Synthesis and Ligand Binding of Nortropane Derivatives: N-Substituted 2β-Carbomethoxy-3β-(4′-iodophenyl)nortropane and *N*-(3-Iodoprop-(2*E*)-enyl)-2β-carbomethoxy-3β-(3′,4′-disubstituted phenyl)nortropane. New High-Affinity and Selective Compounds for the Dopamine Transporter

Patrick Emond, Lucette Garreau, Sylvie Chalon, Miriam Boazi, Mireille Caillet, Jacques Bricard, Yves Frangin, Laurent Mauclaire,† Jean-Claude Besnard, and Denis Guilloteau*

INSERM U316, Laboratoire de Biophysique Médicale et Pharmaceutique, 31 avenue Monge, 37200 Tours, France

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Two novel series of iodinated N-substituted analogs of 2β-carbomethoxy-3β-(4′-iodophenyl)-tropane (β-CIT) and *N*-(3-iodoprop-(2*E*)-enyl)-2β-carbomethoxy-3β-(3′,4′-disubstituted phenyl)-nortropane were synthesized. They were evaluated for their inhibitory properties on dopamine (DA_T), serotonin ($5\text{-}HT_T$), and norepinephrine (NE_T) transporters in rat brain homogenates using [^{3}H]GBR-12935, [^{3}H]paroxetine, and [^{3}H]nisoxetine as specific ligands. All new N-substituted analogs of β-CIT exhibited higher DA_T selectivity over both $5\text{-}HT_T$ and NE_T than β-CIT. Moreover compounds with the N-substituents propynyl (**6**), crotyl (**4**), 2-bromoprop-(2*E*)-enyl (**5**), and 3-iodoprop-(2*E*)-enyl (**3d**) showed similar to higher DA_T affinities than β-CIT (respectively 14, 15, 30, and 30 nM vs 27 nM). Compound **3d** was found to be the most selective DA_T agent of this series ($5\text{-}HT_T/DA_T = 32.0$ vs 0.1 for β-CIT). The *N*-(3-iodoprop-(2*E*)-enyl) chain linked to the tropane nitrogen was therefore maintained on the tropane structure, and phenyl substitution was carried out in order to improve DA_T affinity. K_i values of *N*-(3-iodoprop-(2*E*)-enyl)-2β-carbomethoxy-3β-(3′,4′-disubstituted phenyl)nortropanes revealed that phenyl, 4′-isopropyl, and 4′-*n*-propyl derivatives weakly inhibited specific binding to DA_T, whereas phenyl substitution with 4′-methyl (**3c**), 3′,4′-dichloro (**3b**), and 4′-iodo (**3d**) yielded high-DA_T reuptake agents with increased DA_T selectivity compared to β-CIT. These results demonstrate that the combination of a nitrogen and a phenyl substitution yields compounds with high affinity and selectivity for the dopamine transporter which are usable as SPECT markers for DA neurons.

Introduction

Nuclear imaging techniques are increasingly applied to the exploration of neurodegenerative diseases. In particular, it is known that Parkinson's disease is due to the degeneration of dopamine neurons. Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) exploration of the dopaminergic system are therefore of great interest to evaluate disease evolution and the therapeutic effects of treatments. Several iodinated cocaine derivatives have been synthesized for SPECT exploration and have been tested *in vitro* and *in vivo* for their monoamine transporter affinities.[1,2] These works have shown the lack of affinity and specificity for the dopamine transporter (DA_T) and the *in vivo* dissociation of these compounds from DA_T[1,2] that have led to several structure−activity relationship studies on cocaine derivatives.

Several structural modifications can be envisaged to improve biological properties of cocaine derivatives. In particular, different substituents attached at the 2, 3β, and nitrogen positions have been evaluated for their transporter−ligand interactions.[3,4] From these studies, it has been demonstrated that a substituent at the 2 position, and especially in the axial position, is required for high DA_T affinity.[3,5] Moreover, replacement of the carbomethoxy group can offer an increase in selectivity with only small effects on DA_T affinity.[6,7] By contrast, the nature of the substituent on the aromatic ring directly attached at the 3β position strongly influences the dopamine transporter−ligand recognition interaction. For example, the 4′-methyl-, 4′-halogeno-, and 3′,4′-dichlorophenyl analogs of 2β-carbomethoxy-3β-phenyltropane (β-CT) are more efficient for DA_T than the unsubstituted phenyl derivative.[3,8−11] These and more recent results demonstrate that an increase in electronic density at this part of the molecule is associated with high DA_T affinity.[10,12] For example, the well-known iodinated derivative used for SPECT brain exploration, 2β-carbomethoxy-3β-(4′-iodophenyl)tropane (β-CIT), has a high affinity for DA_T. However, this compound also has high affinity for the serotonin transporter ($5\text{-}HT_T$)[13,14] leading to the visualization of the hypothalamus and midbrain in addition to the striatum. Moreover, β-CIT has slow *in vivo* kinetics resulting in long delays in obtaining optimal striatum to cerebellum ratios which are necessary for quantitative methods.[15,16]

Recent structure−activity studies to improve specificity properties for DA_T have been performed to determine the effect of *N*-allyl[11] and *N*-haloalkyl[17,18] substitutions of tropane derivatives at the bridgehead nitrogen. They have demonstrated that these N-substituent pharmacophores do not affect DA_T affinity compared to their *N*-methyl analogs. Moreover, other authors have demonstrated that N-substitutions could increase the speci-

† Cis-Bio Industrie, 91192 Gif-sur-Yvette, France.
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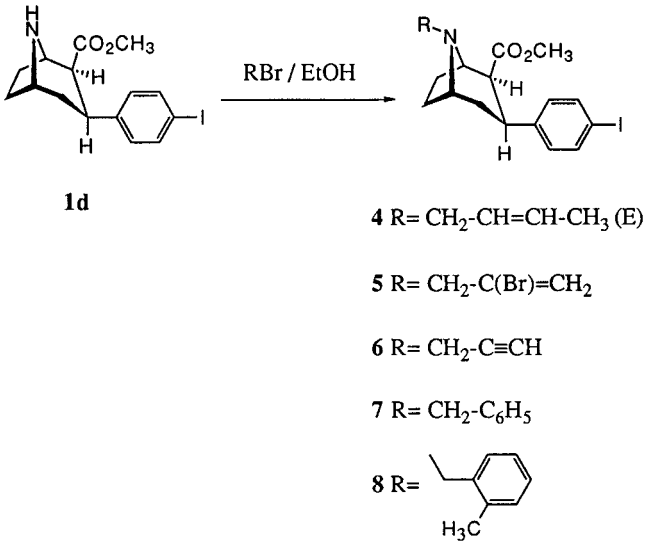
Scheme 1



ficity for DA_T.[19,20] This demonstrates that a steric space is available in this part of the molecule and suggests that *N*-alkynyl-, *N*-alkenyl-, and *N*-benzyltropane derivatives of nor-*β*-CIT are also attractive candidates for obtaining DA_T ligands with high affinity and specificity. In addition, as 3*β*-phenyl substitution plays an important role in transporter−ligand recognition interaction and as a *N*-(3-iodoprop-(2*E*)-enyl) chain may be labeled with iodine-123 for cerebral SPECT exploration, examination of the binding potency to monoamine transporters of several *N*-(3-iodoprop-(2*E*)-enyl)-2*β*-carbomethoxy-3*β*-(substituted phenyl)nortropane derivatives should be helpful to determine whether the combination of a nitrogen and aromatic substitution would yield highly selective DA_T reuptake agents.

The goals of the present investigations were firstly to synthesize and characterize a new series of N-modified derivatives of nor-*β*-CIT containing an alkynyl, alkenyl, or benzyl group for their *in vitro* monoamine transporter affinities. Secondly, we synthesized and tested a new series of *N*-(3-iodoprop-(2*E*)-enyl)-3*β*-(substituted phenyl)nortropanes for their *in vitro* monoamine transporter affinities which may yield highly specific dopamine reuptake agents.

Chemistry

N-Substituted nortropane derivatives **3a**−**f** and **4**−**8** were prepared by the general route described in Schemes 1 and 2. 2*β*-Carbomethoxy-3*β*-(substituted phenyl)-nortropanes **1a**−**f** were synthesized according to previously reported methods.[3,11,21] N-Alkylation reactions of nor-*β*-CIT (**1d**) were performed with the appropriate alkyl bromide in absolute ethanol to yield the corresponding *N*-alkyl-2*β*-carbomethoxy-3*β*-(4′-iodophenyl)-nortropanes **4**−**8** (Scheme 1).

N-(3-Iodoprop-(2*E*)-enyl)nortropane derivatives **3a**−**f** were obtained by iododestannylation of compounds **2a**−**f** by treatment with iodine in chloroform (Scheme 2). The first route to prepare tributyltin precursors **2a**−**f** consisted of obtaining *N*-prop-2-ynyl-2*β*-carbomethoxy-3*β*-(substituted phenyl)nortropanes as starting materials by reacting nortropane derivatives **1a**−**f** with propargyl bromide. As described in the literature,[19] we verified that the hydrostannylation of *N*-prop-2-ynylnortropane derivatives with $HSnBu_3$ in the presence of AIBN as catalyst supplied *E*-compounds **2a**−**f** with their *Z* isomers.

Another method of preparing tributyltin precursors **2a**−**f** from *N*-prop-2-ynylnortropane derivatives consisted of adding a Lipshutz reagent[22] ($Bu_3SnCuBuCNLi_2$) to the triple bond at −78 °C. For this reaction we obtained the *E* and gem isomers. Poor yields and difficult separation of the *E* isomer for both methods led us to choose a previously reported synthesis.[19] In this case tributyltin precursors **2a**−**f** were prepared by reacting 3-(tributylstannyl)prop-(2*E*)-enyl chloride (**11**) with nortropanes **1a**−**f** (Scheme 2). The alkylating agent **11** was prepared by chlorination of pure 3-(tri-*n*-butylstannyl)prop-(2*E*)-en-1-ol with triphenylphosphine and carbon tetrachloride.[19] The pure (*E*)-stannyl alcohol was obtained by hydrostannylation of propargyl alcohol[23] followed by flash chromatography separation using petroleum ether/ethyl acetate (9/1).

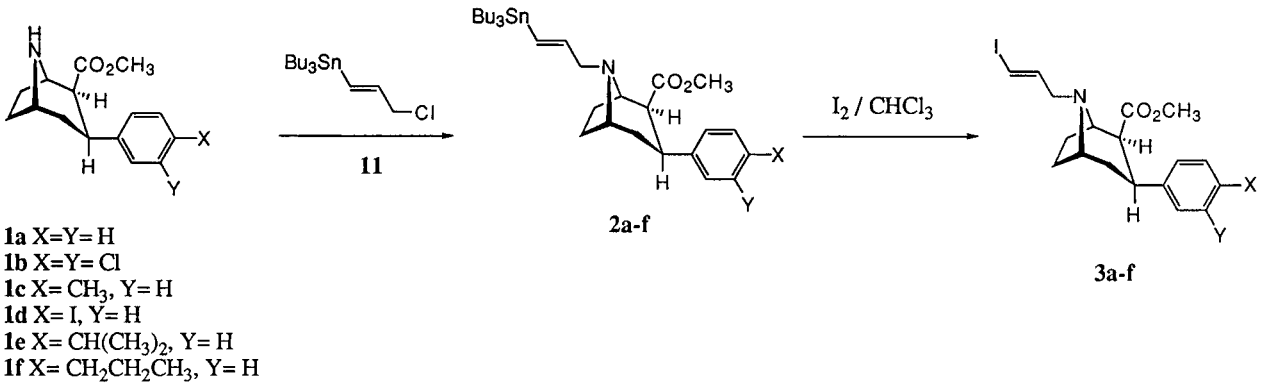
Results and Discussion

The affinities for monoamine transporters of the new compounds described here were determined by *in vitro* competitive binding assays. [^{3}H]GBR-12935, [^{3}H]paroxetine, and [^{3}H]nisoxetine were used as transporter ligands for DA_T, 5-HT_T, and NE_T sites, respectively. It is possible that GBR and tropane derivatives do not bind to exactly the same site on the DA_T; however, we and others[17,18] have used this ligand because it has high affinity for the DA_T and also high selectivity compared to serotonin and noradrenaline transporters. Moreover, the inhibition constants (K_i) of our tropane derivatives in competition with GBR permitted comparison of compounds for their displacement potency and thus for their affinity to the DA_T. The results are expressed as inhibition constants and are summarized in Tables 3 and 4 with compounds ranked in descending order of DA_T affinity.

The results for N-substituted analogs of nor-*β*-CIT (**1d**) and *N*-(3-iodoprop-(2*E*)-enyl)-2*β*-carbomethoxy-3*β*-(3′,4′-disubstituted phenyl)nortropanes were separated to dissociate the effects of different molecular changes on binding affinities. The monoamine transporter affinities of N-substituted *β*-CIT are given in Table 3, and the rank order of DA_T affinity was propynyl = crotyl > methyl = 2-bromoprop-(2*E*)-enyl = 3-iodoprop-(2*E*)-enyl > benzyl > *o*-methylbenzyl. In this series, two compounds (**6**, **4**) with a *N*-propynyl or a *N*-crotyl group were more potent than *β*-CIT for DA_T affinity (K_i = 14 and 15 nM vs 27 nM). Two others (**5**, **3d**) with a 2-bromoprop-(2*E*)-enyl or a 3-iodoprop-(2*E*)-enyl chain possessed similar binding potency to *β*-CIT. Replacement of the *N*-methyl function by a larger sterically bulky group such as benzyl (**7**) or *o*-methylbenzyl (**8**) led to compounds with moderate DA_T affinity (K_i = 42 and 93 nM). These observations and previous reports[11,18,19,24] concerning the synthesis and ligand binding of several N-substituted tropane derivatives support the conclusion that the DA_T can accommodate a steric group on the tropane nitrogen. Moreover, appropriate N-substitution could lead to tropane derivatives with similar to higher DA_T affinity than *β*-CIT itself (**3d**, **4**−**6**).

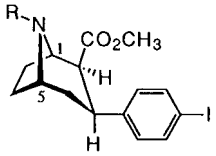
Although high DA_T affinity is necessary for the selection of a new iodinated DA_T ligand, DA_T selectivity

Scheme 2



1a X=Y= H
1b X=Y= Cl
1c X= CH_3, Y= H
1d X= I, Y= H
1e X= $CH(CH_3)_2$, Y= H
1f X= $CH_2CH_2CH_3$, Y= H

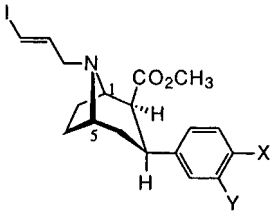
Table 1. Physical Properties of N-Substituted Analogs of *β*-CIT



			^{1}H NMR						
compd	R	molecular formula[a]	OCH_3	H-1	H-2	H-3	H-4α	H-4*β*	H-5
4	$-CH_2-CH=CH-CH_3$	$C_{19}H_{24}INO_2$	3.43	3.61	2.79−2.92	2.79−2.92	1.50−1.73	2.48	3.35
5	$-CH_2-C(Br)=CH_2$	$C_{18}H_{21}BrINO_2$	3.42	3.61	2.78−2.91	2.78−2.91	1.53−1.75	2.57	3.35
6	$-CH_2-C\equiv CH$	$C_{18}H_{20}INO_2$	3.45	3.47	2.84−2.91	2.84−2.91	1.54−1.68	2.51	3.42
7	$-CH_2-C_6H_5$	$C_{22}H_{24}INO_2$	3.28	3.24−3.52	2.74	2.89	1.54−1.74	2.58	3.24−3.52
8	$-CH_2-o(CH_3)C_6H_4$	$C_{23}H_{26}INO_2$	3.18	3.54	2.73	2.88	1.47−1.74	2.48	3.23−3.42

[a] All compounds were analyzed for C, H, N. The results agreed with the theoretical values to ±0.4% for each compound.

Table 2. Physical Properties of *N*-(3-Iodoprop-(2*E*)-enyl)-2*β*-carbomethoxy-3*β*-(3′,4′-disubstituted phenyl)nortropanes

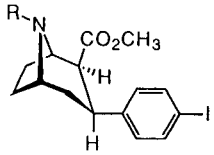


				^{1}H NMR					
compd	X	Y	molecular formula[a]	OCH_3	H-1	H-2, H-3, N-CH_2	H-4α	H-4*β*	H-5
3a	H	H	$C_{18}H_{22}INO_2$	3.44	3.56	2.75−2.98	1.58−1.69	2.55	3.41
3b	Cl	Cl	$C_{18}H_{20}Cl_2INO_2$	3.49	3.61	2.68−2.92	1.52−1.72	2.46	3.33
3c	CH_3	H	$C_{19}H_{24}INO_2$	3.45	3.58	2.76−2.95	1.51−1.70	2.53	3.41
3d	I	H	$C_{18}H_{21}I_2NO_2$	3.47	3.59	2.68−2.91	1.51−1.73	2.49	3.31
3e	$CH(CH_3)_2$	H	$C_{21}H_{28}INO_2$	3.45	3.57	2.68−2.95	1.56−1.73	2.54	3.31
3f	$CH_2CH_2CH_3$	H	$C_{21}H_{28}INO_2$	3.45	3.57	2.68−2.96	1.44−1.73	2.53	3.32

[a] All compounds were analyed for C, H, N. The results agreed with the theoretical values to ±0.4% for each compound.

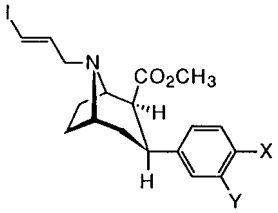
over both 5-HT_T and NE_T is also an important criterion in order to evaluate disease evolution or therapeutic effects by reuptake site quantification. As shown in Table 3, our results demonstrated that *β*-CIT has high 5-HT_T affinity (K_i = 3 nM), in agreement with previous reports.[13,14] By contrast, all the new N-substituted derivatives of *β*-CIT have weak 5-HT_T affinities. Compared to *β*-CIT (5-HT_T/DA_T = 0.1), DA_T selectivity was increased 21-fold for compound **7** (5-HT_T/DA_T = 2.3) to 290-fold for compound **3d** (5-HT_T/DA_T = 32.0). The same type of result was found for NE_T affinities. Although *β*-CIT has weak NE_T inhibition, its NE_T affinity value was the highest of the series, K_i = 80 nM, thus being the least DA_T selective agent. The N-substituted analogs of nor-*β*-CIT (**1d**), ranked by NE_T affinity as 3-iodoprop-(2*E*)-enyl = crotyl > benzyl > propynyl = 2-bromoprop-(2*E*)-enyl = 2′-methylbenzyl, exhibited 3.7−12.5 times less NE_T binding potency than *β*-CIT. All these observations demonstrate that the replacement of the *N*-methyl moiety by an alkenyl or alkynyl group slightly influences DA_T binding with a possible gain in potency for compounds **4** and **6**. In addition, these results demonstrate that an alkenyl, alkynyl, or benzyl chain linked to the tropane nitrogen could dramatically decrease the binding potency to 5-HT_T, thereby increasing specific DA_T binding. By contrast, other studies have shown that several *N*-haloalkyl derivatives of *β*-CIT and N-demethylated tropane derivatives possess high 5-HT_T affinity.[18,25] All these studies demonstrate the important role played by the N-substituent of tropane derivatives on 5-HT_T binding affinity and that, according to the N-substitution, a ligand specific for either DA_T or 5-HT_T could be obtained.

Table 3. K_i Values of N-Substituted Derivatives of β-CIT in Displacing Binding of [^{3}H]GBR-12935, [^{3}H]Paroxetine, and [^{3}H]Nisoxetine in Rat Brain Membranes



		affinity (K_i, nM)			selectivity	
compd	R	[^{3}H]GBR-12935 DA_T	[^{3}H]paroxetine 5-HT_T	[^{3}H]nisoxetine NE_T	5-HT_T/DA_T	NE_T/DA_T
6	$-CH_2-C\equiv CH$	14 ± 1	100 ± 30	>1000	7.1	>71.0
4	$-CH_2-CH=CH-CH_3$	15 ± 1	75 ± 5	400 ± 80	5.0	26.6
β-CIT	CH_3-	27 ± 2	3 ± 0.2	80 ± 28	0.1	2.9
3d	$-CH_2-CH=CHI$	30 ± 5	960 ± 60	295 ± 33	32.0	9.8
5	$-CH_2-C(Br)=CH_2$	30 ± 5	200 ± 40	>1000	6.6	>33.0
7	$-CH_2-C_6H_5$	42 ± 12	100 ± 17	600 ± 100	2.3	14.2
8	$-CH_2-o(CH_3)C_6H_4$	93 ± 19	225 ± 40	>1000	2.4	>10.6

Table 4. K_i Values of *N*-(3-Iodoprop-(2*E*)-enyl)-2β-carbomethoxy-3β-(3′,4′-disubstituted phenyl)nortropanes in Displacing Binding of [^{3}H]GBR-12935, [^{3}H]Paroxetine, and [^{3}H]Nisoxetine in Rat Brain Membranes



			affinity (K_i, nM)[a]			selectivity	
compd	X	Y	DA_T	5-HT_T	NE_T	5-HT_T/DA_T	NE_T/DA_T
3c	CH_3	H	17 ± 7	500 ± 30	>1000	29.4	>58.0
3b	Cl	Cl	29 ± 4	50 ± 6	500 ± 120	1.7	17.2
3d	I	H	30 ± 5	960 ± 60	295 ± 33	32.0	9.8
3a	H	H	113 ± 41	100 ± 20	>1000	0.8	>8.8
3e	$CH(CH_3)_2$	H	500 ± 120	450 ± 80	>1000	0.9	>2.0
3f	$CH_2CH_2CH_3$	H	500 ± 100	300 ± 12	750 ± 160	0.6	1.5

[a] K_i values of β-CIT for DA_T, 5-HT_T, and NE_t were 27 ± 2, 3.0 ± 0.2, and 80 ± 28 nM, respectively.

Because compound **3d** had the highest DA_T vs 5-HT_T selectivity and as the *N*-(3-iodoprop-(2*E*)-enyl) chain may be labeled for SPECT exploration, substituents were carried out on **3d**. The aromatic part was selected for its well-known importance in transporter−ligand interactions and in order to determine whether further aromatic substitutions may contribute to the improvement in DA_T affinity and specificity of these ligands. Results concerning *N*-(3-iodoprop-(2*E*)-enyl)-2β-carbomethoxy-3β-(3′,4′-substituted phenyl)nortropane derivatives are shown in Table 4. The rank order of DA_T affinity was 4′-methylphenyl > 3′,4′-dichlorophenyl = 4′-iodophenyl > phenyl > 4′-isopropylphenyl = 4′-*n*-propylphenyl. The 4′-methyl derivative **3c** was shown to be the most DA_T potent agent of this series. Examination of K_i values revealed that aromatic substitution 4′-methyl, 3′,4′-dichloro, or 4′-iodo provides compounds with high DA_T affinity (K_i = 17, 29, and 30 nM). By contrast weak inhibitions were observed for phenyl, 4′-isopropylphenyl, and 4′-*n*-propylphenyl derivatives (K_i = 113, 500, and 500 nM). These results showed that the nature of the aromatic substituent influences DA_T affinity.

The potencies of compounds **3a**−**f** are consistent with the pharmacophore model proposed by Carroll *et al.*[10] This model demonstrated that increased electron density around both the aromatic ring and the 4′-substituent itself correlated with high DA_T binding potency. In addition, this model associated large steric bulk around the aryl ring with decreased DA_T ligand affinity. The high affinities observed for compounds **3b**−**d** and low affinities observed for compounds **3a**,**e**,**f** are in agreement with the features of this model. The most selective derivative in this series was **3d**, and inhibition constants related to 5-HT_T binding indicated that none of the derivatives decreased 5-HT_T affinity compared to **3d**. However, 4′-methyl, 3′,4′-dichloro, and 4′-iodo derivatives exhibited a 16−290-fold greater DA_T vs 5-HT_T specificity than β-CIT. In addition these compounds (**3b**−**d**) exhibited very low NE_T affinity (K_i = 500, > 1000, and 295 nM, respectively). These results demonstrate that aromatic changes affected the DA_T binding potency of these derivatives and that the combination of a nitrogen and phenyl substitution could lead to compounds with high affinity and selectivity for the dopamine transporter.

In conclusion, two series of N-substituted derivatives of nor-β-CIT and *N*-(3-iodoprop-(2*E*)-enyl)-2β-carbomethoxy-3β-(3′,4′-disubstituted phenyl)nortropanes were synthesized and evaluated for their *in vitro* affinity for DA, 5-HT, and NE transporters in rat brain tissue. N-Substitutions with alkenyl or alkynyl groups yielded compounds with high DA_T affinity. These results are in agreement with previous reports and support the conclusion that a steric tolerance exists in the N-substituent region. Moreover, those compounds exhibited high DA_T selectivity, suggesting that these N-substituents play an important selective role. As compounds **3c,d** possess

high selective binding to the DA_T, it could be assumed that the combination of a nitrogen and a phenyl substitution is a good method to obtain highly selective DA_T compounds. In view of the promising *in vitro* results, we are currently labeling and testing compounds **3c,d** *in vivo* in rats and in nonhuman primates.

Experimental Section

NMR spectra were recorded on a Brüker DPX Advance 200 spectrometer (200 MHz for ^{1}H, 50.3 MHz for ^{13}C). $CDCl_3$ was used as solvent; chemical shifts are expressed in ppm relative to TMS as an internal standard. Mass spectra were obtained on a GC−MS Hewlett Packard 5989A spectrometer (electronic impact at 70 eV). All optical rotations were measured at the sodium D line using a REF polarimeter (20 cm cell, *c* g of solute/100 mL of solution). The thin-layer chromatographic (TLC) analyses were performed using Merck 60F-254 silica gel plates. Flash chromatography was used for routine purification of reaction products using silica gel (230−400 mesh). Visualization was accomplished under UV or in an iodine chamber. All chemicals and solvents were of commercial quality and were purified following standard procedures. Elemental analyses of new compounds, determined by the Service d'Analyse du CNRS, Vernaison, France, were within ±0.4% of theoretical values.

Chemistry. General Procedure of N-Alkylation of 2β-Carbomethoxy-3β-(substituted phenyl)nortropane. 2β-Carbomethoxy-3β-(substituted phenyl)nortropanes **1a**−**f** were prepared according to previously reported methods.[3,11,17,21] The appropriate alkyl bromide or alkyl chloride was added to a solution of 2β-carbomethoxy-3β-(substituted phenyl)nortropane in absolute EtOH (10 mL/mmol) containing Et_3N (140 μL/mmol) and a catalytic amount of KI. The mixture was refluxed under nitrogen atmosphere for 16 h. The solvent was then removed under reduced pressure, and the residue was purified by flash chromatography. Physical data (^{1}H NMR and elemental analysis) for iodinated compounds are given in Table 1.

***N*-((2*E*)-Butenyl)-2β-carbomethoxy-3β-(4′-iodophenyl)-nortropane (4).** Compound **4** was prepared from nor-β-CIT (**1d**) (100 mg, 0.27 mmol) and crotyl bromide (66 mg, 0.43 mmol) as described by the preceding general procedure to obtain a waxy solid (69 mg, 60%) after flash chromatography (Et_2O:Et_3N, 9:1): ^{13}C NMR δ 16.8, 24.7, 24.9, 32.9, 33.0, 50.1, 51.5, 54.6, 60.4, 61.1, 90.5, 127.7, 128.4, 128.5, 135.9, 142.4, 171.8; MS *m*/*z* 425 (M^+, 16), 366 (5), 195 (6), 136 (24), 123 (65), 122 (100), 108(20), 68 (28), 55 (58).

***N*-(2-Bromo-2-propenyl)-2β-carbomethoxy-3β-(4′-iodophenyl)nortropane (5).** Compound **5** was prepared from nor-β-CIT (**1d**) (100 mg, 0.27 mmol) and 2-bromo-2-propenyl bromide (143 mg, 0.32 mmol) as described by the preceding general procedure to obtain a wax (99 mg, 74%) after flash chromatography (Et_2O:Et_3N, 10:1): ^{13}C NMR δ 25.0, 25.4, 32.7, 50.1, 51.6, 60.1, 61.3, 62.3, 90.7, 116.1, 128.5, 131.4, 135.9, 142.2, 171.0; MS *m*/*z* 491 (M^+, 2), 489 (M^+, 3), 411 (21), 410 (100), 202 (8), 200 (8), 189 (23), 187 (26), 188 (26), 186 (22), 122 (84), 108 (30), 68 (23).

***N*-Prop-2-ynyl-2β-carbomethoxy-3β-(4′-iodophenyl)-nortropane (6).** Compound **6** was similarly prepared from nor-β-CIT (**1d**) (180 mg, 0.48 mmol) and propargyl bromide (64 mg, 0.54 mmol) to give an oil (151 mg, 77%) after flash chromatography (Et_2O:Et_3N, 95:5): MS *m*/*z* 409 (M^+, 9), 408 (8), 350 (12), 120 (44), 107 (100), 106 (46).

***N*-Benzyl-2β-carbomethoxy-3β-(4′-iodophenyl)nortropane (7).** Compound **7** was prepared from nor-β-CIT (**1d**) (100 mg, 0.27 mmol) and benzyl bromide (124 mg, 0.72 mmol) as described by the preceding general procedure to obtain a wax (105 mg, 84%) after flash chromatography (Et_2O:Et_3N, 10:1): ^{13}C NMR δ 25.0, 32.8, 49.9, 51.6, 56.8, 60.0, 61.3, 90.4, 125.8, 127.0, 127.6, 128.6, 135.9, 139.4, 142.6, 171.3; MS *m*/*z* 462 (M + 1, 4), 461 (M^+, 16), 370 (4), 173 (13), 172 (28), 159 (89), 158 (37), 91 (100).

***N*-(2-Methylbenzyl)-2β-carbomethoxy-3β-(4′-iodophenyl)nortropane (8).** Compound **8** was prepared from nor-β-CIT (**1d**) (100 mg, 0.27 mmol) and 2-methylbenzyl bromide (51 mg, 0.36 mmol) as described by the preceding general procedure to obtain a wax (119 mg, 92%) after flash chromatography (Et_2O:Et_3N, 10:1): ^{13}C NMR δ 18.6, 25.4, 25.6, 33.3, 37.5, 50.1, 52.1, 55.6, 59.9, 62.1, 90.3, 124.7, 126.5, 129.0, 129.6, 136.3, 137.0, 137.4, 142.6, 170.9; MS *m*/*z* 475 (M^+, 19), 416 (3), 370 (5), 173 (58), 172 (100), 105 (84), 104 (12), 82 (32).

***N*-[3-(Tri-*n*-butylstannyl)prop-(2*E*)-enyl]-2β-carbomethoxy-3β-phenylnortropane (2a).** Compound **2a** was prepared from **1a** (300 mg, 1.22 mmol) and **11** (447 mg, 1.22 mmol) to give a colorless oil (250 mg, 50%) after flash chromatography (petroleum ether 40−65 °C:AcOEt, 7:3): ^{1}H NMR δ 0.81 (t, 9H, ^3J = 7.0 Hz, $3CH_3$), 1.08-1.64 [m, 21H, $(CH_2CH_2CH_2)_3Sn$, H-4α, H-6α, H-7α], 1.97 (m, 2H, H-6β, H-7β), 2.58 (td, 1H, $^3J_{4\beta,5}$ = 3.1 Hz, $^2J_{4\alpha,4\beta}$ = $^3J_{3,4\beta}$ = 12.4 Hz, H-4β), 2.73−2.99 (m, 3H, H-2, H-3, H-9′), 3.08 (dd, 1H, $^2J_{9,9'}$ = 13.9 Hz, $^3J_{9,10}$ = 3.4 Hz, H-9), 3.34 (m, 1H, H-5), 3.40 (s, 3H, OCH_3), 3.61 (m, 1H, H-1), 5.72−6.01 (ABXX′, 2H, $^3J_{10,11}$ = 19.1 Hz, $^3J_{9',10}$ = 5.6 Hz, $^3J_{9,10}$ = 3.4 Hz, CH=CH), 7.06−7.19 (m, $5H_{arom}$).

***N*-[3-(Tri-*n*-butylstannyl)prop-(2*E*)-enyl]-2β-carbomethoxy-3β-(3′,4′-dichlorophenyl)nortropane (2b).** Compound **2b** was prepared from **1b** (430 mg, 1.37 mmol) and **11** (500 mg, 1.37 mmol) as described by the preceding general procedure to obtain a colorless oil (215 mg, 25%) after flash chromatography (petroleum ether 40−65 °C:AcOEt, 8:2): ^{1}H NMR δ 0.82 (t, 9H, ^3J = 7.0 Hz, $3CH_3$), 1.10−1.62 [m, 21H, $(CH_2CH_2CH_2)_3Sn$, H-4α, H-6α, H-7α], 1.98 (m, 2H, H-6β, H-7β), 2.48 (td, 1H, $^3J_{4\beta,5}$ = 2.9 Hz, $^2J_{4\alpha,4\beta}$ = $^3J_{3,4\beta}$ = 12.4 Hz, H-4β), 2.72−2.93 (m, 3H, H-9′, H-2, H-3), 3.06 (dd, 1H, $^2J_{9,9'}$ = 13.5 Hz, $^3J_{9,10}$ = 3.7 Hz, H-9), 3.35 (m, 1H, H-5), 3.45 (s, 3H, OCH_3), 3.64 (m, 1H, H-1), 5.68−6.01 (ABXX′, 2H, $^3J_{10,11}$ = 19.1 Hz, $^3J_{9',10}$ = 5.9 Hz, $^3J_{9,10}$ = 3.7 Hz, CH=CH), 7.05 (dd, $1H_{arom}$, ^3J = 8.3 Hz, ^4J = 2.0 Hz), 7.25 (d, $1H_{arom}$, ^3J = 8.3 Hz), 7.26 (d, $1H_{arom}$, ^4J = 2.0 Hz).

***N*-[3-(Tri-*n*-butylstannyl)prop-(2*E*)-enyl]-2β-carbomethoxy-3β-(4′-methylphenyl)nortropane (2c).** Compound **2c** was similarly prepared from **1c** (3.52 g, 13.61 mmol) and **11** (5.52 g, 15.10 mmol) to yield a colorless oil (8.0 g, 81%) after flash chromatography (petroleum ether 40−65 °C:AcOEt:Et_3N, 85:15:1): ^{1}H NMR δ 0.82 (t, 9H, ^3J = 7.0 Hz, $3CH_3$), 1.18−1.59 [m, 21H, $(CH_2CH_2CH_2)_3Sn$, H-4α, H-6α, H-7α], 1.96 (m, 2H, H-6β, H-7β), 2.21 (s, 3H, $ArCH_3$), 2.56 (td, 1H, $^3J_{4\beta,5}$ = 3.0 Hz, $^2J_{4\alpha,4\beta}$ = $^3J_{3,4\beta}$ = 12.5 Hz, H-4β), 2.75−2.98 (m, 3H, H-9′, H-2, H-3), 3.11 (dd, 1H, $^2J_{9,9'}$ = 13.6 Hz, $^3J_{9,10}$ = 3.8 Hz, H-9), 3.37 (m, 1H, H-5), 3.42 (s, 3H, OCH_3), 3.62 (m, 1H, H-1), 5.75−6.01 (ABXX′, 2H, $^3J_{10,11}$ = 19.2 Hz, $^3J_{9',10}$ = 6.1 Hz, $^3J_{9,10}$ = 3.8 Hz, CH=CH), 6.97−7.10 (2d, $4H_{arom}$, ^3J = 8.0 Hz).

***N*-[3-(Tri-*n*-butylstannyl)prop-(2*E*)-enyl]-2β-carbomethoxy-3β-(4′-iodophenyl)nortropane (2d).** Compound **2d** was prepared by the general procedure from **1d** (520 mg, 1.40 mmol) and **11** (512 mg, 1.40 mmol) to give a colorless oil (373 mg, 40%) after flash chromatography (petroleum ether 40−65 °C:AcOEt, 8:2): ^{1}H NMR δ 0.81 (t, 9H, ^3J = 7.0 Hz, $3CH_3$), 1.20−1.56 [m, 21H, $(CH_2CH_2CH_2)_3Sn$, H-4α, H-6α, H-7α], 1.98 (m, 2H, H-6β, H-7β), 2.50 (td, 1H, $^3J_{4\beta,5}$ = 2.7 Hz, $^2J_{4\alpha,4\beta}$ = $^3J_{3,4\beta}$ = 12.3 Hz, H-4β), 2.75−2.82 (m, 3H, H-9′, H-2, H-3), 3.04 (dd, 1H, $^2J_{9,9'}$ = 13.1 Hz, $^3J_{9,10}$ = 2.4 Hz, H-9), 3.34 (m, 1H, H-5), 3.44 (s, 3H, OCH_3), 3.63 (m, 1H, H-1), 5.69−6.00 (ABXX′, 2H, $^3J_{10,11}$ = 19.1 Hz, $^3J_{9',10}$ = 5.9 Hz, $^3J_{9,10}$ = 4.1 Hz, CH=CH), 7.06 (d, $2H_{arom}$, ^3J = 8.2 Hz), 7.61 (d, $2H_{arom}$, ^3J = 8.2 Hz).

***N*-[3-(Tri-*n*-butylstannyl)prop-(2*E*)-enyl]-2β-carbomethoxy-3β-(4′-isopropylphenyl)nortropane (2e).** Compound **2e** was prepared by the general procedure from **1e** (184 mg, 0.64 mmol) and **11** (260 mg, 0.71 mmol) to give a colorless oil (277 mg, 70%) after flash chromatography (petroleum ether 40−65 °C:AcOEt:Et_3N, 95:5:1): ^{1}H NMR δ 0.81 (t, 9H, ^3J = 7.0 Hz, $3CH_3$), 1.14 [d, 6H, $CH(CH_3)_2$], 1.27−1.64 [m, 21H, $(CH_2CH_2CH_2)_3Sn$, H-4α, H-6α, H-7α], 1.96 (m, 2H, H-6β, H-7β), 2.58 (td, 1H, $^3J_{4\beta,5}$ = 2.8 Hz, $^2J_{4\alpha,4\beta}$ = $^3J_{3,4\beta}$ = 12.3 Hz, H-4β), 2.74−2.96 [m, 4H, H-9′, H-2, H-3, $CH(CH_3)_2$], 3.08 (dd, 1H, $^2J_{9,9'}$ = 13.1 Hz, $^3J_{9,10}$ = 3.1 Hz, H-9), 3.34 (m, 1H, H-5), 3.42 (s, 3H, OCH_3), 3.61 (m, 1H, H-1), 5.73−6.01 (ABXX′, 2H, $^3J_{10,11}$ = 19.0 Hz, $^3J_{9',10}$ = 5.4 Hz, $^3J_{9,10}$ = 3.4 Hz, CH=CH), 7.04 (d, $2H_{arom}$, ^3J = 8.0 Hz), 7.14 (d, $2H_{arom}$, ^3J = 8.0 Hz).

***N*-[3-(Tri-*n*-butylstannyl)prop-(2*E*)-enyl]-2β-carbomethoxy-3β-(4′-*n*-propylphenyl)nortropane (2f).** Compound **2f** was prepared by the general procedure from **1f** (200 mg, 0.70 mmol) and **11** (278 mg, 0.76 mmol) to give a colorless oil (326 mg, 76%) after flash chromatography (petroleum ether 40−65 °C:AcOEt:Et_3N, 90:10:1): ^{1}H NMR δ 0.81 (t, 9H, ^3J = 6.9 Hz, $3CH_3$), 1.14−1.63 [m, 26H, $(CH_2CH_2CH_2)_3Sn$, CH_2CH_3, H-4α, H-6α, H-7α], 1.99 (m, 2H, H-6β, H-7β), 2.45 (t, 2H, ^3J = 8.0 Hz, $ArCH_2$), 2.57 (td, 1H, $^3J_{4\beta,5}$ = 3.1 Hz, $^2J_{4\alpha,4\beta} = {}^3J_{3,4\beta}$ = 12.6 Hz, H-4β), 2.73−2.97 (m, 3H, H-9′, H-2, H-3), 3.09 (dd, 1H, $^2J_{9,9'}$ = 13.6 Hz, $^3J_{9,10}$ = 3.1 Hz, H-9), 3.35 (m, 1H, H-5), 3.42 (s, 3H, OCH_3), 3.62 (m, 1H, H-1), 5.73−6.01 (ABXX′, 2H, $^3J_{10,11}$ = 19.1 Hz, $^3J_{9',10}$ = 5.4 Hz, $^3J_{9,10}$ = 3.1 Hz, CH=CH), 6.99 (d, $2H_{arom}$, ^3J = 8.2 Hz), 7.10 (d, $2H_{arom}$, ^3J = 8.2 Hz).

General Procedure of Iododestannylation of *N*-[3-(Tri-*n*-butylstannyl)prop-(2*E*)enyl]-2β-carbomethoxy-3β-(3′,4′-disubstituted phenyl)nortropane. Stannyl derivatives **2** were dissolved in $CHCl_3$ (6 mL/mmol), and the resulting mixture was cooled to 0 °C. A solution of iodine in $CHCl_3$ (0.1 N) was then added dropwise to the stirred mixture until a color solution resulted. The $CHCl_3$ solution was washed with brine and dried (Na_2SO_4). $CHCl_3$ was removed *in vacuo*, and the crude product was finally purified by flash chromatography. Physical data (^{1}H NMR and elemental analysis) are given in Table 2.

***N*-(3-Iodoprop-(2*E*)-enyl)-2β-carbomethoxy-3β-phenylnortropane (3a).** Compound **3a** was prepared from **2a** (132 mg, 0.23 mmol) to give an oil (65 mg, 69%) after flash chromatography (Et_2O): MS *m*/*z* 411 (M^+, 15), 380 (4), 352 (7), 284 (100), 252 (28), 235 (39), 234 (33), 180 (18), 167 (57), 122 (66).

***N*-(3-Iodoprop-(2*E*)-enyl)-2β-carbomethoxy-3β-(3′,4′-dichlorophenyl)nortropane (3b).** Compound **3b** was prepared from **2b** (200 mg, 0.31 mmol) to give an oil (77 mg, 52%) after flash chromatography (Et_2O): ^{13}C NMR δ 26.2, 26.4, 34.0, 34.2, 51.8, 52.7, 58.3, 61.5, 62.7, 77.6, 126.7, 129.4, 129.6, 129.7, 131.7, 143.2, 143.8, 171.3; MS *m*/*z* 481 (M^+, 9), 479 (M^+, 10), 354 (38), 352 (60), 320 (16), 248 (20), 235 (54), 234 (54), 180 (24), 167 (94), 68 (100).

***N*-(3-Iodoprop-(2*E*)-enyl)-2β-carbomethoxy-3β-(4′-methylphenyl)nortropane (3c).** Compound **3c** was prepared from **2c** (6.4 g, 10.29 mmol) to give a white solid (2.28 g, 50%) after flash chromatography (Et_2O): mp 76−78 °C; $[\alpha]^{25}_D$ −16.5° (*c* 5.0, $CHCl_3$); ^{13}C NMR δ 20.9, 25.7, 26.0, 33.6, 33.9, 51.0, 52.5, 57.9, 61.3, 62.2, 77.1, 127.1, 128.5, 135.1, 139.6, 144.2, 171.8; MS *m*/*z* 425 (M^+, 24), 366 (8), 299 (23), 298 (100), 248 (19), 235 (62), 234 (40), 167 (56), 122 (83).

***N*-(3-Iodoprop-(2*E*)-enyl)-2β-carbomethoxy-3β-(4′-iodophenyl)nortropane (3d).** Compound **3d** was prepared from **2d** (193 mg, 0.31 mmol) to give an oil (77 mg, 47%) after flash chromatography (petroleum ether 40−65 °C:Et_2O:Et_3N, 55:40:5): ^{13}C NMR δ 25.6, 25.9, 33.7, 33.8, 51.1, 52.4, 57.8, 61.0, 62.2, 77.2, 91.1, 129.4, 136.8, 142.6, 144.1, 171.5; MS *m*/*z* 537 (M^+, 26), 478 (6), 411 (24), 410 (100), 378 (12), 350 (12), 248 (15), 235 (50), 234 (41), 167 (55), 122 (50).

***N*-(3-Iodoprop-(2*E*)-enyl)-2β-carbomethoxy-3β-(4′-isopropylphenyl)nortropane (3e).** Compound **3e** was prepared from **2e** (220 mg, 0.36 mmol) to give an oil (138 mg, 85%) after flash chromatography (Et_2O:Et_3N, 95:5): ^{13}C NMR δ 24.4, 26.3, 26.5, 34.0, 34.3, 34.5, 51.6, 53.1, 58.4, 61.8, 62.8, 77.1, 126.4, 127.7, 140.4, 144.8, 146.9, 172.3; MS *m*/*z* 453 (M^+, 38), 394 (9), 327 (26), 326 (100), 235 (77), 234 (45), 167 (49), 122 (67).

***N*-(3-Iodoprop-(2*E*)-enyl)-2β-carbomethoxy-3β-(4′-*n*-propylphenyl)nortropane (3f).** Compound **3f** was prepared from **2f** (290 mg, 0.47 mmol) to give an oil (213 mg, 78%) after flash chromatography (Et_2O:Et_3N, 95:5): ^{13}C NMR δ 13.8, 24.4, 25.7, 25.9, 33.7, 33.9, 37.5, 51.0, 52.6, 57.8, 61.2, 62.3, 77.1, 127.1, 127.9, 139.8, 140.0, 144.2, 171.7; MS *m*/*z* 453 (M^+, 39), 394 (9), 326 (100), 235 (71), 234 (45), 167 (44), 122 (57).

Transporter Affinity Assays. Stock solutions (8 mg/mL) of test agents were constituted in absolute EtOH and stored at −20 °C until used for transporter affinity assays. Agents were tested in duplicate with a crude membrane fraction of homogenates of rat brain striatum (for DA_T assays) in sodium hydrogenocarbonate buffer (pH 7.5) or frontoparietal cerebral cortex (for 5-HT_T and NE_T assays) in 50 mM Tris-HCl buffer (pH 7.4) containing NaCl (120 mM) and KCl (5 mM).

For the DA_T assays,[26] each sample contained 2.4 mL of incubation buffer with 0.01% bovine serum albumin, 0.4 mL of [^{3}H]GBR-12935 (45.7 Ci/mmol; NEN) at a concentration of 1 nM (K_d = 1.6 nM), 0.2 mL of the tested agent at various concentrations ranging from 10^{-5} to 10^{-10} M, and 1 mL of a 100 μg membrane protein preparation. Nonspecific binding was determined with 10^{-6} M mazindol (a gift from Sandoz). Samples were incubated at 37 °C for 1 h, filtered on glass fiber filters (GF/B, Whatman), and washed with ice-cold buffer, and the residual radioactivity was measured with a beta counter (LKB, Rack Beta 1215).

For the 5-HT_T assays,[27] each sample contained 1.2 mL of Tris-NaCl buffer, 0.2 mL of [^{3}H]paroxetine (23.8 Ci/mmol; NEN) at a concentration of 0.5 nM (K_d = 0.5 nM), 0.1 mL of competitors at various concentrations ranging from 10^{-5} to 10^{-10} M, and 0.5 mL containing 70 μL of membrane protein preparation in a total volume of 2 mL. Samples were incubated at 22 °C for 1 h, filtered, and treated as described for DA_T assays. Nonspecific binding was determined with 10^{-6} M fluvoxamine (a gift from Duphar).

For NE_T assays,[28] each sample contained 0.2 mL of incubation buffer, 0.1 mL of [^{3}H]nisoxetine (86 Ci/mmol; NEN) at a concentration of 0.5 nM (K_d = 1.3 nM), 0.1 mL of competitors at various concentrations ranging from 10^{-5} to 10^{-10} M, and 0.2 mL containing 125 μL of membrane protein preparation in a total volume of 0.6 mL. Samples were incubated at 2 °C for 5 h, filtered, and treated as described for DA_T assays. Nonspecific binding was determined with 10^{-6} M desipramine (RBI Bioblock). K_i values were calculated from IC_{50} values according to the method of Cheng and Prusoff:[29] $K_i = IC_{50}/[1 + (L/K_d)]$.

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