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Fluorine-18 labelled building blocks for PET tracer synthesis

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Positron emission tomography (PET) is an important driver for present day healthcare. Fluorine-18 is the most widely used radioisotope for PET imaging and a thorough overview of the available radiochemistry methodology is a prerequisite for selection of a synthetic approach for new fluorine-18 labelled PET tracers. These PET tracers can be synthesised either by late-stage radiofluorination, introducing fluorine-18 in the last step of the synthesis, or by a building block approach (also called modular build-up approach), introducing fluorine-18 in a fast and efficient manner in a building block, which is reacted further in one or multiple reaction steps to form the PET tracer. This review presents a comprehensive overview of the synthesis and application of fluorine-18 labelled building blocks since 2010.

1 Introduction

Positron emission tomography (PET) is a powerful molecular imaging technique with a broad range of applications including diagnosis of disease, monitoring of treatment and early phase determination of pharmacokinetics and pharmacodynamics of novel drug candidates.[1–6] *Via* detection of the γ-radiation formed by annihilation of positrons (β^+) emitted by radionuclides, such as carbon-11 ($t_{1/2}$ = 20 min), nitrogen-13 ($t_{1/2}$ = 10 min), oxygen-15 ($t_{1/2}$ = 2 min), fluorine-18 ($t_{1/2}$ = 110 min), gallium-68 ($t_{1/2}$ = 68 min) and zirconium-89 ($t_{1/2}$ = 78 h), PET is able to provide well-defined, three-dimensional quantitative images of the distribution of biologically active compounds labelled with these radionuclides.[2,7,8] The sensitivity of PET is superior to other molecular imaging techniques, since only picomolar concentrations of the labelled compounds have to be used. At these concentrations, biological targets of interest can

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Dion van der Born

Dion van der Born received his MSc in chemistry in 2016 at the VU University in Amsterdam, where he is also currently finishing his PhD thesis under the supervision of Dr D. J. Vugts, Prof. Dr ir. R. V. A. Orru and Prof. Dr A. D. Windhorst on the development of novel radiochemical methodology for the incorporation of the fluorine-18 labelled tri-fluoromethyl group directly onto arenes. This methodology enables radiolabelling and biological evaluation of active pharmaceutical ingredients containing the trifluoromethyl group. Dion is currently employed as a radiochemist at FutureChemistry, where he is involved in the development of radiolabelled compounds and their biological evaluation.

Anna Pees

Anna Pees studied biomedical chemistry at the University of Mainz, Germany. She performed her Master's thesis in the group of Prof. Dr F. Rösch focusing on the synthesis of lipophilic gallium-68 chelators. Since 2016, she is working as a doctoral student under supervision of Prof. Dr A. D. Windhorst and Dr D. J. Vugts in the field of radiopharmaceutical chemistry at the VU University Medical Center Amsterdam, The Netherlands. Her research interest is the development of new radiofluorination methods which enable the synthesis of new PET tracers for imaging cancer and neurological disorders.

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be visualised without causing a biological effect by the radiolabelled compound, thus truly meeting the tracer principle of Hevesy.[1]

The principal application of PET is to diagnose disease in patients by administering a PET tracer which visualises the biological pathway or the therapeutic target which is involved with the disease. Such clear visualization techniques greatly facilitate physicians to establish the correct diagnosis and decide on an effective treatment strategy. The most popular PET tracer is 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG), which allows visualisation of glucose metabolism. Therefore [^{18}F]FDG is widely used for the diagnosis of cancer and monitoring of cancerous lesions that often show increased glucose metabolism (Fig. 1).[9,10]

PET is also a useful asset in the development of drugs. PET can be used to investigate the effect of the drug on a biological

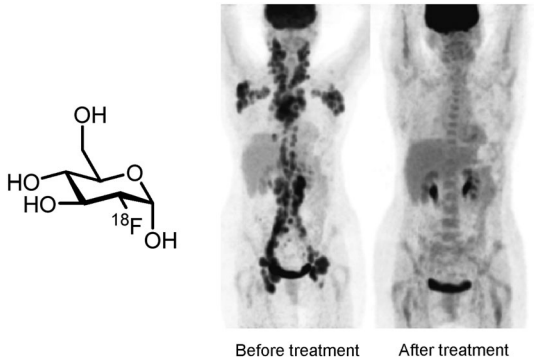

Fig. 1 PET imaging with [^{18}F]FDG.[10]

Alex J. Poot

In 2008 Alex J. Poot obtained his PhD in Medicinal Chemistry from Utrecht University under supervision of Prof. Liskamp. As post-doctoral researcher at the VU University Medical Center (VUmc), Amsterdam, he developed radiolabelled anticancer drugs for PET imaging. In 2014, he accepted a research fellowship from Memorial Sloan Kettering Cancer Center New York to develop carbon-13 labelled probes for tumour metabolism imaging with MRI. In 2015 he was appointed as assistant professor at the VUmc, where his research focusses on novel radiolabelling methods with carbon-11 and fluorine-18, and the application of radiolabelled drugs for oncology PET imaging.

Romano V. A. Orru

Romano V. A. Orru studied molecular sciences at the Agricultural University in Wageningen, the Netherlands, where he obtained his PhD in 1994. From 1996–2000 he worked in the group of K. Faber at the Technical and Karl-Franszens Universities (Graz, Austria). In 2000 he was appointed assistant professor and later associate professor at the VU University Amsterdam. In 2007 he became a full professor of synthetic and bioorganic chemistry. His current research focuses on the development of novel diversity-oriented synthetic methodology for the synthesis of pharmaceutically relevant compounds and natural products.

Albert D. Windhorst

Albert D. Windhorst received his PhD in radiopharmaceutical chemistry in 1998 and was appointed as chair of radiopharmaceutical chemistry in 2014 at the VU University Medical Center Amsterdam, The Netherlands. His research interests are the development of new radio-labelling methods for fluorine-18 and carbon-11 and application of these new techniques in the synthesis of PET tracers for oncology, neurology and cardiology and the translation of these new PET tracers to clinical research. He is immediate past president of the Society of Radiopharmaceutical Sciences, editor of Journal of Labelled Compounds & Radio-pharmaceuticals and associate editor of Nuclear Medicine & Biology.

Danielle J. Vugts

Danielle J. Vugts received her PhD in organic chemistry from the VU University Amsterdam, The Netherlands under the supervision of Prof. Orru. During a post-doctoral period at the VU University Medical Center (VUmc), Amsterdam, The Netherlands she worked on (pre-targeted) immuno-PET. She was appointed assistant professor in 2012 at VUmc. Her research interests are immuno-PET as well as development of new radiolabelling methods for fluorine-18, carbon-11 and zirconium-89 and application of these new techniques in the synthesis of PET tracers for oncology and neurology.

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target or pathway by visualisation with a PET tracer, probing the drug response downstream of the target, or by labelling the drug candidate itself and charting its distribution and kinetics.[3,11]

Of the many positron emitting radionuclides available for the production of PET tracers, fluorine-18 is amongst the most frequently used due to the unique and ideal combination of a 110 minute half-life (allowing transport to satellite PET scan facilities), a clean decay profile (97% positron emission and 3% electron capture), and a low positron energy (max. 0.635 MeV), resulting in high-resolution PET images with a maximum positron range of 2.4 mm in water.[7]

To enable radiochemists to label a wide range of compounds, including naturally occurring compounds and pharmaceuticals, the availability of a large toolkit of fluorine-18 labelling methods is important. Two major strategies can be identified to access fluorine-18 labelled tracers: (1) late-stage radiofluorination, introducing fluorine-18 in the last step of PET tracer synthesis by direct labelling of the precursor with [^{18}F]fluoride and (2) the building block approach (also called modular build-up approach), where fast and efficient introduction of fluorine-18 into the building block by radiolabelling with [^{18}F]fluoride occurs prior to one or more additional reaction steps to arrive at the actual PET tracer.

In recent years, new and very promising methodologies for late-stage aromatic radiofluorination reactions have been developed and excellently reviewed by Preshlock *et al.*[12] and Brooks *et al.*[13] The overview of the different late-stage aromatic radiofluorination reactions given in Table 1, nicely demonstrates the progress in this area.[12–35] For several reasons however, we believe that application of fluorine-18 labelled building blocks for radiolabelling of biologically active molecules as an alternative for late-stage fluorination, is still of high value. In the first place the building block approach allows a modular build-up of fluorine-18 labelled PET tracers which cannot be made by direct late-stage radiofluorination methods. Second, using a labelling strategy that employs fluorine-18 labelled building blocks, the desired PET tracers can be obtained in higher radiochemical yields and radiochemical purity compared to application of late-stage radiofluorination techniques. Finally, once a building block is developed, the same generic labelling methodology can easily be applied to other compounds, *e.g.* *N*-succinimidyl 4-[^{18}F]fluorobenzoate ([^{18}F]SFB) for peptides or a library of analogues of a lead compound. This in contrast to late-stage radiofluorination techniques that only allow the synthesis of a dedicated precursor and where labelling conditions always need to be optimised for every new compound.

The aim of this review is to summarise the recent developments in fluorine-18 labelled building blocks containing a carbon–fluorine bond and their applications in PET tracer synthesis. A comprehensive overview of publications since 2010 that describe the synthesis and development of fluorine-18 labelled building blocks and their potential application to radiolabel low molecular weight compounds for PET tracers, is provided. To demonstrate that these building blocks are indeed a valuable asset, in each case the following characteristics will be discussed:

- Overall radiochemical yield, specific activity and radiochemical purity.
- Ease of synthesis of the labelling precursors.
- Technical ease of labelling.
- Labelling conditions (types of conditions, reaction times, and commercial availability of reagents).
- Purification method (distillation, solid phase extraction (SPE), high performance liquid chromatography (HPLC)).

2 Fluorine-18 labelled aliphatic building blocks

A broad spectrum of aliphatic fluorine-18 labelled building blocks has been utilised in PET tracer synthesis. The spectrum ranges from simple molecules such as radiofluorinated methyl and ethyl halides and sulfonates to complex structures such as [^{18}F]FDG. Fluorine-18 labelled aliphatic building blocks have been used to synthesise either the radiolabelled lead structure or a structural derivative of the lead structure. In the following sections, the synthesis and application of aliphatic fluorine-18 labelled building blocks applied since 2010 will be discussed with respect to their ease of synthesis, stability and application in follow-up reactions.

2.1 [^{18}F]Fluoromethyl halides and sulfonates

The replacement of a methyl group by a [^{18}F]fluoromethyl group is a relatively minor modification in the structure of most small molecules and the chance of significantly influencing the physicochemical and biological properties is minimal. Therefore, [^{18}F]fluoromethylation is often considered as labelling approach for molecules that contain no native fluorine, or where labelling in another position is less preferred. However, the [^{18}F]fluoromethyl group is prone to metabolic instability, resulting in bone uptake of released free [^{18}F]fluoride.[36] The metabolic stability can however be enhanced by deuteration of the [^{18}F]fluoromethyl group[37] or by inhibiting enzyme reactivity with a pharmacological intervention employing disulfiram or miconazole.[38,39]

Multiple [^{18}F]fluoromethylation agents are described and available: [^{18}F]fluoromethyl bromide and iodide are most established, while more recently, [^{18}F]fluoromethyl tosylate as a reagent is of increased interest. This is especially due to the ease of handling and purification of [^{18}F]fluoromethyl tosylate compared to its volatile bromine and iodine analogues. [^{18}F]Fluoromethyl triflate can also be used for [^{18}F]fluoromethylation, but it needs to be synthesised in a two-step procedure from dibromomethane, and is therefore less preferred over other reagents.[40]

Hereafter, synthesis and application of every [^{18}F]fluoromethylation agent for PET tracer synthesis reported since 2010 will be discussed.

2.1.1 [^{18}F]Fluoromethyl bromide. [^{18}F]Fluoromethyl bromide **2** was until the early 2000s the most established agent for [^{18}F]fluoromethylation. Although the interest in this building

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Table 1 Late-stage direct aromatic radiofluorination using [^{18}F]fluoride[a]

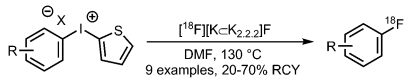
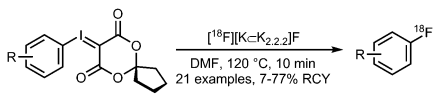
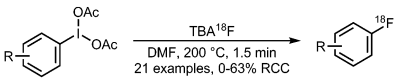
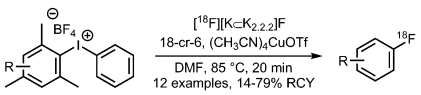
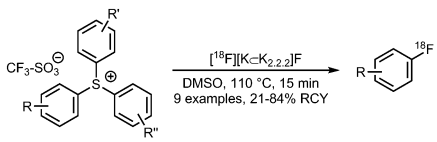
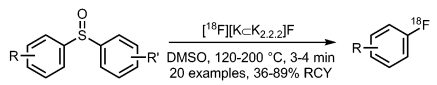
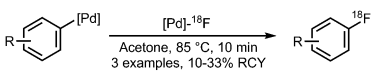
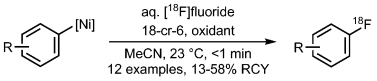
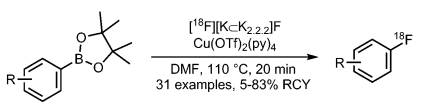
Method	Highlights		Tested on complex molecules?	Ref.
01 Radiofluorination of (hetero)aryl iodonium salts 	• Low to moderate radiochemical yields on electron-rich and electron-neutral precursors. • Reasonable selectivity towards the less electron rich arene. • Precursors can be challenging to prepare.	• Precursors have modest shelf lives. • Harsh reaction conditions, temperatures of >150 °C. • Limited tolerance to common functional groups.	✓	13, 14, 34 and 35
02 Radiofluorination of (hetero)aryl iodonium ylides 	• Low to good radiochemical yields on electron rich and electron-deficient precursors. • Precursors are stable crystalline materials.	• Method has been successfully applied to highly functionalised molecules and existing PET radiopharmaceuticals.	✓	13, 15 and 16
03 Radiofluorination of (diacetoxyiodo)arenes 	• Low to moderate radiochemical conversions on electron-neutral to electron-deficient precursors. • Limited scope concerning arene electron density.	• Synthesis of precursors can be challenging. • Method has not yet been tested on highly functionalised molecules.		17
04 Cu-Mediated radiofluorination of (mesityl)(aryl) iodonium salts 	• Low to good radiochemical yields on electron-rich and electron-deficient precursors. • High reproducibility of radiochemical yields. • Relatively mild reaction conditions.	• No reduced specific activity due to isotopic exchange on BF_4 anion. • Precursors can be challenging to prepare. • Copper catalyst is air stable and commercially available.	✓	12, 13, 18 and 19
05 Radiofluorination of triarylsulfonium salts 	• Low to good radiochemical yields on electron-neutral and electron-deficient precursors. • Precursors can be challenging to prepare. • Precursors show high thermal and chemical stability.	• ^{18}F-Fluorination proceeds in presence of basic functional groups and heterocyclic moieties.	✓	12, 20 and 21
06 Radiofluorination of diaryl sulfoxides 	• Moderate to excellent radiochemical yields on electron-deficient precursors. • No or very low radiochemical yield on electron-rich or electron-neutral precursors. • Precursors can be challenging to prepare.	• Good regioselectivity towards more electron-deficient arenes. • No results yet available on the reaction with complex substrates.		12 and 22
07 Pd-Catalysed radiofluorination of Pd-precursors 	• Low to moderate radiochemical yields on electron-rich precursors. • Two-step procedure, synthesis of [Pd]–^{18}F complex and subsequent radiofluorination of a [Pd]-arene.	• [Pd]–^{18}F complex is sensitive to air and moisture.	✓	13 and 23–25
08 Radiofluorination of arylnickel complexes 	• Low to moderate radiochemical yields on a wide scope of precursors. • Room temperature reaction and short reaction times (<1 min). • The volume of aqueous [^{18}F]fluoride must be kept <1% to prevent degradation of Ni-precursor.	• Basicity of the [^{18}F]fluoride must be reduced/tuned, when [^{18}F]fluoride is dried by classic azeotropic distillation. • Synthesis of Ni-precursors may be challenging.	✓	13, 26 and 27
09 Copper mediated radiofluorination of (hetero)aryl boronic acid pinacolesters 	• Low to good radiochemical yields on electron-rich and electron-deficient precursors. • Precursors are stable, however challenging to synthesise. • Reasonable functional group tolerance.	• Challenging to reproduce. • Products are difficult to purify due to the presence of aryl-H, formed from aryl-BPin during the reaction. • Copper catalyst is air stable and commercially available, but sensitive for basic conditions.	✓	13 and 28

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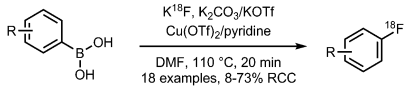
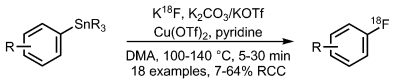
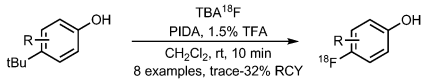
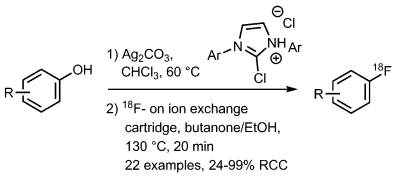
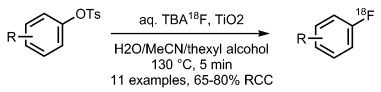
Table 1 (*continued*)

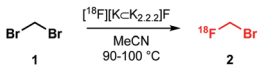
Method	Highlights		Tested on complex molecules?	Ref.
10 Copper mediated radiofluorination of aryl boronic acids 	• Low to good radiochemical yields on electron-rich and electron-deficient precursors. • Precursors are stable, however challenging to prepare. • Reasonable functional group tolerance.	• Not yet tested on heteroaryl precursors. • Not extensively tested yet on more complex precursor structures.		12 and 29
11 Copper mediated radiofluorination of aryl-stannanes 	• Low to good radiochemical conversions on electron deficient arenes. • Precursors are stable, however may be challenging to prepare.	• Method has been successfully applied to highly functionalised molecules and existing PET radiopharmaceuticals.	✓	30
12 Oxidative radiofluorination of phenols 	• Low to moderate radiochemical yields on electron-rich and electron-deficient precursors. • Reasonable functional group tolerance.	• Not yet evaluated on structural more complex precursors. • Not yet evaluated on hetero-arenes.		13 and 31
13 Deoxyradiofluorination of phenols 	• Moderate to excellent radiochemical yields on electron-neutral and electron-deficient precursors. • Phenolic precursors are relatively easy to synthesise and stabile. • Excellent functional group tolerance.	• Radiochemical conversions are based on eluted [18F]fluoride, which is 62% of the total fluoride activity.	✓	32
14 TiO_2 mediated radiofluorination of tosylated precursors 	• Good yields on electron-neutral and electron-deficient precursors. • Precursors are simple to synthesise from phenolic precursors. • No azeotropic drying of [18F]fluoride required, may be performed in up to 25% v/v water.	• Method has been successfully applied to existing PET radio-pharmaceuticals. • Scaling up the amount of aqueous [18F]fluoride had limited success.	✓	12 and 33

[a] Yields: low = 0–30%; moderate = 0–70%; good = 70–90%; excellent = 90–100%.

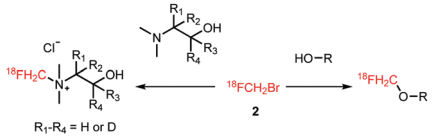
block has decreased since Neal and co-workers developed the synthesis and optimised the production of the tosyl analogue, [18F]fluoromethyl tosylate, for [18F]fluoromethylation, [18F]fluoromethyl bromide is still applied in various reactions for PET tracer production.

[18F]Fluoromethyl bromide is synthesised in one step by reacting dibromomethane **1** with [18F]fluoride in MeCN at 90–100 °C (Scheme 1). The main challenge is in the purification of the volatile product. Although [18F]fluoromethyl bromide has a much lower boiling point (b.p. 9 °C) than its precursor (b.p. 97 °C) and the solvent MeCN (b.p. 82 °C), no pure product could be obtained by straightforward distillation.[41] Purification using gas chromatography is an alternative, however it is incompatible with automation.[40] Distillation over 3 to 4 silica plus Sep-Pak cartridges however provides pure [18F]fluoromethyl bromide in an automation-compliant manner, as impurities are retained on the cartridges while most of the product passes through.[41,42] Reported radiochemical yields of [18F]fluoromethyl bromide vary strongly, from 37 to 74% (dc), which is a major drawback for widespread application of this radiolabelled building block.[40,43]

The subsequent reactions that can be performed with [18F]fluoromethyl bromide to obtain a PET tracer can be divided into two categories; *O*-alkylation and *N*-alkylation (Scheme 2). Although *O*-alkylation comprises the reaction with aliphatic as



Scheme 1 Synthesis of [18F]fluorobromomethane.



Scheme 2 *N*-Alkylation and *O*-alkylation reactions with [18F]fluoromethyl bromide.

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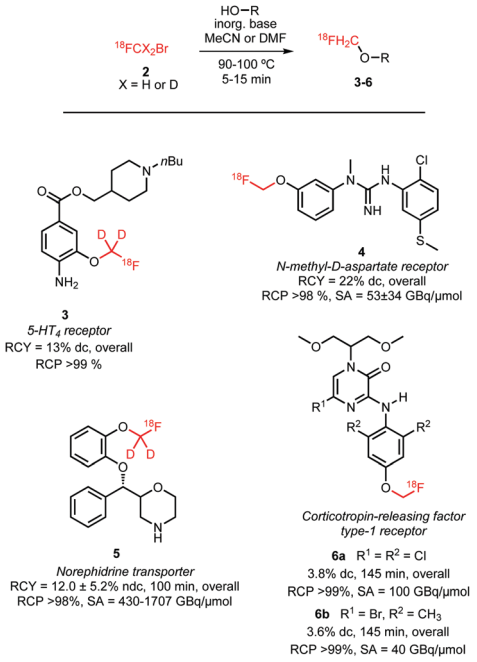
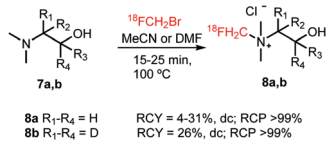


Scheme 3 Recently produced tracers using *O*-alkylation with [^{18}F]fluoromethyl bromide.[42–45]

well as aromatic hydroxyl groups, since 2010 only aromatic *O*-alkylations with [^{18}F]fluoromethyl bromide have been described. An overview of all labelled structures is given in Scheme 3. All syntheses were conducted under comparable reaction conditions. Mostly, reactions were performed in MeCN, only Lodge and co-workers described the use of *N*,*N*-dimethylformamide (DMF).[44] The reactions required high reaction temperatures (90–100 °C) and the addition of an inorganic base. The choice of base proved to have an impact on the yield as reported by Klein *et al.* Purification of the final ^{18}F-fluoromethylated PET tracers was carried out by semi-preparative HPLC.[42–45]

There is only one example of the application of [^{18}F]fluoromethyl bromide in *N*-alkylation reported since 2010, namely, the synthesis of [^{18}F]fluorocholine **8**. This is an established oncologic PET tracer for imaging prostate cancer (Scheme 4). This tracer is routinely synthesised at numerous laboratories and in some cases even commercially available. An automated synthesis of [^{18}F]fluorocholine has been developed by Shao and co-workers. Synthesis and purification of the alkylating reagent was carried out as described above, by distilling [^{18}F]fluoromethyl bromide over three silica Sep-Pak cartridges. This approach proved to be the most efficient regarding yield as well as radiochemical and chemical purity. The volatile product



Scheme 4 Synthesis of [^{18}F]fluorocholine and deuterated derivatives with [^{18}F]fluoromethyl bromide.

was trapped on a C18 cartridge, where it reacted with the [^{18}F]fluorocholine precursor, dimethylaminoethanol. The tracer was obtained after a cartridge purification procedure with a radiochemical yield of 4–6% (dc).[41]

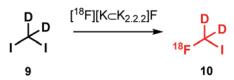
Smith and co-workers investigated the influence of different [^{18}F]fluoromethylation agents in the [^{18}F]fluorocholine synthesis. Next to [^{18}F]fluoromethyl bromide, less volatile [^{18}F]fluoromethyl tosylate was used for [^{18}F]fluoromethylation, to simplify handling and purification. However, for both synthesis routes, a synthesis time of about 150 minutes and similar yields have been observed, both for deuterated **8b** as well as non-deuterated [^{18}F]fluorocholine **8a**.[40]

Thus, [^{18}F]fluoromethyl bromide **2** is a useful building block for [^{18}F]fluoromethylation, providing comparable yields to its more popular and easy-to-handle analogue [^{18}F]fluoromethyl tosylate. Purification and handling of the gaseous compound have been mastered and translated to automated production, making [^{18}F]fluoromethyl bromide **2** easily accessible for novel PET tracer development.

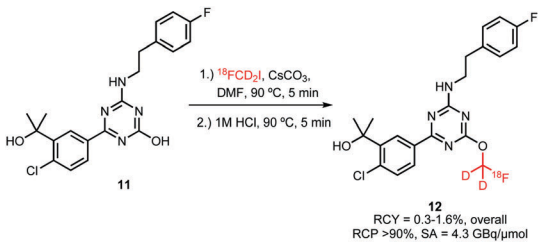
2.1.2 [^{18}F]Fluoromethyl iodide. Although the more reactive [^{18}F]fluoromethyl iodide can be employed analogously to [^{18}F]fluoromethyl bromide or tosylate for [^{18}F]fluoroalkylation, its synthesis and use has only been reported once since 2010. Hortala and co-workers developed the synthesis of a deuterated variant of a [^{18}F]fluoromethylated CB2 cannabinoid receptor ligand, making use of [^{18}F]-d_2-fluoromethyl iodide.

Deuterated [^{18}F]fluoromethyl iodide **10** was obtained *via* a nucleophilic substitution reaction of diiodomethane-d_2 **9** with [^{18}F]fluoride in the presence of potassium carbonate and kryptofix $K_{2.2.2}$ (Scheme 5). Separation of the volatile building block (b.p. 54–56 °C)[46] from the precursor (b.p. 181 °C)[47] was achieved by distillation in a stream of helium. Unfortunately the radiochemical yield of [^{18}F]fluoromethyl iodide was not reported, which makes the comparison between the production of this reagent with other [^{18}F]fluoromethyl alkylating agents difficult.

For [^{18}F]fluoroalkylation, the distilled [^{18}F]FCD_2I **10** was reacted with the radiolabelling precursor in DMF in the presence of cesium carbonate for 5 minutes at 90 °C (Scheme 6). Purification by semi-preparative HPLC resulted in only 0.3–1.6%



Scheme 5 Synthesis of [^{18}F]fluoromethyl iodide.[46]



Scheme 6 [^{18}F]Fluoroalkylation of a CB2 cannabinoid receptor ligand.[46]

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(overall) product, which was attributed to the complexity of the [^{18}F]fluoromethylation reagent synthesis.

It remains unclear why this [^{18}F]fluoroalkylation agent was chosen, the choice possibly depended on the availability of the deuterated precursor. This building block has the same disadvantages as the corresponding bromide, being gaseous and difficult to separate from its precursor. Unfortunately, there is not enough data available to draw a conclusion whether this building block can be synthesised in similar yields as its analogues and whether it shows comparable reactivity in [^{18}F]fluoroalkylation reactions.[36]

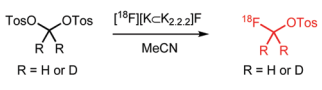
2.1.3 [^{18}F]Fluoromethyl tosylate. Although first published in 1987 by Block and Coenen, the synthesis of [^{18}F]fluoromethyl tosylate **14** did not draw much attention and was initially only applied occasionally. This changed when Neal and co-workers reported an improved synthesis of [^{18}F]fluoromethyl tosylate in 2005, after which application of [^{18}F]fluoromethyl bromide and iodide decreased considerably in favour of using [^{18}F]fluoromethyl tosylate as [^{18}F]fluoromethylating agent. The increasing preference for [^{18}F]fluoromethyl tosylate is easy to understand as handling and purification are straightforward in comparison to its volatile analogues.[48]

[^{18}F]Fluoromethyl tosylate **14** is synthesised in a one-step reaction from methylene ditosylate **13** in MeCN at temperatures between 80 and 120 °C (Scheme 7). Unfortunately, in addition to the desired [^{18}F]fluoromethyl tosylate, [^{18}F]tosylfluoride is formed as side product.[40] Many efforts have been undertaken to reduce the amount of this side product and thus increase the yield of [^{18}F]fluoromethyl tosylate. Neal and co-workers were first to recognise that traces of water have a positive influence on the reaction and reduce side product formation.[48] Up to 20% of water can be beneficial to the reaction outcome.[49]

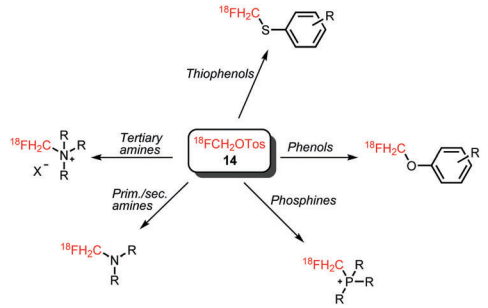
Another approach, pursued by Beyerlein *et al.*, is to replace water by the protic solvent *tert*-butanol. The optimal yield of **14** using this approach was achieved in a solvent mixture of 75% MeCN and 25% *tert*-butanol. Furthermore, it was shown that with the commonly used combination of potassium carbonate and kryptofix $K_{2.2.2}$, degradation of the precursor occurred. Tetrabutylammonium bicarbonate and the combination of potassium carbonate and 18-crown-6 proved better alternatives.[37,40]

In contrast to the volatile analogues [^{18}F]fluoromethyl bromide and iodide, purification of [^{18}F]fluoromethyl tosylate can be easily carried out by semi-preparative HPLC, and even successful [^{18}F]fluoromethylations without intermediate purification have been described.[50,51] Automated procedures have been developed using conventional synthesis units as well as microfluidic devices. Both provide the radiolabelled building block in a radiochemical yield of 44% (dc).[37,49]

[^{18}F]Fluoromethyl tosylate can be used for a variety of alkylation reactions, next to the common *N*- and *O*-alkylation reactions,



Scheme 7 Synthesis of [^{18}F]fluoromethyl tosylate.

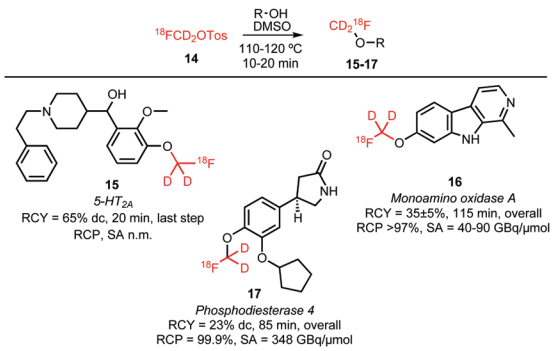


Scheme 8 Reactions with [^{18}F]fluoromethyl tosylate.

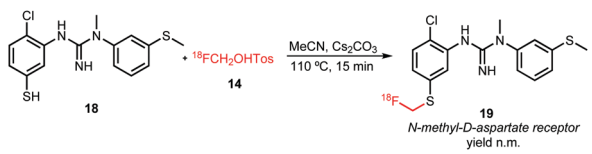
even *S*- and *P*-alkylations have been reported with this reagent (Scheme 8).

O-Alkylations of phenolic hydroxyl groups form besides *N*-alkylations the major part of the conducted [^{18}F]fluoromethylations with deuterated [^{18}F]fluoromethyl tosylate. Scheme 9 shows the reported tracers obtained *via* [^{18}F]fluoromethyl tosylate. *O*-Alkylations were all conducted under similar reaction conditions, proving that the reaction is generally applicable without the need to intensively adjust the different reaction parameters. Dimethyl sulfoxide (DMSO) served as solvent and the reactions were carried out at 110–120 °C for 10–20 minutes. Sodium hydroxide and cesium carbonate have been used as base in the nucleophilic substitution reactions. Radiochemical yields are comparable and range from 60 to 80% for the final alkylation step.[37,52,53]

Analogous to the *O*-alkylation, aromatic *S*-alkylation of guanidine derivative **18** has been performed (Scheme 10). The reaction was carried out in MeCN at 110 °C for 15 minutes using cesium carbonate as base. After purification by semi-preparative HPLC, the compound however decomposed to give free [^{18}F]fluoride. Hence, no yield has been determined for the synthesis of tracer **19**.[54]



Scheme 9 *O*-Alkylated tracers with [^{18}F]fluoromethyl tosylate.[37,52,53]



Scheme 10 Synthesis of a *S*-fluoroalkyl guanidine derivative.[54]

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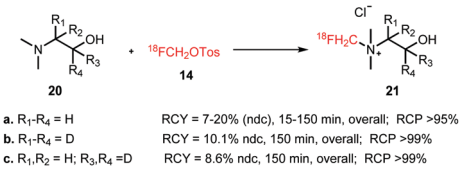


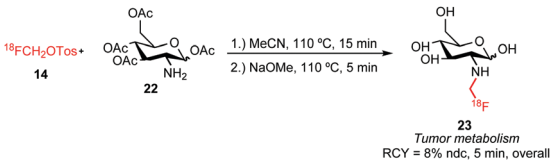
Scheme 11 Synthesis of [^{18}F]fluorocholine and deuterated derivatives with [^{18}F]fluoromethyl tosylate.[40,49,50]

Similar to [^{18}F]fluoromethyl bromide, the main application of [^{18}F]fluoromethyl tosylate in *N*-alkylation reactions is the production of the PET tracer [^{18}F]fluorocholine for the imaging of prostate cancer (Scheme 11). Extensive studies have been performed to establish optimal labelling conditions and to develop an automated synthesis procedure. Smith and co-workers were the first to report [^{18}F]fluoromethylation of the choline precursor using [^{18}F]fluoromethyl tosylate. They compared [^{18}F]fluorocholine and its d_2 and d_4 derivatives (Scheme 11) and showed enhanced stability of the deuterated species towards *in vivo* oxidation during metabolism. They reported that temperature had a strong influence on *N*- or *O*-alkylation. At 100 °C, desired *N*-alkylation was favoured whereas higher temperatures directed the reaction towards *O*-alkylation. Compared to MeCN, the use of DMF resulted in higher radiochemical yields (70 ± 5% dc, n = 5, alkylating step) that could be achieved in decreased reaction times. This was especially beneficial for the deuterated analogues, which required a longer reaction time compared to the non-deuterated compound. The optimised procedure gave the tracers in an overall radiochemical yield of about 10% (ndc) for the d_4 and the non-deuterated compound and 8% (ndc) for [^{18}F]d_2-fluorocholine with a total synthesis time of 150 minutes.[40]

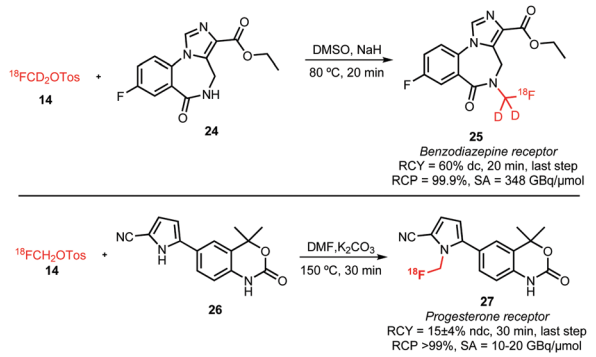
Almost simultaneously, Pascali *et al.* developed a microfluidic synthesis procedure for dose-on-demand [^{18}F]fluorocholine production. They produced [^{18}F]fluorocholine in 13–15 minutes with a radiochemical yield of 20 ± 2% (ndc, overall) without intermediate purification of [^{18}F]fluoromethyl tosylate.[49]

Further proof that intermediate purification is not required for successful [^{18}F]fluorocholine production is provided by the fully-automated one-pot synthesis developed by Rodnick and co-workers. To the mixture of crude [^{18}F]fluoromethyl tosylate, dimethylamino ethanol was added and heated for 10 minutes at 120 °C to yield 7% (ndc, overall) in a total synthesis time of 75 minutes.

Not only [^{18}F]fluorocholine but also other tracers obtained by *N*-alkylation have been reported using [^{18}F]fluoromethyl tosylate. As can be seen in Schemes 12 and 13, next to tertiary nitrogen atoms also primary and secondary nitrogen atoms can



Scheme 12 *N*-Alkylation reactions of primary amines.[55]



Scheme 13 *N*-Alkylation reactions of secondary amines.[37,56]

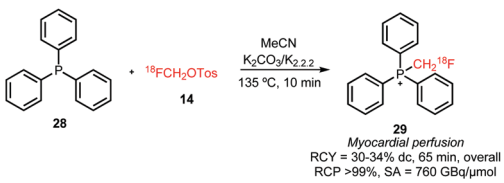
be alkylated. This is rarely found in literature because reactivity of the nitrogen increases in each step leading to polyalkylation. However, the huge excess of precursor compared to alkylation agent (in this case [^{18}F]fluoromethyl tosylate) used in radiochemistry allows in this case selective monoalkylation.

An example of [^{18}F]fluoroalkylation of primary amines is the synthesis of the glucosamine derivative **23** (Scheme 12). Using the conditions of Smith and co-workers, [^{18}F]fluoromethyl glucosamine derivative **23** could be obtained in a radiochemical yield of 8 ± 2% (n = 15, ndc).[55]

Two successful [^{18}F]fluoromethylations of secondary amines with [^{18}F]fluoromethyl tosylate (Scheme 13) are (1) the synthesis of [^{18}F]fluoro-d_2-methylflumazenil **25** for imaging benzodiazepine receptors and (2) the synthesis of the progesterone receptor agonist **27**. Very different reaction conditions were applied in each reaction. While Beyerlein *et al.* reported the [^{18}F]fluoro-d_2-methyl-flumazenil **25** radiosynthesis with a radiochemical yield of 60% dc over the last step using sodium hydride at 80 °C in DMSO,[37] Merchant *et al.* reported the synthesis of **27** in DMF at 150 °C in presence of potassium carbonate as base. Lower temperatures led in the latter case to yields lower than 1% and the addition of base was necessary for a clean reaction. Thus, **27** was synthesised from [^{18}F]fluoromethyl tosylate in 30 minutes with a radiochemical yield of 15 ± 4% (ndc).[56]

Since 2010 only one case of *P*-alkylation with [^{18}F]fluoromethyl tosylate has been reported. [^{18}F]Fluoromethyl triphenylphosphonium cation **29** was synthesised in a one-pot reaction from [^{18}F]fluoromethyl tosylate **14** and triphenylphosphine **28** with an overall radiochemical yield of 30–34% dc (Scheme 14).[51]

In conclusion, [^{18}F]fluoromethyl tosylate is a building block, which can be applied in many different alkylation reactions. Due to its ease of handling and purification compared to the volatile analogues [^{18}F]fluoromethyl bromide and [^{18}F]fluoromethyl iodide,



Scheme 14 Synthesis of [^{18}F]fluoromethyl triphenylphosphonium cation.[51]

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it has gained increased interest for PET tracer development and routine production.

2.2 [^{18}F]Fluoroethyl halides and sulfonates

Like the [^{18}F]fluoromethyl halides and sulfonates, [^{18}F]fluoroethyl halides and sulfonates find widespread application in fluorine-18 labelling. Especially for molecules which contain no native fluorine atom or where the fluorine atom is difficult to introduce. [^{18}F]Fluoroethylation often allows for the radiofluorination of easier accessible precursors under milder reaction conditions and can therefore be advantageous over direct labelling. Furthermore, it facilitates separation of the labelled compound from the precursor by HPLC purification.[57]

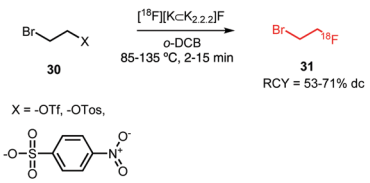
[^{18}F]Fluoroethyl groups are often used as a substitute for a methyl group and in contrast to [^{18}F]fluoromethylated tracers they offer the advantage of showing high *in vivo* stability.

Next to the most popular [^{18}F]fluoroethylation agent [^{18}F]fluoroethyl tosylate ([^{18}]FETos), the bromide and different sulfonates have found application in PET tracer synthesis. The different building blocks and their advantages will be discussed in the following sections.

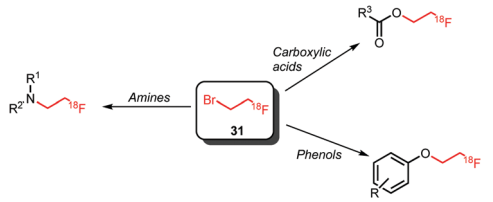
2.2.1 [^{18}F]Fluoroethyl bromide. [^{18}F]Fluoroethyl bromide **31** is after [^{18}F]FETos the most frequently used [^{18}F]fluoroethyl building block and has been employed in many PET tracer syntheses.

All syntheses of this building block followed established procedures by Zhang *et al.* (Scheme 15).[58,59] Typically, 2-bromoethyl triflate served as precursor, but also the use of the corresponding tosylate or nosylate has been reported.[60,61] The radiofluorination reaction was carried out in *o*-dichlorobenzene as solvent, reaction temperatures varied between 85–135 °C and reaction times between 2–15 minutes. [^{18}F]Fluoroethyl bromide **31** was distilled during or after the reaction and transferred to a second reaction vial where it was trapped in a solution at around −15 °C, containing the precursor and base for the subsequent reaction. Distillation was straightforward and the product was produced in high (radio)chemical purity due to the much lower boiling point of [^{18}F]fluoroethyl bromide (71.5 °C) compared to *o*-dichlorobenzene (179 °C) and the triflate precursor (230 °C). Decay-corrected radiochemical yields of 53–71% have been reported.[60,62] Schmaljohann and co-workers reported a cartridge-based purification procedure instead of distillation. They obtained the building block in a radiochemical yield of 63% (dc).[63]

Labelling reactions with [^{18}F]fluoroethyl bromide can be divided into two main categories, being *N*- and *O*-alkylation (Scheme 16). Whereas *N*-alkylation of various amines is performed,



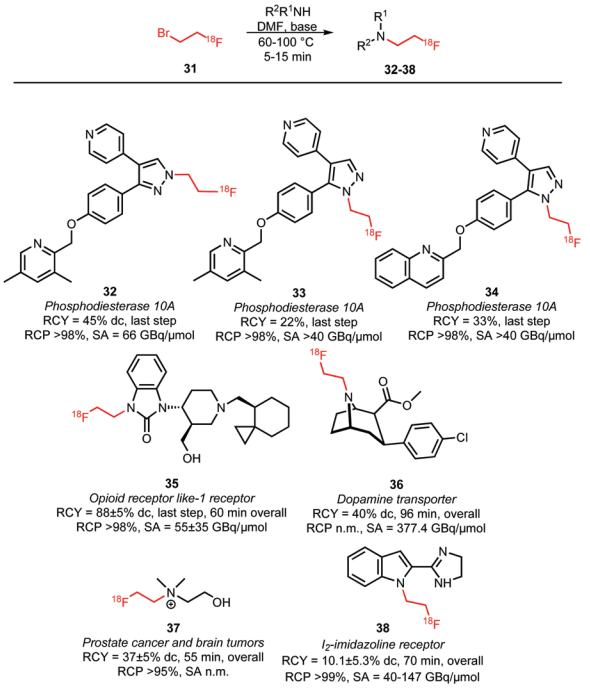
Scheme 15 Synthesis of the building block [^{18}F]fluoroethyl bromide.



Scheme 16 Reaction scope of [^{18}F]fluoroethyl bromide as building block.

O-alkylation is almost exclusively applied and reported for phenolic precursors. Apart from phenolic *O*-alkylation, two ester formations with carboxyl groups have been reported.

An overview of tracers obtained by *N*-alkylation is given in Scheme 17.[60,63–67] Typical reaction conditions for *N*-alkylations are the use of DMF as solvent and the addition of a base in the presence of the amine precursor. As base, either TBAOH or cesium carbonate were used. After heating to 60–100 °C for 5–15 minutes, the products were usually purified by (semi-)-preparative HPLC and obtained in overall radiochemical yields of 10–40% (dc). However, some variations were reported depending on the labelling precursor. Murali and co-workers describe alkylation without any addition of base as otherwise epimerisation of the chiral centre occurs. Consequently, the coupling step required long reaction times and afforded the dopamine transporter (DAT) tracer **36** in a relatively low radiochemical yield of 34% (dc, last step). By performing the same reaction with the more reactive [^{18}F]fluoroethyl triflate, the radiochemical yield could be increased to 84% for the coupling step and the overall reaction time was reduced from 148 to 96 minutes.[60] Schmaljohann *et al.* succeeded in the development of a cartridge based purification procedure for fast and reliable automated



Scheme 17 *N*-Alkylation with [^{18}F]fluoroethyl bromide.[60,63–67]

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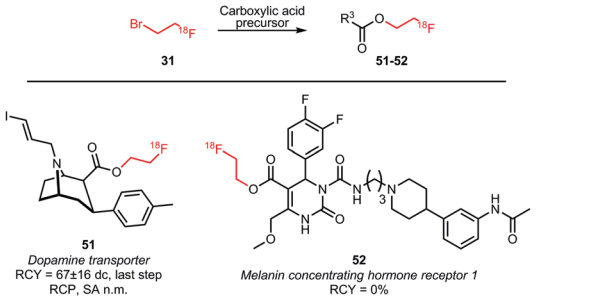
synthesis. They produced [^{18}F]fluoroethyl choline **37**, an imaging agent for prostate cancer and brain tumours, on two different commercially available synthesis units obtaining comparable overall radiochemical yields of 33% and 37% (dc) in 55 minutes.[63] Though, comparable synthesis times could also be achieved including an HPLC purification procedure.[66]

Phenolic *O*-alkylation is the most popular application using [^{18}F]fluoroethyl bromide as the building block. A variety of PET tracers have been synthesised based on this labelling strategy (Scheme 18).[61,62,68–74] The general reaction conditions are similar to *N*-alkylation: the phenolic precursor was reacted with [^{18}F]fluoroethyl bromide under basic conditions at elevated temperatures for 2–20 minutes in DMF or DMSO. Although sodium hydroxide was often employed as base, the use of other bases has been reported depending on the reactivity of the precursor. Liu and co-workers for example described in their synthesis of **46** a coupling reaction with the weaker base potassium carbonate, to prevent degradation of the lactone moiety.[62] Furthermore, addition of sodium iodide to the coupling reaction increased the reactivity of the building block by *in situ* formation of the more reactive [^{18}F]fluoroethyl iodide.[59,62]

Next to *O*-alkylation of phenolic precursors, esterification of carboxylic acid precursors has been investigated (Scheme 19). Rami-Mark and co-workers obtained radiochemical yields of 67 ± 16% (dc) in the coupling reaction forming the dopamine transporter ligand **51**. The reaction was carried out under TBAOH catalysis at a reaction temperature of 100 °C. In contrast to phenolic *O*-alkylation, no increase in yield was observed in the presence of sodium iodide.[75] Another coupling reaction with an

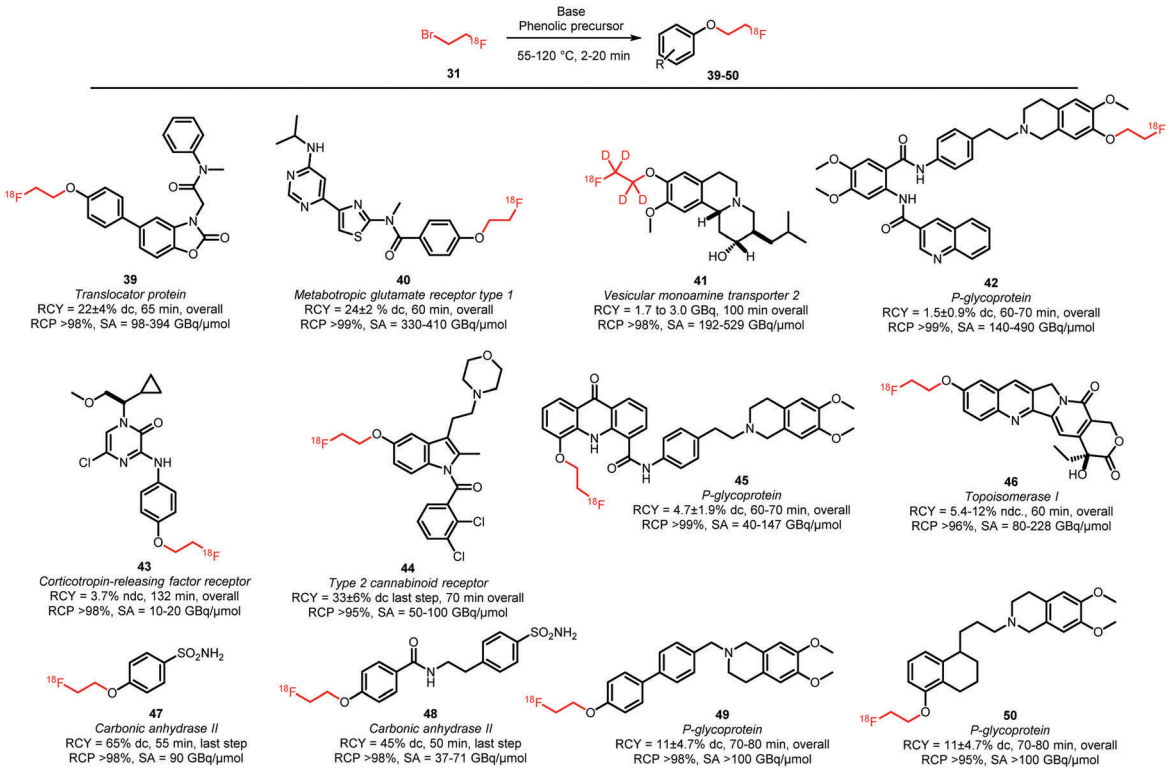


Scheme 19 Esterification of carboxylic acids with [^{18}F]fluoroethyl bromide.[75,76]

acid precursor was conducted by Philippe *et al.*, in order to obtain a derivative of the melanin concentrating hormone receptor 1 antagonist SNAP-7941 **52**. Despite screening different solvents, temperatures and reaction times, no reaction of the radiolabelled building block was observed.[76]

In conclusion, [^{18}F]fluoroethyl bromide can be regarded a convenient reagent for radiofluorination of amines, phenols and carboxylic acids *via* alkylation. [^{18}F]Fluoroethyl bromide can be synthesised fast and reliably and likewise the coupling reactions proceed fast, providing in one step the fluoroalkylated products in decay-corrected overall radiochemical yields of up to 40%.

2.2.2 [^{18}F]Fluoroethyl tosylate ([^{18}F]FETos). The synthesis of [^{18}F]FETos **54** was for the first time reported in 1987 by Block *et al.*[77] Since then, it has gained increasing interest as a building block in fluorine-18 chemistry. In comparison to its halide and sulfonate analogues, it offers favourable properties: its low



Scheme 18 Phenolic *O*-alkylation with [^{18}F]fluoroethyl bromide.[61,62,68–74]

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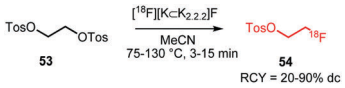


Scheme 20 Radiosynthesis of [18F]FETos.

volatility makes it more applicable to automation, the precursor ethylene ditosylate has a high chemical stability and the building block is highly reactive in alkylating reactions.[78]

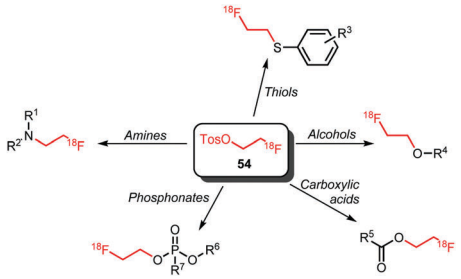
The synthesis procedures of [18F]FETos **54** follow similar reaction conditions (Scheme 20). The kryptofix-potassium carbonate-[18F]fluoride complex ([18F][K⊂K2.2.2]F) reacted, after azeotropic drying, with the precursor ethylene ditosylate **53** in MeCN. Temperatures for this reaction varied between 75 °C and 130 °C and reaction times were between 3 and 15 minutes. Radiochemical yields of 20–90% were reported depending on purification and whether the production was executed manually, semi-automated, automated or by using a microfluidic system. In addition to manual synthesis of the building block, production using automated modules has frequently been carried out, either for only [18F]FETos synthesis or also for subsequent alkylation reactions.[78] Pascali *et al.* developed a microfluidic approach providing the crude radiolabelled building block in a radiochemical yield of 67% (based on radio-TLC analysis).[49]

Of the different approaches to purify [18F]FETos, semi-preparative HPLC generally provided the product with the highest chemical purity, leading to better conversions in the subsequent alkylation reaction. Furthermore, reduced formation of non-radioactive by-products was observed during the alkylation reaction which made final purification of the tracer easier.[57]

As HPLC purification is time-consuming, several SPE-based purification procedures have been developed. However, most of them focus on the removal of free [18F]fluoride, potassium carbonate and kryptofix only.[78] Moreover, significant losses of radioactivity during cartridge purification or the subsequent drying step were observed.[79,80] Schoultz *et al.* presented a SPE procedure including precipitation of the precursor with acetic acid, followed by filtration. The building block was obtained in high radiochemical purity (>99%) and in radiochemical yields of over 45%.[78]

Next to that, many successful one-pot methods have been described where [18F]FETos was used without intermediate purification before the subsequent alkylation reaction. Heinrich *et al.* reported an increased yield when using a one-pot strategy compared to a two-pot reaction with intermediate SPE purification, because they could avoid the activity losses on the cartridge.[79] Majo *et al.* on the other hand obtained in a one-pot procedure only half of the radiochemical yield (20–25%) that was achieved when using a two-pot procedure, with intermediate purification by semi-preparative HPLC.[81]

[18F]FETos has found widespread application as a building block (Scheme 21). Besides *N*- and *O*-alkylation, reactions of [18F]FETos with phosphonates and thiols are known. Further, next to phenolic *O*-alkylation aliphatic hydroxyl groups and aromatic carboxylic acids can also be labelled with [18F]FETos.



Scheme 21 Reaction scope of [18F]FETos as building block.

Numerous *N*-alkylations with [18F]FETos have been performed (Scheme 22).[49,57,82–95] General reaction conditions involve the use of polar aprotic solvents such as DMSO, DMF or MeCN and temperatures ranging from 82 to 130 °C. Mostly, inorganic bases with a range of different pK_a-values were employed depending on the reactivity of the corresponding amine reactant. Alkylation in absence of base has been reported for **56** and **58**, which are potential imaging agents for matrix metalloproteinases and phosphatidylinositol 3-kinase, respectively.[83,88] To achieve [18F]fluoroalkylation of **61** and **64**, the amine reactants were treated with base (NaH or NaOH) prior to radiolabelling to generate the corresponding sodium salt. Radiolabelled **61** and **64** are important PET tracers for translocator protein and VEGF, respectively.[85,90]

Studies that involve Finkelstein-type alkylation reactions by addition of alkali iodides showed promising results indicating that *in situ* iodide exchange indeed could increase the yield of *N*-alkylation.[96] However, this strategy has only been applied to access the serotonin 4 receptor tracer **60** and actually did not appear beneficial for the overall reaction outcome.[89]

The majority of tracers produced by alkylation with [18F]FETos were purified by semi-preparative HPLC. Only two SPE-based purification procedures were described in literature. They were developed for the cancer tracer fluoroethylcholine **68** and for tracer **59** that targets phosphatidyl serine to image cell death.[49,93] Fluoroethyl-ceritinib **55**, an imaging agent for anaplastic lymphoma kinase, was purified by normal phase flash chromatography because no HPLC conditions were found to obtain the tracer in decent purity.[94]

For some of the tracers in Scheme 22, direct and indirect labelling methods of the molecule were compared. In general no clear preference for either method could be concluded as in some cases (**61** and **66**) higher yields with direct labelling were found whereas in other cases (**55** and **62**) the indirect labelling strategy was more successful.[91,94]

Many *O*-alkylations with [18F]FETos have been performed and Scheme 23 shows all tracers synthesised by fluoroalkylation of phenolic precursors.[52,80,81,97–120] The synthesis is overall similar to the *N*-alkylations and reactions were carried out in DMF, DMSO, MeCN or mixtures of these solvents with water at elevated temperatures (80–130 °C). Reaction times ranged from 10 to 20 minutes. A variety of bases have been employed: amongst others cesium carbonate, sodium hydroxide and sodium hydride have mostly been described. The choice of base and its

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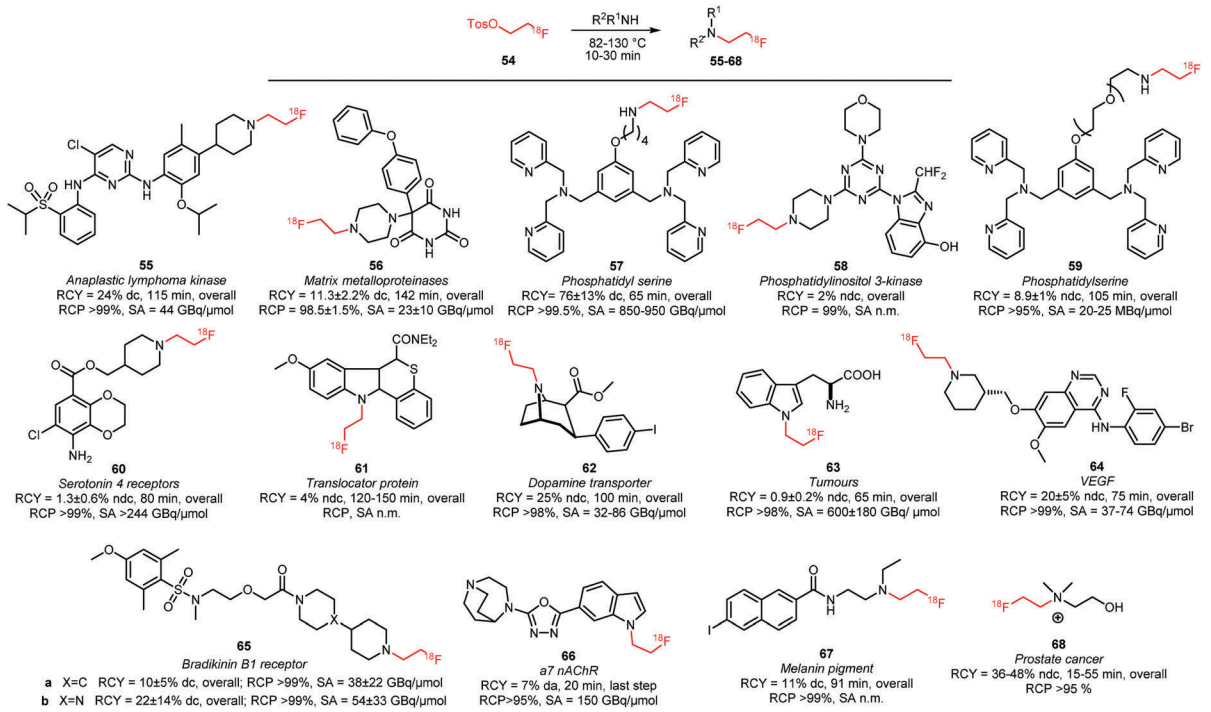

Scheme 22 PET tracers synthesised by *N*-alkylation with [^{18}F]FETos.[49,57,82–95]

concentration has a big influence on the yield of the alkylation reaction. Basic formation of the phenolate generates the nucleophile that will react with [^{18}F]FETos in the radiolabelling.[117] In approximately one third of all synthesis procedures, the phenolic precursor was deprotonated prior to alkylation to form the corresponding phenolate. The time of this preformation of phenolate varied from a few minutes up to several hours.[104,105] The base was either filtered off after phenolate formation was complete or added together with the precursor to the reaction mixture containing [^{18}F]FETos.[98,104]

For some of the synthesised PET tracers, direct and indirect radiolabelling has been compared. For the tracers **71**, **73**, **103** and **105**, higher labelling yields for indirect labelling compared to direct labelling have been reported. For example, Schieferstein *et al.* obtained an overall radiochemical yield of 47 ± 2% in the synthesis of the monoamino oxidase A tracer **73** with [^{18}F]FETos as labelling reagent, whereas the direct labelling approach in their hands only led to decomposition of the precursor.[52] In another study, **73** was obtained *via* direct labelling in 23% decay-corrected radiochemical yield.[121]

For the tracers **85** and **83** however, direct labelling was superior to the indirect method. Purification of the phosphodiesterase 10A tracer **85**, which was synthesised by the two-step reaction *via* [^{18}F]FETos, turned out to be challenging and provided **85** in variable radiochemical purities, ranging from 92–99%. Therefore, direct labelling was performed which afforded **85** in high purity (≥99%) and comparable overall yields (25 ± 9%).[102]

Next to aromatic *O*-alkylation, alkylation of aliphatic hydroxyl groups has also been reported with [^{18}F]FETos. Schoultz *et al.* studied an automated synthesis procedure for the opioid receptor tracers **109a–c**. The tracers were synthesised in a two-step one-pot procedure from [^{18}F]FETos and the trityl-protected precursor **108**. The aliphatic hydroxyl group in the precursor was first deprotonated by treatment for 5 minutes with sodium hydride to generate the alkoxide. Then [^{18}F]FETos was added and efficient alkylation occurred within 10 minutes at 100 °C. In the second step, the trityl-protected hydroxyl group was removed under acidic conditions. After HPLC purification, all derivatives of **109** were obtained in decay-corrected radiochemical yields of 26 ± 8% (Scheme 24).[78,122]

Esterification of carboxylic acids with [^{18}F]FETos has been studied by Heinrich *et al.* and Philippe *et al.*[76,79] Effective esterification towards **111**, a potential imaging agent for the melanin concentrating hormone receptor 1, was not observed when using [^{18}F]FETos, and only direct radiofluorination in a microfluidic procedure proved successful.[76] In contrast, **110**, a tracer for myocardial perfusion, was synthesised successfully *via* esterification of the carboxylic acid precursor with [^{18}F]FETos, performed in a one-pot procedure. After formation of [^{18}F]FETos, the carboxylic acid was added under base catalysis in anhydrous MeCN for 30 minutes at 165 °C. The resulting product **110** was isolated by SPE or HPLC purification in an overall radiochemical yield of 36% (dc). Evaporation of the solvent during alkylation resulted in higher yields due to increased concentration of the reactants (Scheme 25).[79]

James *et al.* described the synthesis of an acetylcholine esterase tracer *via* *O*-alkylation of a phosphonate precursor (Scheme 26). The reaction was carried out in a microwave reactor with addition of cesium carbonate as base and with molecular sieves. Without intermediate purification of [^{18}F]FETos and after semi-preparative HPLC, the desired tracer was obtained in a yield of 6.5% (dc) after the alkylation step.[123]

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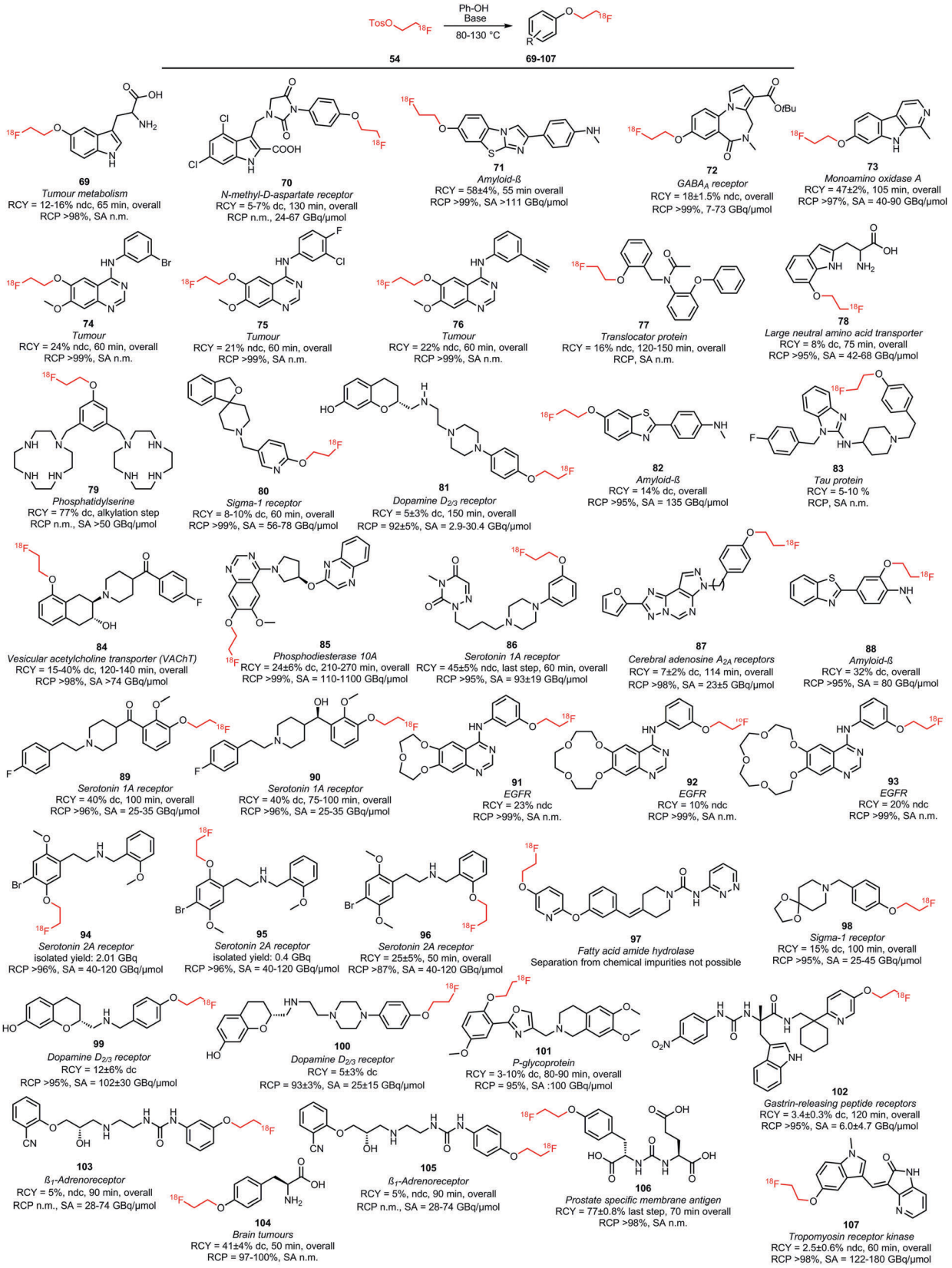

Scheme 23 PET tracers synthesised by *O*-alkylation of phenolic precursors with [^{18}F]FETos.[52,80,81,97–120]

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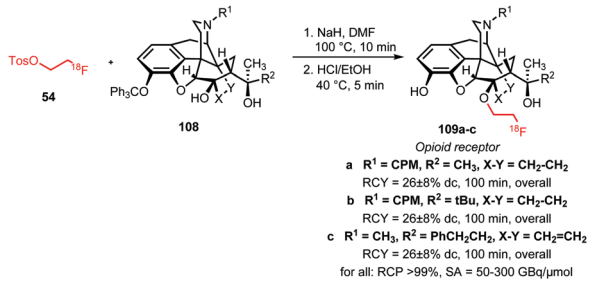
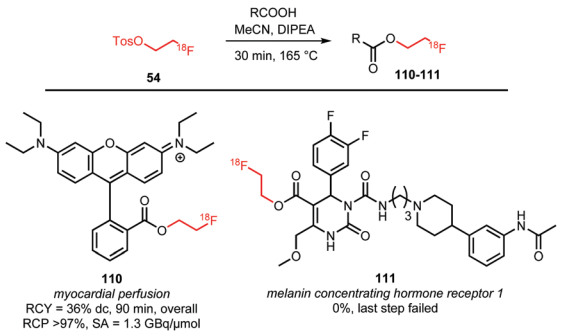
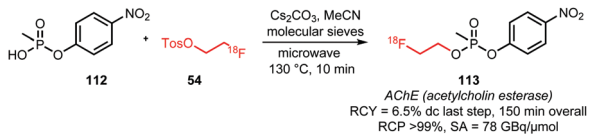


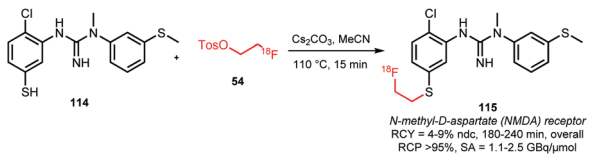
Scheme 24 Aliphatic *O*-alkylation with [^{18}F]FETos.[78,122]



Scheme 25 *O*-Alkylation of carboxylic acids with [^{18}F]FETos.[76,79]



Scheme 26 *O*-Alkylation of a phosphonate with [^{18}F]FETos.[123]



Scheme 27 Synthesis of **115** by *S*-alkylation.[54]

Analogous to *N*- and *O*-alkylation, *S*-alkylation has been successful to obtain the NMDA receptor tracer **115** (Scheme 27). Overall radiochemical yields were 4–9% (ndc) in a synthesis time of 3 to 4 hours. In contrast, direct radiolabelling conditions led to degradation of the precursor and no radiofluorinated product was obtained.[54]

In conclusion, [^{18}F]FETos is an easy to synthesise, versatile building block which has been employed in the synthesis of many tracers because of its versatility and stability. It shows several advantages over the other [^{18}F]fluoroethyl halides and sulfonates such as low volatility and decent reactivity. Furthermore, in many cases, [^{18}F]FETos performs better or as good as the direct radiolabelling approach regarding conversion and purification of the PET tracer.

2.2.3 [^{18}F]Fluoroethyl sulfonate esters. In addition to the two most applied [^{18}F]fluoroethyl building blocks discussed above, a number of other [^{18}F]fluoroethyl sulfonate esters have been employed for fluorine-18 labelling. Most notably, [^{18}F]fluoroethyl nosylate, brosylate, 3,4-dibromobenzenesulfonate and triflate have been used and selection of such alternative [^{18}F]fluoroethylation agents is mainly determined by *e.g.* enhanced stability or increased reactivity in the alkylation reaction.

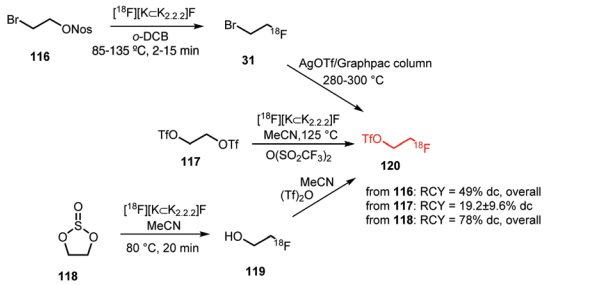
2.2.3.1 [^{18}F]Fluoroethyl triflate. [^{18}F]Fluoroethyl triflate **120** is more reactive towards alkylation than [^{18}F]fluoroethyl bromide and therefore affords [^{18}F]fluoroethylated products under very mild reaction conditions such as room temperature and without the need to add a base. Furthermore, it enables [^{18}F]fluoroethylation of less nucleophilic precursors.

Three different strategies for [^{18}F]fluoroethyl triflate synthesis have been developed (Scheme 28). Philippe *et al.* reported a one-step procedure starting from ethylene glycol bistriflate **117** and [^{18}F][K⊂K$_{2.2.2}$]F complex. The building block was obtained using triflic anhydride at elevated temperatures. Purification was performed with an alumina cartridge providing the product in a radiochemical yield of 19.2 ± 9.6% (dc).[76]

Murali *et al.* on the other hand discovered that the moisture-sensitive bistriflate precursor **117** suffers from poor stability even when stored at −20 °C. They observed low radiolabelling yields and therefore followed a two-step synthesis procedure with [^{18}F]fluoroethyl bromide **31** as intermediate product. The bromide was distilled over an AgOTf/Graphpac column heated to 280–300 °C where it was converted to the corresponding triflate **120**. They reported a total decay-corrected radiochemical yield of 49%, which is more than twice as high as the yield reported for the one-step procedure.[60]

A third approach was developed by Peters *et al.* They used [^{18}F]fluoroethanol **119** as an intermediate that was synthesised from ethylene sulfate **118** in MeCN at 80 °C. After passing the crude reaction mixture through a QMA light cartridge, [^{18}F]fluoroethanol was treated with triflic anhydride. The reaction proceeded smoothly (1 min) and did not require elevated temperatures. [^{18}F]Fluoroethyl triflate was obtained after purification using an Alumina N light cartridge in a radiochemical yield of 78% (dc) starting from dried [^{18}F]fluoride.[124]

Triflate building block **120** has been used in both *N*-alkylations and *O*-alkylations.[60,76,125] While *O*-alkylation of **121**, which is the acid precursor of a potential PET tracer for the melanin concentrating hormone receptor 1, proved unsuccessful under common



Scheme 28 [^{18}F]Fluoroethyl triflate synthesis from [^{18}F]fluoroethyl bromide or ethylene glycol bistriflate.[60,76,124]

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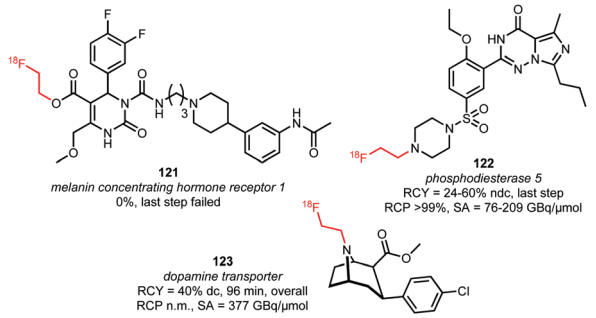
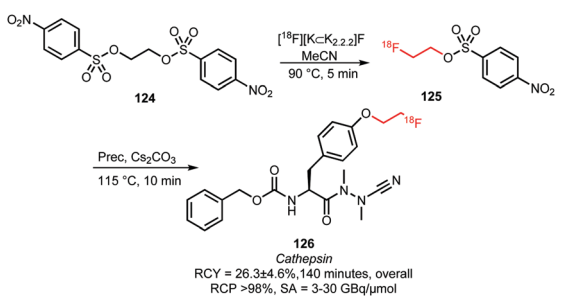


Fig. 2 Tracers labelled with [^{18}F]fluoroethyl triflate.[60,76,125]

[^{18}F]fluoroethylation conditions (the tracer could only be synthesised using direct radiofluorination in a microfluidic system), two successful *N*-alkylations were described (Fig. 2).[76] As the triflate is more reactive than the bromide, milder reaction conditions could be applied resulting in potential imaging agents, **122** and **123**, which were obtained at room temperature without the presence of base or any other additives, after a few minutes, in good radiochemical yields.[60,125] The base-free reaction conditions proved to be a big advantage particularly in the synthesis of the dopamine transporter ligand **123**, avoiding epimerisation of the chiral centre at the C2-position.[60]

2.2.3.2 [^{18}F]Fluoroethyl nosylate. Since 2010, [^{18}F]fluoroethyl nosylate has only been described once as building block in a radiosynthesis. Löser and co-workers presented the synthesis of the fluorinated cathepsin inhibitor **126** in a two-step one-pot process (Scheme 29). [^{18}F]Fluoroethyl nosylate was selected for the alkylation because the use of [^{18}F]FETos resulted in low radiochemical yields (<26% based on radio-TLC analysis) due to degradation of the [^{18}F]FETos under the reaction conditions. Furthermore, separation of the final product from [^{18}F]FETos by semi-preparative HPLC was difficult and resulted in low radiochemical purity.

The selected [^{18}F]fluoroethyl nosylate **125** building block could be prepared from the corresponding ethylene dinosylate **124** in MeCN at 90 °C in 5 minutes (Scheme 29). After cooling the reaction mixture to room temperature, the subsequent coupling reaction was conducted without intermediate purification. Nosylate **125** was treated with the phenolic precursor using catalytic amounts of base at 115 °C for 10 minutes. This gave product **126** in 74% radiochemical yield (based on radio-TLC analysis; 26% after HPLC purification) in an overall synthesis time of 140 minutes.[107]



Scheme 29 [^{18}F]Fluoroethyl nosylate synthesis and reaction to the cathepsin inhibitor **126**.[107]

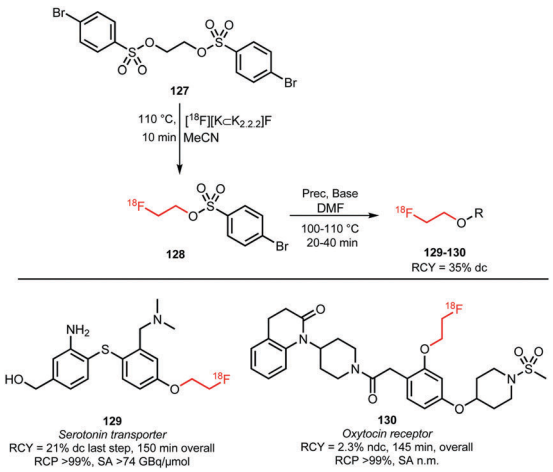
2.2.3.3 [^{18}F]Fluoroethyl brosylate. Like the other sulfonates discussed above, 2-[^{18}F]fluoroethyl-4-bromobenzene sulfonate ([^{18}F]fluoroethyl brosylate) can be used as building block for the introduction of a [^{18}F]fluoroethyl group. Its main advantage is that phenolic *O*-alkylation proceeds more efficiently compared to the use of the corresponding tosylate.[126] Moreover, it is less volatile compared to [^{18}F]FETos, which makes [^{18}F]fluoroethyl brosylate more suitable for application in open vessel reactors (Scheme 30).[127]

The brosylate building block can be prepared by a procedure established by Voll and co-workers. *Via* a nucleophilic substitution reaction, ethylene-1,2-4-bromobenzene sulfonate precursor **127** could be radiofluorinated at elevated temperatures resulting in the desired brosylate in 35% (dc) radiochemical yield after HPLC purification.[127,128]

The follow-up coupling reactions were conducted analogously to those with the other ethyl sulfonate building blocks. The phenolic precursors were reacted in DMF with [^{18}F]fluoroethyl brosylate **128** under basic conditions at 100–110 °C. Catalytic amounts of cesium carbonate or TBAOH were employed as base. In this way the serotonin transporter imaging agent **129** was obtained in an overall radiochemical yield of 21% (dc). This is quite efficient compared to the alternative preparation of fluorine-18 labelled oxytocin receptor ligand **130**, which was obtained in a non-decay corrected overall radiochemical yield of only 2.3%. Total synthesis time of both tracers was about 150 minutes.

Smith and co-workers also investigated the synthesis of PET tracer **130** *via* direct radiofluorination of the respective tosylate precursor and reported a non decay-corrected radiochemical yield of 19%, which is 8 times higher than the two-step synthesis.[127,129]

2.2.3.4 [^{18}F]Fluoroethyl-3,4-dibromobenzenesulfonate. In 2005 Musachio *et al.* studied other [^{18}F]2-fluoroethyl brosylates to mediate [^{18}F]fluoroethylation. Their studies revealed that



Scheme 30 [^{18}F]Fluoroethyl brosylate synthesis and subsequent [^{18}F]fluoroethylation.[127,129]

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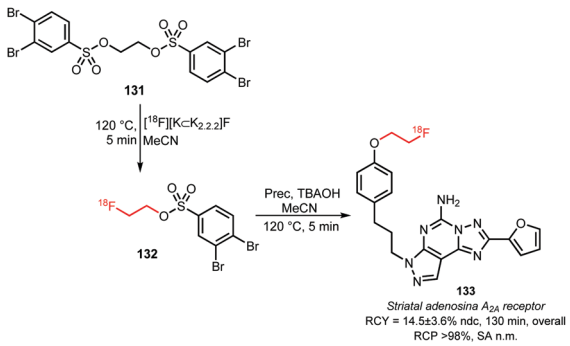


Scheme 31 [^{18}F]Fluoroethyl-3,4-dibromobenzene sulfonate synthesis and reaction to the A_{2A} receptor tracer **133**.[130]

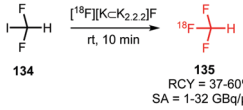
[^{18}F]fluoroethyl-3,4-dibromobenzenesulfonate **132** is highly reactive and quite stable and achieves high yields in alkylating reactions (Scheme 31).[126]

Still, thusfar only one tracer synthesis based on [^{18}F]fluoroethylation with [^{18}F]fluoroethyl-3,4-dibromobenzene sulfonate **132** has been reported. Bhattacharjee and co-workers described the synthesis of a fluorine-18 labelled tracer for A_{2A} receptor imaging. In the first step, ethyleneglycol-1,2-3,4-dibromobenezenesulfonate **131** was reacted with the dried [^{18}F]fluoride at 120 °C for 5 minutes. After that, the resulting building block was purified by semi-preparative HPLC and reacted with the respective phenolic precursor in presence of TBAOH as base. Purification by semi-preparative HPLC afforded the radiotracer **133** for the striatal adenosine A_{2A} receptor in an overall radiochemical yield of 14.5 ± 3.6% (ndc).[130]

2.3 [^{18}F]Fluoroform

The trifluoromethyl functional group is well established for its favourable *in vivo* properties. Therefore it is a group incorporated in many active pharmaceutical ingredients. Consequently, the introduction of fluorine-18 using trifluoromethylation has found widespread interest. A highly effective way to achieve this is to couple [^{18}F]fluoroform to aryl boronic acids and iodides in a copper(I) mediated reaction. However, this approach mostly gave the products in poor specific activity, which is a disadvantage for PET imaging of low density receptors in particular.

Difluoroiodomethane **134** and the difluoromethylsulfonium salt **142** have been explored as alternative precursors for [^{18}F]fluoroform synthesis (Schemes 32 and 35). Based on the precursor difluoroiodomethane **134**, van der Born *et al.* developed two different methods to synthesise [^{18}F]fluoroform, providing the product either in high yield or increased specific activity. In one method, [^{18}F]fluoride was eluted with $K_2CO_3/K_{2.2.2}$ and azeotropically dried following standard procedures. Subsequent reaction with difluoroiodomethane **134** for 10 minutes at room temperature afforded [^{18}F]fluoroform **135** in a radiochemical yield of 60% with a specific activity of 1 GBq μmol^{-1}. Purification was carried out by distillation over a silica Sep-Pak cartridge. The low specific activity is most probably caused by the polyfluorinated precursor. Reducing the amount of precursor 40-fold together with decreasing the amount of base for [^{18}F]fluoride elution from the cartridge gave an average radiochemical yield of only 37%, but specific activity increased to 32 GBq μmol^{-1}.[131]

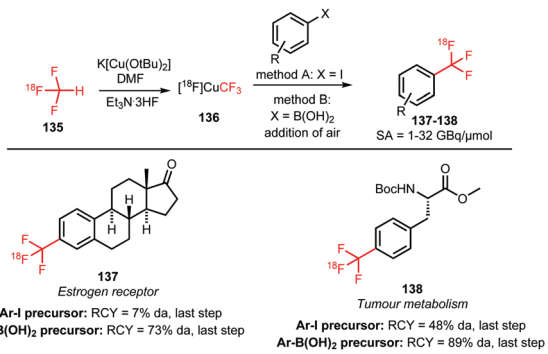


Scheme 32 [^{18}F]Fluoroform synthesis with difluoroiodomethane as precursor.

To introduce the [^{18}F]trifluoromethyl group into PET tracers **137** and **138** for imaging breast cancer and other tumours, copper-mediated reactions with aryl iodides and aryl boronic acids showed promising results. [^{18}F]Trifluoromethylation of aryl iodides was carried out in the presence of copper(I) bromide and potassium *tert*-butoxide as a base. Further, triethylamine trihydrofluoride was employed to stabilise the resulting copper–CF_3 complex. Reactions were complete after 10 minutes at 130 °C. The procedure was similar for trifluoromethylation of aryl boronic acids, but oxidation of copper(I) was required by purging the reaction solution with air. Reactions were complete within 1 min at room temperature, which is considerably faster compared to the reactions using analogous iodide precursors. In Scheme 33, the radiosynthesis of two tracers labelled by [^{18}F]trifluoromethylation using [^{18}F]fluoroform is depicted. Both were synthesised from the available iodide precursor as well as from the boronic acid precursor. Direct comparison of both procedures showed that use of the boronic acid precursors offered more favourable coupling conditions and ultimately higher radiochemical yields.[131]

In addition to the above methods, a one-pot procedure to synthesise [^{18}F]trifluoromethylated tracers in an automation-compliant manner has been developed by Rühl *et al.* In order to find the most efficient Cu–ligand system for the [^{18}F]trifluoromethylation reaction in presence of the dried [^{18}F]fluoride, different ligands and sources of reactive [^{18}F]fluoride were screened. Optimal yields of [^{18}F]trifluoromethylated product were obtained with a $KHCO_3$/kryptofix/DIPEA mixture. Utilizing the optimised conditions, three potential PET tracers **139**, **140** and **141** were synthesised in good radiochemical yields of 73 to 85%. A drawback is that the tracers were obtained in only a very low specific activity of 139 MBq μmol^{-1} (Scheme 34).[132]

Ivashkin *et al.* employed difluoromethylsulfonium salt **142** as precursor for the [^{18}F]fluoroform synthesis (Scheme 35).



Scheme 33 PET tracer synthesis by [^{18}F]trifluoromethylation of iodide and boronic acid precursors.[131]

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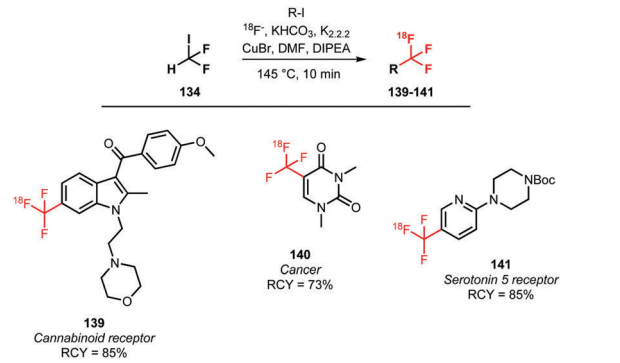
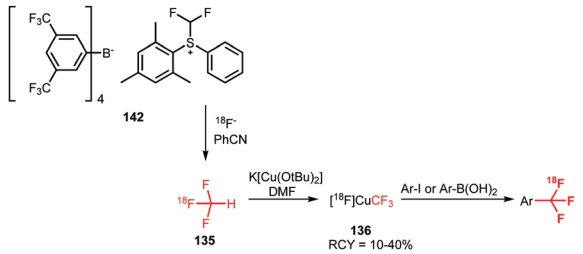
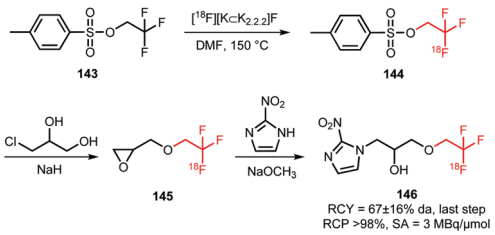


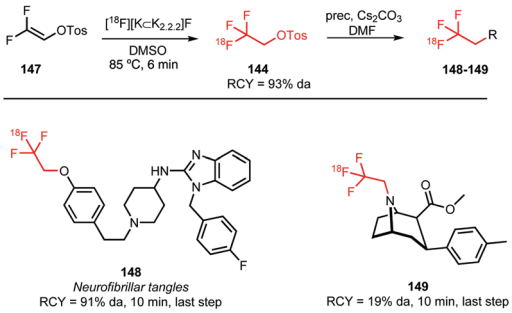
Scheme 34 One-pot synthesis of [^{18}F]trifluoromethylated arenes.[132]



Scheme 35 [^{18}F]Fluoroform synthesis with the difluoromethylsulfonium salt **142** as precursor.[133]



Scheme 36 Synthesis of the hypoxia tracer [^{18}F]TFMISO.[134]



Scheme 37 [^{18}F]Trifluoroethyl tosylate synthesis and coupling towards **148** and **149**.[108,135,136]

However, [^{18}F]fluoroform was not isolated, but distilled into a solution containing a copper(I) halide and potassium *tert*-butoxide. This instantaneously formed the [^{18}F]$CuCF_3$ complex **136**, which was subsequently treated with a range of different model iodides or boronic acids. Again, the tracers were obtained in very low specific activity of 100 MBq μmol^{-1}, comparable to the one-pot procedure described by Rühl *et al.*[133]

In conclusion, production of [^{18}F]fluoroform with high specific activity remains a challenge. A method has however been developed providing [^{18}F]fluoroform with an acceptable specific activity of 32 GBq μmol^{-1}. Aryl iodides and boronic acids have successfully been labelled with [^{18}F]fluoroform as building block. [^{18}F]Trifluoromethylation of boronic acids proceeds fast and under mild reaction conditions and aryl iodides have shown to be valuable precursors in one-pot syntheses of relevant tracers. Hence, [^{18}F]trifluoromethylation with [^{18}F]fluoroform holds great promise for fluorine-18 labelling of compounds containing native trifluoromethyl groups.

2.4 [^{18}F]Trifluoroethyl tosylate

Application of [^{18}F]trifluoroethyl tosylate as a building block enables the introduction of fluorine-18 *via* the trifluoroethyl group. Two different PET tracers have been synthesised using [^{18}F]trifluoroethyl tosylate (Schemes 36 and 37).

Suehiro *et al.* developed the synthesis of [^{18}F]trifluoromisonidazole ([^{18}F]TFMISO) **146**, a hypoxia tracer for bimodality imaging with MRI and PET. In this context, 2,2,2-[^{18}F]trifluoroethyl tosylate **144** was found to be an excellent [^{18}F]trifluoroethylation agent, as it reacts smoothly with alcohols to the corresponding [^{18}F]trifluoroethyl ethers.

The building block was synthesised *via* ^{18}F–^{19}F exchange from 2,2,2-trifluoroethyl tosylate **143**. For this, the unlabelled compound was heated in presence of [^{18}F][K⊂K$_{2.2.2}$]F at 150 °C. After 10 minutes, the product was separated from unreacted [^{18}F]fluoride by extraction with ether. A specific activity of this building block is not reported, but a low specific activity is expected due to the isotopic exchange methodology that was employed here.

Starting from [^{18}F]trifluoroethyl tosylate, the hypoxia tracer was subsequently prepared *via* a 2-step procedure. First, [^{18}F]trifluoroethyl tosylate was treated with deprotonated 3-chloro-1,2-propanediol, in the presence of sodium hydride. After a 45–60 minutes reaction at room temperature, the desired [^{18}F]trifluoroethoxy intermediate **145** was obtained with good radiochemical yields of 57 ± 10% (analytically determined). In the next step, intermediate **145** was converted to [^{18}F]TFMISO in a reaction with 2-nitroimidazole under basic conditions using NaOMe. The final product **146** was obtained in a radiochemical yield of 67 ± 16% (analytically determined) (Scheme 36).

Besides the procedure described above, other routes have been investigated to arrive at the same final compound. The analogue 2,2,2-[^{18}F]trifluoroethyl iodide was synthesised with an excellent labelling efficiency (90–95%), but underwent nucleophilic substitution at the fluorinated carbon atom instead of substitution of the iodide. Furthermore, Suehiro *et al.* tried to directly label the complete precursor molecule of **146**, however this led to intramolecular nucleophilic substitution of the nitro group.[134]

Riss *et al.* synthesised [^{18}F]trifluoroethyl tosylate *via* nucleophilic addition of [^{18}F]fluoride to 1,1-difluorovin-2-yl-4-toluene sulfonate **147** (Scheme 37). Extensive studies to find optimal reaction conditions were conducted and in the end 5 minutes

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reaction in DMSO at 85 °C proved sufficient to produce the desired compound. Trace amounts of water were crucial for product formation as in the absence of water the precursor was subject to an addition–elimination reaction resulting in fluorine-18 labelled **147**. As the addition of ppm amounts of water appears to be rather cumbersome, the influence of low molecular weight alcohols on the reaction has been explored. Best results were obtained with 1 M 2-propanol in DMSO and radiochemical yields up to 67% (based on radio-HPLC analysis) were observed. Furthermore, specific activity of the fluoroethyl building block has been examined. A good specific activity (86 GBq μmol^{-1}) was obtained even with low quantities of [^{18}F]fluoride at the start of synthesis (5 GBq).[135]

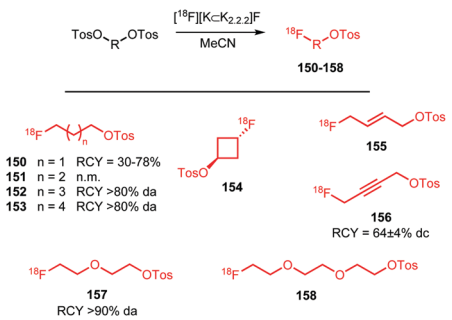
[^{18}F]Trifluoroethyl tosylate was applied in both *O*- and *N*-alkylations resulting in two potential imaging agents, **148** and **149** (Scheme 37). The coupling reaction was conducted in DMF using cesium carbonate as base. *N*-Alkylation (19%) proceeded in a much lower yield than *O*-alkylation (91%), which was attributed to the tropane scaffold used in this specific case.[136]

In summary, 2,2,2-[^{18}F]trifluoroethyl tosylate is a useful building block, forming [^{18}F]trifluoroethyl ethers under relatively mild conditions. The possibility of native radiofluorination and the enhanced stability of the trifluoroethyl group towards metabolic degradation compared to [^{18}F]fluoroethylates make it a promising building block for fluorine-18 labelling in the future.

2.5 Long chain ($n > 2$) fluorine-18 labelled aliphatic halides and sulfonates

Apart from [^{18}F]fluoromethyl and [^{18}F]fluoroethyl halides and sulfonates, building blocks with longer alkyl chains have been used for PET tracer synthesis. PET tracers with longer alkyl chains show enhanced *in vivo* stability, improved target affinity or selectivity and more favourable pharmacokinetics compared to the corresponding fluoroethylated or fluoromethylated analogues.[80,100,137]

Scheme 38 summarises various long chain aliphatic building blocks containing a tosylate as leaving group. Especially [^{18}F]fluoropropyl tosylate **150** is quite popular. Fluoroalkylations to access homologues with a chain length of n = 6 proved successful with this reagent. Furthermore, unsaturated and cyclic derivatives of [^{18}F]fluorobutyl tosylate (**154–156**) as well as polyethyleneglycol derived building blocks (**157** and **158**) have been employed in PET tracer synthesis.



Scheme 38 Synthesis of various long chain aliphatic building blocks from the corresponding ditosylate.

The synthesis of all these tosylate fluorine-18 labelled aliphatic building blocks was similar to the synthesis of [^{18}F]FETos **54**. The ditosylate precursor was reacted with dried [^{18}F][K⊂K$_{2.2.2}$]F complex in MeCN at temperatures of 85–130 °C. The reported yields of the radiofluorination are comparable to those using [^{18}F]FETos, which demonstrates that the procedure is generally applicable and not depending on chain length. The resulting fluorine-18 labelled aliphatic building blocks can be purified in different ways. For example, [^{18}F]fluoropropyl tosylate **150** was purified by either HPLC or silica Sep Pak. In addition, one-pot procedures including the alkylation step were also applied. Although similar radiochemical yields for the one-pot strategy and two-step procedure including HPLC purification have been described,[89] low specific activities for the products from the one-pot synthesis have been reported. The main reason for this is that the coupling product of the remaining ditosylate and the tracer precursor could not be separated from the actual PET tracer.[137] For two of the butane derived fluorine-18 labelled building blocks, **151** and **156**, HPLC purification has been reported. 1-[^{18}F]Fluoro-4-tosylbut-2-ene **155**, the longer chain [^{18}F]fluoroalkyl halides (**152** and **153**) and the PEG derived building blocks (**157** and **158**) were purified by silica Sep-Pak, while 1-[^{18}F]fluoro-3-tosyl cyclobutane **154** was purified by C18 Sep-Pak.[142] For [^{18}F]fluoropropyl tosylate **150**, automated synthesis procedures have been developed including a microfluidic approach.[49]

As discussed, [^{18}F]fluoropropyl tosylate **150** is used most often for longer chain alkylations. Using this building block, the compounds **160**, **162** and **164** were obtained by *N*-alkylation of amine precursors (Fig. 3). Reactions were carried out in DMF at 130 °C for 20 to 30 minutes. When intermediate purification of the building block **150** was necessary, cesium carbonate was added as base. When a one-pot method was applied, the potassium carbonate present from the first reaction served as a base to catalyse the subsequent coupling reaction of **150**. Generally, moderate to good radiochemical yields have been obtained,[49,89,138] (except for the 5-HT$_4$ receptor tracer **164**). The other tracers depicted in Fig. 3 were synthesised by *O*-alkylation of the phenolic precursor with **150**.[49,68,80,89,99,100,137–140] The alkylation reactions were performed in DMSO, DMF or MeCN at around 100 °C and different bases were employed (NaH, NaOH, K_2CO_3 or TBAOH). The precursor of the serotonin transporter ligand **167** was pre-incubated with the base prior to [^{18}F]fluoropropylation to form the phenolate, thereby facilitating nucleophilic substitution.[140]

Overall radiochemical yields of the tracers synthesised with [^{18}F]fluoropropyl tosylate **150** were variable and ranged from low to good. Shalgunov *et al.* conducted a comparative study on the two dopamine D$_{2/3}$ receptor tracers **161** and **166**, labelled with [^{18}F]fluoropropyl tosylate as well as [^{18}F]fluorobutyl tosylate (**169**, **170**) and [^{18}F]FETos (**81**, **99**). Similar yields were obtained for **161**, **169** and **81** as well as **166**, **170** and **99**, showing that the chain length of the building block had no major effect on the reaction kinetics.[100]

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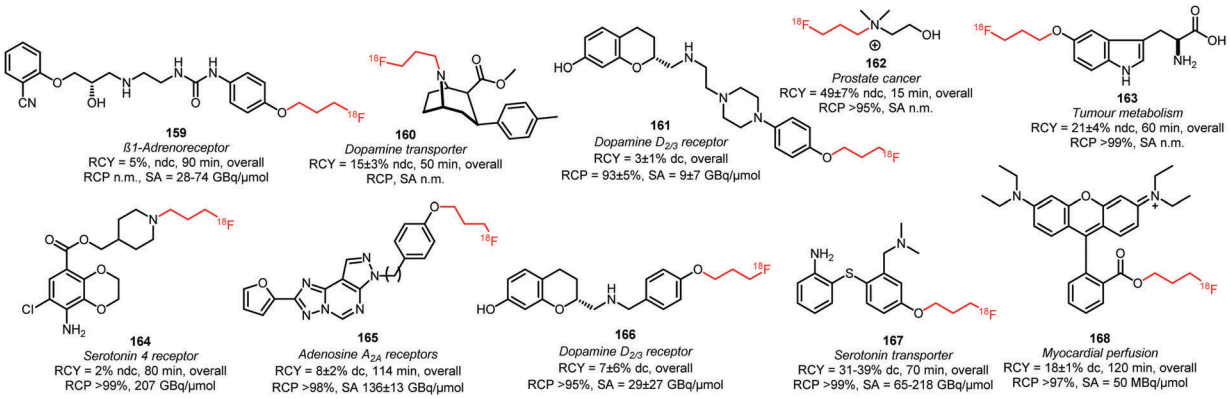

Fig. 3 PET tracers synthesised from the building block [^{18}F]fluoropropyl tosylate.[49,68,80,89,99,100,137–140]

Bartholomä *et al.* developed a synthesis of **168**, which is a known imaging agent for myocardial perfusion, by esterification of the carboxyl group with [^{18}F]fluoropropyl tosylate **150**. In this case, the corresponding lactone served as precursor and the reaction was carried out in MeCN at 165 °C with DIPEA as base. They reported a decay-corrected radiochemical yield of 18 ± 1% in a total synthesis time of 120 minutes. In comparison to the [^{18}F]fluoroethyl analogue, [^{18}F]fluoroproyl tracer **168** showed and improves stability.[137]

Four different butane derived building blocks have been employed for PET tracer synthesis. Next to the parent *n*-butane derivative **151**, also cyclobutane **154**, butene **155** and butyne **156** analogues have been used in *N*- and *O*-alkylations (Fig. 4). The two imaging agents for the dopamine $D_{2/3}$ receptor, **169** and **170**, were synthesised by Wieringen *et al.* and Shalgunov *et al.* *via* *O*-alkylation of the phenolic precursor with [^{18}F]fluorobutyl tosylate **151** in moderate overall radiochemical yields of 5–6% (dc) and 7–8% (dc), respectively. Using building block **151**, resulted in increased lipophilicity of the tracer and thereby enhanced ability to penetrate the blood brain barrier.[100,113] Also, four tropane derivatives, **171a–c** and **172**, were developed for imaging the dopamine transporter. The fluoroalkylation reactions could be carried out without base catalysis.[57,141] Riss *et al.* reported a quite efficient automated alkylation of the amine present in the tropane scaffold employing [^{18}F]fluorobutyne **156** in an overall radiochemical yield of 25% (ndc). Direct labelling of tropane **172** was also reported and proceeds in higher yield (32–36%) under microwave conditions, but this approach did not allow for automation.[57] Furthermore, Franck *et al.* introduced the [^{18}F]fluorocyclobutyl group the amino acid tyrosine **173** using **154**, to enhance the metabolic stability of the PET tracer (cycloalkanes show in general better metabolic stability than the *n*-alkyl counterparts).[142]

[^{18}F]Fluoroalkyl tosylates with a carbon chain length longer than 4 were only applied in the synthesis of triphenylphosphonium salts for myocardial perfusion imaging (Fig. 5). [^{18}F]Fluoropentyl tosylate **152** and [^{18}F]fluorohexyl tosylate **153** were coupled to triphenyl phosphine in toluene at 220 °C. After purification by semi-preparative HPLC, both PET tracers were obtained in decay-corrected radiochemical yields of 15 to 20%, respectively.[143]

The polyethylene glycol derived building blocks 2-(2-[^{18}F]fluoroethoxy)ethyl tosylate **157** and 2-(2-(2-[^{18}F]fluoroethoxy)ethoxy)ethyl tosylate **158** have also been used in the synthesis of myocardial perfusion imaging agents (Fig. 6). Kim *et al.* reported the synthesis of [^{18}F]fluoroPEGylated phosphonium salts **175** and **177** *via* reaction of triphenyl phosphine with 2-(2-[^{18}F]fluoroethoxy)ethyl tosylate **158** in toluene at 220 °C, followed by purification over a small silica cartridge.[143,144] Bartholomä *et al.* presented several 2-(2-[^{18}F]fluoroethoxy)ethyl esters (**178a–c** and **179**) and a (2-(2-[^{18}F]fluoroethoxy)ethoxy)ethyl ester (**176**) of rhodamine B as myocardial perfusion imaging agents. For the labelling of the lactone precursors, a one-pot method was applied in which the coupling reaction was performed in MeCN at 160 to 165 °C under

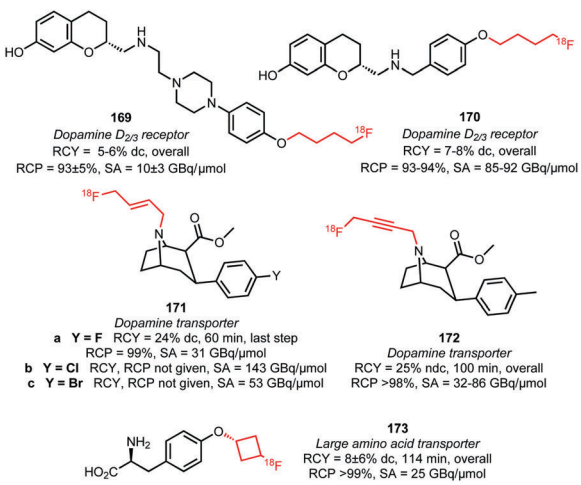

Fig. 4 PET tracers synthesised by indirect labelling with [^{18}F]fluorobutyl tosylate and derivatives.[57,100,113,141,142]

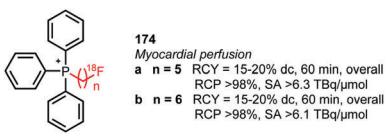

Fig. 5 [^{18}F]Fluoroalkyl triphenylphosphonium salts for myocardial perfusion imaging.[143]

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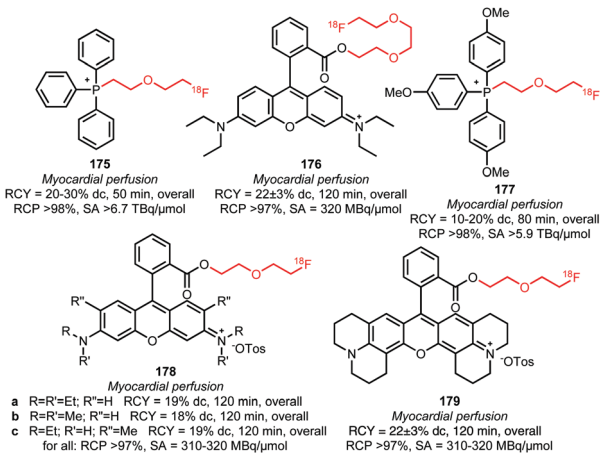
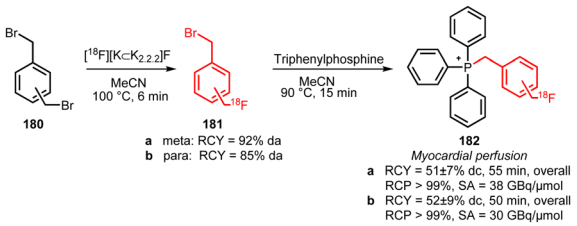


Fig. 6 [^{18}F]FluoroPEGylated tracers for myoardial perfusion imaging.[137,143–145]

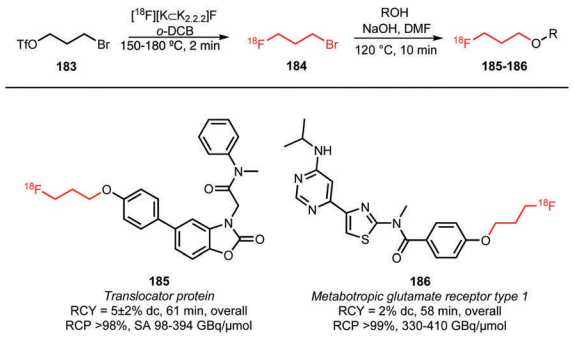
base-catalysis (DIPEA). All tracers were obtained in good overall radiochemical yields (~20% (dc)) in a synthesis time of 20 minutes. *In vitro* and *in vivo* biological evaluations of **179** showed that this tracer is superior to the ethyl, propyl and triethyleneglycol analogues with respect to imaging characteristics and metabolic stability. This shows that the prosthetic group significantly influences the pharmacokinetics and metabolism of the PET tracer.[137,145]

Two other building blocks for indirect labelling of triphenyl phosphines have been presented by Zhao *et al.* in 2014. They synthesised 1-bromomethyl-3-[^{18}F]fluoromethylbenzene **181a** and 1-bromomethyl-4-[^{18}F]fluoromethylbenzene **181b** building blocks using a modified procedure of De Vries *et al.* (Scheme 39).[146] The myocardial perfusion tracers **182a** and **182b** were obtained *via* a one-pot procedure without intermediate purification of the building blocks in decay-corrected radiochemical yields of 52 ± 9% and 51 ± 7%, respectively.[147]

Not only [^{18}F]fluoropropyl tosylate **150**, but also the corresponding bromide has been employed as building block for fluoroalkylation (Scheme 40). [^{18}F]Fluoropropyl bromide **184** was synthesised by treatment of the bromopropyl triflate with dried [^{18}F][K⊂K$_{2.2.2}$]F complex in *o*-dichlorobenzene and subsequent distillation at 150 to 180 °C into cooled DMF (−15 to −20 °C) containing the precursor and sodium hydroxide. After distillation, the trapping solution was heated for 10 minutes at 120 °C to react the building block with the phenolic precursors and generate the two PET tracers **185** and **186**, albeit in rather low overall radiochemical yields (5% and 2%, respectively).[68,69]



Scheme 39 Synthesis and reaction of *meta*- and *para*-[^{18}F]bromomethylfluoromethylbenzene.[147]



Scheme 40 [^{18}F]Fluoropropyl bromide as building block for [^{18}F]fluoroalkylation.[68,69]

Fujinaga *et al.* hypothesised that this can be explained by a decreased inductive effect of the fluorine atom further along the chain.[69]

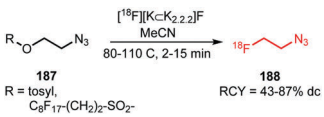
2.6 Fluorine-18 labelled azides

Many labelled azides have found widespread application in tracer synthesis. In particular, [^{18}F]fluoroethyl azide **188** (Scheme 41) and deoxy-[^{18}F]fluoroglucopyranosyl azides have been employed as building block. They can be coupled to PET tracers by the Huisgen 1,3-dipolar cycloaddition, also called copper(I)-catalysed azide-alkyne cycloaddition (CuAAC) or 'click'-reaction. Alternatively, the traceless Staudinger ligation has been employed.

In the CuAAC, 1,4-disubstituted triazoles are formed by reaction of an azide group with an alkyne functionality under copper(I) catalysis. Using the CuAAC protocol introduces fluorine-18 under mild aqueous conditions. Conditions that are compatible with highly functionalised polar biomolecules.[148] Furthermore, these 'click'-reactions usually show high specificity, robustness and yields.[149] Many different functional groups are well tolerated, making additional protection and deprotection steps unnecessary.[150] Moreover, the click reaction is an excellent method to build up libraries of compounds for screening campaigns to ultimately select the best PET tracer.[151]

As an alternative coupling reaction to the CuAAC, the traceless Staudinger ligation can be employed. This reaction of an azide with a phosphine-substituted thioester leads to the formation of an amide bond. Therefore, it represents a useful strategy for the labelling of amino acids and peptides. It proceeds under mild reaction conditions and no metal catalysis is required.[152,153]

Both the CuAAC and the Staudinger ligation methods however have also disadvantages, for example, the *in vivo* toxicity of the copper(I) used in the CuAAC and the instability of phosphine reagents used in the Staudinger ligation due to oxidation.[154]



Scheme 41 Synthesis of [^{18}F]fluoroethyl azide.

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In the following sections, the synthesis of [^{18}F]fluoroethyl azide and deoxy-[^{18}F]fluoroglucopyranosyl azides as well as their application in PET tracer syntheses will be discussed.

2.6.1 [^{18}F]Fluoroethyl azide. [^{18}F]Fluoroethyl azide **188** was introduced as building block in the CuAAC by Glaser and Årstad in 2007.[155] Since then, it has been applied in the synthesis of many PET tracers. Besides [^{18}F]FETos, [^{18}F]fluoroethyl azide is the most used building block in aliphatic indirect fluorine-18 labelling. Many of the syntheses of [^{18}F]fluoroethyl azide **188** followed the established protocol of Glaser and Årstad, treating 2-azidoethyl 4-toluenesulfonate with the dried [^{18}F][K$\subset$K$_{2.2.2}$]F complex in MeCN at 80 °C (Scheme 41). The product was subsequently co-distilled with MeCN at 130 °C into a trapping vial containing MeCN. Typically, high radiochemical yields of >80% (analytically determined) were observed using this procedure, but due to the moderate distillation efficiency, the building block was only obtained in decay-corrected radiochemical yields of 40–65%.[155–157] Hence, some modifications of the procedure have been reported. Besides varying the reaction temperatures (80–110 °C) and times (2–15 minutes), particular attention was paid to the purification procedure of the building block after the reaction was complete. Distillation temperatures ranging between 130 and 140 °C and cooling with liquid nitrogen or dry ice to make trapping more efficient were tried to improve the yields.[148,158,159]

Hugenberg *et al.* described distillation during the reaction time to increase the non decay-corrected yield by shortening the synthesis time.[160] However, none of the modifications of the distillation procedure described above led to a significant increase in radiochemical yield of **188**. Kelly *et al.* found that addition of more MeCN to the reaction vial during distillation did increase the efficiency, but the higher MeCN content in the purified building block solution led to lower yields in the subsequent click reaction.[161] This was also reported by other research groups.[149]

Next to the flow-and-trap-distillation method, a vacuum distillation method has been developed by Zhou *et al.* They reported radiochemical yields of over 80% (dc) within 10 minutes including formation of [^{18}F]fluoroethyl azide, distillation into a dry ice cooled trapping vial and warming up to room temperature.[162] However, due to co-distillation of the side-product vinyl azide, the precursor for the follow-up reaction was needed in large excess. This makes the method unsuitable for the high specific activity labelling of macromolecules due to the pseudo-carrier present.

Furthermore, two different cartridge purification procedures have been developed in order to facilitate automation. Bejot *et al.* and Carroll *et al.* employed a polyfluorinated sulfonate precursor instead of 2-azidoethyl 4-toluenesulfonate (Scheme 41), which could be separated from [^{18}F]fluoroethyl azide **188** by fluorous solid phase extraction (FSPE).[151,163] Another approach used a silica-based C18 cartridge and a Water Oasis HLB cartridge in series.[149]

For some tracer syntheses, successful one-pot procedures have been described.[164,165] However, the one-pot method often promotes side-reactions, which necessitates elaborate purification of the PET tracer. Automated syntheses have been developed as well. Ackermann *et al.*, for example, reported an automated synthesis on the Flex Lab module including purification by vacuum distillation.[166]

Scheme 42 lists all PET tracers synthesised using the [^{18}F]fluoroethyl azide building block *via* the CuAAC method.[55,148,149,151,156–160,163,164,166–180] In most cases, the [^{18}F]fluoroethyl azide reacts with an alkyne precursor in the presence of a Cu(I)- or Cu(II)-catalyst and sodium ascorbate as reducing agent. Copper sulfate was used in the majority of the tracer syntheses reported. Here, Cu(II) is reduced by sodium ascorbate to the reactive Cu(I) species.[158,164,180] In addition, the use of Cu(II) acetate[171] as well as Cu(I) iodide has been reported. Although when Cu(I) iodide is employed the catalyst is already present in its active species, sodium ascorbate is still used since oxidation from Cu(I) to Cu(II) during the reaction is well known.[167,172] Ackermann *et al.* reported that with a freshly prepared mixture of Cu(I) iodide and sodium ascorbate, better results in the labelling of the tumour cell proliferation imaging agent **207** were obtained than with the conventional $CuSO_4$/Na-ascorbate system.[167] In another article, Ackermann *et al.* investigated $Cu(CH_3CN)_4PF_6$ as a catalyst system, because it is soluble in organic solvent and would be more compatible for use in an automated synthesis module. Unfortunately, a lower yield of the tracer **207** was observed with the new catalyst system.[166]

Different solvent systems have been used in the CuAAC. Often water or an aqueous buffer solution such as phosphate buffer is used to dissolve the copper catalyst and the sodium ascorbate.[157,161] On the other hand, the alkyne precursor is mostly added in DMF, but also MeCN, DMSO and aqueous media were used.[148,161,167,175] Depending on the applied purification procedure, the azide building block is added either in the distillation trapping solution or in the solvent eluted from the intermediate SPE purification cartridge.[171,173] The MeCN from co-distillation or trapping led in some cases to a decrease in coupling efficiency.[178] For the prostate-specific membrane antigen (PSMA) tracers **222** and **223**, higher MeCN content led to a decrease in yield from 50% to <25% (measured by radio-HPLC).[161] However, a few successful click reactions were also performed in MeCN.[55,167] The presence of DMF has been described as a necessary condition to maintain the level of Cu(I) in the reaction solution.[162]

Other additives have been employed in some of the tracer syntheses too. The use of the base DIPEA[172] as well as the Cu(I) stabilizing agents TBTA (tris(benzyltriazolylmethyl)amine) and BPDS (bathophenanthroline disulfonic acid disodium salt) have been reported.[168,179] TBTA and BPDS served as auxiliary copper(I) chelators[164] and accelerated the reaction. They were found to be especially helpful in one-pot strategies, for example in the synthesis of imaging agents **217–220** for the multidrug resistance-associated protein 1.[164] However, the presence of BPDS or TBTA was not necessary for successful one-pot synthesis. Chen *et al.* demonstrated this in the synthesis of PSMA inhibitor **221** without ligand in an overall radiochemical yield of 14 ± 1% (ndc).

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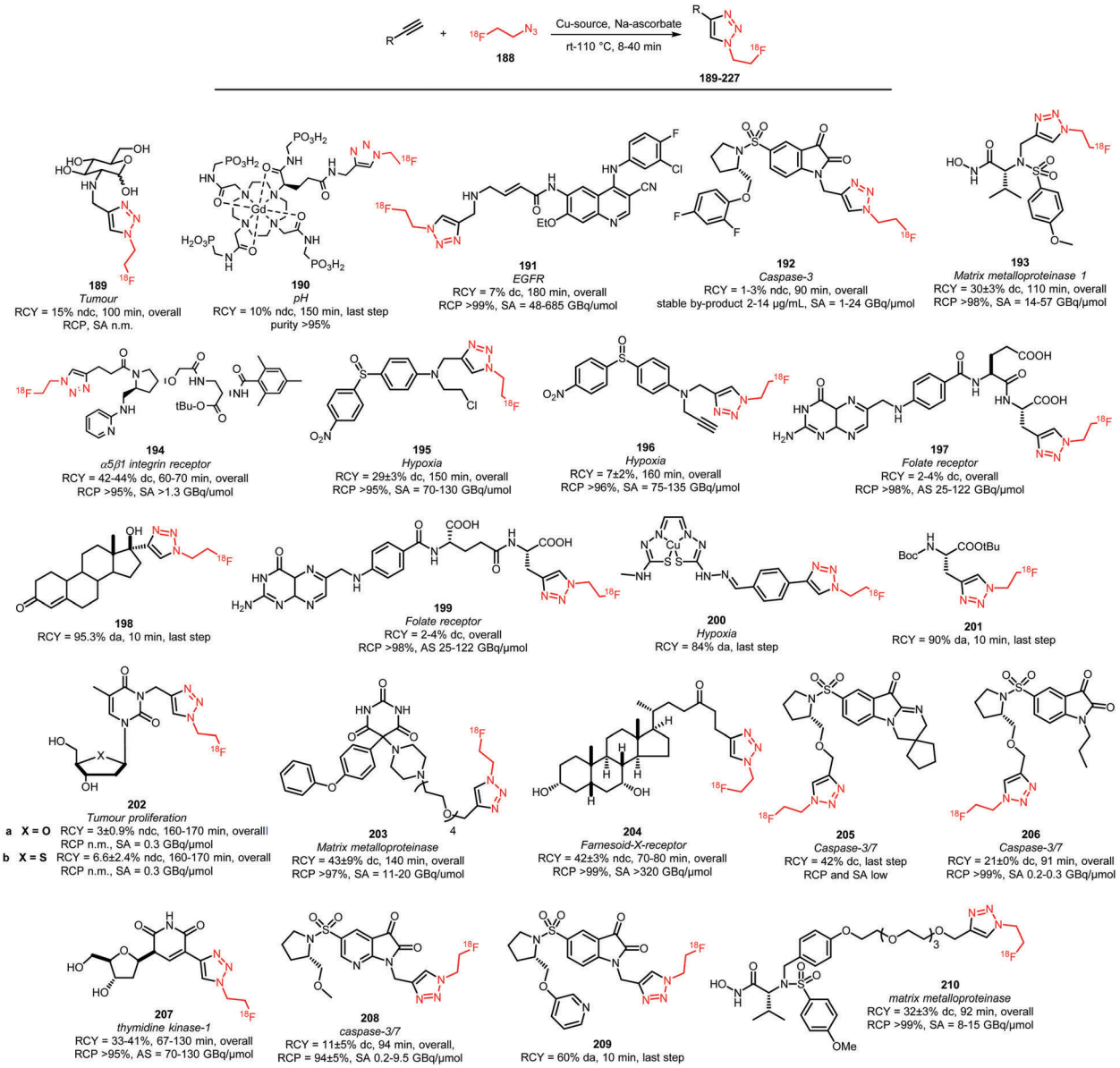
Most of the PET tracers shown in Scheme 42 were purified by semi-preparative HPLC, but purification was not always successful. In some cases, the alkyne precursor could not be separated from the product, leading to low specific activities.[174,177] For the tumour proliferation imaging agents **202a** and **202b**, direct labelling was more successful giving increased specific activities (20–210 GBq μmol^{-1} instead of 0.3 GBq μmol^{-1}) at comparable overall radiochemical yields (7% ndc).[174]

Based on the CuAAC with [^{18}F]fluoroethyl azide, a ''multi-click'' approach has been developed for the synthesis of the apoptosis tracers **227b–d**. Up to four different alkynes were synthesised in one pot from one batch of [^{18}F]fluoroethyl azide at the same time. This makes the CuAAC a valuable tool for the screening of potential PET tracers. However, the purification of the reaction mixtures turned out to be challenging and tracers with low purity were obtained, because the alkyne precursors could not be separated from the labelled compounds.[150,180]

Carroll *et al.* presented the first examples (compounds **229–232**) of fluorine-18 labelled compounds synthesised by traceless Staudinger ligation with [^{18}F]fluoroethyl azide (Scheme 43). The reaction was carried out either in a mixture of tetrahydrofuran (THF) and water or DMF and water, at 80 °C for 30 minutes or at 120 °C for 15 minutes. The labelled compounds could be obtained in radiochemical yields of >95% (analytically determined).[152] Gaeta *et al.* were the first to synthesise and isolate a PET tracer (**228**) *via* this method. Labelling proceeded in a mixture of DMF and MeCN within 15 minutes at 130 °C and provided the $GABA_A$ tracer **228** in an overall radiochemical yield of 7% (ndc).[153]

In conclusion, [^{18}F]fluoroethyl azide is a useful building block for the fluorine-18 labelling of biomolecules and small



Scheme 42 PET tracers synthesised from [^{18}F]fluoroethyl azide in a CuAAC.[55,148,149,151,156–160,163,164,166–180]

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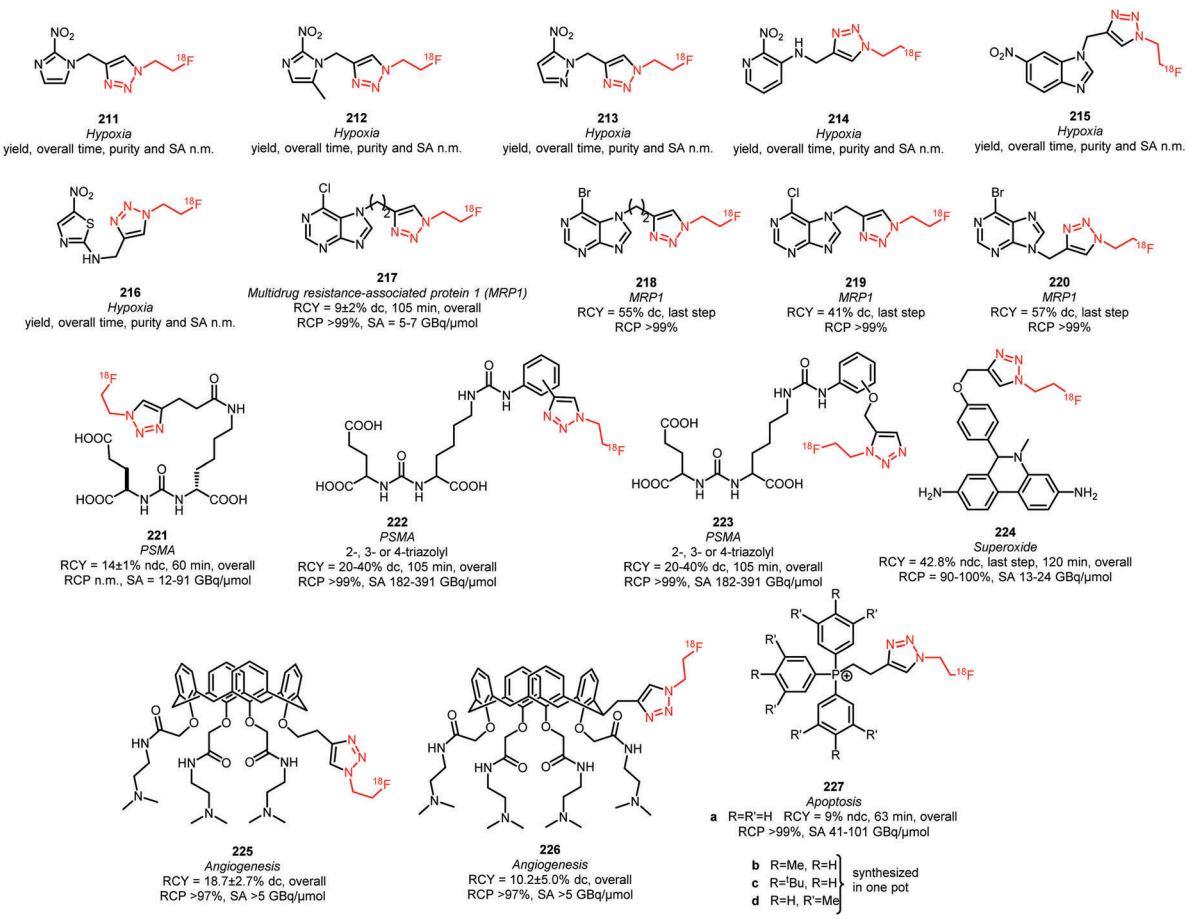
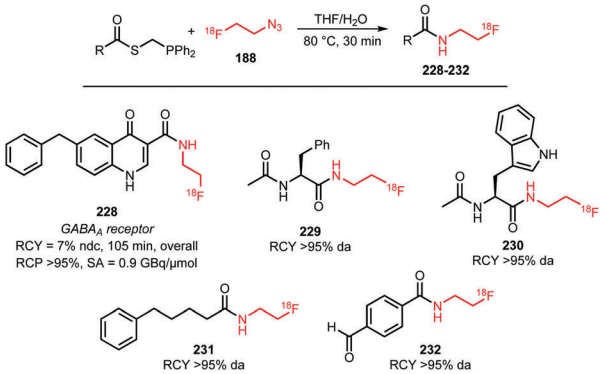


Scheme 42 (cont.)

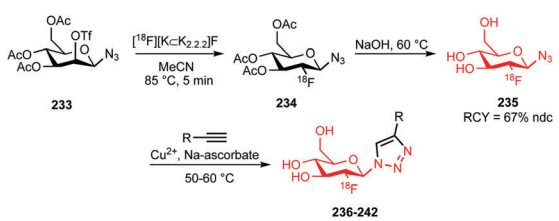


Scheme 43 PET tracers synthesised from [^{18}F]fluoroethyl azide in a traceless Staudinger reaction.[152,153]

molecule PET tracers under mild conditions without need of protecting groups.

2.6.2 Deoxy-[^{18}F]fluoroglucopyranosyl azide. Deoxy-[^{18}F]fluoroglucopyranosyl azides have been used as building blocks in CuAAC and were first introduced by Maschauer *et al.* in 2009.[181] Besides introduction of fluorine-18, this building block was employed frequently to increase polarity of the PET tracer and thereby improve its pharmacokinetic properties.

2-Deoxy-2-[^{18}F]fluoroglucopyranosyl azide can be prepared in a two-step procedure starting from the mannosyl precursor **233** (Scheme 44). In the first step, nucleophilic substitution of the triflate group with [^{18}F][K⊂K$_{2.2.2}$]F was conducted at 85 °C for 5 minutes. HPLC purification provided the acetyl-protected product **234** in a radiochemical yield of 67% (ndc). In the second step, deprotection of the hydroxyl groups was carried out by addition of aqueous sodium hydroxide at 60 °C. After complete deacetylation, the solution was neutralised with hydrogen chloride solution and directly used in the CuAAC reaction.[182] Only minor alterations since the initially developed synthesis of the building block have been reported. Fischer *et al.* showed that



Scheme 44 Synthesis of 2-deoxy-2-[^{18}F]fluoroglucopyranosyl azide with subsequent Cu-catalysed click reaction.

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a cartridge based purification procedure instead of a time consuming HPLC purification yielded 75% of protected 2-deoxy-2-[^{18}F]fluoroglucopyranosyl azide **234**.[183]

Maschauer *et al.* described also the synthesis of 6-deoxy-6-[^{18}F]fluoroglucopyranosyl azide, analogous to the synthesis of 2-deoxy-2-[^{18}F]fluoroglucopyranosyl azide **235**, obtained from its tosyl precursor. They found that addition of all reactants in buffered solution made neutralisation prior to the coupling reaction unnecessary.[184]

The coupling of building block **234** to the alkyne precursors was carried out in a CuAAC reaction, resulting in the PET tracers which are shown in Fig. 7.[171,181,183,185–188] The CuAAC proceeded in a one-pot two-step reaction together with the deprotection of **234**. After deacylation and neutralisation, 2-deoxy-2-[^{18}F]fluoroglucopyranosyl azide **235** was reacted with the corresponding alkyne precursor in an aqueous solution of copper(II)acetate or sulfate and sodium ascorbate. The desired product was formed in 10 to 15 minutes at slightly elevated temperatures (50–60 °C). Typically, the products were purified by semi-preparative HPLC and obtained in overall radiochemical yields of 1–40% (dc) in a total reaction time of 70–180 minutes. Several improvements to the original reaction conditions have been published by Maschauer *et al.* They described a significant increase of product formation in the presence of ethanol in the aqueous reaction solution.[184] Furthermore, THPTA (tris(3-hydroxypropyltriazolylmethyl)amine) and BPDS (bathophenanthroline disulfonic acid disodium salt) were presented as agents accelerating the CuAAC reaction. The use of BPDS enables click reactions in 5 minutes at room temperature.[185]

To conclude, 2-deoxy-2-[^{18}F]fluoroglucopyranosyl azide **235** is a useful building block for fluorine-18 labelling and proved to be especially useful for labelling peptides. It has several advantages: the glucosyl moiety enhances, due to its hydrophilicity, the *in vivo* properties of the PET tracer and the CuAAC is a reliable and efficient procedure with high regioselectivity.[171,183]

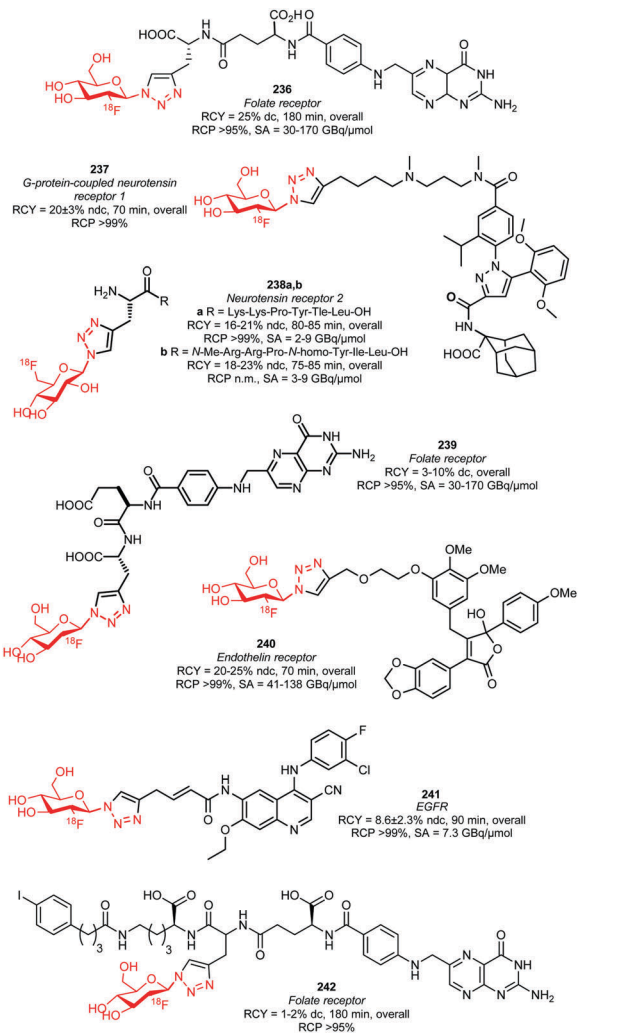


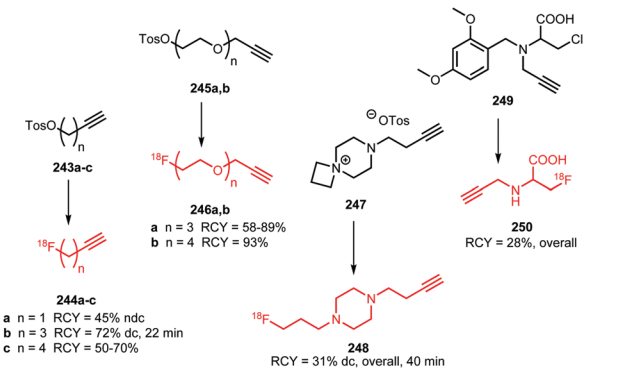
Fig. 7 PET tracers labelled with 2-deoxy-2-[^{18}F]fluoroglucopyranosyl azide.[171,181,183–188]

2.7 ^{18}F-Labelled alkynes

A large range of different fluorine-18 labelled alkynes have been used in PET tracer synthesis. Scheme 45 summarises the different types of precursor used since 2010. Alkyl precursors **243** and polyethylene glycol (PEG) derived precursors **245** are popular precursors for radiofluorination and have been applied many times. By varying the chain length these precursors can be easily adapted to specific requirements without the need to change the labelling procedure significantly.

Small fluorine-18 labelled alkynes such as **244** have relatively low boiling points, which is advantageous for distillation, avoiding time-consuming preparative HPLC purification procedures. In addition, they have little influence on the (bio)chemical properties of the developed PET tracer.

Typical reaction temperatures are between 95–110 °C and distillation is quite fast (2–5 minutes). The solvent used for trapping the product after distillation may depend on the click reaction which is performed afterwards. As a leaving group, predominantly the tosylate is used, as it provides in general the best results in a nucleophilic substitution.[171,189,190] The same applies for the PEG derived precursors **245**. In contrast to alkyl derived fluorine-18 labelled alkynes, PEG derived fluorine-18 labelled alkynes show low volatility which simplifies handling but makes preparative HPLC purification necessary in most cases. Their amphiphilicity makes them ideal reactants in the



Scheme 45 Different types of alkyne precursors.

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CuAAC reaction. Nucleophilic substitution was performed at temperatures between 110 and 140 °C in MeCN or DMSO for 10 to 15 minutes. High radiochemical yields could be obtained, ranging from 58 to 93%.[191–193]

Other alkyne building blocks have been developed as well. The piperazine based building block **248** was chosen because of its high hydrophilicity compared to the alkyl derived fluorine-18 labelled alkynes, facilitating the radiofluorination of peptides in aqueous conditions. It was synthesised from spiro precursor **247**, which could be easily separated from the resulting product **248** using reversed phase C-18 or silica gel cartridges.[194] Building block **249** on the other hand is an amino acid derivative of alanine, functionalised with the alkyne moiety at the N-terminus. It is also a convenient prosthetic group for radiofluorination of biomolecules based on amino acids. The tosylated precursor however showed poor stability during purification, hence the chlorinated precursor was used yielding the product in 28 ± 5% (RCY, overall).[195]

Scheme 46 shows that a large set of structurally diverse PET tracers can be prepared by the application of fluorine-18 labelled alkynes in the CuAAC reaction.[171,189–195] Nonetheless, labelling conditions for all click reactions are comparable. The Cu(I) catalyst in the 1,3-dipolar cycloaddition, was in every case generated *in situ* from a Cu(II) salt by reduction with sodium ascorbate. Attempts to directly employ the active Cu(I) species led to significant precursor degradation and poor radiochemical yields.[191] Mostly, aqueous solutions of the salts were combined with polar aprotic organic solvents like MeCN or DMF containing the radiolabelled building block and/or precursor. Temperatures up to 110 °C have been reported, but in general the CuAAC proceeds under mild temperatures of 20 to 40 °C. In cases of elevated temperatures, microwave heating was shown to be more efficient than conventional heating.[191,193]

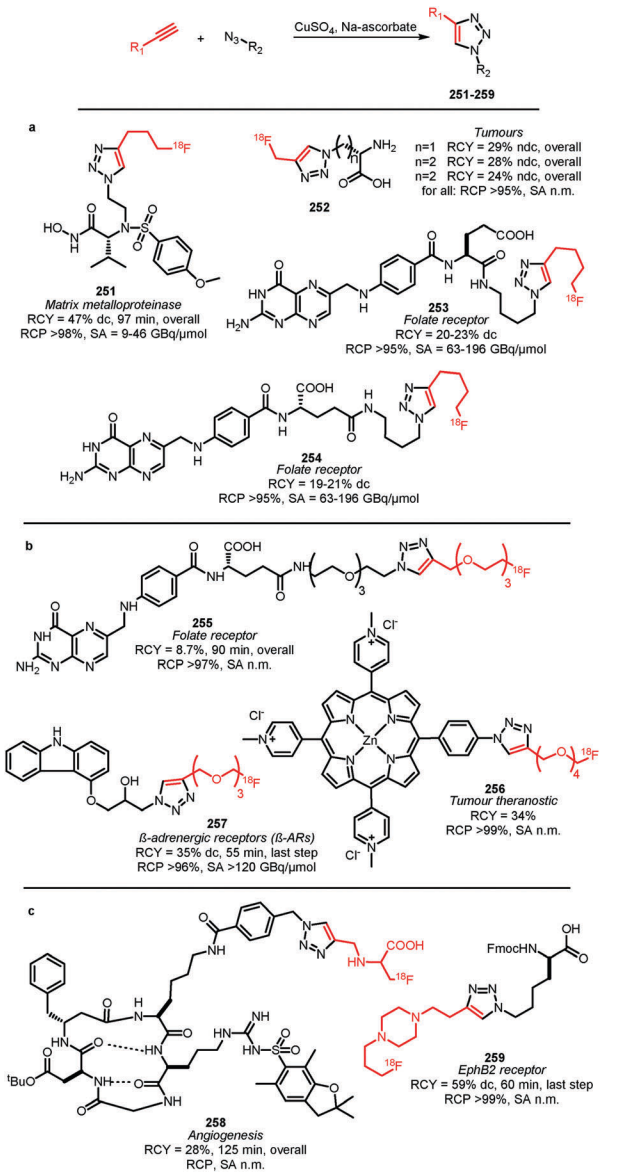
Purification was usually carried out by (semi-)preparative HPLC. However, Yook and co-workers reported a synthesis procedure using an additional, more lipophilic alkyne to react with residual precursor and increase its lipophilicity to allow for separation of the tracer **252** by a SPE purification procedure.[189]

In summary, many different fluorine-18 labelled alkynes have been successfully employed as building blocks in CuAAC reactions for PET tracer syntheses. Due to their structural diversity, the use of fluorine-18 labelled alkynes significantly expand the spectrum of PET tracers that can be accessed.

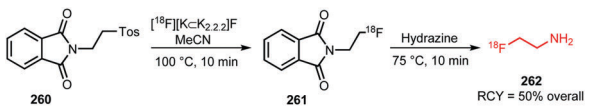
2.8 Fluorine-18 labelled alkyl amines

[^{18}F]Fluoroalkyl amines such as [^{18}F]fluoroethyl amine but also quite complex molecules like **267** (Scheme 48) have been used as small versatile building blocks for radiofluorination. They can be introduced into the precursor by amide, carbamate and urea formation, functional groups that are often present in biomolecules.

Two general methods for the synthesis of [^{18}F]fluoroalkyl amines have been reported: one uses phthalimide protected alkyl amines such as **260** as precursor for [^{18}F]fluorination (Scheme 47) whereas the other method employs Boc-protected alkyl amines **263** (Scheme 48).



Scheme 46 PET tracers synthesised *via* click reaction with different fluorine-18 labelled alkynes: (a) alkyl-derived building blocks;[171,189,190] (b) PEG-derived building blocks;[191–193] (c) others.[194,195]



Scheme 47 Synthesis of [^{18}F]fluoroethylamine *via* the procedure of Tewson *et al.*[195]

The method using phthalimide protected amines as starting materials is based on a Gabriel reaction and was first published by Tewson and co-workers in 1997. Scheme 47 shows the 2-step synthesis of [^{18}F]fluoroethyl amine **262.** The intermediate phthalimide protected aminoethyl tosylate **260** is obtained by reaction of phthalimide with 2-bromoethanol followed by tosylation. Subsequent radiofluorination at 100 °C for 10 minutes in MeCN,

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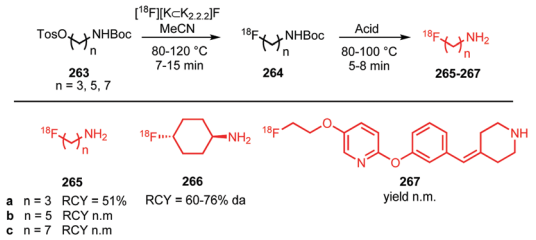


Scheme 48 Synthesis of different types of [^{18}F]fluoroalkyl amines *via* Boc-protected amines.[200,202]

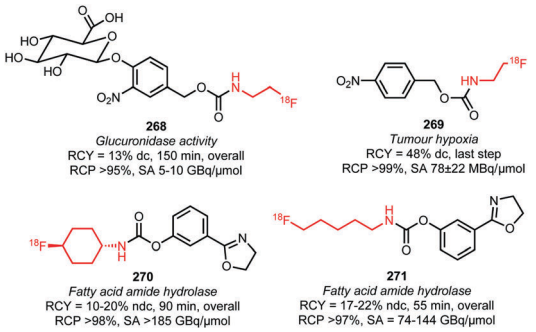


Fig. 8 [^{18}F]Fluorocarbamates synthesised *via* reaction with [^{18}F]fluoroalkyl amines.[146,198,200,201,205]

followed by deprotection with hydrazine, gave [^{18}F]fluoroethyl amine **262**, which was purified by simultaneous distillation into a second reaction vessel. Although the labelling strategy itself is quite straightforward, the deprotection step proved quite complex and several reaction parameters required careful examination. Especially, the presence of water appeared mandatory for the reaction. A complicating factor was that the MeCN, which was left behind from the previous reaction step, led to azeotropic evaporation of the water. Therefore, the MeCN had to be evaporated until dryness before hydrated hydrazine was added. Furthermore, to avoid co-distillation of hydrazine, the reaction temperatures could not exceed 75 °C and the reaction time was kept between 10 and 15 minutes.[196]

The original procedure of Tewson *et al.* is still largely employed as it was first published.[197,198] For example, Huang and co-workers applied it to the synthesis of [^{18}F]fluorooctyl amine. Due to the high boiling point, purification by HPLC was explored but neither normal nor reversed phase HPLC gave satisfactory pure product. However, a radiochemical yield of 53% (dc, based on radio-HPLC analysis) was observed, which is consistent with the yields reported for [^{18}F]fluoroethyl amine **262**.[199]

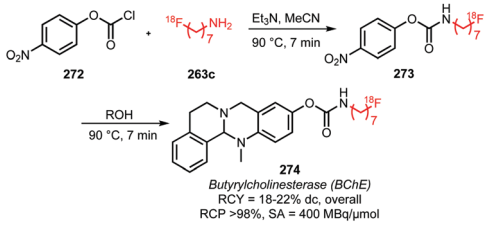
The second method to synthesise [^{18}F]fluoroalkyl amines starts from the corresponding Boc-protected amino tosylates (Scheme 48). [^{18}F]Fluorination is performed in MeCN at 80–120 °C for 7–15 minutes. Radiochemical yields up to 80% (analytically determined) have been reported using this strategy. Subsequent deprotection is performed under acidic conditions at temperatures of 80 to 100 °C. Sulfuric acid as well as trifluoroacetic acid have been employed, both resulting in high conversions. After neutralisation of the sulfuric acid with phosphate buffer or evaporation of trifluoroacetic acid, the [^{18}F]fluoroalkyl amine could be used without further purification in the next reaction.[200–203] A range of structurally diverse amines have been radiofluorinated applying this method (Scheme 48). Apart from primary amines with linear alkyl chains, the cyclic primary amine **266** and the more complex secondary amine **267** were labelled in this manner with fluorine-18.[201,203]

In addition to the above discussed more generally established methods to access [^{18}F]fluoroalkyl amines, Glaser *et al.* reported an alternative method. They described the reduction of [^{18}F]fluoroethyl azide (**188**) with elemental copper under acidic conditions providing [^{18}F]fluoroethyl amine (**262**) in radiochemical yields of over 90% (analytically determined).[204]

[^{18}F]Fluoroalkyl amines can undergo three different types of reactions forming either carbamates, amide bonds, or carbamines. Carbamate formation is most widely applied (Fig. 8).[146,198,200,201,205] The radiofluorination reaction was carried out using the purified (distilled) fluorine-18 labelled building block, but also successful one-pot three step reactions including [^{18}F]fluorination and deprotection of the amine have been reported. In most syntheses, the carbamate formation was carried out at room temperature without additives. Antunes and co-workers prepared **268**, a PET tracer for imaging glucuronidase activity, in an overall radiochemical yield of 13% (dc) including deprotection of the product with 2 M sodium hydroxide solution, while trapped on a tC18 cartridge.[146] Zhang and co-workers used an additional base (triethylamine, TEA) in the synthesis of the tumour hypoxia imaging agent **269**, which was obtained in a radiochemical yield of 48% (dc, last step).[198] Sadovski *et al.* reported that a temperature of 80 °C is optimal to obtain **271**, a radiotracer for fatty acid amide hydrolase imaging, with a radiochemical yield of 17–22% (ndc, overall).[200] In all cases, purification of the products was conducted by semi-preparative HPLC.

Sawatzky *et al.* reported the use of [^{18}F]fluoroheptyl amine **263c** as building block in the multi-step synthesis of the butyrylcholinesterase tracer **274**. To activate [^{18}F]fluoroheptyl amine **263c**, it was first treated with 4-nitrophenyl chloroformate in MeCN under basic conditions resulting in carbamate **273**. Subsequently, **273** was coupled with the phenol to obtain the butyrylcholinesterase tracer **274** in a radiochemical yield of 18–22% (dc) (Scheme 49).[207]

For the synthesis of amides from [^{18}F]fluoroalkyl amines, Silvers *et al.* described the use of an acyl chloride precursor, which was reacted with [^{18}F]fluoropropylamine in MeCN under basic conditions (TEA) for 14 minutes at room temperature. This provided stearoyl-CoA desaturase-1 tracer **275** in an overall radiochemical yield of 21% (dc) (Fig. 9).[203] Huang *et al.* reported



Scheme 49 Synthesis of the butyrylcholinesterase tracer **274**.[206]

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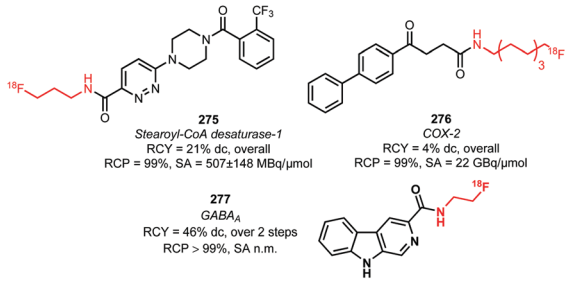


Fig. 9 [^{18}F]Fluoroamides.[198,201,204]

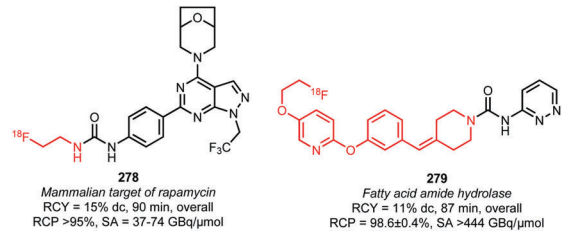


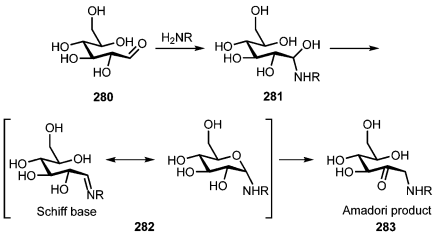
Fig. 10 Fluorine-18 labelled urea derivatives.[197,203]

amide formation starting from the carboxylic acid, using the coupling reagent 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) in the presence of DIPEA as base in DMF. The reaction was carried out at room temperature and yielded cyclooxygenase-2 (COX-2) inhibitor **276** in 4% (dc).[199] In a third approach for amide bond formation, 9*H*-β-carboline pentafluorophenyl ester was used as a precursor. One-pot reaction at 80 °C with 2-[^{18}F]fluoroethyl azide-derived [^{18}F]fluoroethylamine under basic conditions (TEA) gave GABA$_A$ tracer **277** in 46% decay-corrected radiochemical yield (calculated from 2-[^{18}F]fluoroethyl azide).[205]

Since 2010 the synthesis of two fluorine-18 labelled urea derivatives has been reported. In the procedure described by Majo *et al.*, the potential PET ligand for mTOR **278** was synthesised from an amine precursor, which was pre-treated with trisphosgene and TEA in dichloromethane. The building block [^{18}F]fluoroethyl amine was directly distilled into the solution containing the pre-treated precursor. A radiochemical yield of 15% (dc, overall) was achieved.[197] Skaddan and co-workers performed a one-pot synthesis, obtaining **279** from the corresponding carbamate precursor by reaction in MeCN under basic conditions (DIPEA) at 80 °C in a radiochemical yield of 10% (dc, overall) (Fig. 10).

2.9 [^{18}F]FDG

[^{18}F]FDG is the most applied radiopharmaceutical for PET imaging and serves as generic tumour tracer. Because of its widespread use and availability in almost every PET centre, as well as its favourable pharmacokinetics, several attempts have been made to employ [^{18}F]FDG not only as tracer, but also as a building block for other PET tracers. As such, it could enable convenient radiolabelling in a one-step synthesis starting from [^{18}F]FDG.[207] As [^{18}F]FDG is readily available, the synthesis of [^{18}F]FDG will not be discussed in this review.



Scheme 50 Maillard reaction.[208]

When amines are reacted with [^{18}F]FDG, glycosylamines are formed, which are biochemically important for many metabolic pathways. The mechanism of the reaction between [^{18}F]FDG as building block and an amine, is based on the Maillard reaction (Scheme 50). In a Maillard reaction, an amine reacts with the aldehyde of glucose at the 1-position to form Schiff base **282** after elimination of water. After that, the Schiff base can rearrange to the Amadori product **283** leading to ketone formation at the 2′-position. As [^{18}F]FDG contains a fluorine atom instead of a hydroxyl group at the 2-position, it cannot undergo rearrangement to the Amadori product. Thus, in this case the Maillard reaction is blocked at the stage of Schiff base **282**, which is also called a quasi-Amadori product.[208]

An overview of tracers radiolabelled with [^{18}F]FDG is given in Fig. 11.[207–212] The tracers **284–291** were synthesised from the corresponding amine precursor whereas tracers **292–296** were synthesised from oxy-amine precursors. The [^{18}F]FDG building block was employed either in solution (saline or PBS) or azeotropically dried with MeCN prior to use.[207,210]

As solvent, the use of methanol, ethanol, DMSO and mixtures of them with water have been described. Furthermore, acetic acid was present in all reactions mentioned. Reaction temperatures varied between 60–99 °C with reaction times varying between 10–120 minutes.

In the reactions with [^{18}F]FDG as labelling reagent, aniline can serve as catalyst forming [^{18}F]FDG–aniline as an intermediate. Flavell and co-workers could shorten reaction times from 30 to 1 minute using aniline, whereas Baranwal *et al.* were able to perform the reactions at room temperature (instead of 99 °C) when aniline was present.[207,208]

Usually the tracers synthesised from [^{18}F]FDG needed purification and a range of methods to achieve this have been applied. However, it is noteworthy that Al Jammaz and co-workers obtained the PET myocardial perfusion imaging agent **293** in a radiochemical yield of 97% by just simply passing the reaction mixture through a membrane filter, resulting in >98% radiochemical purity.[212] The *in vitro* stability of the glycosyl amine tracers are in general high.[210,211] However, at low pH, increased decomposition of the [^{18}F]FDG amines was observed whereas the [^{18}F]FDG oximes were stable towards hydrolysis under these conditions. Flavell and co-workers took advantage of this characteristic and designed acid-labile pro-drug tracers **284–286**, **288** and **290** for imaging acidic tumour microenvironments.[207]

In summary, because of its commercial availability, [^{18}F]FDG is a very easily accessible building block and allows mild radiofluorination. Valuable PET tracers have been obtained

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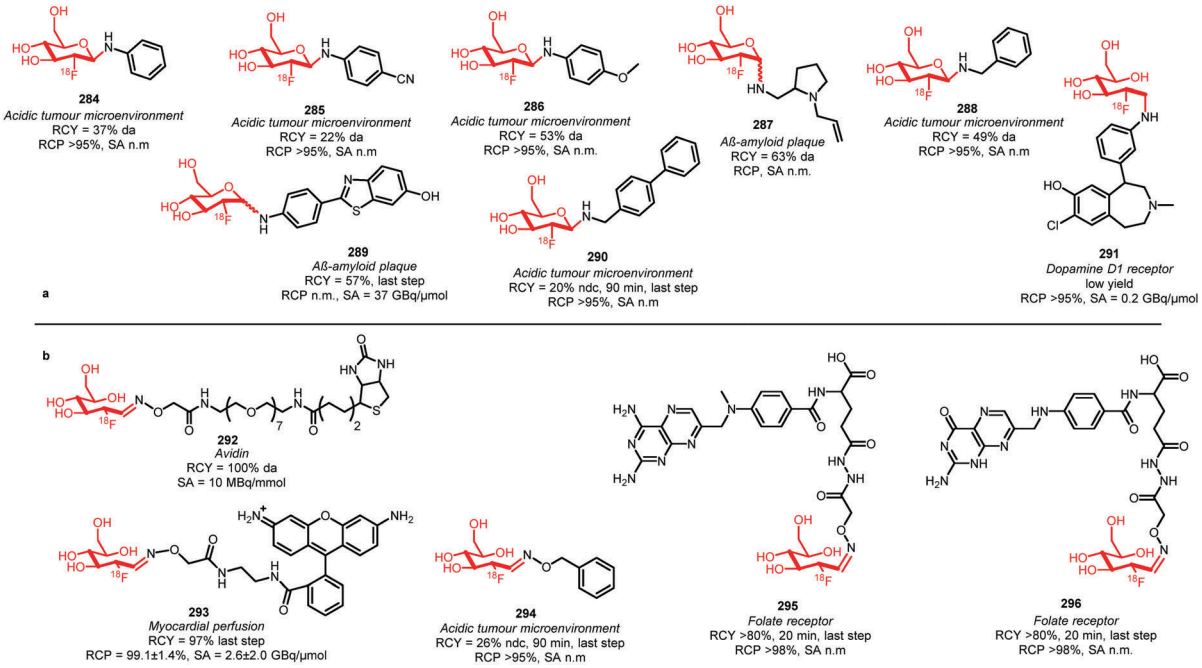


Fig. 11 PET tracers synthesised from [^{18}F]FDG and (a) amine precursors, (b) oxy-amine precursors.[207–212]

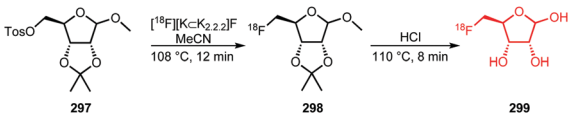
using [^{18}F]FDG. Though, due to its size and hydrophilicity it can have a significant influence on the pharmacokinetics and the targeting of the resulting PET tracer.

2.10 5-[^{18}F]Fluoro-5-deoxyribose

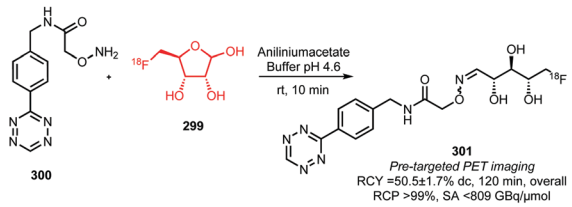
Initially developed as PET tracer for tumour imaging,[213,214] 5-[^{18}F]fluoro-5-deoxyribose has also found application as a building block. Besides in peptide radiolabelling,[215] it has been used to prepare tetrazine **301**, a fluorine-18 labelled compound for pre-targeted PET imaging. The synthesis of the fluorinated tetrazine from an ^{18}F-building block was necessary, because tetrazines are unstable under commonly used direct radiofluorination conditions. 5-[^{18}F]Fluoro-5-deoxyribose can be used under mild conditions and in addition, the 5-[^{18}F]fluoro-5-deoxyribose moiety contributes positively to the overall hydrophilicity of the PET tracer, reducing unspecific binding.[216]

5-[^{18}F]Fluoro-5-deoxyribose **299** could be obtained in a two-step procedure (Scheme 51). First, the protected tosylate precursor **297** was radiofluorinated by nucleophilic substitution in MeCN at 108 °C. Intermediate **298** was purified by semi-preparative HPLC and then deprotected with hydrochloric acid. After neutralisation, the obtained 5-[^{18}F]fluoro-5-deoxyribose **299** was used without further purification.

Another elegant way to synthesise 5-[^{18}F]fluoro-5-deoxyribose was reported by Onega and co-workers. They converted



Scheme 51 Synthesis of 5-[^{18}F]fluoro-5-deoxyribose **299**.



Scheme 52 Synthesis of compound **301** by reaction of 5-[^{18}F]fluoro-5-deoxyribose **299** with tetrazine **300**.[216]

S-adenosyl-L-methionine (SAM) and [^{18}F]fluoride in a two-step enzymatic reaction using fluorinase and adenosine hydrolase to access the product. Radiochemical yields of 75–98% (determined by radio-HPLC) were achieved and the overall synthesis time was 100–120 minutes.[217]

Furthermore, 5-[^{18}F]fluoro-5-deoxyribose **299** was conjugated with the amino-oxy functionalised tetrazine **300** by oxime ether formation (Scheme 52). The reaction was carried out in anilinium acetate buffer (pH 4.6). After 10 minutes at room temperature, product **301** was purified by semi-preparative HPLC and obtained in an overall radiochemical yield of 50.5 ± 1.7% (dc).[216]

In conclusion, the amino-oxy functionalised tetrazine **300** could be labelled fast and in high overall yields, proving the suitability of 5-[^{18}F]fluoro-5-deoxyribose **299** as building block for PET tracer synthesis. In its function as building block, 5-[^{18}F]fluoro-5-deoxyribose may serve as a valuable alternative to [^{18}F]FDG.

2.11 2-Deoxy-2-[^{18}F]fluoroarabinofuranose

Derivatives of 2′-[^{18}F]fluoro-2′-deoxy-1-β-D-arabinofurano-syluracil ([^{18}F]FXAU) **307** can act as potential PET tracers to image the

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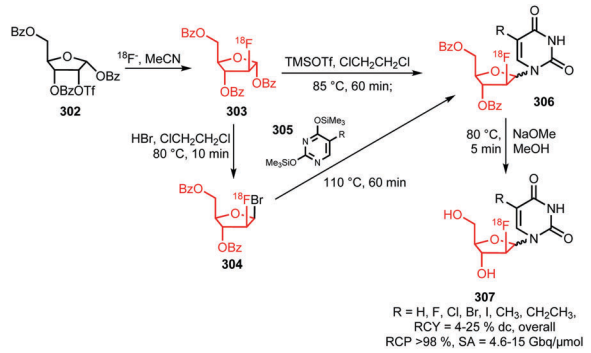


Scheme 53 Synthesis of [^{18}F]FXAU (**307**).[218,220]

expression of the herpes simplex virus type-1 thymidine kinase (Scheme 53). As direct radiofluorination at the 2′-position of the sugar moiety provides extremely low yields (<1%), and therefore does not allow for routine clinical production, many efforts have been made to develop a high-yielding multi-step synthesis based on the building block 2-deoxy-2-[^{18}F]fluoro-arabinofuranose **303**.

Formation of the building block [^{18}F]2-deoxy-2-fluoro-arabinofuranose **303** is in all reported procedures based on the same strategy. In that strategy, the benzyl protected ribose triflate **302** is treated during 20 to 30 min with dried [^{18}F]fluoride in MeCN at 80–90 °C. Alauddin and co-workers reported radiochemical yields of 58–68% for **303** and a radiochemical purity of >90% after passing the reaction mixture over a silica Sep-Pak cartridge to remove unreacted [^{18}F]fluoride.[218] However, depending on the follow-up chemistry, purification of **303** was not always required. Manual as well as automated synthesis procedures on conventional synthesis units and microfluidic devices have been performed.[219,220]

Two different synthesis procedures for [^{18}F]FXAU **307** starting from building block [^{18}F]2-deoxy-2-fluoroarabinofuranose **303** have been developed (Scheme 53). The first method, reported by Alauddin and co-workers in 2002, includes the formation of an α-bromo derivative **304** to promote β-selective coupling to the uracil moiety. For the conversion of the 1-benzoxy group of **303** to the corresponding bromide **304**, hydrogen bromide in acetic acid is used. However, the highly corrosive hydrogen bromide makes this step challenging to automate. The building block was subsequently coupled to a silyl precursor **305** in a non-polar solvent which induced product formation in a favourable anomeric ratio of $\alpha:\beta = 1:3$–$1:9$.[218,221] The reaction time of 60 minutes was rather long, and led to low overall yields.[222]

Although this method is described as very reliable, major disadvantages such as the use of corrosive hydrogen bromide make it not amenable for clinical production. Therefore, an alternative method suitable for automated synthesis of [^{18}F]FXAU has been developed, which employs trimethylsilyl trifluoromethanesulfonate (TMSOTf) as Friedel Crafts catalyst in the coupling reaction that enables direct coupling between building block **303** and silyl precursor **305**. Building block **303** could be employed without purification and added to the *in situ* generated **305**. The reaction optimally performs at 85 °C. No coupling could be observed at lower temperatures while higher temperatures led to decomposition.[220]

In a final step, **306** was deprotected with potassium methoxide in methanol. The product was obtained after neutralisation with HCl and subsequent purification by semi-preparative HPLC. For the 3-step reaction route, radiochemical yields of 10–12% (dc) have been reported, with synthesis times of 114–150 min. The relatively low yields can be attributed to poor α/β anomer selectivity (6 : 4 instead of 1 : 4).[219,220,223] Furthermore, the product has a poor specific activity of 5 GBq µmol^{-1}, probably caused by the excess of TMSOTf.[219]

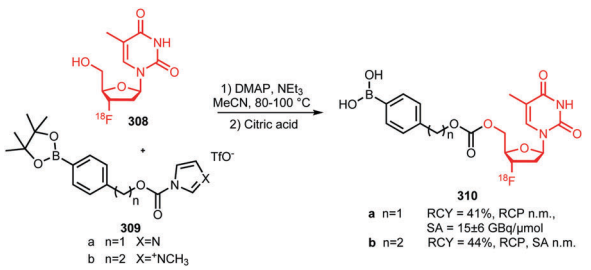
To further improve the synthesis route, Chen *et al.* have investigated the influence of microwave heating and Lewis acid catalysis on the coupling reaction. Microwave heating can have a positive influence on the coupling reaction by reducing the reaction time from 1 hour to 10 minutes, delivering the product in a radiochemical yield of 20% (dc). However, currently this microwave approach is only suitable for manual production.[224]

Application of the Lewis acid catalyst $SnCl_4$ shortens the reaction time of the coupling reaction to 15 minutes while it is compatible with automation. Though, neither microwave heating nor the use of $SnCl_4$ influenced the anomeric ratio positively.[222]

In conclusion, synthesis of the building block 2-deoxy-2-[^{18}F]fluoroarabinofuranose is straightforward, but the anomeric C-1 atom makes the follow-up chemistry challenging. So far, the scope of the building block is limited to the synthesis of 2′-[^{18}F]fluoro-2′-deoxy-1-β-D-arabinofuranosyl-uracil and -thymidine derivatives.

2.12 2′-Deoxy-2′-[^{18}F]fluorothymidine

2′-Deoxy-2′-[^{18}F]fluorothymidine ([^{18}F]FLT) has been applied only once as a building block. Carroll and co-workers reported on the synthesis of a prodrug-like tracer in 2014, PC-[^{18}F]FLT **310a**, for H_2O_2 detection and tumour imaging. Firstly, [^{18}F]FLT was synthesised according to an established procedure. Thereafter it was reacted with imidazole ester precursor **309** (Scheme 54) in the presence of dimethylaminopyridine (DMAP) and TEA. After deprotection with citric acid, the product was purified by semi-preparative HPLC to afford PC-[^{18}F]FLT **310a** and CC-[^{18}F]FLT **310b** in a radiochemical yield of 41% and 44%, respectively, starting from [^{18}F]FLT.[225]



Scheme 54 Production of PC-[^{18}F]FLT **310a** and CC-[^{18}F]FLT **310b** with [^{18}F]FLT.[225]

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2.13 4-(2-[^{18}F]Fluoroethoxy)-3-methoxybenzaldehyde

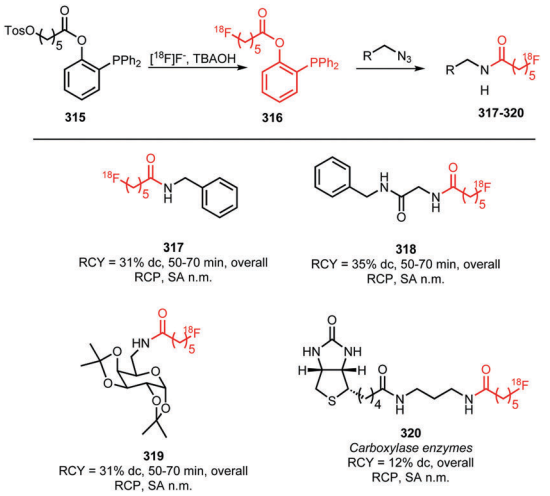
4-(2-[^{18}F]Fluoroethoxy)-3-methoxybenzaldehyde **312** has been applied as a building block in the synthesis of 1-(4-[^{18}F]fluoroethyl)-7-(4′-methyl)curcumin **314**, a tracer for β-amyloid plaque imaging. Compared to direct labelling, the 2-step synthesis shown in Scheme 55 provided higher yields and higher specific activities.

4-(2-[^{18}F]Fluoroethoxy)-3-methoxybenzaldehyde **312** was synthesised from its nosylate precursor **311**. [^{18}F]Fluorination was performed with *n*-Bu$_4$N[^{18}F]F$^-$ in MeCN at 120 °C and resulted in radiochemical yields of over 70% (based on radio-TLC analysis). In the follow-up aldol condensation, **312** was reacted with a 5-hydroxy-1-phenyl-hexa-1,4-dien-3-one (**313**) in the presence of B_2O_3, (*n*-BuO)$_3$B and piperidine at 120 °C. After treatment with hydrochloric acid, the final product **314** was purified by semi-preparative HPLC and obtained in a radiochemical yield of 15–25% with a specific activity of 37.6 GBq μmol^{-1}.[226]

2.14 Fluorine-18 labelled phosphines

Pretze *et al.* explored the synthesis of fluorine-18 labelled triarylphosphine **316** and its performance in a traceless Staudinger ligation. In the traceless Staudinger ligation, triarylphosphines carrying an ester group at the *ortho* position of the phosphorus atom can undergo a reaction with an azide resulting in amide bond formation. The ligation usually proceeds under mild conditions, however with slower reaction kinetics than the CuAAC reaction and it suffers from the disadvantage of oxidation of the phosphine precursor. Nevertheless, it provides a "clean" alternative to the CuAAC reaction and complex biomolecules have been radiolabelled using this strategy.[227]

Fluorine-18 labelled triarylphosphine **316** was prepared by reaction of [^{18}F]tetrabutylammonium fluoride ([^{18}F]TBAF) with the tosylated precursor **315** (Scheme 56). The choice of solvent to obtain **316** proved to be crucial: whereas no reaction was observed in DMF or DMSO, a mixture of MeCN and *tert*-butanol afforded the desired product in 65% (dc) radiochemical yield. The traceless Staudinger ligation was carried out without additional intermediate purification. Water and the azide were directly added and the reaction was stirred at different temperatures. Low temperatures required longer reaction times compared to high temperatures, but provided **317–320** in similar overall yields of 31–35%. The more complex biotin derivative **320** however required a longer reaction time at medium temperatures (60 °C) and resulted in lower yields compared to the other compounds.[228]

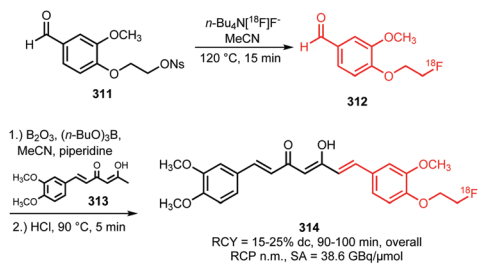


Scheme 56 Synthesis of fluorine-18 labelled phosphine building block **316** and subsequent traceless Staudinger ligation.[228]

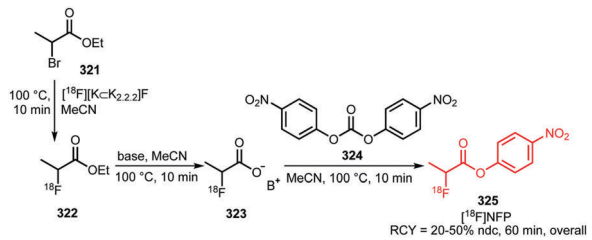
2.15 [^{18}F]4-Nitrophenyl 2-fluoropropionate ([^{18}F]NFP)

[^{18}F]4-Nitrophenyl 2-fluoropropionate ([^{18}F]NFP, **325**) is commonly used for fluorine-18 labelling of amino acids, peptides and other amine derivatives. It can be coupled under very mild reaction conditions with the amine functionality of an amino acid, resulting in amide bond formation.

[^{18}F]NFP can be synthesised *via* a one-pot three-step procedure (Scheme 57). *Via* halogen exchange of ethyl-2-bromopropionate **321** with dried [^{18}F]fluoride, ethyl-2-[^{18}F]fluoropropanoate **322** was obtained, which was subsequently saponified under basic conditions. Usually an aqueous solution of potassium hydroxide is used, however since the subsequent step requires anhydrous conditions, Li *et al.* have used TBAOH which can be employed in a smaller volume, thereby shortening the time-consuming drying procedure. In the third step, bis-4-nitrophenyl carbonate **324** is added, followed by semi-preparative HPLC purification. As the [^{18}F]NFP needs to be absolutely free from water for subsequent coupling to an amine, it was transferred *via* a cartridge procedure to a volatile organic solvent (*e.g.* ether) and then evaporated to dryness. Overall radiochemical yields of 20–50% (ndc) are reported.[84,229] Reaction of **325** with amino precursors proceeds in general under mild conditions (room temperature to 60 °C) in short reaction times with good radiochemical yields. Scheme 58 summarises the molecules labelled with [^{18}F]NFP.[84,229–231] In addition to two amines, also the two amino acids, L-methionine **329** and L-arginine **327**, have been radiofluorinated using this



Scheme 55 Synthesis of 1-(4-[^{18}F]fluoroethyl)-7-(4′-methyl)curcumin.[226]



Scheme 57 One-pot three-step synthesis of [^{18}F]NFP.[84]

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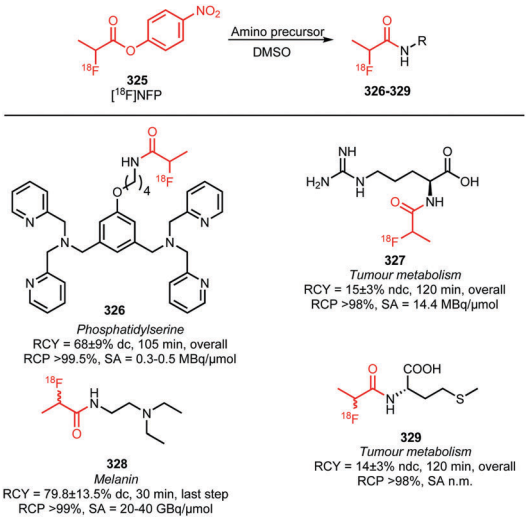


Scheme 58 PET tracer synthesis by coupling to [18F]4-nitrophenyl 2-fluoropropionate **325**.[84,229–231]

building block. Whereas Gao and co-workers described the use of the protected amino acid arginine ethyl ester dihydrochloride as precursor, Hu *et al.* state fast and efficient coupling of [18F]NFP to unprotected methionine. Overall radiochemical yields are comparable and approximately 15% (ndc) with reaction times of 120 minutes.[229,231]

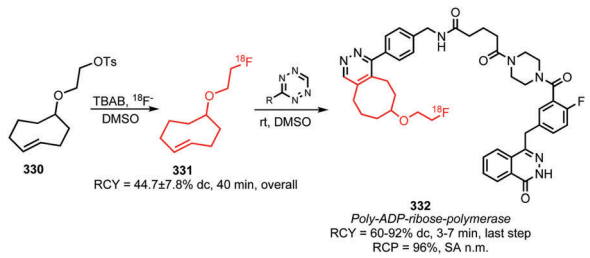
To summarise, [18F]NFP offers fast, mild and simple radiofluorination of amines and amino acids. The only challenge in the application of [18F]NFP is the complex and time-consuming three-step one-pot synthetic procedure of the building block itself.

2.16 Fluorine-18 labelled *trans*-cyclooctenes

In [4+2] inverse electron demand Diels-Alder cycloadditions, *trans*-cyclooctenes (TCO) and tetrazines (Tz) react very fast and selectively with each other under mild reaction conditions. Keliher *et al.* and Reiner *et al.* used this strategy to radiolabel poly-ADP-ribose-polymerase 1 inhibitor AZD2281 **332** (Scheme 59). Compared to native labelling, which requires multiple steps including intermediate purifications, higher yields and reduced reaction times have been reported using this strategy.

As tetrazines are unstable under radiofluorination conditions,[232] fluorine-18 was introduced into the *trans*-cyclooctene reactant **331**. This building block was synthesised from its tosyl precursor in a nucleophilic substitution reaction and obtained after HPLC purification in a radiochemical yield of 44.7 ± 7.8% (dc) in 40 minutes from the start of drying the [18F]fluoride. The tetrazine moiety was integrated into the structure of the AZD2281 derivative **332** by attaching it to the piperazine unit. Reaction between the tetrazine and **331** was very fast (3 min at room temperature). HPLC purification afforded the product in a radiochemical yield of 59.6 ± 5.0% (dc).[233] To allow routine production, an alternative way of purification was developed: excess amount of precursor was extracted by using magnetic beads functionalised with *trans*-cyclooctene. The radiochemical yield was improved to 92.1 ± 0.4% (dc).[234]

In conclusion, as the [4+2] cycloaddition proceeds very fast under mild reaction conditions with high selectivity, it is a very interesting alternative to the popular CuAAC reaction for radiofluorination of biomolecules.



Scheme 59 Synthesis of the fluorine-18 labelled TCO **331** and [4+2] cycloaddition with Tz precursor.[233,234]

2.17 5-(1,3-Dioxolan-2-yl)-2-(2-(2-(2-[18F]fluoroethoxy)ethoxy)-ethoxy)pyridine

Carberry and co-workers introduced a novel fluorine-18 labelled building block, 5-(1,3-dioxolan-2-yl)-2-(2-(2-(2-[18F]fluoroethoxy)-ethoxy)ethoxy)pyridine **334**, which can react after hydrolysis with aminooxy groups, resulting in oxime formation (Scheme 60).[235]

Building block **334** was prepared in a 71 ± 2% radiochemical yield *via* nucleophilic substitution of the corresponding tosylate **333** using [18F][K⊂K2.2.2]F in MeCN at 110 °C, followed by purification using solid-phase extraction.

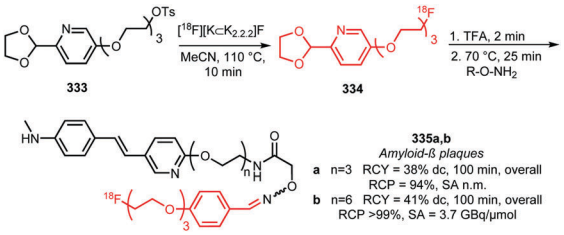
Next, building block **334** was converted *in situ* to the corresponding aldehyde under the same acidic conditions which are used in the oxime formation. Attempts to perform this step prior to radiofluorination were unsuccessful, because the presence of the free aldehyde led to formation of various side products under the radiolabelling conditions.

Two model compounds **335a and b**, both potential tracers for β-amyloid plaque imaging, were synthesised by Carberry *et al.* using building block **334** and were obtained in comparable overall radiochemical yields (around 40% (dc)) in 100 minutes (Scheme 60).[235]

Successful labelling of small molecules using this building block has been demonstrated. The utility of this prosthetic group in radiofluorination of more complex biomolecules such as peptides and proteins has yet to be proven.

2.18 [18F]Fluorobutyl ethacrynic amide ([18F]FBuEA)

[18F]FBuEA **337** was used in the synthesis of the glutathione (GSH) conjugate [18F]FBuEA-GSH **338**, a potential imaging agent



Scheme 60 Radiosynthesis and coupling reaction of building block **334**.[235]

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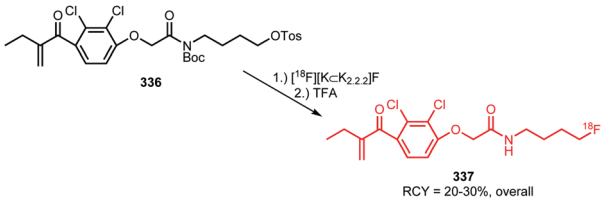
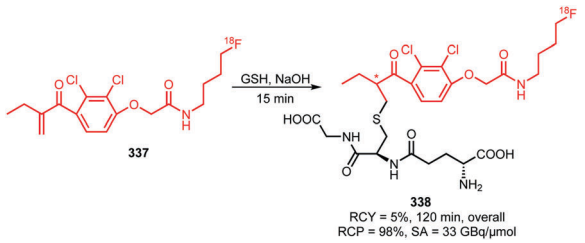


Scheme 61 Radiosynthesis of [^{18}F]FBuEA **337**.[237]



Scheme 62 Conjugation of [^{18}F]FBuEA with glutathione.[237]

for brain tumours targeting the lipocalin-type prostaglandin D synthase.[236]

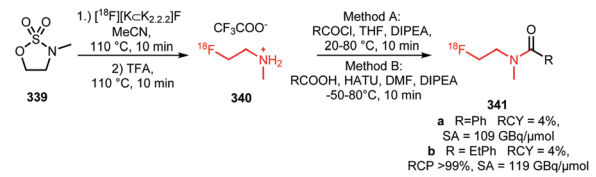
[^{18}F]FBuEA was synthesised from the corresponding tosylate precursor **336** in a nucleophilic substitution reaction and obtained after Boc deprotection and HPLC purification in 20–30% radiochemical yield in 60 minutes reaction time (Scheme 61). Coupling of [^{18}F]FBuEA with glutathione was accomplished in aqueous medium at pH 8.2, followed by semi-preparative HPLC purification, providing the racemic product in an overall radiochemical yield of 5% (dc) and an overall synthesis time of 2 hours (including the synthesis of the building block (Scheme 62)).[237]

2.19 New aliphatic building blocks and coupling methods with potential for PET tracer synthesis

In the following sections, new radiolabelled aliphatic building blocks as well as novel conjugation methods with aliphatic building blocks, which have not been applied yet in PET tracer synthesis, will be summarised.

2.19.1 *N*-(2-[^{18}F]Fluoroethyl)-*N*-methylamine. Hoareau *et al.* reported in 2014 on the one-pot two-step synthesis of *N*-(2-[^{18}F]fluoroethyl)-*N*-methylamine **340** as potential building block for PET tracer synthesis (Scheme 63).

Precursor **339** was radiofluorinated in MeCN at 110 °C within 10 minutes. Next, trifluoroacetic acid (TFA) was added and the reaction mixture was heated again at 110 °C for 10 min. After evaporation of TFA, *N*-(2-[^{18}F]fluoroethyl)-*N*-methylamine **340** was obtained in 81% radiochemical yield and directly employed in the coupling reactions without further purification.



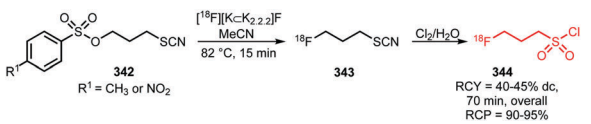
Scheme 63 Synthesis and reaction of *N*-(2-[^{18}F]fluoroethyl)-*N*-methylamine.[238]

For the subsequent conversion to amides **341a** and **341b**, two methods were studied: method A employed benzyl chloride and hydrocinnamoyl chloride, respectively, in THF in presence of DIPEA as base and in method B, the corresponding carboxylic acids were reacted with *N*-(2-[^{18}F]fluoroethyl)-*N*-methylamine **340** in presence of DIPEA and the coupling reagent 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU). Radio-TLC and HPLC analyses showed higher conversion using method B for both products. The yield of amides **341a** and **341b** resulting from method B were 4 and 17% in a synthesis time of 93 minutes and 134 minutes, respectively.[238]

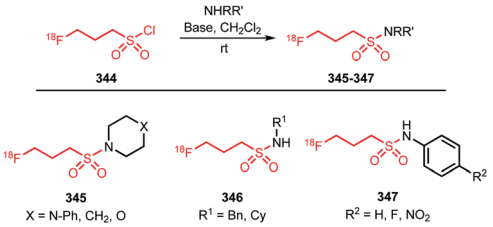
2.19.2 3-[^{18}F]Fluoropropanesulfonyl chloride. In 2009 Li *et al.* introduced 3-[^{18}F]fluoropropanesulfonyl chloride **344**, a potential building block for PET tracer synthesis *via* sulfonamide formation.[239]

An optimised synthesis procedure of building block **344** and its reaction with various amines was reported by Löser *et al.* in 2013. First, [^{18}F]fluoride was introduced by nucleophilic substitution, providing thiocyanate **343** in 75–85% yield from the nosylate precursor. Compound **343** was used without intermediate purification and converted to sulfonyl chloride **344** by repetitive addition of a saturated solution of chlorine in water over a C18 SPE cartridge containing **343**. 3-[^{18}F]Fluoropropanesulfonyl chloride **344** was obtained in 40–45% decay-corrected radiochemical yield in a synthesis time of 70 minutes (Scheme 64).

Different amines were subjected to reaction with 3-[^{18}F]fluoropropanesulfonyl chloride **344** to assess the usability of the building block in PET tracer synthesis (Scheme 65). Aliphatic sulfonamide **345** and **346** were formed in 2–3 minutes with high radiochemical yields of 77 to 89% (determined by radio-TLC). Addition of bases (TEA or DMAP) did not improve the yield. However, for the aniline derivatives **347**, only low yields (<10%) were observed in absence of additive. Addition of TEA or DMAP improved the conversion of aniline and 4-fluoroaniline



Scheme 64 Two-step synthesis 3-[^{18}F]fluoropropanesulfonyl chloride.[240]



Scheme 65 Reaction of 3-[^{18}F]fluoropropanesulphonyl chloride with different amines.[240]

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and provided radiochemical yields of 50–65% (analytically determined). For the poorly nucleophilic 4-nitroaniline, only addition of potassium trimethylsilanolate led to formation of satisfying amounts of product (RCY = 45%, analytically determined).[240]

2.19.3 2-[^{18}F]Fluoroethanol and 3-[^{18}F]fluoropropanol. As an alternative strategy to fluoroalkylation using [^{18}F]fluoroalkyl halides and sulfonates (see Sections 2.1–2.5), 2-[^{18}F]fluoroethanol **119** and 3-[^{18}F]fluoropropanol have been used to synthesise [^{18}F]fluoroalkyl aryl esters and ethers.

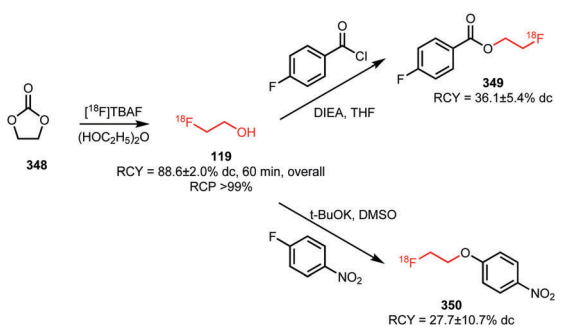
2-[^{18}F]Fluoroethanol **119** was synthesised in a one-step reaction *via* nucleophilic substitution of ethylene carbonate **348**. The reaction was carried out at 165 °C in diethylene glycol with dry [^{18}F]TBAF as fluoride source. After 20 minutes, 2-[^{18}F]fluoroethanol (b.p. 103.5 °C) was co-distilled with THF and trapped into a second vial containing THF in a decay-corrected radiochemical yield of 88.6 ± 2.0%. The total synthesis time including drying of [^{18}F]fluoride was about 60 minutes.

The same procedure was applied to the synthesis of 3-[^{18}F]fluoropropanol resulting in a decay-corrected radiochemical yield of 65.6 ± 10.2%. The lower yield in the latter case was attributed to the higher boiling point of 3-[^{18}F]fluoropropanol (127.8 °C) and the resulting reduced distillation efficiency.

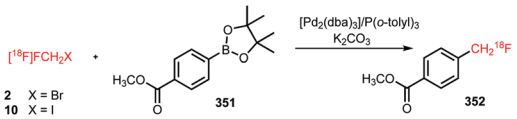
2-[^{18}F]Fluoroethanol was reacted in two model reactions to prove its usability in the formation of [^{18}F]fluoroalkyl aryl esters and ethers (Scheme 66). Under non-optimised reaction conditions, 2-[^{18}F]fluoroethyl 4-fluorobenzoate **349** and 1-(2-[^{18}F]fluoroethoxy)-4-nitrobenzene **350** were synthesised with decay-corrected radiochemical yields of 36.1 ± 5.4% and 27.7 ± 10.7%, respectively. In the synthesis of **350**, the strong base *tert*-butoxide was employed to increase the reactivity of the building block in the nucleophilic substitution by generating 2-[^{18}F]fluoroethoxide.

Due to the slightly higher nucleophilicity of 3-[^{18}F]fluoropropanol compared to [^{18}F]fluoroethanol, similar performance of 3-[^{18}F]fluoropropanol was expected. But formation of 3-[^{18}F]fluoropropyl aryl esters and ethers has not been investigated.[241]

2.19.4 Pd(0)-mediated *C*-[^{18}F]fluoromethylation. To expand the toolbox of radiofluorination methods, Pd(0)-mediated *C*-[^{18}F]fluoromethylation of pinacolborane substituted arenes has been explored. This method offers the possibility not only to introduce the [^{18}F]fluoromethyl group *via* *N*-,*O*-, *S*- or *P*-alkylation but also to allow for C–C bond formation.



Scheme 66 2-[^{18}F]Fluoroethanol as building block in the synthesis of 2-[^{18}F]fluoroethyl aryl esters and ethers.[241]



Scheme 67 Pd(0)-Mediated C-[^{18}F]fluoromethylation.[242]

[^{18}F]Fluoromethyl iodide **10** as well as [^{18}F]fluoromethyl bromide **2** have been investigated as building blocks in a coupling reaction with the pinacolborane-substituted benzoate **351** (Scheme 67). Initial experiments with [^{18}F]fluoromethyl iodide **10** in DMF, using the catalyst system [$Pd_2(dba)_3$]/P(*o*-tolyl)$_3$ and potassium carbonate as base, provided [^{18}F]fluoromethylated benzoate **352** in a radiochemical yield of 23% (based on radio-HPLC analysis). Unfortunately, decomposition of building block [^{18}F]fluoromethyl iodide **10** was observed under the coupling conditions and attempts to reduce decomposition of the precursor failed. When using [^{18}F]fluoromethyl bromide **2**, the yield of **352** could be increased up to 86% (based on radio-HPLC analysis) under optimised conditions. Due to the lower reactivity of the bromide **2** compared to the iodide **10**, higher reaction temperatures of 120 °C were required and the solvent system 1,3-dimethyltetrahydropyrimidin-2(1*H*)-one (DMPU, *N*,*N*′-dimethyl propylene urea)/water (9 : 1) was found to be superior to DMF or *N*-methyl-2-pyrrolidone (NMP). Addition of small amounts of water suppressed side product formation, providing product **352** in 66% decay-corrected radiochemical yield in a total synthesis time of 40 minutes starting from [^{18}F]fluoromethyl bromide.[242]

3 Fluorine-18 labelled aromatic building blocks

Since 2010 a wide variety of fluorine-18 labelled aromatic building blocks have been developed and applied to synthesise PET tracers. These building blocks are mostly used for PET tracers which cannot be prepared by direct radiofluorination of the corresponding precursors, since sufficient electron withdrawing functionalities at the *ortho* or *para* position to the site of fluorination are absent, or because the precursor or product is unstable under the relatively harsh radiolabelling reaction conditions.

In most cases, fluorine-18 labelled aromatic building blocks are synthesised by introduction of [^{18}F]fluoride on phenyl precursors containing one good leaving group (–NO_2 or –NMe_3^+) and at least one strong electron withdrawing functional group (aldehyde, ester, cyanide) positioned *ortho* or *para* from each other. Due to the electron withdrawing functional group, the benzene ring is electron deficient, allowing nucleophilic aromatic substitution with [^{18}F]fluoride, exchanging the leaving group for fluorine-18. After radiofluorination, in the follow-up chemistry, the functional group is either (1) reacted directly in a second reaction with a precursor towards the desired PET tracer or (2) further transformed to a more useful functional group and then reacted with a precursor towards the desired PET tracer.

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3.1 [^{18}F]Fluorobenzaldehydes

The aldehyde functionality is a versatile functional group; it is therefore not surprising that [^{18}F]fluorobenzaldehydes are often reported and used in a wide variety of subsequent chemical reactions (Scheme 68).

Of these reactions, reductive amination is the most commonly used, and will be discussed in Section 3.1.2. Furthermore, [^{18}F]fluorobenzaldehydes are used in the condensation with various types of amines towards imines, oximes and hydrazones, which will be discussed in Section 3.1.3, 3.1.4 and 3.1.5. A well-known reaction for aldehydes is the aldol condensation, which has been used in the synthesis of PET tracers with the dibenzalacetone core structure, as can be seen in Section 3.1.6. Finally, a very innovative application of [^{18}F]fluorobenzaldehydes is discussed in Section 3.1.7, being the use as a reagent in multi-component reactions, opening up the synthesis of a wide diversity of potential PET tracers.

3.1.1 Synthesis of [^{18}F]benzaldehydes. Because the aldehyde functional group is strongly electron withdrawing, 4-[^{18}F]fluorobenzaldehydes and 2-[^{18}F]fluorobenzaldehydes can be synthesised in one reaction step by nucleophilic aromatic substitution with [^{18}F]fluoride of nitro- or trimethylammonium triflate benzaldehydes. Kügler *et al.* and Lemaire *et al.* compared the conversions towards various 4-[^{18}F]fluorobenzaldehydes (Scheme 69) and 2-[^{18}F]fluorobenzaldehydes.[243,244] Comparable conversions were observed for both leaving groups, however reactions were in general faster for the trimethylammonium triflate containing precursors (5 minutes *versus* 15 minutes respectively).

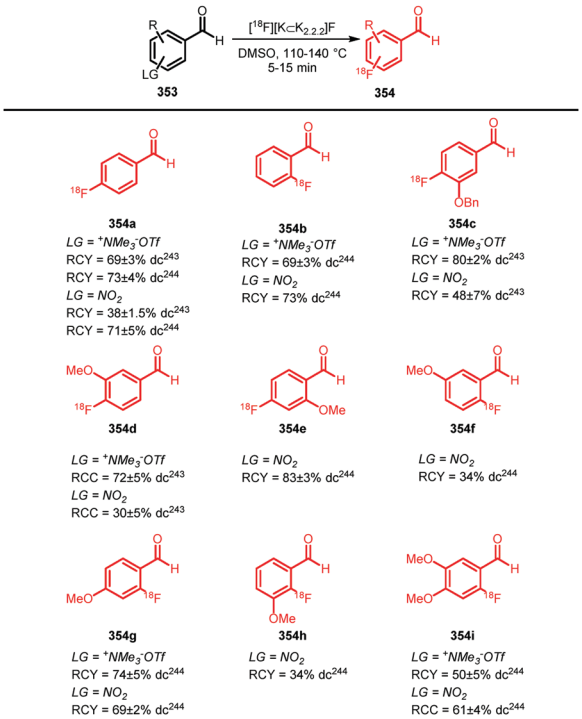
Furthermore, in the case of the trimethylammonium precursors, purification of the 4-[^{18}F]fluorobenzaldehydes from the trimethyl ammonium precursors can be carried out *via* a straightforward C18 SPE procedure. Apolar 4-[^{18}F]fluorobenzaldehyde is retained on the C18 cartridge, while the polar, ionic, trimethylammonium precursor can be removed by washing the cartridge with aqueous media.

In case of the nitro precursors, which are also apolar molecules, such a simple purification procedure to obtain 4-[^{18}F]fluorobenzaldehydes is not possible. As a result, trimethylammonium precursors are currently preferred for the synthesis of 4-[^{18}F]fluorobenzaldehyde.

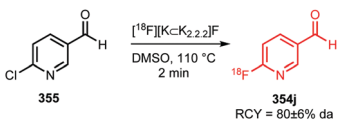
When a nitrogen atom is included in the aromatic ring, directly next to the fluorine-18 labelling position (thus being a pyridine derivative), the electron withdrawing effect of the nitrogen atom highly activates the labelling position, making it possible to obtain high conversions even with less reactive leaving groups. As shown by Kügler *et al.* (Scheme 70), a radiochemical yield of 80 ± 6% (analytically determined) was obtained when labelling the commercially available precursor 6-chloronicotinaldehyde **355**.[243]

Labelling the 3-position of benzaldehyde towards 3-[^{18}F]fluorobenzaldehyde is more challenging because this position is relatively electron rich compared to the 2- and 4-position. Attempts to prepare 3-[^{18}F]fluorobenzaldehyde from nitro- or trimethylammonium benzaldehyde precursors resulted in very low radiochemical yields.[245–247]

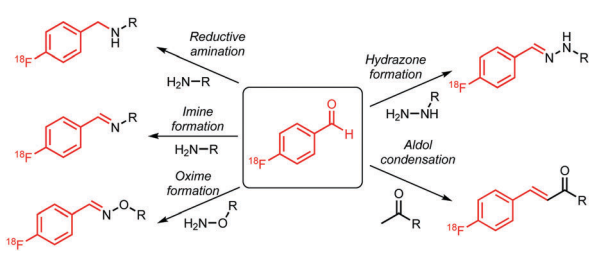
For the synthesis of 3-[^{18}F]fluorobenzaldehyde in higher radiochemical yields, various new radiofluorination techniques have recently been investigated (Scheme 71).[18,28,34,35] These methods enable the formation of 3-[^{18}F]fluorobenzaldehyde in moderate to good radiochemical yields (analytically determined) and thereby open up the possibility to synthesise PET tracers based on this building block. Applications of this building block have not been published yet, except in the synthesis of Lapatinib, which will be discussed in Section 3.2.3.3 (Application of [^{18}F]fluorobenzyl halides in alkylation of phosphines and benzyl alcohols).



Scheme 69 Synthesis of 2- and 4-[^{18}F]fluorobenzaldehydes.[243,244]



Scheme 70 Synthesis of 6-[^{18}F]fluoronicotinaldehyde.[243]



Scheme 68 Possible applications of [^{18}F]fluorobenzaldehydes.

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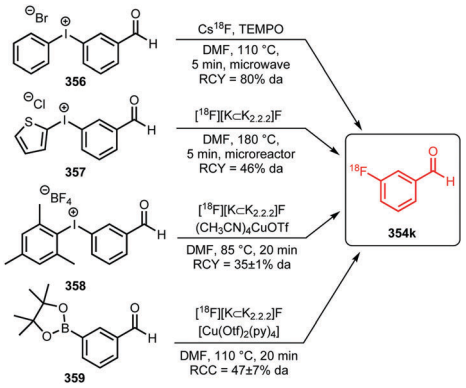


Scheme 71 Novel fluorine-18 labelling methods for the synthesis of 3-[^{18}F]fluorobenzaldehydes.[18,28,34,35]

3.1.2 Application of [^{18}F]fluorobenzaldehydes in reductive aminations. [^{18}F]fluorobenzaldehydes are predominantly used in reductive amination reactions, of which the first examples were published in 1990.[248] Scheme 72 summarises the small molecule PET tracers that have recently been prepared by reductive amination.[243,249–256] Except for tracer **365**, in which sodium borohydride was used as a reductant at 60 °C and tracers **366a** and **366b**, in which sodium triacetoxyborohydride was used as a reductant at room temperature, all tracers were produced using sodium cyanoborohydride as the reductant at temperatures >100 °C. In general, the overall radiochemical yields, starting from [^{18}F]fluoride, were reasonable, in the range of 20–40% decay corrected with synthesis times of 80–150 minutes.

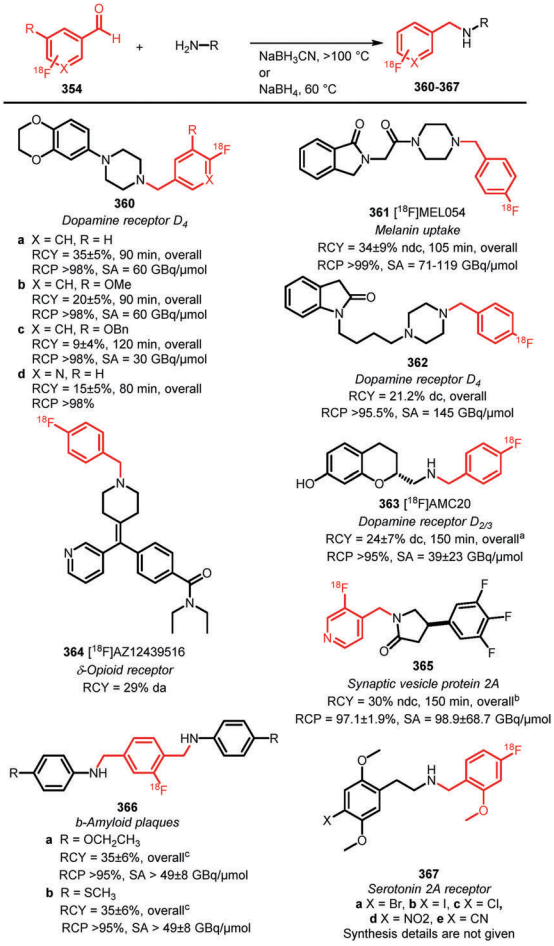
Intermediate purification of [^{18}F]fluorobenzaldehydes as building blocks by SPE or HPLC could be omitted in some cases, resulting in a faster and easier to automate overall synthetic procedure. For example, in the case of the benzodioxin piperazines **360a–d** and *N*-benzyl-phenethylamines **367a–e**, one-pot [^{18}F]benzaldehyde production and subsequent reductive amination was possible.[243,256]

Another example of a successful two-step reaction without intermediate purification is the synthesis of the delta opioid agonist [^{18}F]AZ12439516 **364**. In this case, both the [^{18}F]benzaldehyde synthesis and subsequent reductive amination could be performed using a microfluidic apparatus.[250] Although a significant reduction of overall reaction time can be achieved with the one-pot procedure, it does not always yield satisfactory results. The final purification of the PET tracer can be challenging or even prove to be impossible, due to the formation of significantly more side products.

In a recent publication describing the reductive amination approach using [^{18}F]fluorobenzaldehyde, the synthesis of fluorine-18 labelled histone deacetylase class-I tracer derivatives of [^{11}C]Martinostat can be found. Developed originally as a carbon-11 tracer that showed excellent imaging results in preclinical studies, Strebl *et al.* developed a fluorine-18 derivative, which would allow multicentre clinical studies and ultimately commercialisation of the PET tracer.

Initial approaches to create a fluorine-18 derivative aimed to replace the *N*-methyl functionality with a [^{18}F]fluoroethyl group showed that the [^{18}F]fluoroethyl group led to a significant decrease in target affinity and selectivity.[257] As an alternative, Strebl *et al.* published a fluorine-18 labelled Martinostat derivative where the aromatic ring was substituted with fluorine-18.[257] Since the aromatic ring does not contain an electron withdrawing group that allows for direct nucleophilic aromatic substitution, a building block approach was used, starting from [^{18}F]fluorobenzaldehyde **354l** or **354m**, followed by a multi-step procedure including a reductive amination for further functionalisation (Scheme 73). As the hydroxamate moiety is incompatible with radiofluorination conditions, two approaches were examined: (a) protecting the hydroxamic acid group with 2,2-diethoxypropane to form aprotic 5,5-dimethyl-1,4,2-dioxazole; (b) starting from the methyl ester which is converted in the last step to the hydroxamate using hydroxylamine.

Both approaches led to the desired fluorine-18 labelled Martinostat derivative. Although the overall radiochemical yields were low, due to the multistep procedure requiring two HPLC purifications and multiple solid phase extractions, the radiochemical yields were sufficient for the preclinical evaluation of these compounds.



Scheme 72 Recently produced tracers using reductive amination with [^{18}F]fluorobenzaldehydes. [a] Including deprotection after reductive amination. [b] Including ring closure after reductive amination. [c] In the synthesis of this PET tracer, the dibenzaldehyde 2-[^{18}F]fluoroterephthalaldehyde was used, leading to double reductive amination.[243,249–256]

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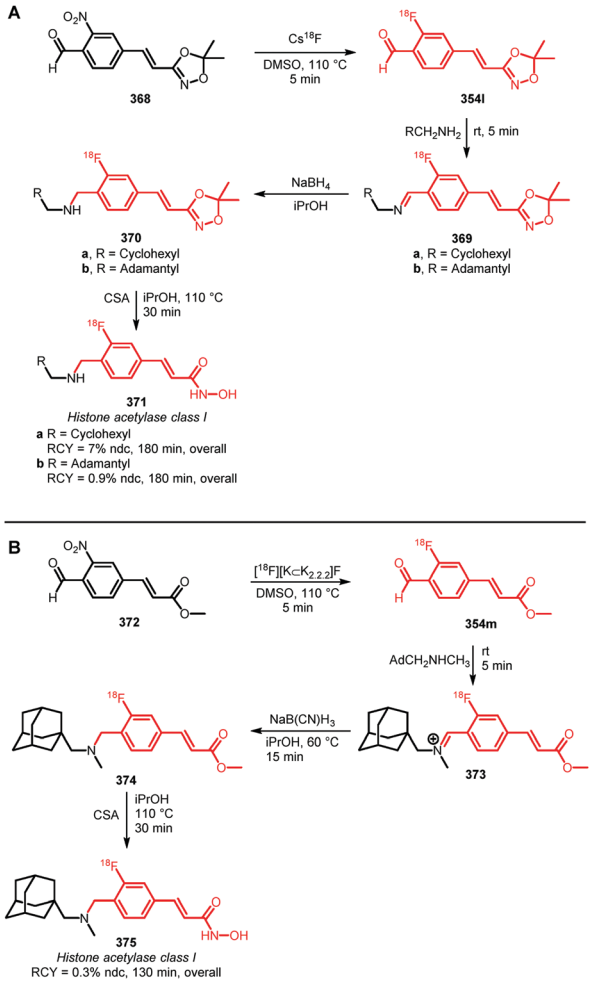
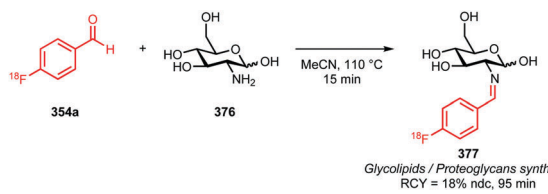


Scheme 73 Synthesis of aromatic fluorine-18 labelled Martinostat derivatives.[257]

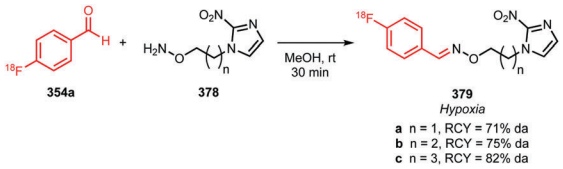
3.1.3 Application of [18F]fluorobenzaldehydes in imine formation.

[18F]fluorobenzaldehydes are also reacted with amines to form imines. This reaction is however not commonly used as imines are generally unstable and can be easily hydrolysed. One example of a PET tracer consisting of an imine formed *via* reaction of [18F]fluorobenzaldehyde with an amine is compound **377** (Scheme 74).[55]

The main advantage of this approach over the use of other fluorine-18 labelled building blocks to label glucosamine **376**, is that the alcohol groups do not require protection due to the high selectivity of [18F]benzaldehydes for reaction with amines.



Scheme 74 Imine formation with 4-[18F]fluorobenzaldehyde as a method to label glucosamine.[55]



Scheme 75 Synthesis of a hypoxia tracer by oxime formation.[259]

3.1.4 Application of [18F]fluorobenzaldehydes in oxime formation.

Oximes formed by condensation of [18F]fluorobenzaldehydes with hydroxamines are generally very stable. It is therefore not surprising that the reaction of [18F]fluorobenzaldehyde with aminooxy-functionalised peptides is a commonly applied method to label peptides.[258] For the synthesis of low molecular weight PET tracers this method is rarely used, as only one report has been published recently.[259]

Abdel-Jalil *et al.* reported on the synthesis of a series of hypoxia tracers **379a–c** by reacting [18F]4-fluorobenzaldehyde **354a** with aminoxy-functionalised precursors **378a–c** (Scheme 75).[259] These precursors are synthesised in only 3 steps and the subsequent oxime formation proceeds in high conversions (RCY > 70% da) in 30 minutes reaction time. Since high yields and short synthesis times in general are ideal for the synthesis PET tracers, this oxime formation using [18F]4-fluorobenzaldehyde has great potential to develop fluorine-18 labelled PET tracers.

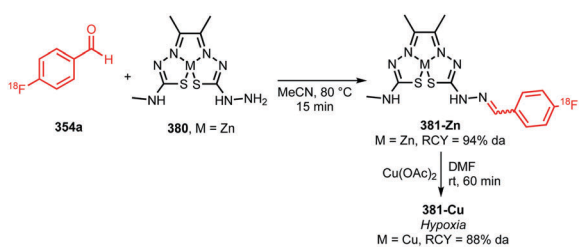
3.1.5 Application of [18F]fluorobenzaldehydes in hydrazone formation.

Another example of stable imine based PET tracers are hydrazones, which can be formed *via* condensation of [18F]fluorobenzaldehydes with hydrazines. A recent example is the publication of Carrol *et al.* on the synthesis of fluorine-18 labelled bis(thiosemicarbazonato) complexes, variations of Cu-ATSM, known as tracers for hypoxia imaging.[163]

A series of derivatives was synthesised using various fluorine-18 labelled building blocks: amide formation with 4-[18F]fluorobenzoic acid, click reaction with [18F]fluoroethyl azide and imine condensation with 4-[18F]fluorobenzaldehyde. The condensation of 4-[18F]fluorobenzaldehyde with hydrazine precursor **380** resulted in 94% radiochemical yield (analytically determined) (Scheme 76). In contrast, the amide formation on the same hydrazine precursor **380** with 4-[18F]fluorobenzoic acid resulted in only 32% radiochemical yield (analytically determined).

3.1.6 Application of [18F]fluorobenzaldehydes in aldol condensation.

The aldol condensation of benzaldehydes with benzylideneacetones is well known.[260] Li *et al.* and Cui *et al.* use this



Scheme 76 Imine formation with 4-[18F]fluorobenzaldehyde for the synthesis of a bis(thiosemicarbazonata) hypoxia tracer.[163]

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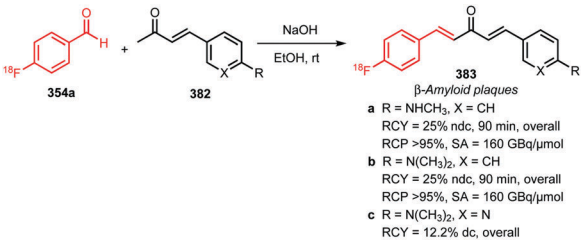


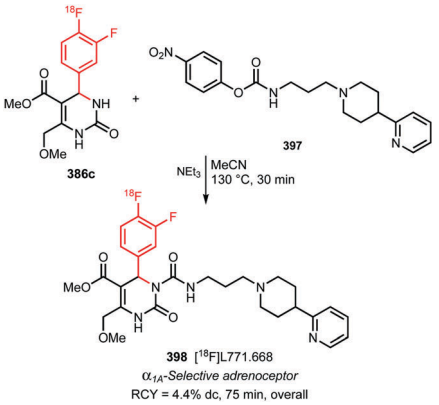
Scheme 77 Synthesis of fluorine-18 labelled benzylidene acetones by aldol condensation with 4-[^{18}F]fluorobenzaldehyde.[261,262]

method in the production of benzylideneacetones **383a–c** as PET tracers for the imaging of β-amyloid plaques by reacting 4-[^{18}F]fluorobenzaldehyde **354a** with benzylideneacetones **382a–c** (Scheme 77).[261,262]

Benzylideneacetones **383a–c** were successfully synthesised within 90 min in moderate radiochemical yields (12–25% ndc). The aldol condensation with [^{18}F]benzaldehydes has thereby proven to be suitable for the synthesis of PET tracers. Unfortunately the scope of the aldol condensation is limited, as an α-acidic ketone is required and the presence of other nucleophilic functional groups is not allowed.

3.1.7 Application of [^{18}F]fluorobenzaldehydes in multicomponent reactions. Multicomponent reactions are important in bio-organic chemistry, since they can deliver structurally diverse compounds in a single reaction step, starting from relatively easy to obtain starting materials. Benzaldehydes are frequently used as reaction partners in multicomponent reactions due to the versatility of the aldehyde functional group. It is therefore not surprising that [^{18}F]fluorobenzaldehydes are the first building block investigated for fluorine-18 based multicomponent reactions (Scheme 78).[263]

Li *et al.* reacted [^{18}F]fluorobenzaldehydes in Biginelli, Groebke, Ugi or Passerini multicomponent reactions, resulting in a diversity of complex radiolabelled molecules with the fluorine-18 label on a position where direct aromatic nucleophilic substitution



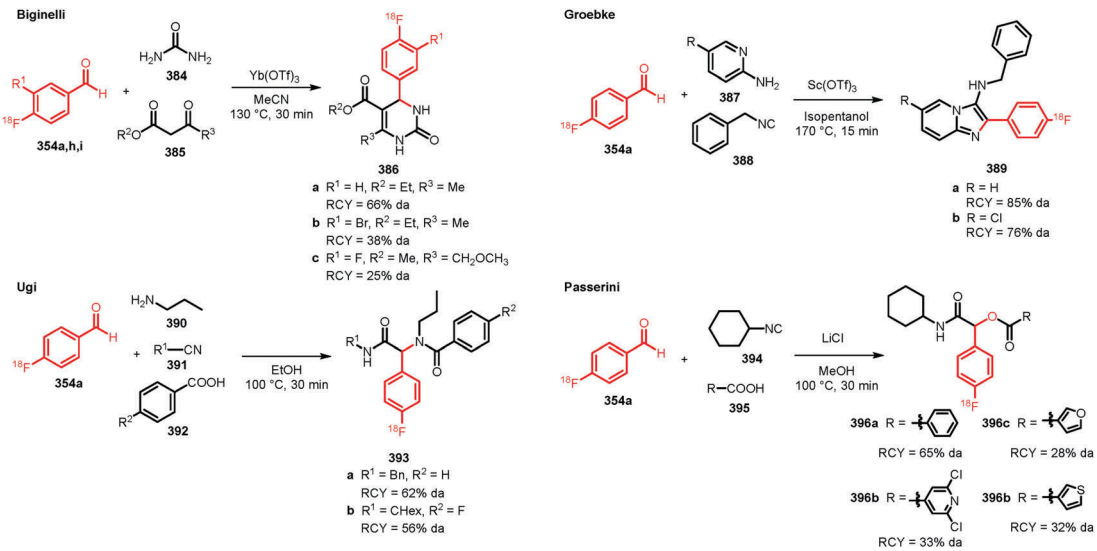
Scheme 79 Synthesis of [^{18}F]L771.668 using the Biginelli MCR.[263]

was not possible. By combining the Biginelli multicomponent reaction with an additional condensation reaction, α_{1A}-selective adrenoceptor antagonist [^{18}F]L771.668 was synthesised in a 4.4% decay-corrected overall radiochemical yield in 75 minutes (Scheme 79).

As shown in this section, [^{18}F]4-fluorobenzaldehydes are ideal building blocks as they can be synthesised efficiently and are able to participate in a wide range of reactions in a efficient manner.

3.2 [^{18}F]Fluoroaryl halides & [^{18}F]fluorobenzyl halides

In recent literature, there are various building blocks described in which the fluorine-18 atom is attached to an aromatic ring and the functional group is an aromatic or aliphatic halide. The most commonly used aryl halide building block is [^{18}F]4-fluoroiodobenzene, which is used in metal catalysed cross-coupling reactions (Section 3.2.1). Other aryl halides, which have very recently been applied are 1-bromo-3-[^{18}F]fluorobenzene (Section 3.2.2) and 2-bromo-6-[^{18}F]fluoropyridine (Section 3.2.3). The group of ^{18}F-labelled benzyl halide building blocks will be



Scheme 78 Multicomponent reactions with [^{18}F]fluorobenzaldehydes.[263]

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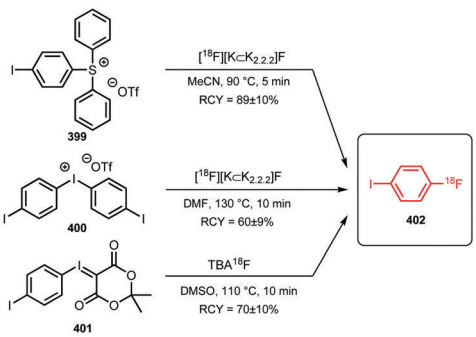
shown in Section 3.2.3 and finally, the novel building block [^{18}F]4-fluorophenetylhalide, prepared using novel fluorine-18 chemistry, will be shown in Section 3.2.5.

3.2.1 Synthesis and application of 4-[^{18}F]fluoroiodobenzene. 4-[^{18}F]fluoroiodobenzene has great potential in PET tracer synthesis, since it can be used as a reagent in metal-catalysed cross-coupling reactions, as recently reviewed by Way *et al.*[261] The aromatic ring is only moderately electron deficient and conventional direct nucleophilic radiofluorination of its $N_2^+BF_4$, triazine, Br, I, IO_2, N^+Me_3 or NO_2 precursor results only in low radiochemical yield.[264] To obtain 4-[^{18}F]fluoroiodobenzene in a higher radiochemical yield, novel late stage radiofluorination methodologies are recently explored (Scheme 80).[20,265–268]

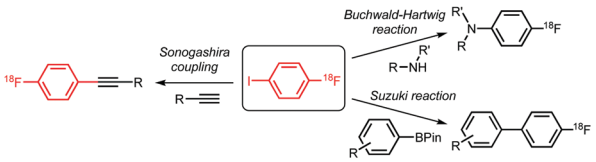
All three reported methods provide 4-[^{18}F]fluoroiodobenzene **402** in moderate to excellent radiochemical yields, thereby demonstrating the advantage of novel radiofluorination technology in the synthesis of building blocks. Because these methods are rather new, applications of 4-[^{18}F]fluoroiodobenzene are still scarce. Only 3 examples have been recently reported, each reporting a different type of metal catalysed cross-coupling (Scheme 81).

The first example is the synthesis of 2-amino-5-(4-[^{18}F]fluorophenyl)pent-4-ynoic acid ([^{18}F]FPhPa) **404**, a novel amino acid for the PET imaging of tumours.[266] The tracer was obtained *via* a Sonogashira coupling between alkyne **403** and 4-[^{18}F]fluoroiodobenzene **402** (Scheme 82). This publication shows that using 4-[^{18}F]fluoroiodobenzene as a building block, Sonogashira derived PET tracers to image amino acid transport can be produced in sufficient radiochemical yields without the use of additional protecting groups.

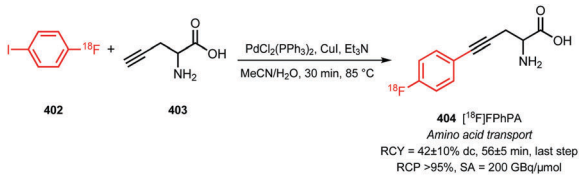
The second example is the synthesis of dopamine D_4 ligand [^{18}F]FAUC 316 (**408**). This tracer is synthesised in two steps from 4-[^{18}F]fluoroiodobenzene **402**, first by a Buchwald–Hartwig reaction of amine **405** and followed by a reductive amination



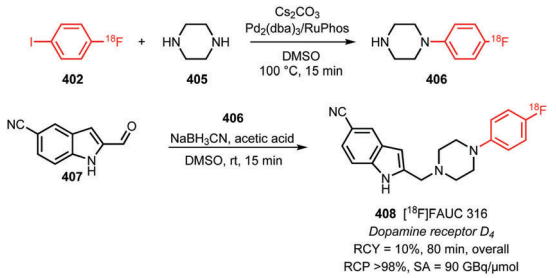
Scheme 80 Synthesis of 4-[^{18}F]fluoroiodobenzene.[20,265–268]



Scheme 81 Metal catalysed coupling reactions with 4-[^{18}F]fluoroiodobenzene.



Scheme 82 Synthesis of [^{18}F]FPhPA by Sonogashira coupling with 4-[^{18}F]fluoroiodobenzene.[266]



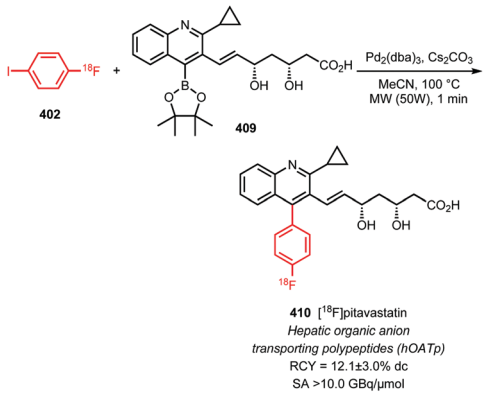
Scheme 83 Buildup synthesis of [^{18}F]FAUC 316.[262]

with aldehyde **407** (Scheme 83).[265] The low overall radiochemical yield of 10% and the long synthesis time of 80 minutes show the disadvantage and challenge of the multistep synthesis for PET tracers.

The last example is the synthesis of [^{18}F]pitavastatin **410**, which is prepared by Suzuki coupling between 4-[^{18}F]fluoroiodobenzene **402** and boronic acid pinacol ester **409** (Scheme 84).[268] A relatively low overall radiochemical yield (12% decay corrected) is also reported here.

In summary, the relatively low radiochemical yield of the cross-coupling reactions is most probably the main reasons that 4-[^{18}F]fluoroiodobenzene is not very often used for PET tracer development. The building block itself however can be prepared in high radiochemical yields.

3.2.2 Synthesis and application of 1-bromo-3-[^{18}F]fluorobenzene. A synthetic strategy towards building block 1-bromo-3-[^{18}F]fluorobenzene **412** has been developed by Yuang *et al.*, specifically for the synthesis of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor targeting PET tracer **414** (Scheme 85).[269]



Scheme 84 Synthesis of [^{18}F]pitavastatin.[268]

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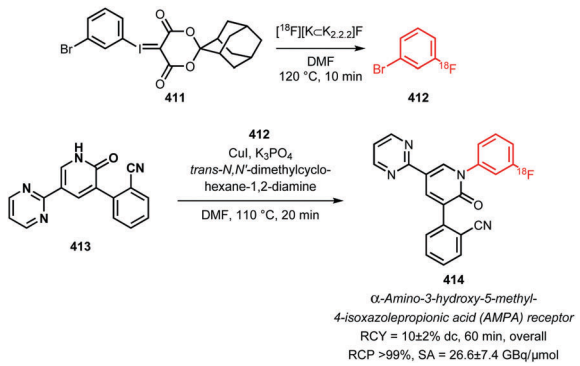
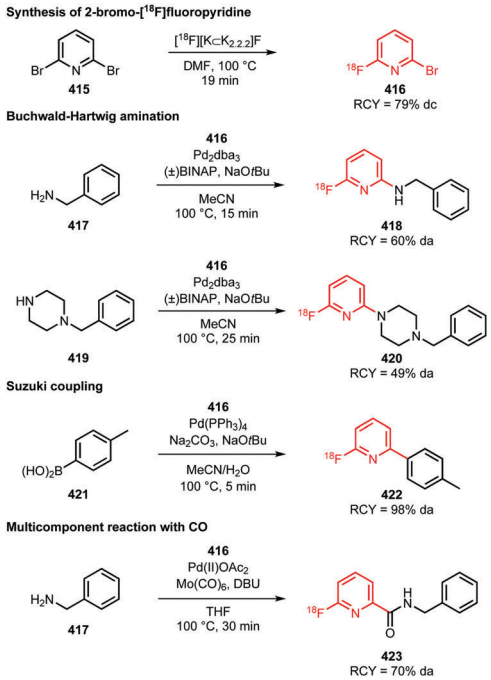


Scheme 85 Synthesis of AMPA receptor PET tracer **414** by Cu-mediated *N*-arylation with 1-bromo-3-[^{18}F]fluorobenzene.[269]

The fluorine-18 atom in 1-bromo-3-[^{18}F]fluorobenzene **412** is positioned at the 3-position from the bromine atom and is thereby challenging to synthesise. Yuang *et al.* however did succeed in the synthesis of this building block in a radiochemical yield of 72 ± 3% (analytically determined) by radiofluorination of precursor **411**.

In the same reaction vessel, 1-bromo-3-[^{18}F]fluorobenzene **412** was further reacted by copper-mediated *N*-arylation resulting in the desired PET tracer **414** in an overall radiochemical yield of 10 ± 2% (dc, calculated from starting amount of [^{18}F]fluoride) in a short 60 min synthesis time with an excellent radiochemical purity and good specific activity.

Thereby, Yuan *et al.* show that novel late-stage fluorination methods, in this case the fluorine-18 labelling of spirocyclic iodonium ylides, can be effectively used for the synthesis of aromatic fluorine-18 labelled building blocks which cannot be made by conventional nucleophilic aromatic substitution due to unfavourable electronic properties.



Scheme 86 Synthesis and application of 2-bromo-6-[^{18}F]fluoropyridine.[271]

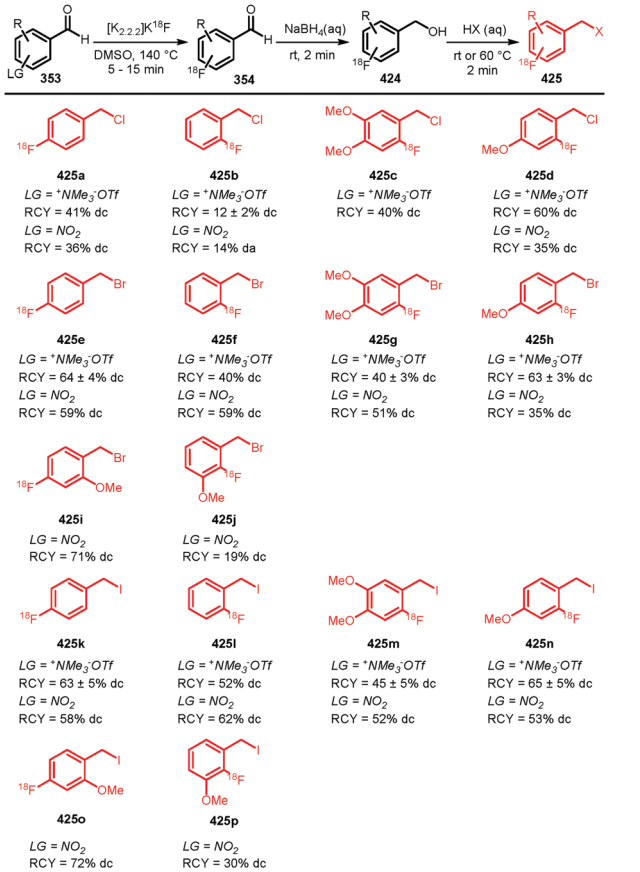
3.2.3 Synthesis and application of 2-bromo-6-[^{18}F]fluoropyridine. 2-Bromo-6-[^{18}F]fluoropyridine **416** can be synthesised from commercially available 2,6-dibromopyridine in radiochemical yields up to 79% (dc), since the nitrogen in the pyridine activates the radiolabelling position (Scheme 86).[270,271]

Betts *et al.* investigated the reaction of this building block with model substrates in the Buchwald–Hartwig amination, Suzuki coupling and in a multicomponent reaction with CO and benzylamine (Scheme 86). The application in the synthesis of PET tracers has not yet been demonstrated, these first results are however promising.

3.2.4 Synthesis and application of [^{18}F]fluorobenzyl halides

3.2.4.1 Synthesis of [^{18}F]fluorobenzyl halides. Benzyl halides are generally very useful in organic chemistry due to their versatile use in alkylation reactions at oxygen, nitrogen, sulfur, phosphor or carbon. It is therefore not surprising that multiple methods have been developed to synthesise [^{18}F]fluorobenzyl halides.[272,273]

The most commonly described approach towards 4-[^{18}F]fluorobenzyl halides and 2-[^{18}F]fluorobenzyl halides is *via* a three step procedure, starting with the synthesis of [^{18}F]fluorobenzaldehyde, followed by a reduction and finally the halogenation of the benzylalcohol. Lemaire *et al.* recently optimised this synthetic strategy towards various 4- and 2-[^{18}F]fluorobenzyl halides (Scheme 87).[244]



Scheme 87 Conventional synthesis of 2- and 4-[^{18}F]fluorobenzyl halides.[244]

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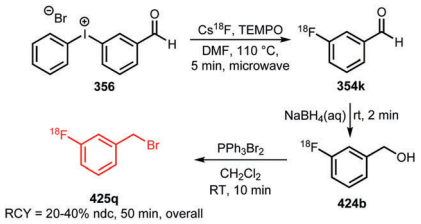


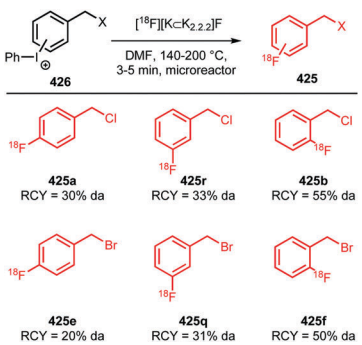
Scheme 88 Three step strategy towards 3-[^{18}F]fluorobenzyl bromide.[240]

Synthesis of 3-[^{18}F]fluorobenzyl halides using this strategy is almost impossible due to the electron rich properties of the aromatic ring as a consequence of substitution at the 3-position. Therefore, Basuli *et al.* synthesised 3-[^{18}F]fluorobenzyl bromide from iodonium salt benzaldehyde precursor **356** (Scheme 88).[243]

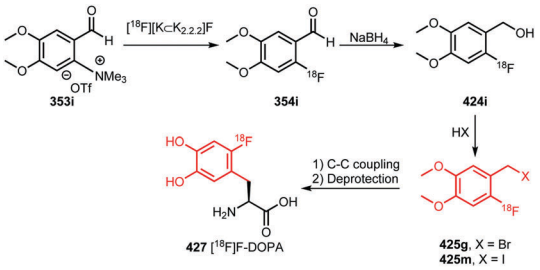
For both three-step strategies, moderate radiochemical yields of the 2-, 3- and 4-[^{18}F]fluorobenzyl halides could be obtained. The multi-step nature however makes this method rather complex and therefore challenging to automate and sensitive to failures.

Because not only electron deficient, but also electron neutral and electron rich iodonium salt precursors can be labelled with [^{18}F]fluoride, Chun *et al.* investigated a direct one-step labelling towards 2-, 3- and 4-[^{18}F]fluorobenzyl halides using iodonium salt precursors (Scheme 89).[34] Using this strategy, the desired [^{18}F]fluorobenzyl halides could be generated with radiochemical yields up to 55% (analytically determined) in just one synthesis step.

3.2.4.2 Application of [^{18}F]fluorobenzyl halides in the synthesis of [^{18}F]F-DOPA. Since 1991, [^{18}F]fluorobenzyl halides have been used as useful building blocks in the synthesis of [^{18}F]F-DOPA **427** (Scheme 90).[274] Due to the electron rich properties of the aromatic ring, [^{18}F]F-DOPA can only be synthesised by direct labelling *via* electrophilic fluorination using [^{18}F]F_2 gas. Drawbacks of this method is a relatively low yield (up to 5 GBq) and low specific activity, typically less than 1 GBq μmol^{-1}.[275–279] To overcome these issues, a method using a building block approach was developed, where fluorine-18 was incorporated *via* a nucleophilic substitution reaction in the first reaction of a five step total synthesis: (1) reaction of trimethylammonium benzaldehyde precursor **353i** with [^{18}F]fluoride towards [^{18}F]benzaldehyde **354i**, (2) reduction to [^{18}F]fluorobenzylalcohol **424i**, (3)



Scheme 89 Preparation of [^{18}F]fluorobenzylhalides in one step from diaryliodonium precursors.[34]



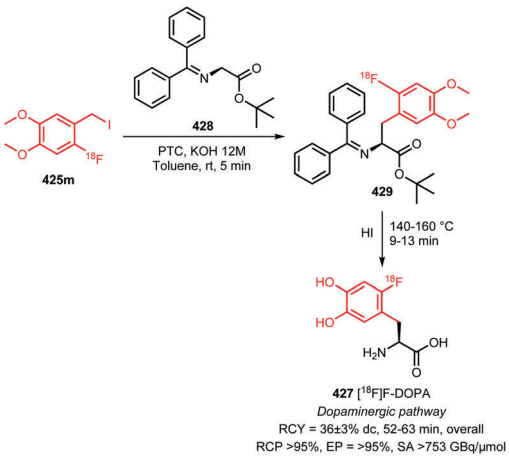
Scheme 90 Synthesis of [^{18}F]F-DOPA *via* multistep approach using a [^{18}F]fluorobenzyl halide as a building block.[274,280–288]

halogenation towards benzyl halide **425g** or **425m** and (4) chiral C–C coupling using a chiral catalyst and (5) deprotection to yield [^{18}F]F-DOPA **427** (Scheme 90).[274,280–288]

For the enantioselective C–C coupling reaction, Lemaire *et al.* developed a method in 2004, where [^{18}F]fluorobenzyl halide (bromide or iodide) is coupled with *N*-(diphenylmethylene)glycine *tert*-butyl ester **428** under basic conditions and in the presence of a phase transfer catalyst (PTC) (Scheme 91).[280] This approach yielded [^{18}F]F-DOPA **427** in an enantiomeric excess of >95%, an overall radiochemical yield of 25–30% (dc) and a specific activity of >100 GBq μmol^{-1} in 100 minutes.

Recently, Lemaire *et al.* optimised and automated this method by studying various reaction conditions and various new PTCs for the C–C coupling.[287,288] [^{18}F]F-DOPA was synthesised using a FASTlab synthesiser in an improved radiochemical yield of 36% ± 3% (dc) and >45 GBq at the end of synthesis, an enantiomeric excess of >95% and a synthesis time of 52–63 min (Scheme 91). In a similar fashion, 2-[^{18}F]fluoro-L-tyrosine was synthesized by Libert *et al.* in an overall radiochemical yield of 50.5 ± 2.7% (dc).[287,288]

Pretze *et al.* evaluated the [^{18}F]F-DOPA synthesis procedure, however was not able to synthesize [^{18}F]F-DOPA in the same radiochemical yield.[289] It was determined that this was caused by a combination of factors: (1) decomposition of the trimethyl ammonium triflate group of the precursor molecule into



Scheme 91 C–C coupling and hydrolysis of a [^{18}F]fluorobenzyl halide with *N*-(diphenylmethylene)glycine *tert*-butyl ester and a phase transfer catalyst (PTC).[280,287,288]

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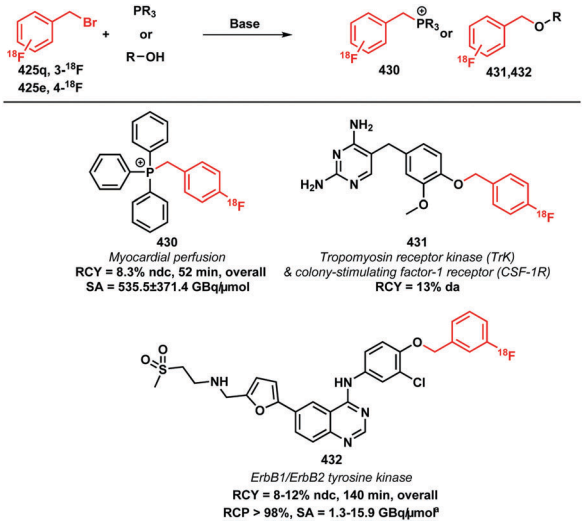
4-aminobenzaldehyde; (2) problematic automation due to formation of precipitates during the C–C coupling reaction.

Because of these drawbacks, Pretze *et al.* investigated a late-stage fluorination approach, based on the radiofluorination of a nitrobenzaldehyde precursor and conversion of the aldehyde functional group to a phenol by Baeyer–Villiger oxidation. With this method, [^{18}F]F-DOPA was synthesized in a radiochemical yield of 20 ± 1% (dc).[289]

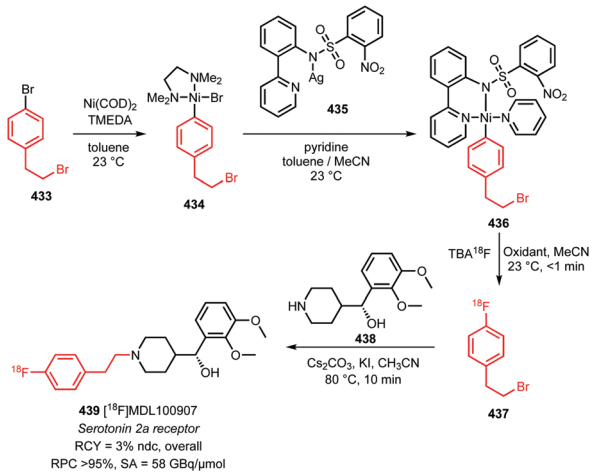
3.2.4.3 Application of [^{18}F]fluorobenzyl halides in alkylation of phospines and benzyl alcohols. Three new tracers have been synthesised using [^{18}F]fluorobenzyl halides since 2010 (Scheme 92).[290–292] Only [^{18}F]fluorobenzyl bromides were used, probably due to a balance between a high reactivity as an alkylating agent for the alkylation of alcohols and phoshines, and a good stability.

Tropomyosin receptor kinase and colony-stimulating factor-1 receptor tracer **431** (Scheme 92) was prepared *via O*-alkylation of the corresponding hydroxyl precursor with 4-[^{18}F]fluorobenzyl bromide **425e**.[292] The yield as measured by HPLC was found to be 13%. Together with the low radiochemical yield for the three step synthesis to obtain 4-[^{18}F]fluorobenzyl bromide of 25–30% (ndc), the main conclusion of Bernard-Gauthier *et al.* was that another synthesis route should be developed for this tracer. They suggested the use of diaryliodonium salts as a precursor for either 4-[^{18}F]fluorobenzyl bromide synthesis, or even for a direct late-stage labelling approach towards **431**.

The myocardial perfusion tracer 4-[^{18}F]fluorobenzyltriphenylphosphonium ion **430**, as reported by Ravert *et al.*, was synthesised *via* microwave assisted alkylation using 4-[^{18}F]fluorobenzyl bromide (Scheme 92).[291] The overall radiochemical yield was 8.3% (ndc). Also in this case, a multistep procedure towards 4-[^{18}F]fluorobenzaldehyde was used. However by performing all steps in one pot and by using microwave irradiation, the total synthesis time could be kept at 52 minutes.



Scheme 92 PET tracers synthesised using [^{18}F]fluorobenzyl bromide as a building block. [a] The specific activity is low due to the low amount of starting activity of [^{18}F]fluoride.[290–292]



Scheme 93 Preparation of serotonin 2a receptor tracer [^{18}F]MDL100907 using 4-[^{18}F]fluorophenethyl bromide.[27]

In the synthesis of the ErB1/ErB2 tracer [^{18}F]lapatinib **432**, 3-[^{18}F]fluorobenzyl bromide **425q** was synthesised in a three step procedure, using an iodonium salt precursor for the synthesis of 3-[^{18}F]fluorobenzaldehyde (Scheme 88) in an overall radiochemical yield of 12% (ndc).[290]

In summary, [^{18}F]fluorobenzyl halides have proven to be successful in the synthesis of [^{18}F]F-DOPA. In the synthesis of new PET tracers however only relatively low radiochemical yields were obtained. It is not clear yet what is causing these relatively low radiochemical yields.

3.2.5 Synthesis and application of 4-[^{18}F]fluorophenethyl bromide. The synthesis of the building block 4-[^{18}F]fluorophenethyl bromide **437** was developed by Ren *et al.* and was applied in the synthesis of serotonin 2a receptor PET tracer [^{18}F]MDL100907 **439** (Scheme 93).[27] This building block cannot be synthesised in one step using conventional nucleophilic aromatic fluorination techniques, due to the high electron density of the aromatic ring. However, 4-[^{18}F]fluorophenethyl bromide **437** was prepared recently in one step by radiofluorination of Ni-precursor **436**.[26] Immediately after formation, 4-[^{18}F]fluorophenethyl bromide **437** was reacted with amine **438** to yield [^{18}F]MDL100907 **439**.

The overall radiochemical yield for the synthesis of [^{18}F]MDL100907 is low (2.2%, ndc), which can be explained by a combination of a low radiofluorination yield and a low alkylation yield. Irrespective of the synthesis results, [^{18}F]fluorophenylethyl bromide is still an attractive building block. More research is required towards the synthesis of [^{18}F]fluorophenylethyl bromide to make this method useful for high yield tracer synthesis.

3.3 [^{18}F]Fluorophenyl amines

Various PET tracers have been synthesised using fluorine-18 labelled aromatic amine containing building blocks since 2010. Their high versatility and selectivity in reactions with electrophiles including acid chlorides, sulfonyl halides, Michael acceptors and various others make them attractive building blocks.

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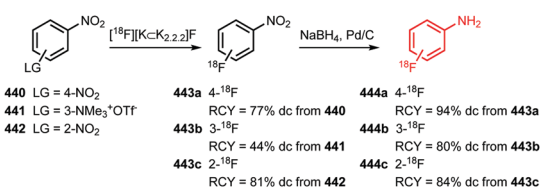
In this chapter, the synthesis and application of [^{18}F]fluoroanilines (Section 2.3.1), [^{18}F]fluorobenzylamines (Section 2.3.2), [^{18}F]fluorophenylhydrazides (Section 2.3.3) and [^{18}F]phenethylamines (Section 2.3.4) will be described.

3.3.1 Synthesis and application of [^{18}F]fluoroanilines. Both 1,4-dinitrobenzene and 1,2-dinitrobenzene are highly activated for nucleophilic aromatic substitution due to the fact that the nitro functional group is very strongly electron withdrawing and also an excellent leaving group. Starting from these precursors, 4-[^{18}F]fluoronitrobenzene and 2-[^{18}F]fluoronitrobenzene can be formed in radiochemical yields of >70% (Scheme 94). The remaining nitro group can be reduced to an amine in >80% radiochemical yield, giving 2- or 4-[^{18}F]fluoroaniline in high overall radiochemical yields.[202,293–297]

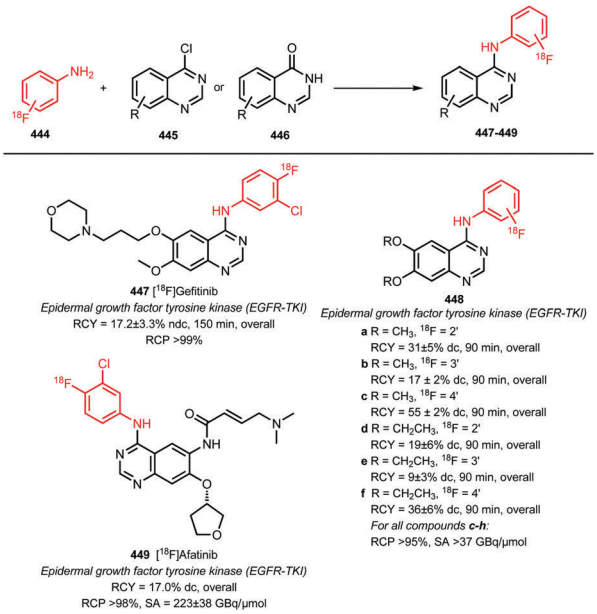
Radiofluorination of 1,3-dinitrobenzene gives 3-[^{18}F]fluoronitrobenzene, however in only low radiochemical yields due to the increased electron density of the aromatic ring due to substitution of the 3-position. The yield can be increased if trimethylammonium precursor **441** is used as a precursor, because the trimethylammonium group is a better leaving group then the nitro group (Scheme 94).[295,298,299]

One group of compounds in which [^{18}F]fluoroanilines as reagents for PET tracers have proven to be useful are the epidermal growth factor receptor (EGFR) kinase inhibitors (Scheme 95).[295,298,299] The anilinoquinazoline structure can be built-up by the reaction of 4-[^{18}F]fluoroanilines with chloroquinazoline **445** or cyclic amide **446**, in which, for the latter, a strong base (1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)) and a coupling reagent (*O*-benzo-triazole-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (BOP)) are required. Using this pathway Gefitinib **447** could be synthesised in an overall radiochemical yield of 17.2 ± 3.3% (dc) and Afatinib **449** in an overall radiochemical yield of 17.0 ± 2.5% (dc).[298,299] Vasdev *et al.* explored this strategy by synthesizing a library of anilinoquinazolines **448a–f**, showing that these tracers can be obtained in 9–55% overall radiochemical yield (dc).[295]

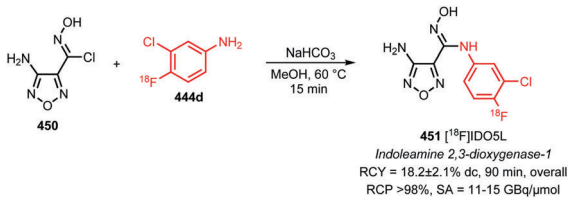
In a similar approach, Huang *et al.* synthesised the potential indoleamine 2,3-dioxygenase-1 tracer [^{18}F]IDO5L **451** in a radiochemical yield comparable to the EGFR inhibitors (Scheme 96).[297] A direct ^{18}F-radiolabelling towards **451** using the corresponding trimethylammonium precursor did not yield **451**, due to decomposition of the precursor under the relatively harsh (120 °C, 30 min) reaction conditions. The coupling reaction with 3-chloro-4-[^{18}F]fluoroaniline, however, only required a temperature of 60 °C, showing a clear benefit of the building block approach.



Scheme 94 Preparation of [^{18}F]fluoroanilines in a two-step fluorine-18 labelling and nitro reduction procedure.[202,293–297]

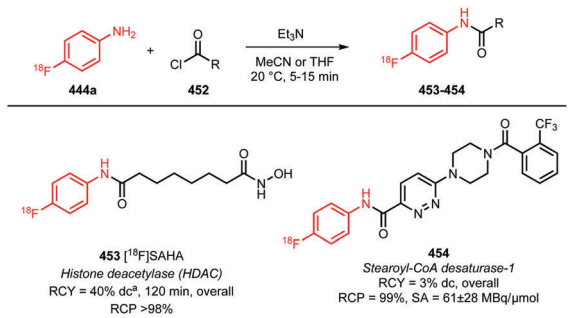


Scheme 95 Synthesis of PET tracers for the EGFR-TKI by reaction of chloroquinazolines or cyclic amides with [^{18}F]fluoroanilines.[295,298,299]



Scheme 96 Synthesis of indolamine 2,3-dioxygenase-1 tracer [^{18}F]IDO5L using 3-chloro-4-[^{18}F]fluoroaniline.[297]

4-[^{18}F]Fluoroaniline has been used for the synthesis of amides by reaction with acid chlorides. The first reported tracer is [^{18}F]SAHA **453** (Scheme 97).[296] The authors reported various efforts to introduce fluorine-18 by late-stage fluorination, but all approaches were unsuccessful. However, with the use of 4-[^{18}F]fluoroaniline as building block they were successful, [^{18}F]SAHA was obtained in a good overall 40% decay-corrected radiochemical yield. Considering this excellent yield for a



Scheme 97 PET tracer synthesis *via* amide formation with 4-[^{18}F]fluoroaniline; [a] Includes formation of the hydroxamide from the methyl ester after the building block is introduced.[202,296]

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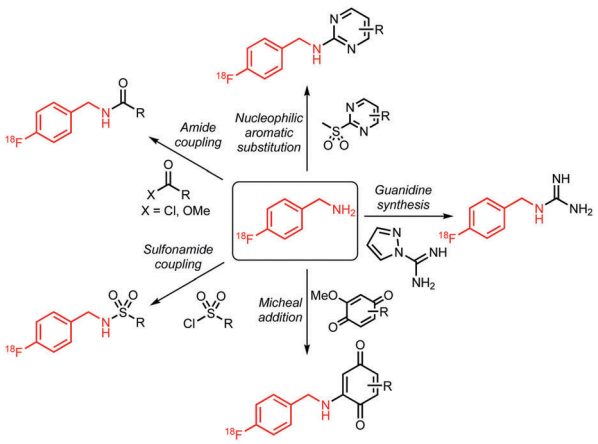
4-step synthesis, the question arises whether other strategies are actually needed at all. Stearoyl-CoA tracer **454** was also synthesised by reaction of 4-[^{18}F]fluoroaniline with an acid chloride.[202] However, this time only an overall radiochemical yield of 3% (dc) was obtained. The low yield was attributed by the authors to the poor reactivity of 4-[^{18}F]fluoroaniline, since the same acid chloride precursor gave a radiochemical yield of 21% (dc) with the aliphatic 3-[^{18}F]fluoropropylamine.

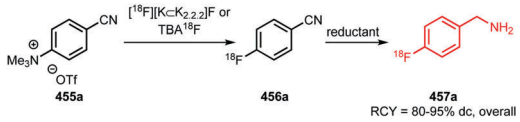
In summary, [^{18}F]fluoroanilines have been successfully applied in the synthesis of multiple PET tracers. The major challenges in using this building block however are in the relative low radiochemical yield caused by the required two step synthesis to produce the building block and the poor nucleophilicity of the aniline.

3.3.2 Synthesis and application of [^{18}F]fluorobenzylamines. [^{18}F]Fluorobenzylamines are versatile building blocks, because they act as a nucleophile in many types of reactions (Scheme 98). Although not very commonly used, [^{18}F]fluorobenzyl amine has recently been used for (sulfon)amide coupling (Section 3.3.2.2), Michael addition (Section 3.3.2.2) nucleophilic substitution on (methylsulfonyl)-pyrimidines (Section 3.3.2.3) and guanidine synthesis (Section 3.3.2.4).[300–305]

3.3.2.1 Synthesis of [^{18}F]fluorobenzylamines. [^{18}F]Fluorobenzylamines are generally synthesised from cyanophenyl derivatives, since the cyano functional group provides an electron withdrawing character for a nucleophilic aromatic substitution of [^{18}F]fluoride on 4-*N*,*N*,*N*-trimethylammonium-benzonitrile triflate **455a** (Scheme 99).[300–304,306,307] After formation of [^{18}F]fluorobenzonitrile, the cyano group is reduced to an amine. Using this synthetic pathway, 4-[^{18}F]fluorobenzylamine **457a** can be obtained in a radiochemical yield of 80–95%.



Scheme 98 Recent examples of reactions with [^{18}F]fluorobenzylamines.



Scheme 99 General synthesis route towards [^{18}F]fluorobenzylamines.[300–304,306,307]

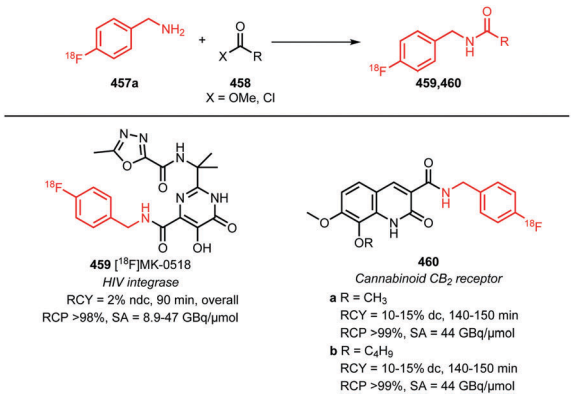
For the reduction, various reducing agents have been used including $LiAlH_4$, borane dimethyl sulfide and mixtures of sodium borohydride with transition metal salts.[300–304,307] Both $LiAlH_4$ and borane dimethyl sulfide resulted in high radiochemical yields of [^{18}F]fluorobenzylamines, but are, for practical reasons, less suited for automated synthesis procedures. Firstly, due to the highly anhydrous reaction conditions which are required and are difficult to achieve using an automated synthesis unit. Secondly, due to the formation of aluminium salts in the case of $LiAlH_4$, which can lead to clogging of transfer lines and filters.

To prevent the issues with the automated synthesis of [^{18}F]benzylamines, Koslowsky *et al.* and Way *et al.* developed a new method for the reduction step. By performing the reduction on a cartridge containing borohydride exchange resin (BER), 4-[^{18}F]fluorobenzylamine could be produced in a synthesis unit in $>85\%$ decay corrected radiochemical yield in 60 minutes starting from [^{18}F]fluoride.[303,307]

3.3.2.2 Application of [^{18}F]fluorobenzylamine in (sulfon)amide coupling reactions. Both human immunodeficiency virus 1 integrase (HIV-1 IN) inhibitor **459** and CB_2 receptor ligands **460a** and **460b** have been synthesised utilizing amide coupling reaction of a methyl ester or acid chloride precursor with 4-[^{18}F]fluorobenzylamine (Scheme 100).[300,302] In the case of the HIV-1 IN inhibitor **459**, the labelled product was obtained in an overall radiochemical yield of 2% (ndc) in 90 minutes synthesis time and in the case of CB_2 receptor ligands, **460a** and **460b** were obtained in an overall radiochemical yield of 15% (dc) in 140 minutes.

4-[^{18}F]Fluorobenzylamine was used for the synthesis of a sulfonamide, *via* a reaction with sulfonyl chloride **461**, to obtain COX-2 tracer **462** in a radiochemical yield of 20% (dc) in 85 min, calculated from 4-[^{18}F]fluorobenzylamine (Scheme 101).[305]

3.3.2.3 Application of [^{18}F]fluorobenzylamine in Michael addition reactions. The natural product geldanamycin **463** is a potent heatshock protein-90 inhibitor which contains a methoxy quinone moiety. The methoxy quinone can undergo a Michael addition reaction with various primary amines, such as [^{18}F]fluorobenzylamine, to obtain fluorine-18 labelled derivatives (Scheme 102).



Scheme 100 Amide coupling reactions with [^{18}F]fluorobenzylamine.[300,302]

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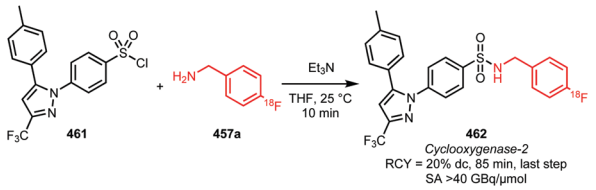
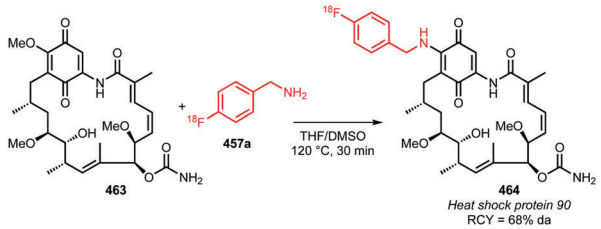


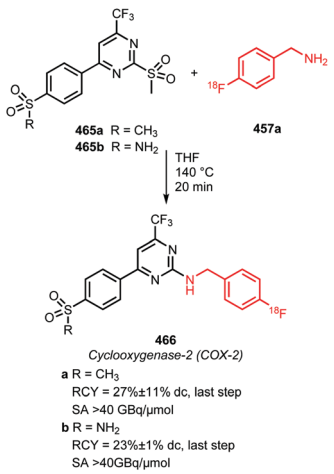
Scheme 101 Coupling of [^{18}F]fluorobenzylamine with sulfonyl chloride **461**.[305]



Scheme 102 Synthesis of [^{18}F]geldanamycin *via* Michael addition using [^{18}F]4-fluorobenzylamine.[303]

The coupling of 4-[^{18}F]fluorobenzylamine with geldanamycin **463** was investigated by Way *et al.*[303] A radiochemical yield of 68% (determined by radio-TLC) after 30 minutes at 120 °C was reported. The labelled product was not isolated, thus no overall radiochemical yield and synthesis time could be given. However, since the new $NaBH_4/NiCl_2$ reduction methodology was used to synthesise 4-[^{18}F]fluorobenzylamine, decent radiochemical yields can be expected despite the multistep procedure.

3.3.2.4 Application of [^{18}F]fluorobenzylamine in nucleophilic-aromatic substitution on (methylsulfonyl)-pyrimidines. Tietz *et al.* reported the synthesis of two COX-2 inhibitors by the nucleophilic aromatic substitution of 4-[^{18}F]fluorobenzylamine on the (methylsulfonyl)pyrimidine moiety of two precursors (Scheme 103).[301] Radiochemical yields of the coupling reactions were moderate, 27 ± 11% (dc) for product **466a** and 23 ± 1% for product **466b**.



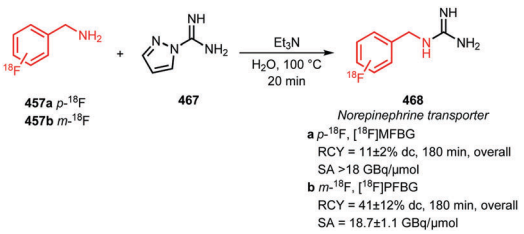
Scheme 103 Synthesis of COX-2 inhibitors by nucleophilic aromatic substitution with 4-[^{18}F]fluorobenzylamine.[301]

3.3.2.5 Application of [^{18}F]fluorobenzylamine in guanidine synthesis. The first syntheses of the tracers *para*-[^{18}F]fluorobenzylguanidine [^{18}F]PFBG **468a** and *meta*-[^{18}F]fluorobenzylguanidine [^{18}F]MFBG **468b**, using [^{18}F]fluorobenzylamines, were reported by Garg *et al.* in 1994 as an alternative to the commonly used cardiology and oncology tracer [^{123}I]MIBG.[306] Following this publication, two articles were published in 1996 and 2002 in which [^{18}F]PFBG was investigated in rat and dog.[308,309] It took until 2014, when Zhang *et al.* showed a renewed interest in [^{18}F]MFBG and [^{18}F]PFBG.[304] For the synthesis of [^{18}F]MFBG and [^{18}F]PFBG, the route used was similar to that of Garg *et al.* (Scheme 104). A few modifications to the radiolabelling were made to improve the overall radiochemical yields, in particular by using lower reaction temperatures and shorter reaction times for the [^{18}F]fluorobenzonitrile synthesis and by using the more reactive 1*H*-pyrazole-1-carboximidamide **467** instead of 2-methyl-2-thiopseudourea sulfate for the guanidine formation.

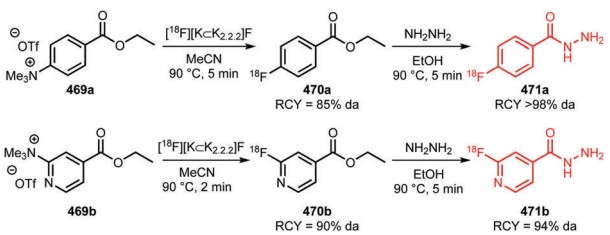
The overall radiochemical yields using the improved synthesis were 11 ± 2% (dc) for [^{18}F]MFBG and 41 ± 12% (dc) for [^{18}F]PFBG. The lower overall radiochemical yield for [^{18}F]MFBG was mainly due to the low radiochemical yield of the synthesis of 3-[^{18}F]fluorobenzonitrile of 21 ± 5% where 4-[^{18}F]fluorobenzonitrile could be synthesised in 75 ± 7%.

In summary, as can be seen by the examples mentioned in Sections 3.3.2.1 to 3.3.2.4, [^{18}F]fluorobenzylamine is a useful building block which was successfully applied in the synthesis of several PET tracers. Nevertheless, the overall radiochemical yields from PET tracer synthesis performed with [^{18}F]fluorobenzylamine are in general moderate to low and the reactions times are quite long, which challenges the use of this methodology.

3.3.3 Synthesis and application of [^{18}F]fluorobenzohydrazides. The [^{18}F]fluorobenzohydrazide building blocks **471a** and **471b** have been developed by Al Jammaz *et al* (Scheme 105).[305] They were synthesised in a two-step procedure starting with the synthesis of ethyl 4-[^{18}F]fluorobenzoate **470a** and ethyl 2-[^{18}F]fluoro-4-pyridinecarboxylate **470b**. The esters were subsequently converted to



Scheme 104 Synthesis of [^{18}F]MFBG and [^{18}F]PFBG.[304]



Scheme 105 Synthesis of [^{18}F]fluorobenzohydrazide building blocks.[310]

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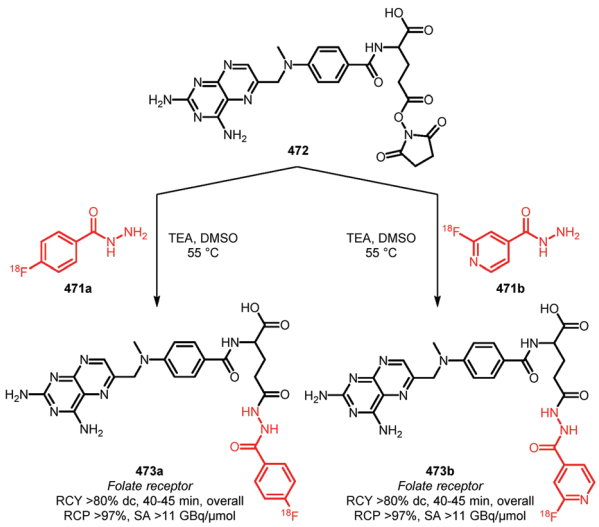


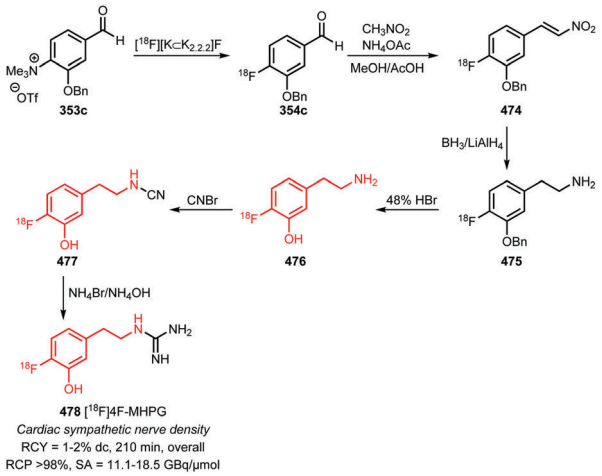
Scheme 106 Fluorine-18 labelling of methotrexate using [^{18}F]fluorobenzohydrazide building blocks.[311]

[^{18}F]fluorobenzohydrazides **471a** and **471b** by reacting with hydrazine hydrate.[310,311]

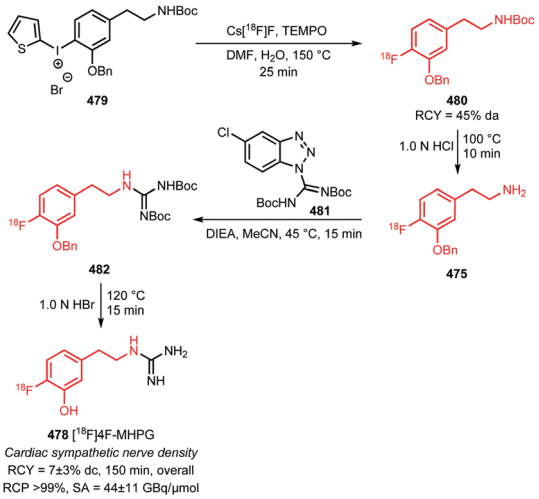
These building blocks have recently been applied in the synthesis of fluorine-18 labelled derivatives of methotrexate (Scheme 106).[311] In this synthesis, the activated *N*-succinimidyl-methotrexate carboxylate **472** was reacted with [^{18}F]fluorobenzohydrazide **471a** or **471b** under mild conditions to obtain the methotrexate derivatives **473a** and **473b**, labelled with fluorine-18. The overall decay corrected radiochemical yields, starting from [^{18}F]fluoride, were $>80\%$ with a synthesis time of 40–45 minutes, which is excellent for a multistep procedure. Furthermore, the products were obtained in $>97\%$ radiochemical purity and a specific activity of 11 GBq μmol^{-1} without the need of a HPLC purification.

The multistep procedure towards fluorine-18 labelled methotrexate is superior to other reported methods in which the PET tracers are synthesised in one step by direct nucleophilic aromatic substitution, because these methods only provide fluorine-18 labelled methotrexate derivatives in overall radiochemical yields of less than 10%.[312,313]

3.3.4 Synthesis and application of [^{18}F]fluorophenethylamines. Since 2010, there have been two PET tracers published containing the fluorophenethyl moiety.[314–316] In the synthesis of the guanidine PET tracer **478**, described by Jang *et al.*, a three-step procedure for the synthesis of [^{18}F]fluorophenethylamine building block **476** has been reported (Scheme 107).[314] First, [^{18}F]fluorobenzaldehyde **354c** is synthesised by nucleophilic aromatic substitution of trimethylammonium precursor **353c** with [^{18}F]fluoride. Next, [^{18}F]fluorobenzaldehyde **354c** is reacted with nitromethane in a nitroaldol condensation to nitroalkene **474**. After reduction and benzyl deprotection, phenethylamine building block **476** is obtained. This building block is reacted with cyanogen bromide and subsequently treated with NH_4Br/NH_4OH, resulting in PET tracer **478**. The overall radiochemical yield over all 6 steps was 1–2% (dc) and the overall synthesis time was 210 minutes.



Scheme 107 Synthesis of 4-[^{18}F]fluoro-3-hydroxyphenylethylguaninidine in six steps.[314]



Scheme 108 Synthesis of 4-[^{18}F]fluoro-3-hydroxyphenylethylguaninidine in four steps.[315]

To improve the overall synthesis time and radiochemical yield, Jang *et al.* reduced the number of reaction steps to a total of four steps by first synthesizing Boc/benzyl protected phenethylamine building block **480** in one step by ^{18}F-fluorination of iodonium salt precursor **479** (Scheme 108).[315] Subsequently the Boc protecting group was removed and the primary amine reacted with reagent **481** to form guanidine **482**. In the last step, all remaining protecting groups were removed to obtain PET tracer **478**. This time, an increased overall radiochemical yield of $7 \pm 3\%$ (dc) was obtained and the synthesis time was decreased to 150 min.

The second PET tracer with a fluorophenethyl moiety is neuronal nitric oxide synthase (nNOS) tracer **488**. This tracer was obtained with 3-[^{18}F]fluorophenethyl amine **485** (Scheme 109),[316] which was synthesised in two steps by radiofluorination of Boc-protected iodonium ylide precursor **483** and subsequent removal of the Boc protecting group with HCl in dioxane. 3-[^{18}F]Fluorophenethylamine was subsequently coupled to aldehyde **486** by reductive

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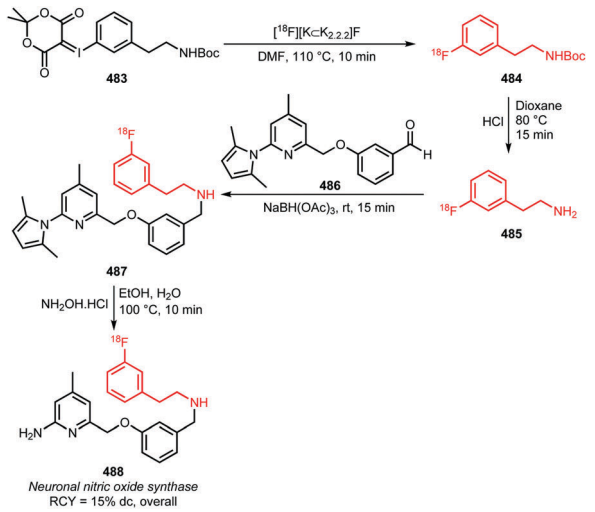
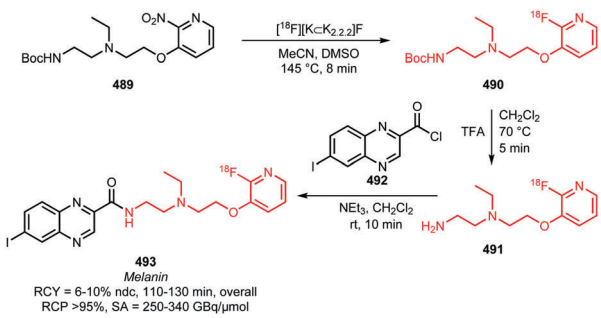


Scheme 109 Building block approach towards neuronal nitric oxide synthase tracer **488**.[316]

amination, followed by deprotection of the primary amine to obtain **488**. Using this strategy, PET tracer **488** could be obtained in an overall radiochemical yield of 15% (dc). This procedure was not further optimised due to issues with reproducibility of the reductive amination step and because promising results were obtained with the novel late-stage radiofluorination of boronic acid pinacol esters (Table 1, entry 9).

3.3.5 Synthesis and application of *N*-(2-aminoethyl)-*N*-ethyl-*N*-[2-(2-[^{18}F]fluoropyridin-3-yloxy)ethyl]-amine. Amine building block **491** was specifically developed by Maisonial *et al.* for the synthesis of melanin targeting PET tracer **493** (Scheme 110).[317] A direct fluorine-18 labelling approach was initially envisaged by Maisonial *et al.*, however was not explored due to a lack of reports about direct radiofluorination in these type of structures. Therefore, a three step approach, as shown in Scheme 110, was pursued as alternative. Nitro precursor **489** was reacted to **490** in 20–40% (dc) radiochemical yield. Deprotection resulted in amine **491** and subsequent coupling with acid chloride **492** yielded the product in an overall radiochemical yield (dc) of 6–10% and total synthesis time of 110–130 minutes.



Scheme 110 Multistep radiosynthesis of fluorine-18 labelled melanoma PET tracer **493**.[317]

3.4 [^{18}F]Fluorobenzoic acid & [^{18}F]fluorobenzoic acid esters

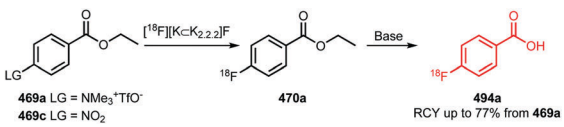
[^{18}F]Fluorobenzoic acids and [^{18}F]fluorobenzoic acid esters are often applied in reactions with amines to form amides. Activated esters are either formed *in situ* from [^{18}F]fluorobenzoic acid (Section 3.4.1), or the active esters are isolated before use, as is the case with [^{18}F]SFB (Section 3.4.2) and [^{18}F]6-fluoronicotinic acid 2,3,5,6-tetrafluorophenyl ester ([^{18}F]FPy-TFP, Section 3.4.3).

3.4.1 Synthesis and application of 4-[^{18}F]fluorobenzoic acid. 4-[^{18}F]Fluorobenzoic acid is synthesised *via* nucleophilic aromatic substitution with [^{18}F]fluoride on either ethyl 4-nitrobenzoate **469c** or (4-ethoxycarbonylphenyl)-trimethylammonium triflate **469a**, followed by basic hydrolysis of the ethyl ester using tetramethylammonium hydroxide or sodium hydroxide and purification by SPE (Scheme 111).[163,318,319]

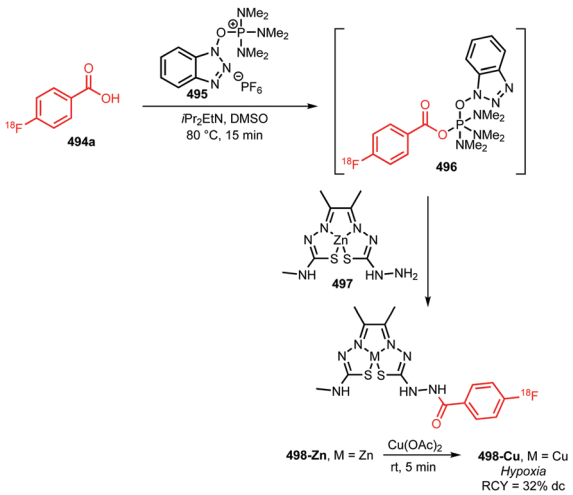
In these recent articles, no radiochemical yields of the obtained 4-[^{18}F]fluorobenzoic acid are mentioned, however, in publications from before 2010, radiochemical yields up to 77% are described when started from trimethylammonium triflate precursor **469a**.[320]

Various coupling reagents can be used to activate benzoic acid for nucleophilic substitution. Caroll *et al.* used BOP **495** together with *N*,*N*-diisopropylethylamine as a base to couple [^{18}F]4-fluorobenzoic acid to hydrazine derivative **497**, followed by a Cu for Zn exchange resulting in hypoxia tracer bis(thiosemicarbazonate) complex **498-Cu** in 32% radiochemical yield, starting from 4-[^{18}F]fluorobenzoic acid (Scheme 112).[163]

Another coupling agent to activate 4-[^{18}F]fluorobenzoic acid, *N*,*N*′-dicyclohexylcarbodiimide (DCC) **499**, is applied by Ackermann *et al.* for the synthesis of fluorine-18 labelled naphthoquinone



Scheme 111 Synthesis of 4-[^{18}F]fluorobenzoic acid.[163,318,319]



Scheme 112 Activation of 4-[^{18}F]fluorobenzoic acid with BOP and coupling to hydrazine derivative **497**.[163]

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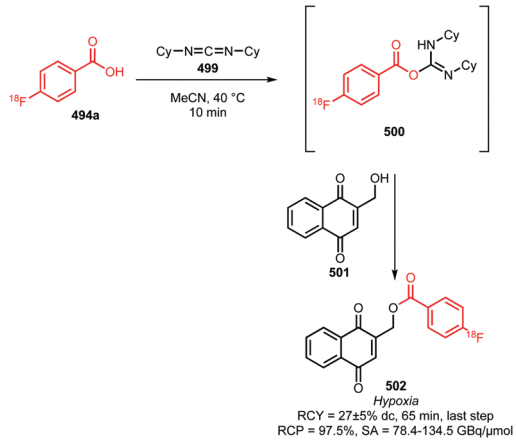


Scheme 113 Activation of 4-[^{18}F]fluorobenzoic acid with DCC and coupling to alcohol **501**.[318]

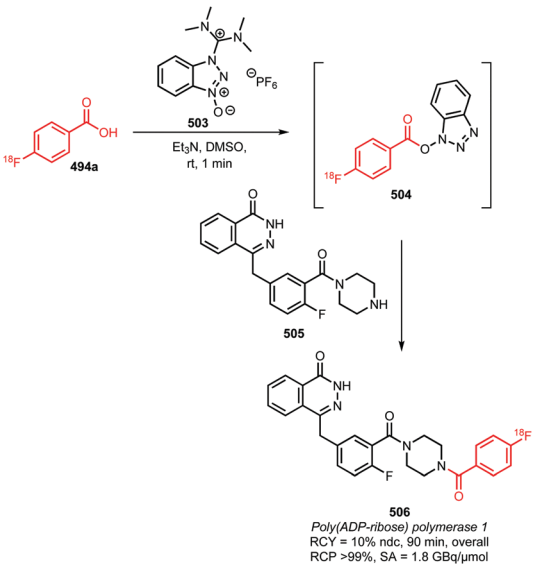
as a PET tracer for hypoxia (Scheme 113).[318] This approach resulted in the desired labelled compound **502** in a moderate radiochemical yield of 27 ± 5% starting from 4-[^{18}F]fluorobenzoic acid, showing that DCC can be used efficiently as reagent to couple 4-[^{18}F]fluorobenzoic acid with primary alcohols.

The last and most recent example of the use of a coupling agent to activate 4-[^{18}F]fluorobenzoic acid is in the synthesis of PARP1 inhibitor [^{18}F]PARPi **506** by activation of 4-[^{18}F]fluorobenzoic acid using HBTU and subsequent reaction with secondary amine precursor **505** in an overall radiochemical yield of 10% (ndc) (Scheme 114).[319] This is a low but acceptable radiochemical yield, considering the 4-[^{18}F]fluorobenzoic acid is reacted with a bulky secondary amine.

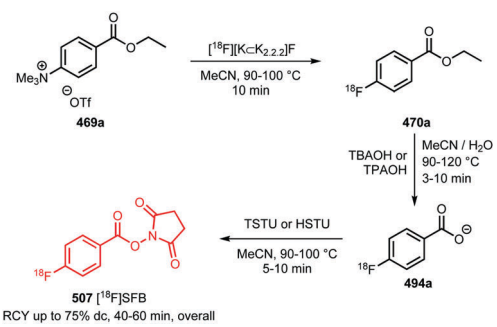
3.4.2 Synthesis and application of *N*-succinimidyl 4-[^{18}F]-fluorobenzoate ([^{18}F]SFB). [^{18}F]SFB is one of the most applied fluorine-18 labelled building blocks to form amides from amines. It is mainly applied to label large peptides, due to its high selectivity for the reaction with amines in a peptidic structure in the presence of various unprotected functional groups.[321] Furthermore, the reaction of [^{18}F]SFB with primary amines proceeds under mild reaction conditions, which is ideal for the labelling of peptides because their secondary structure is readily lost under harsh reaction conditions. These characteristics are of less importance for the labelling of small molecules, as these generally are more stable and selectivity is not a big issue because a protective group strategy can be applied easily. For the labelling of small molecules, [^{18}F]SFB would be less preferred, as various building blocks are available which are more simple to synthesise such as 4-[^{18}F]fluorobenzaldehyde and 2-[^{18}F]fluoroethyl tosylate. Still, in the past years, [^{18}F]SFB has been used 21 times in the labelling of small molecules.[84,93,322–336] The main reason is the fact that at various PET imaging centres, the method to synthesise [^{18}F]SFB is readily available and automated for its use in the labelling of peptides. From a practical point of view, it is thus a small step to also use [^{18}F]SFB for the labelling of small molecules. Currently, there are three methods in use for the synthesis of [^{18}F]SFB. The most convenient and commonly used method is the synthesis of [^{18}F]SFB *via* a one-pot, three-step procedure (Scheme 115).[84,93,322–326] This approach was first published by Tang *et al.* and starts with the radiofluorination of ethyl 4-(trimethylammonium triflate)benzoate **469a** in MeCN, followed by addition of tetrabutylammonium hydroxide (TBAOH) or tetrapropylammonium hydroxide (TPAOH) in water to hydrolyse ethyl 4-[^{18}F]fluorobenzoate **470a** to 4-[^{18}F]fluorobenzoic acid **494a**. After azeotropic drying with additional MeCN, [^{18}F]SFB **507** is prepared by reaction with *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(*N*-succinimidyl)uronium tetrafluoroborate (TSTU) or *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(*N*-succinimidyl)uronium hexafluorophosphate (HSTU) (Scheme 115).

Purification of [^{18}F]SFB is performed by trapping on a C18 SPE cartridge, washing the cartridge with water and eluting the building block in an organic solvent of choice, preferably through alumina and SCX cartridges to remove any remaining [^{18}F]fluoride and other impurities. With these methods, decay corrected radiochemical yields can be obtained up to 75%, and due to the absence of time consuming HPLC purifications and the use of just one SPE purification, the overall synthesis time can be less than 40 minutes.

The second method to synthesise [^{18}F]SFB is a two-pot procedure, in which 4-[^{18}F]fluorobenzoate **494a** is formed by



Scheme 114 Activation of 4-[^{18}F]fluorobenzoic acid with HBTU and coupling to secondary amine **505**.[319]



Scheme 115 One pot, three step synthesis of [^{18}F]SFB.[84,93,322–326]

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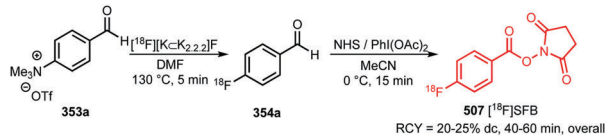

Scheme 116 Two-step synthesis of [^{18}F]SFB.[330,331]

hydrolysis of ethyl 4-[^{18}F]fluorobenzoate **470a** with NaOH or HCl, which is subsequently purified by SPE before formation of [^{18}F]SFB.[327–329] This method is however not recommended, as it only results in longer synthesis times and lower radiochemical yields, without having any advantages over the one-pot procedure.

The third method to synthesise [^{18}F]SFB is a very different, two-step approach, first reported by Glaser *et al.* in 2009 and which is recently used by Ganguly *et al.* (Scheme 116).[330,331] In this method, purified 4-[^{18}F]fluorobenzaldehyde **354a**, is oxidised with (diacetoxyiodo)benzene in the presence of *N*-hydroxysuccinimide (NHS). HPLC purification is necessary to obtain [^{18}F]SFB in sufficient radiochemical purities (>99%) for further reactions. Glaser *et al.* reported a decent overall radiochemical yield of 66 ± 6% (dc), which could however not be reproduced by Ganguly *et al.*, reporting only a 25% (dc) overall radiochemical yield. Although this method only requires two synthetic steps, it still seems that the three-step, one-pot procedure as depicted in Scheme 115 is currently the most convenient, as it is more simple to purify [^{18}F]SFB.

As a building block for the synthesis of low molecular weight PET tracers, [^{18}F]SFB is used solely in the base catalysed acylation of primary amine precursors, as shown in Scheme 117.[84,93,322–329,331–336] The main advantages of labelling amine precursors with [^{18}F]SFB over other fluorine-18 labelled building blocks such as 4-[^{18}F]fluorobenzaldeyde and [^{18}F]FETos is that the acylation with [^{18}F]SFB can be performed under very mild reaction temperatures (typically 20–50 °C, mild basic) and with very high selectivity for the primary amine functional group. Due to the high selectivity of [^{18}F]SFB towards primary amines, protection of other functional groups in the precursor molecule is generally not required (Table 2). As a consequence, the precursors are easier to synthesise and no removal of the protecting groups is necessary afterwards.

Typically, reaction of primary amines with [^{18}F]SFB are performed underbasic conditions. Interestingly, for this reaction not just one type of base, but a wide range of bases in various solvents are reported. Two categories for the solvents and bases can be identified:

(1) Reactions in water using water soluble bases or buffers, including borate buffer, carbonate buffer, sodium phosphate and potassium carbonate. Organic solvents, generally MeCN, can be added to increase solubility of the precursors. These conditions are used when the precursor is highly water soluble.[93,323,325,327–329,331,335]

(2) Reactions in organic solvents (DMSO, DMF, MeCN), using bases which readily dissolve in these solvents (DIPEA, NEt_3). These conditions are used when the precursor is insoluble in water.[84,322,326,332,336]

Two recent publications compared the reaction of [^{18}F]SFB, [^{18}F]fluoroethyl tosylate and 2-[^{18}F]fluoro-4-nitrophenyl-propionate [^{18}F]NFP with amine precursors **525** and **526** in the synthesis of pycolylamine based cell death imaging agents (Fig. 12 and Table 3).[84,93]

Labelling of these precursors with [^{18}F]SFB resulted in fluorine-18 labelled derivatives **508** and **509** (Scheme 117) in overall radiochemical yields of 71 ± 11% (dc) and 13 ± 2% (ndc), respectively. Comparable radiochemical yields were obtained when the precursors were reacted with [^{18}F]FETos at 100 °C and 2-[^{18}F]fluoro-4-nitrophenylpropionate ([^{18}F]NFP) at room temperature. This indicates that precursors **525** and **526** are stable under high temperatures. The reason for the large difference in radiochemical yield between labelling precursor **525** *versus* **526** was not explained.

In general, [^{18}F]SFB is used to label aliphatic amines, however there are two recent examples of labelling aniline derivatives. Neto *et al.* tried to synthesise a PET tracer for imaging EGFR tyrosine kinase **510** (Scheme 117).[333] Unfortunately, reaction of the aniline precursor with [^{18}F]SFB in DMSO using various buffers did not lead to the formation of **510**. Because stronger alkaline conditions are probably required to facilitate labelling of aniline derivatives, the pH was increased to >9, this however resulted in undesired rapid hydrolysis of [^{18}F]SFB. Svensson *et al.*, however, have successfully reacted their aromatic amine precursor with [^{18}F]SFB in the synthesis of cyclin-dependent kinase-2 inhibitor **512** in a decent radiochemical yield of 36–43% (dc).[334] A major difference from the method of Neto *et al.* is that the reaction is performed under water-free conditions using NaH as a base. Due to the absence of water, [^{18}F]SFB does not hydrolyse and is able to react with the amine.

Derivatives of [^{18}F]SFB can potentially be made by changing the position of the fluorine-18 atom and by the addition of substituents on the aromatic ring. Yang *et al.* used this strategy to improve the properties of Prostate-Specific Membrane Antigen tracers **514** and **515**.[324] By changing the location of the fluorine-18 atom to the 2-position and adding a bromine or iodine atom to the 4-position, they were able to produce tracers **529a** and **529b**, which have increased PSMA binding, presumably due to increased interaction with a hydrophobic subpocket in the enzyme (Scheme 118).

3.4.3 Synthesis and application of 6-[^{18}F]fluoronicotinic acid 2,3,5,6-tetrafluorophenyl ester ([^{18}F]FPy-TFP). Olberg *et al.* reported on a different benzoic acid activated ester, [^{18}F]FPy-TFP **531** (Scheme 119).[337] [^{18}F]FPy-TFP can be made in just one synthesis step, due to the stability of the TFP ester under the applied radiolabelling conditions. Furthermore, as for [^{18}F]SFB, also [^{18}F]FPy-TFP can be purified by simple solid phase extraction procedures.

Besides labelling of large peptides, [^{18}F]FPy-TFP is also used for the labelling of small molecules, more specifically, in the labelling of PSMA targeting tracers (Scheme 120).[338,339] The carboxylic acids in the precursor were protected with 4-methoxybenzyl ether (PMB) protecting groups before reaction with [^{18}F]FPy-TFP in case of tracer **532**, therefore requiring an acidic deprotection after the coupling.[338]

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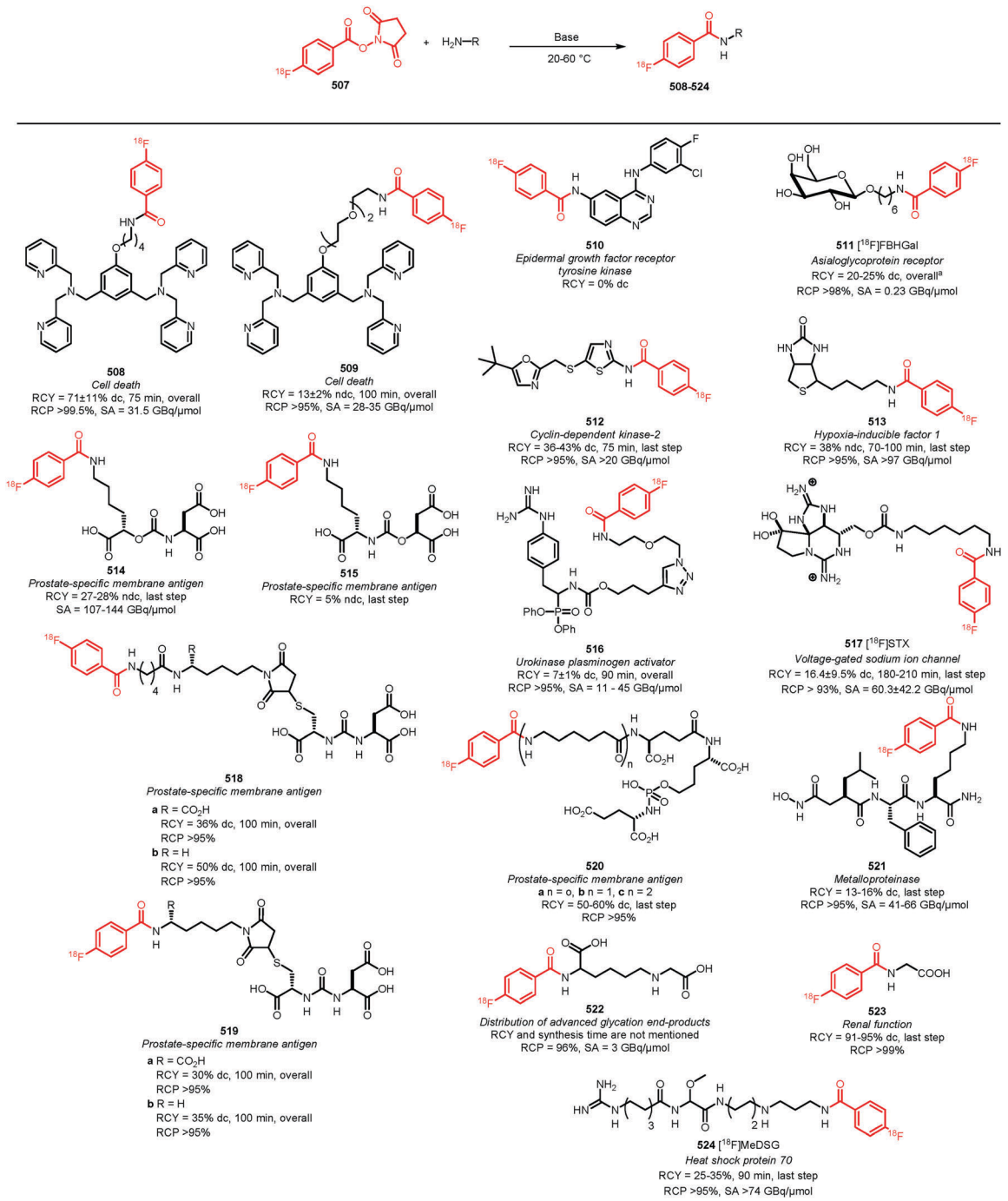

Scheme 117 PET tracers synthesised by amide formation using [^{18}F]SFB. [a] Includes removal of acetyl protecting groups.[84,93,322–329,331–336]

Protection of the carboxylic acids is however not required, as seen in the synthesis of tracer **533**, in which the coupling went smoothly while the carboxylic acid functional groups were unprotected.[339] Most probably because [^{18}F]FPy-TFP already contains an activated ester, therefore no additional coupling reagents are needed.

In conclusion, both PSMA targeting tracers could be made in decent overall radiochemical yields, showing that [^{18}F]FPy-TFP is also a suitable building block for the synthesis of low molecular weight PET tracers.

3.5 Other fluorine-18 labelled aromatic building blocks

3.5.1 Synthesis and application of 4-[^{18}F]fluorophenyldiazonium ion. [^{18}F]Fluoroaniline **444a**, of which its synthesis and direct use has been described in Section 3.3.1, can be further transformed to fluorine-18 labelled fluorophenyldiazonium ion **534**. Phenyldiazonium ions are potentially interesting building blocks in radiochemistry, since radical arylation reactions with these building blocks proceeds generally mild and diazonium ions are insensitive to the presence of functional groups. There is

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Table 2 Functional groups tolerated in acylation of amines with [^{18}F]SFB

Functional group	Compounds (Scheme 117)
Carboxylic acid	**514**,[324] **515**,[24] **522**,[329] **523**,[323] **520a**,[335] **520b**,[331] **520c**,[335] **518a**,[336] **518b**,[336] **519a**,[336] **519b**[336]
Guanidine	**516**,[326] **524**,[328] **517**[325]
Alcohol	**517**[325]
Hydroxamide	**521**[327]

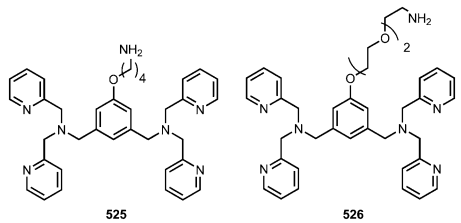


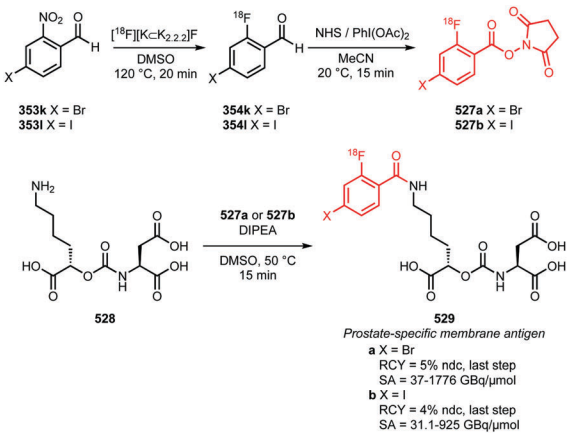
Fig. 12 Alkylamine modified picolylamine derivatives.[84,93]

only one recent publication which describes the use of this building block, in the synthesis of dopamine D_3-selective ligand [^{18}F]SH317 (Scheme 121).[294] The overall radiochemical yield of [^{18}F]SH317 is 1–3% non-decay corrected with an overall synthesis time of 100 minutes.

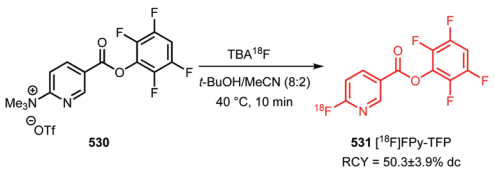
3.5.2 Synthesis and application of *N*-phenyl-*C*-(4-[^{18}F]fluorophenyl)nitrone. Zlatopolskiy *et al.* developed *N*-phenyl-*C*-(4-[^{18}F]fluorophenyl) nitrone **538**, a building block capable of undergoing [3+2]-dipolar cycloadditions with a variety of dipolarophiles.[340,341] 4-[^{18}F]Fluorobenzaldehyde **354a** is synthesised *via* nucleophilic substitution of trimethylammonium salt **353a** with [^{18}F]fluoride (Section 3.1.1), followed by reaction with *N*-phenylhydroxylamine **537** resulting in *N*-phenyl-*C*-(4-[^{18}F]fluorophenyl) nitrone **538** in a decay corrected radiochemical yield of 73.6 ± 5.8%, starting from 4-[^{18}F]fluorobenzaldehyde (Scheme 122).

Zlatopolskiy *et al.* investigated the reaction of *N*-phenyl-*C*-(4-[^{18}F]fluorophenyl) nitrone **538** with a variety of *N*-substituted maleimides, which can be easily introduced in peptides (Scheme 123).[340] The radiochemical yields towards the mixtures of *endo* and *exo* bicyclic isoxazolidines **540a–c**, as measured by HPLC, were 87% for **540a**, 91% for **540b** and 91% for **540c**. The *endo*/*exo* ratio was around 2 : 1 for compounds **540a–c**.

Furthermore Zlatopolskiy *et al.* investigated the Kinugasa reaction by reacting alkynes **541a–d** with *N*-phenyl-*C*-(4-[^{18}F]fluorophenyl) nitrone **538** under copper catalysis resulting in β-lactams **542a–d** (Scheme 124).[341] Radiochemical yields of 65–89% (analytically determined) were obtained with *trans*–*cis* ratios varying between 2 : 3 and 1 : 5 depending on the used alkyne.



Scheme 118 PET tracers for imaging PSMA, labelled using [^{18}F]SFB derivatives.[324]



Scheme 119 Synthesis of [^{18}F]FPy-TFP.[337]

Both the reaction towards isoxazolidines as well as the Kinugasa reaction can potentially be used for the labelling of peptides equipped with maleimide or terminal alkyne functional groups, as long as the high reaction temperature of 110–120 °C would not lead to degradation of the peptides. For the synthesis of low molecular weight PET tracers these reactions could also be useful for the synthesis of PET tracers with an isoxazolidine or β-lactam core structure.

3.5.3 Synthesis and application of 4-[^{18}F]fluorophenyl nitrile oxide. Next to the development of *N*-phenyl-*C*-(4-[^{18}F]fluorophenyl) nitrone **538** (Section 3.5.2), Zlatopolskiy *et al.* also developed 4-[^{18}F]fluorophenyl nitrile oxide **544** (Scheme 125), which can be used as building block for a copper free [2+3]

Table 3 Labeling of picolylamine precursors **525** and **526** with various ^{18}F-labelled building blocks[84,93]

Precursor	Building block	Labelling conditions	Overall RCY (dc)	Overall synthesis time (min)
525	[^{18}F]SFB	DMSO, DIPEA, RT, 10 min	71 ± 11%	75
	[^{18}F]FETos	DMSO, DIPEA, 100 °C, 10 min	76 ± 13%	65
	[^{18}F]NFP	RT, 10 min	68 ± 9%	105
526	[^{18}F]SFB	Borate buffer pH 8.5, 50 °C, 10 min	24 ± 4%	100
	[^{18}F]FETos	MeCN, K_2CO_3, 120 °C, 30 min	17 ± 2%	105

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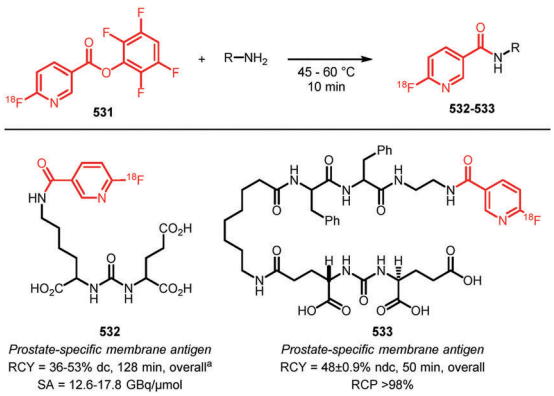
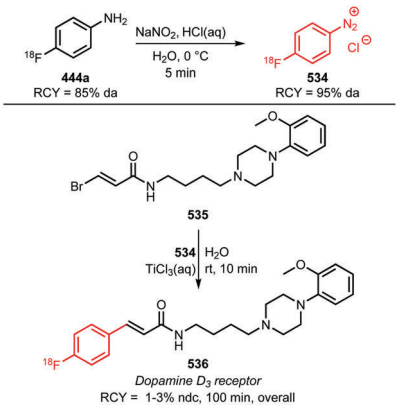
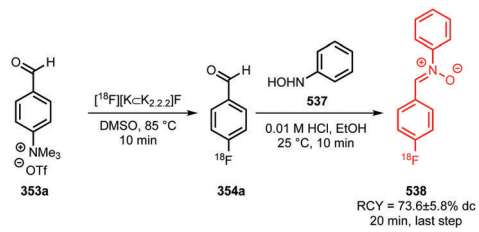


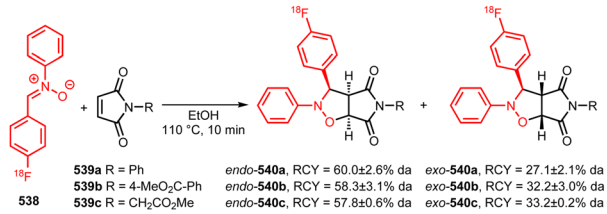
Scheme 120 Synthesis of PSMA targeting tracers using [^{18}F]FPy-TFP. [a] Includes deprotection of the PMB protected carboxylic acids using trifluoroacetic acid.[338,339]



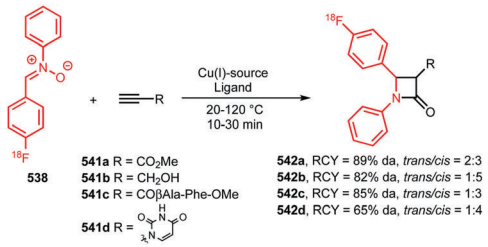
Scheme 121 Synthesis of dopamine D_3-selective ligand [^{18}F]SH317 using 4-[^{18}F]fluorophenyldiazonium chloride.[294]



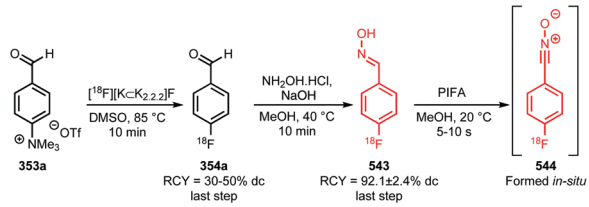
Scheme 122 Synthesis of *N*-phenyl-*C*-(4-[^{18}F]fluorophenyl) nitrone.[340,341]



Scheme 123 Reaction of *N*-phenyl-*C*-(4-[^{18}F]fluorophenyl) nitrone with *N*-substituted maleimides.[340]



Scheme 124 Application of *N*-phenyl-*C*-(4-[^{18}F]fluorophenyl) nitrone in the synthesis of fluorine-18 labelled β-lactams.[341]



Scheme 125 Three step synthesis of the building block 4-[^{18}F]fluorophenyl nitrile oxide.[342]

cycloaddition alternative to the Huisgen 1,3-dipolar cycloaddition ('click'-reaction).[342]

4-[^{18}F]Fluorophenyl nitrile oxide **544** can be synthesised in three steps. Firstly, 4-[^{18}F]fluorobenzaldehyde is synthesised, (Section 3.1.1) followed by reaction with hydroxylamine and sodium hydroxide yielding benzaldoxime **543** in 92.1 ± 2.4% (ndc) in 10 minutes. Because 4-[^{18}F]fluorophenyl nitrile oxide **544** is very reactive, it was not isolated but formed *in situ* and reacted in one pot with various dipolarophiles.

Initial studies in which 4-[^{18}F]fluorophenyl nitrile oxide **543** was formed *in situ* from oxime **543** and reacted with various model dipolarophiles showed high radiochemical yields of 57–95% as measured by HPLC. To prove that this building block is also suitable for the synthesis of PET tracers for COX-2, it was reacted with three indomethacin derivatives which contain a dipolarophile functional group (Scheme 126). Fluorine-18 labelled indomethacin derivatives **545** and **546** could be isolated in 86% and 55% (ndc) radiochemical yield, starting from building block **543**. ^{18}F-Indomethacin derivative **547** was less easily formed and could initially only be obtained in a low radiochemical yield. However, when the oxidant in the reaction was changed from phenyliodine bis(trifluoroacetate) (PIFA) to [bis(acetoxy)iodo]-benzene (BAIB), this indomethacin derivative could also be obtained in a radiochemical yield of 35% (ndc), starting from **543**. Since BAIB is a weaker oxidant, leading to the slower generation of 4-[^{18}F]fluorophenyl nitrile oxide **544** from oxime **543**, the alkene precursor has more time to react before nitrile oxide **544** decomposes by acid-promoted decomposition, solvolysis or reaction with contaminants.

Whether this building block is useful for low molecular weight PET tracers remains unclear, as its multistep synthesis is time consuming and results in low to moderate radiochemical yields. For the labelling of biomolecules, such as peptides it can be beneficial because of the mild reaction conditions, regiospecificity and good cycloaddition yields. Zlatapolsky *et al.* did however

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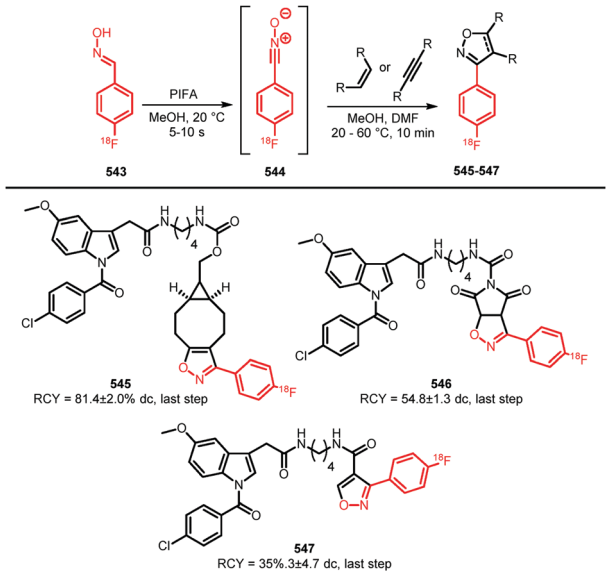


Scheme 126 Application of 4-[^{18}F]fluorophenyl nitrile oxide **544** in the synthesis of fluorine-18 labelled indomethacin.[342]

notice that the amount of precursor needed for acceptable cycloaddition radiochemical yields was high, leading to low specific activities as it is generally difficult to separate a large biomolecule precursor from its labelled product. This issue was solved by *in situ* conversion of 4-[^{18}F]fluorobenzaldoxime **543** to an imidoyl chloride by treatment with chloramine-T. Using this more stable derivative of 4-[^{18}F]fluorobenzaldoxime **543**, the amount of required precursor could be lowered to 5 nmol, thus making this method also useful for the labelling of biomolecules.

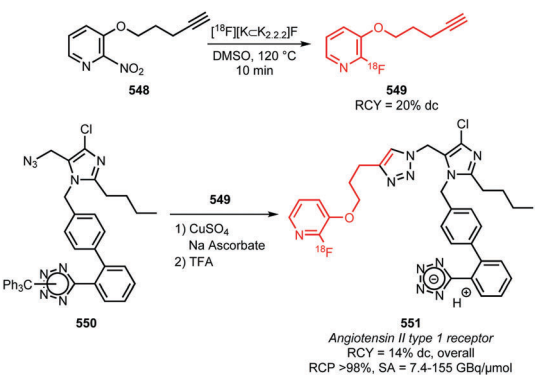
3.5.4 Synthesis and application of [^{18}F]fluorophenyl alkynes. Despite the fact that the Huisgen 1,3-dipolar cycloaddition ('click'-reaction) is generally and widely applied in the synthesis of small molecule PET tracers, there are only three reports which describe 'click'-reactions with aromatic fluorine-18 labelled alkyne building blocks. The first report describes the synthesis and application of building block 2-[^{18}F]fluoro-3-pent-4-yn-1-yloxypyridine ([^{18}F]FPyKYNE) **549** (Scheme 127). This building block has been originally developed by Kuhnast *et al.* as a prosthetic group for the labelling of azide modified macromolecules using the click reaction.[343]

Arksey *et al.* showed that [^{18}F]FPyKYNE **549** can be used as a building block in the synthesis of a fluorine-18 labelled derivative of the AT_1 inhibitor losartan (Scheme 127).[344] The 'click'-reaction of [^{18}F]FPyKYNE **549** with the azide modified losartan **550**, followed by trityl deprotection, proceeded in good radiochemical yields of 44–70% (dc). Unfortunately, the overall radiochemical yield starting from [^{18}F]fluoride was quite low (7–14% dc) due to the low yielding aromatic nucleophilic substitution on nitro precursor **548**.

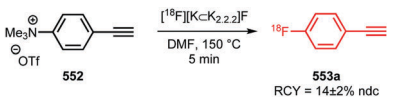
A recent publication by Roberts *et al.* describes the synthesis of another fluorine-18 labelled alkyne building block: (4-[^{18}F]fluorophenyl)acetylene **553a**, which can be obtained by direct labelling of its trimethylammonium precursor (Scheme 128).[345] Although the aromatic ring is only marginally electron deficient, the (4-[^{18}F]fluorophenyl)acetylene building block could still be obtained in a radiochemical yield of 14% (ndc). Purification of this building block was done by HPLC, because SPE methods did not lead to desired radiochemical purities of this reagent.

To demonstrate the application of (4-[^{18}F]fluorophenyl)-acetylene in the synthesis of PET tracers, Roberts *et al.* reacted this building block with a variety of azide precursors (Scheme 129).[345] Compounds **554** and **555** were formed in radiochemical yields of 67% and 56% (analytically determined) respectively. Unfortunately, overall non-decay corrected radiochemical yields, based on starting [^{18}F]fluoride were low due to the low yielding synthesis of 4-([^{18}F]fluorophenyl)acetylene **553a**.

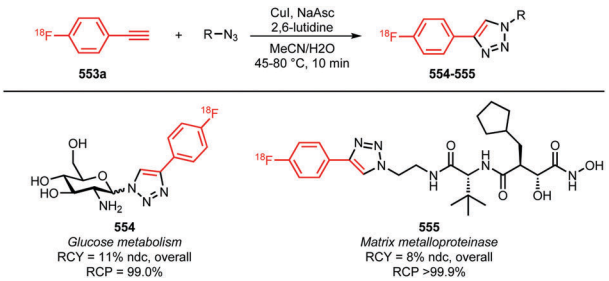
A different approach towards the synthesis of ([^{18}F]fluorophenyl)acetylenes was recently published by Krapf *et al.* (Scheme 130).[346] Instead of a direct labelling approach, they reported a two-step method, consisting of first the synthesis of [^{18}F]fluorobenzaldehydes **363a,b,k** in 20–75% radiochemical yield (ndc) and subsequent Seyferth–Gilbert Homologation towards ([^{18}F]fluorophenyl)acetylenes **553a–c** using the Bestmann–Ohira reagent in 40–60% radiochemical yield (ndc). The two step approach seems more promising than the direct approach



Scheme 127 Synthesis of a fluorine-18 labelled losartan derivative using [^{18}F]FPyKYNE as a building block.[343,344]



Scheme 128 Synthesis of (4-[^{18}F]fluorophenyl)acetylene by direct nucleophilic aromatic substitution with [^{18}F]fluoride.[345]



Scheme 129 'Click'-reaction with (4-[^{18}F]fluorophenyl)acetylene.[345]

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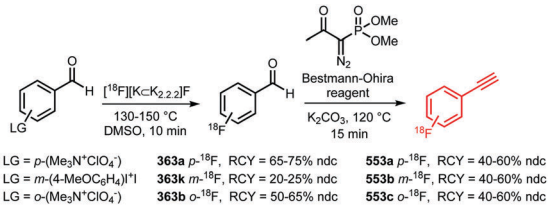


Scheme 130 Synthesis of ([^{18}F]fluorophenyl)acetylenes by Seyferth–Gilbert homologation.[346]

employed by Roberts *et al.*,[345] as exemplified by the overall radiochemical yield for (4-[^{18}F]fluorophenyl)acetylene of 26–45% instead of 14 ± 2%. For the purification of (4-[^{18}F]fluorophenyl)-acetylene, Krapf *et al.* discovered that radiochemical purities of >98% can be achieved by distillation, thereby avoiding cumbersome HPLC purification.[346]

Using small model substrates, it was demonstrated that these alkynes can participate successfully in (1) click reactions with various dipoles (RCY = 20–53%, determined analytically), (2) the Sonogashira reaction (RCY = 83%, determined analytically) and (3) alkyne trimerisation (RCY = 18%, determined analytically). As a proof of principle, (2-[^{18}F]fluorophenyl)acetylene was reacted with azides in the click reaction towards potential COX-2 PET tracer **559** and PSMA PET tracer **560** in a reasonable overall radiochemical yield of 30% and a short 60 min overall synthesis time (Scheme 131).[346]

In summary, ([^{18}F]fluorophenyl)acetylenes are a new class of building blocks with high versatility. The building blocks can be synthesised in decent radiochemical yields and reacted in cycloadditions as well as transition metal catalysed reactions.

3.5.5 Synthesis and application of [^{18}F]fluorophenyl substituted azides. As is the case with [^{18}F]fluorophenyl alkynes (Section 3.5.4), [^{18}F]fluorophenyl substituted azides are also potentially interesting building blocks for use as reagents in the widely used Huisgen 1,3-dipolar cycloaddition ('click'-reaction). Even more, because the aryl C–^{18}F bond is usually more stable than the alkyl C–^{18}F bond, it is even expected that tracers made by 'click'-reaction using [^{18}F]fluorophenyl substituted azides are less prone to *in vivo* defluorination than when the much more commonly used aliphatic [^{18}F]fluoroethyl azide is used (Section 2.6.1).

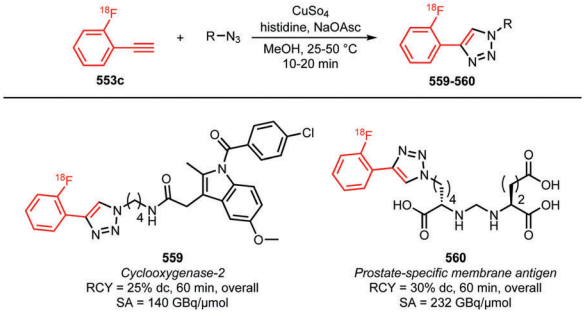
Although [^{18}F]fluorophenyl substituted azides have interesting properties for the use as a reagent in click reactions, there are no recent publications on the use of these building blocks in the synthesis of small molecule PET tracers. The obvious reason is the challenge to synthesise these building blocks. The azide functional group is not a strong electron withdrawing group. Therefore, the synthesis of 2- and 4-[^{18}F]fluorophenyl azide by conventional nucleophilic aromatic substitution with [^{18}F]fluoride leads only to very low radiochemical yields.[347] When the azide functional group is attached to the aromatic ring *via* an aliphatic chain, as in for example [^{18}F]fluorobenzyl azides, the electron density on the aromatic ring is too high to allow successful conventional nucleophilic aromatic substitution. Because [^{18}F]fluorophenyl substituted azides would be a valuable addition to the radiochemist's toolkit, various late-stage fluorination methods have recently been investigated for the synthesis of these building blocks.

Chun *et al.* investigated the radiolabelling of diaryliodonium salt precursors towards [^{18}F]fluorophenyl azides and [^{18}F]fluorobenzyl azides (Scheme 132).[348] For the synthesis of [^{18}F]fluorophenyl azides **562a** and **562b**, the use of diaryliodonium salt precursors was unsuccessful, giving the desired building blocks only in low radiochemical yields. For the synthesis of [^{18}F]fluorobenzyl azides **563a–c**, moderate radiochemical yields were obtained for the *ortho*, *meta* and *para* isomers (39–45% RCY, analytically determined).

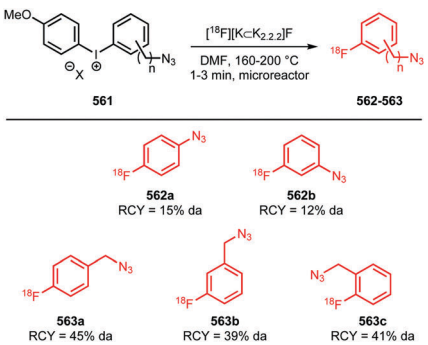
Another approach towards [^{18}F]fluorophenyl substituted azides was reported by Rotstein *et al.* and Wang *et al.* They investigated the radiofluorination of spirocyclic hypervalent iodine(III) precursors (Scheme 133).[16,349] Using this novel radiofluorination method, various [^{18}F]fluorophenyl substituted azides could be formed in moderate to excellent radiochemical yields.

To demonstrate the potential of these building blocks for the synthesis of PET tracers, Wang *et al.* showed that fluorine-18 labelled amino acid **570** could be formed in 49% radiochemical yield (analytically determined) by the 'click'-reaction of building block **567** with alkyne modified precursor **569** (Scheme 134).[344]

In conclusion, novel methodologies have recently become available to synthesise [^{18}F]fluorophenyl substituted azide building blocks in moderate to good radiochemical yields, making this group of building blocks available for the synthesis of PET tracers.



Scheme 131 Click reaction with (2-[^{18}F]fluorophenyl)acetylene.[346]



Scheme 132 Synthesis of [^{18}F]fluorophenyl azides and [^{18}F]fluorobenzyl azides from iodonium salt precursors.[348]

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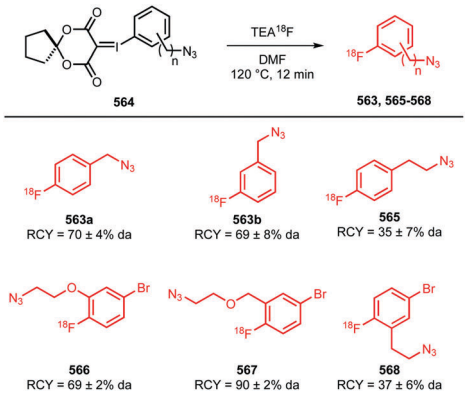
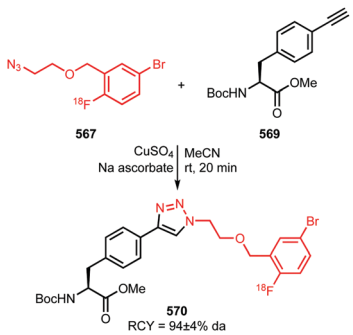


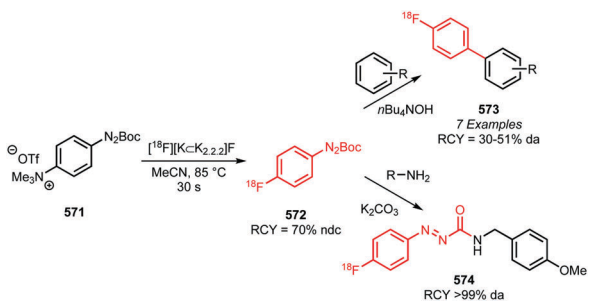
Scheme 133 Synthesis of various [^{18}F]fluorophenyl substituted azides from spirocyclic hypervalent iodine(III) precursors.[16,349]



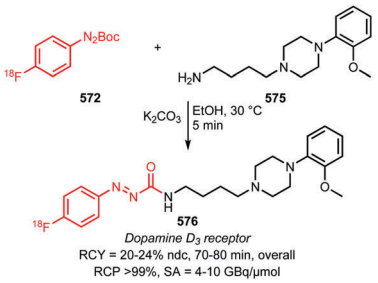
Scheme 134 Synthesis of fluorine-18 labelled amino acid **570** using [^{18}F]fluorophenyl substituted azide **567**.[349]

3.5.6 Synthesis and application of *tert*-butyl 2-(4-[^{18}F]fluorophenyl)azocarboxylate. Fluorine-18 labelled azocarboxylic ester **572** is a novel building block developed by Fehler *et al.*[350] This building block can be synthesised in one step by nucleophilic aromatic substitution of trimethylammonium triflate **571** with [^{18}F]fluoride resulting in a radiochemical yield of 70%, because of the excellent electron withdrawing property of the azocarboxylic ester group at the *para*-position of the trimethylammonium leaving group (Scheme 135).

The application of this building block in radical arylations toward compounds **573** resulted in reasonable radiochemical yields of 30–51% (analytically determined) with simple model



Scheme 135 Synthesis and application of [^{18}F]4-fluorophenylazocarboxylic *tert*-butyl ester.[350]



Scheme 136 Application of [^{18}F]4-fluorophenylazocarboxylic *tert*-butyl ester in the synthesis of dopamine-D_3 ligand **576**.[350]

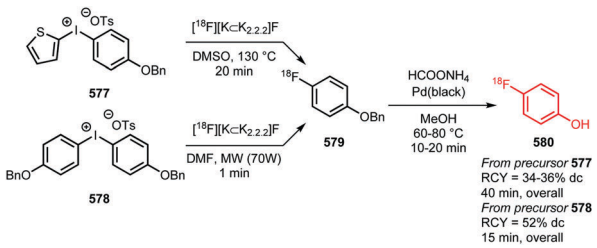
substrates. Examples of more complex molecules resembling PET tracers however have not yet been published. The reaction of building block **575** with amines to amides is very promising, as shown by the quantitative conversion towards compound **574** (Scheme 135) and the successful synthesis of dopamine D_3 ligand **576** in an overall radiochemical yield of 20–24% (ndc) (Scheme 136).[350]

In conclusion, this building block is a good candidate for the synthesis of various PET tracers, as it is easy to synthesise and reacts in high yields. As it is a fairly new building block, its potential needs to be further explored.

3.5.7 Synthesis of 4-[^{18}F]fluorophenol. Various synthetic strategies towards 4-[^{18}F]fluorophenol have already been published before 2010. These are however all challenging three-step low yielding procedures.[351–355]

Recently, Ross *et al.* and Helfer *et al.* developed a novel two-step synthesis of 4-[^{18}F]fluorophenol from iodonium salt precursors **577** and **578** (Scheme 137).[356,357] These iodonium salt precursors are benzyl protected phenols with the reactive iodonium salt at the 4-position. After radiofluorination, benzyl protected 4-[^{18}F]fluorophenol **579** is obtained, which is deprotected by hydrogenation to result in 4-[^{18}F]fluorophenol. When microwave heating was used for the radiofluorination reaction, 4-[^{18}F]fluorophenol could be obtained in an overall synthesis times of 15 minutes with radiochemical yields of 52% (dc). The only disadvantage is that complex iodonium salt precursors need to be synthesised, which are somewhat unstable.

Gao *et al.* developed a novel one-pot method starting from 4-*tert*-butyl precursors **579**.[31] *Via* oxidative radiofluorination and using phenoliodine diacetate (PIDA), various 4-[^{18}F]fluorophenols were prepared in only 30 minutes overall synthesis time (Scheme 138). The synthesis of 4-*tert*-butyl precursors is



Scheme 137 Synthesis of 4-[^{18}F]fluorophenol from iodonium salt precursors.[356,357]

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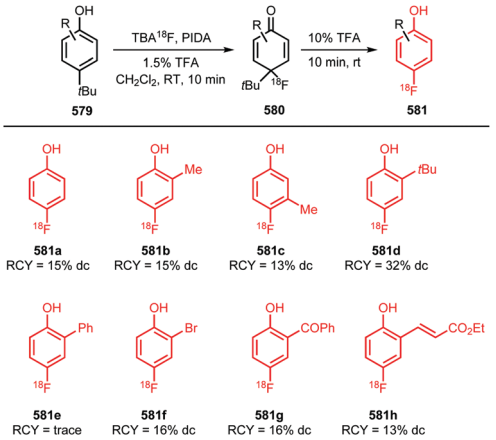


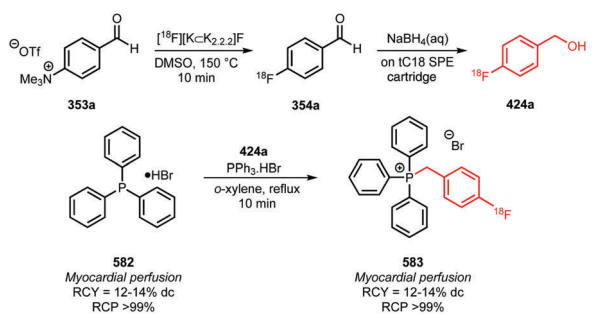
Scheme 138 Synthesis of 4-[^{18}F]fluorophenols by oxidative fluorination of 4-*tert*-butyl phenols.[31]

simpler than of the iodonium salt precursors, some of them are even commercially available. If the radiochemical yields can be further improved, this method will be highly valuable for the synthesis of 4-[^{18}F]fluorophenols.

4-[^{18}F]Fluorophenol has not been applied in the synthesis of new PET tracers. However with these novel methods, 4-[^{18}F]fluorophenol becomes accessible as a fluorine-18 labelled building block and its application in the synthesis of PET tracers can therefore be expected in the future.

3.5.8 Synthesis and application of 4-[^{18}F]fluorobenzyl alcohol. 4-[^{18}F]Fluorobenzyl alcohol is most commonly used as intermediate in the synthesis of benzyl halides (Section 3.2.3). The direct use of 4-[^{18}F]fluorobenzyl alcohol is only reported once in recent literature by Tominaga *et al.* in the synthesis of myocardial perfusion tracer 4-[^{18}F]fluorobenzyltriphenylphosphonium bromide ([^{18}F]FBnTP).[358] This tracer has been previously synthesised by Ravert *et al.* in 8.3 ± 1.4% (ndc) radiochemical yield in a synthesis time of 52 minutes by reaction of 4-[^{18}F]fluorobenzyl bromide with triphenylphosphine.[291]

Tominaga *et al.* showed that [^{18}F]FBnTP can also be synthesised by direct reaction of 4-[^{18}F]fluorobenzyl alcohol with triphenylphosphine hydrobromide (Scheme 139) in an overall radiochemical yield of 12–14% (dc). In comparison, the radiochemical yield obtained by Ravert *et al.* was 8.3% (ndc), which converts to 11.5% (dc). Besides the similar radiochemical



Scheme 139 Application of [^{18}F]4-fluorobenzyl alcohol in the synthesis of [^{18}F]FBnTP.[358]

yields, both methods use SPE purifications in the building block synthesis and a final HPLC purification of the tracer. Therefore, there seems no significant preference for either method in the synthesis of [^{18}F]FBnTP.

4 Conclusion and future perspectives

The interest in the development of novel fluorine-18 labelled PET tracers has increased significantly over the last two decades. For the synthesis of these tracers, radiochemists prefer late stage radiofluorination reactions for various reasons. The use of building blocks is however still of significant importance. Besides the use of fluorine-18 labelled building blocks for the modular build-up of PET tracers, which cannot be obtained *via* direct radiofluorination, several aromatic and aliphatic fluorine-18 labelled building blocks have been developed for generic applications. As such, fluorine-18 labelled building blocks are a good alternative to late stage radiofluorination. For example, building blocks which have been proven valuable due to their simple, easy to automate synthesis and effective reaction with precursors are the alkylating agents [^{18}F]fluoroethyl bromide, [^{18}F]FETos and 'click'-reagent [^{18}F]fluoroethyl azide. These three building blocks account, since 2010, for the synthesis of more than 120 PET tracers. A building block which has proven to be very useful due to its versatility is 4-[^{18}F]fluorobenzaldehyde, as it has been applied as prosthetic group in at least five different types of coupling chemistry as well as in various multicomponent reactions. *N*-Succinimidyl-4-[^{18}F]fluorobenzoate has proven to be valuable as one of the most selective building blocks, as it reacts rather selectively with primary amines.

Other building blocks are less broadly applied, but still find applications in the synthesis of PET tracers. Many aromatic building blocks are for example used in the development of PET tracers which cannot be synthesised easily by late-stage radiofluorination. Although the overall yields *via* the building block approach can be low due to a challenging building block synthesis or low yielding subsequent reactions, the final PET tracer is often produced in sufficient yields for initial preclinical studies. Various aliphatic building blocks are used as an alternative to [^{18}F]fluoroethyl halides and sulfonates to improve the biological characteristics of the PET tracer by modifying the chain length and chain structure. For the synthesis of PET tracers which are difficult to obtain by late-stage radiofluorination as well as the synthesis of PET tracer derivatives with improved biological activity, an elaborate toolkit is required which contains many different types of building blocks. With that perspective in mind, it is clear that the current set of building blocks available to the radiochemist is still rather limited and further expansion to allow the introduction of fluorine-18 at any desired position in any molecule is highly desired.

It should be noted that nowadays novel late-stage radiofluorination chemistry also provides radiochemists with opportunities to develop and access a larger variety of structurally diverse PET tracers that were previously only accessible by elaborate multistep fluorine-18 building block chemistry. These novel

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late-stage radiofluorination chemistry methods significantly increase the tools available for PET tracer synthesis. Nevertheless, despite these recent developments, it is still not possible to access and develop every desired PET tracer. Precursors can be difficult to synthesise and may not be very stable, the functional group tolerance and scope can still be too limited, and the reaction conditions for the fluorine-18 labelling reactions are often still harsh. It is therefore very likely that the building blocks described in this review, that have proven to be particularly successful and are widely applied, will not be replaced by late-stage radiofluorination chemistry, but will remain important in the radiochemists toolkit.

In conclusion, this review shows that building blocks are vital tools for radiochemists and will continue to be important in the future of PET tracer development, as complementary techniques to late-stage radiofluorination methods.

Abbreviations

aq.	Aqueous
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
b.p.	Boiling point
BAIB	[Bis(acetoxy)iodo]-benzene
BOP	(Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
BuEA	Fluorobutyl ethacrynic amide
COX	Cyclooxygenase
CSA	Camphorsulfonic acid
CuAAC	Copper(I)-catalysed azide-alkyne cycloaddition
da	Determined analytically
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
dc	Decay-corrected
DCC	*N*,*N*′-Dicyclohexylcarbodiimide
DIPEA	*N*,*N*-Diisopropylethylamine
DMA	Dimethylacetamide
DMAP	*N*,*N*-Dimethylpyridin-4-amine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
EGFR	Epidermal growth factor receptor
FBnTP	4-Fluorobenzyl-triphenylphosphonium bromide
FBuEA	Fluorobutyl ethacrynic amide
FDG	2-Deoxy-2-fluoroglucose
FETos	2-Fluoroethyl tosylate
FPy-TFP	6-Fluoronicotinic acid 2,3,5,6-tetrafluorophenyl ester
FPyKYNE	2-Fluoro-3-pent-4-yn-1-yloxypyridine
FLT	2′-Deoxy-2′-fluorothymidine
FXAU	2′-Fluoro-2′-deoxy-1-β-D-arabinofuranosyl-uracil
GSH	Glutathione
HATU	1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate
HBTU	(2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate)
HPLC	High-performance liquid chromatography
HSTU	*N*,*N*,*N*′,*N*′-Tetramethyl-*O*-(*N*-succinimidyl)uronium hexafluorophosphate
LG	Leaving group
M	Molar
min	Minute
MRP	Multi-drug resistance protein
MW	Microwave
N	Normal
ndc	Non decay-corrected
NFP	4-Nitrophenyl 2-fluoropropionate
NHS	*N*-Hydroxysuccinimide
n.m.	Not mentioned
o-DCB	1,2-Dichlorobenzene
PDE5	Phosphodiesterase
PIDA	Phenoliodine diacetate
PIFA	Phenyliodine bis(trifluoroacetate)
PEG	Poly(ethylene glycol)
PET	Positron emission tomography
PMB	4-Methoxybenzyl ether
PSMA	Prostate-specific membrane antigen
PTC	Phase-transfer catalyst
py	Pyridine
quant.	quantitative
RCP	Radiochemical purity
RCY	Radiochemical yield (isolated, if not stated otherwise)
rt	Room temperature
SA	Specific activity
SFB	*N*-Succinimidyl 4-fluorobenzoate
SPE	Solid-phase extraction
TBA	*tert*-Butanol
TEA	Triethylamine
TBAB	Tetrabutylammonium bromide
TBAF	Tetrabutylammonium fluoride
TBAOH	Tetrabutylammonium hydroxide
TCO	*trans*-Cyclooctenes
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
TPAOH	Tetrapropylammonium hydroxide
TSTU	*N*,*N*,*N*′,*N*′-Tetramethyl-*O*-(*N*-succinimidyl)uronium tetrafluoroborate
Tz	Tetrazines
VEGF	Vascular endothelial growth factor

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