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

John L. Neumeyer,*,†,‡ Shaoyin Wang,‡ Yigong Gao,† Richard A. Milius,† Nora S. Kula,§ Alexander Campbell,§ Ross J. Baldessarini,§ Yolanda Zea-Ponce,⊥ Ronald M. Baldwin,⊥ and Robert B. Innis⊥

Research Biochemicals International, One Strathmore Road, Natick, Massachusetts 01760, Section of Medicinal Chemistry, Bouve College of Pharmacy and Allied Health Professions, Northeastern University, Boston, Massachusetts 02115, Department of Psychiatry and Neuroscience Program, Harvard Medical School and Mailman Research Center, McLean Division of Massachusetts General Hospital, Belmont, Massachusetts 02178, and Department of Psychiatry, Yale University, School of Medicine and VA Medical Center, West Haven, Connecticut 06516

Received February 25, 1994

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.*, ^{13}C, 20 min; ^{18}F, 109 min) that usually require an on-site cyclotron for their production, whereas SPECT nuclides have longer half-lives (*e.g.*, ^{123}I, 13 h) and can be supplied commercially.

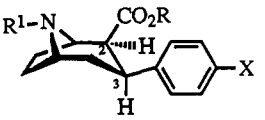
One potentially important application of PET or SPECT methods has been to demonstrate degeneration of dopamine neurons in the brain tissue of patients with Parkinson's disease. Though it had been proposed that profound loss of dopamine innervation of the basal ganglia (≥85%) was required for clinical 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 [^{18}F]-DOPA (6-[^{18}F]fluoro-L-3,4-dihydroxyphenylalanine) for PET studies of the corpus straitum in animal models and later in clinical neurological studies,[2,3] with demonstrated loss of uptake of [^{18}F]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 have been reported for use in PET brain scanning. These include [^{11}C]cocaine,[5] the dopamine transport blockers [^{11}C]nomifensine[6] and [^{18}F]GBR-133,119,[7] and the analogs of cocaine, [^{11}C]-β-CIT ([^{11}C]-2β-carbomethoxy-3β-(4-iodophenyl)tropane)[8,9] and [^{11}C]-β-CFT ([^{11}C]-2β-carbomethoxy-3β-(4-fluorophenyl)tropane) (Table 1).[10,11] Recently, we[12] and others[13,14] demonstrated that SPECT brain scanning with [^{123}I]-(1R)-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 1R[8] and 1S[15,16] stereoisomers of β-CIT and demonstrated enantioselectivity for the 1R 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-hydroxytrypamine) 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 [^{123}I]-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 (^{123}I-labeled) and PET (^{18}F-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 **3b**[19] by alkylation with the appropriate fluoroalkyl bromide in triethylamine. The iodophenyl compounds **4a–7a** were stannylated by Pd(0)-catalyzed reaction with hexamethylditin[20] to give the corresponding 3β-[4-(trimethylstannyl)phenyl]tropane precursors **4b–7b** (Table 2). The ^{123}I-labeled form of β-CIT-FP (**4a**) was prepared as previously described for [^{123}I]-β-CIT[8,21] by iododestannylation of the trimethylstannyl precursor with Na[^{123}I] in the presence of peracetic acid at pH 3–4 and purified by HPLC on a Novapak C18 column (4.6 × 300 mm) with MeOH/H_2O/

Table 1. N-(Fluoroalkyl)tropane Analogs

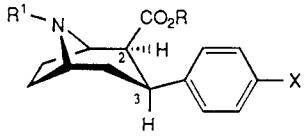


compd	R	R¹	X
1	CH_3	CH_3	I (β-CIT)
2	CH_3	CH_3	F (CFT)
3a	CH_3	H	I (nor-β-CIT)
3b	$CH(CH_3)_2$	H	I (IP-nor-β-CIT)
3c	$CH(CH_3)_2$	CH_3	I (IP-β-CIT)
4a	CH_3	$CH_2CH_2CH_2F$	I (β-CIT-FP)
4b	CH_3	$CH_2CH_2CH_2F$	$Sn(CH_3)_3$
5a	CH_3	CH_2CH_2F	I (β-CIT-FE)
5b	CH_3	CH_2CH_2F	$Sn(CH_3)_3$
6a	$CH(CH_3)_2$	$CH_2CH_2CH_2F$	I (IP-β-CIT-FP)
6b	$CH(CH_3)_2$	$CH_2CH_2CH_2F$	$Sn(CH_3)_3$
7a	$CH(CH_3)_2$	CH_2CH_2F	I (IP-β-CIT-FE)
7b	$CH(CH_3)_2$	CH_2CH_2F	$Sn(CH_3)_3$

* Address Correspondence to: Dr. J. L. Neumeyer, Research Biochemicals International, One Strathmore Road, Natick, MA 01760. Tel: 508-651-8151. Fax: 508-655-1359.
† Research Biochemicals International.
‡ Bouve College of Pharmacy and Allied Health Professions.
§ Harvard Medical School and Mailman Research Center.
⊥ Yale University.

0022-2623/94/1837-1558$04.50/0

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



compd	R^1	R	X	mp (°C)	$[\alpha]^{24}_D$ (deg)	formula[a]
4a (β-CIT-FP)	$CH_2CH_2CH_2F$	CH_3	I	82–83	−12.8	$C_{18}H_{23}NO_2FI$
5a (β-CIT-FE)	CH_2CH_2F	CH_3	I	99–101	−6.4[b]	$C_{17}H_{21}NO_2FI$
6a (IP-CIT-FP)	$CH_2CH_2CH_2F$	$CH(CH_3)_2$	I	94–95	−14.7	$C_{20}H_{27}NO_2FI$
7a (IP-CIT-FE)	CH_2CH_2F	$CH(CH_3)_2$	I	79–80	−11.1	$C_{19}H_{25}NO_2FI$
4b	$CH_2CH_2CH_2F$	CH_3	$Sn(CH_3)_3$	*d*	−14.6	$C_{21}H_{32}NO_2FSn$
5b	CH_2CH_2F	CH_3	$Sn(CH_3)_3$	*d*	−12.4	$C_{20}H_{30}NO_2FSn$
6b	$CH_2CH_2CH_2F$	$CH(CH_3)_2$	$Sn(CH_3)_3$	*d*	−17.6	$C_{23}H_{36}NO_2FSn$
7b	CH_2CH_2F	$CH(CH_3)_2$	$Sn(CH_3)_3$	*d*	−16.2	$C_{22}H_{34}NO_2FSn$

[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 ($CDCl_3$) 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 [^{3}H]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 IC_{50} ± SEM and converted to K_i values from the relationship $K_i = IC_{50}/(1 + [L/K_d])$ (ref 22).

Table 4. Behavioral Activity of *N*-(Fluoroalkyl)tropanes: Locomoter Arousal in Rat[a]

compd	*N* (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	6898 ± 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 previously[23] 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**; $F_{2,6} \geq 29$; for **5a**: $F_{2,6} > 56$; all $p < 0.001$). An asterisk (*) indicates significant differences from corresponding vehicle controls by post-hoc t tests ($t \geq 6.0, p < 0.001$).

Et_3N (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 ^{123}I) or PET (labeled with ^{18}F). 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 [^{123}I]-β-CIT-FP (**4a**) to a 10-kg adult female baboon under isofluorane anesthesia as previously described for [^{123}I]-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

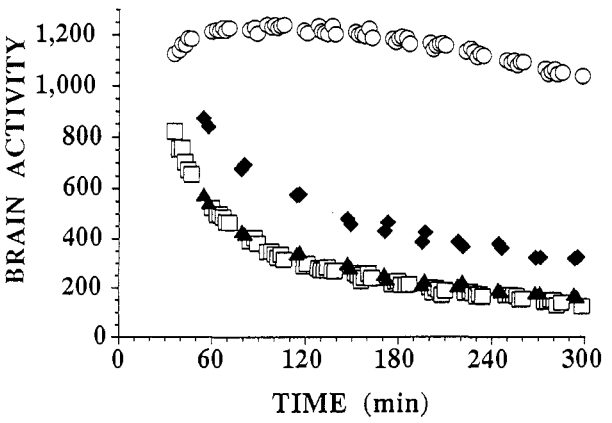


Figure 1. Dynamic regional brain uptake after intravenous administration of 7.8 mCi [^{123}I]-β-CIT-FP (**4a**) in an adult female baboon. Uptake was measured in the region of the striatum (○), occipital cortex (□), midbrain (◆), and cerebellum (▲). Activity is expressed in units provided by the camera 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 (≈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)-2β-carboxy-3β-(4-iodophenyl)nortropane esters in baboons is reported elsewhere.[24] Human studies and labeling experiments with ^{18}F imaging are currently in progress.

Acknowledgment. This work was supported in part by U.S. Public Health Service (NIMH) Grants MH-49533 (to J.L.N.) and MH-34006 and MH-47370 (to R.J.B.), an award from the Bruce J. Anderson Foundation (to R.J.B.), and a grant in aid from RBI to S.W. at Northeastern University.

References

(1) Leenders, K. L.; Salmon, E. P.; Tyrell, P.; Perani, D.; Brooks, D. J.; Sager, H.; Jones, T.; Marsden, D.; Frackowiak, R. S. J. The nigrostriatal dopaminergic system assessed *in vivo* by positron emission tomography in healthy volunteer subjects and patients with Parkinson's disease. *Arch. Neurol.* **1990**, *47*, 1290–1298.

(2) Garnett, E. S.; Firnau, G.; Chan, P. K. H.; Sood, S.; Belbeck, L. W. [^{18}F]-Fluoro-dopa, and analogue of dopa, and its use in direct external measurements of storage, degradation, and turnover of intracerebral dopamine. *Proc. Natl. Acad. Sci. U.S.A.* **1978**, *75*, 464.

(3) Garnett, E. S., Firnau, G.; Nahmias, C. Dopamine visualized in the basal ganglia of living man. *Nature* **1983**, *305*, 137.

(4) Calne, D. B.; Langston, J. W.; Martin, W. R. W.; Stoessl, A. J.; Ruth, T. J.; Adam, M. J.; Pate, B. D.; Schulzer, M.: Positron emission tomography after MPTP: observations relating to the cause of Parkinson's disease. *Nature* **1985**, *317*, 246–248.

(5) Fowler, J. S.; Volkow, N. D.; Wolf, A. P.; Dewey, S. L.; Schyler, D. J.; MacGregor, R. R.; Hitzemann, R.; Logan, J.; Bendriem, B.; Gatley, S. J.; Christman, D.: Mapping cocaine binding sites in human and baboon brain *in vivo*. *Synapse* **1989**, *4*, 371–377.

(6) Aquilonius, S. M.; Bergström, K.; Eckernas, S. A.; Hartvig, P.; Leenders, K. L.; Lundquist, H.; Antoni, G.; Gee, A.; Rimland, A.; Uhlin, J.; Langstrom, B. *In vivo* evaluation of striatal dopamine reuptake sites using ^{11}C-nomifensine and positron emission tomography. *Acta Neurol. Scand.* **1987**, *76*, 283–287.

(7) Kilbourn, M. R.; Carey, J. E.; Koeppe, R. A.; Haka, M. S.; Hutchines, G. D.; Sherman, P. S.; Kuhl, D. E. Biodistribution, dosimetry, metabolism, and monkey PET studies of [18F]GBR 13119. Imaging the dopamine uptake system *in vivo*. *Nucl. Med. Biol.* **1989**, *16*, 569–576.

(8) Neumeyer, J. L.; Wang, S.; Milius, R. A.; Baldwin, R. M.; Zea-Ponce, Y.; Hoffer, P. B.; Sybirska, E.; Al-Tikriti, M.; Charney, D. S.; Malison, R. T.; Laruelle, M.; Innis, R. B. [^{123}I]-2β-Carbomethoxy-3β-(4-iodophenyl)tropane: High affinity SPECT radiotracer of monoamine reuptake sites in brain. *J. Med. Chem.* **1991**, *34*, 3144–3146.

(9) Müller, L.; Halldin, C.; Farde, L.; Karlsson, P.; Hall, H.; Swahn, C. G.; Neumeyer, J. L.; Gao, Y.; Milius, R.: [^{11}C]β-CIT, a cocaine analogue: preparation, autoradiography and preliminary PET investigations. *Nucl. Med. Biol.* **1993**, *20*, 249–255.

(10) Wong, D. F.; Yung, B.; Dannals, R. F.; Shaya, E. K.; Ravert, H. T.; Chen, C. A.; Chan, B.; Folio, T.; Scheffel, U.; Ricaurte, G. A.; Neumeyer, J. L.; Wagner, H. N., Jr.; Kuhar, M. J. *In Vivo* Imaging of baboon and human dopamine transporters by Positron Emission Tomography Using [^{11}C]CFT. *Synapse* **1993**, *15*, 130–142.

(11) Hantraye, P.; Brownell, A.-L.; Elmaleh, D.; Spealman, R. D.; Wullner, U.; Brownell, G. L.; Madras, B. K.; Isacson, O. Dopamine fiber detection by [^{11}C]CFT and PET in a primate model of parkinsonism. *NeuroReport* **1992**, *3*, 265–268.

(12) Innis, R. B.; Seibyl, J. P.; Scanley, B. E.; Laruelle, M.; Abi-Dargham, A.; Wallace, E.; Baldwin, R. M.; Zea-Ponce, Y.; Zoghbi, S.; Wang, S.; Gao, Y.; Neumeyer, J. L.; Charney, D. S.; Hoffer, P. B.; Marek, K. L. Single photon emission computed tomographic imaging demonstrates loss of striatal dopamine transporters in Parkinson's disease. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 11965–11969.

(13) Kuikka, J. T.; Bergström, K. A.; Vanninen, E.; Laulumaa, V.; Hartikainen, P.; Länsimies, E. Initial experience with single-photon emissionm tomography using iodine-123-labelled 2β-carbomethoxy-3β-(4-iodophenyl)tropane in human brain. *Eur. J. Nucl. Med.* **1993**, *20*, 783–786; **1994**, *21*, 53–56.

(14) Brucke, T.; Kornhuber, J.; Angelberger, P.; Aenbaum, S.; Frassine, H.; Podreka, I. SPECT imaging of dopamine and serotonin transporters with [^{123}I]β-CIT. Binding kinetics in the human brain. *J. Neural Transm.* [Gen Sect] **1993**, *94*, 137–146.

(15) Wang, S.; Gao, Y.; Laruelle, M.; Baldwin, R. M.; Scanley, B. E.; Innis, R. B.; Neumeyer, J. L.: Enantioselectivity of cocaine recognition sites: binding of (1S)- and (1R)-2β-carbomethoxy-3β-(4-iodophenyl) tropane (β-CIT) to monoamine transporters. *J. Med. Chem.* **1993**, *36*, 1914–1917.

(16) Scanley, B. E.; Baldwin, R. M.; Laruelle, M.; Al-Tikriti, M. S.; Zea-Ponce, Y.; Zoghbi, S.; Giddings, S. S.; Cheney, D. S.; Wang, S.; Gao, Y.; Neumeyer, J. L.; Hoffer, P. B.; Innis, R. B. Active and inactive enantiomers of β-CIT: comparison using homogenate binding and SPECT imaging. *Mol. Pharmacol.* **1994**, *45*, 136–141.

(17) Laruelle, M.; Baldwin, R. M.; Malison, R. T.; Zea-Ponce, Y.; Zoghbi, S. S.; Al-Tikriti, M. S.; Sybirska, E. H.; Zimmermann, R.; Wisniewski, G.; Neumeyer, J. L.; Milius, R. A.; Wang, S.; Smith, E. O.; Roth, R. H.; Charney, D. S.; Hoffer, P. B.; Innis, R. B. SPECT imaging of dopamine and serotonin transporters with [^{123}I]β-CIT: Pharmacological characterization of brain uptake in nonhuman primates, *Synapse* **1993**, *13*, 295–309.

(18) Carroll, F. I.; Abraham, P.; Lewin, A. H.; Parham, K. A.; Boja, J. W.; Kuhar, M. J. Isopropyl and phenyl esters of 3β-(4-substituted phenyl) tropan-2β-carboxylic acids—potent and selective compounds for the dopamine transporter, *J. Med. Chem.* **1992**, *35*, 2497–2500.

(19) The isopropyl ester **3b** was prepared from β-CIT (1) by hydrolysis of the ester in water to yield the corresponding carboxylic acid (mp 288–289 °C), which was converted to the acid chloride with thionyl chloride followed by addition of isopropyl alcohol in Et_3N to yield (58%) of **3b** (mp 119–120 °C).

(20) Azizian, H.; Eaborn, C.; Pidcock, A. Synthesis of organotrialkylstannanes. The reaction between organic halides and hexaalkyldistannanes in the presence of palladium complexes. *J. Organomet. Chem.* **1981**, *215*, 49–58.

(21) Baldwin, R. M.; Zea-Ponce, Y.; Zoghbi, S. S.; Laruelle, M.; Al-Tikriti, M. S.; Sybirska, E. H.; Malison, R. T.; Neumeyer, J. L.; Milius, R. A.; Wang, S.; Stabin, M.; Smith, E. O.; Charney, D. S.; Hoffer, P. B.; Innis, R. B. Evaluation of the monamine uptake site ligand [^{123}I] methyl 3β-(4-iodophenyl)tropane-2β-carboxylate ([^{123}I]β-CIT) in nonhuman primates: pharmacokinetics, biodistribution, and SPECT brain imaging coregistered with MRI. *Nucl. Med. Biol.* **1993**, *20*, 597–606.

(22) Kula, N. S.; Baldessarini, R. J.: Lack of increase in dopamine transporter binding or function in rat brain tissue after treatment with blockers of neuronal uptake of dopmine. *Neuropharmacology* **1991**, *30*, 89–92.

(23) Campbell, A.; Baldessarini, R. J.; Neumeyer, J. L. Altered spontaneous behavior and sensitivity to apomorphine in rats following pretreatment with S(+)-apomorphine or fluphenazine. *Psychopharmacology* **1993**, *111*, 351–358.

(24) Baldwin, R. M.; Zea-Ponce, Y.; Al-Tikriti, M. S.; Zoghbi, S. S.; Seibyl, J. P.; Charney, D. S.; Hoffer, P. B.; Wang, S.; Milius, R. A.; Neumeyer, J. L.; Innis, R. B. *Nucl. Med. Biol.* In press.

(25) Kessler, R. M.; Ansan, M. S.; de Paulis, T.; Schmidt, D. E.; Clanton, J. A.; Smith, H. E.; Manning, R. G.; Gillespie, D.; Ebert, M. H. High affinity D_2 receptor radioligands. Regional rat brain distribution of iodinated benzamides. *J. Nucl. Med.* **1991**, *32*, 1593–1600.