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# Tropane-derived $^{11}$C-labelled and $^{18}$F-labelled DAT ligands†

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**Radiolabelling of cocaine-derived 3-phenyltropanes for dopamine transporter positron emission tomography with $^{18}$F and $^{11}$C is reviewed.**

**Keywords:** fluorine-18; carbon-11; dopamine transporter; PET; 3-phenyltropane

## Introduction

Positron emission tomography (PET) studies of dopamine transporter (DAT) availability provide valuable insights into the presynaptic integrity of dopaminergic neurons in vivo.[1–5] Several key challenges persist in the development of DAT ligands, these are DAT selectivity, due to close homology of the serotonin transporter and the noradrenalin transporter, and slow equilibration of binding, caused by high binding affinity and adverse metabolic degradation. A DAT ligand with ideal characteristics has to be identified.[6–14] Initial candidates included [$^{11}$C]nomifensine, [$^{18}$F]GBR13119, D-*threo*-[$^{11}$C]methylphenidate and the tropane (**1**) (−)-*N*-[$^{11}$C]cocaine (**2**). These suffered from low striatum to cerebellum ratios (1.5–2.4), fast washout and low selectivity.[5,6] Despite the equipotent inhibition of DAT, serotonin transporter and noradrenalin transporter, **2** emerged as the lead for DAT radiotracer development regardless of its short biological half-life and low selectivity. Substitution of the benzoate ester by an arene moiety to afford 3-phenyltropanes (**3**) resulted in a 40 times longer biological half-life.[15,16]

Most cocaine-derived candidates share the distinctive absolute configurations at carbons 1, 2, 3 and 5 of a mutual bicyclic tropane ((1*R*,5*S*)-8-methyl-8-azabicyclo[3.2.1]octane) scaffold (**1**) (Figure 1). A variety of synthetic ligands has been developed, and a large number of sophisticated modifications were introduced to tailor desired characteristics.[17] Progress in $^{18}$F-labelled and $^{11}$C-labelled radiotracers have been summarised occassionally.[5,18–21] This review focuses on radiolabelling of the 3-phenyltropane scaffold using $^{18}$F and $^{11}$C.

## $^{11}$C-Labelling

Substitution of a stable carbon atom with $^{11}$C provides an elegant way of radiotracer development, although incorporation of the radiolabel into a substrate should ideally be achieved in a single synthetic transformation.[22] Considerable effort has been spent on the development of $^{11}$C-synthons starting from [$^{11}$C]$CH_4$ and [$^{11}$C]$CO_2$.[23–25] To date, most $^{11}$C-radiotracers are obtained by alkylation of heteroatom nucleophiles using [$^{11}$C]$CH_3$I or [$^{11}$C]$CH_3$OTf (Schemes 1 and 2).[26–28]

Although precautions have to be taken to suppress side reactions and improve trapping of the synthon, a wide range of viable conditions for *N*-methylation of 3-phenyltropanes exist. These comprise the use of an excess of precursor without any base, inorganic bases and trialkylamines in a dipolar aprotic solvent.

(−)-Cocaine has been labelled at two sites to obtain [*O*-methyl-$^{11}$C]cocaine and [*N*-methyl-$^{11}$C]cocaine.[29–32] Cocaine is hydrolysed by butyryl choline esterase (E.C. 3.1.1.8) in blood to obtain ecgonine methyl ester and the free acid. Both metabolites fail to enter the brain or penetrate the blood–brain barrier (BBB).[33,34] Nevertheless, [$^{11}$C]4′-fluorococaine (**4**) was briefly considered as an alternative to [$^{11}$C]cocaine in an attempt to overcome hydrolytic cleavage of the ester function.[32] The most problematic alteration of cocaine is cytochrome-P450-mediated oxidative dealkylation of the nitrogen. The (−)-norcocaine formed by *N*-demethylation penetrates the BBB, binds to monoamine transporters and confounds reference tissue modelling.[33,34] *N*-dealkylation represents a major shortcoming of the 3-phenyltropane lead.[11–14]

### *O*-$^{11}$C-Methylation of 3-phenyltropanes

Radiolabelling via *O*-$^{11}$C-methylation might offer distinct advantages over *N*-$^{11}$C-methylation methods. The precursors are easily synthesised via ester hydrolysis under mild conditions, and the resultant carboxylic acids can be separated by a simple aqueous extraction.[35]

An $^{11}$C-labelled analogue of WIN 35,428 (*β*-CFT) **5**, the gold standard for DAT studies in molecular biology and pharmacology, was obtained by *O*-methylation of *O*-desmethyl-*β*-CFT.[36,61,104] This early study used [$^{11}$C]$CH_3$I, and multiple

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## Biography

**Patrick Riss** was born in Aachen, Federal Republic of Germany, in 1979. He studied Chemical Engineering and Nuclear Chemistry in Jülich and Mainz before obtaining a doctorate 'summa cum laude' in natural sciences in 2008. Throughout his time in Mainz he was engaged in the development of $^{11}C$, $^{18}F$ and $^{68}Ga$ labelled 3-phenyltropanes for dopamine transporter imaging with PET. He spent time working overseas at the Medical Department, Brookhaven National Laboratory, Upton, NY in 2008 and at the National Institute of Mental Health, National Institutes of Health, Bethesda, MD in 2011. In his current position as a Senior Research Associate at the University of Cambridge, UK, he is affiliated with the Wolfson Brain Imaging Centre and the Behavioural and Clinical Neuroscience Institute. His research interests include biocatalysis, development of radiolabelling methodology, discovery and validation of PET radiotracers and application of PET imaging in animal models of human disease.

## Biography

**Katharina Stockhofe** was born in Duisburg, Germany in 1986. She graduated from the Landfermann-Gymnasium with Abitur in 2006 and started to study Biomedical Chemistry at the Johannes Gutenberg-University Mainz. In 2012 she obtained her Diploma in radiopharmaceutical and bioinorganic chemistry. For her diploma thesis in the group of Prof. Tobias Ross and Prof. Frank Rösch at the Institute of Nuclear Chemistry in Mainz she investigated new DAT-Ligands for $^{68}Ga$-labelling. In her work she synthesized phenyltropanes as model structures for such labeling studies. In 2012 she started her PhD in the group of Prof. Ross and Prof. Rösch and continued the research on metal-based brain ligands. In another project she is developing different nanodimensional structures, nanomaterials and makromolekules for labeling with chelator needing metals like $^{68}Ga$ and with $^{18}F$.

## Biography

**Frank Rösch** was born in Chemnitz, Germany, in 1955. He studied nuclear and radiochemistry at the Technical University Dresden graduated in 1981 and obtained a PhD in 1984. Subsequently, he spent a fellowship at the Laboratory for Nuclear Problems, Joint Institute for Nuclear Research, Dubna, Sowjet Union, investigating physicochemical properties of radiometals in aqueous solution. In 1987 he continued research on the production and application of radionuclides in life sciences at the ZfK Rossendorf, and since 1992 at the Research Centre Juelich, Germany. Isotopes covered were e.g. $^{86}Y$ and $^{94m}Tc$. In 1992 he was appointed professor of nuclear chemistry at the Institute of Nuclear Chemistry at the Johannes Gutenberg-University Mainz, Germany. He is carrying out developments on fundamental and applied radiochemistry and radiopharmaceutical chemistry with a focus on radiometals and radionuclide generators. Here, the pathway to carrier-free $^{177}Lu$ was developed. New approaches towards the design and use of generators such as $^{68}Ge/Ga$, $^{44}Ti/Sc$, $^{140}Nd/Pr$ etc. have been elaborated. He is involved in teaching, training and education and is one of the editors of the "Handbook of Nuclear Chemistry".

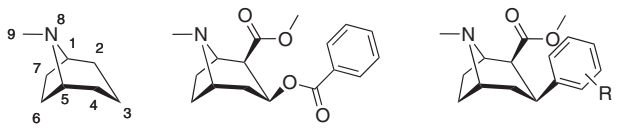
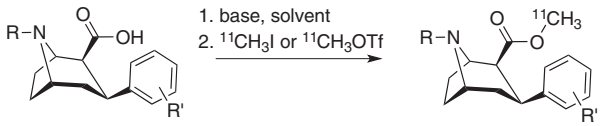
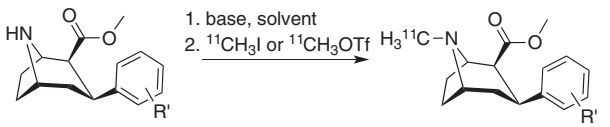



**Figure 1.** Tropane (**1**), (−)-cocaine (**2**) and 3-phenyltropane (**3**).




**Scheme 1.** *O*-$^{11}C$-methylation of 3-phenyltropanes.

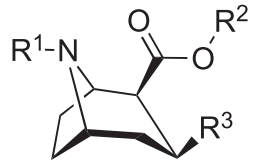



**Scheme 2.** *N*-$^{11}C$-methylation of phenyltropanes.

examples of similar conditions were to follow for a variety of 3-phenyltropanes, for example, $\beta$-CMT **6** and $\beta$-CCT **7** (Table 1).[38–40] Purification of the $^{11}C$-labelled products is achieved by semi-preparative HPLC providing the radiotracers in high specific activity and radiochemical purity. The *N*-(3-fluoroprop-1-yl) analogue of **8**, FP-$\beta$-CIT **9**, was evaluated because of a faster washout rate and higher target to non-target ratio, as established in a preliminary $^{123}I$-SPECT (Single Photon Emission Tomography) study.[41,42] A similar observation was made with [$^{123}I$]altropane® **10**, and its much more rapid kinetic profile warranted $^{11}C$-labelling and evaluation.[43] PE2I **11**, a close analogue of **10**, was developed, and $^{11}C$-labelling as well as $^{123}I$-labelling was investigated.[44–46] PR04.MZ **12** was synthesised using [$^{11}C$]$CH_3I$ and the carboxylic acid precursor TFA salt in combination with rubidium carbonate as base, to result in quantitative incorporation of $^{11}C$.[47]

Considerable effort has been spent to optimise the labelling protocols for 3-phenyltropanes. In particular, substitution of [$^{11}C$]$CH_3I$ with [$^{11}C$]$CH_3OTf$ facilitated synthesis of **8** under more mild conditions. A minor modification was also employed in the $^{11}C$-methylation of FE-$\beta$-CIT **13**, and few precursors were required in a shorter reaction time.[46,48] Remarkably improved $^{11}C$-methylation yields were also reported for **11** by several groups. Despite its appealing preliminary characteristics, the radiotracer suffered from rapid degradation in vivo. Only 15–20% of the compound was found intact in plasma 40-min post-injection. Shetty *et al.*[11] identified the radiometabolites that readily entered the brain and distributed unevenly throughout the investigated regions. Compound **14** was derived from **11** via bio-isosteric substitution

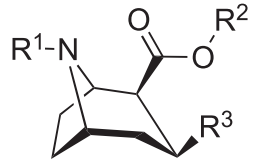
**Table 1.** 3-Phenyltropanes labelled with $^{11}C$




| Compound | Method (conditions) | $A_S$ (MBq/nmol) | RCY/ % (activity) | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|---|---|---|
| **2** [$^{11}$C]cocaine | **A**[29] (MeCN/DMF/DMSO, 135 °C, 5′[c], 35′[d] RCP > 98%) | 9.25 | n.a. | [$^{11}$C]$CH_3$ | $CH_3$ | $OCOC_6H_5$ |
| | **C**[32] (NaOH/DMF 135 °C) | >3.7 | n.a. | $CH_3$ | [$^{11}$C]$CH_3$ | |
| **4** [$^{11}$C]4-fluorococaine[32] | **A** (MeCN/DMF/DMSO, 135 °C, 5′[c], 35′[d], RCP > 98%) | >3.7 | n.a. | [$^{11}$C]$CH_3$ | $CH_3$ | 4′-$FC_6H_4C$(O)O |
| **5** β-CFT (WIN35,428)[35,54,55,61,102,104] | **A** (MeCN/DMF, 110 °C, 4′[c],20–30′[d], RCP > 97%) | 15 | n.a. (≤2.4 GBq) | [$^{11}$C]$CH_3$ | $CH_3$ | 4′-$C_6H_4F$ |
| | **A** (DMF, 80 °C, 1′[c], 21′[d], RCP > 97%) | 111 | 21[b] | | | |
| | **B** (DMF, 1′[c], 60 °C) | n.a. | 70–80[b] | $CH_3$ | [$^{11}$C]$CH_3$ | |
| | **D** (MeCN, 80 °C, 3′[c], <25′[d], RCP > 99%) | 258 ± 30 | 40–50[b] | | | |
| **6** β-CMT | **A**[58] (DMSO; 110 °C, 5′[c], 23′[d], RCP > 98%) | 22–37 | 15–20[b] | [$^{11}$C]$CH_3$ | $CH_3$ | 4′-$C_6H_4CH_3$ |
| | **C**[36] (DMF; 80 °C, 1′[c], 19–21′[d], RCP > 99%) | 29–111 | 40–55[b] | $CH_3$ | [$^{11}$C]$CH_3$ | |
| **7** β-CCT[36,57] (RTI-131) | **A** (DMSO; 110 °C, 5°[c], 23°[d], RCP > 98%), | 22–37 | 15–20[b] | [$^{11}$C]$CH_3$ | $CH_3$ | 4′-$C_6H_4Cl$ |
| | **C** (DMF, 80 °C, 1′[c], 19–21′[d], RCP > 99%) | 29–111 | 40–55[b] | $CH_3$ | [$^{11}$C]$CH_3$ | |
| **8** β-CIT[37,39,40,102] (RTI-55) | **A** (acetone, 110 °C, 5′, 19–21′[d], RCP > 99%) | 37 | 40–50[b] | [$^{11}$C]$CH_3$ | $CH_3$ | 4′-$C_6H_4I$ |
| | **B** (DMF, 50 °C, 1′[c], 30–40′, RCP > 99%) | 11.1–41 | 30–60[a] | | | |
| | **B** (DMF, 60 °C, 1′[c]) | n.a. | 60–70[b] | | | |
| | **D** (DMF, TBAOH, 50 °C, 1′[c], 30–40′[d], RCP > 99%) | n.a. | 25–50[b] | $CH_3$ | [$^{11}$C]$CH_3$ | |
| | **D** (DMF,TBAOH, 50 °C, 1′[c], ~20′[d], RCP > 99%) | n.a. | 50–60[b] | | | |
| **9** FP-β-CIT | **C**[42] (DMF, TBAOH, 80 °C, 1′, 30′, RCP > 99%) | 37 | 50–60[b] | $F(CH_2)_3$ | [$^{11}$C]$CH_3$ | 4′-$C_6H_4I$ |
| **10** Altropane®[43] | **C** (DMSO, 5′, 30′, RCP > 97%,) | ≤75 | n.a. (<2.8 GBq[a]) | *E*-$I(CH)_2CH_2$ | [$^{11}$C]$CH_3$ | 4′-$C_6H_4F$ |
| **11** PE2I[46] | **C** (acetone, NaOH, 105 °C, 25′) | 30–44 | 49–74[b] | *E*-$I(CH)_2CH_2$ | [$^{11}$C]$CH_3$ | 4′-$C_6H_4CH_3$ |
| **12** PR04.MZ[47,52] | **C** (DMF, $Rb_2CO_3$, 75 °C, 5′[c], 45′[d], RCP > 98%) | 67 | 20[a] | $FCH_2(C)_2CH_2$ | [$^{11}$C]$CH_3$ | 4′-$C_6H_4CH_3$ |
| | **C** (DMF, TBAOH, 3′[c], 35′[d], RCP > 97%, 30′) | 185 ± 30 | 4–15[a] | | | |
| **13** FE-β-CIT[38,103] | **C** (DMF,TBAOH, 80 °C, 1′[c], ~30′[d]) | 37 | 50–60[b] | $F(CH_2)_2$ | [$^{11}$C]$CH_3$ | 4′-$C_6H_4I$ |
| | **D** (acetone, TBAOH, 50 °C, 3–4′[c], 25–30′, RCP > 99%) | 37–93 | 40–50[b] | | | |
| **14** LBT-999[19] | **D** (acetone, NaOH, 110 °C, 2′[c], 25–30′[d], RCP > 99%) | 30–45 | 19–45[b] | *E*-$FCH_2(CH)_2CH_2$ | [$^{11}$C]$CH_3$ | 4′-$C_6H_4CH_3$ |
| **15** β-CPPIT (RTI-177)[60] | **A** (DMF, 120 °C, 10′[c], 60′[d], RCP ≥ 99%) | 110–130 | 60–70[b] | [$^{11}$C]$CH_3$ | 2α-3-phenyl-1,2-oxazol-5-yl | 4′-$C_6H_4Cl$ |
| **16** β-CDCT[57] | **A** (DMSO, 110 °C, RCP > 98%) | 22–37 | 15–20 | [$^{11}$C]$CH_3$ | $CH_3$ | |

(*Continues*)

**Table 1.** (Continued)




| Compound | Method (conditions) | $A_S$ (MBq/nmol) | RCY/ % (activity) | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|---|---|---|
| **17** NS-2214[59] | **A** (DMSO, 130 °C, 5′[c], 30′[d], RCP > 98) | >50 | 24–30 | [$^{11}$C]$CH_3$ | 2α-formyl-*O*-methyl oxime | 3′,4′-$C_6H_3Cl_2$ |
| **18** β-IP-CIT (RTI-121)[58] | **A** (DMF, 90 °C, 5′[c], 40′[d], RCP > 97%) | 20–38 | 95[b] | [$^{11}$C]$CH_3$ | $CH(CH_3)_2$ | 3′,4′-$C_6H_3Cl_2$<br>4′-$C_6H_4I$ |

RCY, radiochemical yield (conversion of the total radioactivity); RCP, radiochemical purity; $A_s$, specific activity; DMF, dimethylformamide; DMSO, dimethyl sulfoxide; n.a., not available; EOB, end of bombardement.
**A**: *N*-$^{11}$C-methylation with [$^{11}$C]methyl iodide; **B**: *N*-$^{11}$C-methylation with [$^{11}$C]$CH_3$OTf; **C**: *O*-$^{11}$C-methylation with [$^{11}$C]methyl iodide; **D**: *O*-$^{11}$C-methylation with [$^{11}$C]$CH_3$OTf.
[a]Decay-corrected to EOB;
[b]Non-decay-corrected;
[c]Reaction time;
[d]Total duration of radiotracer production.

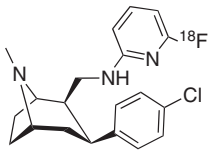



**Figure 2.** [$^{18}$F]-labelled NPPCT.

of iodine by a fluoromethyl group. $^{11}$C-labelling followed a procedure similar to the one used for **11**.[29,49] Metabolite studies substantiated similar shortcomings in terms of BBB-penetrating radiometabolites.[12–14] Recently, **12** was prepared under GMP (good manufacturing practice) compliant conditions using a GE TRACERlab FX C synthesis module, adapted to the captive solvent method.[47,50–52] Only 0.1 mg of the *O*-desmethyl-**12** TFA salt was used. A preliminary study did not show metabolite uptake into the rat brain.[53]

### *N*-$^{11}$C-Methylation of 3-phenyltropanes

Several early DAT imaging studies were conducted with *N*-$^{11}$C-labelled derivatives. Compounds **5**, **7–8** and **15–18** were synthesised via *N*-$^{11}$C-methylation of the appropriate *nor*-methyl precursors.[35,39,54–58] Although individual reaction conditions varied in between different researchers, sufficient yields in a comparable range were obtained, highlighting the robustness of the *N*-$^{11}$C-methylation. Few α-epimers of the phenyltropane class have been reported for PET, for example, the 2α-epimer **17**.[59] The authors obtained higher yields when the free amine was used as precursor.

Concurrent to *O*-$^{11}$C-methylation, the performance of [$^{11}$C]$CH_3OTf$ as labelling reagent was compared with [$^{11}$C]$CH_3I$ for *N*-$^{11}$C-methylation of **5** and **8**. In accordance with *O*-alkylation, a reliable improvement of about 20% was observed within shorter reaction times and at lower temperatures. A reduction of the amount of labelling precursor to 0.15 mg did not have an impact on the specific activity.[36–38,56] Higher specific activity was achieved in a rare example of a gas phase conversion of [$^{11}$C]$CO_2$ into [$^{11}$C]$CH_3OTf$ for **5**.[61] In general, the use of [$^{11}$C]$CH_3OTf$ provided some advantages compared with [$^{11}$C]$CH_3I$. In all reports the amount of precursor was lower, and more mild reaction conditions were feasible. Specifically lower temperatures were used, with no adverse effects on the conversion of the radionuclide into the desired product. However, these are well-accepted benefits of this highly reactive reagent and entirely unrelated to the 3-phenyltropane class of compounds. It is generally expected that most research groups will use modifications of established in-house methylation conditions.

## $^{18}$F-Labelling

$^{18}$F provides a high positron yield, very low positron energy and an expedient half-life allowing for multi-step reactions, commercial distribution of radiotracers and convenient handling in imaging studies. High specific radioactivities of >150 MBq/nmol are feasible in routine production.[62–64] This allows for PET imaging of saturable biological systems under genuine tracer conditions, even in small animals (Figure 2).[65,66]

One particular driving force for derivatisation was the introduction of aliphatic C–F bonds to allow for direct nucleophilic radiofluorination.[18] Few electrophilic pathways have been described for $^{18}$F-labelling of tropanes, instead (Table 2). Direct nucleophilic radiofluorination is the most straightforward option to afford the title class of compounds labelled with $^{18}$F, and recent reports described automated cGMP compliant processes. However, two-step procedures are equally useful. Given the widespread availability of automated two-step procedures for a variety of radiotracers, preference of either method will most likely come down to available equipment and individual expertise from PET centre to PET centre.

### Aromatic fluorination of 3-phenyltropanes

4′-[$^{18}$F]fluorococaine **4** was prepared by nucleophilic aromatic substitution from 4′-nitrococaine.[32] As mentioned earlier, **5** is the most frequently used reference compound for selective dopamine reuptake inhibitors, and [$^{3}$H]**5** is widely used for *in vitro* binding studies. Although its structure contains a 'native' fluorine atom, straightforward synthesis of **5** has been hampered by poor accessibility of labelling sites for nucleophilic fluorination in electron-rich aromatic systems. However, a number of studies using **5** synthesised by electrophilic radiofluorination have been reported.[49,67,68]

To date only a small number of brain imaging agents targeting saturable biochemical processes can be used in low to moderate specific activity, in particular when small animals are studied.[65,66] Nevertheless, it has been shown that tracer conditions can be achieved using low to moderate affinity radioligands in combination with high numbers of available binding sites. This is feasible with **5** in moderate specific activity (15 MBq/nmol) using [$^{18}$F]$F_2$ made from [$^{18}$F]fluoride. However, in a human PET study, peak uptake into the striatum was achieved only after 225 min, owing to the high affinity and long plasma half-life of **5**.[49,67,68]

In an attempt to overcome the limitations of electrophilic fluorination and to circumvent the elaborate conversion of [$^{18}$F]fluoride ion into an electrophilic fluorination reagent, an innovative radical 4-[$^{18}$F]fluoroarylation[69] was employed for labelling of **4**. However, under these conditions, the 3α-epimer **19** was formed as major product, albeit in high diastereoselectivity. Compound **19** retained an inhibition potency similar to **4** but has not been used for PET imaging as of yet.

### [$^{18}$F]Fluoromethylarenes

Petric *et al.* considered the use of [$^{18}$F]fluoromethyl-substituted analogues of **3**. The fluoromethyl derivatives **20–21** were obtained using a direct nucleophilic labelling reaction and evaluated.[70,71]

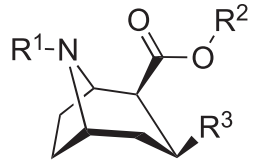
### [$^{18}$F]Fluoroalkylated 3-phenyltropanes

*N*- and *O*-ω-[$^{18}$F]fluoroalkyl 3-phenyltropane derivatives were investigated with respect to the development of DAT-selective ligands suitable for $^{18}$F-labelling. Their mutual characteristic is a heteroatom bound ω-[$^{18}$F]fluoroalkyl chain. Two principal routes for efficient radiolabelling of these compounds exist: direct nucleophilic substitution of an aliphatic leaving group by [$^{18}$F]fluoride ion, and ω-[$^{18}$F]fluoroalkylation using ω-[$^{18}$F]fluoroalkyl halides or ω-[$^{18}$F]fluoroalkyl sulfonates (Scheme 3).

### *O*-Alkylation

2-[$^{18}$F]fluoroethyl bromide was used to synthesise the 2-[$^{18}$F]fluoroethyl ester analogues of **6** and **7**. Both products, **22** and **23**, were obtained in good yields after a single HPLC purification. By-product formation was largely suppressed by distillation of 2-[$^{18}$F]fluoroethyl bromide.[53] Essentially the same method was

**Table 2.** $^{18}$F-labelled 3-phenyltropanes




| Compound | Method (results) | $A_S$ (MBq/nmol) | RCY (%) | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|---|---|---|
| **4** (−)-4-[$^{18}$F]fluoro-cocaine[32] | **B** (DMSO, heating) | >3.7 | 10–15[f] | $CH_3$ | $CH_3$ | 4′-[$^{18}$F]$FC_6H_4C$(O)O |
| **5** β-CFT[49,67,68] | **A** (AcO[$^{18}$F]F, $AcO_2H$, 5–15′[c], 65–75′[d], RCP > 98%) | ≤16 | 0.9–2[f] | $CH_3$ | $CH_3$ | 4′-$C_6H_4$[$^{18}$F]F |
| **9** FP-β-CIT[79,81–83] | **B** (MeCN, 90 °C,10′[d], 80′[e], RCP > 98%)[a] | n.a. | 1–2[e] | [$^{18}$F]F$(CH_2)_3$ | $CH_3$ | 4′-$C_6H_4$I |
| | **C** (MeCN, 150°°C, 30′[d], 125′[e], RCP > 98%)[i] | 94 ± 50 | 25 ± 5 | | | |
| | **B** (MeCN-2-methylbutan-2-ol 1 : 9, 100 °C, 20′[d], 60′[e], RCP > 97%)[a] | 64.4 ± 4.5 | 28 | | | |
| **12** PR04.MZ[74,93,96] | **B** (MeCN, 120 °C, 3′[d], 50′[e], RCP > 97%)[a] | 89 ± 45 | 13 ± 3 | [$^{18}$F]F$CH_2C_2CH_2$ | $CH_3$ | 4′-$C_6H_4CH_3$ |
| | **B** (MW (18 atm, 255 W), 180 °C, 45″[d], 35′[e], RCP > 98%)[a] | 18 ± 95 | 34 ± 2 | | | |
| **13** FE-β-CIT[96] | **C** (DMSO, 120 °C, 20′[d], 95′[e],, RCP > 98%)[h] | 32–86 | 25[e] | [$^{18}$F]F$(CH_2)_2$ | $CH_3$ | 4′-$C_6H_4$I |
| **14** LBT-999[74,92] | **B** (DMSO, 165 °C, 10′[d] 90′[e],RCP > 95%)[a] | 37–111 | 10–16[f] | *E*-[$^{18}$F]F$CH_2$ (CH$_2$)$_2$$CH_2$ | $CH_3$ | 4′-$C_6H_4CH_3$ |
| | **B** (MW (19 atm, 255 W), 180 °C, 45″[d], 40′[e], RCP > 98%)[a] | 89 ± 45 | 27 ± 2 | | | |
| **19** α-CFT[69] | **B**[a+] | n.a. | ≤16 | $CH_3$ | $CH_3$ | 3α-4′-$C_6H_4$[$^{18}$F]F |
| **20** 2-FMT[70,71] | **B** (MeCN, 90 °C, 20′[e], 65′[d], RCP > 95%)[a] | 74–185 | 22 | $CH_3$ | $CH_3$ | 2′-$C_6H_4CH_2$[$^{18}$F]F |
| **21** 4-FMT[70,71] | **B** (MeCN, 90 °C, 65′[d], 20′[e], RCP > 95%)[a] | 74–185 | 36 | $CH_3$ | $CH_3$ | 4′-$C_6H_4$ $CH_2$[$^{18}$F]F |
| **22** FECT[53] | **D** (DMF, 80 °C, 10′[d], 65′[e])[i] | 11 | 18[g] | $CH_3$ | [$^{18}$F]F$(CH_2)_2$ | 4′-$C_6H_4Cl$ |
| **23** FETT[53] | **D** (DMF, 80 °C, 10′[d], 65′[e])[i] | 11 | 18[g] | $CH_3$ | [$^{18}$F]F$(CH_2)_2$ | 4′-$C_6H_4CH_3$ |
| **24** FE@CIT (MCL301)[72] | **D** (DMF, 150 °C, 10′[c])[i] | 416 | n.a. | $CH_3$ | [$^{18}$F]F$(CH_2)_2$ | 4′-$C_6H_4$I |
| **25** FE-PE2I[73] | **D** (DMF, 85 °C, 20′[d], 90′[e], RCP > 95%)[i] | 113–385 | 7[f] | *E*-I$(CH)_2CH_2$ | [$^{18}$F]F$(CH_2)_2$ | 4′-$C_6H_4CH_3$ |
| **26** FiPr-β-CCT[75] | **B** (MeCN, 80 °C, 100′[e])[a] | 74 | 4.6 | $CH_3$ | $CH(CH_3)$ $CH_2$[$^{18}$F]F | 4′-$C_6H_4Cl$ |
| **27** MCL-322[77] | **B** (MeCN, 80 °C, 20′[d], 60′[e], RCP > 95%)[a] | 60–90 | 30–40[f] | $CH_3$ | [$^{18}$F]F$(CH_2)_2$ | 4′-$C_6H_4Br$ |
| **28** FP-β-CCT (FPCT)[85] | **C** (MeCN, 85 °C, 45′[d], 122′[e], RCP > 99%)[i] | 74 | 10[g] | [$^{18}$F]F$(CH_2)_3$ | $CH_3$ | 4′-$C_6H_4Cl$ |
| **29** FP-β-CMT[84] | **C** (DMF, 150 °C, 30′[d], 90′[e], RCP > 99%)[h] | n.a. | 4–5[g] | [$^{18}$F]F$(CH_2)_3$ | $CH_3$ | 4′-$C_6H_4CH_3$ |
| **30** FECNT[9] | **C** (MeCN, 135 °C, 45′[d], 122′[e], RCP > 99%)[h] | 74 | 21[f] | [$^{18}$F]F$(CH_2)_2$ | $CH_3$ | 4′-$C_6H_4Cl$ |
| **31** FE-β-CFT[86] | **C** (DMF, 130 °C, 10′[d], 85′[e], RCP = 100%)[h] | 208–383 | 6.6[g] | [$^{18}$F]F$(CH_2)_2$ | $CH_3$ | 4′-$C_6H_4F$ |
| **32** FP-β-CBT[87] | **C** (DMF, 150 °C, 30′[d], 90′[e], RCP > 96%)[h] | n.a. | 5[g] | [$^{18}$F]F$(CH_2)_3$ | $CH_3$ | 4′-$C_6H_4Br$ |
| **33** FP-β-CFT[88] | **C** (DMF, 135 °C, 25′[d], 105[e], RCP > 99%)[h] | 15–30 | 10[g] | [$^{18}$F]F$(CH_2)_3$ | $CH_3$ | 4′-$C_6H_4F$ |
| **34** PR17.MZ[94] | **B**[94] (MeCN, 90 °C, 3′[d], RCP > 98%)[a] | 180 | 45[f] | *E*-[$^{18}$F]F$CH_2$(CH$_2$)$_2$$CH_2$ | $CH_3$ | $-C_6H_5$ |
| | **B** (MW, 180 °C, 50″[d], RCP > 98%)[a] | 180 | 86[f] | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **35** FBFNT[21] | **C** (DMF, 105 °C, 15′[d], RCP = 99%)[h] | 31.5 | 24[f] | *E*-[$^{18}$F]FCH$_2$(CH)$_2$CH$_2$ | $CH_3$ | 4′-$C_6H_4F$ |
| **36** FBCNT | **C** (DMF, 105 °C, 15′[d], RCP = 99%)[h] | 142 | 24[f] | *E*-[$^{18}$F]FCH$_2$(CH)$_2$CH$_2$ | $CH_3$ | 4′-$C_6H_4Cl$ |
| **37** FBBNT | **C** (DMF, 105 °C, 15′[d], RCP = 99%)[h] | 53 | 24[f] | *E*-[$^{18}$F]FCH$_2$(CH)$_2$CH$_2$ | $CH_3$ | 4′-$C_6H_4Br$ |
| **38** TFENT (TECMT)[97] | **C** (DMF, 135 °C, 10′[d])[h] | 85 | 19[f] | [$^{18}$F]$F_3CCH_2$ | $CH_3$ | 4′-$C_6H_4CH_3$ |
| **39** FBnCT[99] | **C**[i] | 55.5–111 | 25[f] | [$^{18}$F]$FCH_2C_6H_4$ | $CH_3CH_2$ | 4′-$C_6H_4Cl$ |
| **40** NPCCT[100] | **B** (DMSO, 150 °C, 10′[d], 100′[e], RCP > 99%)[b] | 110–225 | 5[g] | $CH_3$ | See Figure 2 | 4′-$C_6H_4Cl$ |
| **41** $\beta$-FE-CNC[75] | **C** (MeCN, 85 °C)[h] | n.a. | 15[f] | [$^{18}$F]$F(CH_2)_2$ | $CH_3$ | 3′-$NO_2C_6H_5C(O)O$ |
| **42** $\beta$-FP-CNC[75] | **C** (MeCN, 85 °C)[h] | n.a. | 15[f] | [$^{18}$F]$F(CH_2)_3$ | $CH_3$ | 3′-$NO_2C_6H_5C(O)O$ |

RCY, radiochemical yield (conversion of the total radioactivity); RCP, radiochemical purity; $A_s$, specific activity; DMF, dimethylformamide; DMSO, dimethyl sulfoxide; n.a., not available; MW: microwave heating.
**A**: electrophilic radiofluorination; **B**: nucleophilic radiofluorination; **C**: *N*-$^{18}$F-alkylation; **D**: *O*-$^{18}$F-alkylation.
[a]Potassium 1,10-diaza-4,7,13,16,21,24-hexaoxabicyclo[8.8.8]hexacosane (K222 or [2.2.2]cryptand) cryptate [$^{18}$F]F$^{\circ}$ complex was used;
[b]Tetrabutylammonium [$^{18}$F]fluoride (TBA[$^{18}$F]F) was used;
[c]Cesium [$^{18}$F]fluoride was used;
[d]Reaction time;
[e]Total duration of radiotracer production;
[f]Decay-corrected;
[g]Non-decay-corrected;
[h]A fluoroalkyl sulfonate was used;
[i]A fluoroalkyl halide was used, [+]followed by radical arylation using an [$^{18}$F]fluorophenyl prosthetic group.





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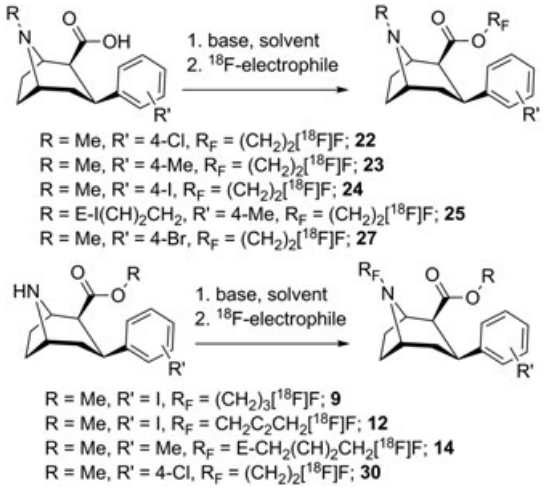


**Scheme 3.** Examples of [$^{18}$F]fluoroalkylation of 3-phenyltropanes.

used later for **24**, an *O*-2-[$^{18}$F]fluoroethyl ester of **8**, this time using a commercially available synthesis module.[72] A slightly modified version of the 2-[$^{18}$F]fluoroethyl bromide route was used to synthesise **25** only recently.[73] The carboxylate function in 3-phenyltropane-derived ligands has been described as relatively tolerant to structural modification with respect to DAT inhibition. Even the introduction of bulky $^{99m}$Tc complexes did not reduce potency.[74] However, the exchange of the methyl ester for a fluoroprop-2-yl ester in **6** to give **26** significantly improved the relative potency at the DAT resulting in an improved selectivity. Both diastereoisomers of **26** were investigated, and the *S*-isomer (1*R*,2*S*,3*S*,5*S*)-(*S*)-1-fluoropropan-2-yl 8-methyl-3-phenyl-8-azabicyclo[3.2.1] octane-2-carboxylate ((S)-**26**) showed remarkable selectivity and high DAT inhibition potency. When (*R*,*S*)-**26** was labelled using direct nucleophilic substitution, the 2$\alpha$-epimer was formed as a by-product. Notably, the high affinity diastereoisomer (*S*)-**26** showed a much slower kinetic profile than its *R*-configured counterpart.[75,76] Indirect labelling of *O*-2-[$^{18}$F]fluoroalkyl derivatives was preferred until a direct nucleophilic fluorination approach towards **27** was reported. Direct nucleophilic substitution on a 4-methylbenzenesulfonate precursor furnished the 2-[$^{18}$F]fluoroethyl ester **27** in a good yield.[77] An improved radiosynthesis of **22** using [$^{18}$F]fluoroethyl triflate was reported recently. Interestingly, metabolite analysis did not suggest significant degradation of this compound *in vivo*, paralleling the observations in [$^{18}$F]**5** PET studies.[78]

### *N*-Alkylation

The $^{18}$F-analogue of the commercialised SPECT radiotracer DATscan® **9** stands out as a highly sought after compound among 3-phenyltropanes. Compound **9** elegantly offers the opportunity to introduce an $^{11}$C-label, an $^{18}$F-label or an $^{123}$I-label. Compared with its congener **8**, a more rapid kinetic profile affords a transient equilibrium within the time frame of a clinical PET examination. Moreover, *N*-desalkylation does not occur.[76] *N*-(3-methanesulfonyloxyprop-1-yl)-*nor*-**8** was labelled using direct nucleophilic radiofluorination to obtain **9**, albeit in low radiochemical yield of 1–2%.[79,80] These issues were overcome when a reliable two-step radiosynthesis was devised.[81] The use of tertiary alcohols as additives[82] or co-solvents[83] was explored as a means to further improve the radiosynthesis of **9**. A variety of analogues of **9** were investigated using *N*-alkylation with $\omega$-[$^{18}$F]fluoroalkylating agents. For example, the synthesis and evaluation of **28** from 3-[$^{18}$F]fluoroprop-1-yl iodide has been reported.[79]

Bioisosteric replacement of the iodo substituent by a methyl group to afford **29** was inspired by a report concerning the rapid kinetic profile of **11** in rats.[44] Notably, the authors identified 2$\alpha$-epimerisation as a yield-reducing culprit.[84]

Compound **28** and its close analogue **30** were labelled with $^{18}$F and characterised in rhesus monkeys. The lower, yet more appropriate affinity of **30** gave rise to more favourable characteristics. By using 2-[$^{18}$F]fluoroeth-1-yl tosylate it was obtained in good yields and used in human subjects.[85] Because of a polar metabolite formed in vivo by *N*-desalkylation, quantification of **30** requires blood sampling.[12,13]

Compound **31** was obtained using the same two-step labelling procedure.[85] **31** was obtained in sufficient yields, although the authors report 'very polar metabolites' leading to less than 20% of intact parent compound in plasma 20-min post-injection.[86] When the 4′-bromo-analogue **32** was investigated, a two-step procedure was more satisfying than direct labelling.[87] Its 4′-fluoro-analogue **33** was reported, albeit a surprisingly low specific activity was obtained. The authors explicitly state that the use of 3-[$^{18}$F]fluoroprop-1-yl tosylate facilitated an improved yield.[88] Radioactivity uptake into bone confounded the utility of **33**, although this is not relevant for DAT imaging in striatal brain regions, whereas cortical regions located close to the skull are prone to radiation spill over from the skull.[89]

Compound **14** was synthesised via an indirect approach using 4-[$^{18}$F]fluorobut-2-ene-1-yl tosylate as well as by direct nucleophilic radiofluorination.[90–92] A microwave reactor was also used for indirect heating at 100 W for 2 min but without significant improvement.[90]

Following the discovery of a slow conformational change in the DAT upon binding to tropane-based inhibitors, a series of conformationally constrained analogues was investigated.[93] Two of these candidates **12** and **34** were evaluated.[74,93–96] Initial labelling was conducted under conventional conditions, but promising preliminary characterisation warranted investigation of microwave-enhanced radiosynthesis.[74] Thereby, the compounds were obtained in higher yield after a very short reaction time. Compound **34** was synthesised from a bromide precursor because of stability issues observed with the tosylate analogue.

4-Fluorobut-2-ene-1-yl substituted tropanes, introduced about a decade ago, were re-investigated recently to afford the prospective DAT radiotracers **35–37**. Candidate **36** was synthesised from *E*-4-[$^{18}$F]fluorobut-2-ene-1-yl tosylate and provided a favourable kinetic profile.[21] In an approach to improve the metabolic stability of *N*-alkylated tropane derivatives, a 2,2,2-[$^{18}$F]trifluoroethyl prosthetic group was introduced into **6** to obtain **38**.[97]

A more exceptional 3-phenyltropane derivative, FBnCT **39**, was obtained by grafting a 4-[$^{18}$F]fluoromethylphenyl prosthetic group onto the tropane nitrogen; however, current state of the art in aromatic radiofluorination complicates the radiosynthesis, and a four-step procedure is necessary to obtain the labelled compound.[98,99]

Recent progress involves *N*-pyridylamides and *N*-pyridylamines, which provide high DAT selectivity, combined with a convenient site for $^{18}$F-labelling. The most promising candidate **40** shows good results in *ex vivo* autoradiographic studies, which warrants further investigation including detailed metabolite studies.[100] Early on in the development of cocaine analogues for PET, Goodman *et al.* reported carbamoyl analogues of (−)-cocaine bearing *N*-(2-[$^{18}$F]fluoroethyl) **41** and *N*-(3-[$^{18}$F]fluoropropyl) **42** modifications, although no further evaluation of the compounds was disclosed.

## Conclusions and outlook

Over the decades, significant effort has been spent on the development and evaluation of DAT-selective PET radiotracers. In parallel, numerous studies have focussed on labelling conditions and automation of the radiosynthesis. As a result, an extensive set of chemical entities has been studied towards potential DAT radiotracers.

There are two sites for convenient alkylation of the compound, the carboxylate function and the amino function. Consequently, 3-phenyltropanecarboxylic acids and *N*-desmethyl ('nor')-tropanes are key substrates for radiolabelling. Treatment of the restricted bicyclic tropane system bearing two adjacent *exo*-substituents with base is difficult. CH-acidity on carbons 2 and 3 is elevated by the 2-carboxylate or 3-aryl substituents and augmented by conformational strain. Strong bases in combination with elevated temperature readily inverts the stereocenter at C-2 of the bicyclic structure. This is reflected in most of the reaction conditions used to furnish the free acid; a medley of neutral, mildly basic and mildly acidic conditions. Some labelling conditions are prone to C-2-inversion. This 2-epimerisation may compete with formation of the desired product, imposing a limitation on the radiochemical yield.[101] Today, soft, moderately basic alkaline metal or ammonium salts are preferred.

In terms of radiolabelling, there is no clear preference of any single method. Labelling with $^{11}C$ has been achieved in sufficient yields using ubiquitously available reagents such as $[^{11}C]CH_3I$ or $[^{11}C]CH_3OTf$. A variety of different solvents, bases and precursors have been employed.

For $^{18}F$-labelling, each individual route provides specific advantages. However, the use of secondary labelling reagents, such as $\omega$-[$^{18}$F]fluoroalkylating agents, comes at the expense of prolonged synthesis duration and more complex process automation. Notably, whereas prosthetic groups are often understood as means to label radiotracers using more gentle conditions than those used for direct fluorination, the opposite effect is found in *N*-alkylation of tropanes. In this case, much harsher reaction conditions are common, and epimerisation competes with product formation.

Although good yields are routinely obtained in automated processes, one shortcoming still has to be overcome: Most of the clinically employed DAT radiotracers are rapidly metabolised to furnish BBB-penetrating metabolites, which confound non-invasive imaging. Hence, future work has to be committed to avoid metabolically sensitive functional groups towards a more favourable metabolic profile.

## Conflict of Interest

The authors did not report any conflict of interest.

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