

***N*- ω -Fluoroalkyl Analogs of (1*R*)-2 β -Carbomethoxy-3 β -(4-iodophenyl)-tropane (β -CIT): Radiotracers for Positron Emission Tomography and Single Photon Emission Computed Tomography Imaging of Dopamine Transporters**

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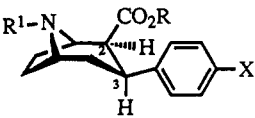
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Imaging techniques are increasingly applied to neurochemical and neuropharmacological studies of brain function. PET (positron emission tomography) and SPECT (single photon emission computed tomography) methods can be applied with high sensitivity in such studies. Though spatial resolution remains somewhat greater with PET, several advantages are offered by SPECT technology. Positron-emitting nuclides have short half-lives (e.g., ¹³C, 20 min; ¹⁸F, 109 min) that usually require an on-site cyclotron for their production, whereas SPECT nuclides have longer half-lives (e.g., ¹²³I, 13 h) and can be supplied commercially.

One potentially important application of PET or SPECT methods has been to demonstrate degeneration of dopamine neurons in the brain tissue of patients with Parkinson's disease. Though it had been proposed that profound loss of dopamine innervation of the basal ganglia ($\geq 85\%$) was required for clinical manifestation of Parkinsonism, recent imaging studies indicate that early symptoms can be detected with losses of only 50–60%.¹ This finding has increased interest in developing practical clinical methods to detect changes in dopamine neurons by brain scanning. The first successful application for this purpose used [¹⁸F]-DOPA (6-[¹⁸F]fluoro-L-3,4-dihydroxyphenylalanine) for PET studies of the corpus striatum in animal models and later in clinical neurological studies,^{2,3} with demonstrated loss of uptake of [¹⁸F]DOPA in the basal ganglia of Parkinson's disease patients compared to neurologically normal controls.⁴

Another approach to developing novel, selective neuron-labeling agents is to use radioligands with selective affinity for dopamine transporters—membrane proteins which are highly specific to dopamine neurons. Several such ligands

Table 1. *N*-(Fluoroalkyl)tropane Analogs



compd	R	R¹	X
1	CH₃	CH₃	I (β -CIT)
2	CH₃	CH₃	F (CFT)
3a	CH₃	H	I (nor- β -CIT)
3b	CH(CH₃)₂	H	I (IP-nor- β -CIT)
3c	CH(CH₃)₂	CH₃	I (IP- β -CIT)
4a	CH₃	CH₂CH₂CH₂F	I (β -CIT-FP)
4b	CH₃	CH₂CH₂CH₂F	Sn(CH₃)₃
5a	CH₃	CH₂CH₂F	I (β -CIT-FE)
5b	CH₃	CH₂CH₂F	Sn(CH₃)₃
6a	CH(CH₃)₂	CH₂CH₂CH₂F	I (IP- β -CIT-FP)
6b	CH(CH₃)₂	CH₂CH₂CH₂F	Sn(CH₃)₃
7a	CH(CH₃)₂	CH₂CH₂F	I (IP- β -CIT-FE)
7b	CH(CH₃)₂	CH₂CH₂F	Sn(CH₃)₃

have been reported for use in PET brain scanning. These include [¹¹C]cocaine,⁵ the dopamine transport blockers [¹¹C]nomifensine⁶ and [¹⁸F]GBR-133,119,⁷ and the analogs of cocaine, [¹¹C]- β -CIT ([¹¹C]-2 β -carbomethoxy-3 β -(4-iodophenyl)tropane)^{8,9} and [¹¹C]- β -CFT ([¹¹C]-2 β -carbomethoxy-3 β -(4-fluorophenyl)tropane) (Table 1).^{10,11} Recently, we¹² and others^{13,14} demonstrated that SPECT brain scanning with [¹²³I]-(1*R*)- β -CIT also can be used to demonstrate loss of dopamine innervation of the basal ganglia of Parkinson's disease patients. We had previously reported the synthesis of the 1*R*⁸ and 1*S*^{15,16} stereoisomers of β -CIT and demonstrated enantioselectivity for the 1*R* antipode at dopamine and serotonin transporters. All of these dopamine transporter labeling agents appear to have some technical shortcomings for use as imaging agents. For example, β -CIT has high affinity for serotonin (5-hydroxytryptamine) transporters as well as for those of dopamine, though most of the striatal labeling with this ligand after intravenous administration of a tracer dose of [¹²³I]- β -CIT appears to represent dopamine neurons.¹⁷

To extend the structure-activity relationships in tropanes as potential neuroradiological ligands, and to facilitate direct comparison of the same molecules in SPECT (¹²³I-labeled) and PET (¹⁸F-labeled) applications, we synthesized and characterized a series of *N*- ω -fluoroalkyl analogs of β -CIT (4a and 5a), as well as their isopropyl ester congeners IP- β -CIT (6a and 7a). The isopropyl esters were selected because of the observation that IP- β -CIT (3c) had greater affinity for the dopamine transporter than β -CIT.¹⁸ We also prepared the corresponding 4-trimethylstannyl derivatives (4b–7b), which can be used as precursors in the synthesis of radiolabeled β -CIT derivatives.

N-Fluoroalkyl analogs were prepared from nor- β -CIT (3a)⁸ or the corresponding isopropyl ester 3b¹⁹ by alkylation with the appropriate fluoroalkyl bromide in triethylamine. The iodophenyl compounds 4a–7a were stannylated by Pd(0)-catalyzed reaction with hexamethylditin²⁰ to give the corresponding 3 β -[4-(trimethylstannyl)phenyl]tropane precursors 4b–7b (Table 2). The ¹²³I-labeled form of β -CIT-FP (4a) was prepared as previously described for [¹²³I]- β -CIT^{8,21} by iododestannylation of the trimethylstannyl precursor with Na¹²³I in the presence of peracetic acid at pH 3–4 and purified by HPLC on a Novapak C18 column (4.6 \times 300 mm) with MeOH/H₂O/

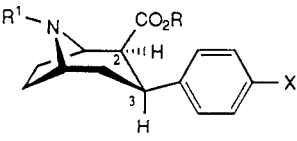
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Table 2. Physical Chemical Properties of *N*-(Fluoroalkyl)tropane Analogs


compd	R ¹	R	X	mp (°C)	[α] _D ²⁴ (deg)	formula ^a
4a (β-CIT-FP)	CH ₂ CH ₂ CH ₂ F	CH ₃	I	82–83	–12.8	C ₁₈ H ₂₃ NO ₂ FI
5a (β-CIT-FE)	CH ₂ CH ₂ F	CH ₃	I	99–101	–6.4 ^b	C ₁₇ H ₂₁ NO ₂ FI
6a (IP-CIT-FP)	CH ₂ CH ₂ CH ₂ F	CH(CH ₃) ₂	I	94–95	–14.7	C ₂₀ H ₂₇ NO ₂ FI
7a (IP-CIT-FE)	CH ₂ CH ₂ F	CH(CH ₃) ₂	I	79–80	–11.1	C ₁₉ H ₂₅ NO ₂ FI
4b	CH ₂ CH ₂ CH ₂ F	CH ₃	Sn(CH ₃) ₃	<i>d</i>	–14.6	C ₂₁ H ₃₂ NO ₂ FSn
5b	CH ₂ CH ₂ F	CH ₃	Sn(CH ₃) ₃	<i>d</i>	–12.4	C ₂₀ H ₃₀ NO ₂ FSn
6b	CH ₂ CH ₂ CH ₂ F	CH(CH ₃) ₂	Sn(CH ₃) ₃	<i>d</i>	–17.6	C ₂₃ H ₃₆ NO ₂ FSn
7b	CH ₂ CH ₂ F	CH(CH ₃) ₂	Sn(CH ₃) ₃	<i>d</i>	–16.2	C ₂₂ H ₃₄ NO ₂ FSn

^a The analytical results of C, H, N were within ±0.4% of the theoretical values. ^b Measured at 18 °C. ^c The 300-MHz NMR spectra (CDCl₃) were consistent with their assigned structures. ^d Colorless oil.

Table 3. Affinity (*K_i*) of *N*-(Fluoroalkyl)tropanes at Dopamine Transporters (DA_T) in Rat Brain Tissue^a

compd	K _i (nM)
cocaine	510 ± 110
β-CIT (1)	1.40 ± 0.20
β-CFT (2)	14.7 ± 2.9
β-CIT-FP (4a)	3.50 ± 0.39
β-CIT-FP-Sn(CH ₃) ₃ (4b)	>10000
β-CIT-FE (5a)	4.00 ± 0.73
β-CIT-FE-Sn(CH ₃) ₃ (5b)	>10000
IP-β-CIT-FP (6a)	1.20 ± 0.29
IP-β-CIT-FP-Sn(CH ₃) ₃ (6b)	>10000
IP-β-CIT-FE (7a)	4.40 ± 0.35
IP-β-CIT-FE-Sn(CH ₃) ₃ (7b)	1150 ± 320

^a Agents were tested, at six concentrations in duplicate, with a crude membrane fraction of homogenates of rat brain corpus striatum with radioligand concentration (*L*) = 0.4 nM [³H]GBR-12935 (13 Ci/mmol; *K_d* = 1.0 nM) and 30 μM methylphenidate as blank for DA_T (ref 22). Concentration–inhibition curves were computer-fit to determine IC₅₀ ± SEM and converted to *K_i* values from the relationship *K_i* = IC₅₀/(1 + [*L*/*K_d*]) (ref 22).

Table 4. Behavioral Activity of *N*-(Fluoroalkyl)tropanes: Locomotor Arousal in Rat^a

compd	<i>N</i> (rats)	dose (mg/kg)	counts/h ± SEM		
			hour 1	hour 2	hour 3
vehicle control	7	0	815 ± 27	427 ± 25	162 ± 20
cocaine	3	1	14940 ± 1030*	1960 ± 319*	–
	3	3	15710 ± 1150*	712 ± 113*	–
β-CIT (1)	4	1	6820 ± 373*	9990 ± 615*	9710 ± 413*
β-CIT-FP (4a)	3	0.3	759 ± 38	403 ± 26	210 ± 33
	3	1	1943 ± 36*	1071 ± 20*	325 ± 51
	3	3	3791 ± 253*	2109 ± 123*	1410 ± 203*
β-CIT-FE (5a)	3	0.3	2030 ± 61*	2945 ± 167*	3459 ± 212*
	3	1	4180 ± 116*	4200 ± 97*	4400 ± 117*
	3	3	6398 ± 244*	7796 ± 348*	7562 ± 434*

^a Adult (150–200 g) male Sprague–Dawley rats were injected intraperitoneally (ip) with saline containing DMSO (vehicle control) or a test agent, and locomotion was quantified in an electronic activity monitor at hourly intervals, as described previously²³ with data expressed as mean ± SEM activity counts/hour at 0–1, 1–2, and 2–3 h. By ANOVA, there was a very significant overall effect of treatment (*F*_{4,15} = ≥18.6 at each hour, *p* < 0.0001), and by dose of the novel fluoroalkyl derivatives of β-CIT (for 4a; *F*_{2,6} ≥ 29; for 5a; *F*_{2,6} ≥ 56; all *p* < 0.001). An asterisk (*) indicates significant differences from corresponding vehicle controls by post-hoc *t* tests (*t* ≥ 6.0, *p* < 0.001).

Et₃N (75:25:0.2, 1.0 mL/min, *t_R* 10.8) min. The product, obtained in 64% radiochemical yield and 98% radiochemical purity, was formulated in 5% ethanol/isotonic saline solution containing 0.1 mM L-ascorbic acid.

Affinities of the fluoroalkyl analogues 4a–7a for DA transporter were determined from radioligand displacement studies using corpus striatum tissue homogenates

prepared from rat brain and compared with β-CIT, its fluorinated congener, CFT (2), CIT (1) (Table 3), and cocaine.

The (trimethylstannyl)phenyl-substituted derivatives (4b, 5b, 6b, 7b) all showed very low affinity, and all of the other para-iodinated β-CITs (4a, 5a, 6a, 7a) had similarly much higher affinity (1–4 nM) than cocaine (510 nM). Compound 6a showed slightly greater affinity than β-CIT itself, while compounds 4a, 5a, and 7a had slightly less. That is, *N*-alkyl substitution with a fluoroethyl or fluoropropyl moiety yielded compounds with similar high affinity to the DA transporter.

Preliminary behavior testing compared compounds 4a and 5a to cocaine and β-CIT (1) (Table 4). All three β-CIT congeners induced somewhat less initial behavioral arousal than cocaine during the first hour of behavioral monitoring for locomotion (all at a dose of 1 mg/kg, ip) but produced sustained effects above control levels that persisted for at least 3 h. β-CIT itself showed the greatest stimulatory effect in the third hour of monitoring, while compound 4a (the *N*-fluoropropyl analog of β-CIT) more rapidly lost its efficacy by the third hour and had little effect at the lowest dose tested (0.3 mg/kg) at any time. This *in vivo* activity suggests that a functional antagonistic interaction at dopamine transporter may contribute significantly to the arousal-inducing activity of these compounds. However, *in vivo* activity was not consistently predicted by *in vitro* affinity. Thus, while both 4a and 5a had somewhat lower affinity at the dopamine transporter than β-CIT itself and seemed correspondingly less potent *in vivo*, compound 4a had slightly higher *in vitro* affinity than 5a but was clearly less potent *in vivo* (Tables 3 and 4). These differences may reflect dissimilarities in tissue distribution or metabolism of the compounds tested *in vivo*.

The high affinity of these agents for the DA transporter suggests that they may be useful imaging agents for either SPECT (labeled with ¹²³I) or PET (labeled with ¹⁸F). To assess this possibility, SPECT imaging was carried out with a Strichman 810X Brain Imager for 5 h after intravenous administration of 7.8 mCi [¹²³I]-β-CIT-FP (4a) to a 10-kg adult female baboon under isoflurane anesthesia as previously described for [¹²³I]-β-CIT.¹⁷ Data were acquired in the striatum (an area rich in dopamine transporters) and midbrain (rich in serotonin transporters) compared to reference regions in the occipital cortex and cerebellum (Figure 1). There was significant uptake in the striatal region, with total uptake peaking (100%) at 90 min postinjection (pi), and washing out at a rate of 4.8%/h; in contrast, lower uptake and more rapid washout

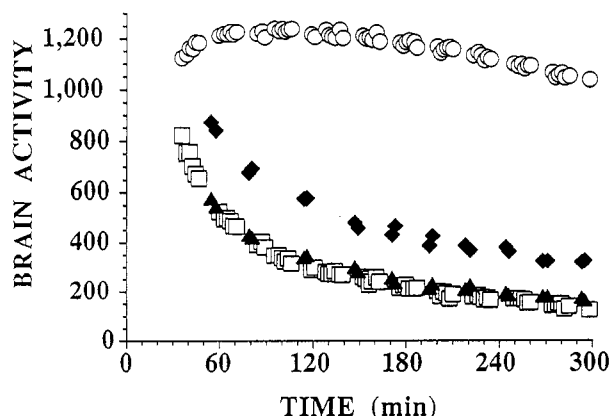


Figure 1. Dynamic regional brain uptake after intravenous administration of 7.8 mCi [^{123}I]- β -CIT-FP (4a) in an adult female baboon. Uptake was measured in the region of the striatum (O), occipital cortex (□), midbrain (◆), and cerebellum (▲). Activity is expressed in units provided by the camera manufacturer (Strichman Medical Equipment, Medfield, MA) such that 1 unit of activity represents approximately 100 Bq/mL.

was observed in the midbrain region, peaking before 60 min and washing out at a rate of 16%/h over the same period. The ratio of uptake in striatum to the occipital cortex was 3.4 at peak striatal uptake and increased with time, reaching 5.0 at 5 h, when the experiment ended, whereas the ratio of midbrain to cerebellum remained at 1.9 to 1.7 over the same period. The striatal washout of [^{123}I]- β -CIT-FP ($\approx 5\%/h$) was faster than that reported for [^{123}I]- β -CIT (0.6%/h)¹⁷ but had approximately similar distribution of activity in striatal and midbrain regions. The short brain clearance time for [^{123}I]- β -CIT-FP is in accord with the short behavioral action of β -CIT (Table 4).

We are currently measuring the relative *in vitro* affinities of these analogs for the 5-HT transporter, but these results may not reflect their *in vivo* selectivity, since discrepancies are common between *in vivo* and *in vitro* characteristics of radiotracers. For example, homogenate binding studies have shown that β -CIT has similar affinity for both DA and 5-HT transporters (with IC_{50} values of 2–4 nM).⁸ In contrast, SPECT imaging studies have shown that midbrain activity is closely associated with DA transporters in the striatum.¹⁷ Such differences between *in vivo* and *in vitro* results for neuroreceptor tracers are fairly common and have been postulated to reflect either physical characteristics of the tracer (e.g., lipophilicity) or anatomic organization of the target site (e.g., a "synaptic barrier" which impedes the removal of tracer from the brain).²⁵ The fact that a single compound such as [^{123}I]- β -CIT shows similar affinity for two target sites but still demonstrates differential washout rates suggests that the "synaptic barrier" associated with the 5-HT transporter is different from that of the DA transporter. Although the relative affinities of a series of compounds may be compared with regard to a common target, extrapolation to different targets may not be valid.

In summary, this series of fluoroalkyl phenyltropane derivatives showed high affinity for the dopamine transporter and are promising agents for imaging with either PET (labeled with ^{18}F) or SPECT (labeled with ^{123}I). One compound ([^{123}I]- β -CIT-FP) evaluated in this preliminary study when imaged with SPECT showed high ratios of target to background activity. This agent showed somewhat faster washout rate than [^{123}I]- β -CIT, and together

with its high uptake in the striatum and relative specificity with respect to cortical, midbrain, and cerebellar areas may be a valuable tracer for studying the dopamine system *in vivo* by tomographic imaging.

The regional brain uptake and pharmacokinetics of [^{123}I]- N -(ω -fluoroalkyl)-2 β -carboxy-3 β -(4-iodophenyl)nortropane esters in baboons is reported elsewhere.²⁴ Human studies and labeling experiments with ^{18}F imaging are currently in progress.

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