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Synthesis and Biological Evaluation of a Series of Novel *N*- or *O*-Fluoroalkyl Derivatives of Tropane: Potential Positron Emission Tomography (PET) Imaging Agents for the Dopamine Transporter

Xiao-Hui Gu,[a,c] Rushi Zong,[a,c] Nora S. Kula,[b] Ross J. Baldessarini[b] and John L. Neumeyer[a,c,*]

[a]*Medicinal Chemistry Laboratory, Alcohol and Drug Abuse Research Center, Belmont, MA 02478-9106, USA*
[b]*Neuroscience Program, Mailman Research Center, McLean Hospital, Harvard Medical School, Belmont, MA 02478-9106, USA*
[c]*Natural Pharmacia International, Inc., 115 Mill Street, Belmont, MA 02478-9106, USA*

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Abstract—A series of novel fluoroalkyl-containing tropane derivatives was synthesized, and their binding affinities for the dopamine transporter (DAT), serotonin transporter (SERT), and norepinephrine transporter (NET) were determined via competitive binding assays. Among these derivatives, the fluoropropyl ester of β-CIT (**19**), the fluoroethyl ester of β-CIT (**20**), the *N*-fluoropropyl derivative of β-CBT (**12**), and the fluoropropyl ester of β-CMT (**18**) displayed higher affinity and greater selectivity for the DAT versus SERT and NET than FP-CIT, which indicates that they are attractive candidates for the development of ^{18}F-labeled PET imaging agents for the DAT.

Positron emission tomography (PET) is a sensitive and specific non-invasive imaging technology that can provide information about the functional status of neurotransmitter systems in vivo.[1–3] PET has emerged as an important tool in drug discovery, research and development.[4–8] Desirable properties of a PET radiotracer include: (1) high affinity for target and low affinity for nontargets, (2) sufficient lipophilicity or carrier system to cross cell membranes, (3) low peripheral metabolism, and (4) efficient labeling with radioactive isotopes.

The dopamine transporter (DAT) is a membrane-bound protein with 12 putative transmembrane segments, selectively expressed by dopamine neurons and located with relatively high density at the presynaptic dopaminergic nerve terminals. The function of the DAT is to terminate the neurochemical action of released dopamine by reuptake into the presynaptic dopaminergic neurons.[9] Changes in the density and function of DAT have been implicated in neurodegenerative and neuropsychiatric diseases such as Parkinson's disease,[10,11] major depression,[12] Huntington's chorea,[13] schizophrenia,[14] and attention deficit-hyperactivity disorder (ADHD).[15,16] DAT also plays a prominent role in the reinforcing effects of cocaine and other stimulants.[17–20]

There has been a great deal of recent effort to prepare PET-based radiotracers for use in studies of DAT abundance and pharmacology. Most such PET radiotracers for DAT labeling have been carbon-11 labeled 2β - carbomethoxy - 3β - (4 - substituted - phenyl)tropane derivatives.[21–28] Several fluorine-18 labeled tropane derivatives are also known. These include CFT,[29] FP-CFT,[28] FP-CIT,[30–32] FECT,[33] FETT,[33] FPCT,[34] FECNT,[35] and FIPCT,[36] in which the methyl group at the 8-position of the tropane was replaced by a 3-fluoropropyl group or a 2-fluoroethyl group or the 2β-methyl ester by a 2β-2′-fluoroethyl ester and a 2β-1′-fluoro-isopropoxy ester. Most recently, the fluorine-18 labeled 2β-propanoyl-3β-(4-substituted-phenyl)tropane derivatives FTT and FCT, which contain a 2β-ketone moiety instead of a 2β-ester group, were reported by Mach et al.[37] Some of these radioligands show promise

*Corresponding author. Tel.: +1-617-855-3388; fax: +1-617-855-2519; e-mail: neumeyer@mclean.harvard.edu

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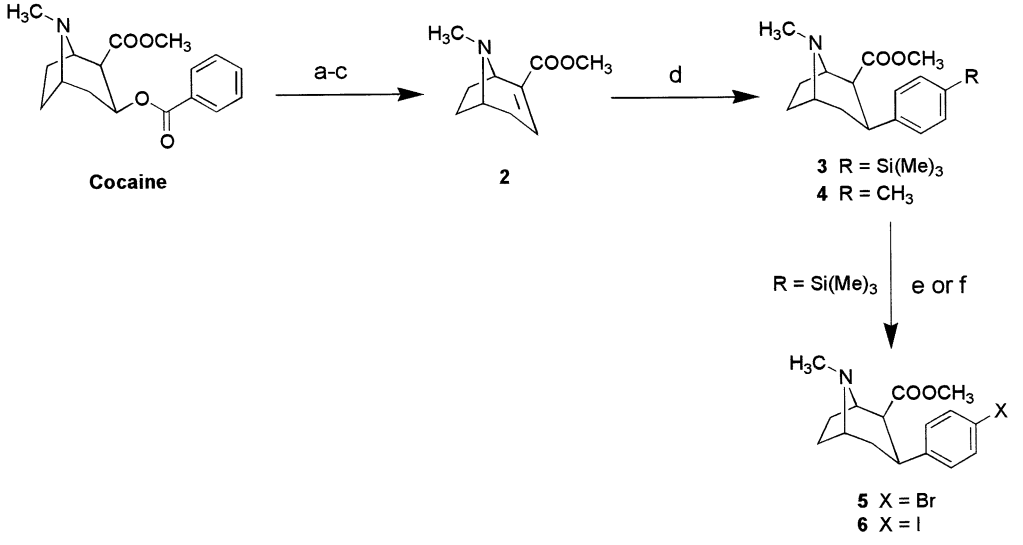
as clinical PET imaging agents for the DAT, but their affinity and selectivity for the DAT still require improvement.

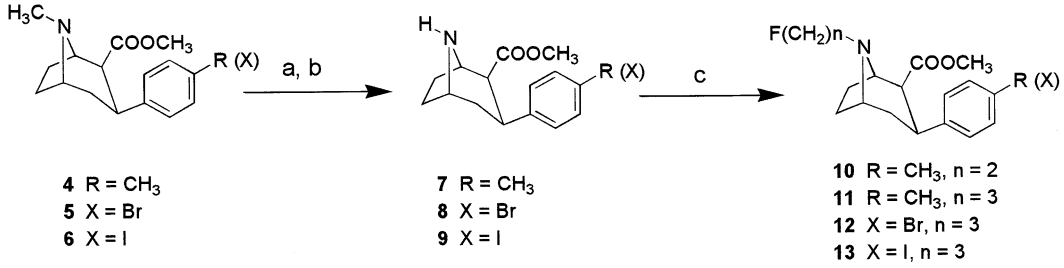
Fluorine-18 is a more attractive positron-emitting radionuclide for radiolabeling because it has a longer half-life ($t_{1/2}$ = 110 min) than carbon-11 ($t_{1/2}$ = 20.4 min), enabling imaging studies to be carried out over longer periods of time (2–4 h). Further, fluorine-18 is also the lowest energy positron emitter (0.635 MeV, 97% abundant) and it affords the highest resolution images (maximum 2.4 mm positron range). Accordingly, we have focused our recent efforts on developing ^{18}F-labeled tropane derivatives as DAT imaging agents.[30,31] We now report the synthesis and monoamine transporter binding evaluation of a series of novel fluoroalkyl-substituted derivatives of tropane. The results of our study indicate that several fluoroalkyl-containing tropane derivatives possess high affinity and selectivity for DAT, and so are attractive potential PET radioligands for in vivo imaging the DAT in human forebrain.

Anhydroecgonine methyl ester (**2**) was initially prepared from cocaine in 97% overall yield after bulb-to-bulb distillation by the procedure of Clarke et al. (Scheme 1).[38] Treatment of **2** with appropriate 4-substituted phenylmagnesium bromide afforded the 2β-carbomethoxy-3β-(4-substituted phenyl) tropanes (**3**–**4**) after quenching the reaction with trifluoroacetic acid at low temperature.[39] Reaction of the trimethylsilyl **3** with NaBr and NCS in HOAc[40] afforded β-CBT (**5**)[41] in nearly quantitative yield. β-CIT (**6**) was obtained in excellent yield after treatment of **3** in absolute MeOH with ICl or iodine in the presence of $AgBF_4$.[42] We also found that treatment of **3** with iodine or ICl in HOAc without the expensive catalyst $AgBF_4$ gave 75% yield of β-CIT. *N*-Demethylation of **4**–**6** using α-chloroethyl chloroformate (ACE-Cl) in ethylene dichloride followed by treatment with MeOH[43] afforded the nortropanes (**7**–**9**) (Scheme 2). The *N*-(fluoroalkyl)phenyltropanes (**10**–**13**) were prepared by alkylation of the corresponding nortropanes (**7**–**9**) with fluoroethyl bromide or fluoropropyl bromide according to the procedure we reported previously.[44,45]

The fluoroalkyl-containing ester analogues of tropane **18**–**20** were synthesized according to the general synthetic route shown in Scheme 3. Hydrolysis of **4** and **6** in aqueous dioxane[46] gave the corresponding acids **14** and **15** in excellent yields. Treatment of **14** and **15** with $POCl_3$ yielded the acid chlorides, which were treated with 1,3-propane-diol monomesylate[47] yielding esters **16**–**17**. Treatment of the mesylate **16**–**17** with TBAF in refluxing THF afforded the 3-fluoropropyl ester **18**–**19** in good yields. The acid chloride of **14** was treated with 2-fluoroethanol in dry CH_2Cl_2 in the presence of Et_3N to give the desired 2-fluoroethyl ester **20** in good yield. Hydrolysis of FP-CIT (**13**) in aqueous dioxane afforded the acid **21** (Scheme 4). Without isolation, the acid **21**



Scheme 1. Reagents and conditions: (a) HCl (6 N), reflux; (b) $POCl_3$; (c) MeOH; (d) ArMgBr, Et_2O; (e) ICl or I_2, $AgBF_4$, MeOH; (f) NaBr, NCS, HOAc.



Scheme 2. Reagents and conditions: (a) ACE–Cl, $ClCH_2CH_2Cl$, reflux; (b) MeOH, rt; (c) $F(CH_2)_nBr$, KI, Et_3N, EtOH, reflux.

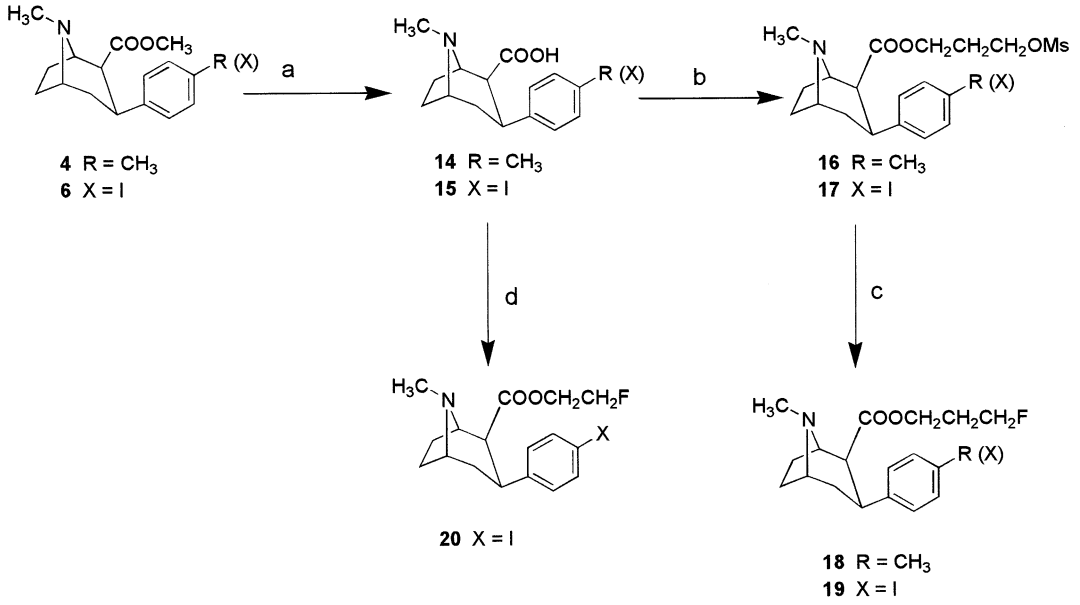
was converted to the acid chloride by treatment with $POCl_3$, and the resulting acid chloride was reacted with 2-fluoroethanol to give **22** in good yield. The physical data of all these novel derivatives are listed in Table 1.

The K_i values for the inhibition of radioligand binding at the DAT, SERT, and NET in rat forebrain tissue by these novel fluoroalkyl-containing tropane derivatives are summarized in Table 2 along with our previously reported K_i values for β-CIT, nor-CIT, and FP-CIT for comparison. Binding potencies at DAT, SERT, and NET were determined with competitive binding assays using previously reported procedures.[48,49] Ratios of K_i values (SERT/DAT and NET/DAT) were used to indicate the in vitro selectivity of these novel compounds for the DAT.

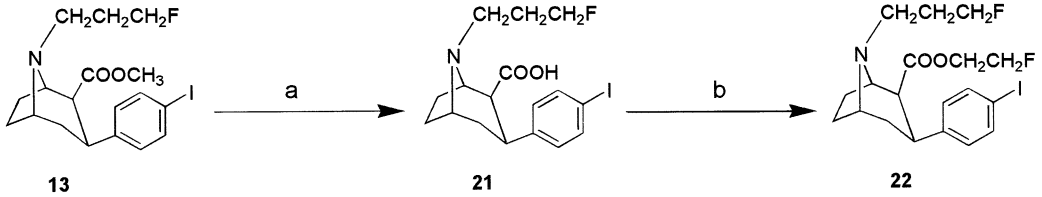
In marked contrast to β-CIT and FP-CIT, all of these novel derivatives displayed selectivity for the DAT versus both the SERT and the NET. Among them, the fluoropropyl ester of β-CMT (**18**) displayed the highest selectivity (45-fold) for the DAT over the SERT while the fluoroethyl ester of β-CIT (**20**) exhibited the highest affinity for the DAT ($K_i = 0.93$ nM) and the highest selectivity (125-fold) for the DAT over the NET. Compared to FP-CIT, the *N*-fluoropropyl derivative of β-CBT (**12**) showed enhanced affinity (2.5-fold) for DAT and decreased affinity at both SERT (22-fold) and NET (3.1-fold), resulting in enhanced selectivity for DAT over SERT and NET. However, the *N*-fluoroethyl (**11**) and *N*-fluoropropyl (**10**) derivatives of β-CMT showed lower affinity for all three transporters than FP-CIT, but the decrease is relatively greater for the SERT and the NET, resulting in higher selectivity for DAT than was shown by FP-CIT.

It is interesting to note that the *N*-fluoropropyl derivative of β-CMT (**11**) showed higher (3-fold and 4-fold, respectively) selectivity for the DAT over the SERT and the NET than the corresponding *N*-fluoroethyl derivative **10** due to its lower affinity for the SERT and the similar affinity for the DAT. Remarkably, all fluoroalkyl esters except **22** displayed higher binding affinity and selectivity for the DAT than FP-CIT. The fluoropropyl ester of β-CIT (**19**) had similar affinity for the DAT to that of β-CIT, whereas the fluoroethyl ester **20** showed somewhat higher DAT affinity. The fluoroethyl ester of FP-CIT (**22**) possessed similar affinity, but increased selectivity for the DAT relative to the methyl ester FP-CIT. The fluoropropyl ester of β-CMT (**18**) had similar affinity for the DAT as FP-CIT, but **18** possessed 193-fold and 4-fold lower affinity for the SERT and the NET, respectively, than FP-CIT.

In summary, we have synthesized and determined the cerebral monoamine transporter binding affinity of a series of novel fluoroalkyl-containing tropane derivatives. All of these derivatives except the *N*-fluoroalkyl

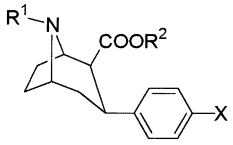


Scheme 3. Reagents and conditions: (a) dioxane/H_2O (1:1), reflux; (b) $POCl_3$; $HOCH_2CH_2CH_2OMs$, Et_3N, CH_2Cl_2; (c) TBAF, THF, reflux; (d) $POCl_3$; $HOCH_2CH_2F$, Et_3N, CH_2Cl_2.



Scheme 4. Reagents and conditions: (a) dioxane/H_2O (1:1), reflux; (b) $POCl_3$; $HOCH_2CH_2F$, Et_3N, CH_2Cl_2.

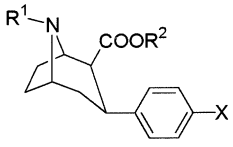
Table 1. Physical properties of novel fluoroalkyl derivatives of tropane



Compd	R^1	R^2	X	Mp (°C)	Formula[a]	Analysis[b]
10	CH_2CH_2F	CH_3	CH_3	95–96	$C_{22}H_{30}FNO_8 \cdot 0.5H_2O$[c]	C, H, N
11	$CH_2CH_2CH_2F$	CH_3	CH_3	62–63	$C_{19}H_{26}FNO_2$	C, H, N
12	$CH_2CH_2CH_2F$	CH_3	Br	84–85	$C_{18}H_{23}BrFNO_2$	C, H, N
18	CH_3	$CH_2CH_2CH_2F$	CH_3	Syrup	$C_{19}H_{26}FNO_2 \cdot 0.25H_2O$	C, H, N
19	CH_3	$CH_2CH_2CH_2F$	I	80–81	$C_{18}H_{23}FINO_2$	C, H, N
20	CH_3	CH_2CH_2F	I	117–118	$C_{17}H_{21}FINO_2$	C, H, N
22	$CH_2CH_2CH_2F$	CH_2CH_2F	I	Syrup	$C_{19}H_{24}F_2INO_2$	C, H, N

[a]All compounds exhibit ^{1}H NMR spectra in agreement with their assigned structures.
[b]CHN analyses were within ±0.4% of the theoretical values.
[c]This compound was characterized and tested as its tartrate salt.

Table 2. Transporter binding affinity and SAR of fluoroalkyl derivatives of tropane



				Affinity (K_i ± SE, nM)[a]			Selectivity[b]	
Compd	R^1	R^2	X	DAT [^{3}H]β-CIT	SERT [^{3}H]paroxetine	NET [^{3}H]nisoxetine	SERT/DAT	NET/DAT
10	CH_2CH_2F	CH_3	CH_3	32.1 ± 2.2	375 ± 26	268 ± 25	11.7	8.4
11	$CH_2CH_2CH_2F$	CH_3	CH_3	37.6 ± 3.8	1311 ± 307	1208 ± 176	34.9	32.1
12	$CH_2CH_2CH_2F$	CH_3	Br	3.33 ± 0.99	36.4 ± 2.2	196 ± 14	10.9	58.9
18	CH_3	$CH_2CH_2CH_2F$	CH_3	7.17 ± 0.71	325 ± 15	260 ± 12	45.3	36.3
19	CH_3	$CH_2CH_2CH_2F$	I	1.54 ± 0.09	1.65 ± 0.23	173 ± 15	1.1	112
20	CH_3	CH_2CH_2F	I	0.93 ± 0.02	4.02 ± 0.48	116 ± 12	4.3	125
22	$CH_2CH_2CH_2F$	CH_2CH_2F	I	8.71 ± 0.50	13.3 ± 3.3	723 ± 38	1.5	83
Nor-CIT[c]	H	CH_3	I	0.64 ± 0.097	0.06 ± 0.001	1.85 ± 0.21	0.1	2.9
β-CIT[c]	CH_3	CH_3	I	1.33 ± 0.15	0.46 ± 0.06	2.80 ± 0.40	0.4	2.1
FP-CIT[c]	$CH_2CH_2CH_2F$	CH_3	I	8.29 ± 0.53	1.68 ± 0.13	63.0 ± 4.0	0.2	7.6

[a]Transporter binding affinity assays are detailed previously:[48,49] rat striatal homogenates with [^{3}H]β-CIT from Tocris-Cookson (64.7 Ci/mmol) for DAT, cerebral cortical homogenates with [^{3}H]paroxetine from NEN (15 Ci/mmol) for SERT, and [^{3}H]nisoxetine from NEN (80 Ci/mmol) for NET.
[b]Selectivity for the DAT is indicated as the ratio of K_i for the SERT or NET to that for the DAT (ratios < 1.0 indicate preference for the non-DAT site).
[c]Reported previously [49] and listed for comparative purpose.

derivatives of β-CMT and the fluoroethyl ester of FP-CIT (**22**) showed higher DAT affinity and selectivity than FP-CIT. Among these novel ligands, the fluoroethyl ester of β-CIT (**20**) had the highest DAT affinity (K_i = 0.93 nM) and highest selectivity for DAT over NET (NET/DAT ratio = 125), while the fluoropropyl ester of β-CMT (**18**) displayed the highest selectivity for DAT over SERT (SERT/DAT ratio = 45). From a practical point of view, tropanes **12**, **18**, **19**, and **20** are especially attractive candidates for the development of ^{18}F-labeled PET radiotracers for clinical imaging DAT in human brain.

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