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PAPER

Direct, nucleophilic radiosynthesis of [^{18}F]trifluoroalkyl tosylates: improved labelling procedures

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A rapid and efficient protocol to afford the title compound 2-[^{18}F]-fluoro-2,2-difluoroethyl tosylate ([^{18}F]**7b**) is described. Starting from [^{18}F]fluoride ion, labelling reagent **7b** was obtained in good yields and a high specific radioactivity. Compound ([^{18}F]**7b**) was then used to synthesise a prospective radiotracer for PET-imaging in dementia.

Introduction

Quantitative imaging of radiotracer distribution with positron emission tomography (PET) provides invaluable information about molecular transactions in living subjects. PET is based on the detection of coincident 511 keV photons originating from the positron decay process in proton rich radionuclides. This allows for spatial localisation and quantification of the decaying radionuclide in tissue.[1]

The true potential of PET, however, lies in the combination of a positron-emitting radionuclide with a molecular entity that participates in a biochemical process of interest. With the increasing application of PET, spanning preclinical small animal imaging, applications in drug development, biomedical research and clinical diagnostic imaging, there is a strong demand for novel radiotracers for a variety of biological targets. Consequently, a wide portfolio of reliable chemical methodology is required, allowing access to novel radiotracers suitable for increasingly complex imaging studies.[2]

^{18}F is the most frequently employed PET nuclide[3] providing a unique combination of beneficial physical and chemical characteristics; high positron yield from an almost exclusive decay *via* the β^+ decay branch (97%) is paired with a very low positron energy (638 keV) limiting the linear range of the emitted positron to a few millimetres in aqueous tissue. This accounts for a high image resolution compared to most other PET nuclides. This profile is rounded by an expedient half-life (109.7 minutes) rendering ^{18}F suitable for multi-step reactions, transport of radiotracer formulations over moderate distances and convenient handling of the tracer in imaging studies.[1] Moreover, its ability to readily form stable bonds with carbon atoms promotes the straightforward minimally invasive introduction of F atoms into most organic molecules. A key advantage is that production batches of up to 370 GBq (10^3 human doses) as [^{18}F]fluoride ion are realistically achievable on standard medical cyclotrons from the ^{18}O(p,n)^{18}F nuclear reaction *via* irradiation of $H_2{}^{18}O$ liquid targets. Using [^{18}F]fluoride ion, high specific radioactivity, *i.e.* a high ratio of radioactive to non-radioactive molecules (>150 GBq μmol^{-1}) in the radiotracer formulation, is easily feasible. This allows for PET-imaging of saturable biological systems under genuine tracer conditions.[1d] Alternative production routes for ^{18}F as electrophilic fluorination agents exist but their comprehensive adaptation into routine application has been hampered by low specific radioactivity, inconvenient handling, and low production yields.[1,4] As a result, nucleophilic fluorination using [^{18}F]fluoride ion is by far the most common and important route for fluorine-18 labelling.[1–4]

The trifluoromethyl (CF_3) group is a common motif in small molecule drugs, *cf.* Fig. 1. Trifluoromethylation of drug scaffolds is a common method of lead optimisation in drug development, thus a constant feed of novel bioactive compounds containing this function can be anticipated.[5]

The CF_3 group is a bioisostere for iodo, bromo, carbonyl, carboxyl, *sec*-propyl and *tert*-butyl groups.[5] With an electronegativity in the range between chlorine and fluorine, it is a strong electron withdrawing group. Consequently, CF_3 substitution is commonly used to manipulate the acidity of neighbouring groups. Notably, CF_3-groups coordinate to two main group metals of biological relevance.[5b]

However, despite the high abundance of CF_3 groups in pharmaceuticals and drug candidates and its high metabolic stability, only a few approaches for ^{18}F labelling of CF_3 groups have been reported. The radiosynthesis of [^{18}F]CF_3-groups has been further complicated by the low reactivity of leaving groups in difluoromethylene precursors, elaborate multi-step synthesis, and low specific activity in particular with carrier added [^{18}F]CF_3-labelled radiotracers obtained *via* electrophilic fluorination.[8] So far, nucleophilic ^{18}F-fluorination of CF_3 groups has mainly been achieved using harsh reaction conditions. This is a major limitation in ^{18}F radiochemistry, since the CF_3 group is present in a

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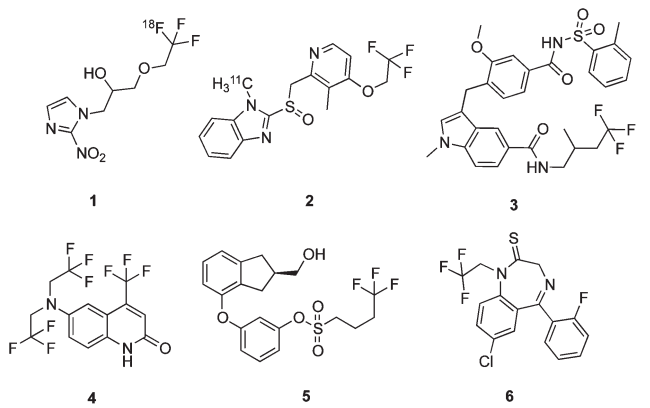
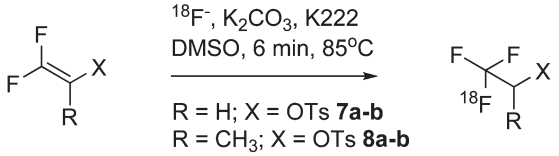


Fig. 1 Examples of aliphatic trifluoromethyl groups in radiotracers, current pharmaceuticals and prospective drugs in clinical trials. **1**: [^{18}F]-TFMISO, a hypoxia PET radiotracer;[6a] **2**: [^{11}C]methyl lansoprazole;[6b] **3**: Flecainide, a cardiovascular sodium channel inhibitor for the treatment of tachycardia;[6c] **4**: LGD-2226, a prospective selective androgen receptor mediator in clinical trials;[6d] **5**: BAY 38-7271 a cannabinoid receptor agonist in clinical trials;[6e] **6**: Quazepam, an α1 selective benzodiazepine derivative.[6f]

large number of well-characterised drug candidates and pharmaceuticals (Fig. 1). Therefore, an efficient method to radiolabel the CF_3 group in high specific radioactivity would open up a wide range of compounds for PET-imaging applications in drug development and medical research. This will also avoid the issue of having to modify leads that already contain 'native' C–F bonds in CF_3 groups by introducing further fluorine atoms in radiotracer development.

Recently, we have reported a rapid, one-step method for nucleophilic radiosynthesis of aliphatic [^{18}F]CF_3-groups in high specific radioactivity under mild conditions.[7] Incorporation of the radiolabel is considered to be achieved *via* the equivalent nucleophilic addition of H[^{18}F]F to 2,2-difluorovinyl groups as shown in Scheme 1.

In addition to direct labelling under mild conditions, secondary labelling agents such as [^{18}F]**7b** provide a novel route for the introduction of metabolically insensitive ^{18}F-labels in heteroatom bound prosthetic groups. In particular defluorination reactions are known to occur to a lower extent than in aliphatic ^{18}F fluorides due to the extraordinarily high stability of C–F bonds in trifluoromethyl groups. This is to the best advantage of brain imaging studies, where uptake of [^{18}F]fluoride ion into the skull will seriously confound PET data. Apart from direct labelling with [^{18}F]F$^-$, indirect labelling using prosthetic groups is often the only way to label sensitive small molecules or peptides for PET. The present study is concerned with synthesis and application of novel [^{18}F]trifluoroalkyl prosthetic groups for PET chemistry.



Scheme 1 Addition of H[^{18}F]F.

Results and discussion

To develop this method, substrate **7a** was used for optimisation of the labelling conditions, investigating the influence of the ^{18}F-fluoride source, reaction time, stoichiometry, temperature and solvent on the radiochemical yields (RCY) as determined by radio-HPLC and/or radio-TLC (Table 1). An alternative substrate, 1,1-difluoroprop-1-en-2-yl tosylate (**8a**, Scheme 2), was labelled with [$K^+ \subset$ K222][^{18}F]F$^-$ under optimised reaction conditions to obtain 1,1,1-[^{18}F]trifluoroprop-2-yl tosylate as a labelling agent.

Synthesis of labelling precursors

The desired difluorovinyl-functionalised labelling precursors are readily accessible using established synthesis methods *e.g. via* sulphur or phosphorus based ylide-reagents, respectively, or *via* HF elimination reactions. In our case, the model compounds were obtained in good yields using known transformations by elimination and Horner–Wadsworth–Emmons olefination.[7]

Compounds **7a** and **8a** were obtained in good yields as described previously.

Optimisation of the labelling reaction

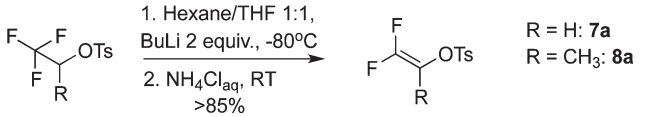
We chose the direct reaction of **7a** with potassium 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (K222) cryptate [^{18}F]fluoride ion complex in DMSO at 130 °C as a starting point for our investigations.

Our effort was then focused on the time course of the reaction, and the time dependent outcome of the reaction from the [^{18}F] fluoride source was investigated (Table 1, entries 1 to 5). Notably all of these can be readily obtained from the target water

Table 1 Optimisation of the reaction conditions for the formation of [^{18}F]**7b**

Entry	M[^{18}F]F	Solvent	*T*/°C	Time/min	RCY[a]/%
1	K[K222][^{18}F]F	DMSO	130	6	61.7 ± 0.4
2	Cs[^{18}F]F	DMSO	130	6	60.3 ± 0.6
3	TBA[^{18}F]F	DMSO	130	6	54.2 ± 0.5
4	Ag[^{18}F]F	DMSO	130	6	58.9 ± 2.2
5	K[K222][^{18}F]F + CuOTf	DMSO	130	6	47.6 ± 0.4
6	K[K222][^{18}F]F	DMSO	110	3	77.9 ± 3.0
7	K[K222][^{18}F]F	DMSO	90	3	91.0 ± 1.0
8	K[K222][^{18}F]F	DMSO	85	3	91.9 ± 1.4
9	K[K222][^{18}F]F	DMSO	70	3	24.8 ± 3.9
10	K[K222][^{18}F]F	DMF	90	3	54.4 ± 2.9
11	K[K222][^{18}F]F	MeCN	82	3	63.4 ± 2.6
12	K[K222][^{18}F]F	THF	66	3	77.2 ± 0.9

[a] $n = 3$.



Scheme 2 Synthesis of labelling precursors **7a**–**8a**.

by solid phase extraction (SPE) in a straightforward sequence on a QMA cartridge, elution in a small volume, concentration and azeotropic removal of excess water. This is highly advantageous for general application of ^{18}F. Currently being the established basis for ^{18}F-chemistry throughout the world, this process has been automated on a variety of commercial systems.

Moderate to good yields were obtained for all [^{18}F]fluoride sources with no clear preference. It was therefore decided to optimise the conditions using potassium 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (crypt-222) cryptate [^{18}F]fluoride ion complex, the most commonly used method for [^{18}F]fluoride ion, which would then enable a more straightforward transfer of the methodology into general application.

In order to determine the best solvent for optimal performance of the radiolabelling step, the dipolar aprotic solvents acetonitrile, DMF, DMSO, and THF were investigated as reaction media. However, substitution of DMSO for either one of the alternative solvents did not have a beneficial effect (Fig. 2). In the case of THF, degradation of the labelled product was accelerated. For this reason, DMSO was the reaction medium of choice in all further experiments.

In the next step the time dependent radiochemical yield was investigated as a function of reaction time at different temperatures in DMSO (Fig. 3).

[^{18}F]fluoride was rapidly incorporated into the labelling precursor and high yields were achieved within 3 minutes at 130 °C. Prolonged reaction times gave lower RCY of [^{18}F]**7b**, due to an increase in the formation of ^{18}F-labelled precursor **7a**. Radiochemical yields of [^{18}F]**7b** were found to improve with decreasing reaction temperature, which was clearly attributable to suppression of a side reaction leading to an unidentified, more polar radioactive product. Highest yields were achieved at 85 °C after a reaction time of 3–6 minutes. Further reduction of the reaction temperature to 70 °C gave unsatisfyingly low yields.

Since rapid chromatographic separation of unlabelled precursor is a key component of radiotracer production processes, and low precursor concentrations generally result in less demanding conditions for separation, we investigated the concentration dependent RCY as a function of reaction time. Highest radiochemical yields were obtained using 5 ± 0.5 mg of precursor **7a** per millilitre of DMSO, equivalent to a final concentration of about 2 mM. Reduction of the concentration of precursor to 1 mM still resulted in a moderate to good labelling yield. Even using a final concentration of 0.4 mM of **7a** in DMSO, [^{18}F]**7b** was obtained in sufficient yield to facilitate production of radiotracers in clinically relevant doses, although at the expense of high variances in the RCY (Fig. 4).

As noted earlier, ^{18}F-labelled "precursor" [^{18}F] **7a** was observed as a by-product of the reaction in some cases (Table 1 entries 1–6, 10–12). The most likely mechanism for its formation is by an addition–elimination mechanism (Scheme 3), rather than nucleophilic substitution of ^{19}F for ^{18}F.

Since this mechanism could also result in an undesired dilution of the final radioactive product with unlabelled **7b** due to the incorporation of $^{19}F^-$ into **7a**, we determined the specific radioactivity (A_S) of [^{18}F]**7a** obtained using the conditions described in Table 1 entry 8. For this experiment, a batch of approximately 5 GBq [^{18}F]fluoride ion was used for the radiosynthesis. The A_S of [^{18}F]**7a** was determined to be 86 MBq nmol^{-1}, which is in good accordance with the typical values obtained in

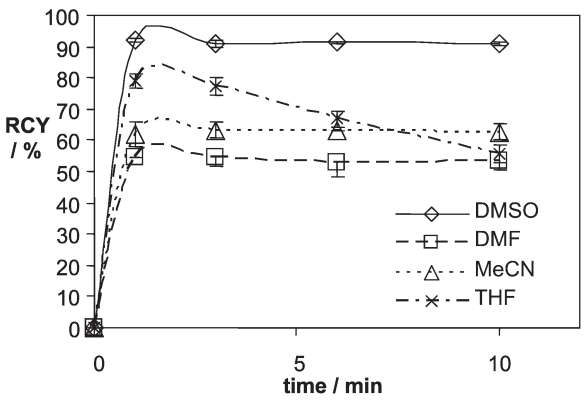


Fig. 2 Radiochemical yield as a function of the solvent.

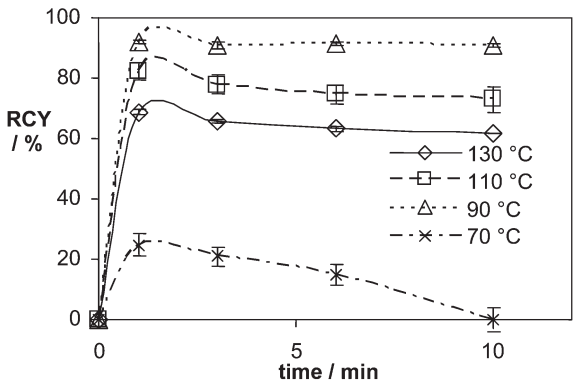


Fig. 3 Radiochemical yield as a function of temperature.

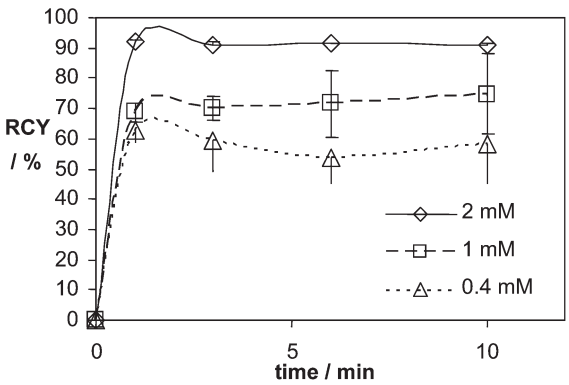
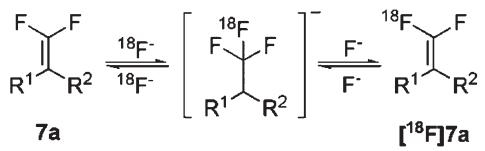


Fig. 4 Plot of radiochemical yield as a function of labelling precursor concentration.



Scheme 3 Addition–elimination mechanism leading to [^{18}F]**7a**.

low activity ^{18}F-production batches. It can therefore be concluded that there is no significant deteriorating effect by equilibration of trifluoro-carbanion and difluorovinyl species. On the other hand, addition of stoichiometric amounts of potassium fluoride to the reaction mixture led to a significant reduction in the reaction rate.

In order to elucidate potential ^{18}F–^{19}F isotopic exchange with fluorine atoms in the product, a control experiment was conducted. Non-radioactive **7b** was reacted with [^{18}F]fluoride ion for 15 minutes and the formation of [^{18}F]**7b** was monitored. Only trace amounts of about 1 percent were formed after 5 minutes and even after 15 minutes at 110 °C only minor amounts of [^{18}F]**7b** were found (<3%). These findings indicate a low susceptibility of aliphatic CF_3 groups to isotopic exchange under our reaction conditions.

Due to the nanomolar quantities of [^{18}F]fluoride ion in the reaction mixture, normally traces of water would strongly affect the labelling efficiency due to solvation of the fluoride ion. Nevertheless, in our assumption, a small amount of water would benefit 'trapping' of the anionic intermediate in the course of the reaction by protonation, thus avoiding excessive equilibration of ^{18}F and ^{19}F addition–elimination products. A high variance between different batches of dried fluoride and between different DMSO qualities gave rise to the assumption that the residual water content might play a key role in the observed yields. For this reason, we investigated the dependency of the radiochemical yield of [^{18}F]**7a** on the water content of the reaction medium (Fig. 5).

When anhydrous DMSO[8] was used, a significant amount of labelled precursor **7a** was formed at 130 °C. In contrast, the ratio between [^{18}F]**7b** and [^{18}F]**7a** gradually improved in favour of the desired product [^{18}F]**7b** when the water content in DMSO was increased.

Maximum yield was obtained with about 5 ppm of water being added to the reaction mixture with only trace amounts of [^{18}F]**7a** being formed. As expected, increasing hydration then impedes the formation of both products at higher water concentrations with the [^{18}F]**7b** being the almost exclusive product at 10 ppm. Only traces of [^{18}F]**7a** were formed at 100 ppm and no labelled product was found at 1000 ppm.[8] We reasoned that the no-carrier-added (n.c.a.) reaction proceeds *via* an intermediate equilibrium where the final labelling product is only obtained in good yields when the intermediate carbanion is rapidly protonated, *i.e.* by trace amounts of water in the reaction mixture.

Conversely, at very low water concentrations, an addition–elimination mechanism as outlined in Scheme 3 will gradually lead to increasing amounts of [^{18}F]**7a** being formed.

Whereas too high concentration of water leads to the loss of reactivity of the n.c.a. [^{18}F]fluoride ion under our optimised reaction conditions (Table 1), excellent radiochemical yields were obtained for [^{18}F]**7b**. However, fine-tuning of the water content might prove difficult in practical application and impede widespread adaptation of the protocol. Hence, we investigated alternative additives that would suppress unwanted side-reactions without affecting the reactivity of $^{18}F^-$, avoiding the necessity of careful adjustment of their concentration. We surmised that an acidic compound with an appropriate pK_a value would be appropriate, simply by protonating the carbanion intermediate without affecting the reactivity of $^{18}F^-$.

Potassium fluoride cryptate and crown ether complexes are known to provide sufficient basicity to deprotonate nitroalkanes and carbonyl compounds in dipolar aprotic solvents and facilitate controlled reactions in condensation reactions. The pK_a value of water in DMSO (31.4) is in the same range as the pK_a values of low molecular weight alcohols (Table 2).[11a] Moreover, alcohols and diols, in particular secondary and tertiary alkyl alcohols, are known to promote reactivity when used in conjunction with alkali metal fluorides of low solubility in aprotic solvents.[2e,11b,c] Considering these facts, we surmised that alcohols would be tolerated in much higher, hence easily controllable concentrations. In contrast, water interferes with the reaction at higher concentration. We therefore focused our effort on low molecular weight alcohols as additives for the reaction mixture, which have been shown to allow for ^{18}F-labelling. In order to investigate the contribution of the pK_a of our additives onto the outcome of the reaction, compounds spanning the pK_a range from 11 to 32 were included at a concentration of 1 M. Based on our earlier findings, DMSO was used as a solvent and [$K^+ \subset$ K222][^{18}F]F^- was used as source of activated $^{18}F^-$.

Using a 1 M concentration of malononitrile and nitromethane did not furnish the desired product in considerable yields. Higher RCY in the range of 20% was found when indole and benzothiazole were used as proton donors, however, the ratio between

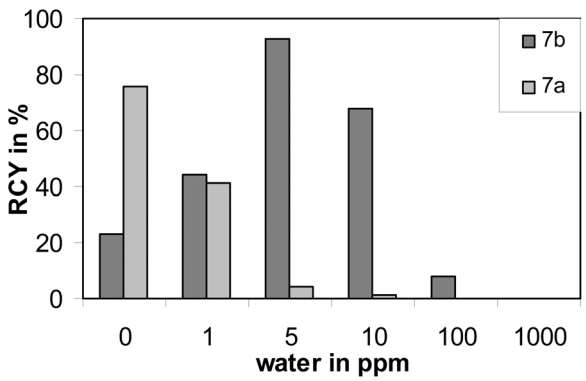


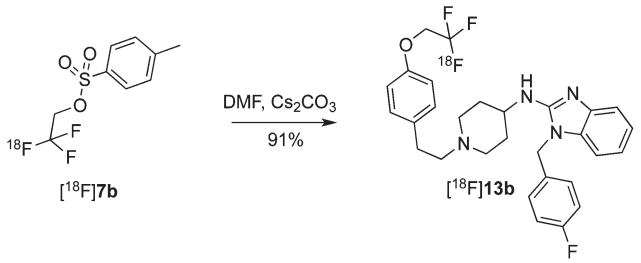
Fig. 5 Dependence of the radiochemical yield on the water content. *X*-axis denotes amounts of water being added to the solvent.

Table 2 Influence of protic additives on labelling outcome

Entry	Additive	pK_a[11]	Time/ min	[^{18}F]**7b** : [^{18}F]**7a**	RCY (product)/%
1	Isoamyl alcohol	n.a.	5	6 : 1	62.2 ± 3.8
2	2-Propanol	30.3	5	10 : 1	66.9 ± 5.8
3	2-Methyl-2-propanol	32.2	5	4 : 1	56.5 ± 7.95
4	Ethanol	29.8	5	5 : 1	45.6 ± 1.4
5	Benzothiazole	27.0	5	2 : 1	22.7 ± 7.35
6	Indole	21.0	5	3 : 2	18.6 ± 0.7
7	Nitromethane	17.2	5	1 : 1	3.7 ± 0.5
8	Malononitrile	11.1	5	Trace	Trace
9	Isoamyl alcohol	n.a.	10	7 : 1	62.3 ± 4.2
10	2-Propanol	30.3	10	10 : 1	72.5 ± 8.3
11	2-Methyl-2-propanol	32.2	10	5 : 1	55.75 ± 2.0
12	Ethanol	29.8	10	6 : 1	50.35 ± 3.9
13	DMSO (neat)	n.a.	5	10 : 1	75.0 ± 11.0
14	2-Propanol (neat)	30.3	5	n.a.	Trace
15	2-Methylaniline	31.4	5	3 : 1	48.5 ± 2.2

Table 3 Two step labelling yields

Compound	Precursor	Product	RCY/%
9a	4-CNC_6H_4OH	4-$CNC_6H_4OCH_2CF_2[^{18}F]F$ (**9b**)	93
10a	2-$ClC_6H_4CO_2H$	2-$ClC_6H_4CO_2CH_2CF_2[^{18}F]F$ (**10b**)	82
11a	$HN(CH_2C_6H_5)$	$(C_6H_5CH_2)_2CH_2CF_2[^{18}F]F$ (**11b**)	77
12a	$(C_6H_5)CSH$	$(C_6H_5)CSCF_2[^{18}F]F$ (**12b**)	86
13a		[^{18}F]**13b**	91



Scheme 4 Radiotracer synthesis.

[^{18}F]**7b** and [^{18}F]**7a** was not satisfactory (Table 2). More striking results were observed when alcohols were used as reaction media (Table 2 entries 1–4). Their use afforded the desired ^{18}F-labelled product [^{18}F]**7b** in much better yields of up to 67% after 5 minutes, combined with a very good ratio between ^{18}F-labelled **7b** and **7a**. Prolonged reaction times did not have a significant effect on the reaction outcome. (Table 2 entries 9–12). Since highest yields were found using 1 M 2-propanol in DMSO and 2.5 mg of precursor in 500 ml, we briefly investigated the use of only 2-propanol. However, only traces of [^{18}F]**7b** were obtained in this case.

Using the optimised conditions (Table 2 entry 2), [^{18}F]**7b** was obtained in an A_S of 56 MBq nmol^{-1}, 5 hours from end-of-bombardment (EOB) for a production scale irradiation.[12] This would correspond to an A_S of approximately 200 MBq nmol^{-1} for a fully automated process of about 90 minutes duration, indicating the A_S has not been diluted under these conditions.

Compound [^{18}F]7b as labelling reagent

As a prosthetic group, the 2-[^{18}F]fluoro-2,2-difluoroethyl group provides great potential as a metabolically insensitive, readily available supplement to PET chemistry. With n.c.a. [^{18}F]**7b** in hand we briefly examined the reactivity of this alkylating agent towards different nucleophiles. For this reason, [^{18}F]**7b** was reacted with N, O and S nucleophiles **9a–12a** in DMF using Cs_2CO_3 as base. The results are summarised in Table 3. Moderate to good yields were obtained within 10 minutes for **9b–12b**. [^{18}F]**7b** was also used to synthesise radiotracer candidate **13b** as a proof of concept for radiotracer synthesis.[10] The results presented in Table 3 clearly show that [^{18}F]**7b** is well suited as a labelling agent.

Compound **13b** is a potential imaging agent for neurofibrillar tangles formed by hyperphosphorylated human τ-protein in several forms of dementia, for example Alzheimer's disease (Scheme 4).

Experimental section

All solvents and reagents were obtained from Alfa Aesar (Alfa Aesar UK Ltd, Heysham, Morecambe, UK), Sigma-Aldrich (Sigma-Aldrich Co. Ltd, Poole, UK) and Fisher Scientific (Fisher Scientific UK Ltd, Loughborough, UK). Solid phase extraction cartridges were obtained from Waters (Waters Ltd, Elstree, UK). Analytical HPLC was performed on an Agilent 1100 series HPLC system (Agilent Technologies UK Ltd, Wokingham, UK), consisting of a G1312 A binary pump and a G1314 variable wavelength UV-detector. A Bioscan (Bioscan Inc., Washington DC, USA) dual BGO metabolite detector system with Flow-Count B-FC-4000 analogue/digital interface and a Bioscan 1″ NaI(Tl) detector with Flow-Count B-FC-4000 analogue/digital interface were used for radioactivity detection. Lablogic Laura 3 and Laura 4 software (Lablogic Systems Ltd, Sheffield, UK) was used for data acquisition and evaluation. For screening of reaction conditions, a Chromolith RP18e (5 μm) 0.4 mm × 100 mm column (Merck KGaA, Darmstadt, Germany) at a flow rate of 2 ml min^{-1} (7 mM NH_4OH–acetonitrile gradient), a Phenomenex Primesphere RP-18 (5 μm) 0.46 × 250 mm column at a flow rate of 1 ml min^{-1} (70–80% MeCN in 0.05 M ammonium formate pH 6.8), a Phenomenex Gemini RP-18 (5 μm) 0.46 × 250 mm column at a flow rate of 1 ml min^{-1} (70–80% MeCN in 0.05 M ammonium formate pH 6.8), and a Chromolith RP18e (5 μm) 0.4 mm × 100 mm column (Merck KGaA, Darmstadt, Germany) at a flow rate of 4 ml min^{-1} (water–acetonitrile, 67 : 33) were used as stationary phase. A GE Healthcare BAS-*IP* MS storage phosphor screen 35 cm × 43 cm was used for radioTLC (Fisher Scientific UK Ltd, Loughborough, UK). Detection and evaluation were performed using a Duerr CR 35 NDT (raytest Isotopenmessgeraete GmbH, Straubenhardt, Germany) and raytest AIDA QWBA software. NMR spectra were recorded on BrukerAvance III 400 QNP Ultrashield Plus Cryo or a BrukerBrukerAvance 500 CryoUltrashield (Bruker UK Ltd, Coventry, UK). Chemical shifts are reported downfield from TMS, relative to the solvent residual signal. Melting points were determined using a Kofler melting point apparatus. Low resolution mass spectrometry was conducted using a Bruker Esquire (Bruker UK Ltd, Coventry, UK) electron spray ion source and detector. Accurate, high resolution mass spectra were recorded on an Orbitrap spectrometer using electron spray ionisation. Flash chromatography was conducted using a Gilson PLC 2020 chromatography system and normal phase silica gel cartridges.

General procedure for radiolabelling

[^{18}F]Fluoride ion was produced using the ^{18}O(p,n)^{18}F nuclear reaction *via* proton bombardment (16 → 3 MeV) of an $H_2{}^{18}O$ liquid target on a GE PETtrace cyclotron at a beam current of 30–40 μA for 5 to 10 minutes. The radionuclide was extracted from the enriched target water *via* solid phase extraction on a Waters Accell plus light QMA strong anion exchanger cartridge (CO_2^{2-}-form). Reactive [^{18}F]F$^-$ was obtained by elution of the trapped radioactivity using a mixture of appropriate bases (20 μmol) in acetonitrile (300 μl) and water (300 μl). Six aliquots of the eluate (100 ml) were transferred to 5 ml conical

bottom reaction tubes and the mixtures were concentrated in a stream of nitrogen. Remaining free water was removed by azeotropic co-evaporation with 3 portions of anhydrous acetonitrile (3 × 1 ml). Labelling precursor dissolved in the appropriate solvent was added to the residue and heated to the desired temperature. Aliquots were withdrawn from the reaction mixture (100 ml) at multiple time points and transferred into water (0.5 ml). The resultant sample was directly injected into radioHPLC or used for radioTLC (1 ml, $CHCl_3$).

Procedure for screening of the proton source

Stock solutions of additive (10 mmol) and **7a** (50 mg, 0.2 mmol) in DMSO (10 ml) were prepared. Aliquots (500 ml) of these solutions were added to $[K^+ \subset K222][^{18}F]F^-$ residues in 2 ml Wheaton reactivials at the desired reaction temperature. Samples were withdrawn at the desired time point, diluted with water and analysed by radio-HPLC.

1-(4-Fluorobenzyl)-*N*-(1-(4-(2,2,2-trifluoroethoxy)phenethyl)-piperidin-4-yl)-1*H*-benzo[*d*]imidazol-2-amine (13b). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.38 (q, J = 10 Hz, 2H), 1.85 (t, J = 11 Hz, 2H), 2.02 (d, J = 11 Hz, 2 H), 2.37 (t, J = 8 Hz, 1H), 2.39 (d, J = 6 Hz, 1H), 2.62 (d, J = 6 Hz, 1 H), 2.64 (t, J = 8 Hz, 1H), 2.79 (d, J = 11 Hz, 2 H), 3.79–3.95 (m, 2 H), 5.03 (s, 2H), 6.82 (d, J = 9 Hz, 2H), 6.94–7.14 (m, 8 H), 7.52 (d, J = 8 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.7, 161.3, 155.7, 153.1, 141.5, 134.2, 130.8, 130.7, 130.6, 129.6, 129.5, 128.3, 128.2, 121.9, 120.2, 116.4, 116.3, 116.1, 113.9, 107.3, 61.4, 52.2, 50.0, 45.1, 32.7, 32.5, 30.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): −77.7, −113.6. MS (ESI) = 526.2, $C_{29}H_{30}F_4N_4O$ requires 526.2356, HRMS $C_{29}H_{30}F_4N_4O$ requires 526.2356, found: 527.2360 [M + H], $C_{29}H_{30}F_4N_4O$ requires C, 66.15; H, 5.74; F, 14.43; N, 10.64; found C, 66.09; H, 5.72, N, 10.86%.

2,2-Difluorovinyl 4-methylbenzenesulfonate (7a).[9] 2,2,2-Trifluoroethyl tosylate (2.57g, 10 mmol) was dissolved in anhydrous THF (15 ml) and cooled to −78 °C. *n*-Butyl lithium (1.6 M in hexanes, 12.5 ml, 20 mmol) was added dropwise and the resultant mixture was stirred at −78 °C for 40 minutes. A mixture of water (4.5 g, 25 mmol) and THF (10 ml) was added and the mixture was allowed to warm to room temperature. The reaction mixture was diluted with diethyl ether and the phases were separated. The aqueous phase was extracted with diethyl ether (20 ml) and discarded. The organic phases were combined, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel (pentane–diethyl ether, 19 : 1). Compound **7a** was obtained as a colourless oil in 79% (1.86 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.46 (s, 3H, $ArCH_3$), 4.38 (q, J = 8 Hz, 1H, CH), 7.38 (d, J = 9 Hz, 2H, ArH), 7.81 (d, J = 9 Hz, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.7, 64.5 (q, J_{CF} = 37.8 Hz), 120.5, 123.2, 128.1, 130.9 (d, J_{CF} = 171 Hz), 131.8, 145.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): −74.06. MS (ESI) = 234.0, $C_9H_8F_2O_3S$ requires: 234.0162.

1,1-Difluoroprop-1-en-2-yl 4-methylbenzenesulfonate (8a). Synthesised from **6b** (2.7 g, 10 mmol) as described for **7a**. Compound **7b** was obtained as a colourless oil in 83% (2.05 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.91 (t, J = 3 Hz, 3H, CH_3), 2.46 (s, 3H, $ArCH_3$), 7.31 (d, J = 8.5 Hz, 2H, ArH), 7.81 (d, J = 9 Hz, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.1, 21.7, 109.6 (dd, J_{CF} = 15.5 Hz, J_{CF} = 49.5 Hz), 128.3, 129.9, 132.5, 145.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): −108.5 (d, J = 55.6 Hz), −94.99 (d, J = 55.6 Hz). MS (ESI) = 247.0, $C_{10}H_{10}F_2O_3S$ requires: 247.0235. HRMS $C_{10}H_9F_2O_3S$ requires: 247.0235, found: 247.0241; $C_{10}H_{10}F_2O_3S$ requires C, 48.38; H, 4.06; F, 15.31; O, 19.33; S, 12.92, found C, 48.41; H, 3.93%.

2,2,2-Trifluoroethyl 4-methylbenzenesulfonate (7b).[1] 2,2,2-Trifluoroethanol (10g, 100 mmol) and triethylamine (14.3 g, 140 mmol) are dissolved in anhydrous diethyl ether (120 ml). Toluenesulfonyl chloride (17.2 g, 90 mmol) was added in portions at room temperature. The mixture was stirred for approximately 48 hours, until the toluenesulfonyl chloride had been consumed. The solids were filtered off and the filter cake is washed with diethyl ether (2 × 30 ml). The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel (hexane–diethyl ether; 9 : 1). Product **6a** was obtained as colourless crystals in 89% (20.3 g) yield. MP = ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.46 (s, 3H, $ArCH_3$), 4.38 (q, J = 8 Hz, 2 H, CH_2), 7.38 (d, J = 9 Hz, 2 H, ArH), 7.81 (d, J = 9 Hz, 2 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.7, 64.5 (q, J_{CF} = 37.8 Hz, 120.5, 123.2, 128.1, 130.1, 131.8, 145.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): −74.06. MS (ESI) = 254.0, $C_9H_9F_3O_3S$ requires 254.0224.

1,1,1-Trifluoropropan-2-yl 4-methylbenzenesulfonate (8b). Synthesised as described for **7b**, from 5.7 g (50 mmol) 1,1,1-trifluoropropan-2-ol. Product **8b** was obtained as colourless oil in 84% (10.1 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.45 (d, J = 7 Hz, 3 H, CH_3), 2.44 (s, 3H, $ArCH_3$), 4.82 (p, J = 6 Hz, 1 H, CH), 7.35 (d, J = 9 Hz, 2 H, ArH), 7.79 (d, J = 9 Hz, 2 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.7, 21.7, 73.2 (q, J_{CF} = 34.2 Hz, 118.7, 121.5, 124.3, 127.9, 132.9, 145.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): −78.66. MS (ESI) = 267.0, $C_{10}H_{10}F_3O_3S$ requires 267.0297, HRMS $C_{10}H_{10}F_3O_3S$ requires 267.0297, found: 267.0303; $C_{10}H_{11}F_3O_3S$ requires C, 44.77; H, 4.13; F, 21.25; O, 17.89; S, 11.95; found C, 45.07 H, 4.07%.

Conclusions

We have demonstrated a novel, versatile methodology for the nucleophilic radiosynthesis of [^{18}F]fluoro-1,1-difluoromethyl-labelled compounds which have not been accessible so far. Direct nucleophilic ^{18}F-fluorination of CF_3 groups in high specific radioactivity opens up a wide range of potential candidates for radiotracer studies. Furthermore, accessing such "native" functionalities in biologically well-characterised molecules will be highly favourable to the invasive introduction of additional fluorine atoms or fluorinated prosthetic groups into radiotracer candidates. Our novel approach is an advancement of utmost utility for the field of radiochemistry and in particular for PET-imaging. Limitations of our protocol involving H_2O addition to the labelling medium have now been overcome by replacement of water by organic proton donors, which do not impair reactivity of fluoride ion at a concentration of 1 M.

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