Biaryl Analogues of Conformationally Constrained Tricyclic Tropanes as Potent and Selective Norepinephrine Reuptake Inhibitors: Synthesis and Evaluation of Their Uptake Inhibition at Monoamine Transporter Sites

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A series of novel conformationally constrained tricyclic tropane derivatives containing a biaryl moiety, (*Z*)-9-(biarylylmethylene)-7-azatricyclo[4.3.1.0^{3,7}]decanes, were synthesized and evaluated for their ability to inhibit reuptake of dopamine (DA), serotonin (5-HT), and norepinephrine (NE) by the DA, 5-HT, and NE transporters. Most of the compounds containing a methoxycarbonyl substituent at C-10 exhibit moderate to high inhibitory activity at the NET but lower activity at the DAT and SERT. Among these new compounds, some potent, NET-selective ligands were identified. The *p*-methoxy derivative **11a** has a K_i value of 39 nM for uptake inhibition at the NET and moderate to high selectivity over the SERT (100-fold) and the DAT (20-fold). Compound **11f** exhibits a remarkable potency (K_i = 9.7 nM) at the NET and a 25-fold selectivity over both the SERT and the DAT. Analogue **23** containing a thiophene ring as a bioisosteric replacement of the phenyl ring Ar^1 displays a high activity (K_i = 10.3 nM) for the NET and similar selectivity over the SERT (50-fold) and the DAT (37-fold). The selectivity profile of biaryl analogues differs from that of the monoaryl series, as most members of that series display excellent potency at and selectivity for the SERT (*J. Med. Chem.* **2002**, *45*, 1930). This finding suggests that the different shape and size of the lipophilic recognition pocket that encompasses the aryl ring(s) of these tropanes are major determinants of a ligand's transporter activity at either the NET or the SERT. Some of the compounds in this series may also be valuable in sorting out the contribution of the individual transporters to cocaine's reinforcing properties.

Introduction

The abuse of cocaine (**1**) (Chart 1) represents a major and increasing threat to our economy, communities, and public health.[1−3] Consequently, considerable effort has been directed toward understanding cocaine's mechanism of action and its behavioral effects as well as toward the discovery of possible medications. Cocaine is known to have multiple effects on endogenous central neurotransmitter systems. It binds with moderate and roughly equal affinity to all three of the monoamine transporters and thereby inhibits the presynaptic reuptake of dopamine (DA), serotonin (5-HT), and norepinephrine (NE) into neurons. Because the importance of the interaction of cocaine with the dopaminergic system ("DA hypothesis") is strongly supported by experimental data, most of the drugs generated to date have targeted either DA receptors or the DA transporter (DAT).[4−6] However, a study employing knockout mice has demonstrated that cocaine provides its rewarding cues through its effects on additional systems besides the dopaminergic system.[7,8] Recent work suggests that both the serotonin (SERT) and the norepinephrine transporters (NET) may also play prominent roles in cocaine addiction.[9−15] Research with compounds that vary both in their transporter selectivity and in reinforcing strength may help unravel the pharmacological mechanisms relevant to drug addiction. To further elucidate the role of the different transporter systems in cocaine reward and craving, novel ligands with defined potency at each of these three transporter sites may be of value. In view of our own recent work, it is even reasonable to suggest that drugs with a differential selectivity for the monoamine transporters may exhibit only partial cocaine-like properties and thus serve as medications in the treatment of cocaine craving.[16]

To date, a large variety of tropane-based or nontropane analogues of cocaine have been synthesized with two general aims in mind: (1) to further elucidate

Chart 1

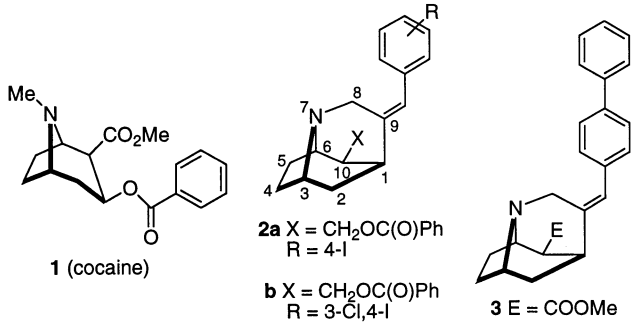

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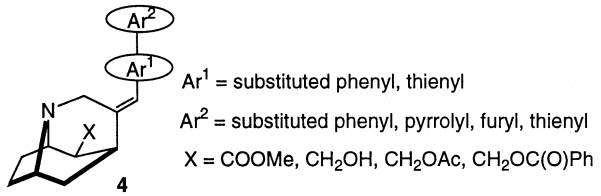
Chart 2

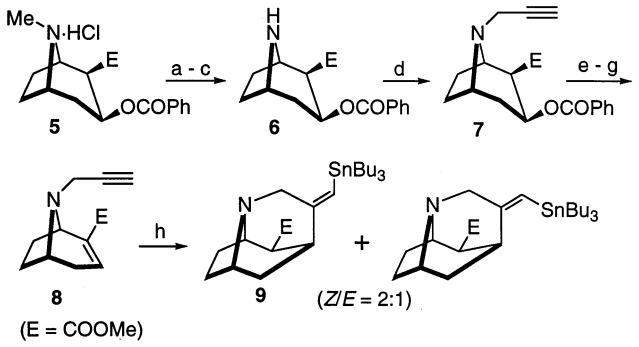


structure−activity relationships (SAR) at the DAT and (2) to identify ligands of improved potency and DAT selectivity that could be used in cocaine addiction.[17−28] In contrast to the substantial body of research on DAT-selective ligands, fewer studies have focused on the SAR relevant to creating ligands imbued with varying levels of transporter selectivity.[3,4,29] As part of our research program aimed at the discovery of possible medications for cocaine abuse, we have been exploring a new series of conformationally constrained analogues in an effort to learn how to "dial in" certain levels of transporter selectivity. For example, in our recent studies,[30−32] a series of tropane analogues (**2**) were synthesized and several highly potent and selective serotonin reuptake inhibitors identified. Compound **2a** exhibited a K_i value of 0.1 nM at the SERT and K_i values of more than 10 000 and 8190 nM at the DAT and NET, respectively, whereas compound **2b** displayed an even higher inhibitory potency and selectivity with a K_i value of 0.06 nM at the SERT and K_i values of more than 10 000 nM both at the DAT and NET.[31] Furthermore, these SAR studies revealed that the selectivity of such compounds for the individual transporters could be tuned through structural modifications to its pharmacophoric group. For example, the biphenylyl analogue **3** is a potent NET-selective inhibitor with a K_i value of 12 nM and about 50-fold selectivity over both the SERT and the DAT.[30] More recently, compound **3** has been investigated by others as a new positron emission tomography (PET) imaging agent displaying good brain uptake in both rats and baboons and a certain degree of selectivity for the NET in vivo.[33]

A growing body of evidence has shown that norepinephrine plays an important role in the central nervous system and, although the exact mechanism still remains unknown, could be involved in a variety of psychiatric disorders.[34−38] For example, reboxetine is a relatively selective NET inhibitor that has demonstrated efficacy in depression and panic disorders.[34,38] Even the broad therapeutic efficacy of paroxetine, which is generally considered to be a selective SERT inhibitor, may result in part from its action on the NET in the treatment of depression, panic disorder, social anxiety disorder, and posttraumatic stress disorder.[39] Biaryls and their homologues represent an important class of organic compounds and comprise important partial structures of natural products, polymers, advanced materials, liquid crystals, supermolecules, and pharmaceuticals.[40] To gain a better understanding of the structural features required for high activity and selectivity at norepinephrine transporters, we have synthesized and evaluated the transporter activities of a series of (*Z*)-9-(biarylylmethylene)-7-azatricyclo[4.3.1.$0^{3,7}$]decanes (**4**) (Chart 2) in a continuation of our previous work.

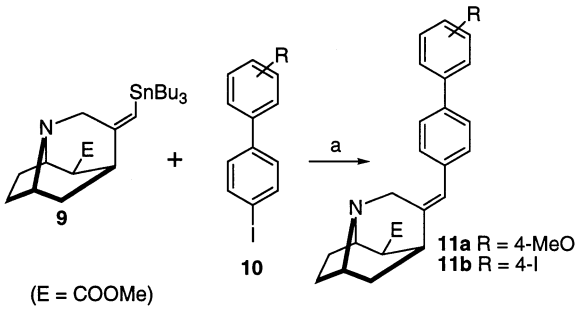
Chemistry. Scheme 1 outlines our synthetic approach to the construction of the tricyclic skeleton

Scheme 1[a]



[a] Reagents and conditions: (a) Saturated $NaHCO_3$, 96%; (b) $CH_3CH(Cl)OCOCl$, 1,2-dichloroethane, reflux, 7 h, 91%; (c) MeOH, reflux, 8 h, 90%; (d) propargyl bromide, K_2CO_3, MeCN, reflux, 24 h, 88%; (e) 2 N HCl, reflux, 16 h; (f) $POCl_3$, reflux, 2 h; (g) MeOH, −78 °C to room temperature, 84% (3 steps); (h) AIBN, *n*-Bu_3SnH, benzene, reflux, 16 h, 75%.

Scheme 2[a]

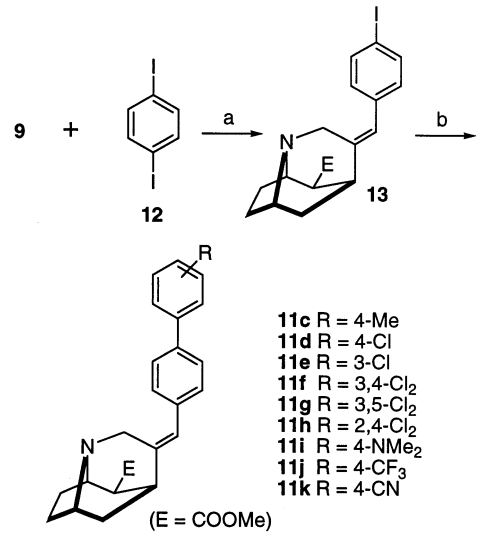


[a] Reagents and conditions: (a) $Pd_2(dba)_3$, Ph_3As, CuI, DMF, 45 °C.

starting from cocaine hydrochloride (**5**).[30] Thus, norcocaine (**6**) was prepared by *N*-demethylation of cocaine with α-chloroethyl chloroformate.[41] The subsequent alkylation with propargyl bromide afforded *N*-propargylnorcocaine (**7**), which was then subjected to saponification, dehydration, and reesterification to provide *N*-propargylnoranhydroecgonine methyl ester (**8**) in good yield. The key step, the radical cyclization of enyne **8** using syringe pump methodology, produced predominantly the *Z*-isomer of vinyl stannane **9**.[42,43]

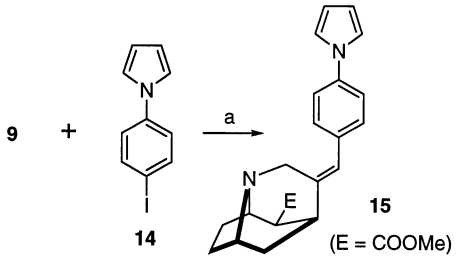
We first modified the substituents on the biphenylyl group while leaving the ester moiety intact. As illustrated in Scheme 2, biaryl analogues **11a**,**b** were prepared by Stille coupling of tin precursor **9** with the corresponding biarylyl iodides in moderate yields. Because of the limited availability of biarylyl iodides, the remaining compounds **11** were prepared in a stepwise manner with the use of a Suzuki coupling in the second step as described in Scheme 3. The key intermediate **13** was obtained by coupling of the vinyl stannane **9** with 1,4-diiodobenzene (**12**) in the presence of $Pd_2(dba)_3$ and Ph_3As in a yield of 57%. The subsequent Suzuki coupling of the iodide **13** with substituted phenylboronic acids in the presence of $Pd(PPh_3)_4$ as the catalyst provided the desired compounds **11c**−**k** in moderate yields. In the course of our synthetic studies, we optimized the Stille coupling conditions for the conformationally constrained tropane substrates and found that the yields were significantly improved by utilizing the catalyst system with the ligand Ph_3As instead of $(o\text{-}CH_3C_6H_4)_3P$ that was previously used.[30−32]

Scheme 3[a]



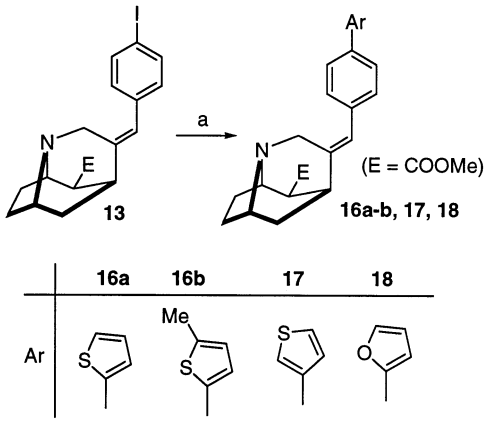
[a] Reagents and conditions: (a) $Pd_2(dba)_3$, Ph_3As, CuI, DMF, 45 °C, 16 h; (b) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, toluene/H_2O, reflux, 31 h.

Scheme 4[a]



[a] Reagents and conditions: (a) $Pd_2(dba)_3$, Ph_3As, CuI, DMF, 45 °C.

Scheme 5[a]

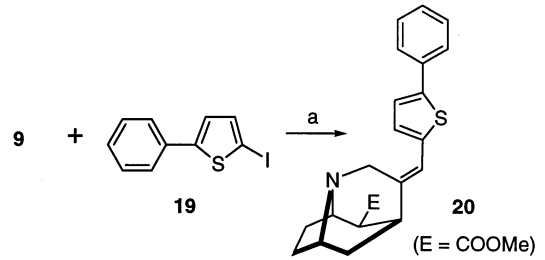


[a] Reagents and conditions: (a) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, toluene/H_2O, reflux.

To investigate the effect of changing Ar^2 to a heteroaromatic ring, compound **15** was prepared by coupling of the vinyl stannane **9** with 1-(4-iodophenyl)-pyrrole (**14**) (Scheme 4). Compounds **16a**,**b**, **17**, and **18** were obtained by Suzuki coupling of the iodide **13** with 2- or 3-thienylboronic acids or 2-furylboronic acid (Scheme 5).

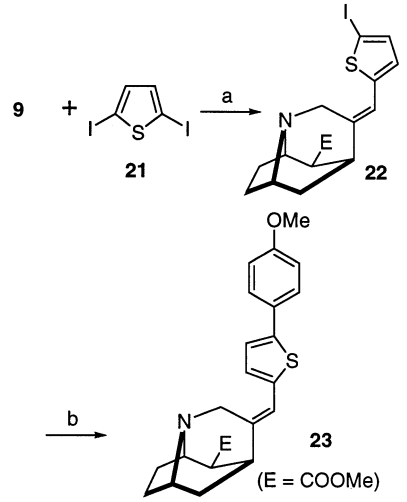
The biaryl analogues **20** and **23** with a thiophene moiety as Ar^1 were synthesized in similar fashion from the iodides **19** or **22** (Schemes 6 and 7).

Scheme 6[a]



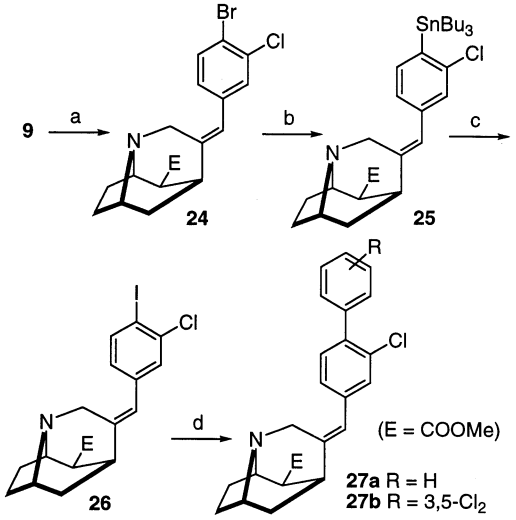
[a] Reagents and conditions: (a) $Pd_2(dba)_3$, Ph_3As, CuI, DMF, 45 °C.

Scheme 7[a]



[a] Reagents and conditions: (a) $Pd_2(dba)_3$, Ph_3As, CuI, DMF, 45 °C; (b) 4-methoxyphenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, toluene/H_2O, reflux.

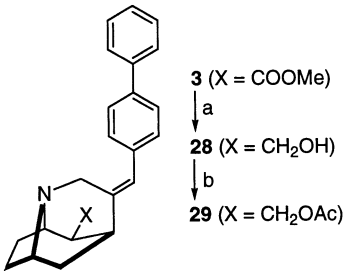
Scheme 8[a]



[a] Reagents and conditions: (a) 1-bromo-2-chloro-4-iodobenzene, $Pd_2(dba)_3$, Ph_3As, CuI, DMF, 45 °C, 24 h; (b) Bu_6Sn_2, $Pd(PPh_3)_4$, toluene, reflux, 9 h; (c) I_2, CH_2Cl_2, room temperature, 15 h; (d) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, toluene/H_2O, reflux, 31 h.

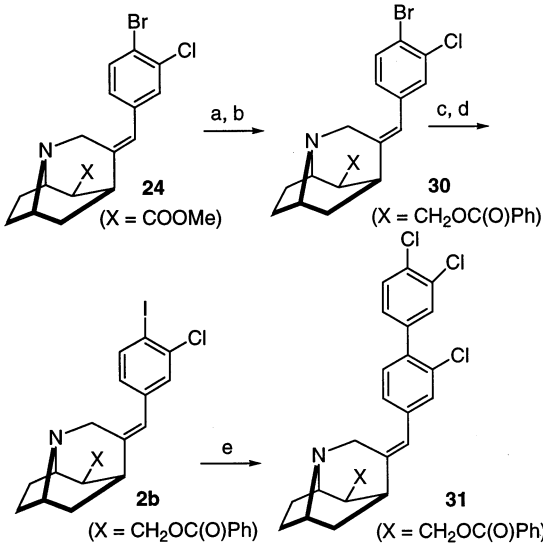
The modification of Ar^1 with different substituents was somewhat limited by the availability of the appropriate precursors. As illustrated in Scheme 8, compounds **27a**,**b** with a 3-chloro substituent on Ar^1 were obtained by coupling with the iodide **26**, which in turn was derived from the corresponding bromide **24** by a two-step conversion.

Scheme 9[a]



[a] Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C to room temperature, 3 h; (b) Ac_2O, pyridine, DMAP, room temperature, 2 h.

Scheme 10[a]



[a] Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C to room temperature, 3 h; (b) benzoyl chloride, pyridine, DMAP, room temperature, 2 h; (c) Bu_6Sn_2, $Pd(PPh_3)_4$, toluene, reflux, 9 h; (d) I_2, CH_2Cl_2, room temperature, 15 h; (e) 3,4-dichlorophenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, toluene/H_2O, reflux.

To prepare the inverse ester **29** (Scheme 9), the methyl ester **3** was reduced with $LiAlH_4$ to give the alcohol **28**, which was further treated with acetic anhydride. For the synthesis of the benzoate **31**, the methyl ester **24** was similarly converted to the benzoate **30**, which was then subjected to the transformation to the iodide **2b**,[31] followed by Suzuki coupling as above (Scheme 10).

Results and Discussion

All final compounds were tested for their ability to inhibit high-affinity reuptake of DA, 5-HT, and NE into nerve endings (synaptosomes) prepared from brain regions enriched in transporters for these biogenic amine neurotransmitters.[31,44] The protocols used are described in the Experimental Section. The uptake data and selectivity profiles (based on the K_i values) of all the new compounds prepared are listed in Table 1. For comparison purposes, data for compound **3** from our preliminary paper[30] and for (−)-cocaine are also included. All data are mean values ± SEM from two to four independent experiments, each consisting of six drug concentrations in triplicate.

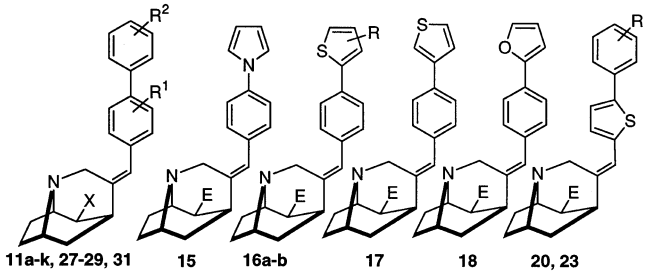
To explore the effect of modifications of Ar^2 in lead compound **3** with different substituents on activity and selectivity, we synthesized and examined compounds **11a**−**k**. Among the compounds with an electron-donating substituent, potency in inhibition of NET reuptake decreases in the sequence 4-Me > 4-MeO > 4-NMe_2, and all of these compounds display a fairly good activity at and selectivity for the NET. The 4-methoxy analogue **11a** exhibits a good potency (K_i = 39 nM) at the NET and selectivity vs the SERT (100-fold) and the DAT (20-fold). The 4-methyl analogue **11c** has a better potency (K_i = 23 nM) at the NET and a 50-fold selectivity vs the SERT and 10-fold vs the DAT. Compound **11i**, containing a bulky 4-(dimethylamino) substituent, displays reduced activity at the NET (K_i = 58 nM) with a 20-fold selectivity vs both the SERT and DAT. Among the compounds with an electron-withdrawing substituent, activity to the NET decreases in the sequence 3-Cl > 4-CN > 4-I > 4-Cl > 4-CF_3. The 3-chloro analogue **11e** exhibits a good potency (K_i = 17 nM) at the NET and a 13-fold selectivity vs the SERT. The 4-cyano analogue **11k** displays a K_i of 32 nM at the NET and a 25-fold selectivity vs the SERT. Both of these two compounds also have a moderate to good activity to the DAT. The disubstituted analogues **11f**−**h** exhibit a moderate to high activity at the NET. The 3,4-dichloro derivative **11f** has a remarkable potency (K_i = 9.7 nM) at the NET and a 25-fold selectivity vs both the SERT and the DAT. It is interesting that the 3,4-dichlorophenyl substitution pattern also led to one of the most DAT-active compounds (IC_{50} = 0.79 nM) in the WIN series[45] and one of the most SERT-active analogues (K_i = 1.6 nM) in the conformationally constrained tricyclic tropane series.[30]

To investigate the effect of using heteroaromatic rings, such as pyrrolyl, thienyl, and furyl, as the group Ar^2, we synthesized and examined compounds **15**−**18**. Analogue **15**, containing a pyrrolyl ring, displays a good activity (K_i = 46 nM) at the NET and moderate selectivity vs the SERT (3-fold) and the DAT (12.5-fold). Analogues **16a**,**b** and **17**, containing a 2-thienyl, 5-methyl-2-thienyl, or 3-thienyl group, display a better potency ($K_i \approx$ 20 nM) at the NET and somewhat better selectivity vs the SERT (4−9-fold) and the DAT (8−33-fold). Compound **18** with a 2-furyl ring exhibits a high activity (K_i = 13.9 nM) at the NET and moderate selectivity vs the SERT (17-fold) and the DAT (7-fold). Compounds **20** and **23** containing a thiophene ring as the aromatic moiety Ar^1 were also explored. Analogue **20** displays a good potency (K_i = 13.5 nM) for the NET and a lower selectivity vs the SERT (5-fold) and the DAT (12.5-fold) in comparison to compound **3**. However, analogue **23** exhibits an improved activity (K_i = 10.3 nM) at the NET and a fairly good selectivity vs the SERT (50-fold) and the DAT (37-fold).

As mentioned above, the introduction of a 3-chloro substituent into Ar^2 resulted in the discovery of **11e**, a NET ligand with good potency (K_i = 17.5 nM). However, both of the compounds **27a** and **27b** with a 3-chloro substituent in Ar^1 display a dramatically decreased activity at the NET, and their selectivity profiles switch to selectivity for the SERT vs NET and DAT.

To investigate the influence of the ester group in the biaryl analogues on transporter potency and selectivity, we converted compound **3** into the alcohol **28** and the inverted ester **29**. In comparison to the methyl ester **3**,

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



compd	substituent	[^{3}H]DA uptake K_i (nM)	[^{3}H]5-HT uptake K_i (nM)	[^{3}H]-NE uptake K_i (nM)	uptake ratio (based on K_i) 5-HT/DA	NE/DA	NE/5-HT
cocaine		423 ± 147	155 ± 0.4	108 ± 3.5	0.37	0.26	0.7
3[b]		477 ± 81	614 ± 105	12 ± 1	1.29	0.02	0.02
11a	R^1 = H, R^2 = 4-MeO X = COOMe	841 ± 85	3394 ± 598	39 ± 7	4.04	0.05	0.01
11b	R^1 = H, R^2 = 4-I X = COOMe	377 ± 53	660 ± 87	114 ± 31	1.75	0.30	0.44
11c	R^1 = H, R^2 = 4-Me X = COOMe	214 ± 5	1489 ± 142	22.7 ± 2.1	6.97	0.11	0.02
11d	R^1 = H, R^2 = 4-Cl X = COOMe	417 ± 25	1260 ± 99	739 ± 148	3.03	1.77	0.59
11e	R^1 = H, R^2 = 3-Cl X = COOMe	89 ± 12	213 ± 51	17.5 ± 2.2	2.4	0.20	0.08
11f	R^1 = H, R^2 = 3, 4-Cl_2 X = COOMe	236 ± 76	239 ± 37	9.7 ± 2.7	1.01	0.04	0.04
11g	R^1 = H, R^2 = 3, 5-Cl_2 X = COOMe	106 ± 14	384 ± 59	61 ± 6	3.62	0.58	0.16
11h	R^1 = H, R^2 = 2, 4-Cl_2 X = COOMe	1595 ± 201	393 ± 18	466 ± 103	0.25	0.29	1.19
11i	R^1 = H, R^2 = 4-NMe_2 X = COOMe	1053 ± 107	1002 ± 60.4	57.9 ± 0.65	0.95	0.05	0.06
11j	R^1 = H, R^2 = 4-CF_3 X = COOMe	3125 ± 0.01	2215 ± 52	1146 ± 185	0.71	0.37	0.52
11k	R^1 = H, R^2 = 4-CN X = COOMe	47 ± 6.6	909 ± 85	32.4 ± 1.2	19.3	0.69	0.04
15	E = COOMe	568 ± 97	149 ± 25	45.9 ± 10.5	0.26	0.08	0.31
16a	R = H, E = COOMe	155 ± 16	73 ± 5	19.8 ± 1.4	0.47	0.13	0.27
16b	R = 5-Me, E = COOMe	674 ± 7	200 ± 10	22.5 ± 4.6	0.30	0.03	0.11
17	E = COOMe	277 ± 48	145 ± 33	20.5 ± 2.8	0.52	0.07	0.14
18	E = COOMe	98 ± 3	248 ± 33	13.9 ± 0.7	2.54	0.14	0.06
20	R = H, E = COOMe	179 ± 19	71 ± 5	13.5 ± 2.0	0.40	0.08	0.19
23	R = 4-MeO, E = COOMe	371 ± 11	531 ± 51	10.3 ± 0.5	1.43	0.03	0.02
27a	R^1 = 3-Cl, R^2 = H X = COOMe	4259 ± 307	366 ± 35	991 ± 139	0.09	0.23	2.71
27b	R^1 = 3-Cl, R^2 = 3, 5-Cl_2 X = COOMe	8742 ± 1843	2771 ± 185	>10000	0.32	N/T	N/T
28	R^1 = H, R^2 = H X = CH_2OH	1298 ± 6	1544 ± 242	183 ± 8	1.19	0.14	0.12
29	R^1 = H, R^2 = H X = CH_2OAc	165 ± 2	46 ± 10	57± 4	0.28	0.35	1.24
31	R^1 = 3-Cl, R^2 = 3, 4-Cl_2 X = $CH_2OC(O)Ph$	5643 ± 332	956 ± 81	>10000	0.17	N/T	N/T

[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. [b] Data taken from ref 30.

a dramatic loss in activity was observed for alcohol **28**, whereas conversion into the inverse ester **29** leads to a significant gain in activity with a favorable SERT selectivity vs NET and DAT. Biaryl analogue **31** with a benzoyloxymethyl moiety derived from the highly potent and selective SERT ligand **2b** displays no NET activity and a dramatically reduced activity at the SERT. The methyl ester group would thus appear to be a critical element for NET activity; however, we have not fully explored all possible chemical modifications at this site.

In summary, a number of conformationally constrained tricyclic tropane derivatives, (*Z*)-9-(biarylylmethylene)-7-azatricyclo[4.3.1.0^{3,7}]decanes with the general structure **4**, have been synthesized and their transporter inhibitory activities explored. Most of the methyl esters exhibit moderate to high inhibitory activity at the NET but lower activities at the DAT and SERT. Among them, some potent and selective NET ligands, such as compounds **11a**, **11f**, and **23**, were identified. This selectivity profile differs from that of the monoaryl series, as most members of that series display excellent potency at and selectivity for the SERT.[31] This finding suggests that the different shape and size of the lipophilic recognition pocket that encompasses the aryl ring(s) of these tropanes are major determinants of a ligand's transporter activity at either the NET or the SERT. Some of the compounds in this series may also be valuable in sorting out the contribution of the individual transporters to cocaine's reinforcing properties.

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). Thin-layer chromatography (TLC) was performed using Merck silica gel 60F-254 plates. Column 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, Alfa Aesar, or Acros. Solvents were obtained from Fisher Scientific (or VWR) and were used without further purification unless otherwise noted. DMF (DriSolv) was obtained from EM Science. Iodide **10a** was obtained from the corresponding bromide.[46] 2-Iodo-5-phenylthiophene (**19**) was prepared from 2-phenylthiophene according to the reported method.[47] The key intermediates **13**, **22**, **26**, and **2b** were synthesized based on previously reported procedures,[31,32] while the catalyst system was optimized with the ligand Ph_3As instead of (o-$CH_3C_6H_4)_3P$.

Representative Procedure for Radical Cyclization. A solution of compound **8 (**1.00 g, 4.88 mmol**)** in deoxygenated anhydrous benzene (100 mL) was heated to 80 °C, and a solution of tri-*n*-butylstannane (2.75 mL, 10.2 mmol) and AIBN (824 mg, 4.92 mmol) in deoxygenated anhydrous benzene (50 mL) was then added via a syringe pump over 8 h. After stirring at 80 °C for a further 15 h, the mixture was cooled to room temperature and concentrated under reduced pressure. The residue was then subjected to column chromatography with hexanes/ethyl acetate (6/1 to 1/1) as the eluent to give the two isomers of **9**. (*Z*)-**9** was used as the starting material to synthesize the biaryl analogues.

Representative Procedure for Stille Coupling (Procedure A): (1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-[4-(4-Methoxyphenyl)-benzylidene]-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (11a). 4-Iodo-4′-methoxybiphenyl (**10a**) (50.5 mg, 0.16 mmol), triphenylarsine (26.6 mg, 0.087 mmol), $Pd_2(dba)_3$ (9.9 mg, 10.8 μmol), and CuI (16.5 mg, 0.087 mmol) were dissolved in anhydrous DMF (2 mL) and stirred at room temperature for 20 min under nitrogen. Then the stannane **9** (53.9 mg, 0.11 mmol) in DMF (2 mL) was added, and the mixture was stirred at 45−55 °C for 16 h. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel using ethyl acetate/triethylamine (98/2) or dichloromethane/methanol (98/2) as the eluents to provide the desired product **11a** as a white solid (17.8 mg, 42%). $[\alpha]^{25}_D$ +77.4° (*c* 0.36, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.41−1.59 (m, 3H), 2.04−2.28 (m, 3H), 2.42 (t, J = 3.3 Hz, 1H), 2.73 (dd, J = 3.0 and 5.8 Hz, 1H), 3.25−3.34 (m, 1H), 3.66 (s, 3H), 3.76−3.82 (m, 1H), 3.85 (s, 3H), 3.95 and 4.08 (ABq, J = 18.6 Hz, both d with J = 2.4 Hz, 2H), 6.16 (t, J = 2.7 Hz, 1H), 6.97 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 7.2 Hz, 2H), 7.51 (d, J = 8.1 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 32.0, 32.6, 36.6, 37.4, 48.4, 51.9, 52.4, 53.7, 55.3, 56.2, 114.2, 121.7, 126.6, 127.9, 128.8, 133.2, 135.8, 138.5, 140.5, 159.1, 174.3; MS *m*/*z* (%): 389 (M^+, 9), 330 (14), 207 (13), 165 (16), 148 (27), 138 (26), 91 (25), 83 (100), 68 (51). Anal. ($C_{25}H_{27}NO_3$·0.5HCl) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-[4-(4-Iodophenyl)benzylidene]-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (11b). Procedure A was followed giving the title compound as an oil. $[\alpha]^{25}_D$ +44.5° (*c* 0.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.40−1.58 (m, 3H), 2.06−2.30 (m, 3H), 2.45 (t, J = 3.0 Hz, 1H), 2.74 (dd, J = 3.3 and 5.7 Hz, 1H), 3.26−3.36 (m, 1H), 3.69 (s, 3H), 3.74−3.82 (m, 1H), 3.96 and 4.08 (ABq, J = 18.0 Hz, both d with J = 2.7 and 2.4 Hz, respectively, 2H), 6.19 (t, J = 2.7 Hz, 1H), 7.29 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.1 Hz, 2H), 7.78 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 32.0, 32.6, 36.5, 37.4, 48.4, 52.0, 52.4, 53.7, 56.3, 105.2, 121.5, 126.8, 128.8, 128.9, 133.2, 135.8, 137.8, 140.5, 142.4, 174.3; MS *m*/*z* (%): 485 (M^+, 15), 426 (19), 207 (8), 149 (26), 106 (9), 83 (100), 68 (37). Anal. ($C_{24}H_{24}INO_2$·0.33H_2O) C, H, N.

Representative Procedure for Suzuki Coupling (Procedure B): (1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-[4-(4-Methylphenyl)benzylidene]-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (11c). To a mixture of the iodide **13** (42 mg, 0.103 mmol) and $Pd(PPh_3)_4$ (5.9 mg, 0.005 mmol) in 1.0 mL of degassed toluene was added *p*-tolylboronic acid (15.3 mg, 0.113 mmol), followed by a solution of sodium carbonate (21.8 mg, 0.205 mmol) in 0.5 mL of water. After reflux at 110 °C for 31 h, the reaction mixture was cooled, diluted with $CHCl_3$, and washed with brine. The organic phase was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (preparative TLC) using ethyl acetate/triethylamine (10/1) and dichloromethane/methanol (95/5) as the eluents to provide the desired product **11c** as a white solid (19.0 mg, 50%). $[\alpha]^{25}_D$ +72.3° (*c* 0.92, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.42−1.60 (m, 3H), 2.02−2.30 (m, 3H), 2.39 (s, 3H), 2.44 (t, J = 2.7 Hz, 1H), 2.74 (dd, J = 3.0 and 5.7 Hz, 1H), 3.28−3.36 (m, 1H), 3.66 (s, 3H), 3.78−3.84 (m, 1H), 3.98 and 4.10 (ABq, J = 18.6 Hz, both d with J = 2.4 Hz, 2H), 6.18 (t, J = 2.7 Hz, 1H), 7.23 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.1, 31.9, 32.5, 36.5, 37.3, 48.3, 51.9, 52.3, 53.8, 56.3, 121.8, 126.7, 126.8, 127.3, 128.6, 128.8, 129.5, 131.9, 137.0, 137.8, 174.2; MS *m*/*z* (%): 373 (M^+, 23), 314 (31), 277 (64), 199 (15), 156 (15), 83 (100), 68 (33), 51 (30). Anal. ($C_{25}H_{27}NO_2$·0.2HCl) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-[4-(4-Chlorophenyl)benzylidene]-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (11d). Procedure B was followed, giving the title compound as an oil. $[\alpha]^{25}_D$ +85.4° (*c* 0.68, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.44−1.58 (m, 3H), 2.05−2.28 (m, 3H), 2.43 (t, J = 3.3 Hz, 1H), 2.74 (dd, J = 3.0 and 5.6 Hz, 1H), 3.26−3.34 (m, 1H), 3.66 (s, 3H), 3.78−3.82 (m, 1H), 3.95 and 4.08 (ABq, J = 18.9 Hz, both d with J = 2.4 Hz, 2H), 6.17 (t, J = 3.0 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 32.0, 32.6, 36.5, 37.4, 48.4, 51.9, 52.4, 53.7, 56.3, 121.5, 126.9, 128.1, 128.8, 128.9, 133.3, 136.8, 137.6, 139.1, 141.3, 174.3; MS *m*/*z* (%): 393 (M^+, 24), 334 (49), 265 (10), 215 (44), 202

(45), 189 (42), 165 (37), 149 (100), 141 (46), 115 (30), 108 (47). Anal. ($C_{24}H_{24}ClNO_2$·0.25HCl) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-[4-(3-Chlorophenyl)benzylidene]-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (11e). Procedure B was followed, giving the title compound as an oil. $[\alpha]^{25}_D$ +47.2° (*c* 1.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$): *δ* 1.46−1.54 (m, 3H), 2.05−2.28 (m, 3H), 2.43 (t, *J* = 3.0 Hz, 1H), 2.73 (dd, *J* = 2.7 and 5.6 Hz, 1H), 3.28−3.34 (m, 1H), 3.66 (s, 3H), 3.78−3.82 (m, 1H), 3.96 and 4.10 (ABq, *J* = 19.2 Hz, both d with *J* = 2.4 Hz, 2H), 6.17 (t, *J* = 2.7 Hz, 1H), 7.27 (d, *J* = 8.7 Hz, 2H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.36 (dd, *J* = 7.5 and 7.8 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.58 (s, 1H); ^{13}C NMR ($CDCl_3$): *δ* 32.0, 32.6, 36.5, 37.4, 48.4, 51.9, 52.4, 53.7, 56.3, 121.5, 125.0, 127.0, 127.2, 127.5, 128.9, 130.0, 134.7, 137.1, 137.4, 141.5, 142.5, 174.3; MS *m*/*z* (%): 393 (M^+, 13), 334 (34), 215 (28), 202 (30), 189 (28), 167 (34), 149 (100), 141 (51), 115 (30), 108 (48). Anal. ($C_{24}H_{24}ClNO_2$·0.33H_2O) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-[4-(3,4-Dichlorophenyl)benzylidene]-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (11f). Procedure B was followed, giving the title compound as a white solid. $[\alpha]^{25}_D$ +80.6° (*c* 0.74, $CHCl_3$); ^{1}H NMR ($CDCl_3$): *δ* 1.42−1.58 (m, 3H), 2.04−2.28 (m, 3H), 2.43 (t, *J* = 3.0 Hz, 1H), 2.73 (dd, *J* = 2.7 and 5.7 Hz, 1H), 3.24−3.34 (m, 1H), 3.66 (s, 3H), 3.78−3.82 (m, 1H), 3.95 and 4.07 (ABq, *J* = 18.3 Hz, both d with *J* = 2.4 and 2.7 Hz, respectively, 2H), 6.16 (t, *J* = 2.7 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.42 (dd, *J* = 2.1 and 8.4 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$): *δ* 31.9, 32.5, 36.4, 37.4, 48.3, 51.9, 52.3, 53.7, 56.2, 121.3, 126.0, 126.9, 128.6, 128.9, 130.6, 131.2, 132.8, 136.2, 137.3, 140.6, 141.7, 174.2; MS *m*/*z* (%): 427 (M^+, 12), 368 (34), 215 (33), 202 (29), 189 (41), 184 (35), 166 (49), 148 (100), 141 (63), 120 (41), 106 (48). Anal. ($C_{24}H_{23}Cl_2NO_2$·0.1H_2O) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-[4-(3,5-Dichlorophenyl)benzylidene]-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (11g). Procedure B was followed, giving the title compound as an oil. $[\alpha]^{25}_D$ +76.9° (*c* 0.38, $CHCl_3$); ^{1}H NMR ($CDCl_3$): *δ* 1.43−1.58 (m, 3H), 2.04−2.28 (m, 3H), 2.44 (t, *J* = 3.0 Hz, 1H), 2.73 (dd, *J* = 2.7 and 5.6 Hz, 1H), 3.26−3.34 (m, 1H), 3.66 (s, 3H), 3.78−3.81 (m, 1H), 3.94 and 4.08 (ABq, *J* = 19.2 Hz, both d with *J* = 2.4 Hz, 2H), 6.17 (t, *J* = 2.7 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.32 (dd, *J* = 1.8 and 2.1 Hz, 1H), 7.45 (d, *J* = 2.1 Hz, 2H), 7.51 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$): *δ* 32.0, 32.6, 36.5, 37.4, 48.4, 51.9, 52.3, 53.7, 56.3, 121.3, 125.3, 126.9, 127.0, 129.0, 135.3, 136.0, 137.7, 142.1, 143.7, 174.3; MS *m*/*z* (%): 427 (M^+, 27), 368 (53), 215 (43), 202 (38), 189 (53), 184 (35), 166 (46), 148 (100), 141 (61), 120 (40), 108 (53), 106 (46). Anal. ($C_{24}H_{23}Cl_2NO_2$·0.4HCl) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-[4-(2,4-Dichlorophenyl)benzylidene]-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (11h). Procedure B was followed, giving the title compound as an oil. $[\alpha]^{25}_D$ +79.4° (*c* 0.80, $CHCl_3$); ^{1}H NMR ($CDCl_3$): *δ* 1.42−1.59 (m, 3H), 2.04−2.26 (m, 3H), 2.43 (t, *J* = 3.3 Hz, 1H), 2.73 (dd, *J* = 2.7 and 5.6 Hz, 1H), 3.26−3.34 (m, 1H), 3.67 (s, 3H), 3.78−3.82 (m, 1H), 3.94 and 4.08 (ABq, *J* = 18.9 Hz, both d with *J* = 2.4 Hz, 2H), 6.18 (t, *J* = 2.7 Hz, 1H), 7.24−7.29 (m, 4H), 7.37 (d, *J* = 8.7 Hz, 2H), 7.48 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): *δ* 32.0, 32.6, 36.6, 37.4, 48.4, 51.9, 52.3, 53.7, 56.3, 121.5, 127.2, 128.1, 129.4, 129.7, 132.0, 133.2, 133.6, 136.0, 137.0, 138.7, 141.7, 174.3; MS *m*/*z* (%): 427 (M^+, 7), 368 (11), 215 (31), 202 (24), 189 (36), 179 (12), 166 (26), 148 (100), 141 (54), 120 (35), 108 (48), 106 (37). Anal. ($C_{24}H_{23}Cl_2NO_2$·0.5H_2O) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-[4-[4-(Dimethylamino)phenyl]benzylidene]-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (11i). Procedure B was followed, giving the title compound as an oil. $[\alpha]^{25}_D$ +97.1° (*c* 0.18, $CHCl_3$); ^{1}H NMR ($CDCl_3$): *δ* 1.42−1.58 (m, 3H), 2.04−2.26 (m, 3H), 2.42 (t, *J* = 3.0 Hz, 1H), 2.72 (dd, *J* = 2.7 and 5.6 Hz, 1H), 2.99 (s, 6H), 3.26−3.34 (m, 1H), 3.65 (s, 3H), 3.76−3.82 (m, 1H), 3.96 and 4.08 (ABq, *J* = 18.0 Hz, both d with *J* = 2.4 Hz, 2H), 6.15 (t, *J* = 3.0 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$): *δ* 31.8, 32.4, 36.4, 37.2, 40.6, 48.2, 52.0, 52.3, 53.9, 56.3, 112.7, 122.2, 126.1, 127.5, 128.8, 132.0, 132.1, 134.9, 139.1, 149.9, 174.0; MS *m*/*z* (%): 403 (M^+ + 1, 49), 402 (M^+, 21), 344 (20), 320 (72), 262 (27), 235 (46), 201 (85), 171 (100), 165 (52), 150 (47), 130 (89), 117 (75), 105 (56). Anal. ($C_{26}H_{30}N_2O_2$·0.6HCl) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-[4-[4-(Trifluoromethyl)phenyl]benzylidene]-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (11j). Procedure B was followed, giving the title compound as a white solid. $[\alpha]^{25}_D$ +55.9° (*c* 0.32, $CHCl_3$); ^{1}H NMR ($CDCl_3$): *δ* 1.44−1.60 (m, 3H), 2.06−2.26 (m, 3H), 2.45 (t, *J* = 3.0 Hz, 1H), 2.75 (dd, *J* = 3.0 and 5.8 Hz, 1H), 3.26−3.36 (m, 1H), 3.67 (s, 3H), 3.80−3.84 (m, 1H), 3.96 and 4.10 (ABq, *J* = 18.0 Hz, both d with *J* = 2.4 and 2.7 Hz, respectively, 2H), 6.19 (t, *J* = 3.0 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.7 Hz, 2H), 7.69 (br s, 4H); ^{13}C NMR ($CDCl_3$): *δ* 32.0, 32.6, 36.5, 37.4, 48.4, 51.9, 52.3, 53.7, 56.2, 121.4, 125.6, 125.7, 127.1, 127.2, 128.9, 130.1, 137.4, 141.9, 174.3 (CF_3 and the adjacent aromatic C not observed); MS *m*/*z* (%): 427 (M^+, 52), 368 (100), 299 (18), 285 (24), 259 (43), 215 (42), 202 (36), 189 (39), 174 (64), 164 (66), 152 (46), 141 (60), 115 (42), 106 (46). Anal. ($C_{25}H_{24}F_3NO_2$·0.5H_2O) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-[4-(4-Cyanophenyl)benzylidene]-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (11k). Procedure B was followed, giving the title compound as an oil. $[\alpha]^{25}_D$ +73.6° (*c* 0.37, $CHCl_3$); ^{1}H NMR ($CDCl_3$): *δ* 1.44−1.60 (m, 3H), 2.06−2.26 (m, 3H), 2.45 (t, *J* = 3.3 Hz, 1H), 2.74 (dd, *J* = 3.3 and 5.8 Hz, 1H), 3.24−3.34 (m, 1H), 3.66 (s, 3H), 3.78−3.82 (m, 1H), 3.95 and 4.08 (ABq, *J* = 18.9 Hz, both d with *J* = 2.4 and 2.7 Hz, respectively, 2H), 6.18 (t, *J* = 3.0 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.7 Hz, 2H), 7.72 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$): *δ* 32.0, 32.6, 36.4, 37.4, 48.4, 51.9, 52.3, 53.7, 56.3, 110.7, 119.0, 121.3, 127.1, 127.4, 129.0, 132.6, 136.6, 137.9, 142.4, 145.1, 174.3; MS *m*/*z* (%): 384 (M^+, 60), 325 (100), 256 (21), 242 (29), 227 (29), 216 (54), 192 (50), 162 (76), 152 (36), 141 (66), 115 (47), 106 (43). Anal. ($C_{25}H_{24}N_2O_2$·2/3HCl) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-[4-(1-Pyrrolyl)benzylidene]-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (15). Procedure A was followed, giving the title compound as an oil. $[\alpha]^{25}_D$ +68.3° (*c* 0.21, $CHCl_3$); ^{1}H NMR ($CDCl_3$): *δ* 1.45−1.58 (m, 3H), 2.02−2.28 (m, 3H), 2.43 (t, *J* = 3.0 Hz, 1H), 2.72 (dd, *J* = 3.0 and 5.7 Hz, 1H), 3.24−3.34 (m, 1H), 3.66 (s, 3H), 3.78−3.82 (m, 1H), 3.92 and 4.06 (ABq, *J* = 19.5 Hz, both d with *J* = 2.4 Hz, 2H), 6.14 (t, *J* = 3.0 Hz, 1H), 6.34 (dd, *J* = 2.1 and 2.4 Hz, 2H), 7.09 (dd, *J* = 2.1 and 2.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): *δ* 32.0, 32.6, 36.5, 37.3, 48.3, 51.9, 52.3, 53.7, 56.3, 110.4, 119.2, 120.3, 121.1, 129.5, 135.6, 137.0, 157.6, 174.2; MS *m*/*z* (%): 348 (M^+, 50), 289 (47), 220 (11), 206 (9), 180 (19), 152 (13), 144 (28), 115 (16), 83 (100), 68 (50), 41 (50). Anal. ($C_{22}H_{24}N_2O_2$·0.75HCl) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-[4-(2-Thienyl)benzylidene]-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (16a). Procedure B was followed, giving the title compound as a white solid. $[\alpha]^{25}_D$ +78.1° (*c* 0.80, $CHCl_3$); ^{1}H NMR ($CDCl_3$): *δ* 1.42−1.60 (m, 3H), 2.02−2.08 (m, 1H), 2.08−2.30 (m, 2H), 2.45 (t, *J* = 3.3 Hz, 1H), 2.74 (dd, *J* = 2.7 and 5.6 Hz, 1H), 3.28−3.36 (m, 1H), 3.68 (s, 3H), 3.78−3.84 (m, 1H), 3.90 and 4.01 (ABq, *J* = 18.9 Hz, both d with *J* = 2.4 and 2.7 Hz, respectively, 2H), 6.16 (t, *J* = 2.7 Hz, 1H), 7.10 (dd, *J* = 3.6 and 3.3 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 3.3 Hz, 1H), 7.33 (d, *J* = 3.6 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$): *δ* 32.0, 32.6, 36.5, 37.4, 48.4, 51.9, 52.4, 53.7, 56.2, 121.5, 122.9, 124.7, 125.8, 126.8, 128.0, 128.8, 132.1, 136.6, 141.1, 174.3; MS *m*/*z* (%): 365 (M^+, 28), 306 (29), 277 (6), 197 (9), 152 (21), 83 (100), 68 (36). Anal. ($C_{22}H_{23}NO_2S$·0.2H_2O) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-[4-(5-Methyl-2-thienyl)benzylidene]-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (16b). Procedure B was followed, giving the title compound as a white solid. $[\alpha]^{25}_D$ +71.8° (*c* 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$): *δ* 1.42−1.60 (m, 3H), 2.04−2.30 (m, 3H), 2.42

(t, J = 3.0 Hz, 1H), 2.50 (s, 3H), 2.72 (dd, J = 3.0 and 5.6 Hz, 1H), 3.24−3.34 (m, 1H), 3.65 (s, 3H), 3.78−3.82 (m, 1H), 3.92 and 4.06 (ABq, J = 18.3 Hz, both d with J = 2.4 and 2.7 Hz, respectively, 2H), 6.12 (t, J = 2.7 Hz, 1H), 6.18 (m, 1H), 7.09 (d, J = 3.3 Hz, 1H), 7.18 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 15.5, 32.0, 32.6, 36.5, 37.4, 48.4, 51.9, 52.4, 53.7, 56.2, 121.6, 122.7, 125.3, 126.2, 128.8, 132.5, 136.1, 139.4, 140.7, 141.7, 174.3; MS *m*/*z* (%): 379 (M^+, 17), 320 (32), 237 (12), 211 (24), 187 (18), 160 (100), 152 (38), 141 (26), 118 (21), 106 (21). Anal. ($C_{23}H_{25}NO_2S$·1HCl·0.75H_2O) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-[4-(3-Thienyl)benzylidene]-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (17). Procedure B was followed, giving the title compound as a white solid. [α]$^{25}_D$ +58.5° (*c* 0.43, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.38−1.56 (m, 3H), 1.98−2.22 (m, 3H), 2.36 (t, J = 3.3 Hz, 1H), 2.66 (dd, J = 2.7 and 5.7 Hz, 1H), 3.18−3.28 (m, 1H), 3.58 (s, 3H), 3.72−3.76 (m, 1H), 3.88 and 4.01 (ABq, J = 18.6 Hz, both d with J = 2.1 and 2.4 Hz, respectively, 2H), 6.08 (t, J = 2.7 Hz, 1H), 7.16 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 0.9 Hz, 1H), 7.32 (dd, J = 2.4 and 0.9 Hz, 1H), 7.38 (dd, J = 2.4 and 0.9 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 32.0, 32.6, 36.5, 37.4, 48.4, 51.9, 52.4, 53.8, 56.3, 120.1, 121.7, 126.2, 126.4, 128.8, 133.6, 136.3, 140.6, 141.9, 174.3; MS *m*/*z* (%): 365 (M^+, 4), 307 (19), 223 (10), 197 (24), 173 (16), 165 (28), 153 (100), 141 (20), 115 (25), 106 (19). Anal. ($C_{22}H_{23}NO_2S$·0.75HCl) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-[4-(2-Furyl)benzylidene]-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (18). Procedure B was followed, giving the title compound as a white solid. [α]$^{25}_D$ +53.1° (*c* 0.31, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.48−1.62 (m, 3H), 2.08−2.38 (m, 3H), 2.45 (t, J = 3.0 Hz, 1H), 2.75 (dd, J = 2.7 and 5.6 Hz, 1H), 3.36−3.44 (m, 1H), 3.68 (s, 3H), 3.86−3.94 (m, 1H), 4.01 and 4.22 (ABq, J = 14.1 Hz, both d with J = 2.4 Hz, 2H), 6.16 (t, J = 3.0 Hz, 1H), 6.49 (dd, J = 1.8 and 3.3 Hz, 1H), 6.66 (dd, J = 0.6 and 3.3 Hz, 1H), 7.22 (d, J = 8.4 Hz, 2H), 7.48 (dd, J = 0.6 and 1.8 Hz, 1H), 7.64 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 31.6, 32.3, 36.2, 37.2, 48.0, 52.0, 52.3, 53.8, 56.3, 105.0, 111.7, 122.3, 123.8, 128.4, 128.7, 131.9, 136.6, 142.1, 153.9, 174.3; MS *m*/*z* (%): 349 (M^+, 38), 290 (34), 277 (100), 199 (17), 183 (16), 152 (23), 83 (88), 68 (35). Anal. ($C_{22}H_{23}NO_3$·0.6H_2O) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-[(5-Phenyl-2-thienyl)methylene]-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (20). Procedure A was followed, giving the title compound as a white solid. [α]$^{25}_D$ +90.6° (*c* 0.29, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.42−1.62 (m, 3H), 2.05−2.20 (m, 1H), 2.20−2.36 (m, 2H), 2.43 (t, J = 3.3 Hz, 1H), 2.76 (dd, J = 2.7 and 5.7 Hz, 1H), 3.40−3.45 (m, 1H), 3.59 (s, 3H), 3.80−3.86 (m, 1H), 3.96 (d, J = 2.4 Hz, 2H), 6.31 (t, J = 2.7 Hz, 1H), 6.79 (d, J = 3.9 Hz, 1H), 7.15 (d, J = 3.6 Hz, 1H), 7.20 (dd, J = 7.5 and 6.9 Hz, 1H), 7.30 (dd, J = 7.5 and 6.6 Hz, 2H), 7.51 (d, J = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 31.5, 32.1, 36.1, 36.4, 47.6, 52.1, 52.2, 53.6, 56.1, 115.7, 123.2, 125.6, 127.3, 127.4, 128.9, 134.2, 136.7, 139.8, 143.9, 173.6; MS *m*/*z* (%): 365 (M^+, 15), 306 (11), 149 (9), 97 (14), 83 (100), 68 (31), 57 (46). Anal. ($C_{22}H_{23}NO_2S$·0.2HCl) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-[2-[5-(4-Methoxyphenyl)thienyl]-methylene]-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (23). Procedure B was followed, using iodide **22** as the starting material and giving the title compound as a white solid. [α]$^{25}_D$ +83.3° (*c* 0.23, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.46−1.58 (m, 3H), 1.98−2.10 (m, 1H), 2.10−2.32 (m, 2H), 2.42 (t, J = 2.7 Hz, 1H), 2.72 (dd, J = 2.7 and 5.6 Hz, 1H), 3.25−3.34 (m, 1H), 3.65 (s, 3H), 3.76−3.80 (m, 1H), 3.83 (s, 3H), 3.88 and 3.98 (ABq, J = 18.6 Hz, both d with J = 2.4 and 2.7 Hz, respectively, 2H), 6.32 (t, J = 2.7 Hz, 1H), 6.81 (d, J = 3.6 Hz, 1H), 6.90 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 3.6 Hz, 1H), 7.62 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 32.0, 32.6, 36.5, 36.6, 48.5, 51.9, 52.3, 53.8, 55.3, 56.3, 114.3, 115.2, 122.1, 126.8, 126.9, 133.2, 139.4, 148.8, 148.9, 159.1, 174.1; MS *m*/*z* (%): 395 (M^+, 48), 336 (30), 255 (24), 228 (23), 203 (28), 184 (28), 168 (100), 151 (47), 115 (32), 108 (26). Anal. ($C_{23}H_{25}NO_3S$·0.1HCl) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(3-Chloro-4-phenylbenzylidene)-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (27a). Procedure B was followed, using iodide **26** as the starting material and giving the title compound as an oil. [α]$^{25}_D$ +73.8° (*c* 0.21, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.46−1.62 (m, 3H), 2.06−2.30 (m, 3H), 2.46 (t, J = 3.0 Hz, 1H), 2.75 (dd, J = 2.7 and 5.6 Hz, 1H), 3.26−3.38 (m, 1H), 3.70 (s, 3H), 3.76−3.84 (m, 1H), 3.96 and 4.10 (ABq, J = 18.0 Hz, both d with J = 2.4 Hz, 2H), 6.13 (t, J = 2.4 Hz, 1H), 7.16 (dd, J = 8.1 and 1.8 Hz, 1H), 7.29 (d, J = 6.6 Hz, 1H), 7.33 (d, J = 1.8 Hz, 1H), 7.36−7.48 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 32.0, 32.6, 36.4, 37.4, 48.3, 51.9, 52.3, 53.7, 56.3, 120.5, 126.7, 127.5, 128.0, 129.4, 129.7, 131.2, 132.4, 137.9, 138.0, 139.1, 142.9, 174.3; MS *m*/*z* (%): 393 (M^+, 8), 334 (19), 149 (17), 91 (11), 83 (97), 68 (36), 44 (100). Anal. ($C_{24}H_{24}ClNO_2$) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-[3-Chloro-4-(3,5-dichlorophenyl)-benzylidene]-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (27b). Procedure B was followed, using iodide **26** as the starting material and giving the title compound as an oil. [α]$^{25}_D$ +80.2° (*c* 0.19, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.44−1.62 (m, 3H), 2.02−2.28 (m, 3H), 2.45 (t, J = 2.7 Hz, 1H), 2.72 (dd, J = 5.6 and 2.7 Hz, 1H), 3.26−3.34 (m, 1H), 3.67 (s, 3H), 3.74−3.84 (m, 1H), 3.94 and 4.06 (ABq, J = 16.2 Hz, both d with J = 2.4 Hz, 2H), 6.11 (t, J = 2.7 Hz, 1H), 7.14 (dd, J = 7.8 and 1.8 Hz, 1H), 7.24 (d, J = 7.8 Hz, 1H), 7.27 (d, J = 1.8 Hz, 1H), 7.30 (d, J = 1.5 Hz, 1H), 7.31 (d, J = 1.8 Hz, 1H), 7.37 (dd, J = 1.5 and 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 32.0, 32.6, 36.3, 37.4, 48.3, 52.0, 52.2, 53.7, 56.3, 120.3, 125.4, 126.5, 126.8, 127.6, 128.0, 129.2, 129.8, 130.2, 130.9, 134.5, 141.8, 174.3; MS *m*/*z* (%): 461 (M^+, 11), 402 (23), 314 (23), 249 (32), 215 (67), 202 (43), 189 (64), 165 (100), 148 (95), 141 (92), 120 (58), 106 (75). Anal. ($C_{24}H_{22}Cl_3NO_2$·0.1HCl) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(4-Biphenylylmethylene)-10-(hydroxymethyl)-7-azatricyclo[4.3.1.0^{3,7}]decane (28). To a solution of **3** (34 mg, 0.0946 mmol) in 4 mL of THF was added portionwise $LiAlH_4$ (11 mg, 0.29 mmol), and the mixture was stirred for 3 h. The reaction mixture was 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 Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel using ethyl acetate/triethylamine (10/1) as the eluent to afford compound **28** as a white solid (29 mg, 92%). ^{1}H NMR ($CDCl_3$): δ 1.48−1.68 (m, 3H), 2.02−2.38 (m, 3H), 2.44 (dd, J = 5.6 and 2.7 Hz, 1H), 2.83 (dd, J = 5.7 and 3.0 Hz, 1H), 3.28−3.32 (m, 2H), 3.32−3.54 (m, 2H), 3.88 and 4.02 (ABq, J = 13.2 Hz, both d with J = 2.4 and 2.1 Hz, respectively, 2H), 6.25 (t, J = 2.7 Hz, 1H), 7.26−7.33 (m, 3H), 7.38−7.43 (m, 2H), 7.57−7.62 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 33.1, 33.6, 36.7, 38.3, 48.9, 50.1, 55.6, 59.8, 66.3, 123.5, 127.9, 128.0, 128.5, 130.0, 130.1, 137.9, 140.3, 141.0, 142.1; MS *m*/*z* (%): 331 (M^+, 44), 314 (16), 300 (48), 205 (22), 191 (18), 178 (18), 165 (33), 149 (17). Anal. ($C_{23}H_{25}NO$·0.33H_2O) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-10-(Acetoxymethyl)-9-(4-biphenylylmethylene)-7-azatricyclo[4.3.1.0^{3,7}]decane (29). To a solution of the alcohol **28** (22 mg, 0.0664 mmol) in pyridine (2 mL) and acetic anhydride (0.5 mL) was added DMAP (1 mg), and the reaction mixture was stirred for 2 h. After removal of the solvent under reduced pressure, the residue was dissolved in 20 mL of EtOAc and washed with a saturated solution of $NaHCO_3$ (2 × 10 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel using ethyl acetate/triethylamine (10/1) as the eluent to give compound **29** as a white solid (19.7 mg, 79%). [α]$^{25}_D$ +167.0° (*c* 0.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.42−1.60 (m, 3H), 1.74−1.84 (m, 1H), 2.05 (s, 3H), 2.02−2.28 (m, 3H), 2.38 (dd, J = 5.6 and 2.7 Hz, 1H), 2.86 (dd, J = 5.7 and 2.7 Hz, 1H), 3.28−3.36 (m, 1H), 3.92−4.08 (m, 4H), 6.18 (t, J = 2.7 Hz, 1H), 7.28−7.36 (m, 3H), 7.41−7.46 (m, 2H), 7.56−7.63 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 20.9, 32.2, 32.8, 36.0, 37.2, 45.3, 48.7, 53.9, 58.2, 67.2, 122.0, 126.9, 127.1, 127.2, 128.8, 136.4, 138.8, 140.6, 140.9, 171.1; MS *m*/*z*

(%): 373 (M^+, 31), 314 (90), 300 (25), 191 (12), 165 (15), 149 (28), 83 (51), 68 (49), 43 (100). Anal. ($C_{25}H_{27}NO_2 \cdot 0.2H_2O$) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-10-(Benzoyloxymethyl)-9-[3-chloro-4-(3,4-dichlorophenyl)benzylidene]-7-azatricyclo[4.3.1.0^{3,7}]-decane (31). Procedure B was followed, using iodide **2b** as the starting material and giving the title compound as an oil. $[\alpha]^{25}_D$ +115.6° (*c* 0.66, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.48−1.68 (m, 3H), 1.92−2.02 (m, 1H), 2.06−2.28 (m, 3H), 2.49 (dd, J = 5.6 and 2.4 Hz, 1H), 2.97 (dd, J = 5.7 and 2.4 Hz, 1H), 3.28−3.38 (m, 1H), 3.96 and 4.06 (ABq, J = 18.6 Hz, both d with J = 2.7 Hz, 2H), 4.16−4.30 (m, 2H), 6.14 (t, J = 2.7 Hz, 1H), 7.14 (dd, J = 8.1 and 1.8 Hz, 1H), 7.25 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 1.8 Hz, 1H), 7.41−7.60 (m, 6H), 7.64−7.71 (m, 1H), 8.02 (dd, J = 8.4 and 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 32.2, 32.8, 36.3, 37.1, 45.4, 48.7, 53.9, 58.2, 67.3, 126.8, 128.4, 128.6, 128.9, 129.5, 129.8, 130.0, 130.1, 130.9, 131.3, 131.8, 131.9, 131.9, 132.0, 132.1, 132.2, 133.0, 138.7, 138.9, 143.7, 166.4; MS *m*/*z* (%): 537 (M^+, 0.5), 416 (4), 277 (41), 199 (19), 183 (16), 155 (14), 152 (12), 105 (100). Anal. ($C_{30}H_{26}Cl_3NO_2 \cdot 0.8H_2O$) C, H, N.

Synaptosomal Uptake of [^{3}H]Dopamine, [^{3}H]5-Hydroxytryptamine, and [^{3}H]Norepinephrine. Compounds were tested as the free base. The effect of candidate compounds in antagonizing biogenic amine high-affinity uptake was determined as previously described.[17f] 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 17 500*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). 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 μM cocaine. Fluoxetine (10 μM) and desipramine (3 μM), 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 67 nM for [^{3}H]DA, 53 nM for [^{3}H]5-HT, and 54 nM for [^{3}H]NE. Even though uptake is a nonequilibrium process, K_i determinations are thought to be appropriate estimates of affinity between these compounds and the biogenic amine transporters because it is likely that the relatively long (45 min) period of incubation of the drug before addition of the [^{3}H] amine is adequate time for equilibrium between the test compound and the biogenic amine transporter to occur.

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