectivity, we converted **5a** and **5b** into their corresponding alcohols **7a** and **7b**. In comparison to the ester **5a**, a drastic loss in activity was observed for the alcohol **7a**. Also, conversion of the alcohol **7a** into the acetate **8a** did not lead to a significant regain in activity. At first sight the ester group would seem to be essential for activity, even if all possible chemical modifications have not been explored.

The size and orientation of the hydrophobic recognition pocket seems to be a major factor in differentiating ligands for either the NET or the SERT. We found that simple phenyl substitution does not lead to high activity at the SERT. However, naphthyl substitution increases the activity at the SERT by a factor of about 10 (**5e** vs

Table 1. Inhibition of Reuptake at Monoamine Transporters, $K_i \pm$ SEM (nM)[a]



5, 7 or 8 **6**

	R^1/R^2	[^{3}H]NE uptake	[^{3}H]5-HT uptake	[^{3}H]DA uptake	NE/DA	NE/5-HT	5-HT/DA
cocaine		108 ± 3	155 ± 1	423 ± 147	0.2	0.7	0.37
5a	R^1 = Ph R^2 = COOMe	53 ± 16	1140 ± 70	481 ± 11	0.11	0.05	2.36
5b	R^1 = 3,4-dichlorophenyl R^2 = COOMe	1000 ± 280	20 ± 1	1920 ± 260	0.52	50.6	0.01
5c	R^1 = 4-MeO-C_6H_4 R^2 = COOMe	187 ± 5	56 ± 4	3130 ± 160	0.06	3.37	0.02
5d	R^1 = 4-F-C_6H_4 R^2 = COOMe	584 ± 163	335 ± 45	6620 ± 460	0.09	1.74	0.05
5e	R^1 = naphthyl R^2 = COOMe	5370 ± 580	121 ± 3	9720 ± 700	0.55	44.5	0.01
5f	R^1 = 2-furyl R^2 = COOMe	111 ± 13	3680 ± 190	2020 ± 190	0.05	0.03	1.82
5g	R^1 = 3-furyl R^2 = COOMe	164 ± 3	498 ± 65	1880 ± 10	0.09	0.33	0.26
5h	R^1 = 2-thienyl R^2 = COOMe	26 ± 2	2050 ± 40	268 ± 17	0.10	0.01	7.65
5i	R^1 = 4-biphenylyl R^2 = COOMe	12 ± 1	614 ± 105	477 ± 81	0.02	0.02	1.29
6	R^1 = Ph R^2 = COOMe	1530 ± 150	7480 ± 250	5070 ± 310	0.3	0.2	1.48
7a	R^1 = Ph R^2 = CH_2OH	2830 ± 630	5300 ± 180	9690 ± 167	0.29	0.53	0.55
7b	R^1 = 3,4-dichlorophenyl R^2 = CH_2OH	10500 ± 800	96 ± 5	21300 ± 2180	0.49	109.	0.005
8a	R^1 = Ph R^2 = CH_2OAc	450 ± 18	1050 ± 190	1030 ± 70	0.44	0.43	1.02
8b	R^1 = 3,4-dichlorophenyl R^2 = CH_2OAc	638 ± 86	1.6 ± 0.4	1870 ± 90	0.34	412	0.001

[a] K_i values are mean ± SEM from two to four independent experiments, each consisting of six drug concentrations (in triplicate) that were selected on the basis of preliminary screening experiments to bracket the approximate IC_{50} value.

Table 2. Binding and Inhibition of Reuptake Performed in Cells Expressing Human Transporters, $K_i \pm$ SEM (nM)[a]

	HEK-hNET cells		HEK-hSERT cells		HEK-hDAT cells		selectivities (uptake)		
	[^{125}I]RTI-55 binding	[^{3}H]NE uptake	[^{125}I]RTI-55 binding	[^{3}H]5-HT uptake	[^{125}I]RTI-55 binding	[^{3}H]DA uptake	NE/DA	NE/5-HT	5-HT/DA
cocaine	1740 ± 180	264 ± 57	343 ± 31	301 ± 53	258 ± 23	276 ± 22			
5a	1040 ± 360	68 ± 13	2330 ± 480	2400 ± 1100	1570 ± 180	910 ± 160	0.07	0.03	2.6
5b	3770 ± 390	640 ± 120	0.56 ± 0.01	30.0 ± 8	3320 ± 550	>10 μM	0.06	21.3	0.03
5c	5440 ± 470	208 ± 75	42 ± 11	53 ± 14	3600 ± 1600	3700 ± 520	0.06	3.9	0.01

[a] Numbers represent the means ± SEM from at least three independent experiments, each conducted with duplicate (for binding assays) or triplicate (for uptake assays) determination.

5a), thus demonstrating the different shape of the recognition site. Since 3,4-dichlorophenyl substitution in the WIN series leads to some of the most DAT active compounds to be reported (IC_{50} = 0.79 nM),[29] we decided to explore this substitution pattern also in our series. Compound **5b** in fact exhibits remarkable potency and selectivity for the SERT, showing about 100-fold higher activity at the SERT vs the DAT and about 50-fold higher activity at the SERT vs the NET. This activity could further be improved by reducing the ester group and acylating the obtained alcohol with acetic anhydride. The resulting compound **8b** is the most active and selective compound in the present series. Its selectivity for the SERT over the NET and DAT of about 410 and 1000 is intriguing. This good selectivity is also retained in the alcohol **7b**, which still has good activity at the SERT. The 3,4-dichlorophenyl substituent pattern constitutes therefore an important element for binding at the SERT, which can be further fine-tuned by modification of the ester group. Compound **5c** has a SERT activity between that of **8b** and **5e**, and its selectivity over the DAT is still good (50-fold for SERT vs DAT).

Additionally, compounds **5a**, **5b**, and **5c** were tested by the Cocaine Treatment Discovery Program (CTDP) of the National Institute on Drug Abuse (NIDA) for their effects on radioligand binding and biogenic amine uptake by HEK cells expressing cDNA for the human DAT, SERT, and NET, respectively (Table 2).[30] The uptake data obtained using cells that express human monoamine transporters correlate well with the data obtained with rat synaptosomes, thus corroborating our initial data. Slight inconsistencies are probably due to species differences. These data revealed an excellent binding affinity within the picomolar range at the human SERT for compound **5b**. The selectivity of this compound over both DAT and NET is about 6000, hence making it one of the most active and selective tropane analogues identified to date at the SERT.

The compounds disclosed in the present series possess several features which distinguish them from other

tropane derivatives synthesized until now, particularly, the additional bridge between the carbon atom 3[19] and the nitrogen, which constrains the tropane ring in the boat conformation. Recent reports on boatlike tropane derivatives revealed a decreased binding at the SERT in comparison to the DAT.[31−33] However, due to the orientation of the nitrogen lone pair over the two-carbon bridge combined with the introduction of additional steric bulk over the three-carbon bridge, these ligands were anticipated to exhibit decreased activity at the DAT, in analogy to the "front-bridged" compounds (Figure 1).[14] This hypothesis was confirmed, since all of the compounds tested showed only moderate or low inhibition of dopamine reuptake. On the other hand, the activity and selectivity for the SERT and NET is mainly influenced by the substitution pattern of the aromatic ring. Initial data for variations of the ester group show that fine-tuning for higher selectivity and activity is possible.

In summary, the synthesis of a novel class of tricyclic tropane analogues which can be viewed as hybrids between tropanes and quinuclidines has been accomplished that makes use of radical cyclization technology in combination with Stille coupling chemistry. These new tropaquinuclidines represent a significant structural departure from many of the other classes of tropane ligands synthesized to date. They are characterized by the boat conformation of the tropane ring and the orientation of the additional bridge (and therefore of the nitrogen lone pair) together with the unusual placement of the aromatic moiety. The potency and selectivity shown by some of these ligands for the NET, SERT, or NET/SERT are striking, particularly in view of the displacement of the aromatic ring in this series from its usual position at the C3 in the WIN analogues. These ligands provide additional pharmacological tools of use in attempting to correlate structure and transporter selectivity with in vivo studies of behavioral outcomes.

Experimental Section

NMR spectra were recorded on a Varian Unity Inova spectrometer at 300 MHz for proton and 75.46 MHz for carbon-13 spectra. $CDCl_3$ was used as solvent. Chemical shifts are reported in ppm relative to internal TMS. Coupling constants are given in hertz (Hz). Analytical thin-layer chromatography was performed using Merck silica gel 60F-254 plates; flash chromatography was performed using Merck silica gel (60−200 mesh). Mass spectra were measured in the EI mode at an ionization potential of 70 eV. Starting materials were obtained from Aldrich or Fluka. Solvents were obtained from Fisher Scientific and were used without further purification unless otherwise noted. DMF (DriSolv) was obtained from EM Science. Norcocaine, 2-iodofuran, and 3-iodofuran were prepared according to literature methods.[20,34] To ensure proper elemental analyses and for easy handling in the biological assays, all final compounds were converted into salts by common methods.

***N*-Propargylnorcocaine.** Norcocaine (2.57 g, 8.88 mmol), propargyl bromide (1.18 mL, 10.6 mmol), and K_2CO_3 (1.46 g, 10.6 mmol) were refluxed in acetonitrile (50 mL) for 12 h. The solvent was removed, and the residue was dissolved in ice-cold ammonia solution (2% v/v). The aqueous solution was extracted with ether (3 × 30 mL) and dried, and the solvent was evaporated under reduced pressure. Flash chromatography (ethyl acetate/hexane 1/3, R_f 0.34) afforded *N*-propargylnorcocaine (2.43 g, 84%) as slightly yellow crystals: ^{1}H NMR δ 1.77 (m, 2H), 1.91 (m, 1H), 2.02 (m, 2H), 2.18 (t, J = 2.4, 1H), 2.45 (dd, J = 11.7, 2.2), 3.05 (m, 1H), 3.09 and 3.19 (ABq, J = 16.1, both parts d with J = 2.4), 3.44 (br s, 1H), 3.72 (s, 3H), 3.95 (m, 1H), 5.27 (quin, J = 5.8, 1H), 7.45 (t, J = 7.8, 2H), 7.54 (t, J = 7.3, 1H), 8.03 (d, J = 7.3, 2H); ^{13}C NMR δ 25.23, 25.92, 35.49, 41.82, 50.06, 51.33, 60.12, 61.95, 66.92, 71.25, 80.94, 128.25, 129.65, 130.18, 132.87, 166.1, 170.23.

***N*-Propargylnoranhydroecgonine Methyl Ester (2).** *N*-Propargylnorcocaine (2.43 g, 7.42 mmol) was refluxed in 2 N hydrochloric acid overnight. The solution was concentrated to dryness, and the residue was dried at room temperature in vacuo for 4 h. Phosphorus oxychloride (50 mL) was added, and the mixture was refluxed for 2 h. The excess of phosphorus oxychloride was removed under reduced pressure, and the residue was dried for 1 h in vacuo. The gummy mass was cooled in a dry ice/acetone bath, and methanol (50 mL) was added very carefully with gentle shaking of the flask. The solution was allowed to return to room temperature slowly and stirred for 1 h at room temperature. The methanol was evaporated, and the product was purified by flash chromatography (ethyl acetate/hexane 1/3, R_f 0.24) to afford **4** (1.25 g, 82%) as a yellow oil: ^{1}H NMR δ 1.52 (m, 1H), 1.84 (m, 2H), 2.15 (m, 2H), 2.21 (t, J = 2.5, 1H), 2.6 (d, J = 19.7, 1H), 3.24 and 3.31 (ABq, J = 16.0, both parts d with J = 2.6, 2H), 3.51 (t, J = 5.1, 1H), 3.74 (s, 3H), 4.0 (d, J = 5.0, 1H), 6.83 (brs, 1H); ^{13}C NMR δ 29.71, 31.13, 34.18, 37.86, 51.48, 54.43, 56.48, 71.45, 80.52, 133.36, 135.91, 166.1.

Radical Cyclization of 2. Compound **2** (1.03 g, 5.02 mmol) was dissolved in benzene (100 mL) and heated to reflux. AIBN (824 mg, 5.02 mmol) and tri-*n*-butylstannane (2.75 mL, 10.0 mmol) were dissolved in benzene to the total volume of 50 mL and added via syringe pump over 8 h to the refluxing solution of **2**. The mixture was refluxed for another 2 h, the solvent was evaporated, and the residue was purified by flash chromatography employing a gradient (ethyl acetate/hexane 30/70 to 100/0) to yield a mixture of **3** and **4**.

(1*S*,3*R*,6*S*)-(*Z*)-9-[(Tri-*n*-butylstannyl)methylene]-7-azatricyclo[4.3.1.0^{3,7}]decane-2β-carboxylic acid methyl ester (3): yield 1.23 g (51%); R_f 0.38 (ethyl acetate); ^{1}H NMR δ 0.75−1.7 (m, 30 H), 2.00 (ddd, J = 22.5, 9.5, 2.2, 1H), 2.14 (m, 2H), 2.35 (t, J = 2.9, 1H), 2.63 (m, 1H), 3.26 (m, 1H), 3.54 and 3.61 (ABq, J = 17.3, both parts d with J = 2.2, 2H), 3.63 (s, 3H), 3.77 (m, 1H), 5.52 (t, J = 2.4, 1H with satellites from J_{Sn-H} = 57.5); ^{13}C NMR δ 9.67, 13.65, 27.24, 29.12, 31.95, 32.61, 36.52, 40.20, 50.34, 51.70, 52.40, 53.80, 55.9, 117.49, 155.96, 174.15.

(1*S*,3*R*,6*S*)-(*E*)-9-[(Tri-*n*-butylstannyl)methylene]-7-azatricyclo[4.3.1.0^{3,7}]decane-2β-carboxylic acid methyl ester (4): yield 540 mg (22%); R_f 0.15 (ethyl acetate); ^{1}H NMR δ 0.75−1.7 (m, 30H), 1.95 (ddd, J = 22.5, 9.5, 2.3, 1H), 2.15 (m, 2H), 2.40 (m, 2H), 3.25 (m, 1H), 3.64 (s, 1H), 3.58−3.8 (m, 3H), 5.47 (t, J = 1.8, 1H with satellites from J_{Sn-H} = 62.6); ^{13}C NMR δ 5.53, 9.22, 22.91, 24.67, 27.52, 28.22, 32.82, 33.30, 46.53, 47.27, 47.47, 49.26, 52.16, 112.27, 151.38, 169.98.

Stille Coupling (General Procedure). The appropriate aryl or hetaryl iodide (0.5 mmol), tris(*o*-tolyl)phosphine (8 mol %), $Pd_2(dba)_3$ (2 mol %), and copper(I) iodide (8 mol %) were dissolved in DMF (2 mL) and stirred at room temperature for 15 min under nitrogen. Then the stannane (0.5 mmol) in DMF (2 mL) was added, and the mixture was stirred at 45−50 °C for 12 h. The solution was poured into ice-cold hydrochloric acid (2 N), and the aqueous phase was extracted with ether (3 × 20 mL). The organic phase was reextracted with hydrochloric acid (2 × 15 mL), and the combined acidic solutions were basified with NH_4OH and extracted with ethyl acetate (4 × 20 mL). The solution was dried over $MgSO_4$, the solvent was evaporated, and the residue was chromatographed on silica gel using ethyl acetate/triethylamine 10/1.

(1*S*,3*R*,6*S*)-(*Z*)-9-(Phenylmethylene)-7-azatricyclo-[4.3.1.0^{3,7}]decane-2β-carboxylic acid methyl ester (5a): yield 66%, colorless oil, solidifies upon standing (white crystals); mp 97−98 °C; $[\alpha]^{25}_D$ +68.5 (*c* 0.35, $CHCl_3$); ^{1}H NMR δ 1.46 (m, 3H), 2.0−2.3 (m, 3H), 2.41 (t, J = 3.2, 1H), 2.71 (dd, J = 5.9, 3.17, 1H), 3.28 (m, 1H), 3.65 (s, 3H), 3.79 (m, 1H), 3.92 and 4.05 (ABq, J = 18.3, both parts d with J = 2.4, 2H), 6.13 (t, J = 2.3), 7.1−7.4 (m, 5H); ^{13}C NMR δ 32.03, 32.65,

36.59, 37.37, 48.26, 51.85, 52.41, 53.76, 56.28, 122.03, 126.15, 128.34, 128.36, 137.42, 140.59, 174.28. Anal. C, H, N.

(1*S*,3*R*,6*S*)-(*Z*)-9-(3,4-Dichlorophenylmethylene)-7-azatricyclo[4.3.1.0^{3,7}]decane-2β-carboxylic acid methyl ester (5b): yield 61%; white crystals; mp 127−28 °C; $[\alpha]^{25}_{D}$ +64.6 (*c* 1.65, $CHCl_3$); ^{1}H NMR δ 1.50 (m, 3H), 2.05 (m, 1H), 2.17 (m, 2H) 2.42 (t, *J* = 2.9, 1H), 2.69 (m, 1H), 3.28 (m, 1H), 3.65 (s, 3H), 3.76 (m, 1H), 3.86 and 3.99 (ABq, *J* = 18.3, both parts d with *J* = 2.3, 2H), 6.03 (br s, 1H), 7.01 (dd, *J* = 8.4, 1.8, 1H), 7.26 (d, *J* = 1.8, 1H), 7.36 (d, *J* = 8.1, 1H); ^{13}C NMR δ 31.94, 32.54, 36.28, 37.26, 48.15, 51.88, 52.12, 53.61, 56.27, 119.77, 127.41, 129.78, 130.01 130.13, 132.26, 137.29, 143.49, 174.15. Anal. C, H, N.

(1*S*,3*R*,6*S*)-(*Z*)-9-(4-Methoxyphenylmethylene)-7-azatricyclo[4.3.1.0^{3,7}]decane-2β-carboxylic acid methyl ester (5c): yield 59%; ^{1}H NMR δ 1.49 (m, 3H), 2.07 (m, 1H), 2.17 (m, 2H), 2.39 (t, *J* = 3.1, 1H), 2.68 (m, 1H), 3.28 (m, 1H), 3.64 (s, 3H), 3.77 (m, 1H), 3.80 (s, 3H), 3.89 and 4.02 (ABq, *J* = 18.1, both parts d with *J* = 2.4, 2H), 6.07 (br s, 1H), 6.86 (d, *J* = 8.7, 2H), 7.13 (d, *J* = 8.7, 2H); ^{13}C NMR δ 32.03, 32.67, 36.67, 37.28, 48.27, 51.85, 52.46, 53.76, 55.26, 56.23, 113.77, 121.29, 129.54, 130.25, 138.07, 157.85, 174.31. Anal. C, H, N.

(1*S*,3*R*,6*S*)-(*Z*)-9-(4-Fluorophenylmethylene)-7-azatricyclo[4.3.1.0^{3,7}]decane-2β-carboxylic acid methyl ester (5d): yield 49%; ^{1}H NMR δ 1.5 (m, 3H), 2.05 (m, 1H), 2.16 (m, 2H), 2.40 (t, *J* = 3.2, 1H), 2.68 (dd, *J* = 6.0, 3.1, 1H), 3.28 (m, 1H), 3.65 (s, 3H), 3.76 (m, 1H), 3.87 and 3.99 (ABq, *J* = 18.2, both parts d with *J* = 2.3, 2H), 6.1 (br s, 1H), 7.0 (t, *J* = 8.8, 2H), 7.14 (dd, *J* = 8.6, 5.6, 2H); ^{13}C NMR δ 31.92, 32.55, 36.40, 37.17, 48.04, 51.77, 52.23, 53.65, 56.19, 115.12 (d, *J* = 21.32), 120.73, 129.75 (d, *J* = 7.7), 133.43 (d, *J* = 3.3), 140.12 (d, *J* = 2.2), 161.0 (d, *J* = 246.7), 174.23; MS *m*/*z* (%) 301 (M$^+$, 34), 242 (59), 159 (29), 146 (45), 120 (46), 109 (39), 83 (100); Anal. C, H, N.

(1*S*,3*R*,6*S*)-(*Z*)-9-(1-Naphthylmethylene)-7-azatricyclo-[4.3.1.0^{3,7}]decane-2β-carboxylic acid methyl ester (5e): yield 46%; ^{1}H NMR δ 1.50 (m, 3H), 2.15 (m, 3H), 2.45 (t, *J* = 3.3, 1H), 2.9, (dd, *J* = 6.0, 3.3, 1H), 3.69 and 3.83 (ABq, *J* = 18.5, both parts d with *J* = 2.4, 2H), 3.74 (s, 3H), 3.76 (m, 1H), 6.68 (br s, 1H), 7.3−8.0 (m, 7H); ^{13}C NMR δ 32.02, 32.56, 36.48, 36.75, 47.06, 51.9, 52.33, 53.82, 56.32, 119.25, 124.45, 125.31, 125.61, 125.66, 125.79, 126.98, 128.37, 131.47, 133.52, 133.83, 141.9, 174.40. Anal. C, H, N.

(1*S*,3*R*,6*S*)-(*Z*)-9-(2-Furylmethylene)-7-azatricyclo-[4.3.1.0^{3,7}]decane-2β-carboxylic acid methyl ester (5f): yield 28%; ^{1}H NMR δ 1.49 (m, 3H), 2.0 (m, 1H), 2.18 (m, 2H), 2.39 (t, *J* = 3.0, 1H), 2.68 (dd, *J* = 6.0, 3.0, 1H), 3.30 (m, 1H), 3.64 (s, 3H), 3.76 (m, 1H), 3.88 and 3.95 (ABq, *J* = 18.9, both parts d with *J* = 2.4, 2H), 6.02 (t, *J* = 2.4, 1H), 6.07 (d, *J* = 3, 1H), 6.37 (dd, *J* = 3.2, 1.9, 1H), 7.35 (d, *J* = 1.4, 1H); ^{13}C NMR δ 32.06, 32.62, 36.28, 36.52, 48.37, 51.88, 52.14, 53.71, 56.30, 107.76, 110.27, 111.23, 139.37, 141.13, 152.90, 174.16; MS *m*/*z* (%) 273 (M$^+$, 26), 214 (26), 69 (37), 68 (36), 43 (100). Anal. C, H, N.

(1*S*,3*R*,6*S*)-(*Z*)-9-(3-Furylmethylene)-7-azatricyclo-[4.3.1.0^{3,7}]decane-2β-carboxylic acid methyl ester (5g): yield 8%; ^{1}H NMR δ 1.51 (m, 3H), 2.1 (ddd, *J* = 12.5, 9.8, 2.3, 1H), 2.2 (m, 2H), 2.4 (t, *J* = 3.1, 1H), 2.68 (dd, *J* = 5.9, 3.0, 1H), 3.31 (m, 1H), 3.64 (s, 3H), 3.75 and 3.83 (ABq, *J* = 17.9, both parts d with *J* = 2.0, 2H), 3.78 (m, 1H), 5.95 (s, 1H), 6.34 (s, 1H), 7.32 (s, 1H), 7.37 (s, 1H); ^{13}C NMR δ 31.89, 32.50, 36.30, 36.40, 48.32, 51.87, 52.19, 53.85, 56.34, 110.47, 111.50, 122.46, 140.25, 142.74, 174.09; MS *m*/*z* (%) 273 (M$^+$, 0.7), 214 (17), 85 (41), 83 (100), 68 (32). Anal. C, H, N.

(1*S*,3*R*,6*S*-(*Z*)-9-(2-Thienylmethylene)-7-azatricyclo-[4.3.1.0^{3,7}]decane-2β-carboxylic acid methyl ester (5h): yield 58%; ^{1}H NMR δ 1.51 (m, 3H), 2.03 (m, 1H), 2.2 (m, 2H), 2.4 (t, *J* = 2.9, 1H), 2.70 (dd, *J* = 5.6, 2.7, 1H), 3.28 (m, 1H), 3.63 (s, 3H), 3.77 (s, 1H) 3.85 and 3.93 (ABq, *J* = 18.4, both parts d with *J* = 2.2, 2H), 6.37 (s, 1H), 6.87 (d, *J* = 3.4, 1H), 7.0 (t, *J* = 3.7 1H), 7.5 (d, *J* = 10, 1H); ^{13}C NMR δ 32.01, 32.58, 36.48, 36.56, 48.43, 51.89, 52.76, 53.76, 56.32, 114.93, 124.80, 125.82, 126.99, 138.72, 140.83, 174.12. Anal. C, H, N.

(1*S*,3*R*,6*S*-(*Z*)-9-(4-Biphenylylmethylene)-7-azatricyclo-[4.3.1.0^{3,7}]decane-2β-carboxylic acid methyl ester (5i): yield 64%; ^{1}H NMR δ 1.50 (m, 3H), 2.1 (m, 1H), 2.2 (m, 2H), 2.42 (t, *J* = 3.0, 1H), 2.75 (dd, *J* = 5.8, 3.1, 1H), 3.3 (m, 1H), 3.79 (s, 3H), 3.8 (s, 1H) 3.96 and 4.09 (ABq, *J* = 18.3, both parts d with *J* = 2.1, 2H), 6.17 (s, 1H), 7.2−7.65 (m, 9H); ^{13}C NMR δ 31.99, 32.61, 36.55, 37.40, 48.38, 51.88, 52.37, 53.74, 56.25, 121.61, 126.89, 127.00, 127.17, 128.73, 128.77, 136.42, 138.83, 140.67, 140.89, 174.27. Anal. C, H, N.

(1*S*,3*R*,6*S*)-(*E*)-9-(Phenylmethylene)-7-azatricyclo-[4.3.1.0.^{3,7}]decane-2β-carboxylic acid methyl ester (6): yield 37%; $[\alpha]^{25}_{D}$ −52.8 (*c* 1.065, $CHCl_3$); ^{1}H NMR δ 1.48 (m, 3 H), 2.05 (m, 1H), 2.17 (m, 2H), 2.30 (t, *J* = 3.1, 1H), 3.33 (m, 2H), 3.43 (s, 3H), 3.71 and 3.82 (ABq, *J* = 17.7, both parts d with *J* = 2.1, 2H), 3.78 (m, 1H), 6.28 (s, 1H), 7.1−7.3 (m, 5H); ^{13}C NMR δ 28.83, 31.98, 32.66, 35.60, 48.99, 51.08, 51.40, 53.85, 56.30, 121.21, 126.09, 128.08, 128.10, 137.06, 139.61, 174.22. Anal. C, H, N.

(1*S*,3*R*,6*S*)-2-(Hydroxymethyl)-(*Z*)-9-(phenylmethylene)-7-azatricyclo[4.3.1.0^{3,7}]decane (7a). To a solution of **5a** (0.5 mmol) in THF (10 mL) was added $LiAlH_4$ (1.5 mmol) portionwise, and the mixture was stirred for 3 h. The mixture was quenched with concentrated Rochelle salt solution (15 mL) followed by extraction with EtOAc (3 × 10 mL). The organic phase was washed with brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure to afford the title compound as a colorless oil: quantitative yield; ^{1}H NMR δ 1.4−1.7 (m, 4H), 2.0−2.35 (m, 3H), 2.41 (dd, *J* = 5.7, 3.1, 1H), 2.80 (m, 1H), 3.26 (m, 1H), 3.45 (m, 2H), 3.88 and 3.97 (ABq, *J* = 18.4, both parts d with *J* = 2.5, 2H), 6.17 (t, *J* = 2.3, 1H), 7.25 (m, 5H); ^{13}C NMR δ 32.20, 32.89, 35.68, 37.26, 48.45, 48.72, 53.98, 58.07, 65.56, 121.85, 126.04, 128.22, 128.36, 137.30, 141.19. Anal. C, H, N.

(1*S*,3*R*,6*S*)-2-(Hydroxymethyl)-(*Z*)-9-(3,4-dichlorophenylmethylene)-7-azatricyclo[4.3.1.0^{3,7}]decane (7b). DIBAL-H (1.5 mmol) was added dropwise to a solution of **5b** (0.5 mmol) in THF (10 mL) under N_2 at room temperature. The reaction mixture was stirred for 3 h, quenched with concentrated Rochelle salt solution (15 mL), and extracted with EtOAc (3 × 10 mL). The organic phase was washed with brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the crude product by flash chromatography on silica gel using EtOAc/NEt_3 10/1 as eluent afforded the title compound as a colorless oil: yield 89%; ^{1}H NMR δ 1.2−1.4 (m, 4H), 2.0−2.35 (m, 3H), 2.43 (dd, *J* = 6.1, 3.4, 1H), 2.81 (m, 1H), 3.30 (m, 1H), 3.5 (d, *J* = 7.6, 2H), 3.85 and 3.93 (ABq, *J* = 18.4, both parts d with *J* = 2.5, 2H), 6.08 (t, *J* = 2.4, 1H), 7.05 (dd, *J* = 8.4, 2.0, 1H), 7.3 (d, *J* = 2.0, 1H), 7.4 (d, *J* = 8.4, 1H); ^{13}C NMR δ 32.20, 32.80, 35.73, 37.06, 48.44, 48.63, 54.00, 58.06, 65.53, 119.74, 127.36, 129.69, 129.93, 130.19, 132.33, 137.33, 144.23. Anal. C, H, N.

(1*S*,3*R*,6*S*)-2-(Acetoxymethyl)-(*Z*)-9-(phenylmethylene)-7-azatricyclo[4.3.1.0^{3,7}]decane (8a). To a solution of **7a** (0.1 mmol) in pyridine (1 mL) and acetic anhydride (0.25 mL) was added DMAP (1 mg), and the solution was stirred for 2 h. The mixture was concentrated under reduced pressure, diluted with EtOAc (20 mL), and washed with a saturated solution of $NaHCO_3$ (2 × 10 mL). The organic solution was dried and concentrated under reduced pressure. Purification of the crude product by flash chromatography on silica gel using $CHCl_3$/MeOH 10/1 as eluent afforded the title compound as a colorless oil: yield 73%; ^{1}H NMR δ 1.5 (m, 3H), 1.77 (m, 1H), 2.04 (s, 3H), 2.05 (m, 3H), 2.36 (dd, *J* = 5.8, 2.9, 1H), 2.85 (dd, *J* = 5.7, 2.8, 1H), 3.30 (m, 1H), 3.91 and 3.99 (ABq, *J* = 18.2, both parts d with *J* = 2.8, 2H), 3.97 (d, *J* = 7.8, 2H), 6.13 (t, *J* = 2.4, 1H), 7.1−7.4 (m, 5H); ^{13}C NMR δ 20.89, 32.20, 32.80, 35.93, 37.20, 45.23, 48.50, 53.87, 67.22, 122.36, 126.10, 128.30, 128.37, 137.29, 140.44, 171.04. Anal. C, H, N.

(1*S*,3*R*,6*S*)-2-(Acetoxymethyl)-(*Z*)-9-(3,4-dichlorophenylmethylene)-7-azatricyclo[4.3.1.0^{3,7}]decane (8b) was prepared in a similar manner as **8a**: yield 80%; ^{1}H NMR δ 1.5 (m, 3H), 1.78 (m, 1H), 2.05 (s, 3H), 2.1 (m, 3H), 2.35 (dd, *J* = 5.6, 2.9, 1H), 2.85 (dd, *J* = 5.7, 3.1, 1H), 3.31 (m, 1H), 3.86 and 3.94 (ABq, *J* = 18.4, both parts d with *J* = 2.5, 2H), 3.95

(d, J = 7.4, 2H), 6.04 (t, J = 2.4, 1H), 7.02 (dd, J = 8.2, 2.0, 1H), 7.29 (d, J = 2.0, 1H), 7.38 (d, J = 8.2, 1H); ^{13}C NMR δ 20.90, 32.15, 32.74, 35.97, 36.97, 45.12, 48.39, 53.87, 58.15, 66.99, 120.29, 127.43, 129.85, 130.03, 130.23, 132.35, 137.22, 143.22, 171.01. Anal. C, H, N.

Synaptosomal Uptake of [^{3}H]Dopamine, [^{3}H]5-Hydroxytryptamine, and [^{3}H]Norepinephrine. All compounds were tested as their respective salts. The effect of candidate compounds in antagonizing biogenic amine high-affinity uptake was determined using a method similar to that previously employed for [^{3}H]DA uptake.[27] Striatum, midbrain, and parietal/occipital cortex were dissected and used as a source of rat DAT, SERT, and NET, respectively. These brain regions were homogenized with a Teflon-glass pestle in ice-cold 0.32 M sucrose and centrifuged for 10 min at 1000*g*. The supernatant was centrifuged at 17500*g* for 20 min. This P_2 synaptosomal pellet was resuspended in 30 volumes of ice-cold modified KRH buffer consisting of (in mM) NaCl (125), KCl (4.8), $MgSO_4$ (1.2), $CaCl_2$ (1.3), KH_2PO_4 (1.2), glucose (5.6), nialamide (0.01), and HEPES (25) (pH 7.4).[28] An aliquot of the synaptosomal suspension was preincubated with the buffer and drug for 30 min at 4 °C and then for 15 min at 37 °C before uptake was initiated by the addition of [^{3}H]biogenic amine (∼5 nM for [^{3}H]DA and [^{3}H]5-HT, 9 nM for [^{3}H]NE, final concentration). After 5 min, uptake was terminated by adding 5 mL of cold buffer containing glucosamine as a substitute for NaCl and then finally by rapid vacuum filtration over GF-C glass-fiber filters, followed by washing with two 5 mL volumes of ice-cold, sodium-free buffer. The bound and free [^{3}H]biogenic amines were separated by rapid vacuum filtration over Whatman GF/C filters, using a Brandel M24R cell harvester, followed by two washes with 5 mL of cold buffer. Radioactivity on the filters was then extracted by allowing the filters to sit overnight with 5 mL of scintillation fluid. The vials were vortexed and counted. Specific uptake of [^{3}H]DA was defined as that which is sensitive to inhibition by 30 mM cocaine; 10 mM fluoxetine and 3 mM desipramine, respectively, were used to define the specific uptake of [^{3}H]5-HT and [^{3}H]NE. In each instance, it was virtually identical to that calculated by subtracting the mean of identical tubes incubated at 0 °C. IC_{50} values were determined using the computer program LIGAND. The Cheng−Prusoff equation for classic, competitive inhibition was used for calculating K_i from IC_{50} values in uptake experiments. The K_m values used were about 67 nM for [^{3}H]-DA, 53 nM for [^{3}H]5-HT, and 54 nM for [^{3}H]NE.

Acknowledgment. We are indebted to the NIH, National Institute on Drug Abuse (DA10458, DA05867, and DA09045), and the Office of Naval Research for their financial support. We thank Dr. Istvan Enedy for the molecular modeling studies.

Supporting Information Available: X-ray structures of **5a** and **6**, tables of crystal data, atomic coordinates, bond lengths and angles, anisotropic and isotropic displacement parameters, and hydrogen coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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Refinement on F^2, $R = 0.059$, wR = 0.122 for all 2687 unique data. Crystal data for **6**: A clear plate 0.44 × 0.09 × 0.07 mm, $C_{25}H_{20}NO_5S$, FW = 455.55, orthorhombic space group $P2_12_12_1$; $a = 8.166(1)$, $b = 10.458(2)$, $c = 26.034(4)$ Å, $V = 2223.4(6)$ Å^3, $Z = 4$, $d_{calc} = 1.361$ gm/cm^3; 7455 reflections were measured to $2q_{max} = 113°$. Refinement on F^2, $R = 0.056$, wR = 0.128 for all 2633 unique data. Crystallographic coordinates have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, deposit@ccdc.cam.ac.uk. Additionally, crystallographic data have been deposited as Supporting Information.

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