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# Synthesis of Tropane and Nortropane Analogues with Phenyl Substitutions as Serotonin Transporter Ligands

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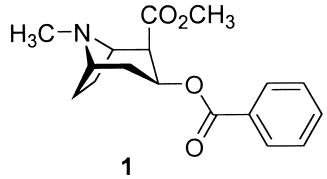
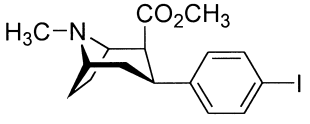
**Abstract**—The effects of structural modifications of 2β-carbomethoxy-3β-phenyl tropane analogues were evaluated on in vitro affinity to the dopamine (DAT) and serotonin (5-HTT) transporters in rat brain tissue. The introduction of a large alkyl group at the 4′-position of the phenyl ring, affording 2β-carbomethoxy-3β-(4′-alkylphenyl) tropane, diminished the affinity for the DAT whereas moderate 5-HTT affinity was obtained. The introduction of an iodine at the 3′-position of the 4′-alkylphenyl, affording 2β-carbomethoxy-3β-(3′-iodo-4′-alkylphenyl) tropane, and *N*-demethylation, affording 2β-carbomethoxy-3β-(3′-iodo-4′-alkylphenyl) nortropane, improved affinity and specificity for the 5-HTT. It could be assumed from these results that the combination of these three modifications of tropane structure yielded highly selective compounds for the 5-HTT. Of the new compounds synthesized, the most selective cocaine derivative, 2β-carbomethoxy-3β-(3′-iodo-4′-isopropylphenyl) nortropane (**8d**) labeled with iodine-123 or carbon-11, could be a potential ligand for exploration of the 5-HT transporter by SPET or PET. © 2001 Published by Elsevier Science Ltd.

## Introduction

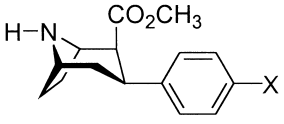
The serotonin transporter (5-HTT) plays a major role in the regulation of synaptic serotonin levels. The serotonin system is involved in several neurologic and psychiatric disorders,[1,2] but its precise role in these diseases remains to be clarified. Although several findings have shown that disturbances in serotoninergic activity could be a major etiological factor in depression, it is still unclear whether the fundamental defect is at the presynaptic or postsynaptic level, or both.[3] In neurodegenerative disorders such as Alzeihmer's disease, the 5-HTT may serve as a marker for the degeneration of 5-HT neurons, as its distribution closely follows that of 5-HT nerve endings.[4] In vivo exploration of the 5-HTT by positron emission tomography (PET) or single photon emission tomography (SPET) would therefore greatly improve understanding of changes in the 5-HT system occurring in disease, and also help in the diagnosis and therapeutic follow-up of these diseases.




**1**
Cocaine




**2**
β-CIT




**3**
X =F, Cl, I, $C_2H_5$

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The natural (−) isomer of cocaine (**1**) is well known to interact with dopamine, serotonin and norepinephrine transporters (DAT, 5-HTT and NET) with slight DAT selectivity.[5] Several attempts have been made in recent years to obtain cocaine derivatives with enhanced affinity and selectivity for one of these monoamine transporters.

The substitution of the benzoyl group of cocaine by a 4′-iodinated phenyl at the 3β position of the tropane structure leads to 2β-carbomethoxy-3β-(4′-iodophenyl) tropane, also called β-CIT (**2**), a compound with high binding affinity for the DAT and the 5-HTT.[6] In the research for high specific radioligands for exploration of the DAT by SPET, several β-CIT analogues differently substituted on the nitrogen or phenyl ring have been investigated. Among them, *N*-(3-iodoprop-2-enyl)-2β-carbomethoxy-3β-(4′-substitutedphenyl) nortropane derivatives with a chlorine (IPT), fluorine (Altropane) or methyl (PE2I) as substituant exhibit high affinity and selectivity for the DAT.[7–10] As appropriate structural modifications on β-CIT lead to high affinity and selective compounds for the DAT, it might be assumed that other structural modifications could afford compounds with high affinity and selectivity for the 5-HTT.

Boja et al.[11] first reported that the *N*-demethylation of 2β-carbomethoxy-3β-(4′-substituted phenyl) tropane derivatives leads to compounds (**3**) with enhanced affinity for the 5-HTT and no significant change in affinity for the DAT; for example the *N*-demethylated analogue of β-CIT (nor-β-CIT) is 10 times more selective for the 5-HTT than β-CIT.[11] Although nor-β-CIT retains good affinity for the DAT, its use has been proposed to explore the 5-HTT distribution in vivo in humans.[12,13] Moreover, nor-β-CIT derivatives in which iodine is replaced by alkyl, alkenyl or alkynyl groups show higher affinity for the 5-HTT than their *N*-methylated analogues.[14] These results confirm that *N*-demethylation of the tropane structure yield compounds with enhanced affinity for the 5-HTT.

Blough et al. recently reported the synthesis of a nortropane structure with an iodine and an ethyl at the 3′ and 4′ position of the phenyl ring, respectively: 2β-carbomethoxy-3β-(3′-iodo-4′-ethylphenyl) nortropane (**4**, EINT).[15] This compound presents high affinity and specificity for the 5-HTT in vitro. In addition EINT inhibits the in vivo accumulation of [$^{125}$I]-β-CIT in rat cerebral regions known to be rich in 5-HTT such as the hypothalamus and thalamus.

As the introduction of an alkyl or an iodine on the phenyl group and *N*-demethylation of the tropane structure markedly influence the binding properties at the 5-HTT, we evaluated whether the combination of these substitutions would yield compounds with high affinity and specificity for the 5-HTT. We report the synthesis of tropane and nortropane derivatives with the general structure **5** and in vitro binding properties at the DAT and the 5-HTT.

## Results

### Chemistry

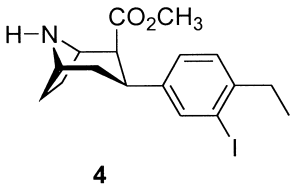
All compounds described, were prepared as outlined in Scheme 1 using ecgonidine methyl ester as starting material. Compounds **6a–e** were obtained by 1-4 Michael addition on ecgonidine methyl ester with the corresponding Grignard reagent, as previously described.[16] Iodination of the aromatic ring of compounds **6a–e** was carried out using a mixture of yellow mercuric oxide, perchloric acid and acetic acid.[11] The structure assignments of compounds **7a–e** were elucidated by NMR hydrogen carbon three-bond correlation which exhibits interaction between only one aromatic hydrogen and the first carbon of the alkyl group linked to the phenyl ring. Moreover, correlation between the carbon 3 of the tropane structure and two aromatic hydrogens corroborates these assignments. Compounds **8a–e** were prepared by *N*-demethylation of compounds **7a–e**. This reaction involved the formation of the corresponding carbamate using 2,2,2-trichloroethylchloroformate, followed by treatment with a Zn–acetic acid mixture according to previously reported procedures.[17]

### In vitro binding assays

Affinity of the described compounds for monoamine transporters was determined by in vitro competitive binding assays. [$^3$H] GBR-12935 and [$^3$H] paroxetine were used as specific ligands for the DAT and 5-HTT sites, respectively. The results are expressed as inhibition constants and are summarized in Table 1.

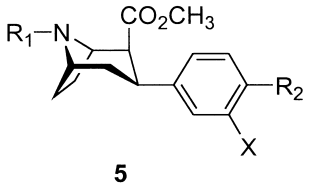
## Discussion

The cocaine derivative β-CIT, which binds with high affinity to the DAT and the 5-HTT has been used to



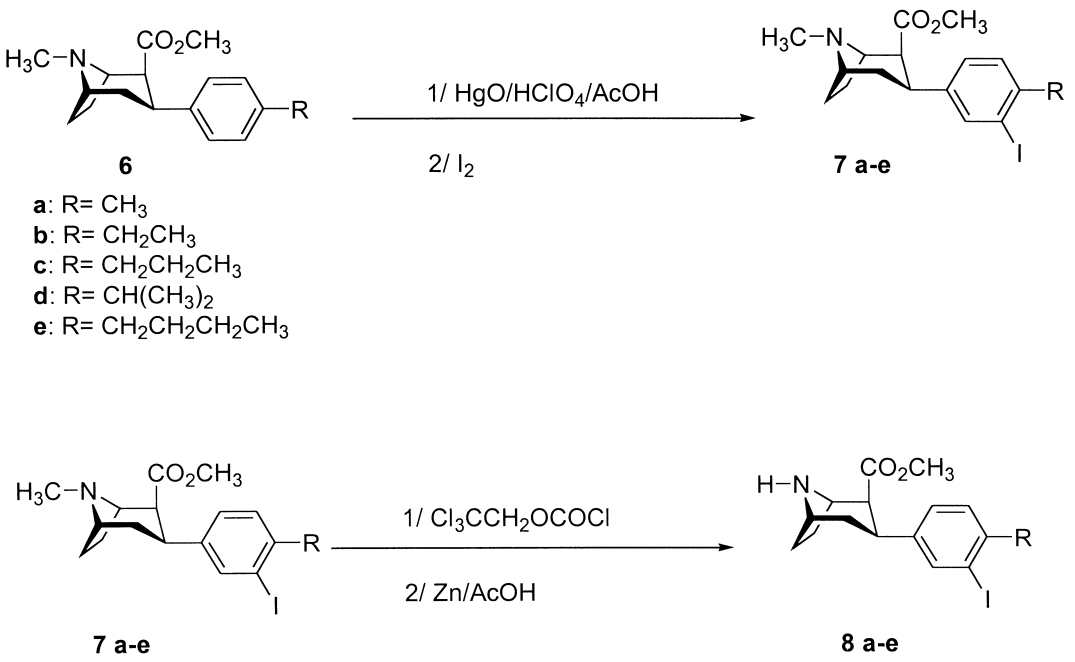

**4**

EINT



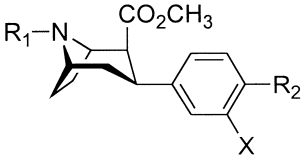

**5**

$R_1$ = $CH_3$, H
$R_2$ = alkyl
X = H, I




**Scheme 1.** Synthesis of tropane and nortropane analogues.

**Table 1.** $K_i$ values in displacing binding of [$^3$H] GBR-12935 and [$^3$H] Paroxetine in rat brain membranes




| Compound | $R_1$ | $R_2$ | X | Affinity ($K_i$, nM) DAT | Selectivity 5-HTT | DAT/5-HTT |
|---|---|---|---|---|---|---|
| **6a** | $CH_3$ | $CH_3$ | H | 32±4 | >500 | <0.1 |
| **7a** | $CH_3$ | $CH_3$ | I | 46±6 | 80±17 | 0.6 |
| **8a** | H | $CH_3$ | I | 111±25 | 31±2 | 3.6 |
| **6b** | $CH_3$ | $CH_2CH_3$ | H | >500 | 35±10 | >14.3 |
| **7b** | $CH_3$ | $CH_2CH_3$ | I | 333±75 | 19±3 | 17.5 |
| **8b** | H | $CH_2CH_3$ | I | 263±55 | 15±8 | 17.5 |
| **6c** | $CH_3$ | $CH_2CH_2CH_3$ | H | >500 | 239±47 | >2.1 |
| **7c** | $CH_3$ | $CH_2CH_2CH_3$ | I | >500 | 316±13 | >1.6 |
| **8c** | H | $CH_2CH_2CH_3$ | I | >500 | 70±21 | >7.4 |
| **6d** | $CH_3$ | $CH(CH_3)_2$ | H | >500 | 275±35 | >1.8 |
| **7d** | $CH_3$ | $CH(CH_3)_2$ | I | >500 | 39±5 | >12.8 |
| **8d** | H | $CH(CH_3)_2$ | I | >500 | 25±6 | >20.0 |
| **6e** | $CH_3$ | $CH_2CH_2CH_2CH_3$ | H | >500 | 126±37 | >4.0 |
| **7e** | $CH_3$ | $CH_2CH_2CH_2CH_3$ | I | 352±22 | 135±31 | >2.6 |
| **8e** | H | $CH_2CH_2CH_2CH_3$ | I | >500 | 57±8 | >8.8 |

explore these monoamine transporters by PET or SPET.[13,18] In order to improve the selectivity for the 5-HTT, several groups have explored the effects of structural modifications on tropane. In particular *N*-demethylation, the introduction of an alkyl group at the 4′ position and an iodine atom at the 3′ position of the phenyl ring have been shown to affect the binding properties of such compounds to DAT and 5-HTT.[11,14,15,19] It is hypothesized that the combination of these substitutions could improve affinity and specificity for the 5-HTT. The binding study of test compounds **6a**–**e** which were *N*-methylated and 4′-phenyl substituted by alkyl groups show that only **6a** ($R_2=CH_3$) had moderate affinity for the DAT ($K_i=32$ nM) whereas the $K_i$ values of test compounds **6b**–**e** were higher than 500 nM. In contrast, **6a** exhibited weak affinity for the 5-HTT (>500 nM) whereas **6b**–**e** presented moderate to low affinity ($K_i=35$–275 nM). From these results it may be concluded that the DAT binding site does not tolerate an alkyl substituent at the phenyl ring which is larger than a methyl group. In contrast, the 5-HTT binding site seems to accommodate larger alkyl groups in this

position. These results comply with the DAT pharmacophore model proposed by Carroll et al., which associates large steric bulk around the aryl ring with decreased DAT ligand affinity.[20] However, it has to be emphasized that high affinity for both DAT and 5-HTT was obtained for 4′-unsaturated substituants such as vinyl, isopropenyl, (*E*/*Z*) propenyl, ethynyl or propynyl.[14] Thus, in contrast to 4′-unsaturated substituants, the introduction of large alkyl group at the 4′-position of the tropane phenyl ring inhibits DAT binding, affording an increase in 5-HTT specificity.

The introduction of the iodine atom at the 3′ position (**7a**–**e**) on the whole seem does not influence the affinity at the DAT site to any great extend when compared to compounds **6a**–**e**. On the other hand, although no increase in 5-HTT binding potency was observed for compounds **7c** and **7e**, compounds **7a**, **7b**, and **7d** presented 2- to 7-fold higher 5-HTT binding potency compared to non-iodinated derivatives **6a**, **6b**, and **6d**. For 2β-carbomethoxy-3β-phenyl tropane (WIN 35,065-2) and its iodinated analogue 2β-carbomethoxy-3β-(3′-iodophenyl) tropane (RTI-92),[15] similar results have been observed; while RTI-92 and WIN 35,065-2 are equipotent at the DAT (26 and 33 nM), the affinity of RTI-92 at the 5-HTT is ca. 50-fold higher than for WIN 35,065-2 (38.8 vs 2000 nM). These findings lead to the conclusion that the introduction of an iodine on the phenyl ring of the tropane structure can contribute to enhancement of 5-HTT affinity and selectivity compared to DAT.

As the introduction of an alkyl group at the 4′ position and an iodine at the 3′ position of the aromatic ring enhance the affinity and the specificity of tropane structures for the 5-HTT overall, we synthesized compounds **8a**–**e** in order to assess whether *N*-demethylation would increase 5-HTT affinity and selectivity. The rank order of 5-HTT affinity is ethyl (**8b**) > isopropyl (**8d**) > methyl (**8a**) > butyl (**8e**) > propyl (**8c**). Except for the 4′-ethyl analogue (**8b**), which exhibited the same 5-HTT affinity as **7b**, other 2β-carbomethoxy-3β-(3′-iodo-4′-substituted phenyl) nortropanes had higher affinity for the 5-HTT than their *N*-methyl analogues. These results corroborate those previously published[11,14] and confirm the hypothesis that *N*-demethylation results in compounds with enhanced 5-HTT affinity. The best selectivity and affinity for the 5-HTT are obtained with *N*-desmethyl-3′-iodophenyl derivatives.

## Conclusion

In conclusion, substituted tropane derivatives were synthesized and evaluated for their in vitro affinity for DA and 5-HT transporters in the rat brain. The introduction of an alkyl group larger than a methyl at the 4′-phenyl position hinders the DAT–ligand interaction, whereas moderate to high 5-HTT affinity was obtained. In addition, iodination of the phenyl ring at the 3′-position and *N*-demethylation improved the affinity and specificity for the 5-HTT. The hypothesis, that the combination of all these structural modifications might lead to compounds with good affinity and selectivity for the 5-HT transporter site, has thus been confirmed. In view of the in vitro results, compounds **8b** and **8d** labeled with iodine-123 or carbon-11 could be useful ligands for scintigraphic exploration of the 5-HTT. Evaluation of these compounds in non-human primates is currently being performed.

## Experimental

NMR spectra were recorded on a Bruker DPX Avance 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 CG–MS Hewlett Packard 5989A spectrometer (electronic impact at 70 eV). 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.

### Chemistry general procedure of synthesis of 2β-carbomethoxy-3β-(3′-iodo-4′-substituted phenyl) tropane (7a-e)

**2β-Carbomethoxy-3β-(3′-iodo-4′-methylphenyl) tropane 7a.** 2β-carbomethoxy-3β-4′-tolyl tropane **6a** (1 g, 3.65 mmol) was dissolved in a mixture of acetic acid (12.5 mL), perchloric acid (4.2 mL) and mercuric oxide yellow (790 mg, 3.66 mmol). A solution of iodine (2.32 g, 9.15 mmol) in a mixture of $CH_2Cl_2$ (33.3 mL) and acetic acid (16.8 mL) was added dropwise. The reaction was stirred at room temperature overnight. The solid was separated by filtration and the filtrate was diluted with $H_2O$ (16.8 mL) and $CH_2Cl_2$ (33.3 mL) and cooled in an ice bath. The mixture was basified with concentrated $NH_4OH$. The organic layer was separated and the aqueous layers were extracted with $CH_2Cl_2$ (3×30 mL). The crude product was purified by flash-chromatography (hexane/AcOEt/$Et_3N$, 70/20/10) to give 580 mg (40%, 1.46 mmol) of a yellow oil. $^1$H NMR, δ 1.52–1.62 (m, 3H, H-4α, H-6α, H-7α), 1.96–2.10 (m, 2H, H-6β, H-7β), 2.14 (s, 3H, N–$CH_3$), 2.28 (s, 3H, Ph–$CH_3$), 2.43 (td, 1H, $^3J_{3-4\beta} = {}^2J_{4\alpha-4\beta} = 12.6$ Hz, $^3J_{4\beta\text{-}5} = 3.8$ Hz, H-4β), 2.77–2.88 (m, 2H, H-2, H-3), 3.26 (m, 1H, H-5), 3.45 (s, 3H, O–$CH_3$), 3.49 (m, 1H, H-1), 7.04 (d, 1H, $^3J = 7.9$ Hz, H-5′), 7.13 (dd, 1H, $^3J = 7.9$ Hz, $^4J = 1.6$ Hz, H-6′), 7.6 (d, 1H, $^4J = 1.6$ Hz, H-2′); $^{13}$C NMR, δ 25.1, 25.7, 27.4, 31.8, 33.9, 52.5, 62.0, 65.1, 100.8, 129.1, 137.7, 138.5, 142.5, 171.9; MS *m*/*z* 399 ($M^+$, 9), 97 (34), 96 (37), 83 (100), 82 (79), 42 (30). Anal. calcd for $C_{17}H_{22}INO_2$: C, 51.14; H, 5.55; N, 3.51. Found: C, 51.22; H, 5.51; N, 3.52.

**2β-Carbomethoxy-3β-(3′-iodo-4′-ethylphenyl) tropane 7b.** Compound **7b** was prepared from **6b** (650 mg, 2.27 mmol) to give an oil (310 mg, 34%) after purification by flash chromatography (hexane/AcOEt/$Et_3N$, 50/50/2); $^1$H NMR, δ 1.09 (t, 3H, $^3J = 7.5$ Hz, C$H_3$–$CH_2$), 1.44–

1.69 (m, 3H, H-4α, H-6α, H-7α), 1.83–2.04 (m, 2H, H-6β, H-7β), 2.14 (s, 3H, N–$CH_3$), 2.44 (td, 1H, $^3J_{3-4\beta} = {}^2J_{4\alpha-4\beta} = 12.2$ Hz, $^3J_{4\beta-5} = 2.7$ Hz, H-4β), 2.59 (q, 2H, $^3J = 7.5$ Hz, $CH_2$–$CH_3$, 2.77–2.90 (m, 2H, H-2, H-3), 3.27 (m, 1H, H-5), 3.45 (s, 3H, O–$CH_3$), 3.42–3.48 (m, 1H, H-1), 7.04 (d, 1H, $^3J = 8.0$ Hz, H-5′), 7.14 (dd, 1H, $^3J = 8.0$ Hz, $^4J = 1.7$ Hz, H-6′), 7.58 (d, 1H, $^4J = 1.7$ Hz, H-2′); $^{13}$C NMR, δ 14.4, 25.1, 25.7, 32.9 , 33.5, 33.9, 41.8, 51.1, 52.5, 62.1, 65.2, 100.1, 127.4, 127.8, 139.2, 142.6, 143.6, 171.9; MS *m*/*z* 413 ($M^+$, 7), 97 (33), 96 (34), 83 (100), 82 (77), 42 (28). Anal. calcd for $C_{18}H_{24}INO_2$: C, 52.31; H, 5.85; N, 3.39. Found: C, 51.49; H, 5.89; N, 3.41.

**2β-Carbomethoxy-3β-(3′-iodo-4′-*n*-propylphenyl) tropane 7c.** Compound **7c** was prepared from **6c** (500 mg, 1.66 mmol) to give an oil (340 mg, 48%) after purification by flash chromatography (hexane/AcOEt/$Et_3N$, 60/40/2); $^1$H NMR, δ 0.95–1.03 (t, 3H, $^3$J = 7.3 Hz, $CH_3$–$CH_2$), 1.52–1.72 (m, 5H, H-4α, H-6α, H-7α, $CH_3$–$CH_2$), 2.10–2.24 (m, 2H, H-6β, H-7β), 2.24 (s, 3H, N–$CH_3$), 2.54 (td, 1H , $^3J_{3-4\beta} = {}^2J_{4\alpha-4\beta} = 12.2$ Hz, $^3J_{4\beta-5} = 2.7$ Hz, H-4β), 2.64 (t, 2H, $^3J = 7.7$ Hz, Ph–$CH_2$), 2.87–2.97 (m, 2H, H-2, H-3), 3.37 (m, 1H, H-5), 3.54 (s, 3H, O–$CH_3$), 3.54–3.58 (m, 1H, H-1), 7.11 (d, 1H, $^3J = 7.9$ Hz, H-5′), 7.20 (dd, 1H, $^3J = 7.9$ Hz, $^4J = 1.7$ Hz, H-6′), 7.68 (d, 1H, $^4J = 1.7$ Hz, H-2′); $^{13}$C NMR, δ 13.8, 23.3, 25.1, 25.7, 32.9, 33.9, 41.9, 42.2, 51.1, 52.5, 62.1, 65.2, 100.4, 127.1, 128.6, 138.2, 142.3, 142.6, 171.9; MS *m*/*z* 427 ($M^+$, 8), 97 (38), 96 (37), 83 (100), 82 (81), 42 (30). Anal. calcd for $C_{19}H_{26}INO_2$: C, 53.40; H, 6.13; N, 3.28. Found: C, 53.54; H, 6.19; N, 3.31.

**2β-Carbomethoxy-3β-(3′-iodo-4′-isopropylphenyl) tropane 7d.** Compound **7d** was prepared from **6d** (440 mg, 1.46 mmol) to give an oil (475 mg, 76%) after purification by flash chromatography ($Et_2O$/$Et_3N$, 95/5); $^1$H NMR, δ 1.10 [d, 6H, $^3J = 6.8$ Hz, $CH(CH_3)_2$], 1.55 (m, 3H, H-4α, H-6α, H-7α), 2.07 (m, 2H, H-6β, H-7β), 2.14 (s, 3H, N–$CH_3$), 2.44 (td, 1H, $^2J_{4\alpha-4\beta} = {}^3J_{3-4\beta} = 12.2$ Hz, $^3J_{4\beta-5} = 2.7$ Hz, H-4β), 2.83 (m, 2H, H-2, H-3), 3.02 (sp, 1H, $^3J = 6.8$ Hz, $CH(CH_3)_2$], 3.40 (m, 1H, H-5), 3.43 (s, 3H, O–$CH_3$), 3.48 (m, 1H, H-1), 7.03 (d, 1H, $^3J = 8.1$ Hz, H-5′), 7.17 (dd, 1H, $^3J = 8.1$ Hz, $^4J = 1.7$ Hz, H-6′), 7.58 (d, 1H, $^4J = 1.7$ Hz, H-2′) ; $^{13}$C NMR, δ 23.7, 25.8, 26.4, 33.7, 34.6, 38.2, 42.6, 51.7, 53.1, 62.8, 65.9, 101.5, 125.8, 128.2, 139.1, 143.3, 148.2, 172.5 ; MS *m*/*z* 427 ($M^+$, 8), 396 (1), 368 (3), 97 (38), 96 (41), 83 (100), 82 (91). Anal. calcd for $C_{19}H_{26}INO_2$: C, 53.40; H, 6.13; N, 3.28. Found: C, 53.51; H, 6.17; N, 3.21.

**2β-Carbomethoxy-3β-(3′-iodo-4′-*n*-butylphenyl) tropane 7e.** Compound **7e** was prepared from **6e** (1 g, 3.17 mmol) to give an oil (275 mg, 21%) after purification by flash chromatography (hexane/$Et_3N$, 90/10): $^1$H NMR, δ 0.98 (t, 3H, $^3J = 7.2$ Hz, $CH_3$–$CH_2$–), 1.25–1.77 (m, 7H, H-4α, H-6α, H-7α? $CH_3$–$CH_2$–$CH_2$), 2.05–2.30 (m, 2H, H-6β, H-7β), 2.28 (s, 3H, N–$CH_3$), 2.58 (td, 1H, $^2J_{4\alpha-4\beta} = {}^3J_{3-4\beta} = 12.0$ Hz, $^3J_{4\beta-5} = 2.5$ Hz, H-4β), 2.68 (t, 2H, $^3J = 7.9$ Hz, Ph–$CH_2$), 2.89–3.00 (m, 2H, H-2, H-3), 3.39 (m, 1H, H-5), 3.56 (s, 3H, O–$CH_3$), 3.60 (m, 1H, H-1), 7.12 (d, 1Har, $^3J = 8.2$ Hz, H-5′), 7.23 (dd, 1Har, $^3J = 8.0$ Hz, $^4J = 1.2$ Hz, H-6′), 7.56 (d, $^4J = 1.6$ Hz, H-2′); $^{13}$C NMR, δ 13.8, 22.3, 25.1, 25.7, 32.3, 32.9, 33.9, 39.9, 41.8, 51.1, 52.5, 62.1, 65.2, 100.3, 127.2, 128.5, 138.2, 142.4, 142.6, 171.9; MS *m*/*z* = 441 ($M^+$, 5), 410 (1), 382 (2), 97 (33), 96 (33), 83 (100), 82 (76), 42 (28). Anal. calcd for $C_{20}H_{28}INO_2$: C, 54.43; H, 6.39; N, 3.17. Found: C, 54.37; H, 6.38; N, 3.19.

**General procedure of synthesis of 2β-carbomethoxy-3β-(3′iodo-4′substituted phenyl) nortropane (8a–e).** Compounds **8a**–**e** have been prepared from compounds **7a**–**e** as described previously.[9]

**2β-Carbomethoxy-3β-(3′-iodo-4′-tolyl) nortropane 8a.** Compound **8a** was prepared from **7a** (223 mg, 0.56 mmol) to give an oil (102 mg, 47%) after purification by flash chromatography (AcOEt/$Et_3N$: 75/5); $^1$H NMR, δ 1.42–1.68 (m, 3H, H-4α, H-6α, H-7α), 1.83–2.00 (m, 2H, H-6β, H-7β), 2.15–2.29 (td, 1H, $^3J_{3-4\beta} = {}^2J_{4\alpha-4\beta} = 13.0$ Hz, $^3J_{4\beta-5} = 2.9$ Hz, H-4β), 2.26 (s, 3H, Ph–$CH_3$), 2.59 (dd, 1H, $^3J_{2-3} = 5.7$ Hz, $^3J_{2-1} = 1.9$ Hz, H-2), 3.04 (dt, 1H, $^3J_{3-4\beta} = 12.8$ Hz, $^3J_{2-3} = {}^3J_{3-4\alpha} = 5.7$ Hz, H-3), 3.32 (s, 3H, O–$CH_3$), 3.59 (m, 2H, H-1, H-5), 6.96 (dd, 1H, $^3J = 7.8$ Hz, $^4J = 1.9$ Hz, H-6′), 7.02 (d, 1Har, $^3J = 7.8$ Hz, H-5′), 7.51 (d, 1Har, $^4J = 1.9$ Hz, H-2′); $^{13}$C NMR, δ 27.4, 27.6, 29.0, 33.7, 34.8, 50.9, 51.1, 53.5, 56.2, 101.0, 127.0, 129.3, 137.8, 139.3, 141.8, 173.6; MS *m*/*z* 385 ($M^+$, 13), 141 (10), 83 (93), 82 (55), 69 (100), 68 (74). Anal. calcd for $C_{16}H_{20}INO_2$: C, 49.88; H, 5.23; N, 3.64. Found: C, 50.03; H, 5.22; N, 3.63.

**2β-Carbomethoxy-3β-(3′-iodo-4′-ethylphenyl) nortropane 8b.** Compound **8b** was prepared from **7b** (230 mg, 0.56 mmol) to give an oil (81 mg, 37%) purification by after flash chromatography (AcOEt/$Et_3N$, 75/25); $^1$H NMR, δ 1.08 (t, 3H, $^3J = 7.5$ Hz, $CH_3$–$CH_2$), 1.41–1.71 (m, 3H, H-4α, H-6α, H-7α), 1.86–2.03 (m, 2H, H-6β, H-7β), 2.25 (td, 1H, $^3J_{3-4\beta} = {}^2J_{4\alpha-4\beta} = 13.0$ Hz, $^3J_{4\beta-5} = 3.0$ Hz, H-4β), 2.56 (q, 2H, $^3J = 7.5$ Hz, $CH_3$–$CH_2$), 2.53–2.65 (m, 2H, N–H, H-2), 3.07 (dt, 1H, $^3J_{3-4\beta} = 13.0$ Hz, $^3J_{2-3} = {}^3J_{3-4\alpha} = 5.5$ Hz, H-3), 3.33 (s, 3H, O–$CH_3$), 3.42–3.48 (m, 1H, H-1), 3.62 (m, 2H, H-1, H-5), 6.97 (s, 2Har), 7.3 (s, 1Har); $^{13}$C NMR, δ 14.4, 27.6, 29.0, 33.5, 33.7, 34.8, 50.9, 51.0, 53.5, 56.2, 100.2, 127.3, 128.0, 138.2, 141.8, 144.5, 173.6; MS *m*/*z* 399 ($M^+$, 12), 368 (2), 340 (2), 141 (12), 83 (95), 82 (52), 69 (100), 68 (71), 41(9). Anal. calcd for $C_{17}H_{22}INO_2$: C, 51.14; H, 5.55; N, 3.51. Found: C, 50.98; H, 5.56; N, 3.50.

**2β-Carbomethoxy-3β-(3′-iodo-4′-*n*-propylphenyl) nortropane 8c.** Compound **8c** was prepared from **7c** (200 mg, 0.47 mmol) to give an oil (120 mg, 53%) after purification by flash chromatography (AcOEt/$Et_3N$, 90/10); $^1$H NMR, δ 0.89 (t, 3H, $^3J = 7.3$ Hz, $CH_3$–$CH_2$), 1.46–1.66 (m, 5H, H-4α, H-6α, H-7α, $CH_3$–$CH_2$), 1.98–2.02 (m, 2H, H-6β, H-7β), 2.27 (td, 1H , $^3J_{3-4\beta} = {}^2J_{4\alpha-4\beta} = 12.4$ Hz, $^3J_{4\beta-5} = 3.0$ Hz, H-4β), 2.47 (broads, 1H, N–H), 2.52–2.64 (m, 3H, H-2, Ph–$CH_2$), 3.06 (dt, 1H, $^3J_{3-4\beta} = 14.0$ Hz, $^3J_{2-3} = {}^3J_{3-4\alpha} = 6.2$ Hz, H-3), 3.34 (s, 3H, O–$CH_3$), 3.61–3.63 (m, 2H, H-1, H-5), 7.02 (s, 2Har), 7.54 (s, 1Har); $^{13}$C NMR, δ13.6, 23.2, 27.5, 28.9, 33.6, 34.8, 42.1, 50.8, 51.1, 53.5, 56.2, 100.7, 127.1, 128.6, 128.9, 142.7, 144.2, 174.4. Anal. calcd for

$C_{18}H_{24}INO_2$: C, 52.31; H, 5.85; N, 3.39. Found: C, 52.38; H, 5.84; N, 3.38.

**2β-Carbomethoxy-3β-(3′-iodo-4′-isopropylphenyl) nortropane 8d.** Compound **8d** was prepared from **7d** (200 mg, 0.47 mmol) to give an oil (140 mg, 72%) after purification by flash chromatography ($AcOEt/Et_3N$, 90/10); $^1H$ NMR, δ 1.12 [d, 6H, $^3J = 6.8$ Hz, CH ($CH_3$)$_2$), 1.64 (m, 3H, H-4α, H-6α, H-7α), 1.98 (m, 2H, H-6β, H-7β), 2.27 (td, 1H, $^3J_{4\beta-5} = 2.6$ Hz, $^2J_{4\alpha-4\beta} = {}^3J_{3-4\beta} = 12.8$ Hz, H-4β), 2.63 (m, 1H, H-2), 3.05 [m, 3H, H-3, N–H, C*H* ($CH_3$)$_2$], 3.34 (s, 3H, O–$CH_3$), 3.64 (m, 2H, H-1, H-5), 7.06 (s, 2Har), 7.55 (s, 1Har); $^{13}C$ NMR, δ 23.7, 28.2, 29.6, 34.3, 35.5, 38.2, 51.5, 51.7, 54.2, 56.9, 101.6, 126.1, 128.1, 139.0, 142.5, 149.1, 174.3; MS *m*/*z* 413 ($M^+$, 10), 382 (1), 354 (2), 141 (13), 83 (92), 82 (57), 80 (11), 69 (100), 68 (94), 43 (20), 41 (26). Anal. calcd for $C_{18}H_{24}INO_2$: C, 52.31; H, 5.85; N, 3.39. Found: C, 52.13; H, 5.83; N, 3.39.

**2β-Carbomethoxy-3β-(3′-iodo-4′-*n*-butylphenyl) nortropane 8e.** Compound **8e** was prepared from **7e** (200 mg, 0.45 mmol) to give an oil (91 mg, 47%) after purification by flash chromatography ($Et_2O/Et_3N$, 75/25Ac); $^1H$ NMR, δ 0.96 (t, 3H, $^3J = 7.2$ Hz, $CH_3$–$CH_2$–), 1.27–1.78 (m, 7H, H-4α, H-6α, H-7α, $CH_3$–$CH_2$–$CH_2$), 1.90–2.17 (m, 2H, H-6β, H-7β), 2.35 (td, 1H, $^2J_{4\alpha-4\beta} = {}^3J_{3-4\beta} = 12.8$ Hz, $^3J_{4\beta-5} = 2.8$ Hz, H-4β), 2.67–2.72 (m, 4H, H-2, Ph–$CH_2$, N–H), 3.19 (dt, 1H, $^3J_{3-4\beta} = 12.8$ Hz, $^3J_{2-3} = {}^3J_{3-4\alpha} = 5.5$ Hz, H-3), 3.43 (s, 3H, O–$CH_3$), 3.68–3.75 (m, 2H, H-1, H-5), 7.11 (s, 2Har), 7.63 (s, 1Har); $^{13}C$ NMR, δ 13.8, 22.3, 27.5, 28.9, 32.2, 33.6, 34.8, 39.9, 50.8, 52.5, 53.5, 56.2, 100.4 (C-I), 127.1, 128.8, 138.2, 141.7, 143.3, 173.6 ; MS *m*/*z* 427 ($M^+$, 6), 83 (83), 82 (46), 69 (100), 68 (72), 41 (15). Anal. calcd for $C_{19}H_{26}INO_2$: C, 53.40; H, 6.13; N, 3.28. Found: C, 53.53; H, 6.15; N, 3.29.

### 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 three independent experiments in duplicate with a crude rat cerebral membrane homogenates from striatum (for DAT assays) in sodium hydrogenocarbonate buffer (pH 7.5) or frontoparietal cortex (for 5-HTT assays) in 50 mM Tris–HCl buffer (pH 7.4) containing NaCl (120 mM) and KCl (5 mM). For the DAT assays,[21] each sample contained 2.4 mL of incubation buffer with 0.01% bovine serum albumin, 0.4 mL [$^3H$] 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 100 g membrane protein preparation. Nonspecific binding was determined with $10^{-6}$ M mazindol provided by Sandoz. Samples were incubated at 37 °C for 1 h, filtered on glass fiber filters GF/B (Whatman), washed with ice-cold buffer and the residual radioactivity was measured with a beta counter (LKB, Rack Beta 1215). For the 5-HTT assays,[22] each sample contained 1.2 mL of Tris–HCl buffer, 0.2 mL [$^3H$] 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 g 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 DAT assays. Nonspecific binding was determined with $10^{-6}$ M fluvoxamine (a gift from Duphar). $K_i$ values were calculated from $IC_{50}$ values according to the method of Cheng and Prussoff:[23] $K_i = IC_{50} / [1 + (L/K_d)]$ where $L$ is the tracer concentration and $K_d$ the dissociation constant of this tracer.

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