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Synthesis and evaluation of novel tropane derivatives as potential PET imaging agents for the dopamine transporter

Hongwen Qiao [a,b], Lin Zhu [a,b], Brian P. Lieberman [b], Zhihao Zha [b], Karl Plössl [b], Hank F. Kung [a,b,c,*]

[a] Key Laboratory of Radiopharmaceuticals, Beijing Normal University, Ministry of Education, Beijing 100875, PR China
[b] Department of Radiology, University of Pennsylvania, Philadelphia, PA 19104, USA
[c] Department of Pharmacology, University of Pennsylvania, Philadelphia, PA 19104, USA

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ABSTRACT

A novel series of tropane derivatives containing a fluorinated tertiary amino or amide at the 2β position was synthesized, labeled with the positron-emitter fluorine-18 ($t_{1/2}$ = 109.8 min), and tested as potential in vivo dopamine transporter (DAT) imaging agents. The corresponding chlorinated analogs were prepared and employed as precursors for radiolabeling leading to the fluorine-18-labeled derivatives via a one-step nucleophilic aliphatic substitution reaction. In vitro binding results showed that the 2β-amino compounds **6b**, **6d** and **7b** displayed moderately high affinities to DAT (K_i <10 nM). Biodistribution studies of **[^{18}F]6b** and **[^{18}F]6d** showed that the brain uptakes in rats were low. This is likely due to their low lipophilicities. Further structural modifications of these tropane derivatives will be needed to improve their in vivo properties as DAT imaging agents.

The dopamine transporter (DAT) is located on the membrane of presynaptic dopaminergic neurons in the central nervous system (CNS). A rapid and efficient reuptake of dopamine from the synaptic cleft back into presynaptic neuronal site terminates and regulates the dopaminergic neurotransmission.[1–4] The concentration of DAT is highest in the caudate, putamen, nucleus accumbens, and olfactory tubercle, while lower in the substantia nigra, amygdala, and hypothalamus. Changes in DAT concentration are associated with numerous neurodegenerative and neuropsychiatric diseases, including Parkinson's disease (PD), attention deficient-hyperactivity disorder (ADHD), drug abuse, Huntington's chorea and schizophrenia. PET imaging is a sensitive technique to measure the density and activity of DAT in the brain, which is potentially useful for diagnosing, monitoring and evaluating treatment of these diseases, especially for movement disorders associated with PD.[5–9]

A large number of positron emission tomography (PET) radiotracers labeled with carbon-11 and fluorine-18 for imaging DAT have been developed extensively in the past three decades.[10–12] An effective DAT imaging tracer should meet a set of minimum requirements[13]: (1) adequate binding affinity to DAT (K_i <10 nM) and more than 50-fold lower binding affinities to the serotonin transporter (SERT) and norepinephrine transporter (NET); (2) appropriate lipophilicity to allow the imaging agents to cross the blood–brain barrier (BBB); (3) reasonable in vivo metabolite profiles from peripheral tissues without producing unwanted radioactive metabolites able to enter the brain; (4) appropriate pharmacokinetics for quantification of the DAT concentration in the brain; (5) simple and effective radiolabeling procedure prepared via a limited number of chemical transformations within a short time to give a radioactive compound with high radiochemical yield, purity and specific activity.

It is well known that ^{18}F has a longer half-life (109.8 min) than ^{11}C (20 min), and has been widely used for labeling DAT imaging tracers.[2,14] Numerous compounds labeled with ^{18}F have been evaluated for imaging DAT binding sites in the brain, and most of them are tropane derivatives. They include leading candidates such as [^{18}F]FECT,[15] [^{18}F]FP-CIT,[16] [^{18}F]FECNT,[17,18] [^{18}F]FE-PE2I[19] and [^{18}F]LBT-999[20,21]. It was reported that [^{18}F]FECNT displayed a high affinity and selectivity to human DAT, and the most favorable DAT binding kinetics in human studies, attaining quasi-equilibrium at 90 min post injection. However, analyses of arterial plasma from rats, monkeys and humans showed an inactive radiometabolite of [^{18}F]FECNT that entered the brain and distributed nonspecifically in the brain, contributing to a higher background.[22] Another tracer, [^{18}F]FE-PE2I, developed from [^{11}C]PE2I,[23–25] displayed a desired high binding affinity (K_i = 12 ± 1.7 nM) to DAT with more than 50-fold lower affinity to other monoamine transporters.[26] A relatively new generation of highly selective DAT ligand, LBT-999, has been reported. It is a close structural analog of [^{11}C]PE2I and has been labeled with ^{18}F as well as with ^{11}C.[20,21,27] However,

* Corresponding author. Tel.: +1 215 662 3096; fax: +1 215 349 5035.
E-mail address: kunghf@sunmac.spect.upenn.edu (H.F. Kung).

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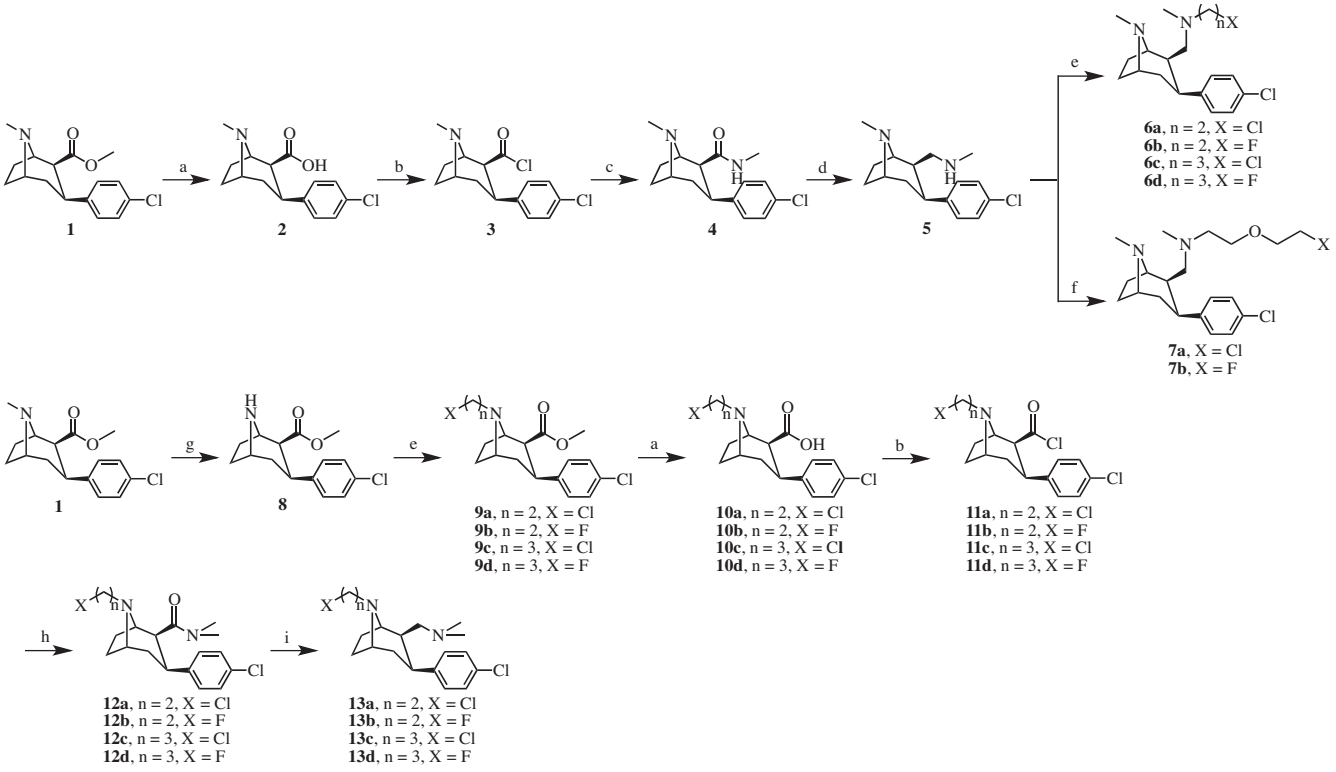
similar to [^{18}F]FECNT, [^{11}C]PE2I also undergoes in vivo metabolism forming polar components: two polar radiometabolites were found in the brain.[28,29] Therefore, it can be expected that [^{18}F]FE-PE2I and [^{18}F]LBT-999 may also undergo similar metabolism.[15,30] The objective of optimization of novel DAT imaging tracers is to improve the metabolic stability, while retaining the high affinity and selectivity to DAT. Based on previously reported structure–activity relationships of tropane derivatives,[31] we have elected a new strategy by introducing a tertiary amino or amide group to replace the ester group at the 2β position of tropane. We reasoned that the 2β substituted tropanes may be less likely to produce undesired brain penetrating metabolites and have less complicated metabolite profiles. Therefore, we have prepared and tested tropane derivatives containing 2β-fluoroalkylamines and their corresponding amides, and we also prepared several *N*-fluoroalkyl substituted tropanes for comparison. Synthesis and evaluation of these tropane derivatives are reported herein.

The general strategy for the synthesis of the tropane derivatives is shown in Scheme 1. Following a published route[32], compound **1** was hydrolyzed in 1 N HCl under reflux for 12 h to give acid **2**. The carboxyl group at 2β position of **2** was transformed to acyl chloride with oxalyl chloride in CH_2Cl_2 at room temperature to give **3**, which reacted directly with methylamine hydrochloride and triethylamine in CH_2Cl_2 to yield **4** in 75% overall yield from **1**. Compound **4** was reduced with BH_3·THF in THF under reflux for 12 h to give **5** in 85% yield. Compound **5** was reacted with 1-bromo-2-chloroethane or 1-bromo-3-chloropropane in the presence of triethylamine to give compounds **6a** or **6c** in 13% and 83% yields as precursors for radiolabeling with fluorine-18 via nucleophilic aliphatic substitution. Reaction of **5** with 1-bromo-2-fluoroethane or 1-iodo-3-fluoropropane afforded compounds **6b** and **6d** as standards under the same reaction conditions in good yields (89% and 84%). In addition, **5** was reacted with 2-(2-chloroethoxy)ethyl-4-methylbenzenesulfonate or its fluorinated analog in the presence of Cs_2CO_3 to give compound **7a** or **7b** in 11% and 64% yields.

Compound **8** was synthesized from **1** following a previously published method[33] in good yield (84%). It was then reacted with 1-bromo-2-chloroethane, 1-bromo-2-fluoroethane, 1-bromo-3-chloropropane or 1-iodo-3-fluoropropane to give **9a–9d** in the range of 68–82% yields. These were hydrolyzed in 1 N HCl, and then changed to 2β-acyl chloride derivatives **11a–11d** with oxalyl chloride. The acyl chloride derivatives, **11a–11d**, were reacted with dimethylamine in CH_2Cl_2 to give fluorinated and chlorinated 2β-amide compounds **12a–12d** in good yields ranging from 71% to 85%. These amide intermediates, **12a–12d**, were successfully reduced with BH_3·THF under reflux for 4 h to give the corresponding 2β-amine derivatives **13a–13d**. The yields of chlorinated analogs **13a** and **13c** were only 18% and 13%, fluorinated analogs **13b** and **13d** were 71% and 74%.

The in vitro binding affinities (K_i) to DAT for the fluorinated tropane derivatives were evaluated by competition binding assays with [^{125}I]IPT, which has high affinity to DAT (K_d = 1.2 nM).[34] Membrane homogenates of transfected LLC-PK1 cell line that overexpress DAT were used for binding assays. The K_i of GBR12909 binding to DAT was also tested for comparison (Table 1). The 2β-amide derivatives **12b** and **12d** showed low affinities to DAT (699 ± 11.3 and 135 ± 4.50 nM), but when the 2β-amide was reduced to 2β-amine, the binding affinities of **13b** and **13d** increased to 18.3 ± 3.10 and 26.9 ± 0.80 nM. Significantly, other 2β-amines, **6b**, **6d** and **7b**, in which the methyl at 8-N position of tropane structure was preserved, displayed high affinities to DAT (3.79 ± 1.04, 2.64 ± 0.03 and 4.63 ± 0.31 nM).

In the literature, most of the ^{18}F labeled tropane derivatives developed as DAT imaging tracers were radiolabeled by a two-step



Scheme 1. Reagents and reaction conditions: (a) 1 N HCl, reflux, 12 h; (b) $(COCl_2)_2$, CH_2Cl_2, rt, 4 h; (c) CH_3NH_2·HCl, Et_3N, CH_2Cl_2, rt, 8 h, **4**: 75%; (d) BH_3·THF, THF, reflux, 12 h, **5**: 85%; (e) $Y(CH_2)_nX$ (Y = Br, I; X = Cl, F), Et_3N, MeCN, rt, 12 h, **6a**: 13%, 6b: 83%, **6c**: 89%, **6d**: 84%, **9a**: 82%, **9b**: 68%, **9c**: 75%, **9d**: 76%; (f) $TsO(CH_2)_2O(CH_2)_2X$ (X = Cl, F), Cs_2CO_3, DMF, rt, 12 h, **7a**: 11%, **7b**: 64%; (g) 1. ACE-Cl, CH_2ClCH_2Cl, reflux, 6 h; 2. MeOH, reflux, 4 h, **8**: 84%; (h) $(CH_3)_2NH$, CH_2Cl_2, rt, 8 h, **12a**: 79%, **12b**: 81%, **12c**: 71%, **12d**: 85%; (i) BH_3·THF, THF, reflux, 4 h, **13a**: 18%, **13b**: 71%, **13c**: 13%, **13d**: 74%.

Table 1
Binding affinity, radiolabeling yield and log*P* of tropane derivatives

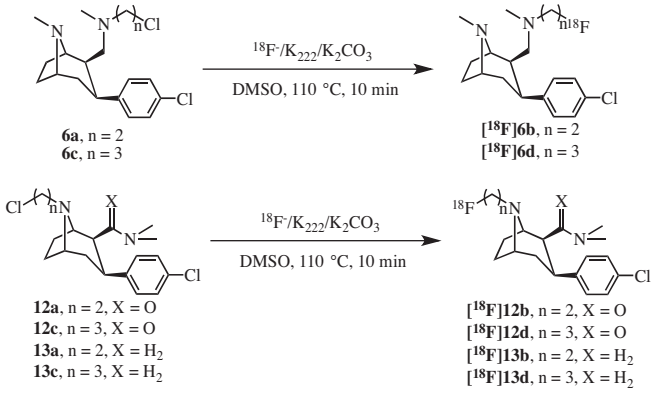
Compound	K_i (n = 3, nM)[a]	RCY[b]	log*P*
[^{18}F]6b	3.79 ± 1.04	33.5 ± 14.9%	1.52
[^{18}F]6d	2.64 ± 0.03	40.3 ± 4.3%	1.72
[^{18}F]7b	4.63 ± 0.31	—	—
[^{18}F]12b	699 ± 11.3	32.9 ± 8.8%	−0.11
[^{18}F]12d	135 ± 4.50	22.9 ± 4.9%	−0.07
[^{18}F]13b	18.3 ± 3.10	24.5 ± 5.3%	1.88
[^{18}F]13d	26.9 ± 0.80	26.7 ± 6.7%	1.98
GBR12909	2.42	—	—

[a] LLC-DAT membrane homogenates incubated with 0.1 nM [^{125}I]IPT (K_d = 1.2 nM).
[b] RCY: radiochemical yield, n = 3, non-decay-corrected. The total time for the radiolabeling was less than 60 min.

reaction: $^{18}F^-$ was first introduced to active intermediates, and the purified ^{18}F labeled intermediates were reacted with tropanes leading to the desired ^{18}F labeled tropane derivatives.[15,19,20,35] One exception is worth-mentioning: the preparation of [^{18}F]LBT-999, that was first performed using a two-step approach as described above and later using a one-step chloro-for-fluorine radiofluorination reaction.[20,21] In this project, we tested an alternative strategy by using a direct one-step nucleophilic fluorination to prepare the ^{18}F labeled tropane. To our surprise, the precursors containing –OTs, –OMs or –Br as the leaving group for direct one-step nucleophilic ^{18}F labeling were unstable. It was found that only the chlorine atom was suitable as the leaving group, which provided the stability for these precursors. Therefore, we prepared, **6a**, **6c**, **7a**, **12a**, **12c**, **13a** and **13c** for ^{18}F radiolabeling via a one-step reaction, through which ^{18}F labeled tropane derivatives were successfully prepared (Scheme 2). A mixture of $^{18}F^-/K_{222}/K_2CO_3$ in acetonitrile was co-evaporated to dryness, and 1 mL solution of 1 mg precursor in anhydrous DMSO was added. The reaction mixture was heated at 110 °C for 10 min, and the resulting mixture was purified with semi-preparative reversed phase HPLC. The radiochemical yields of the desired ^{18}F labeled tropane derivatives are shown in Table 1. The identities of the radiotracers were confirmed by co-injection with standard compounds. As expected the HPLC profiles of these radiotracers showed the same retention time as those of standard cold compounds. The total time for radiolabeling was less than 60 min, radiochemical purities were higher than 99% and specific radioactivities were greater than 80 GBq/μmol. It was found that **[^{18}F]7b** was not produced as expected. This was mostly likely due to the fact that the precursor **7a** was unstable under the labeling condition as described above.

The lipophilicities of these ^{18}F labeled tropane derivatives were measured by partition between 1-octanol and 0.1 M NaH_2PO_4 buffer (pH 7.4). In this experiment a labeled compound was added to 3 g of 1-octanol and 3 g of NaH_2PO_4 buffer. The mixture was vortexed for 1 min, and centrifuged for 3 min. The 1-octanol layer was removed and the partition step was repeated two more times. The partition coefficient was determined by calculating the ratio of counts/mL between 1-octanol and buffer after the third partition. The partition coefficients (log*P*) of the ^{18}F labeled tropane derivatives are shown in Table 1. For an effective brain DAT imaging tracer, appropriate log*P* should be between 1 and 3.[13,36] Compounds **[^{18}F]6b**, **[^{18}F]6d**, **[^{18}F]13b** and **[^{18}F]13d** displayed suitable lipophilicities for imaging DAT in brain. Lipophilicities of 2β-amide derivatives **[^{18}F]12b** and **[^{18}F]12d** were too low for brain penetration, and also their binding affinities to DAT were too low to be useful. Compounds **[^{18}F]6b** and **[^{18}F]6d** have high binding affinities to DAT, **[^{18}F]13d** has similar affinity and slightly better lipophilicity than **[^{18}F]13b**. The three ^{18}F labeled compounds were evaluated with biodistribution studies in rats.

Initial evaluation of **[^{18}F]6b**, **[^{18}F]6d** and **[^{18}F]13d** was performed in normal male Sprague–Dawley rats at 30 min post iv injection (30 μCi per rat, n = 3). The organs of interest were removed and weighed, and the radioactivity was counted with an automatic gamma counter. The percent initial dose per gram of organs was calculated by a comparison of the tissue counts to suitably diluted aliquots of the injected dose. Different regions of rat brain corresponding to striatum (ST), hippocampus (HP), cerebellum (CB) and cortex (CX) were dissected and counted to obtain the regional distribution of the tracers. Biodistribution results showed that all three tested tracers, **[^{18}F]6b**, **[^{18}F]6d** and **[^{18}F]13d**, have high accumulations in lung and kidney at 30 min after injection (Table 2). **[^{18}F]6b** and **[^{18}F]6d** displayed lower uptake in bone than **[^{18}F]13d**, suggesting a slower de-fluorination reaction in vivo. Brain uptakes of these labeled tracers were 0.72 ± 0.04%, 0.52 ± 0.05% and 0.39 ± 0.03% dose per gram, respectively. The results of brain uptake demonstrated that the compounds moderately penetrated the BBB. The lipophilicities of labeling compounds appear to play an important role in brain uptake. The log*P* of **[^{18}F]6b**, **[^{18}F]6d** and **[^{18}F]13d** (1.52, 1.72 and 1.98) was lower than the optimal log*P* value (2.0–3.5) required for crossing the BBB[36]. This may have been the reason that these tracers only displayed a low brain uptake. It will be necessary to improve lipophilicities of these ^{18}F labeled tropane derivatives for better brain penetration. Regional brain distribution of the derivatives



Scheme 2. Radiosynthesis of the series of novel ^{18}F labeled tropane derivatives.

Table 2
Organs and regional brain biodistribution of **[^{18}F]6b**, **[^{18}F]6d** and **[^{18}F]13d** in normal Sprague–Dawley rats (% dose per gram, average of 3 rats ± S.D.)

	[^{18}F]6b	**[^{18}F]6d**	**[^{18}F]13d**
Organs			
Blood	0.10 ± 0.01	0.10 ± 0.01	0.14 ± 0.01
Heart	0.80 ± 0.08	1.56 ± 0.24	0.57 ± 0.04
Muscle	0.27 ± 0.05	0.22 ± 0.07	0.30 ± 0.04
Lung	5.93 ± 0.30	11.5 ± 1.80	5.58 ± 0.60
Kidney	3.65 ± 0.17	4.63 ± 0.19	2.08 ± 0.31
Liver	3.01 ± 0.18	2.08 ± 0.20	0.86 ± 0.12
Bone	0.43 ± 0.06	0.50 ± 0.02	1.04 ± 0.27
Brain	0.72 ± 0.04	0.52 ± 0.05	0.39 ± 0.03
Regions			
Cerebellum	0.65 ± 0.09	0.66 ± 0.09	0.44 ± 0.03
Striatum	1.07 ± 0.12	0.63 ± 0.04	0.49 ± 0.05
Hippocampus	0.79 ± 0.07	0.54 ± 0.04	0.44 ± 0.04
Cortex	0.91 ± 0.11	0.68 ± 0.03	0.52 ± 0.04
Hypothalamus	0.82 ± 0.10	0.63 ± 0.06	0.43 ± 0.03
Ratio (vs CB)			
Striatum	1.63	0.94	1.10
Hippocampus	1.21	0.80	0.99
Cortex	1.39	1.02	1.17
Hypothalamus	1.26	0.94	0.97

suggested that **[^{18}F]6b** exhibited moderate accumulation in the ST region, the ST/CB ratio showed specific binding of this tracer to the region where dopamine neurons are highly concentrated. The brain uptakes of **[^{18}F]6d** and **[^{18}F]13d** were too low to warrant further in vivo studies to measure their regional brain dissection.

In conclusion, a series of novel ^{18}F labeled tropane derivatives containing specific substitution groups at the 2β-position was synthesized, labeled with the positron-emitter ^{18}F ($t_{1/2}$ = 109.8 min) and evaluated as DAT imaging tracers. Compound **6b**, **6d** and **7b** showed moderately high binding affinities to DAT by in vitro binding assays. The ^{18}F labeled tropane derivatives were radiolabeled efficiently via a one-step nucleophilic aliphatic substitution reaction using the corresponding chlorine analogs as precursors. The biodistribution studies of **[^{18}F]6b**, **[^{18}F]6d** and **[^{18}F]13d** demonstrated moderate brain penetration in rats, and **[^{18}F]6b** displayed specific uptake in the striatum region. However, the brain uptakes of these derivatives were relatively low, which is likely due to their low lipophilicities. Further structural modifications of these tropane derivatives are needed to improve their lipophilicities and in vivo brain uptake before they can be useful as DAT imaging agents.

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