Fluorine-18 Labelled Building Blocks for PET Tracer Synthesis

Overview and Recent Advances in ^{18}F-Trifluoromethylation

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Overview and Recent Advances in ^{18}F-Trifluoromethylation

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General introduction

1.1 Positron Emission Tomography

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 hr), PET is able to provide well-defined, three-dimensional quantitative images of the distribution of biologically active compounds labelled with these radionuclides (Figure 1).[2,7,8]

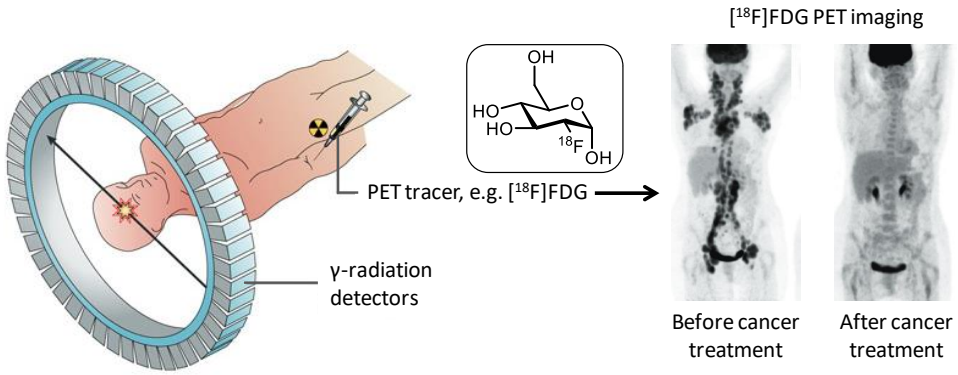


Figure 1 PET imaging before and after cancer treatment using PET tracer [^{18}F]FDG.[10]

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 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 visualisation 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 (Figure 1).[9,10]

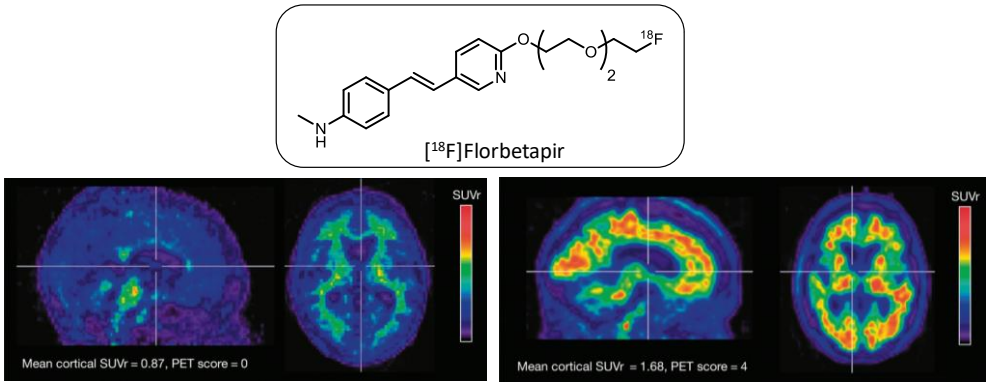


Figure 2 PET imaging of β-amyloid plaques in the brain using [^{18}F]Florbetapir.[11]

A newly developed PET tracer is [^{18}F]Florbetapir (Amyvid) (Figure 2).[11] This tracer targets and thus visualises β-amyloid plaques, formed in Alzheimer's disease. Therefore, PET imaging with [^{18}F]Florbetapir is an excellent method for the diagnosis of this disease.

Table 1 Selection of commonly used fluorine-18 labelled PET tracers.

PET Tracer	Target	Application	Ref.
[^{18}F]Florbetapir	β-amyloid plaques	Neurology - Alzheimer's disease	11
[^{18}F]Flutemetamol	β-amyloid plaques	Neurology - Alzheimer's disease	13
[^{18}F]Florbetaben	β-amyloid plaques	Neurology - Alzheimer's disease	14
[^{18}F]F-DOPA	Striatal Dopaminergic Pathway	Neurology - Parkinson's disease	15-17
[^{18}F]MPPF	Serotonin 1A receptor	Neurology - Various diseases	18-20
[^{18}F]DPA-714	Translocator protein 18 kDa	Neurology - Various diseases	21
[^{18}F]FDG	Glucose metabolism	Oncology - Various cancers	9,10
[^{18}F]FLT	Thymidine kinase 1	Oncology - Various cancers	22
[^{18}F]FET	Amino acid transporters	Oncology - Various cancers	23
[^{18}F]DCFPyL	Prostate-specific membrane antigen	Oncology - Prostate cancer	24
[^{18}F]FES	Estrogen receptor	Oncology - Breast cancer	25
[^{18}F]fluoride	Bone hydroxyapatite crystals	Oncology - Bone cancer	26
[^{18}F]FMISO	Hypoxia	Various - Tissue oxygen deficiency	27-28

Besides the use of PET imaging in diagnosing disease in patients, 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 target or pathway by visualization 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.[3,12]

In the human body, there is a wide range of biological targets available which potentially can be visualised and investigated by PET imaging. For some of these targets, PET tracers have been developed, of which a selection is shown in Table 1. For most targets, there is however not yet a PET tracer available. Therefore, to increase the potential of PET imaging, it is important that novel PET tracers are being developed.

1.2 Synthesis of fluorine-18 labelled PET tracers

Many positron emitting radionuclides are currently 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). This results in relatively high-resolution PET images.[7]

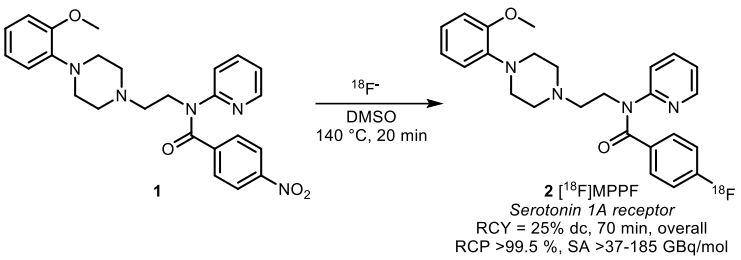
To enable radiochemists to label a wide range of compounds, the availability of a large toolkit of fluorine-18 labelling methods is important. Two major strategies can be identified to access fluorine-18 labelled tracers: (1) late-stage radiofluorination, introducing fluorine-18 in the last step of PET 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.

The [^{18}F]fluoride ($^{18}F^-$) itself is generally obtained by irradiation of oxygen-18 enriched water ($H_2{}^{18}O$) with a proton beam generated in a cyclotron.[29,30] Using this production method, [^{18}F]fluoride in $H_2{}^{18}O$ can be obtained in high amounts of up to 1 TBq.[31]

To be able to introduce [^{18}F]fluoride into a molecule, it must be free from any residual water, including the $H_2{}^{18}O$ target water. The general method to recover the expensive $H_2{}^{18}O$ is by trapping [^{18}F]fluoride on an anion exchange cartridge and collecting the $H_2{}^{18}O$.[30] The [^{18}F]fluoride is subsequently eluted using a solution containing a base and a phase transfer catalyst, such as kryptofix-2.2.2 ($K_{2.2.2}$) or tetra-n-butylammonium hydrogencarbonate in water or a water/acetonitrile mixture. Residual water is removed by azeotropic drying at elevated temperatures. After the drying procedure, the [^{18}F]fluoride can be dissolved using a phase transfer catalyst in a dry

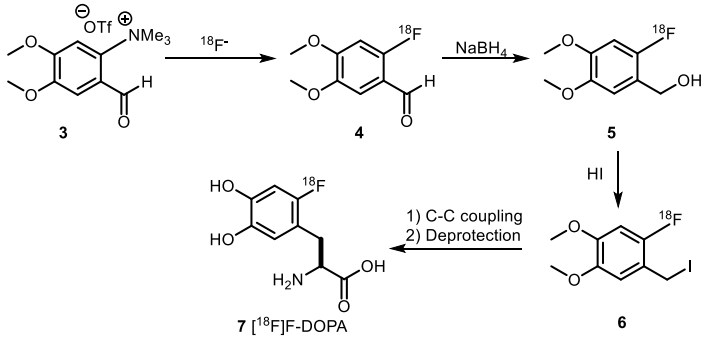
organic non-protic solvent of choice, e.g. acetonitrile (MeCN), *N,N*-dimethylformamide (DMF) or dimethyl sulfoxide (DMSO).

An example of a PET tracer which is made by direct late-stage radiofluorination is [^{18}F]MPPF (Scheme 1).[18] In this case, [^{18}F]fluoride reacts with precursor **1** *via* an aromatic nucleophilic substitution, in which the -NO_2 leaving group is substituted with [^{18}F]fluoride.



Scheme 1 Synthesis of [^{18}F]MPPF *via* direct late-stage fluorination.[18]

In the case of [^{18}F]F-DOPA, late stage radiofluorination is not possible, due to the electron rich character of the aromatic ring. Therefore, to produce [^{18}F]F-DOPA, the building block approach is currently the synthetic procedure of choice (Scheme 2).



Scheme 2 Synthesis of [^{18}F]F-DOPA *via* building block approach.[32-34]

Precursor **3**, which is required for this approach contains an electron withdrawing aldehyde group, which decreases the electron density of the aromatic ring and thereby enables nucleophilic aromatic substitution on the trimethyl ammonium leaving group. This conveniently results in fluorine-18 labelled building block **4**. In two steps, this building block is then converted to benzyl iodide **6**, which can undergo asymmetric C-C coupling towards [^{18}F]F-DOPA.[32-34]

To develop novel radiofluorination methods the following aspects should be considered both for the late-stage and the building block approach methodology:

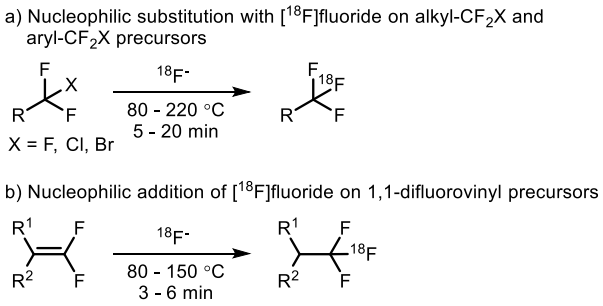
- Radiochemical yields should be high enough to deliver the tracer in sufficient amounts for PET imaging of one or multiple patients.
- Reaction conditions should ideally be mild, as this simplifies purification due to less degradation of the precursor and PET tracers. Furthermore, mild reactions are generally easier to automate and are more reliable.
- Reaction times should be fast, to reduce loss of the fluorine-18 labelled PET tracer by radioactive decay.
- The number of reaction steps should be kept at a minimum, as multiple steps make automation more difficult and increases the risks of failure due to the increased number of handlings.
- The precursors should be bench stable, preferably for several years, to ensure successful synthesis of the PET tracer over time.
- Purification should be as simple as possible, while still maintaining overall radiochemical purities of >95%. Simple methods like solid phase extraction are preferred as it is easy to automate and very fast (<5 minutes). Purification by High Pressure Liquid Chromatography (HPLC) is more challenging and requires more time (10 - 30 min), however is sometimes required to obtain sufficiently high purities.
- Specific activity of the PET tracer should be high, at least >18 GBq/µmol, to allow PET imaging of low abundant targets.

1.3 Synthesis of PET tracers containing the fluorine-18 labelled trifluoromethyl functional group

Many biologically active compounds contain a trifluoromethyl (CF_3) functional group. The CF_3 group is incorporated to improve their binding selectivity, lipophilicity, or metabolic stability.[35-38] The [^{18}F]CF_3-containing compounds and analogues are however not very abundant because only limited synthetic approaches were available before commencing the work described in this thesis (Scheme 3).[39-48]

Both the nucleophilic substitution of X (chlorine or bromine) with [^{18}F]fluoride on alkyl/aryl-CF_2X precursors (Scheme 3a)[39-44] and the nucleophilic addition of [^{18}F]fluoride using 1,1-difluorovinyl precursors (Scheme 3b),[45,46] generate the [^{18}F]trifluoromethyl group in a single synthetic step. However, both approaches suffer usually from limited success. Although rather straightforward substrates gave the desired fluorine-18 containing product in up to 93% yield, the labelling of more complex starting materials

resulted often in very low yields (<15%). Moreover, precursors containing the difluorobromomethyl or 1,1-difluorovinyl functional group are hard to obtain by commercial sources or synthetic methods.



Scheme 3 Methods available for the preparation of [^{18}F]trifluoromethylated compounds using [^{18}F]fluoride as fluorine-18 source, at the start of the development of the methods in this thesis.

Furthermore, the specific activity (SA), which is the ratio of ^{18}F product over the total amount of ^{18}F + ^{19}F product, is low (<1 GBq/µmol) for these methods. Specific activities of at least 18 GBq/µmol are however required to be able to visualise biological targets of interest without inducing any biological effect. Exception is the nucleophilic addition of [^{18}F]fluoride on 1,1-difluorovinyl precursors, as this method yields radiofluorinated compounds in good specific activities up to 86 GBq/µmol (Scheme 3b). Unfortunately, this reaction only yields products with the less common [^{18}F]2,2,2-trifluoroethyl group, and cannot be used for the synthesis of [^{18}F]trifluoromethyl arenes.[45,46]

Lately, many efforts have been put in the development of novel methods towards the synthesis of [^{18}F]CF_3-containing PET tracers. The implication of these methods will be discussed in Chapter 5: Summary and Outlook.

All in all, the number of methods available for radiochemists for the synthesis of radiolabelled compounds with the [^{18}F]trifluoromethyl group is still limited. Furthermore, these methods show several limitations, including low radiochemical yields, difficult to obtain precursors and low specific activities. Therefore, there is a need for methods which supplement and improve the current available methods.

1.4 Aim and outline of this thesis

The aim of this thesis is to expand the toolbox of radiochemical methods with new methods for the synthesis of radiofluorinated PET tracers containing the fluorine-18 labelled trifluoromethyl group, using [^{18}F]trifluoromethane ([^{18}F]HCF_3) as a building block.

Chapter 2 gives an overview of the application of fluorine-18 labelled building blocks in the synthesis of PET tracers since 2010. In this review, both the synthesis and application of both the aliphatic and aromatic building blocks, including [^{18}F]trifluoromethane, are covered.

Chapter 3 describes the synthesis of [^{18}F]trifluoromethane and the application of this building block in the synthesis of [^{18}F]trifluoromethyl carbinols, by reaction with various aldehydes and ketones. Furthermore, the results in this chapter give new insights on the mechanism of the trifluoromethylation of aldehydes and ketones with trifluoromethane.

Chapter 4 describes two novel methods towards the synthesis of [^{18}F]trifluoromethyl arenes using [^{18}F]trifluoromethane as a building block. In both methods, first [^{18}F]trifluoromethane is converted using a Cu(I) source and a strong base towards [^{18}F]$CuCF_3$. In the first method, [^{18}F]$CuCF_3$ reacts with various aryl iodides under elevated temperatures while in the second method, [^{18}F]$CuCF_3$ reacts with various aryl boronic acids at room temperature in very short reaction times under oxidative conditions using air as an oxidant. Besides the development of these new methods, also the specific activity of [^{18}F]trifluoromethane itself, and thus the PET tracers made with this building block, has been improved to allow PET imaging of low abundant targets (SA = 28 ± 5 GBq/μmol). The application of both methods for the synthesis of PET tracers is demonstrated by the synthesis of [^{18}F](trifluoromethyl)estrone and [^{18}F](trifluoromethyl)phenylanaline.

Chapter 5 gives a summary of **Chapter 1-4** and provides an outlook on the future for methods towards the synthesis of PET tracers with the fluorine-18 trifluoromethyl moiety, including the methods described in this thesis.

1.5 References

1 S. M. Ametamey, M. Honer and P. A. Schubiger, *Chem. Rev.*, 2008, **108**, 1501-1516.

2 J. S. Fowler and A. P. Wolf, *Acc. Chem. Res.*, 1997, **30**, 181-188.

3 P. M. Matthews, E. A. Rabiner, J. Passchier and R. N. Gunn, *Br. J. Clin. Pharmacol.*, 2012, **73**, 175-186.

4 H. Gewirtz, *JACC Cardiovasc. Imaging*, 2011, **4**, 292-302.

5 K.-L. Xiong, Q.-W. Yang, S.-G. Gong and W.-G. Zhang, *Nucl. Med. Commun.*, 2010, **31**, 4-11.

6 D. Papathanassiou, C. Bruna-Muraille, J.-C. Liehn, T. D. Nguyen and H. Curé, *Crit. Rev. Oncol. Hematol.*, 2009, **72**, 239-254.

7 P. W. Miller, N. J. Long, R. Vilar and A. D. Gee, *Angew. Chem. Int. Ed.*, 2008, **47**, 8998-9033.

8 M. E. Phelps, *PNAS*, 2000, **97**, 9226-9233.

9 P. F. Rambaldi, *Whole-Body FDG PET Imaging in Oncology*, Springer-Verlag, Mailand, 1st edn., 2013.

10 A. Ellmann and J. Holness, *Contin. Med. Educ.*, 2013, **31**, 279-283.

11 C. M. Clark, J. A. Schneider, B. J. Bedell, T. G. Beach, W. B. Bilker, M. A. Mintun, M. J. Pontecorvo, F. Hefti, A. P. Carpenter, M. L. Flitter, M. J. Krautkamer, H. F. Kung, R. E. Coleman, P. M. Doraiswamy, A. S. Fleisher, M. N. Sabbagh, C. H. Sadowsky, E. M. Reiman, S. P. Zehntner and D. M. Skovronsky, *JAMA*, 2011, **305**, 275–283.

12 P. H. Elsinga, A. van Waarde, A. M. J. Paans and R. A. J. O. Dierckx, *Trends on the Role of PET in Drug* Development, World Scientific, Singapore, 1st edn., 2012.

13 R. Vandenberghe, K. Van Laere, A. Ivanoiu, E. Salmon, C. Bastin, E. Triau, S. Hasselbach, I. Law, A. Andersen, A. Korner, L. Minthon, G. Garraux, N. Nelissen, G. Bormans, C. Buckley, R. Owenius, L. Thurfjell, G. Farrar and D. J. Brooks, *Ann. Neurol.*, 2010, **68**, 319-329.

14 H. Barthel, H. Gertz, S. Dresel, O. Peters, P. Bartenstein, K. Buerger, F. Hiemeyer, S. M. Wittemer-Rump, J. Seibyl, C. Reininger and O. Sabri, *Lancet Neurol.*, 2011, **10**, 424-435.

15 W. D. Heiss, K. Wienhard, R. Wagner, H. Lanfermann, A. Thiel, K. Herholz and U. Pietrzyk, *J. Nucl. Med.*, 1996, **37**, 1180-1182.

16 A. Becherer, G. Karanikas, M. Szabó, G. Zettinig, S. Asenbaum, C. Marosi, C. Henk, P. Wunderbaldinger, T. Czech, W. Wadsak and K. Kletter, *Eur. J. Nucl. Med. Mol. Imaging*, 2003, **30**, 1561-1567.

17 W. Chen, D. H. S. Silverman, S. Delaloye, J. Czernin, N. Kamdar, W. Pope, N. Satyamurthy, C. Schiepers and T. Cloughesy, *J. Nucl. Med.*, 2006, **47**, 904-911.

18 D. Le Bars, C. Lemaire, N. Ginovart, A. Plenevaux, J. Aerts, C. Brihaye, W. Hassoun, V. Leviel, P. Mekhsian, D. Weissmann, J. F. Pujol, A. Luxen and D. Comar, *Nucl. Med. Biol.*, 1998, **25**, 343-350.

19 C. Y. Shiue, G. G. Shiue, P. D. Mozley, M. P. Kung, Z. P. Zhuang, H. J. Kim and H. F. Kung, *Synapse*, 1997, **25**, 147–154.

20 L. Lang, E. Jagoda, B. Schmall, B. Vuong, H. R. Adams, D. L. Nelson, R. E. Carson and W. C. Eckelman, *J. Med. Chem.*, 1999, **42**, 1576–1586.

21 N. Arlicot, J. Vercouillie, M. Ribeiro, C. Tauber, Y. Venel, J. Baulieu, S. Maia, P. Corcia, M. G. Stabin, A. Reynolds, M. Kassiou and D. Guilloteau, *Nucl. Med. Biol.*, 2012, **39**, 570-578.

22 H. Barthel, M. C. Cleij, D. R. Collingridge, O. C. Hutchinson, S. Osman, Q. He, S. K. Luthra, F. Brady, P. M. Price and E. O. Aboagye, *Canc. Res.*, 2003, **63**, 3791-3798.

23 W. A. Weber, H. J. Wester, L. Grosu Anca, M. Herz, B. Dzewas, H. J. Feldmann, M. Molls, G. Stöcklin and M. Schwaiger, *Eur. J. Nucl. Med.*, 2000, **27**, 542-549.

24 Z. Szabo, E. Mena, S. P. Rowe, D. Plyku, R. Nidal, M. A. Eisenberger, E. S. Antonarakis, H. Fan, R. F. Dannals, Y. Chen, R. C. Mease, M. Vranesic, A. Bhatnagar, G. Sgouros, S. Y. Cho and M. G. Pomper, *Mol. Imaging. Biol.*, 2015, **17**, 565-574.

25 S. D. Johnson, M. J. Welch, *Q. J. Nucl. Med.*, 1998, **42**, 8-17.

26 D. C. Bortot, B. J. Amorim, G. C. Oki, S. B. Gapski, A. O. Santos, M. C. L. Lima, E. C. S. C. Etchebehere, M. F. Barboza, J. Mengatti and C. D. Ramos, *Eur. J. Nucl. Med. Mol. Imaging*, 2012, **39**, 1370-1736.

27 P. E. Valk, C. A. Mathis, M. D. Prados, J. C. Gilbert and T. F. Budinger, *J. Nucl. Med.*, 1992, **33**, 2133-2137.

28 S. T. Lee and A. M. Scott, *Sem. Nucl. Med.*, 2007, **37**, 451-461.

29 M. Guillaume, A. Luxen, B. Nebeling, M. Argentini, J. C. Clark and V. W. Pike, *Appl. Radiat. Isot.*, 1991, **42**, 749–762.

30 T. J. Ruth and A. P. Wolf, *Radiochim. Acta*, 1979, **26**, 21-24.

31 L. Cai, S. Lu, V. W. Pike, *Eur. J. Org. Chem.* 2008, 2853-2873.

32 C. Lemaire, M. Guillaume, R. Cantineau, A. Plenevaux and L. Christiaens, *Appl. Radiat. Isot.*, 1991, **42**, 629-635.

33 L. C. Libert, X. Franci, A. R. Plenevaux, T. Ooi, K. Maruoka, A. J. Luxen and C. F. Lemaire, *J. Nucl. Med.*, 2013, **54**, 1154-1161.

34 C. Lemaire, L. Libert, X. Franci, J.-L. Genon, S. Kuci, F. Giacomelli and A. Luxen, *J. Labelled Comp. Radiopharm.*, 2015, **58**, 281-290.

35 H. L. Yale, *J. Med. Pharmaceut. Ch.*, 1959, **1**, 121-133.

36 S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 237-432.

37 J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonk and H. Liu, *Chem. Rev.*, 2014, **114**, 2432-2506.

38 W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359-4369.

39 G. Angelini, M. Speranza, C.-Y. Shiue and A. P. Wolf, *J. Chem. Soc. Chem. Commun.* **1986**, 924-925.

40 M. R. Kilbourn, M. R. Pavia and V. E. Gregor, *Appl. Radiat. Isot.*, 1990, **41**, 823-828.

41 M. K. Das and J. Mukherjee, *Appl. Radiat. Isot.*, 1993, **44**, 835-842.

42 P. Johnström and S. Stone-Elander, *J. Labelled Compd. Rad.*, 1995, **39**, 537-548.

43 J. Prabhakaran, M. D. Underwood, R. V. Parsey, V. Arango, V. J. Majo, N. R. Simpson, R. van Heertum, J. J. Mann and J. S. D. Kumar, *Bioorg. Med. Chem.*, 2007, **15**, 1802-1807.

44 M. Suehiro, G. Yang, G. Torchon, E. Ackerstaff, J. Humm, J. Koutcher and O. Ouerfelli, *Bioorg. Med. Chem.*, 2011, **19**, 2287-2297.

45 P. J. Riss and F. I. Aigbirhio, *Chem. Commun.*, 2011, **47**, 11873-11875.

46 P. J. Riss, V. Ferrari, L. Brichard, P. Burke, R. Smith and F. I. Aigbirhio, *Org. Biomol. Chem.*, 2012, **10**, 6980-6986.

2

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.

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2.1 Introduction

In recent years, new and very promising methodologies for late-stage aromatic radiofluorination reactions have been developed and excellently reviewed by Preshlock *et al.*[1] and Brooks *et al.*[2] The overview of the different late-stage aromatic radiofluorination reactions given in Table 1, nicely demonstrates the progress in this area.[1–24] 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.

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

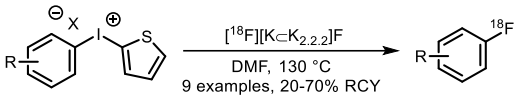
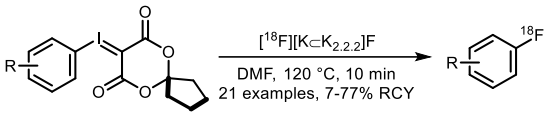
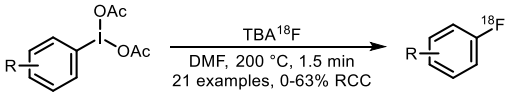
Method & highlights	**Ref.**
01 Radiofluorination of (hetero)aryl iodonium salts  • Low to moderate radiochemical yields on electron-rich and electron-neutral precursors. • Reasonable selectivity towards the less electron rich arene. • Precursors can be challenging to prepare. • Precursors have modest shelf lives. • Harsh reaction conditions, temperatures of >150 °C. • Limited tolerance to common functional groups.	2, 3, 23 and 24
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.	2, 4 and 5
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.	6

Table 1 (Continued)

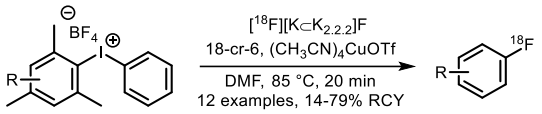
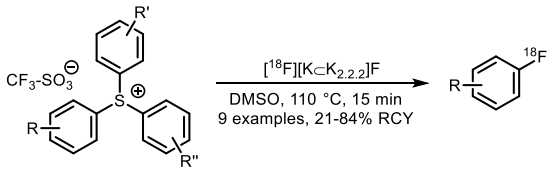
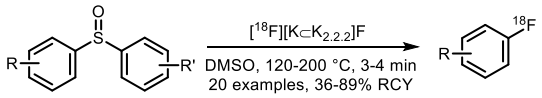
Method & highlights	**Ref.**
04 Cu-mediated radiofluorination of (mesityl)(aryl) iodonium salts  • Low to good radiochemical yields on electron-rich and electron-deficient precursors. • High reproducibility of radiochemical yields. • Relatively mild reaction conditions. • No reduced specific activity due to isotopic exchange on BF_4 anion. • Precursors can be challenging to prepare. • Copper catalyst is air stable and commercially available.	1, 2, 7 and 8
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.	1, 9 and 10
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.	1 and 11

Table 1 (Continued)

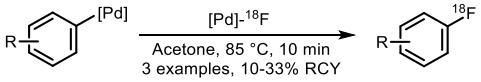
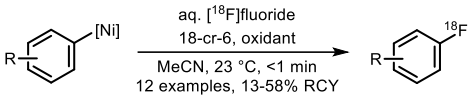
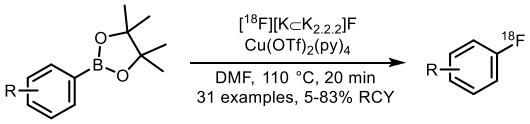
Method & highlights		**Ref.**
07 Pd-Catalysed radiofluorination of Pd-precursors  		
• Low to moderate radiochemical yields on electron-rich precursors. • Two-step procedure, synthesis of [Pd]–^{18}F complex and subsequent radiofluorination of a [Pd]-arene.	• [Pd]–^{18}F complex is sensitive to air and moisture.	2, 12-14
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.	2, 15 and 16
09 Copper mediated radiofluorination of (hetero)aryl boronic acid pinacolesters  		2 and 17
• 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.	

Table 1 (Continued)

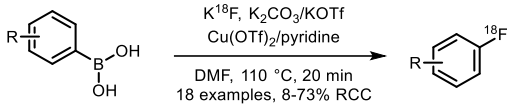
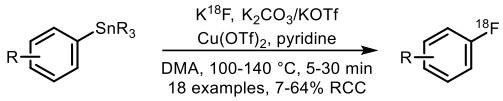
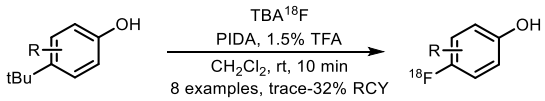
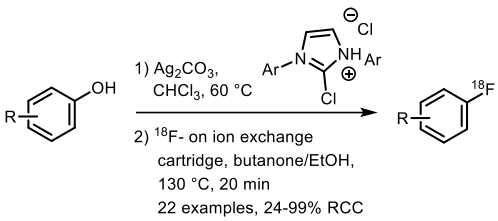
Method & highlights	**Ref.**
10 Copper mediated radiofluorination of aryl boronic acids  • Low to good radiochemical yields on electron-rich and electron deficient precursors. • Precursors are stable, however challenging to prepare. • Reasonable functional group tolerance. • Not yet tested on heteroaryl precursors. • Not extensively tested yet on more complex precursor structures.	1 and 18
11 Copper mediated radiofluorination of arylstannanes  • 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.	19
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 heteroarenes.	2 and 20

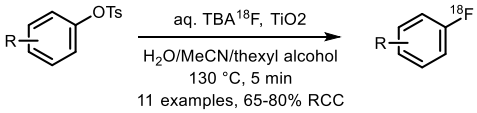
Table 1 (Continued)

Method & highlights	**Ref.**
13 Deoxyradiofluorination of phenols	21



- 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 [^{18}F]fluoride, which is 62% of the total fluoride activity.

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 [^{18}F]fluoride required, may be performed in up to 25% v/v water.
- Method has been successfully applied to existing PET radiopharmaceuticals. 1 and 22
- Scaling up the amount of aqueous [^{18}F]fluoride had limited success.

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

2.2 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 radio-fluorinated 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.

2.2.1 [^{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.[25] The metabolic stability can however be enhanced by deuteration of the [^{18}F]fluoromethyl group[26] or by inhibiting enzyme reactivity with a pharmacological intervention employing disulfiram or miconazole.[27,28]

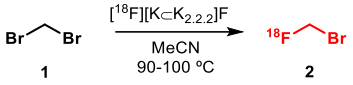
Multiple [^{18}F]fluoromethylation agents are described and available: [^{18}F]fluoro-methyl bromide and iodide are most established, while more recently, [^{18}F]fluoromethyl tosylate as a reagent is of increased interest. This is especially due to the ease of handling and purification of [^{18}F]fluoromethyl 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.[29]

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

2.2.1.1 [^{18}F]Fluoromethyl bromide

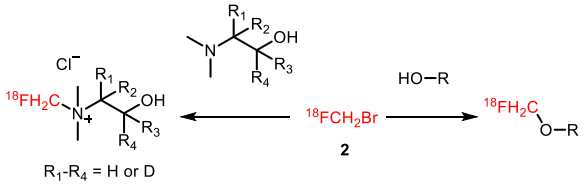
[^{18}F]Fluoromethyl bromide **2** was until the early 2000s the most established agent for [^{18}F]fluoromethylation. Although the interest in this building block has decreased since Neal and co-workers developed the synthesis and optimised the production of the tosyl analogue, [^{18}F]fluoromethyl tosylate, for [^{18}F]fluoromethylation, [^{18}F]fluoromethyl bromide is still applied in various reactions for PET tracer production.

[^{18}F]Fluoromethyl bromide is synthesised in one step by reacting dibromomethane **1** with [^{18}F]fluoride in MeCN at 90–100 °C (Scheme 1).



Scheme 1 Synthesis of [^{18}F]fluorobromomethane.

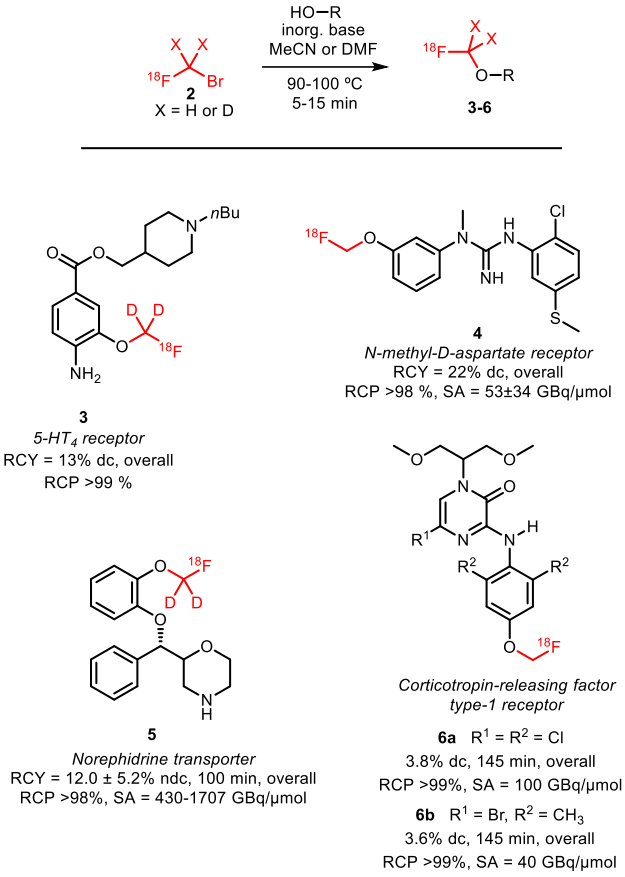
The main challenge is in the purification of the volatile product. Although [^{18}F]fluoromethyl bromide has a much lower boiling point (b.p. 9 °C) than its precursor (b.p. 97 °C) and the solvent MeCN (b.p. 82 °C), no pure product could be obtained by straightforward distillation.[30] Purification using gas chromatography is an alternative, however it is incompatible with automation.[29] Distillation over 3 to 4 silica plus Sep-Pak cartridges however provides pure [^{18}F]fluoromethyl bromide in an automation-compliant manner, as impurities are retained on the cartridges while most of the product passes through.[30,31] Reported radiochemical yields of [^{18}F]fluoromethyl bromide vary strongly, from 37 to 74% (dc), which is a major drawback for widespread application of this radiolabelled building block.[29,32]



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

The subsequent reactions that can be performed with [^{18}F]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 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.

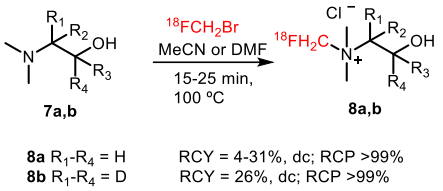
All syntheses were conducted under comparable reaction conditions. Mostly, reactions were performed in MeCN, only Lodge and co-workers described the use of *N*,*N*-dimethylformamide (DMF).[33] The reactions required high reaction temperatures (90–100 °C) and the addition of an inorganic base. The choice 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.[31–34]



Scheme 3 Recently produced tracers using *O*-alkylation with [^{18}F]fluoromethyl bromide.[31–34]

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 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).[30]



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

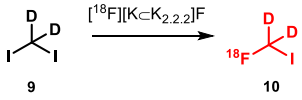
Smith and co-workers investigated the influence of different [^{18}F]fluoromethylation agents in the [^{18}F]fluorocholine synthesis. Next to [^{18}F]fluoromethyl bromide, less volatile [^{18}F]fluoromethyl tosylate was used for [^{18}F]fluoromethylation, to simplify handling and purification. However, 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**.[29]

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.

2.2.1.2 [^{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.

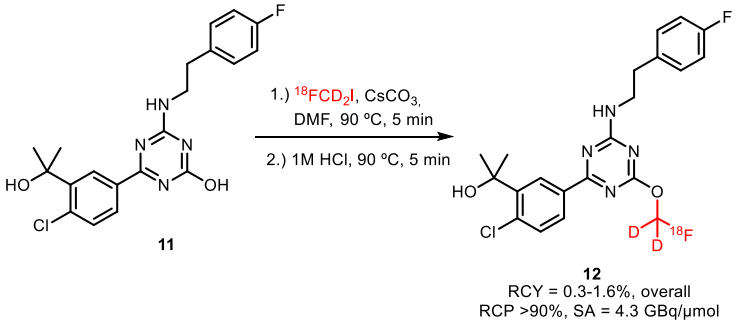
Deuterated [^{18}F]fluoromethyl iodide **10** was obtained *via* a nucleophilic substitution reaction of diiodomethane-d_2 **9** with [^{18}F]fluoride in the presence of potassium carbonate and kryptofix $K_{2.2.2}$ (Scheme 5). Separation of the volatile building block (b.p. 54–56 °C)[35] from the precursor (b.p. 181 °C)[36] 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.



Scheme 5 Synthesis of [^{18}F]fluoromethyl iodide.[35]

For [18F]fluoroalkylation, the distilled [18F]FCD2I **10** was reacted with the radio-labelling 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% (overall) product, which was attributed to the complexity of the [18F]fluoromethylation reagent synthesis.

It remains unclear why this [18F]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 [18F]fluoroalkylation reactions.[25]



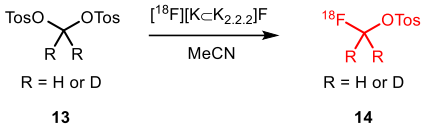
Scheme 6 [18F]Fluoroalkylation of a CB2 cannabinoid receptor ligand.[46]

2.2.1.3 [18F]Fluoromethyl tosylate

Although first published in 1987 by Block and Coenen, the synthesis of [18F]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 [18F]fluoromethyl tosylate in 2005, after which application of [18F]fluoromethyl bromide and iodide decreased considerably in favour of using [18F]fluoromethyl tosylate as [18F]fluoro-methylating agent. The increasing preference for [18F]fluoromethyl tosylate is easy to understand as handling and purification are straightforward in comparison to its volatile analogues.[37]

[18F]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 [18F]fluoromethyl tosylate, [18F]tosylfluoride is formed as side product.[29] Many efforts have been undertaken to reduce the amount of this side product and thus increase the yield of [18F]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.[37] Up to 20% of water can be beneficial to the reaction outcome.[38]

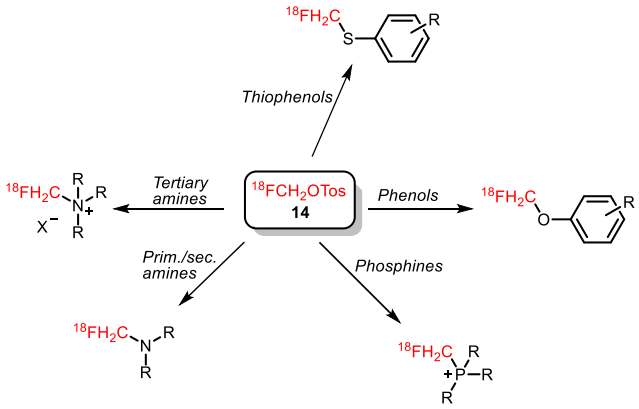


Scheme 7 Synthesis of [18F]fluoromethyl tosylate.

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.[26,29]

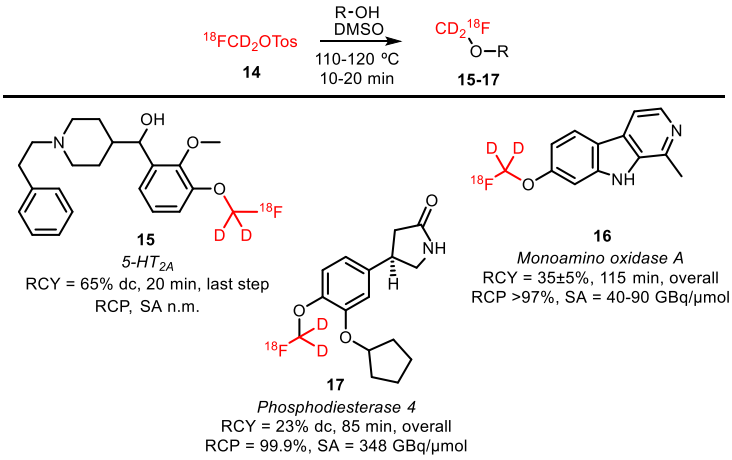
In contrast to the volatile analogues [18F]fluoromethyl bromide and iodide, purification of [18F]fluoromethyl tosylate can be easily carried out by semi-preparative HPLC, and even successful [18F]fluoromethylations without intermediate purification have been described.[39,40] Automated procedures have been developed using conventional synthesis units as well as microfluidic devices. Both provide the radiolabelled building block in a radiochemical yield of 44% (dc).[26,38]

[18F]Fluoromethyl tosylate can be used for a variety of alkylation reactions, next to the common *N*- and *O*-alkylation reactions, even *S*- and *P*-alkylations have been reported with this reagent (Scheme 8).



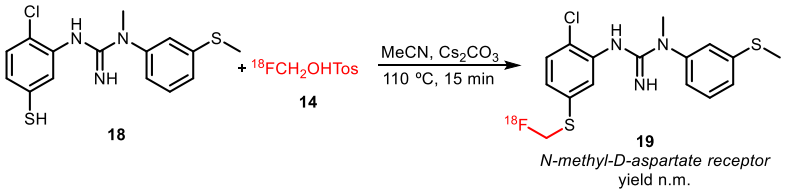
Scheme 8 Reactions with [18F]fluoromethyl tosylate.

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.[26,41,42]



Scheme 9 *O*-Alkylated tracers with [^{18}F]fluoromethyl tosylate.[26,41,42]

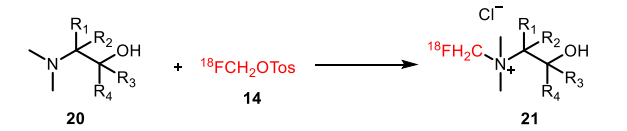
Analogous to the *O*-alkylation, aromatic *S*-alkylation of guanidine derivative **18** has been performed (Scheme 10).



Scheme 10 Synthesis of a *S*-fluoroalkyl guanidine derivative.[43]

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**.[43]

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).



a. R_1-R_4 = H — RCY = 7-20% (ndc), 15-150 min, overall; RCP >95%
b. R_1-R_4 = D — RCY = 10.1% ndc, 150 min, overall; RCP >99%
c. R_1,R_2 = H; R_3,R_4 =D — RCY = 8.6% ndc, 150 min, overall; RCP >99%

Scheme 11 Synthesis of [^{18}F]fluorocholine and deuterated derivatives with [^{18}F]fluoromethyl tosylate.[29,38,39]

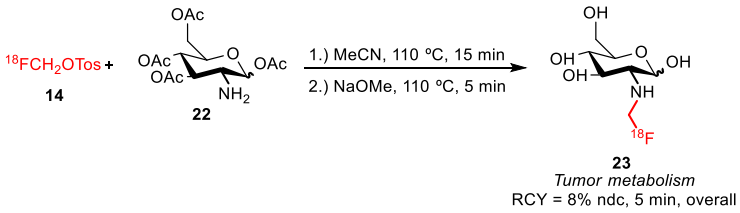
Extensive studies have been performed to establish optimal labelling conditions and to develop an automated synthesis procedure. Smith and co-workers were the first to report [^{18}F]fluoromethylation of the choline precursor using [^{18}F]fluoromethyl tosylate. They compared [^{18}F]fluorocholine and 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.[29]

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.[38]

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

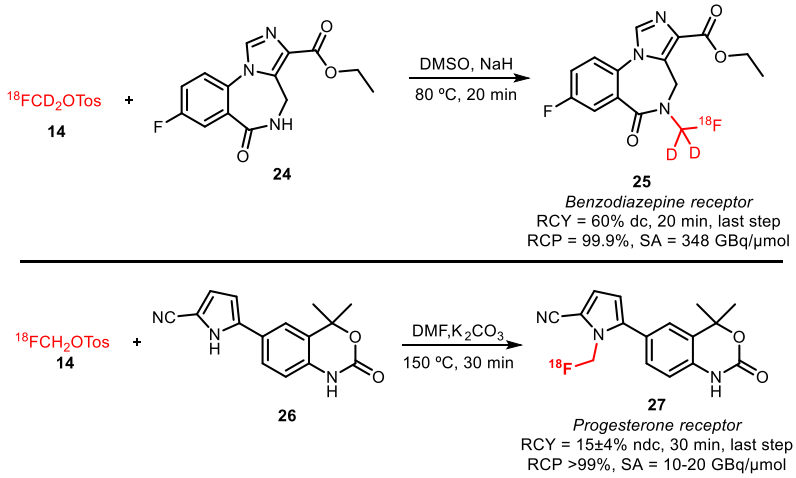
tosylate, dimethylamino ethanol was added and heated for 10 minutes at 120 °C to yield 7% (ndc, overall) in a total synthesis time of 75 minutes.

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 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.



Scheme 12 *N*-Alkylation reactions of primary amines.[44]

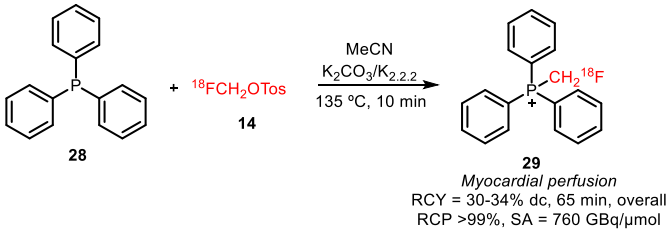
An example of [^{18}F]fluoroalkylation of primary amines is the synthesis of the glucosamine derivative **23** (Scheme 12). Using the conditions of Smith and co-workers, [^{18}F]fluoromethyl glucosamine derivative **23** could be obtained in a radiochemical yield of 8 ± 2% (n = 15, ndc).[44]



Scheme 13 *N*-Alkylation reactions of secondary amines.[26,45]

Two successful [^{18}F]fluoromethylations of secondary amines with [^{18}F]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,[26] 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).[45]

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).[40]



Scheme 14 Synthesis of [^{18}F]fluoromethyl triphenylphosphonium cation.[40]

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

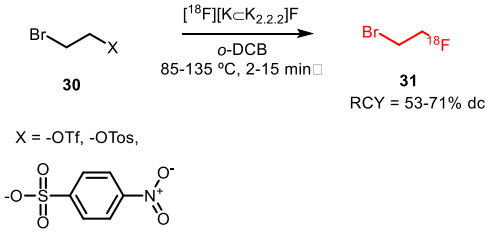
2.2.2 [^{18}F]Fluoroethyl halides and sulfonates

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.[46]

[^{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}F]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.

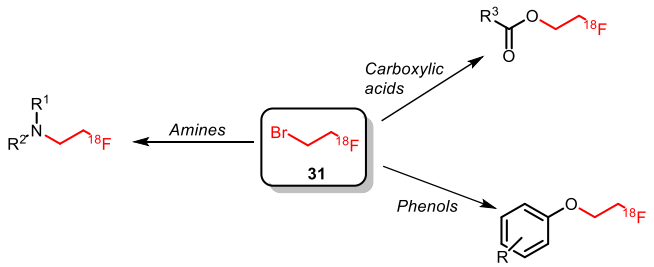
2.2.2.1 [^{18}F]Fluoroethyl bromide

[^{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).[47,48] Typically, 2-bromoethyl triflate served as precursor, but also the use of the corresponding tosylate or nosylate has been reported.[49,50] 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.[49,51] 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).[52]



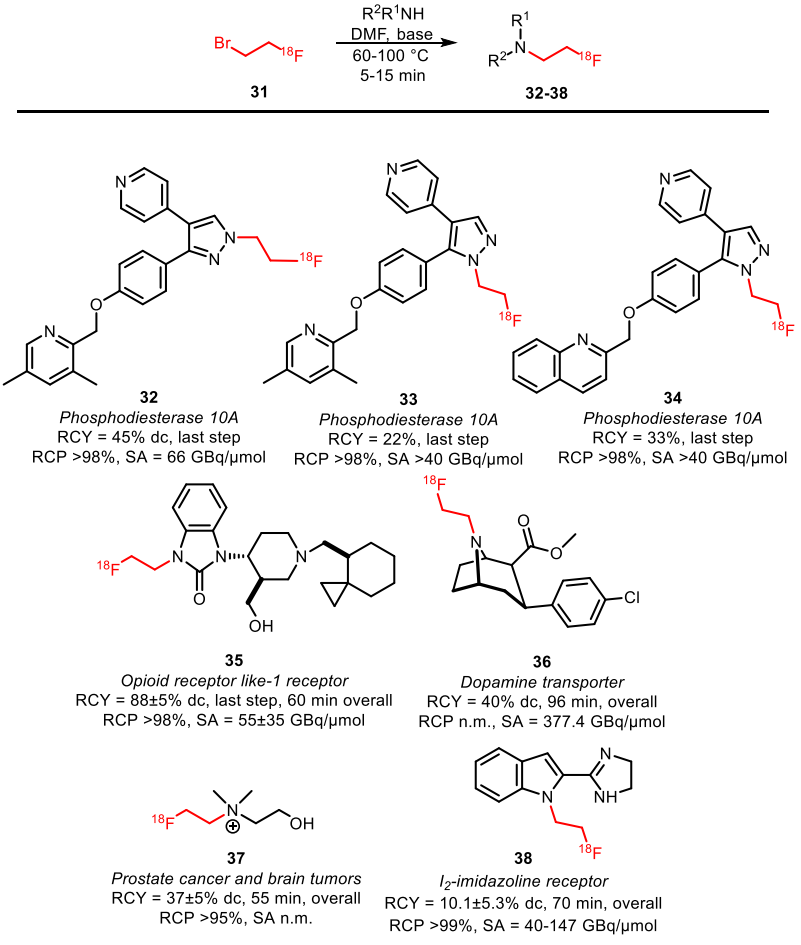
Scheme 15 Synthesis of the building block [^{18}F]fluoroethyl bromide.

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, *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.



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

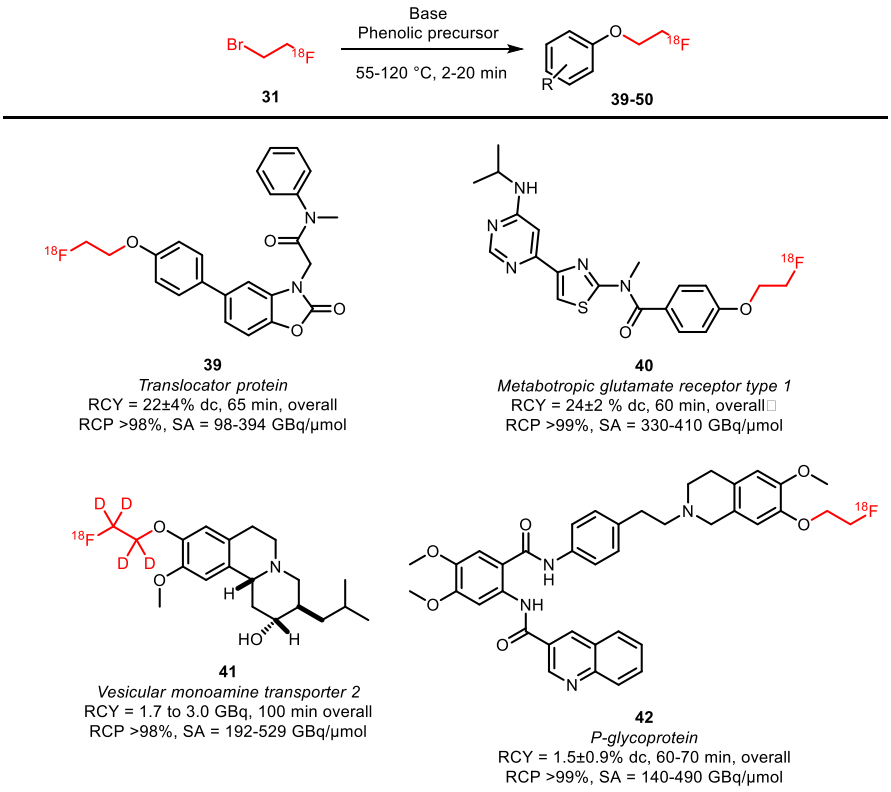
An overview of tracers obtained by *N*-alkylation is given in Scheme 17.[49,52–56] Typical reaction conditions for *N*-alkylations are the use of DMF as solvent and the addition of a base in the presence of the amine precursor.



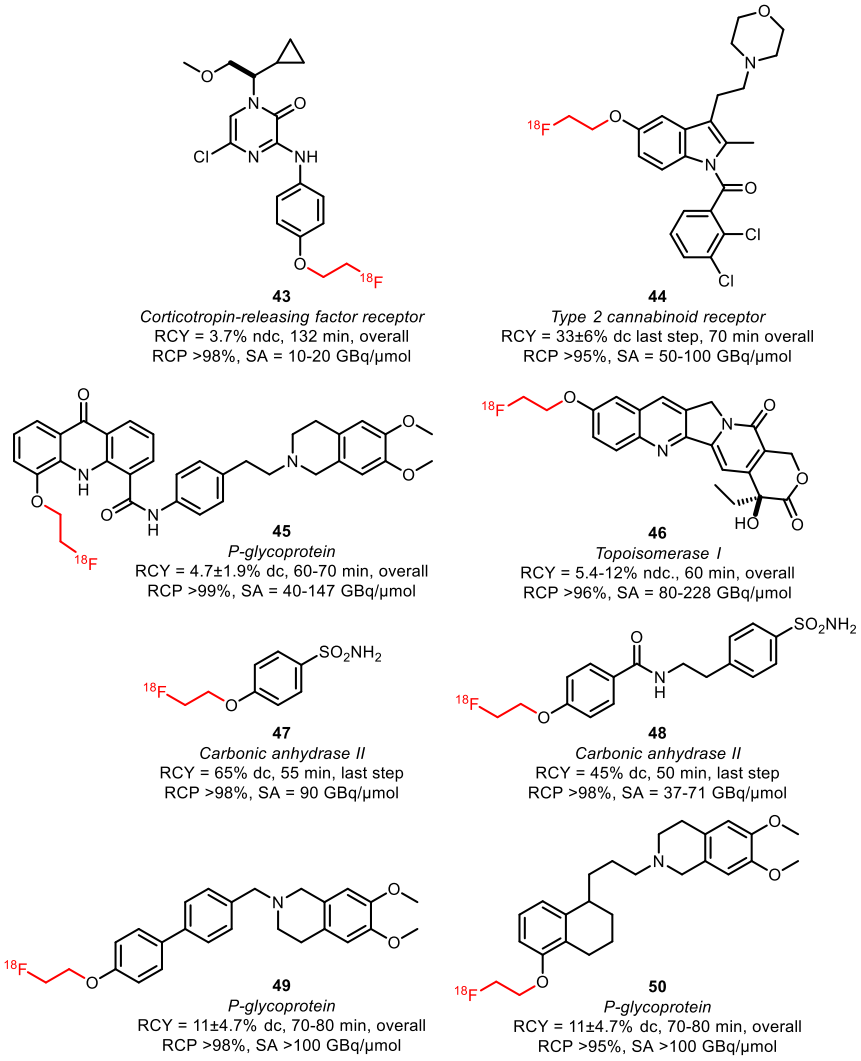
Scheme 17 *N*-Alkylation with [^{18}F]fluoroethyl bromide.[49,52–56]

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.[49]

Schmaljohann *et al.* succeeded in the development of a cartridge based purification procedure for fast and reliable automated 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.[52] Though, comparable synthesis times could also be achieved including an HPLC purification procedure.[55]



Scheme 18 Phenolic *O*-alkylation with [^{18}F]fluoroethyl bromide.[50,51,57–63]



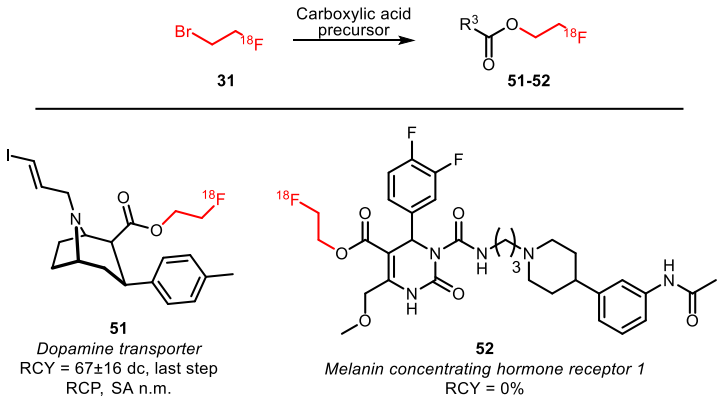
Scheme 18 (continued)

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).[50,51,57–63]

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.[51] 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.[48,51]

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.[64] Another coupling reaction with an 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.[65]



Scheme 19 Esterification of carboxylic acids with [^{18}F]fluoroethyl bromide.[64,65]

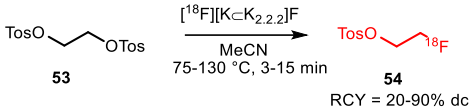
In conclusion, [^{18}F]fluoroethyl bromide can be regarded a convenient reagent for radiofluorination of amines, phenols and carboxylic acids *via* alkylation. [^{18}F]Fluoroethyl bromide can be synthesised fast and reliably and likewise the coupling reactions proceed fast, providing in one step the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

2.2.2.2 [^{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.*[66] 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 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.[67]

The synthesis procedures of [^{18}F]FETos **54** follow similar reaction conditions (Scheme 20). After azeotropic drying, the kryptofix-potassium carbonate-[^{18}F]fluoride complex ([^{18}F][K⊂K$_{2.2.2}$]F) reacted 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 [^{18}F]FETos synthesis or also for subsequent alkylation reactions.[67] Pascali *et al.* developed a microfluidic approach providing the crude radiolabelled building block in a radiochemical yield of 67% (based on radio-TLC analysis).[38]



Scheme 20 Radiosynthesis of [^{18}F]FETos.

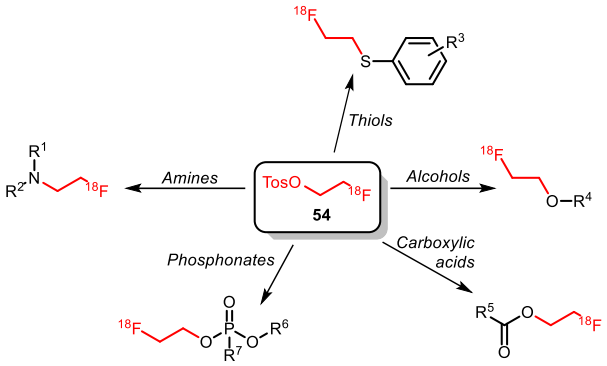
Of the different approaches to purify [^{18}F]FETos, semipreparative HPLC generally provided the product with the highest chemical purity, leading to better conversions in the subsequent alkylation reaction. Furthermore, reduced formation of non-radioactive by-products was observed during the alkylation reaction which made final purification of the tracer easier.[46]

As HPLC purification is time-consuming, several SPE-based purification procedures have been developed. However, most of them focus on the removal of free [^{18}F]fluoride, potassium carbonate and kryptofix only.[67] Moreover, significant losses of radioactivity during cartridge purification or the subsequent drying step were observed.[68,69] 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%.[67]

Next to that, many successful one-pot methods have been described where [^{18}F]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.[68] 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 semipreparative HPLC.[70]

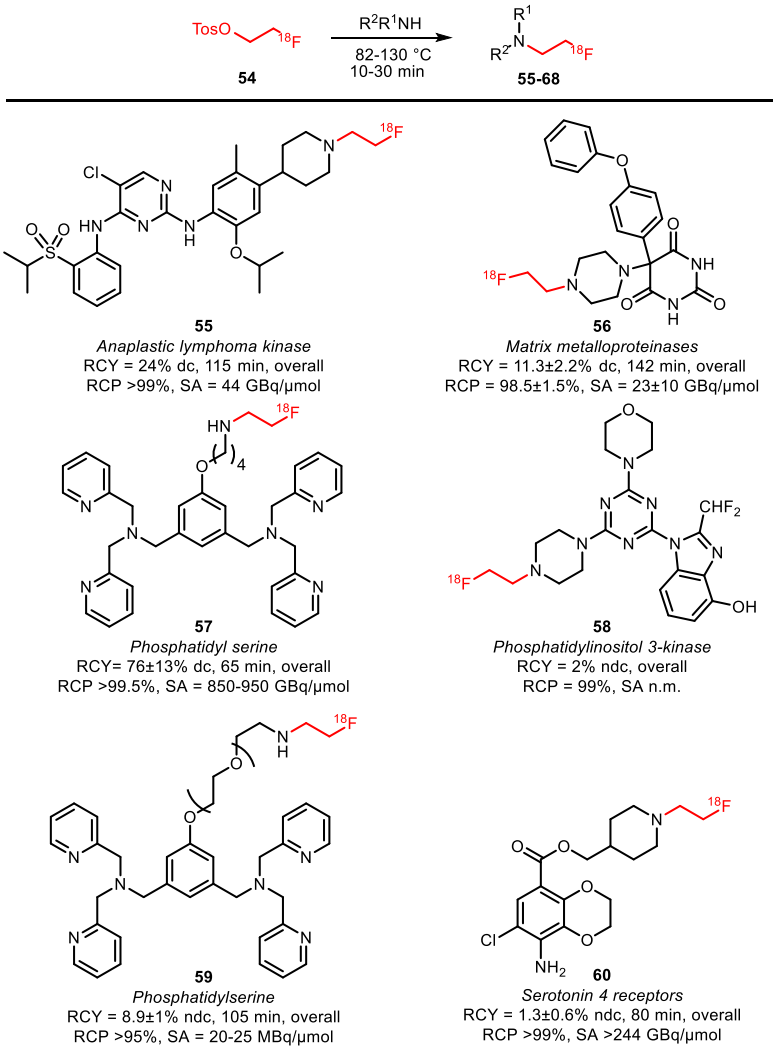
[^{18}F]FETos has found widespread application as a building block (Scheme 21). Besides *N*- and *O*-alkylation, reactions of [^{18}F]FETos with phosphonates and thiols are known. Further, next to phenolic *O*-alkylation aliphatic hydroxyl groups and aromatic carboxylic acids can also be labelled with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



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

Numerous *N*-alkylations have been performed using [^{18}F]FETos as a building block (Scheme 22).[38,46,71-84] 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 pKa-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.[72,77] To achieve [^{18}F]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.[74,79]

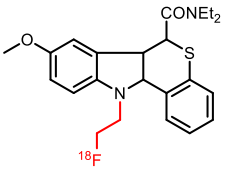
Studies that involve Finkelstein-type alkylation reactions by addition of alkali iodides showed promising results indicating that *in situ* iodide exchange indeed could increase the yield of *N*-alkylation.[85] However, this strategy has only been applied to access the serotonin 4 receptor tracer **60** and actually did not appear beneficial for the overall reaction outcome.[78] The majority of tracers produced by alkylation with [^{18}F]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]



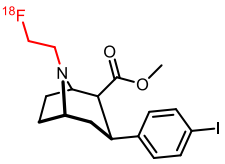
Scheme 22 PET tracers synthesised by *N*-alkylation with [^{18}F]FETos.[49,57,82–95]

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.[83]

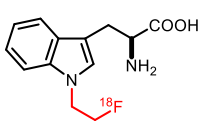
For some of the tracers in Scheme 22, direct and indirect labelling methods of the molecule were compared. In general no clear preference for either method could be concluded as in some cases (**61** and **66**) higher yields with direct labelling were found whereas in other cases (**55** and **62**) the indirect labelling strategy was more successful.[80,83]



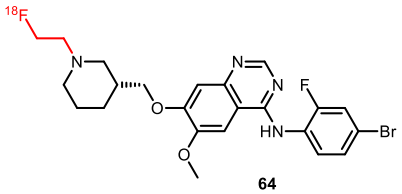
61
Translocator protein
RCY = 4% ndc, 120-150 min, overall
RCP, SA n.m.



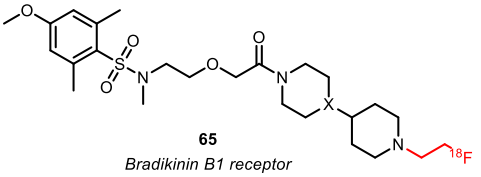
62
Dopamine transporter
RCY = 25% ndc, 100 min, overall
RCP >98%, SA = 32-86 GBq/μmol



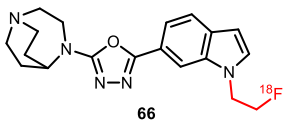
63
Tumours
RCY = 0.9±0.2% ndc, 65 min, overall
RCP >98%, SA = 600±180 GBq/ μmol



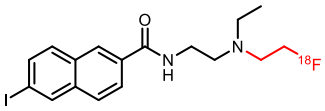
64
VEGF
RCY = 20±5% ndc, 75 min, overall
RCP >99%, SA = 37-74 GBq/μmol



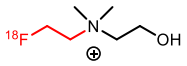
65
Bradikinin B1 receptor
a X=C RCY = 10±5% dc, overall; RCP >99%, SA = 38±22 GBq/μmol
b X=N RCY = 22±14% dc, overall; RCP >99%, SA = 54±33 GBq/μmol



66
a7 nAChR
RCY = 7% da, 20 min, last step
RCP>95%, SA = 150 GBq/μmol



67
Melanin pigment
RCY = 11% dc, 91 min, overall
RCP >99%, SA n.m.

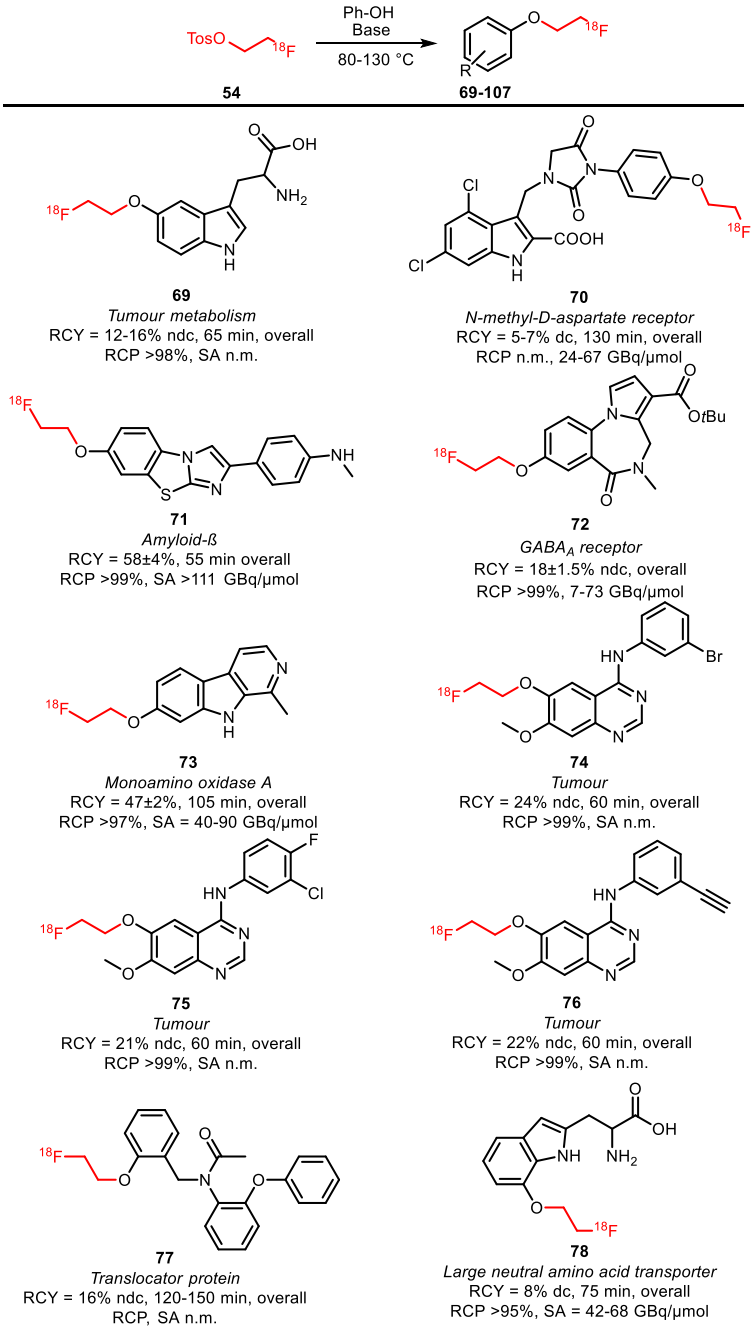


68
Prostate cancer
RCY = 36-48% ndc, 15-55 min, overall
RCP >95 %

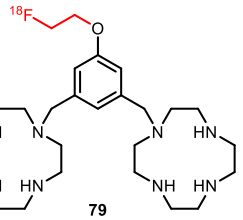
Scheme 22 (continued)

Many *O*-alkylations with [^{18}F]FETos have been performed and Scheme 23 shows all tracers synthesised by fluoroalkylation of phenolic precursors.[41,69,70,86–109] 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 been described. The choice of base and its concentration has a big influence on the yield of the alkylation reaction. Basic formation of the phenolate generates the nucleophile, which reacts with [^{18}F]FETos in the radiolabelling.[106] 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 varied from a few minutes up to

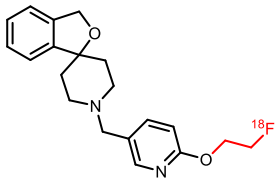
several hours.[93,94] The base was either filtered off after phenolate formation or added together with the precursor to the reaction mixture containing [^{18}F]FETos.[87,93]



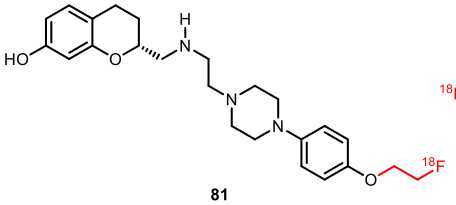
Scheme 23 PET tracers synthesised by *O*-alkylation of phenolic precursors with [^{18}F]FETos.[41,69,70,86–109]



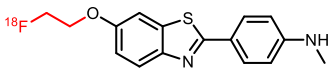
79
Phosphatidylserine
RCY = 77% dc, alkylation step
RCP n.m., SA >50 GBq/µmol



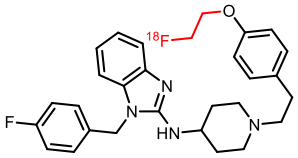
80
Sigma-1 receptor
RCY = 8-10% dc, 60 min, overall
RCP >99%, SA = 56-78 GBq/µmol



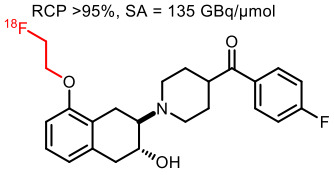
81
Dopamine $D_{2/3}$ receptor
RCY = 5±3% dc, 150 min, overall
RCP = 92±5%, SA = 2.9-30.4 GBq/µmol



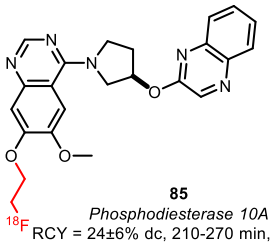
82
Amyloid-ß
RCY = 14% dc, overall
RCP >95%, SA = 135 GBq/µmol



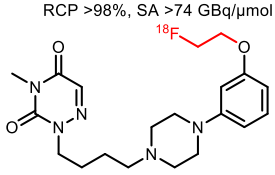
83
Tau protein
RCY = 5-10 %
RCP, SA n.m.



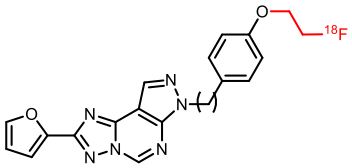
84
Vesicular acetylcholine transporter (VAChT)
RCY = 15-40% dc, 120-140 min, overall
RCP >98%, SA >74 GBq/µmol



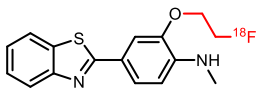
85
Phosphodiesterase 10A
RCY = 24±6% dc, 210-270 min, overall
RCP >99%, SA = 110-1100 GBq/µmol



86
Serotonin 1A receptor
RCY = 45±5% ndc, last step, 60 min, overall
RCP >95%, SA = 93±19 GBq/µmol

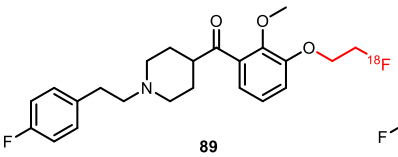


87
Cerebral adenosine A_{2A} receptors
RCY = 7±2% dc, 114 min, overall
RCP >98%, SA = 23±5 GBq/µmol

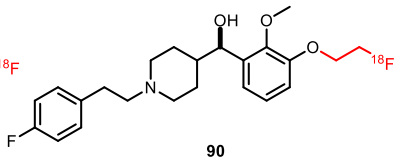


88
Amyloid-ß
RCY = 32% dc, overall
RCP >95%, SA = 80 GBq/µmol

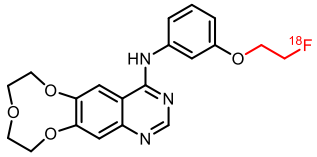
Scheme 23 (continued)



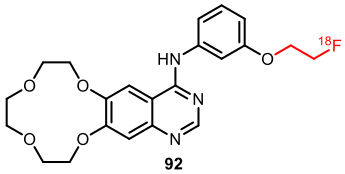
89
Serotonin 1A receptor
RCY = 40% dc, 100 min, overall
RCP >96%, SA = 25-35 GBq/µmol



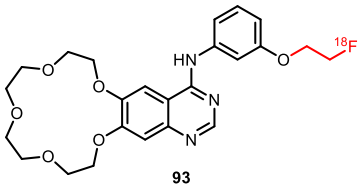
90
Serotonin 1A receptor
RCY = 40% dc, 75-100 min, overall
RCP >96%, SA = 25-35 GBq/µmol



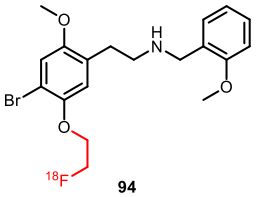
91
EGFR
RCY = 23% ndc
RCP >99%, SA n.m.



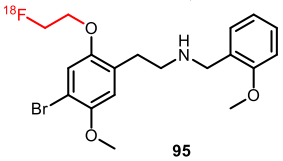
92
EGFR
RCY = 10% ndc
RCP >99%, SA n.m.



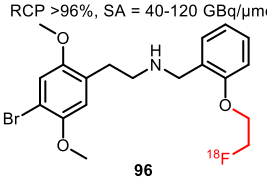
93
EGFR
RCY = 20% ndc
RCP >99%, SA n.m.



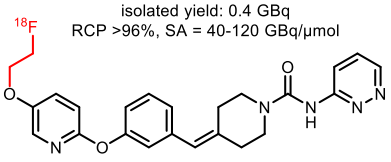
94
Serotonin 2A receptor
isolated yield: 2.01 GBq
RCP >96%, SA = 40-120 GBq/µmol



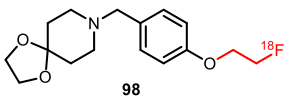
95
Serotonin 2A receptor
isolated yield: 0.4 GBq
RCP >96%, SA = 40-120 GBq/µmol



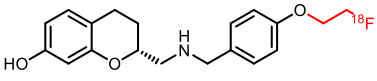
96
Serotonin 2A receptor
RCY = 25±5%, 50 min, overall
RCP >87%, SA = 40-120 GBq/µmol



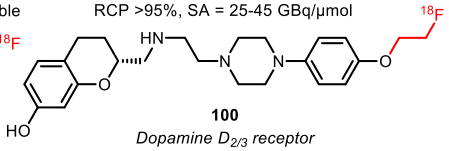
97
Fatty acid amide hydrolase
Separation from chemical impurities not possible



98
Sigma-1 receptor
RCY = 15% dc, 100 min, overall
RCP >95%, SA = 25-45 GBq/µmol

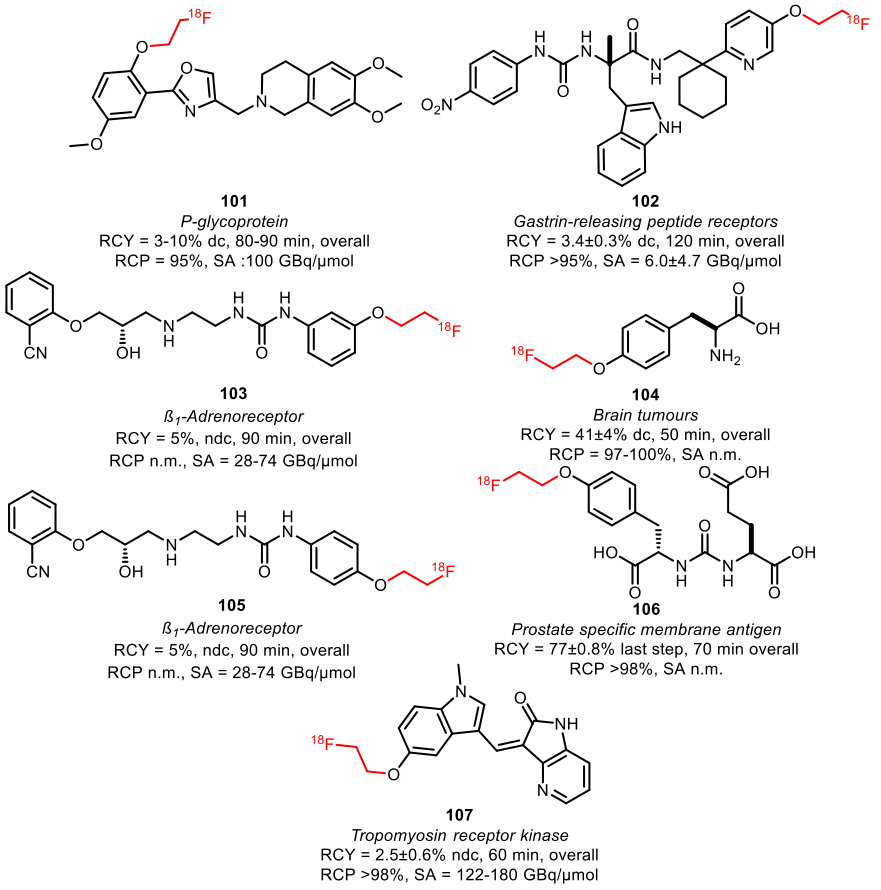


99
Dopamine $D_{2/3}$ receptor
RCY = 12±6% dc
RCP >95%, SA = 102±30 GBq/µmol



100
Dopamine $D_{2/3}$ receptor
RCY = 5±3% dc
RCP = 93±3%, SA = 25±15 GBq/µmol

Scheme 23 (continued)

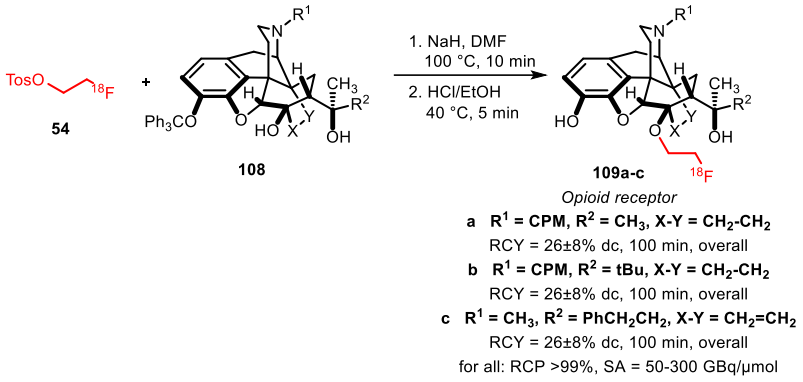


Scheme 23 (continued)

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.[41] In another study, **73** was obtained *via* direct labelling in 23% decay corrected radiochemical yield.[110]

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%).[91]

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).[67,111]

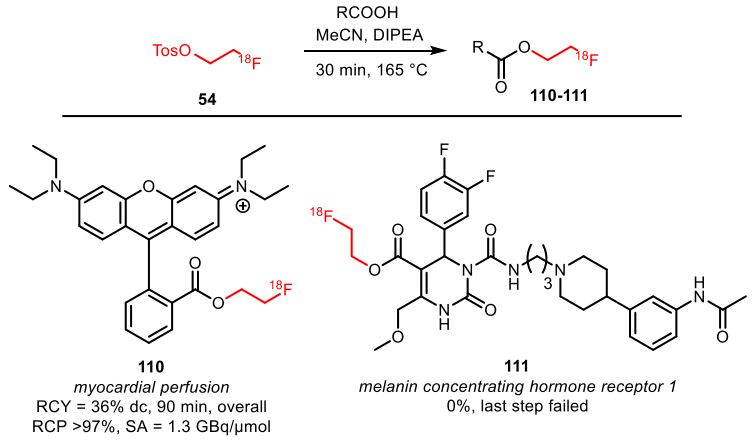


Scheme 24 Aliphatic *O*-alkylation with [^{18}F]FETos.[67,111]

Esterification of carboxylic acids with [^{18}F]FETos has been studied by Heinrich *et al.* and Philippe *et al.*[65,68] 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.[65] 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).[68]

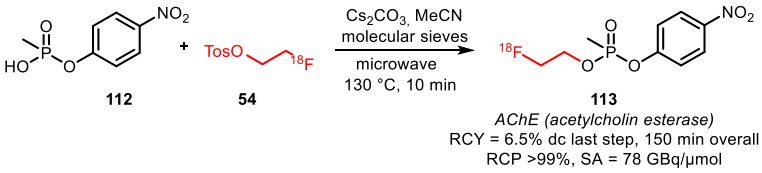
James *et al.* described the synthesis of an acetylcholine esterase tracer *via* *O*-alkylation of a phosphonate precursor (Scheme 26). The reaction was carried out in a microwave reactor with addition of cesium carbonate as base and with molecular sieves.

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.[112]



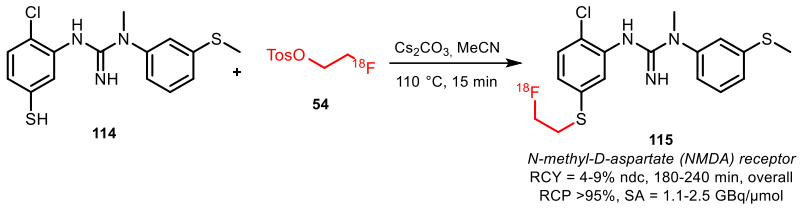
Scheme 25 *O*-Alkylation of carboxylic acids with [^{18}F]FETos.[65,68]

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.[43]



Scheme 26 *O*-Alkylation of a phosphonate with [^{18}F]FETos.[112]

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.



Scheme 27 Synthesis of **115** by S-alkylation.[43]

2.2.2.3 [^{18}F]Fluoroethyl sulfonate esters

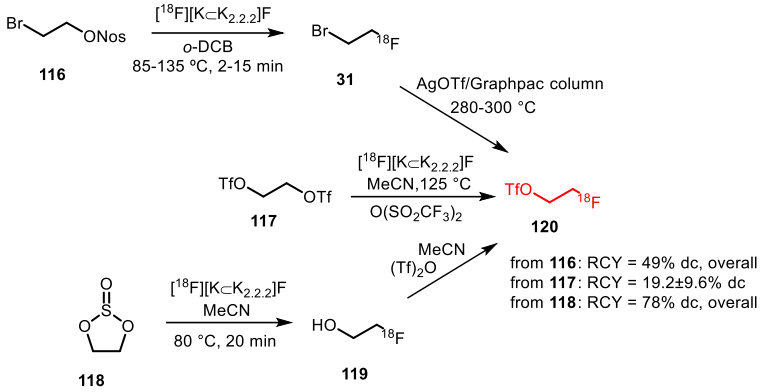
In addition to the two most applied [^{18}F]fluoroethyl building blocks discussed above, a number of other [^{18}F]fluoroethyl sulfonate esters have been employed for fluorine-18 labelling. Most notably, [^{18}F]fluoroethyl nosylate, brosylate, 3,4-dibromobenzene-sulfonate and triflate have been used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

2.2.2.3.1 [^{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).[65]

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.[49]



Scheme 28 [18F]Fluoroethyl triflate synthesis from [18F]fluoroethyl bromide or ethylene glycol bistriflate.[49,65,113]

A third approach was developed by Peters *et al.* They used [18F]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, [18F]fluoroethanol was treated with triflic anhydride. The reaction proceeded smoothly (1 min) and did not require elevated temperatures. [18F]Fluoroethyl triflate was obtained after purification using an Alumina N light cartridge in a radiochemical yield of 78% (dc) starting from dried [18F]fluoride.[113]

Triflate building block **120** has been used in both *N*-alkylations and *O*-alkylations.[49,65,114] While *O*-alkylation towards **121** proved unsuccessful under common [18F]fluoroethylation conditions (the tracer could only be synthesised using direct radiofluorination in a microfluidic system), two successful *N*-alkylations were described (Fig. 1).[65]

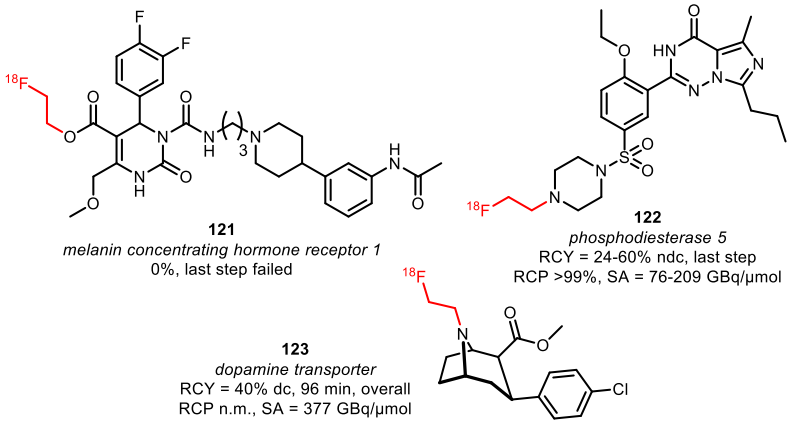
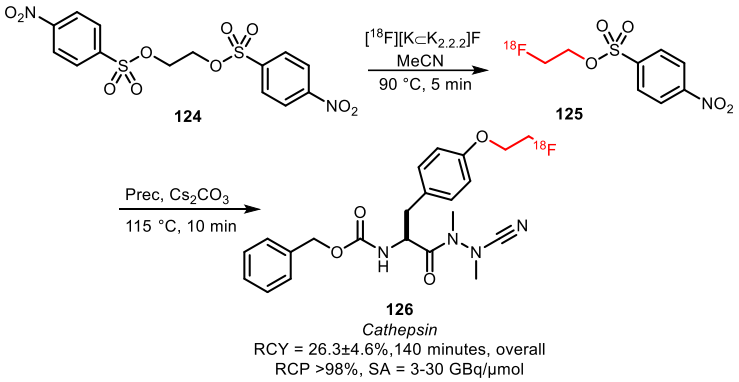


Figure 1 Tracers labelled with [18F]fluoroethyl triflate.[49,65,114]

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.[49,114] 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.[49]

2.2.2.3.2 [^{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).



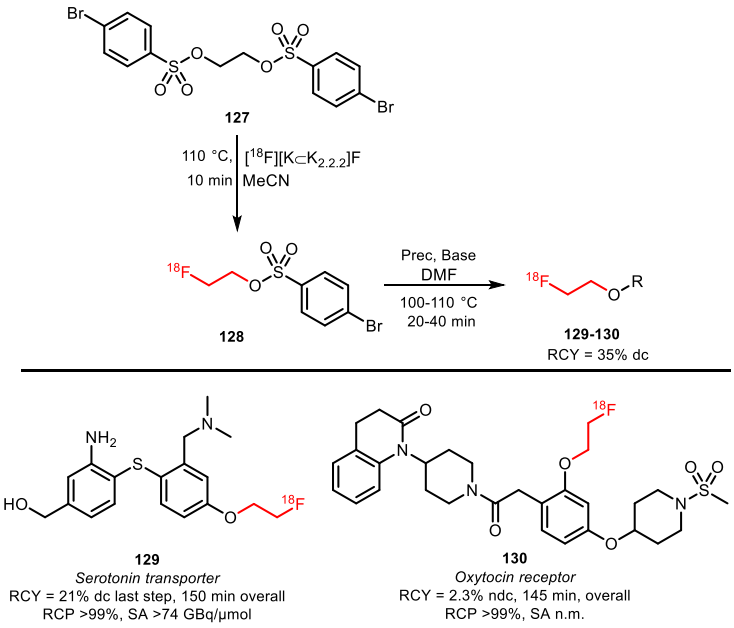
Scheme 29 [^{18}F]Fluoroethyl nosylate synthesis and reaction towards cathepsin inhibitor **126**.[96]

[^{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.[96]

2.2.2.3.3 [^{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.[115] 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).[116]



Scheme 30 [^{18}F]Fluoroethyl brosylate synthesis and subsequent [^{18}F]fluoroethylation.[116,118]

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.[116,117]

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

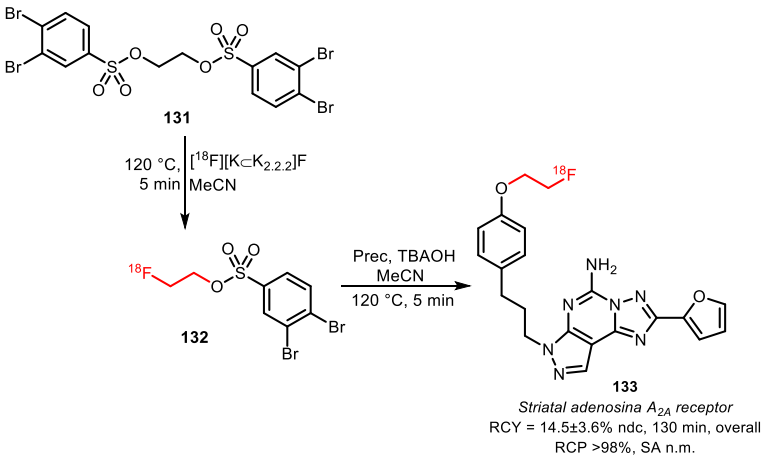
overall radiochemical yield of only 2.3%. Total synthesis time of both tracers was about 150 minutes.

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.[116,118]

2.2.2.3.4 [^{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 [^{18}F]fluoroethyl-3,4-dibromobenzene-sulfonate **132** is highly reactive and quite stable and achieves high yields in alkylating reactions (Scheme 31).[115]

Still, thus far 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 A2A receptor imaging. In the first step, ethane-1,2-diyl-bis(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).[119]

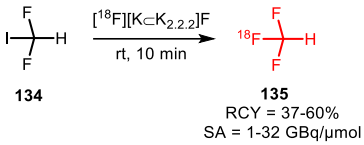


Scheme 31 [^{18}F]Fluoroethyl-3,4-dibromobenzene sulfonate synthesis and reaction to the A_{2A} receptor tracer **133**.[119]

2.2.3 [^{18}F]Trifluoromethane

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]trifluoromethane 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.

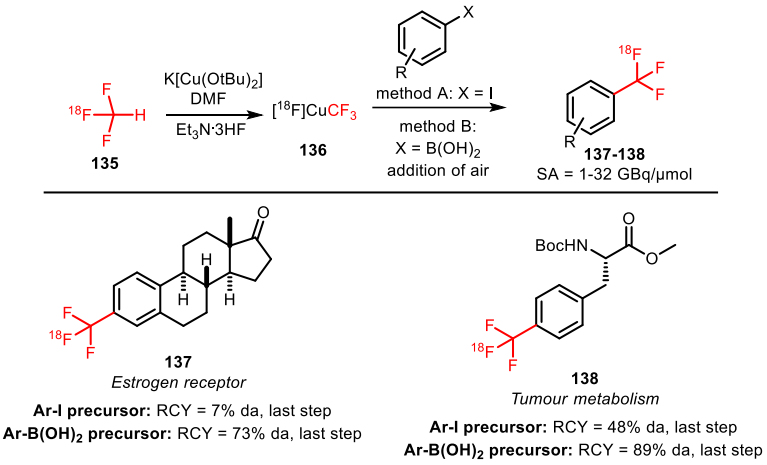
Difluoroiodomethane **134** and the difluoromethylsulfonium salt **142** have been explored as alternative precursors for [^{18}F]trifluoromethane synthesis (Schemes 32 and 35). Based on the precursor difluoroiodomethane **134**, van der Born *et al.* developed two different methods to synthesise [^{18}F]trifluoromethane, 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]trifluoromethane **135** in a radiochemical yield of 60% with a specific activity of 1 GBq/µmol. 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.[120]



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

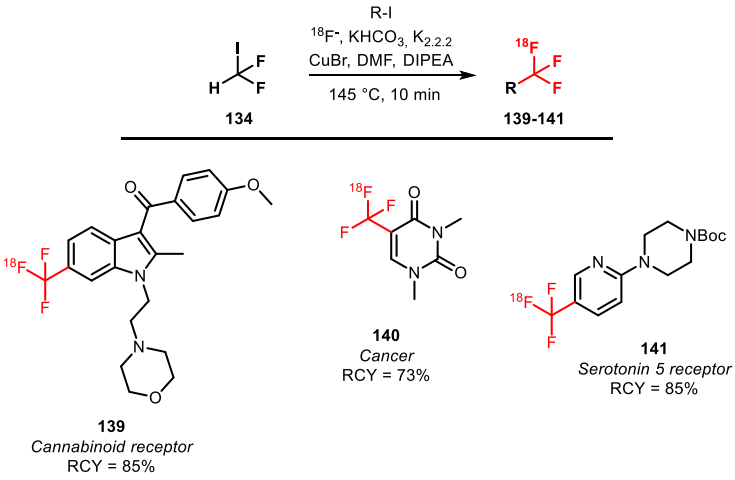
To introduce the [^{18}F]trifluoromethyl group into PET tracers **137** and **138** for imaging breast cancer and other tumours, copper-mediated reactions with aryl iodides and aryl boronic acids showed promising results. [^{18}F]Trifluoromethylation of aryl iodides was carried out in the presence of 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]trifluoromethane 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.[120]



Scheme 33 PET tracer synthesis by [^{18}F]trifluoromethylation of iodide and boronic acid precursors.[120]

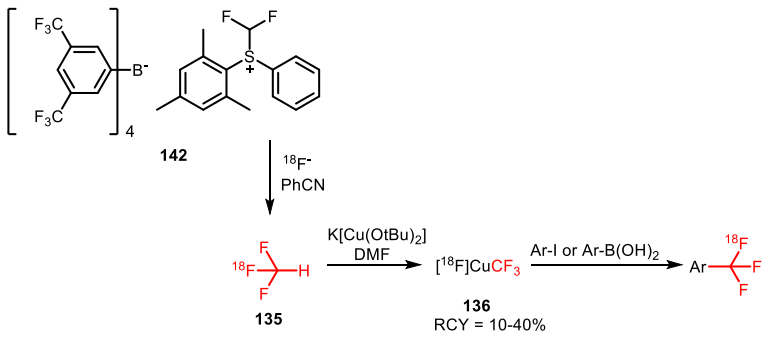
In addition to the above methods, a one-pot procedure to synthesise [^{18}F]trifluoromethylated tracers in an automation compliant manner has been developed by Rühl *et al*. (Scheme 34).



Scheme 34 One-pot synthesis of [^{18}F]trifluoromethylated arenes.[121]

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.[121]

Ivashkin *et al.* employed difluoromethylsulfonium salt **142** as precursor for the [^{18}F]trifluoromethane synthesis (Scheme 35). However, [^{18}F]trifluoromethane 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, comparable to the one-pot procedure described by Rühl *et al.*[122]



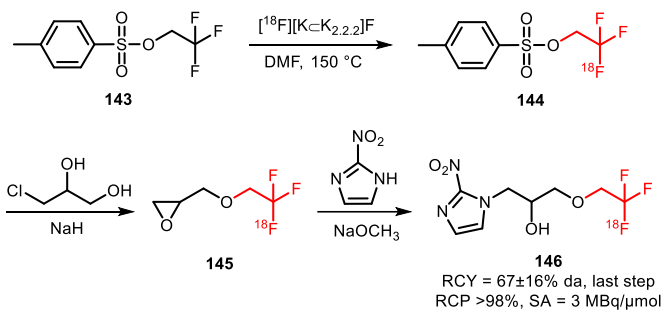
Scheme 35 [^{18}F]Trifluoromethane synthesis with the difluoromethylsulfonium salt **142** as precursor.[122]

In conclusion, production of [^{18}F]trifluoromethane with high specific activity remains a challenge. A method has however been developed providing [^{18}F]trifluoromethane with an acceptable specific activity of 32 GBq/µmol. Aryl iodides and boronic acids have successfully been labelled with [^{18}F]trifluoromethane 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]trifluoromethane holds great promise for fluorine-18 labelling of compounds containing native trifluoromethyl groups.

2.2.4 [^{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 (Scheme 36).



Scheme 36 Synthesis of the hypoxia tracer [^{18}F]TFMISO.[123]

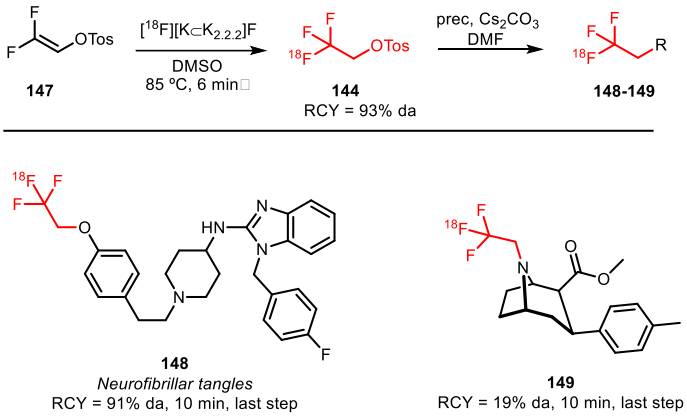
The building block was synthesised *via* ^{18}F–^{19}F exchange from 2,2,2-trifluoroethyl tosylate **143**. For this, the unlabelled compound was heated in presence of [^{18}F][K⊂K$_{2.2.2}$]F at 150 °C. After 10 minutes, the product was separated from unreacted [^{18}F]fluoride by extraction with ether. 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.[123]

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).



Scheme 37 [^{18}F]Trifluoroethyl tosylate synthesis and coupling towards **148** and **149**.[97,124,125]

Extensive studies to find optimal reaction conditions were conducted and in the end 5 minutes 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) was obtained even with low quantities of [^{18}F]fluoride at the start of synthesis (5 GBq).[124]

[^{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.[125]

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

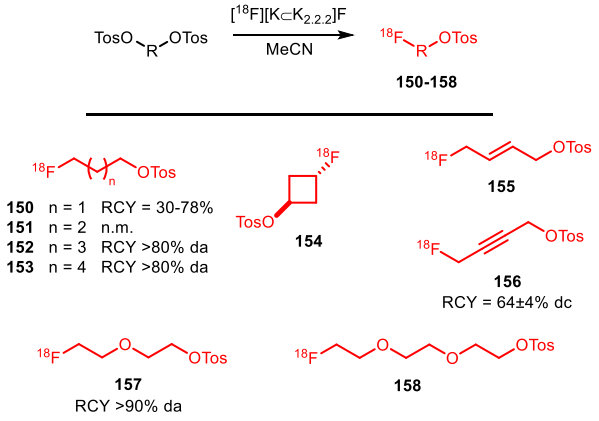
metabolic degradation compared to [^{18}F]fluoroethylates make it a promising building block for fluorine-18 labelling in the future.

2.2.5 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.[69,89,126]

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.

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.



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

Although similar radiochemical yields for the one-pot strategy and two-step procedure including HPLC purification have been described,[78] 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.[126] 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.[131] For [^{18}F]fluoropropyl tosylate **150**, automated synthesis procedures have been developed including a microfluidic approach.[38]

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 (Figure 2).

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,[38,78,127] (except for the 5-HT4 receptor tracer **164**). The other tracers depicted in Figure 2 were synthesised by *O*-alkylation of the phenolic precursor with **150**.[38,76,69,70,88,89,126–129] 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.[129]

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.[89]

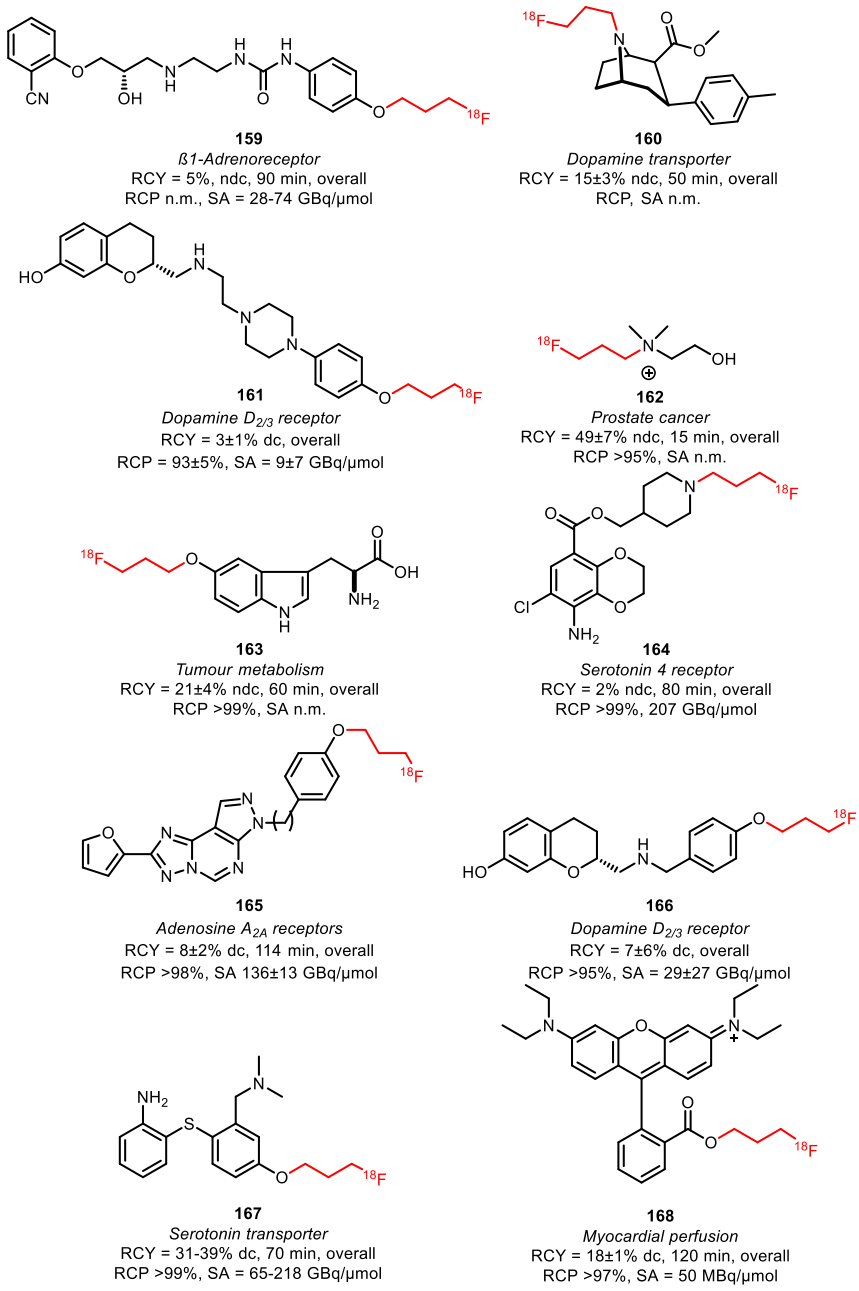


Figure 2 PET tracers synthesised from the building block [^{18}F]fluoropropyl tosylate.[38,57,69,78,88,89,126–129]

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 improved stability.[126]

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 (Figure 3). 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.[89,101]

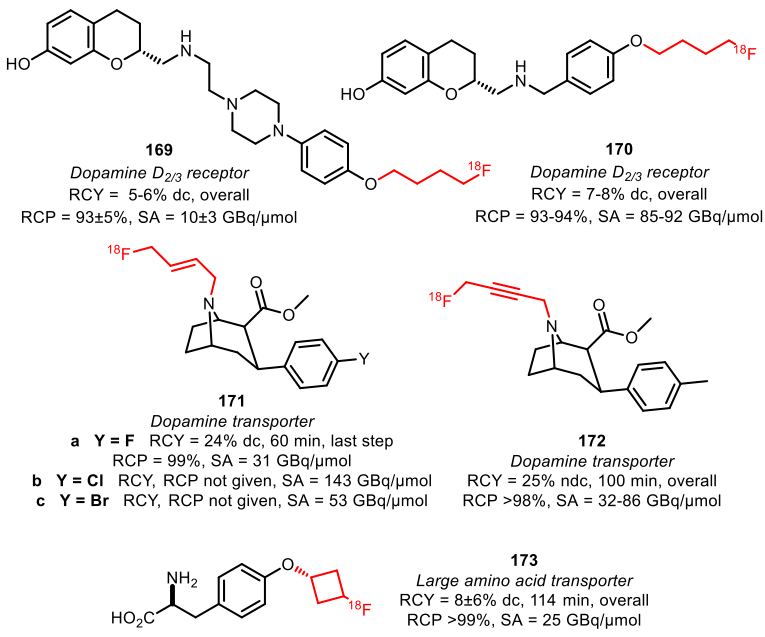
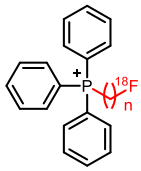


Figure 3 PET tracers synthesised by indirect labelling with [^{18}F]fluorobutyl tosylate and derivatives.[46,89,102,130,131]

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.[46,130] 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.[46] Furthermore, Franck *et al*. introduced the [^{18}F]fluoro-

cyclobutyl group labelled 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).[131]

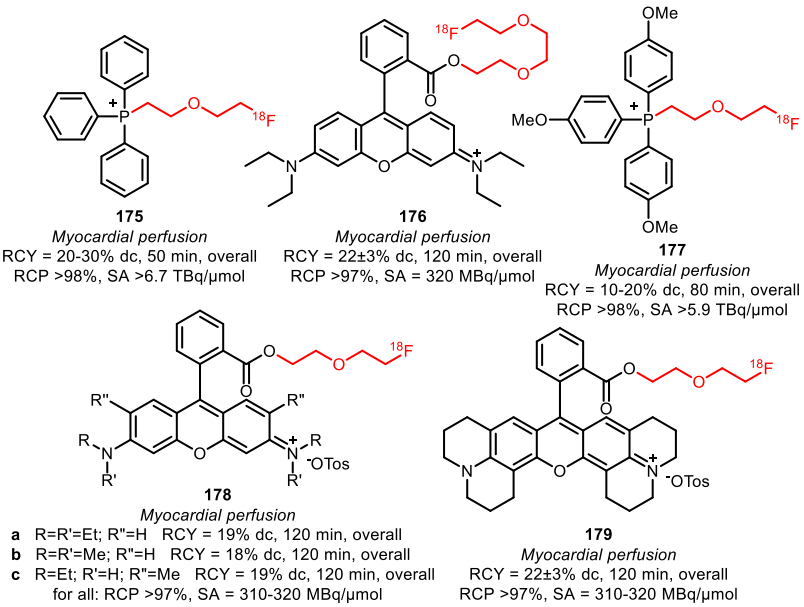
[^{18}F]Fluoroalkyl tosylates with a carbon chain length longer than 4 were only applied in the synthesis of triphenylphosphonium salts for myocardial perfusion imaging (Figure 4). [^{18}F]Fluoropentyl tosylate **152** and [^{18}F]fluorohexyl tosylate **153** were coupled to triphenyl phosphine in toluene at 220 °C. After purification by semi-preparative HPLC, both PET tracers were obtained in decay corrected radiochemical yields of 15 to 20%, respectively.[132]



174
Myocardial perfusion
a **n = 5** RCY = 15-20% dc, 60 min, overall
RCP >98%, SA >6.3 TBq/µmol
b **n = 6** RCY = 15-20% dc, 60 min, overall
RCP >98%, SA >6.1 TBq/µmol

Figure 4 [^{18}F]Fluoroalkyl triphenylphosphonium salts for myocardial perfusion imaging.[132]

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 (Figure 5).



175
Myocardial perfusion
RCY = 20-30% dc, 50 min, overall
RCP >98%, SA >6.7 TBq/µmol

176
Myocardial perfusion
RCY = 22±3% dc, 120 min, overall
RCP >97%, SA = 320 MBq/µmol

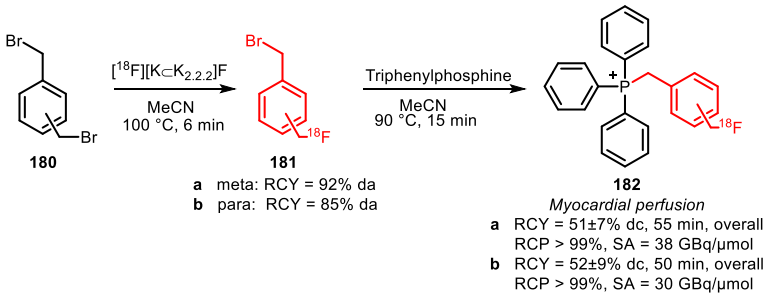
177
Myocardial perfusion
RCY = 10-20% dc, 80 min, overall
RCP >98%, SA >5.9 TBq/µmol

178
Myocardial perfusion
a R=R'=Et; R"=H RCY = 19% dc, 120 min, overall
b R=R'=Me; R"=H RCY = 18% dc, 120 min, overall
c R=Et; R'=H; R"=Me RCY = 19% dc, 120 min, overall
for all: RCP >97%, SA = 310-320 MBq/µmol

179
Myocardial perfusion
RCY = 22±3% dc, 120 min, overall
RCP >97%, SA = 310-320 MBq/µmol

Figure 5 [^{18}F]FluoroPEGylated tracers for myoardial perfusion imaging.[126,132–134]

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.[132,133] 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 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.[126,134]

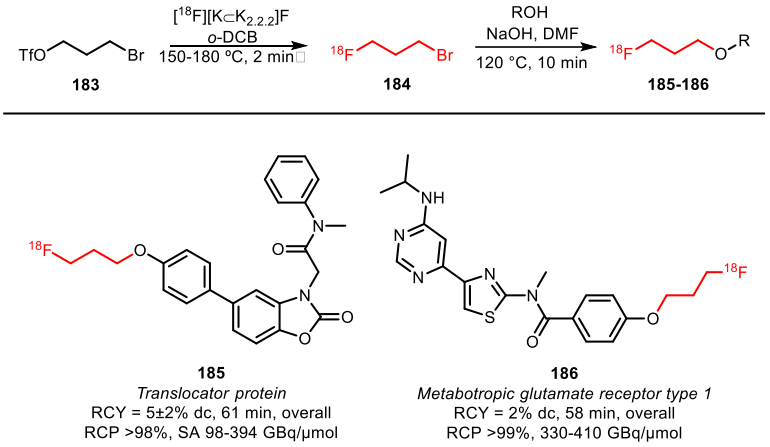


Scheme 39 Synthesis and reaction of *meta*- and *para*-[^{18}F]bromomethylfluoromethylbenzene.[136]

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).[135] 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.[136]

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).[57,58] Fujinaga *et al*. hypothesised that this can be explained by a decreased inductive effect of the fluorine atom further along the chain.[58]



Scheme 40 [18F]Fluoropropyl bromide as building block for [18F]fluoroalkylation.[57,58]

2.2.6 Fluorine-18 labelled azides

Many labelled azides have found widespread application in tracer synthesis. In particular, [18F]fluoroethyl azide **188** (Scheme 41) and deoxy-[18F]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 cyclo-addition (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.[137] Furthermore, these 'click'-reactions usually show high specificity, robustness and yields.[138] Many different functional groups are well tolerated, making additional protection and deprotection steps unnecessary.[139] Moreover, the click reaction is an excellent method to build up libraries of compounds for screening campaigns to ultimately select the best PET tracer.[140]

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

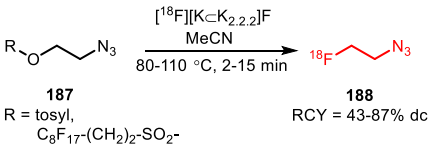
labelling of amino acids and peptides. It proceeds under mild reaction conditions and no metal catalysis is required.[141,142]

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.[143]

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.

2.2.6.1 [^{18}F]Fluoroethyl azide

[^{18}F]Fluoroethyl azide **188** was introduced as building block in the CuAAC by Glaser and Årstad in 2007.[144] 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-toluene-sulfonate with the dried [^{18}F][K⊂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%.[144–146] 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.[137,147,148]



187
R = tosyl, C_8F_{17}-$(CH_2)_2$-SO_2-

188
RCY = 43-87% dc

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

Hugenberg *et al*. described distillation during the reaction time to increase the non decay-corrected yield by shortening the synthesis time.[149] 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.[150] This was also reported by other research groups.[138]

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.[151] 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.

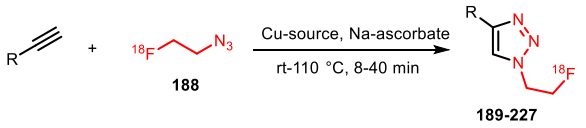
Furthermore, two different cartridge purification procedures have been developed in order to facilitate automation. Bejot *et al*. and Carroll *et al*. employed a polyfluorinated sulfonate precursor instead of 2-azidoethyl 4-toluenesulfonate (Scheme 41), which could be separated from [^{18}F]fluoroethyl azide **188** by fluorous solid phase extraction (FSPE).[140,152] Another approach used a silica-based C18 cartridge and a Water Oasis HLB cartridge in series.[138]

For some tracer syntheses, successful one-pot procedures have been described.[153,154] 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.[155]

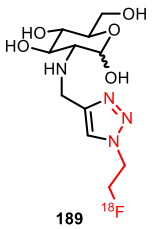
Scheme 42 lists all PET tracers synthesised using the [^{18}F]fluoroethyl azide building block *via* the CuAAC method.[44,137,138,140,140–149,152,153,155–169] In most cases, the [^{18}F]fluoro-ethyl azide reacts with an alkyne precursor in the presence of a Cu(I)- or Cu(II)-catalyst and sodium ascorbate 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.[147,153,169] In addition, the use of Cu(II) acetate[160] 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.[156,161] 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.[156] 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.[155]

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.[146,150] On the other hand, the alkyne precursor is mostly added in DMF,

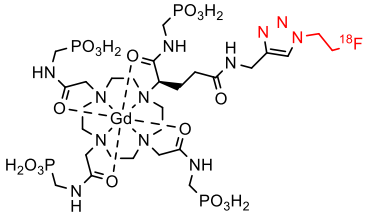
but also MeCN, DMSO and aqueous media were used.[137,150,156,164] Depending on the applied purification procedure, the azide building block is added either in the distillation trapping solution or in the solvent eluted from the intermediate SPE purification cartridge.[160,162] The MeCN from co-distillation or trapping led in some cases to a decrease in coupling efficiency.[167]



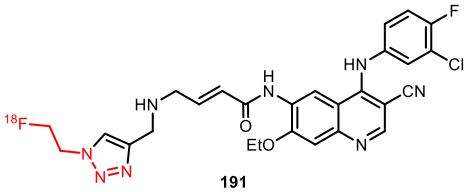
188 **189-227**



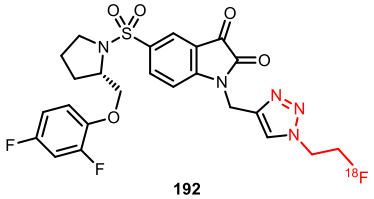
189
Tumour
RCY = 15% ndc, 100 min, overall
RCP, SA n.m.



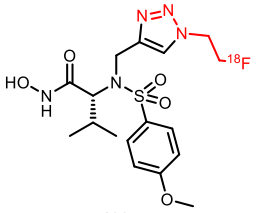
190
pH
RCY = 10% ndc, 150 min, last step
purity >95%



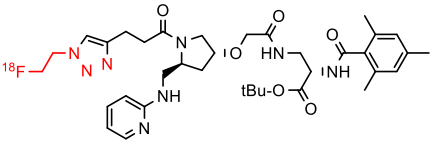
191
EGFR
RCY = 7% dc, 180 min, overall
RCP >99%, SA = 48-685 GBq/umol



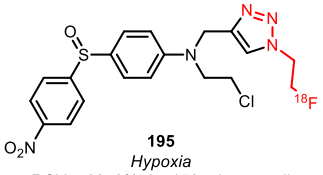
192
Caspase-3
RCY = 1-3% ndc, 90 min, overall
stable by-product 2-14 µg/mL, SA = 1-24 GBq/µmol



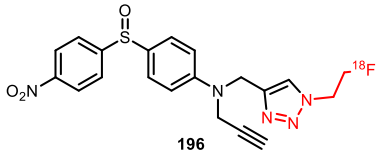
193
Matrix metalloproteinase 1
RCY = 30±3% dc, 110 min, overall
RCP >98%, SA = 14-57 GBq/µmol



194
α5β1 integrin receptor
RCY = 42-44% dc, 60-70 min, overall
RCP >95%, SA >1.3 GBq/umol

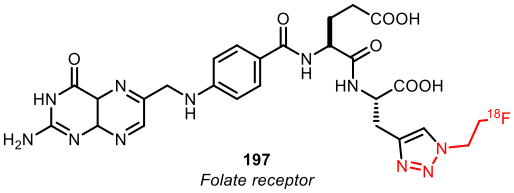


195
Hypoxia
RCY = 29±3% dc, 150 min, overall
RCP >95%, SA = 70-130 GBq/umol

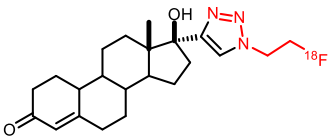


196
Hypoxia
RCY = 7±2%, 160 min, overall
RCP >96%, SA = 75-135 GBq/µmol

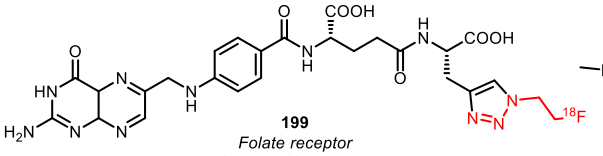
Scheme 42 PET tracers synthesised from [^{18}F]fluoroethyl azide in a CuAAC.[44,137,138,140,145–149,152,153,155–169]



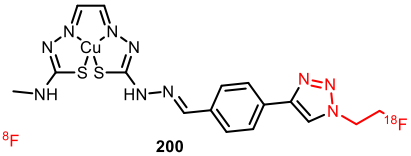
197
Folate receptor
RCY = 2-4% dc, overall
RCP >98%, AS 25-122 GBq/μmol



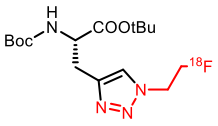
198
RCY = 95.3% da, 10 min, last step



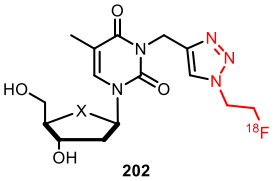
199
Folate receptor
RCY = 2-4% dc, overall
RCP >98%, AS 25-122 GBq/μmol



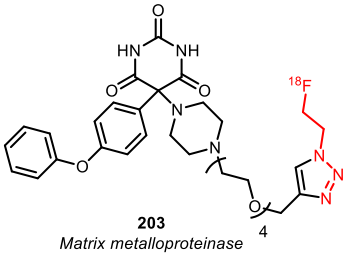
200
Hypoxia
RCY = 84% da, last step



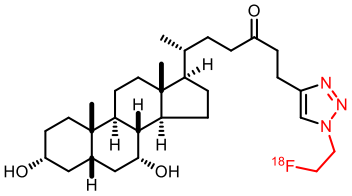
201
RCY = 90% da, 10 min, last step



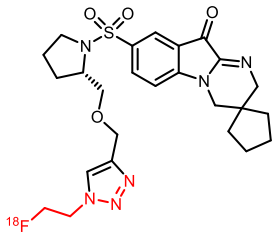
202
Tumour proliferation
a X = O RCY = 3±0.9% ndc, 160-170 min, overall
RCP n.m., SA = 0.3 GBq/μmol
b X = S RCY = 6.6±2.4% ndc, 160-170 min, overall
RCP n.m., SA = 0.3 GBq/μmol



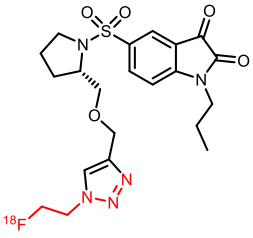
203
Matrix metalloproteinase
RCY = 43±9% dc, 140 min, overall
RCP >97%, SA = 11-20 GBq/umol



204
Farnesoid-X-receptor
RCY = 42±3% ndc, 70-80 min, overall
RCP >99%, SA >320 GBq/μmol

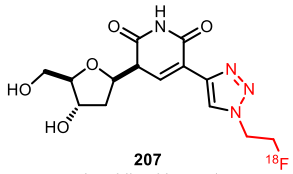


205
Caspase-3/7
RCY = 42% dc, last step
RCP and SA low

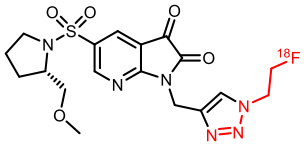


206
Caspase-3/7
RCY = 21±0% dc, 91 min, overall
RCP >99%, SA 0.2-0.3 GBq/μmol

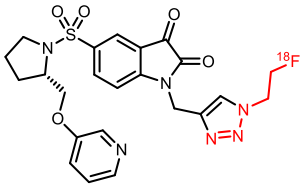
Scheme 42 (Continued)



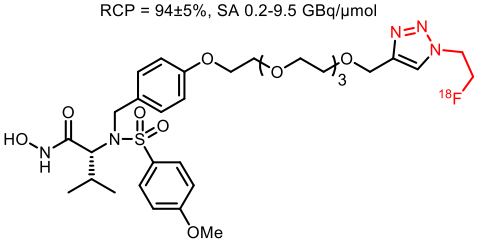
207
thymidine kinase-1
RCY = 33-41%, 67-130 min, overall
RCP >95%, AS = 70-130 GBq/μmol



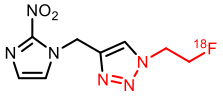
208
caspase-3/7
RCY = 11±5% dc, 94 min, overall,
RCP = 94±5%, SA 0.2-9.5 GBq/μmol



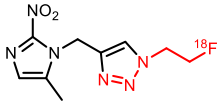
209
RCY = 60% da, 10 min, last step



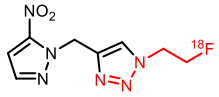
210
matrix metalloproteinase
RCY = 32±3% dc, 92 min, overall
RCP >99%, SA = 8-15 GBq/μmol



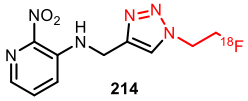
211
Hypoxia
yield, overall time, purity and SA n.m.



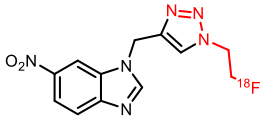
212
Hypoxia
yield, overall time, purity and SA n.m.



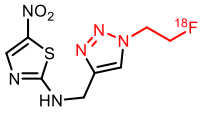
213
Hypoxia
yield, overall time, purity and SA n.m.



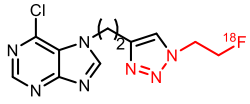
214
Hypoxia
yield, overall time, purity and SA n.m.



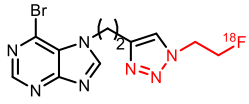
215
Hypoxia
yield, overall time, purity and SA n.m.



216
Hypoxia
yield, overall time, purity and SA n.m.

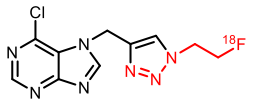


217
Multidrug resistance-associated protein 1 (MRP1)
RCY = 9±2% dc, 105 min, overall
RCP >99%, SA = 5-7 GBq/μmol

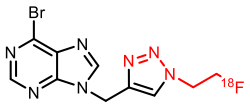


218
MRP1
RCY = 55% dc, last step
RCP >99%

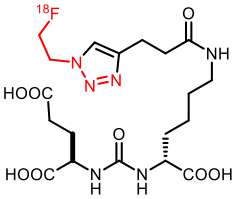
Scheme 42 (Continued)



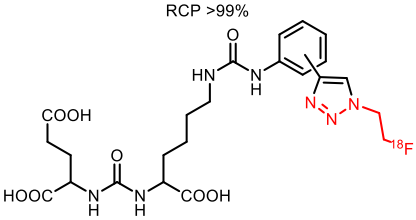
219
MRP1
RCY = 41% dc, last step
RCP >99%



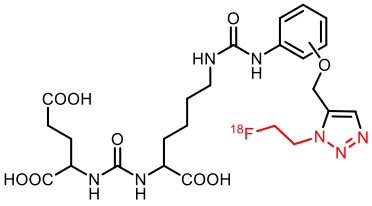
220
MRP1
RCY = 57% dc, last step
RCP >99%



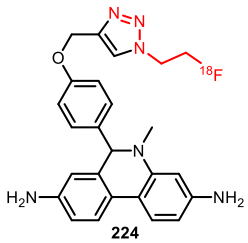
221
PSMA
RCY = 14±1% ndc, 60 min, overall
RCP n.m., SA = 12-91 GBq/µmol



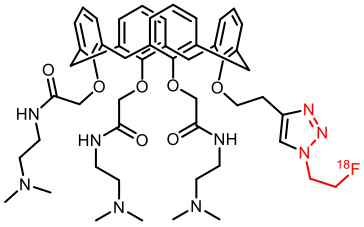
222
PSMA
2-, 3- or 4-triazolyl
RCY = 20-40% dc, 105 min, overall
RCP >99%, SA 182-391 GBq/µmol



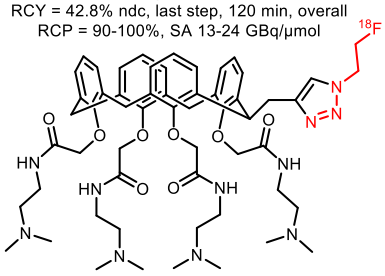
223
PSMA
2-, 3- or 4-triazolyl
RCY = 20-40% dc, 105 min, overall
RCP >99%, SA 182-391 GBq/µmol



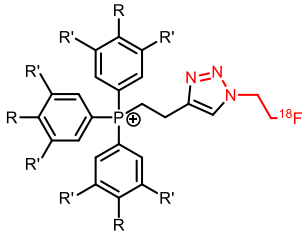
224
Superoxide
RCY = 42.8% ndc, last step, 120 min, overall
RCP = 90-100%, SA 13-24 GBq/µmol



225
Angiogenesis
RCY = 18.7±2.7% dc, overall
RCP >97%, SA >5 GBq/µmol



226
Angiogenesis
RCY = 10.2±5.0% dc, overall
RCP >97%, SA >5 GBq/µmol



227
Apoptosis
a R=R'=H RCY = 9% ndc, 63 min, overall
RCP >99%, SA 41-101 GBq/µmol
b R=Me, R=H
c R=^{t}Bu, R=H } synthesized in one pot
d R=H, R'=Me

Scheme 42 (Continued)

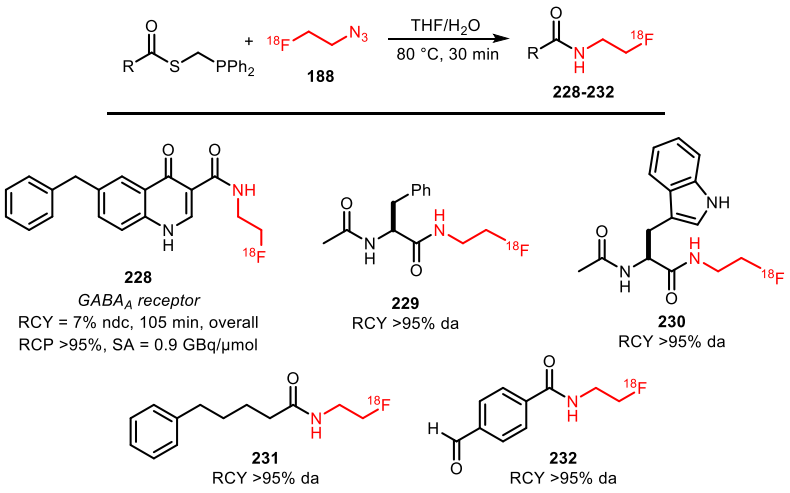
For the prostate-specific membrane antigen (PSMA) tracers **222** and **223**, higher MeCN content led to a decrease in yield from 50% to <25% (measured by radio-HPLC).[150] However, a few successful click reactions were also performed in MeCN.[55,156] The presence of DMF has been described as a necessary condition to maintain the level of Cu(I) in the reaction solution.[151]

Other additives have been employed in some of the tracer syntheses too. The use of the base DIPEA[161] as well as the Cu(I) stabilizing agents TBTA (tris(benzyltriazolyl-methyl)amine) and BPDS (bathophenanthroline disulfonic acid disodium salt) have been reported.[157,168] TBTA and BPDS served as auxiliary copper(I) chelators[153] 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.[153] 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).

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.[163,166] For the tumour proliferation imaging agents **202a** and **202b**, direct labelling was more successful giving increased specific activities (20–210 GBq/μmol instead of 0.3 GBq/μmol) at comparable overall radiochemical yields (7% ndc).[163]

Based on the CuAAC with [^{18}F]fluoroethyl azide, a ‘‘multiclick’’ 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.[139,169]

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).[141] 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 GABAA tracer **228** in an overall radiochemical yield of 7% (ndc).[142]



Scheme 43 PET tracers synthesised from [^{18}F]fluoroethyl azide in a traceless Staudinger reaction.[141,142]

In conclusion, [^{18}F]fluoroethyl azide is a useful building block for the fluorine-18 labelling of biomolecules and small molecule PET tracers under mild conditions without need of protecting groups.

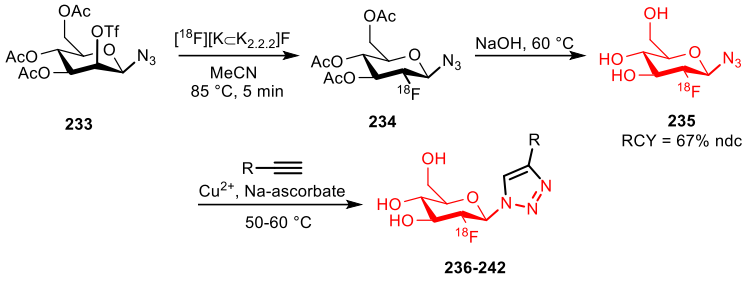
2.2.6.2 Deoxy-[^{18}F]fluoroglucopyranosyl azide

Deoxy-[^{18}F]fluoroglucopyranosyl azides have been used as building blocks in CuAAC and were first introduced by Maschauer *et al*. in 2009.[170] 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⊂K2.2.2]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.[171] Only minor alterations since the initially developed synthesis of the building block have been reported. Fischer *et al*. showed that a cartridge based purification procedure instead of a time consuming HPLC purification yielded 75% of protected 2-deoxy-2-[^{18}F]fluoroglucopyranosyl azide **234**.[172]

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.[173]



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

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 Figure 6.[160,170,172,174–177] 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.[173] 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.[174]

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.[160,172]

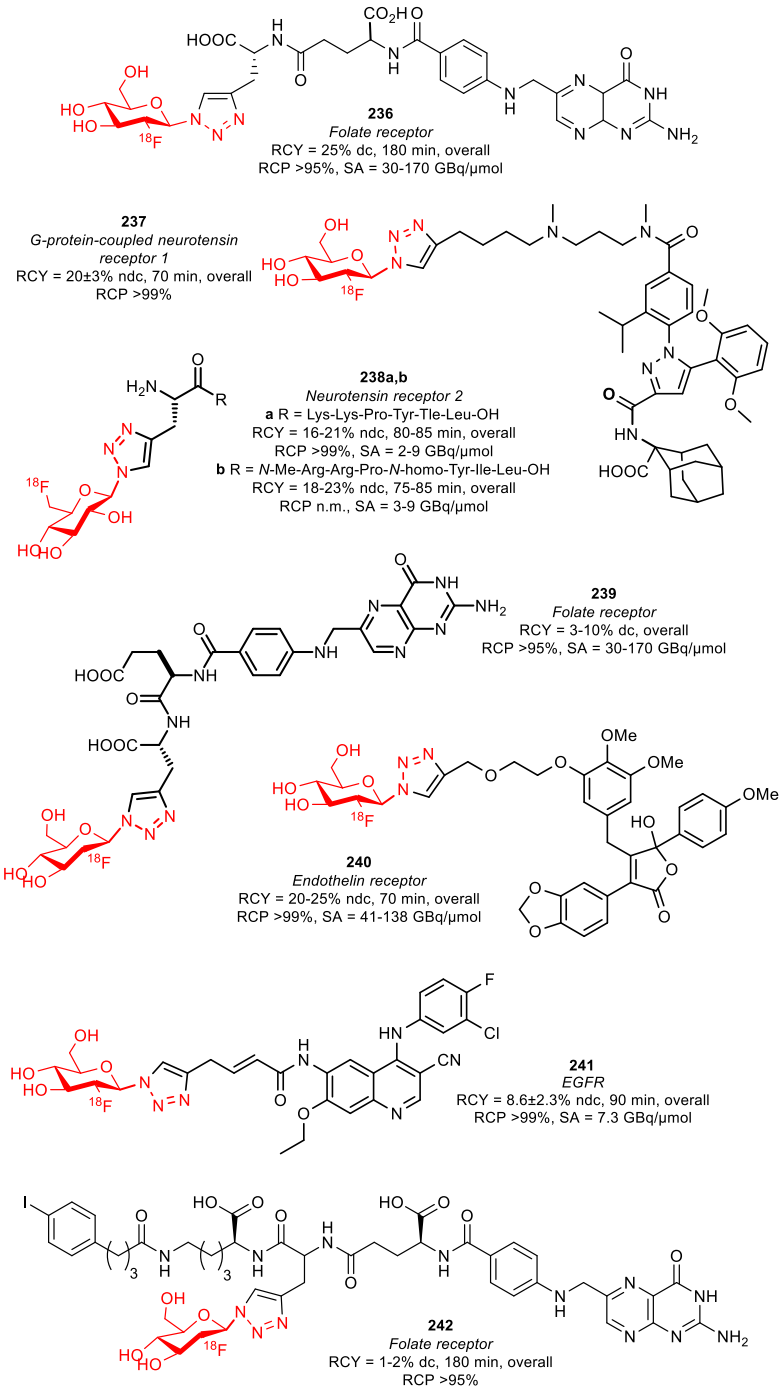


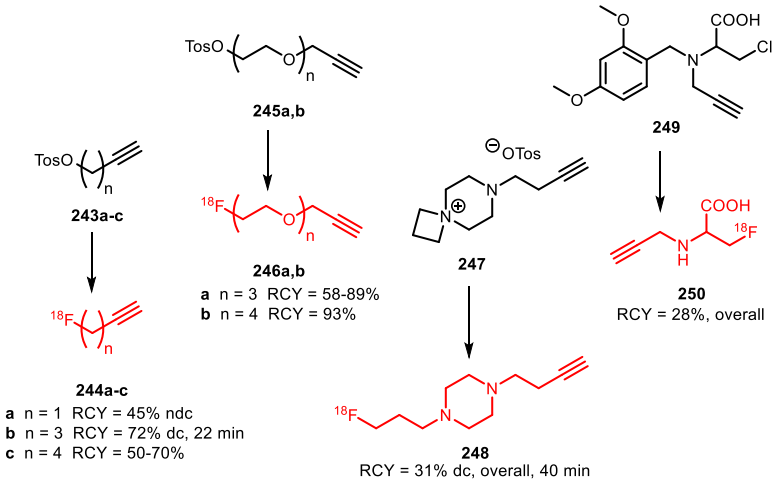
Figure 6 PET tracers labelled with 2-deoxy-2-[^{18}F]fluoroglucopyranosyl azide.[160,170,172–177]

2.2.7 Fluorine-18 labelled alkynes

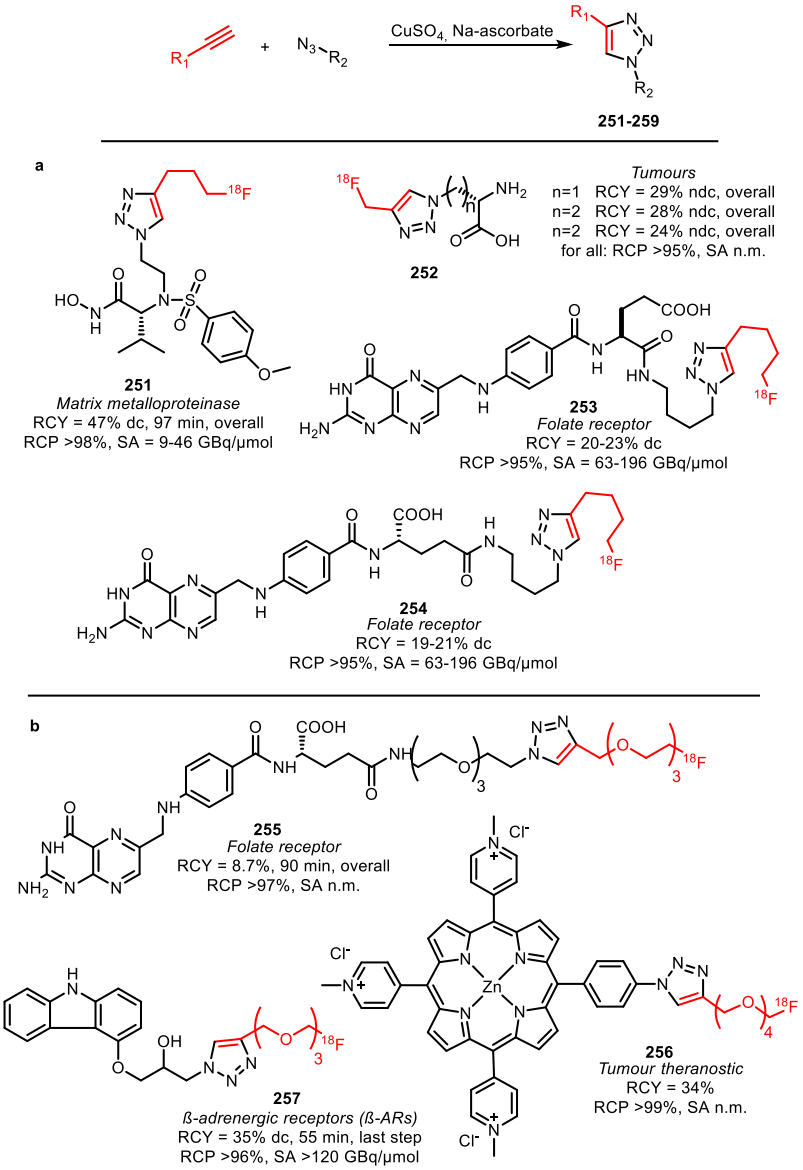
A large range of different fluorine-18 labelled alkynes have been used in PET tracer synthesis. Scheme 45 summarises the different types of precursor used since 2010. Alkyl precursors **243** and polyethylene glycol (PEG) derived precursors **245** are popular precursors for radiofluorination and have 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.

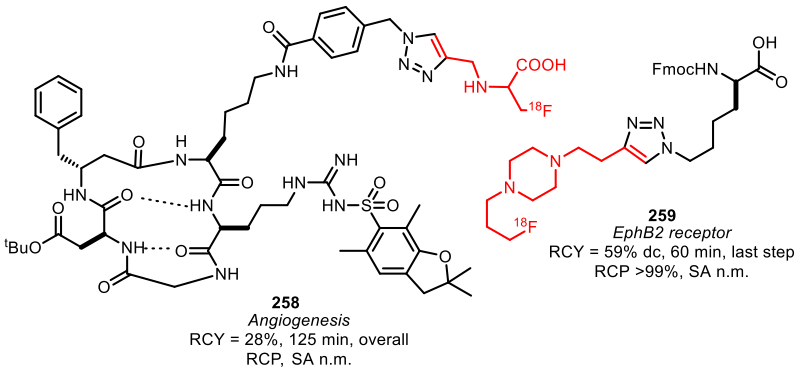
Typical reaction temperatures are between 95–110 °C and distillation is quite fast (2–5 minutes). The solvent used for trapping the product after distillation may depend on the click reaction which is performed afterwards. As a leaving group, predominantly the tosylate is used, as it provides in general the best results in a nucleophilic substitution.[160,178,179] 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 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%.[180–182]



Scheme 45 Different types of alkyne precursors.



Scheme 46 PET tracers synthesised via click reaction with different fluorine-18 labelled alkynes: (a) alkyl-derived building blocks;[160,178,179] (b) PEG-derived building blocks.[180–182]



Scheme 46 (Continued) Other fluorine-18 labelled alkynes.[183,184]

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.[183] 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).[184]

Scheme 46 shows that a large set of structurally diverse PET tracers can be prepared by application of fluorine-18 labelled alkynes in the CuAAC reaction.[160,178–184] 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.[180] 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.[180,182]

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.[178]

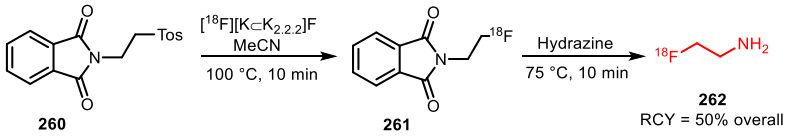
In summary, many different fluorine-18 labelled alkynes have been successfully employed as building blocks in CuAAC reactions for PET tracer syntheses. Due to their structural diversity, the use of fluorine-18 labelled alkynes significantly expand the spectrum of PET tracers that can be accessed.

2.2.8 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 radio-fluorination. 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).

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, 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.[185]

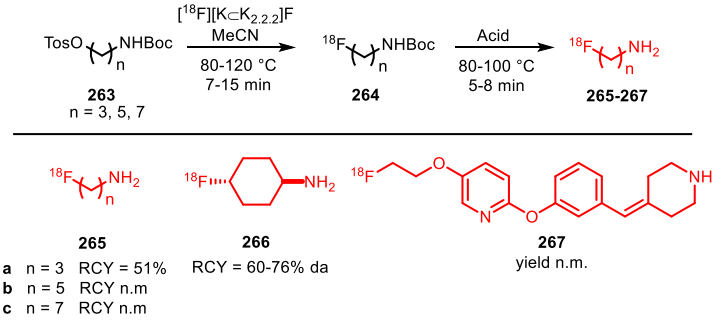


Scheme 47 Synthesis of [^{18}F]fluoroethylamine via the procedure of Tewson *et al*.[184]

The original procedure of Tewson *et al*. is still largely employed as it was first published.[186,187] For example, Huang and co-workers applied it to the synthesis of

[18F]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 [18F]fluoroethyl amine **262**.[188]

The second method to synthesise [18F]fluoroalkyl amines starts from the corresponding Boc-protected amino tosylates (Scheme 48). [18F]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 de-protection 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 [18F]fluoroalkyl amine could be used without further purification in the next reaction.[189–192] 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.[190,192]



Scheme 48 Synthesis of different types of [18F]fluoroalkyl amines via Boc-protected amines.[189,191]

In addition to the above discussed more generally established methods to access [18F]fluoroalkyl amines, Glaser *et al*. reported an alternative method. They described the reduction of [18F]fluoroethyl azide (**188**) with elemental copper under acidic conditions providing [18F]fluoroethyl amine (**262**) in radiochemical yields of over 90% (analytically determined).[193]

[18F]Fluoroalkyl amines can undergo three different types of reactions forming either carbamates, amide bonds, or carbamines. Carbamate formation is most widely applied (Figure 7).[135,187,189,190,194] The radiofluorination reaction was carried out using the purified (distilled) fluorine-18 labelled building block, but also successful one-pot three step reactions including [18F]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.[135]

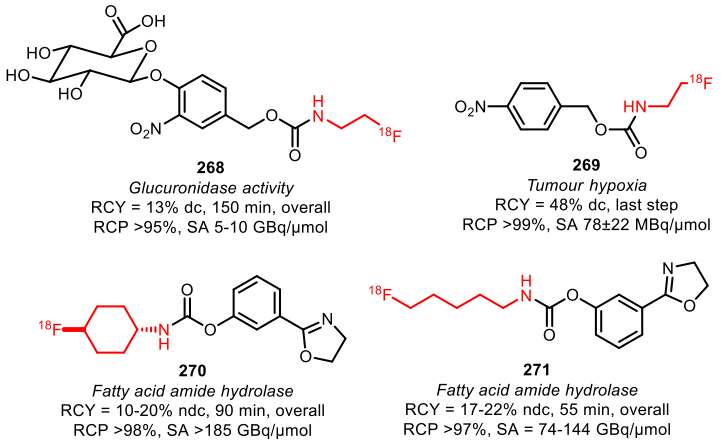
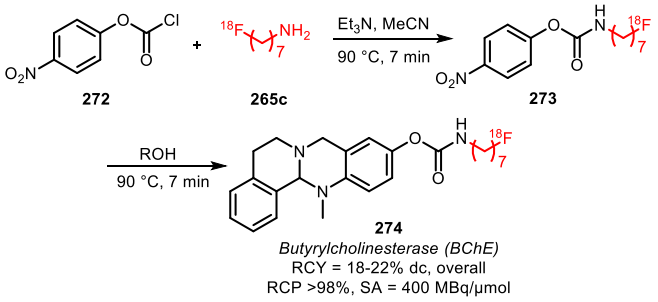


Figure 7 [^{18}F]Fluorocarbamates synthesised via reaction with [^{18}F]fluoroalkyl amines.[135,187,189,190,194]

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).[187] 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).[189] In all cases, purification of the products was conducted by semi-preparative HPLC.



Scheme 49 Synthesis of the butyrylcholinesterase tracer **274**.[195]

Sawatzky *et al*. reported the use of [^{18}F]fluoroheptyl amine **265c** as building block in the multi-step synthesis of the butyrylcholinesterase tracer **274**. To activate [^{18}F]fluoroheptyl amine **265c**, 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).[196]

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) (Figure 8).[192] Huang *et al*. reported 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).[188] In a third approach for amide bond formation, *9H*-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).[194]

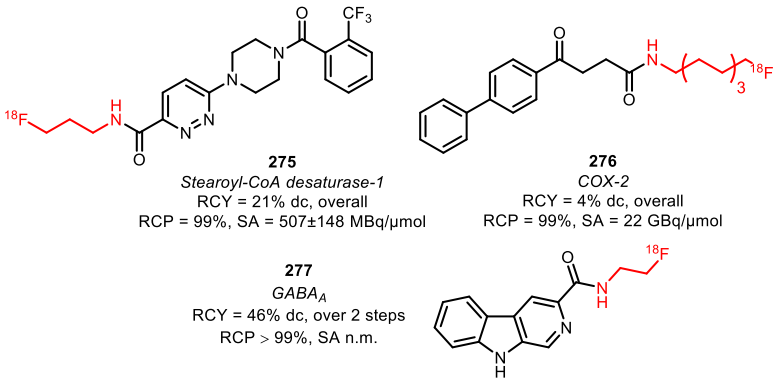


Figure 8 [^{18}F]Fluoroamides.[187,190,193]

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.[186] 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) (Figure 9).

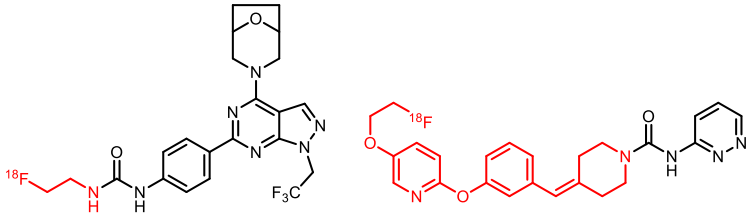
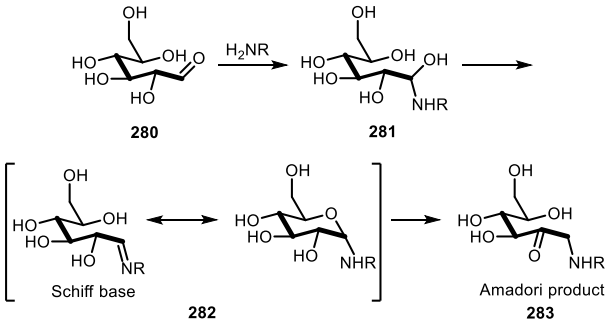


Figure 9 Fluorine-18 labelled urea derivatives.[186,192]

2.2.9 [^{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.[196] As [^{18}F]FDG is readily available, the synthesis of [^{18}F]FDG will not be discussed in this review.



Scheme 50 Maillard reaction.[197]

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.[197]

An overview of tracers radiolabelled with [^{18}F]FDG is given in Figure 10 and Figure 11.[196–201] 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.[196,199]

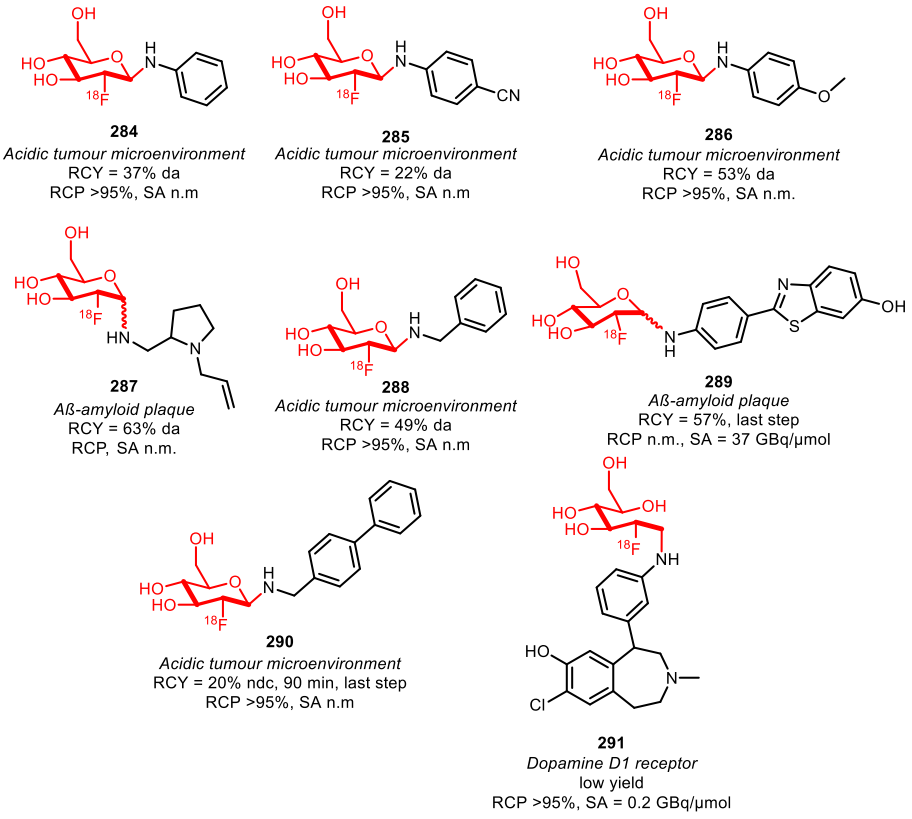


Figure 10 PET tracers synthesised from [^{18}F]FDG and amine precursors.[196–201]

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.[196,197]

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.[201] The *in vitro* stability of the glycosyl amine tracers are in general high.[199,200] 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.[196]

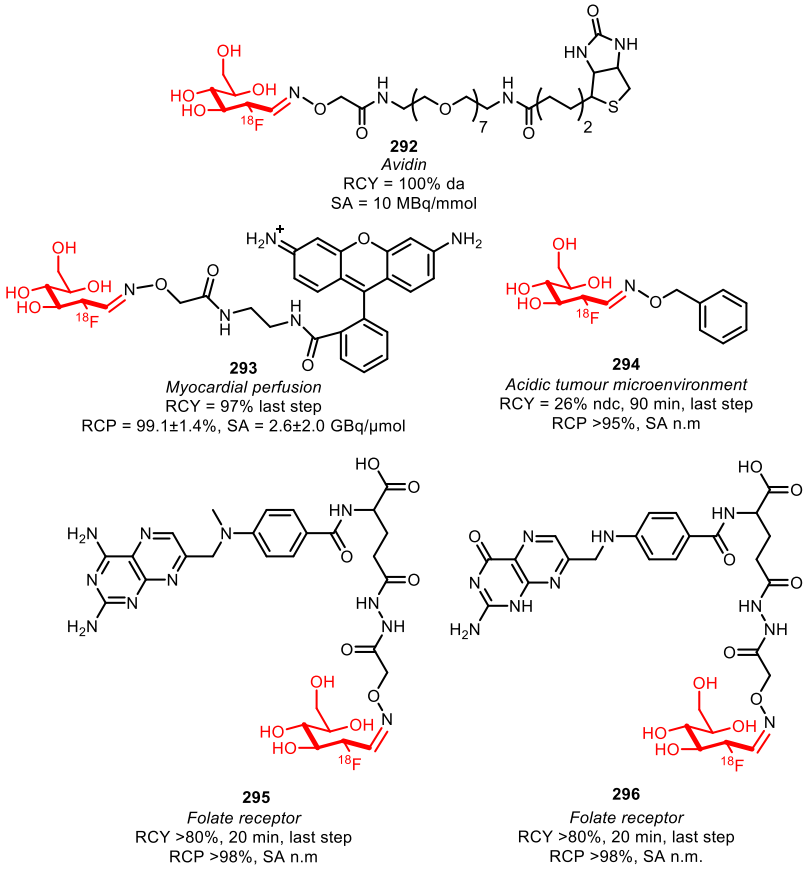


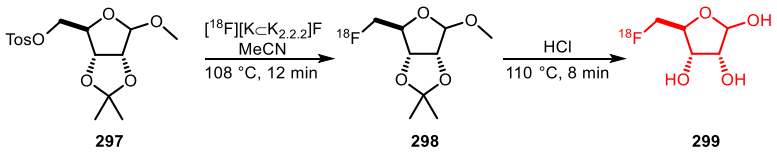
Figure 11 PET tracers synthesised from [^{18}F]FDG and oxy-amine precursors.[196–201]

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 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.

2.2.10 5-[^{18}F]Fluoro-5-deoxyribose

Initially developed as PET tracer for tumour imaging,[202,203] 5-[^{18}F]fluoro-5-deoxyribose has also found application as a building block. Besides in peptide radiolabelling,[204] 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 radio-fluorination 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.

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 semipreparative HPLC and then deprotected with hydrochloric acid. After neutralisation, the obtained 5-[^{18}F]fluoro-5-deoxyribose **299** was used without further purification.

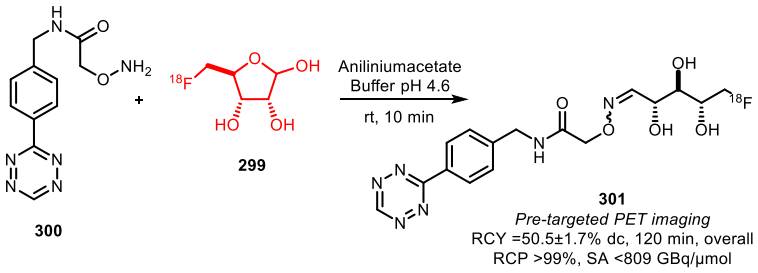


Scheme 51 Synthesis of 5-[^{18}F]fluoro-5-deoxyribose **299**.

Another elegant way to synthesise 5-[^{18}F]fluoro-5-deoxyribose was reported by Onega and co-workers. They converted *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.[206]

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).[205]

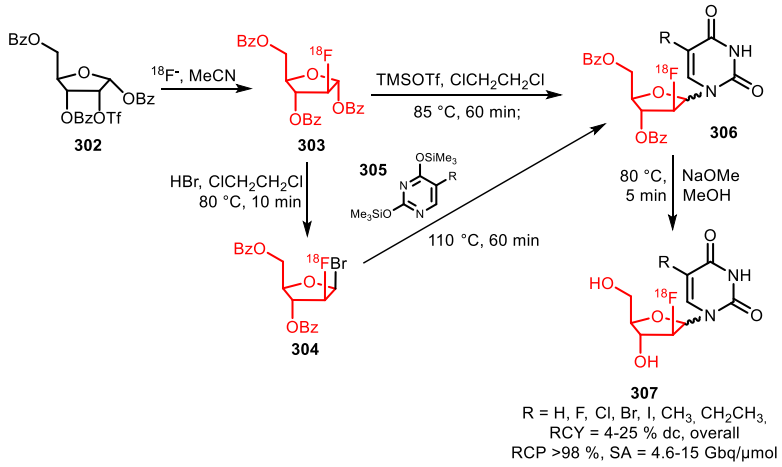
In conclusion, the amino-oxy functionalised tetrazine **300** could be labelled fast and in high overall yields, proving the suitability of 5-[^{18}F]fluoro-5-deoxyribose **299** as building block for PET tracer synthesis. In its function as building block, 5-[^{18}F]fluoro-5-deoxyribose may serve as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



Scheme 52 Synthesis of compound **301** by reaction of building block 5-[^{18}F]fluoro-5-deoxyribose **299** with tetrazine **300**.[205]

2.2.11 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 expression of the herpes simplex virus type-1 thymidine kinase (Scheme 53).



Scheme 53 Synthesis of [^{18}F]FXAU (**307**).[207,209]

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]fluoroarabinofuranose **303**.

Formation of the building block [^{18}F]2-deoxy-2-fluoroarabinofuranose **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 30min 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 490% after passing the reaction mixture over a silica Sep-Pak cartridge to remove unreacted [^{18}F]fluoride.[207] 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.[208,209]

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 α : β = 1 : 3–1 : 9.[207,210] The reaction time of 60 minutes was rather long, and led to low overall yields.[211]

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.[209]

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).[208,209,212] Furthermore, the product has a poor specific activity of 5 GBq/µmol, probably caused by the excess of TMSOTf.[208]

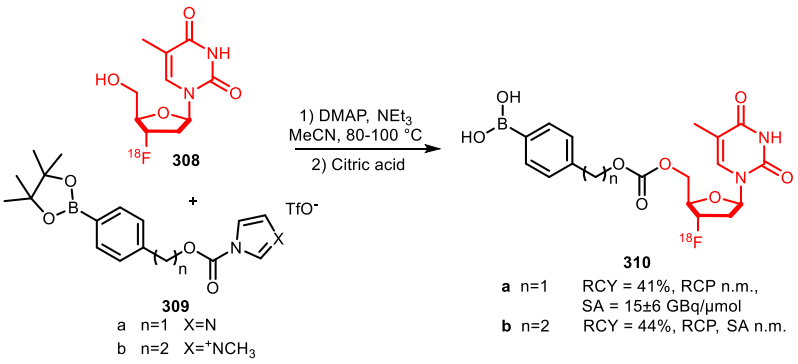
To further improve the synthesis route, Chen *et al*. have investigated the influence of microwave heating and Lewis acid catalysis on the coupling reaction. Microwave heating can have a positive influence on the coupling reaction by reducing the reaction

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.[213] 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.[211]

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.

2.2.12 2'-Deoxy-2'-[^{18}F]fluorothymidine

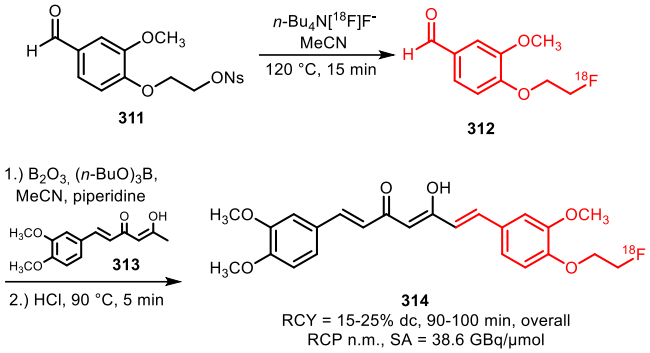
2'-Deoxy-2'-[^{18}F]fluorothymidine ([^{18}F]FLT) has been applied only once as a building block. Carroll and co-workers reported on the synthesis of a prodrug-like tracer in 2014, PC-[^{18}F]FLT **310a**, for H_2O_2 detection and tumour imaging. Firstly, [^{18}F]FLT was synthesised according to an established 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.[214]



Scheme 54 Production of PC-[^{18}F]FLT **310a** and CC-[^{18}F]FLT **310b** with [^{18}F]FLT.[214]

2.2.13 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.



Scheme 55 Synthesis of 1-(4-[^{18}F]fluoroethyl)-7-(4'-methyl)curcumin.[215]

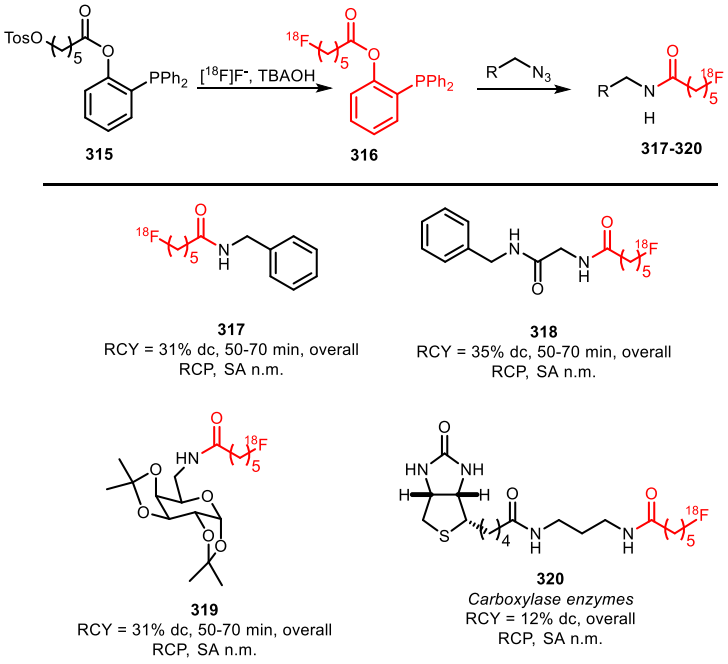
4-(2-[^{18}F]Fluoroethoxy)-3-methoxybenzaldehyde **312** was synthesised from its nosylate precursor **311**. [^{18}F]Fluorination was performed with *n*-Bu$_4$N[^{18}F]F$^-$ in MeCN at 120 °C and resulted in radiochemical yields of over 70% (based on radio-TLC analysis). In the follow-up aldol condensation, **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 semipreparative HPLC and obtained in a radiochemical yield of 15–25% with a specific activity of 37.6 GBq/µmol.[215]

2.2.14 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.[216]

Fluorine-18 labelled triarylphosphine **316** was prepared by reaction of [^{18}F]tetra-butylammonium 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.[217]



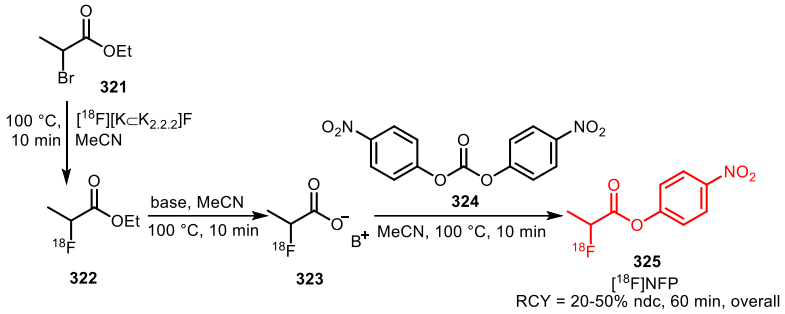
Scheme 56 Synthesis of fluorine-18 labelled phosphine building block **316** and subsequent traceless Staudinger ligation.[217]

2.2.15 [^{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.

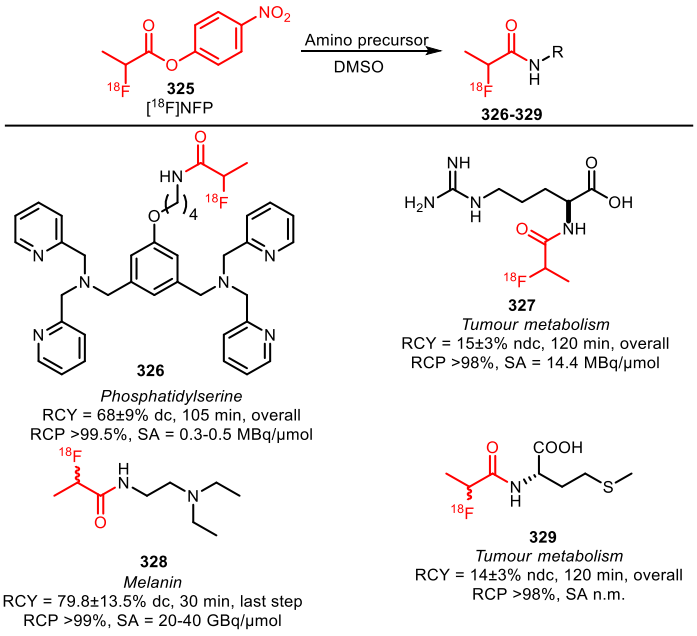
[^{18}F]NFP can be synthesised *via* a one-pot three-step procedure (Scheme 57). *Via* halogen exchange of ethyl-2-bromopropionate **321** with dried [^{18}F]fluoride, ethyl-2-[^{18}F]fluoropropanoate **322** was obtained, which was subsequently saponified under basic conditions. Usually an aqueous solution 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.[73,218]



Scheme 57 One-pot three-step synthesis of [^{18}F]NFP.[73]

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.[73,218–220]



Scheme 58 PET tracer synthesis by coupling to [^{18}F]4-nitrophenyl 2-fluoropropionate **325**.[73,218–220]

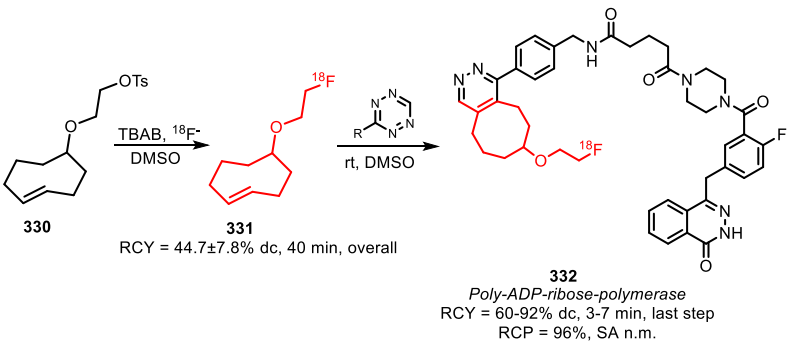
In addition to two amines, also the two amino acids, L-methionine **329** and L-arginine **327**, have been radiofluorinated using this building block. Whereas Gao and co-workers described the use of the protected amino acid arginine ethyl ester dihydro-

chloride as precursor, Hu *et al*. state fast and efficient coupling of [^{18}F]NFP to unprotected methionine. Overall radiochemical yields are comparable and approximately 15% (ndc) with reaction times of 120 minutes.[218,220]

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

2.2.16 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.



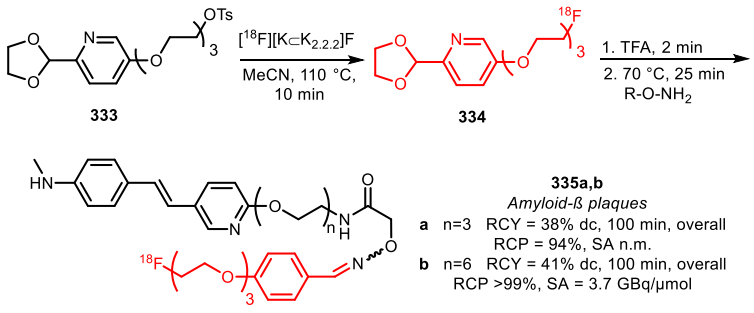
Scheme 59 Synthesis of the fluorine-18 labelled TCO **331** and [4+2]cycloaddition with Tz precursor.[222,223]

As tetrazines are unstable under radiofluorination conditions,[221] 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 [^{18}F]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).[222] 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).[223]

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.

2.2.17 5-(1,3-Dioxolan-2-yl)-2-(2-(2-(2-[^{18}F]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-[^{18}F]fluoroethoxy)ethoxy)ethoxy)pyridine **334**, which can react after hydrolysis with aminooxy groups, resulting in oxime formation (Scheme 60).[224]



Scheme 60 Radiosynthesis and coupling reaction of building block **334**.[224]

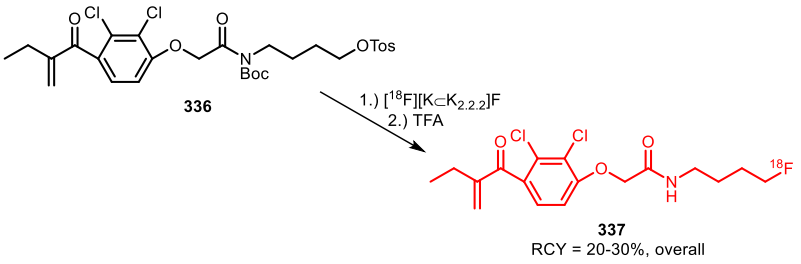
Building block **334** was prepared in a 71 ± 2% radiochemical yield *via* nucleophilic substitution of the corresponding tosylate **333** using [^{18}F][K⊂K2.2.2]F in MeCN at 110 °C, followed by purification using solid-phase extraction. Next, building block **334** was converted *in situ* to the corresponding 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).[224] 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.

2.2.18 [^{18}F]Fluorobutyl ethacrynic amide ([^{18}F]FBuEA)

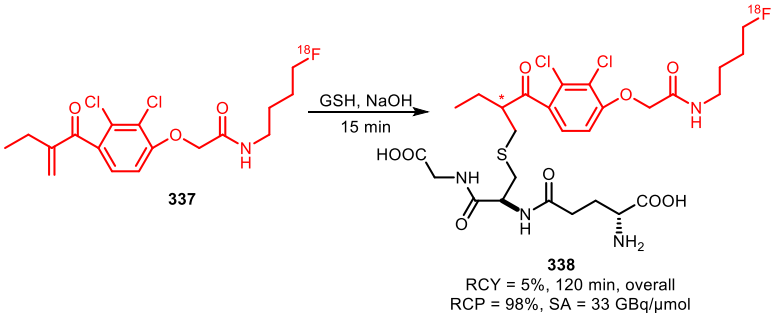
[^{18}F]FBuEA **337** was used in the synthesis of the glutathione (GSH) conjugate [^{18}F]FBuEA-GSH **338**, a potential imaging agent for brain tumours targeting the lipocalin-type prostaglandin D synthase.[225]

[^{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).



Scheme 61 Radiosynthesis of [^{18}F]FBuEA **337**.[226]

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).[226]



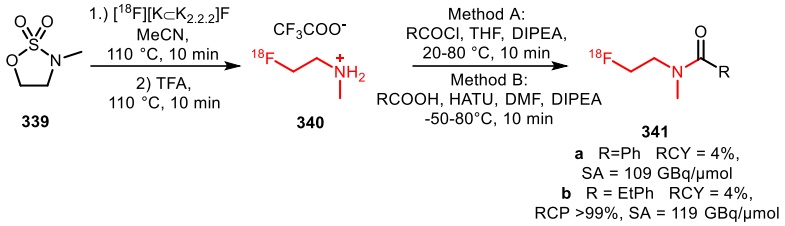
Scheme 62 Conjugation of [^{18}F]FBuEA with glutathione.[226]

2.2.19 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.

2.2.19.1 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).



Scheme 63 Synthesis and reaction of *N*-(2-[^{18}F]fluoroethyl)-*N*-methylamine.[227]

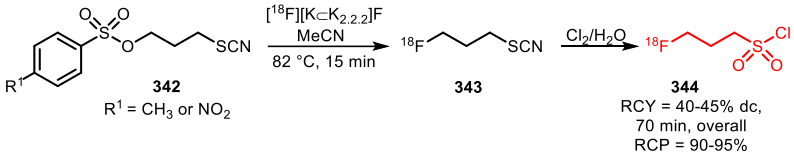
Precursor **339** was radiofluorinated in MeCN at 110 °C within 10 minutes. Next, trifluoroacetic acid (TFA) was added and the reaction mixture was heated again at 110 °C for 10 min. After evaporation of TFA, *N*-(2-[^{18}F]fluoroethyl)-*N*-methylamine **340** was obtained in 81% radiochemical yield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

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.[227]

2.2.19.2 3-[^{18}F]Fluoropropanesulfonyl chloride

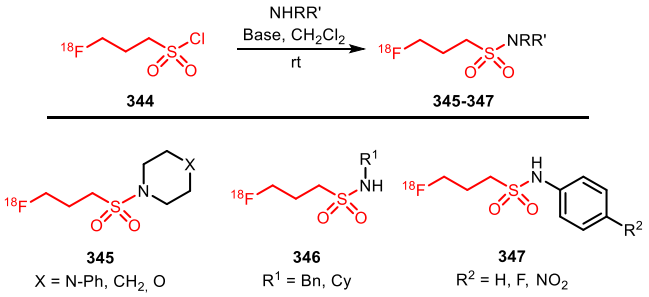
In 2009 Li *et al*. introduced 3-[^{18}F]fluoropropanesulfonyl chloride **344**, a potential building block for PET tracer synthesis *via* sulfonamide formation.[228] An optimised synthesis procedure of building block **344** and its reaction with various amines was reported by Löser *et al*. in 2013. 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).



Scheme 64 Two-step synthesis 3-[^{18}F]fluoropropanesulfonyl chloride.[229]

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 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).[229]



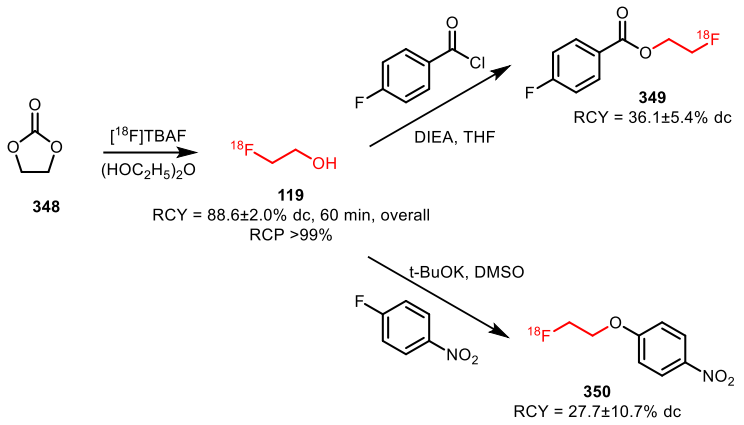
Scheme 65 Reaction of 3-[^{18}F]fluoropropanesulphonyl chloride with different amines.[229]

2.2.19.3 2-[^{18}F]Fluoroethanol and 3-[^{18}F]fluoropropanol

As an alternative strategy to fluoroalkylation using [^{18}F]fluoroalkyl halides and sulfonates (see Sections 2.2.1–2.2.5), 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]Fluoro-ethanol **119** was synthesised in a one-step reaction *via* nucleophilic substitution of ethylene carbonate **348** (Scheme 66). 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]fluoro-ethanol (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.



Scheme 66 2-[^{18}F]Fluoroethanol as building block in the synthesis of 2-[^{18}F]fluoroethyl aryl esters and ethers.[230]

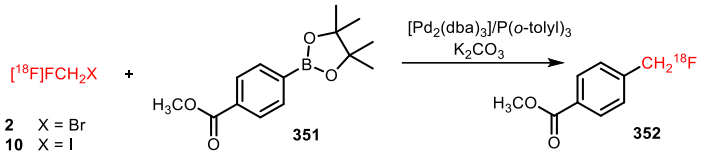
2-[^{18}F]Fluoroethanol was reacted in two model reactions to prove its usability in the formation of [^{18}F]fluoroalkyl aryl esters and ethers (Scheme 66). Under non-optimised reaction conditions, 2-[^{18}F]fluoroethyl 4-fluorobenzoate **349** and 1-(2-[^{18}F]fluoroethoxy)-4-nitrobenzene **350** were 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.[230]

2.2.19.4 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.

[^{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).



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

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.[231]

2.3 Fluorine-18 labelled aromatic building blocks

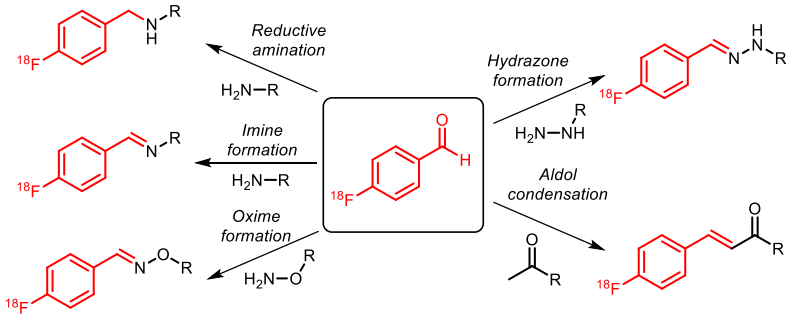
Since 2010 a wide variety of fluorine-18 labelled aromatic building blocks have been developed and applied to synthesise PET tracers. These building blocks are mostly used for PET tracers which cannot be prepared by direct radiofluorination of the corresponding precursors, since sufficient electron withdrawing 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.

2.3.1 [^{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).



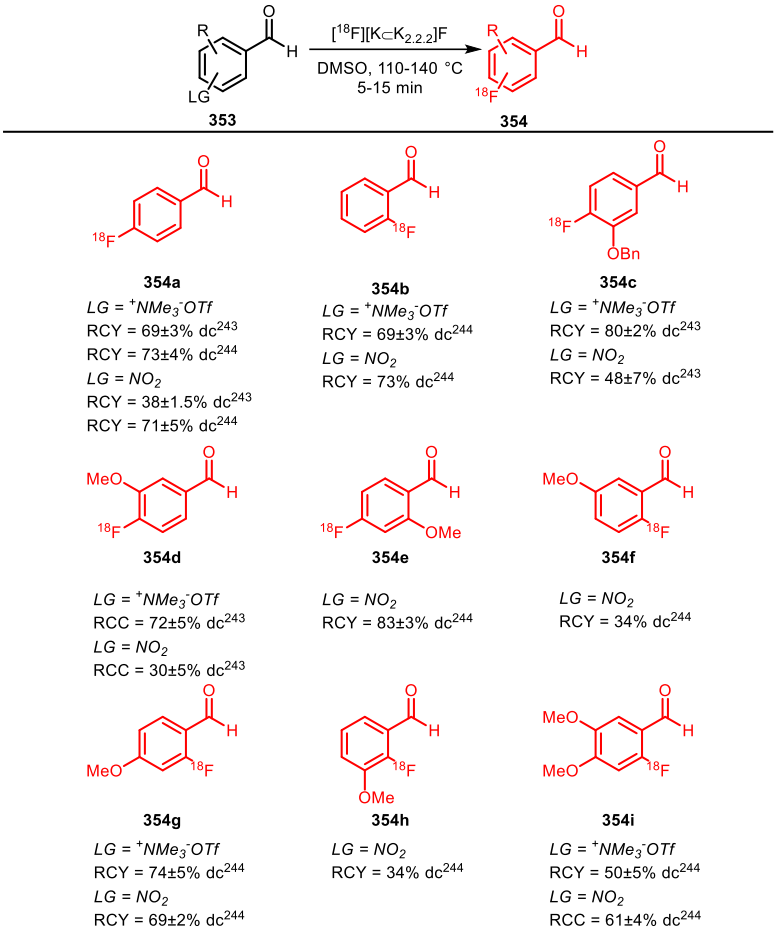
Scheme 68 Possible applications of [^{18}F]fluorobenzaldehydes.

Of these reactions, reductive amination is the most commonly used, and will be discussed in Section 2.3.1.2. 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 2.3.1.3, 2.3.1.4 and 2.3.1.5. 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 2.3.1.6. Finally, a very innovative application of [^{18}F]fluorobenzaldehydes is discussed in Section 2.3.1.7, being the use as a reagent in multicomponent reactions, opening up the synthesis of a wide diversity of potential PET tracers.

2.3.1.1 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.[232,233] 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).

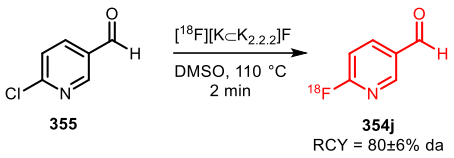


Scheme 69 Synthesis of 2- and 4-[^{18}F]fluorobenzaldehydes.[232,233]

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.

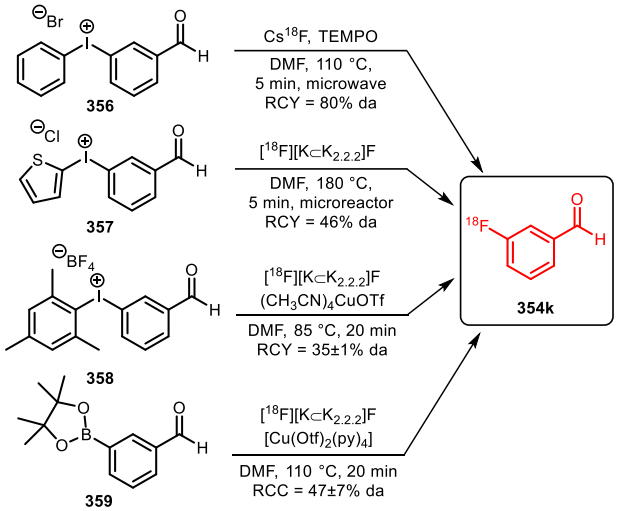
In case of the nitro precursors, which are also apolar molecules, such a simple purification procedure to obtain 4-[^{18}F]fluorobenzaldehydes is not possible. As a result, trimethylammonium precursors are currently preferred for the synthesis of 4-[^{18}F]fluorobenzaldehyde.

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**.[232]



Scheme 70 Synthesis of 6-[^{18}F]fluoronicotinaldehyde.[232]

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.[234–236]



Scheme 71 Novel fluorine-18 labelling methods for the synthesis of 3-[^{18}F]fluorobenzaldehydes.[7,17,23,24]

For the synthesis of 3-[^{18}F]fluorobenzaldehyde in higher radiochemical yields, various new radiofluorination techniques have recently been investigated (Scheme 71).[7,17,23,24] 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 2.3.2.4.3 (Application of [^{18}F]fluorobenzyl halides in alkylation of phosphines and benzyl alcohols).

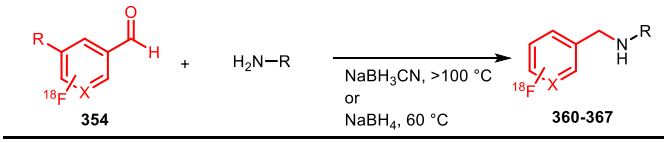
2.3.1.2 Application of [^{18}F]fluorobenzaldehydes in reductive aminations

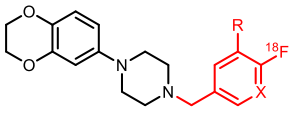
[^{18}F]fluorobenzaldehydes are predominantly used in reductive amination reactions, of which the first examples were published in 1990.[237] Scheme 72 summarises the small molecule PET tracers that have recently been prepared by reductive amination.[232,228–245] Except for tracer **365**, in which sodium 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.[232,245]

Another example of a successful two-step reaction without intermediate purify-cation 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.[239] 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.





360

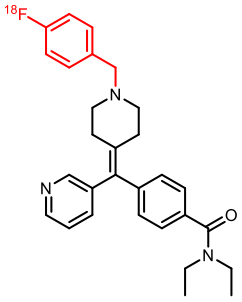
Dopamine receptor D_4

a X = CH, R = H
RCY = 35±5%, 90 min, overall
RCP >98%, SA = 60 GBq/μmol

b X = CH, R = OMe
RCY = 20±5%, 90 min, overall
RCP >98%, SA = 60 GBq/μmol

c X = CH, R = OBn
RCY = 9±4%, 120 min, overall
RCP >98%, SA = 30 GBq/μmol

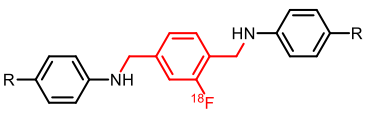
d X = N, R = H
RCY = 15±5%, 80 min, overall
RCP >98%



364 [^{18}F]AZ12439516

δ-Opioid receptor

RCY = 29% da

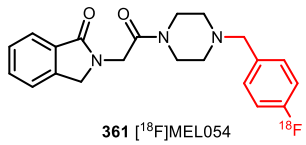


366

b-Amyloid plaques

a R = OCH_2CH_3
RCY = 35±6%, overall[c]
RCP >95%, SA > 49±8 GBq/μmol

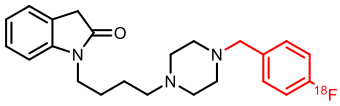
b R = SCH_3
RCY = 35±6%, overall[c]
RCP >95%, SA > 49±8 GBq/μmol



361 [^{18}F]MEL054

Melanin uptake

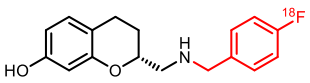
RCY = 34±9% ndc, 105 min, overall
RCP >99%, SA = 71-119 GBq/μmol



362

Dopamine receptor D_4

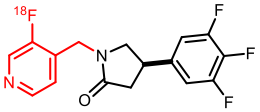
RCY = 21.2% dc, overall
RCP >95.5%, SA = 145 GBq/μmol



363 [^{18}F]AMC20

Dopamine receptor $D_{2/3}$

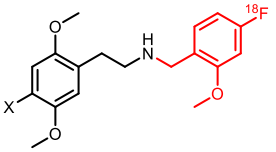
RCY = 24±7% dc, 150 min, overall[a]
RCP >95%, SA = 39±23 GBq/μmol



365

Synaptic vesicle protein 2A

RCY = 30% ndc, 150 min, overall[b]
RCP = 97.1±1.9%, SA = 98.9±68.7 GBq/μmol

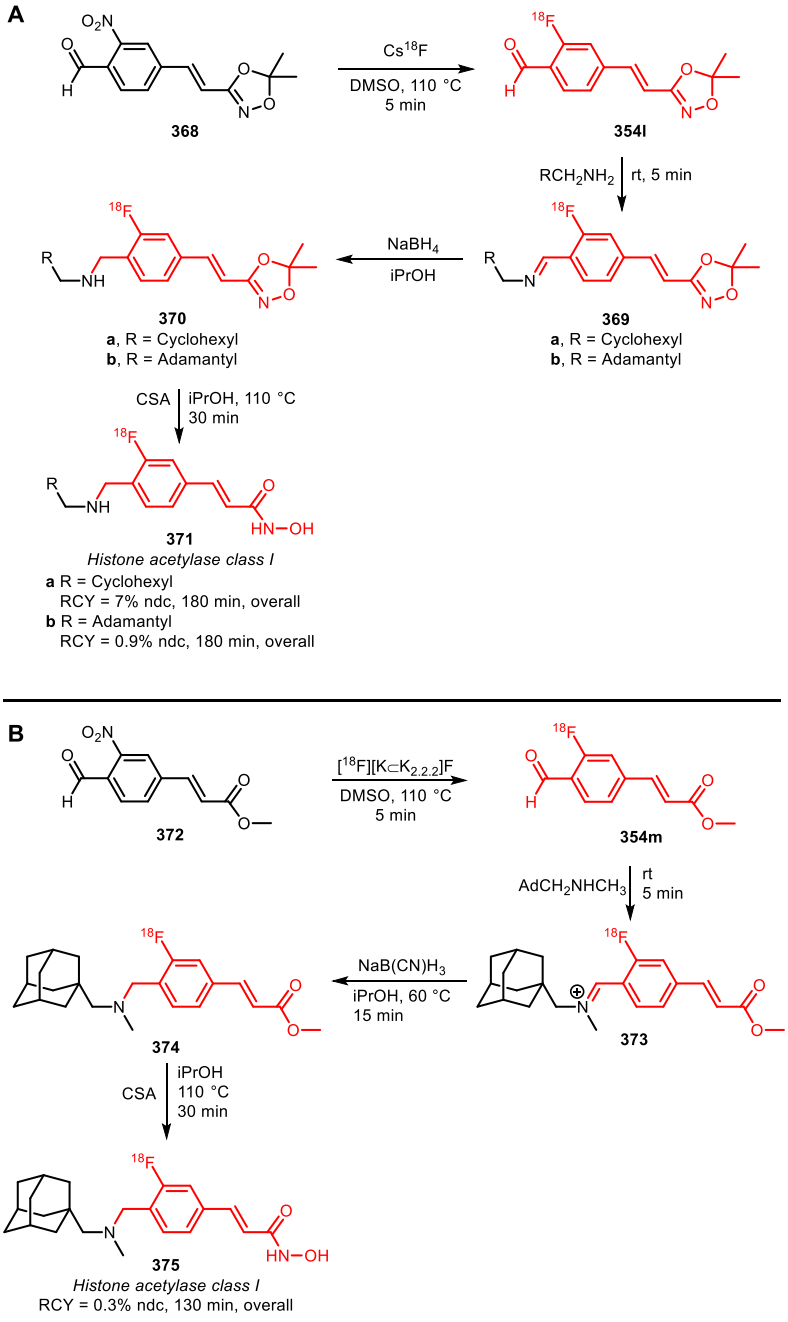


367

Serotonin 2A receptor

a X = Br, **b** X = I, **c** X = Cl,
d X = NO2, **e** X = CN
Synthesis details are not given

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.[232,238–245]



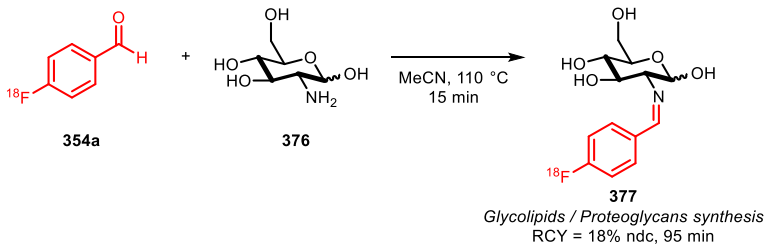
Scheme 73 Synthesis of aromatic fluorine-18 labelled Martinostat derivatives.[246]

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.[246] As an alternative, Strebl *et al*. published a fluorine-18 labelled Martinostat derivative where the aromatic ring was substituted with fluorine-18.[246] 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 hydroxamatemoiety is incompatible with radio-fluorination 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.

2.3.1.3 Application of [^{18}F]fluorobenzaldehydes in imine formation

[^{18}F]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 [^{18}F]fluorobenzaldehyde with an amine is compound **377** (Scheme 74).[44]



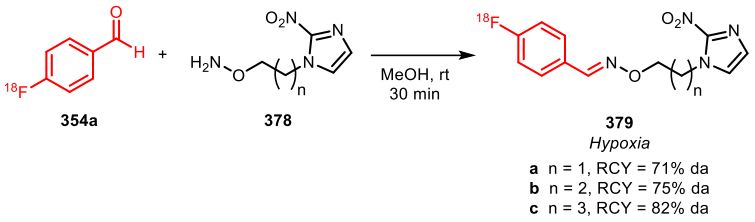
Scheme 74 Imine formation with 4-[^{18}F]fluorobenzaldehyde as a method to label glucosamine.[44]

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 [^{18}F]benzaldehydes for reaction with amines.

2.3.1.4 Application of [^{18}F]fluorobenzaldehydes in oxime formation

Oximes formed by condensation of [^{18}F]fluorobenzaldehydes with hydroxamines are generally very stable. It is therefore not surprising that the reaction of [^{18}F]fluorobenzaldehyde with aminooxy-functionalised peptides is a commonly applied method to label peptides.[247] For the synthesis of low molecular weight PET tracers this method is rarely used, as only one report has been published recently.[248]

Abdel-Jalil *et al*. reported on the synthesis of a series of hypoxia tracers **379a–c** by reacting [^{18}F]4-fluorobenzaldehyde **354a** with aminoxy-functionalised precursors **378a–c** (Scheme 75).[248] 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 of PET tracers, this oxime formation using [^{18}F]4-fluorobenzaldehyde has great potential to develop fluorine-18 labelled PET tracers.

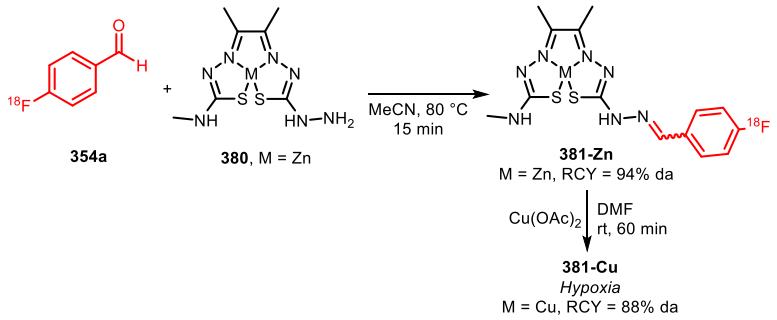


Scheme 75 Synthesis of a hypoxia tracer by oxime formation.[259]

2.3.1.5 Application of [^{18}F]fluorobenzaldehydes in hydrazine formation

Another example of stable imine based PET tracers are hydrazones, which can be formed *via* condensation of [^{18}F]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.[152]

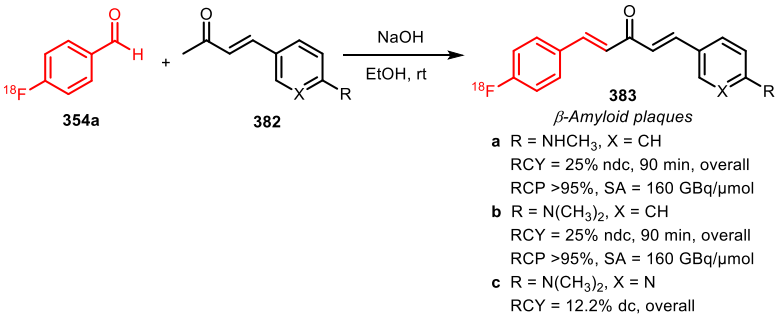
A series of derivatives was synthesised using various fluorine-18 labelled building blocks: amide formation with 4-[^{18}F]fluorobenzoic acid, click reaction with [^{18}F]fluoroethyl azide and imine condensation with 4-[^{18}F]fluorobenzaldehyde. The condensation of 4-[^{18}F]fluorobenzaldehyde with 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-[^{18}F]fluorobenzoic acid resulted in only 32% radiochemical yield (analytically determined).



Scheme 76 Imine formation with 4-[^{18}F]fluorobenzaldehyde for the synthesis of a bis(thiosemicarbazonata) hypoxia tracer.[152]

2.3.1.6 Application of [^{18}F]fluorobenzaldehydes in aldol condensation

The aldol condensation of benzaldehydes with benzylideneacetones is well known.[249] Li *et al*. and Cui *et al*. use this 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).[250,251]

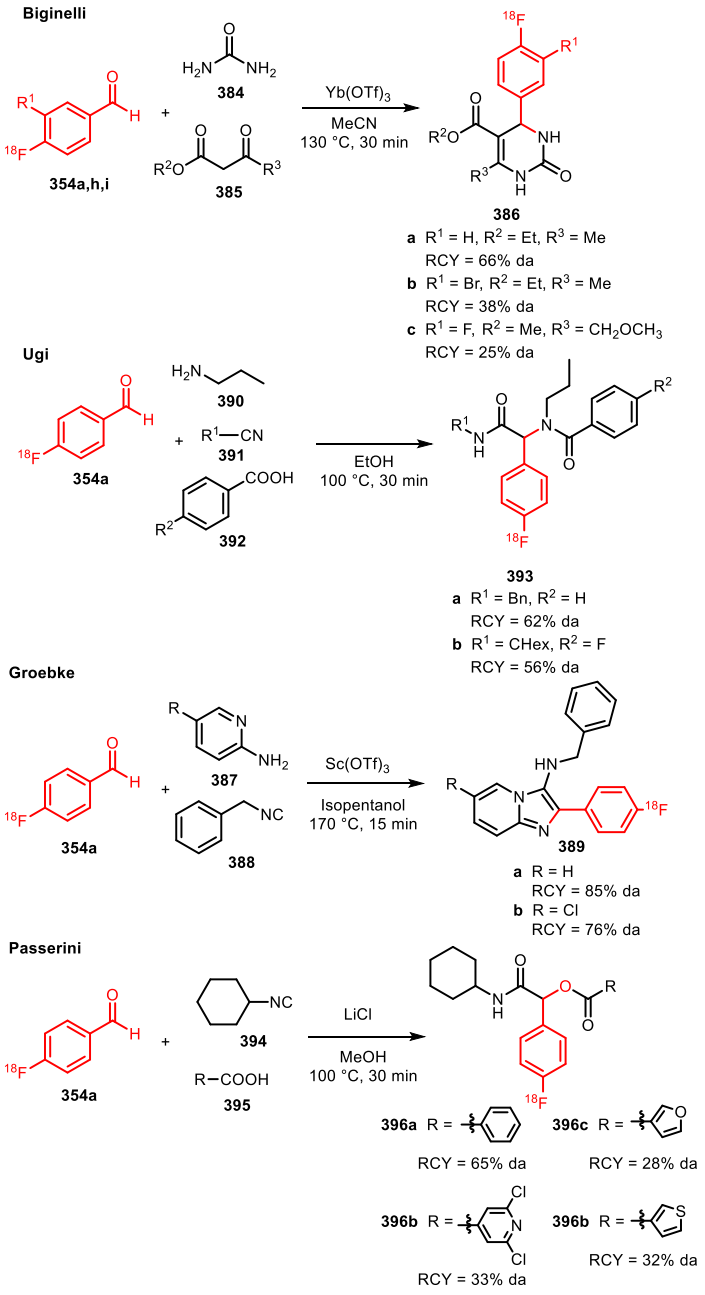


Scheme 77 Synthesis of fluorine-18 labelled benzylidene acetones by aldol condensation with 4-[^{18}F]fluorobenzaldehyde.[250,251]

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.

2.3.1.7 Application of [^{18}F]fluorobenzaldehydes in multicomponent reactions

Multicomponent reactions are important in bio-organic chemistry, since they deliver structurally diverse compounds in a single step from easy to obtain starting materials.



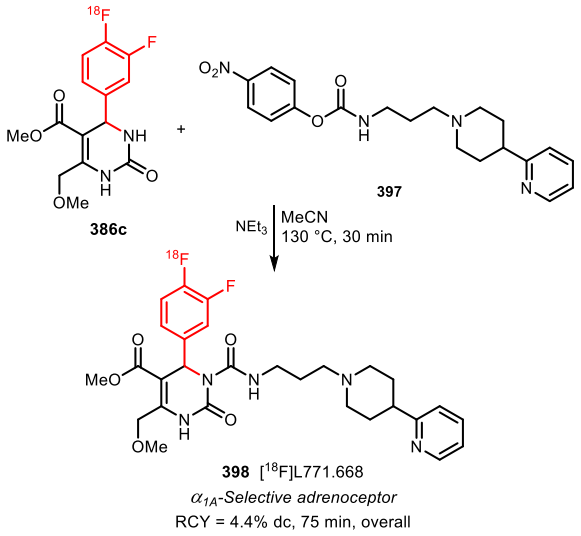
Scheme 78 Multicomponent reactions with [^{18}F]fluorobenzaldehydes.[252]

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 blocks investigated for fluorine-18 based multicomponent reactions (Scheme 78).[252]

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 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 an efficient manner.



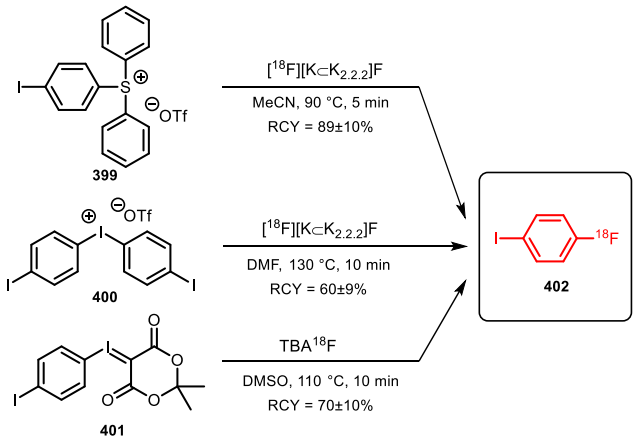
Scheme 79 Synthesis of [^{18}F]L771.668 using the Biginelli MCR.[252]

2.3.2 [^{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 2.3.2.1). Other aryl halides, which have very recently been applied are 1-bromo-3-[^{18}F]fluorobenzene (Section 2.3.2.2) and 2-bromo-6-[^{18}F]fluoropyridine (Section 2.3.2.3). The group of ^{18}F-labelled benzyl halide building blocks will be shown in Section 2.3.2.4 and finally, the novel building block [^{18}F]4-fluorophenetylhalide, prepared using novel fluorine-18 chemistry, will be shown in Section 2.3.2.5.

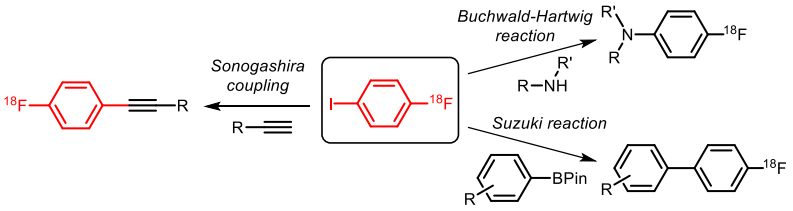
2.3.2.1 Synthesis and application of 4-[^{18}F]fluoroiodobenzene

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.*[250] 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.[253] To obtain 4-[^{18}F]fluoroiodobenzene in a higher radiochemical yield, novel late stage radiofluorination methodologies are recently explored (Scheme 80).[9,254–257]



Scheme 80 Synthesis of 4-[^{18}F]fluoroiodobenzene.[9,254–257]

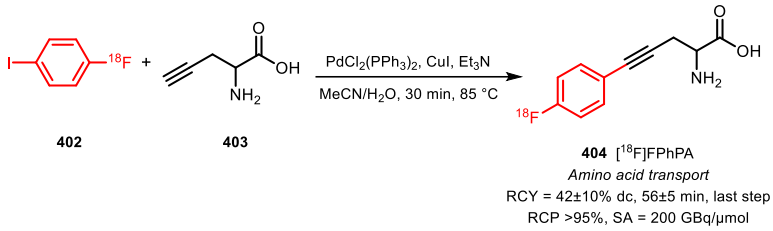
All three reported methods provide 4-[^{18}F]fluoroiodobenzene **402** in moderate to excellent radiochemical yields, thereby demonstrating the advantage of novel radiofluorination technology in the synthesis of building blocks.



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

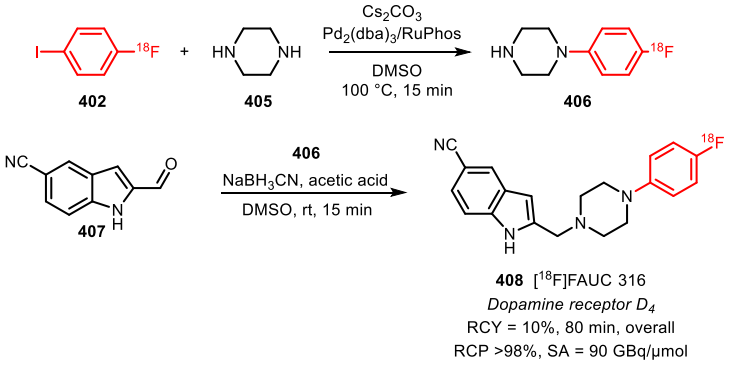
Because these methods are rather new, applications of 4-[^{18}F]fluoroiodobenzene are still scarce. Only 3 examples have been recently reported, each reporting a different type of metal catalysed cross-coupling (Scheme 81).

The first example is the synthesis of 2-amino-5-(4-[^{18}F]fluorphenyl)pent-4-ynoic acid ([^{18}F]FPhPa) **404**, a novel amino acid for the PET imaging of tumours.[255] The tracer was obtained *via* a Sonogashira coupling between alkyne **403** and 4-[^{18}F]fluoro-iodobenzene **402** (Scheme 82). This publication shows that using 4-[^{18}F]fluoroiodo-benzene 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.



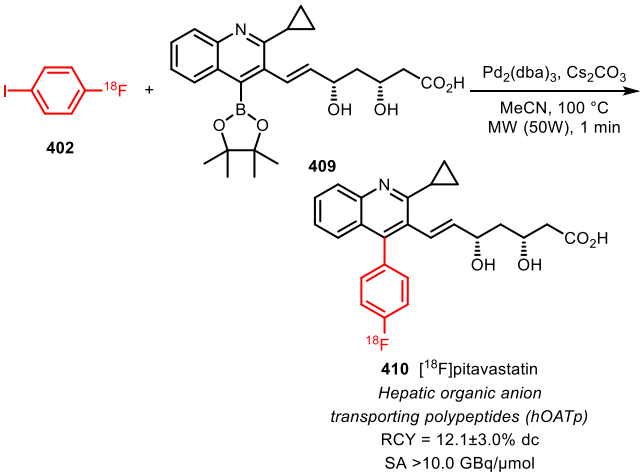
Scheme 82 Synthesis of [^{18}F]FPhPA by Sonogashira coupling with 4-[^{18}F]fluoroiodobenzene.[255]

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 with aldehyde **407** (Scheme 83).[254] 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.



Scheme 83 Buildup synthesis of [^{18}F]FAUC 316.[251]

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).[257] A relatively low overall radiochemical yield (12% decay corrected) is also reported here.



Scheme 84 Synthesis of [^{18}F]pitavastatin.[257]

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.

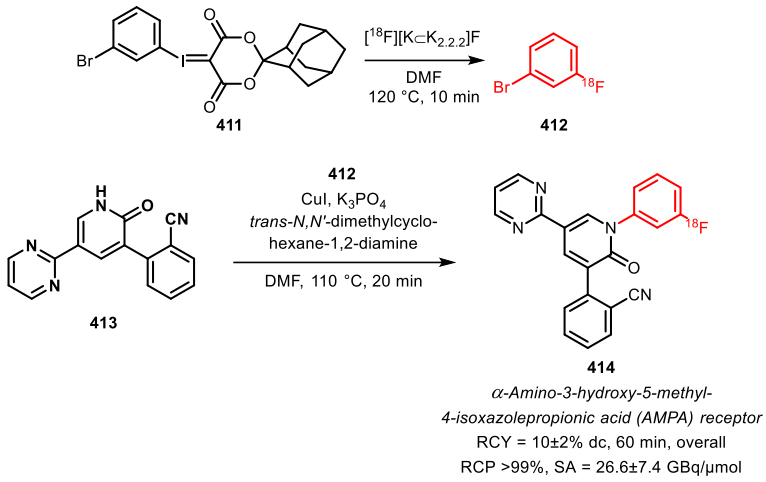
2.3.2.2 Synthesis and application of 1-bromo-3-[^{18}F]fluorobenzene

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).[258]

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.

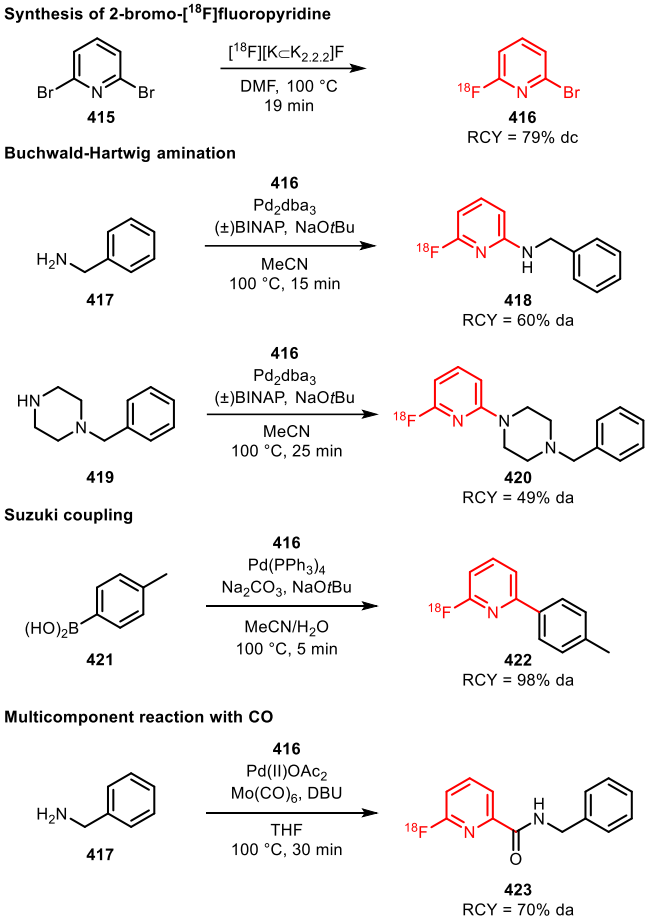


Scheme 85 Synthesis of AMPA receptor PET tracer **414** by Cu-mediated *N*-arylation with 1-bromo-3-[^{18}F]fluorobenzene.[258]

2.3.2.3 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).[259,260]

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.



Scheme 86 Synthesis and application of 2-bromo-6-[^{18}F]fluoropyridine.[260]

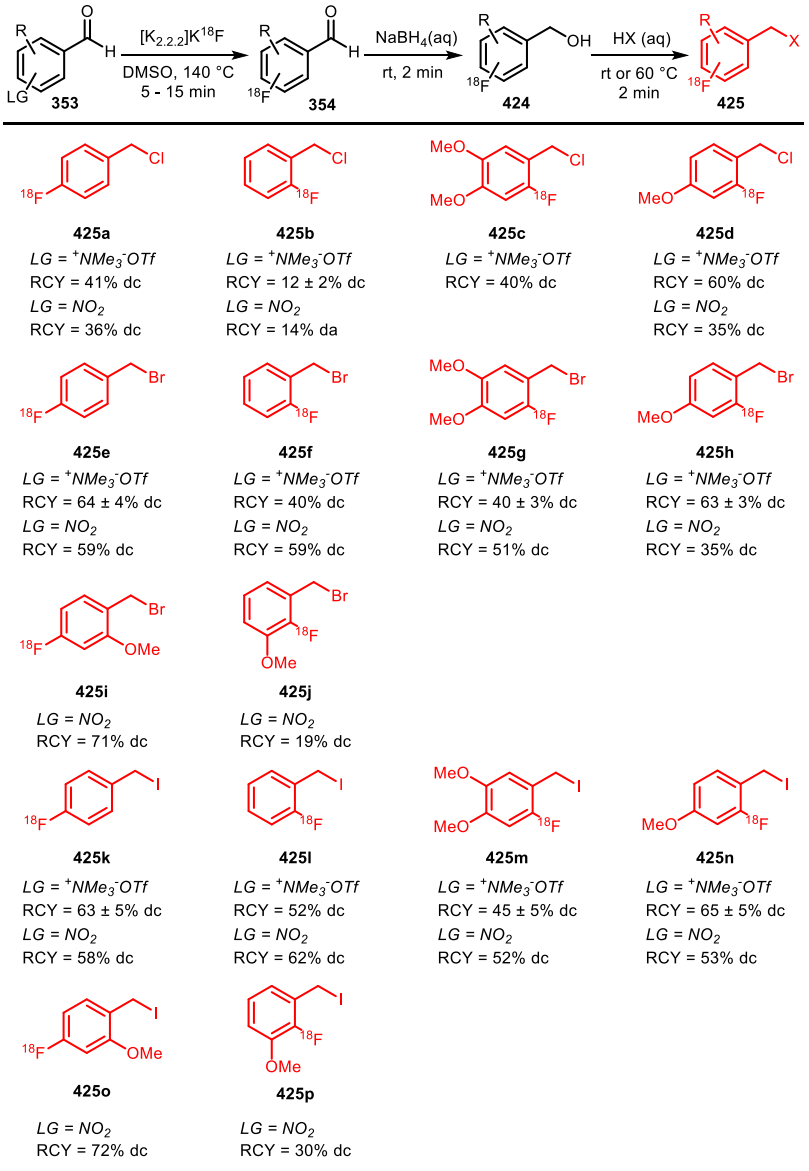
2.3.2.4 Synthesis and application of [^{18}F]fluorobenzyl halides

2.3.2.4.1 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.[261,262]

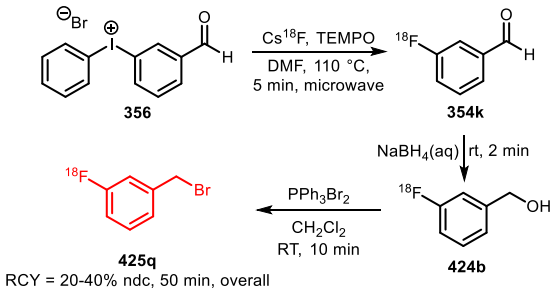
The most commonly described approach towards 4-[^{18}F]fluorobenzyl halides and 2-[^{18}F]fluorobenzyl halides is *via* a three step procedure, starting with the synthesis of [^{18}F]fluorobenzaldehyde, followed by a reduction and finally the halogenation of the benzylalcohol. Lemaire *et al*. recently optimised this synthetic strategy towards various 4- and 2-[^{18}F]fluorobenzyl halides (Scheme 87).[233]

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).[232]



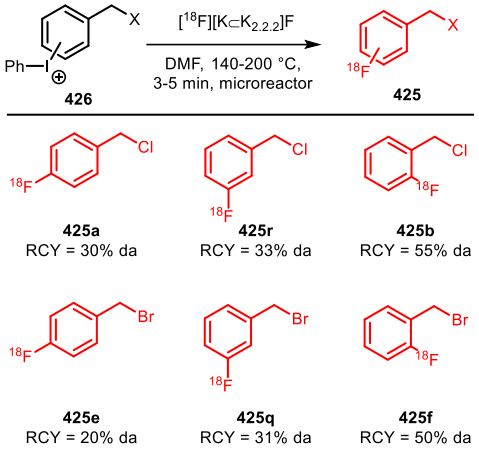
Scheme 87 Conventional synthesis of 2- and 4-[^{18}F]fluorobenzyl halides.[233]

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.



Scheme 88 Three step strategy towards 3-[^{18}F]fluorobenzyl bromide.[229]

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).[23] 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.

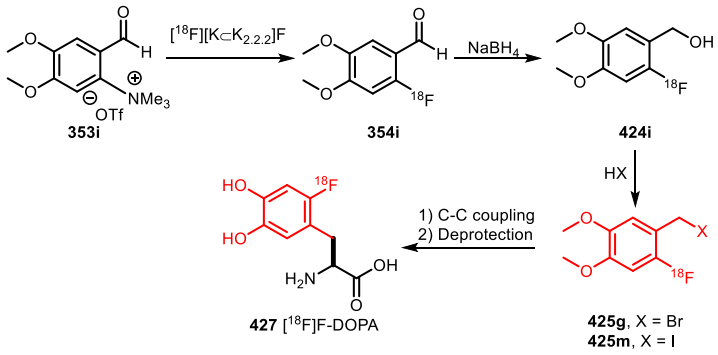


Scheme 89 Preparation of [^{18}F]fluorobenzylhalides in one step from diaryliodonium precursors.[23]

2.3.2.4.2 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).[263]

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.[264–268] 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) 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).[263,269–279]

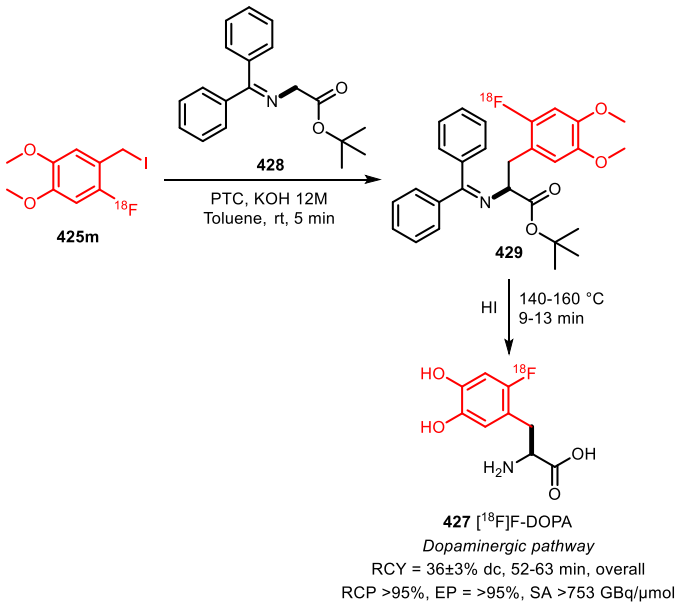


Scheme 90 Synthesis of [^{18}F]F-DOPA via multistep approach using a [^{18}F]fluorobenzyl halide as a building block.[263,269–277]

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).[269] 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 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.[276,277] [^{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 synthesised by Libert *et al*. in an overall radiochemical yield of 50.5 ± 2.7% (dc).[276,277]



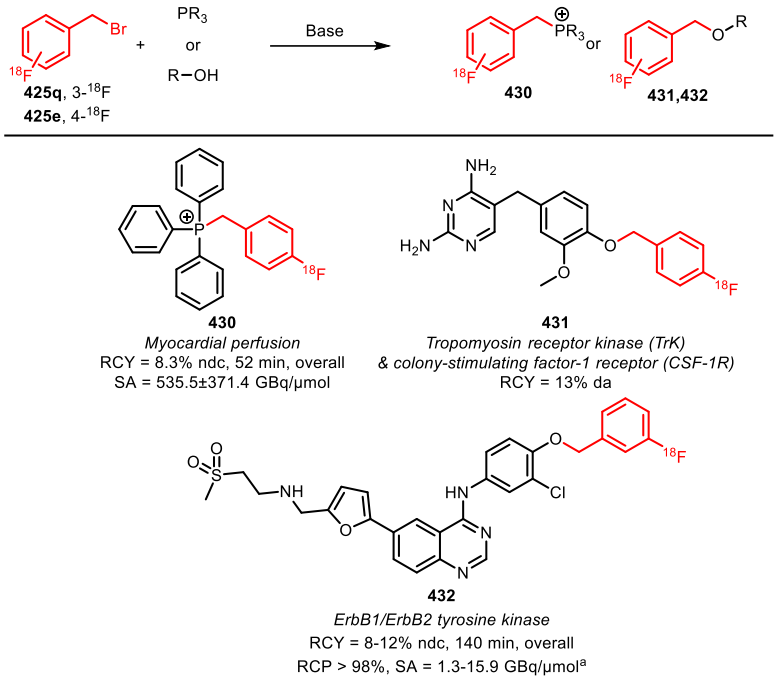
Scheme 91 C–C coupling and hydrolysis of a [^{18}F]fluorobenzyl halide with *N*-(diphenylmethylene)glycine *tert*-butyl ester and a phase transfer catalyst (PTC).[269,276,277]

Pretze *et al*. evaluated the [^{18}F]F-DOPA synthesis procedure, however was not able to synthesise [^{18}F]F-DOPA in the same radiochemical yield.[278] 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 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 synthesised in a radiochemical yield of 20 ± 1% (dc).[278]

2.3.2.4.3 Application of [^{18}F]fluorobenzyl halides in alkylation of phosphines and benzyl alcohols

Three new tracers have been synthesised using [^{18}F]fluorobenzyl halides since 2010 (Scheme 92).[279–281] 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 phosphines, and a good stability.



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.[279–281]

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**.[281] 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**.

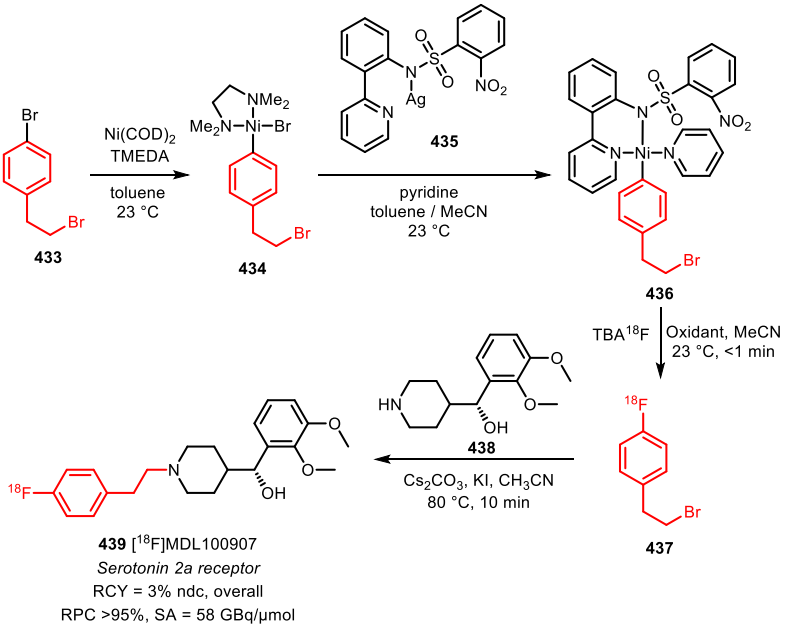
The myocardial perfusion tracer 4-[^{18}F]fluorobenzyltriphenylphosphonium ion **430**, as reported by Ravert *et al*., was synthesised *via* microwave assisted alkylation using 4-[^{18}F]fluorobenzyl bromide (Scheme 92).[280] The overall radiochemical yield was 8.3% (ndc). Also in this case, a multistep 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.

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).[279]

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 this.

2.3.2.5 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).[16] 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 **434** was prepared recently in one step by radiofluorination of Ni-precursor **434**.[15] Immediately after formation, 4-[^{18}F]fluorophenethyl bromide **437** was reacted with amine **438** to yield [^{18}F]MDL100907 **439**.



Scheme 93 Preparation of serotonin 2a receptor tracer [^{18}F]MDL100907 using 4-[^{18}F]fluorophenethyl bromide.[16]

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

[18F]fluorophenylethyl bromide to make this method useful for high yield tracer synthesis.

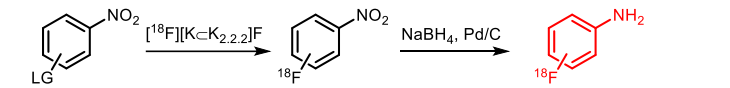
2.3.3 [18F]Fluorophenyl amines

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.

In this chapter, the synthesis and application of [18F]fluoroanilines (Section 2.3.3.1), [18F]fluorobenzylamines (Section 2.3.3.2), [18F]fluorobenzohydrazides (Section 2.3.3.3) and [18F]phenethylamines (Section 2.3.3.4) will be described.

2.3.3.1 Synthesis and application of [18F]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-[18F]fluoronitrobenzene and 2-[18F]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-[18F]fluoroaniline in high overall radiochemical yields.[191,282–286]



440 LG = 4-NO_2
441 LG = 3-$NMe_3^+OTf^-$
442 LG = 2-NO_2

443a 4-18F
RCY = 77% dc from **440**
443b 3-18F
RCY = 44% dc from **441**
443c 2-18F
RCY = 81% dc from **442**

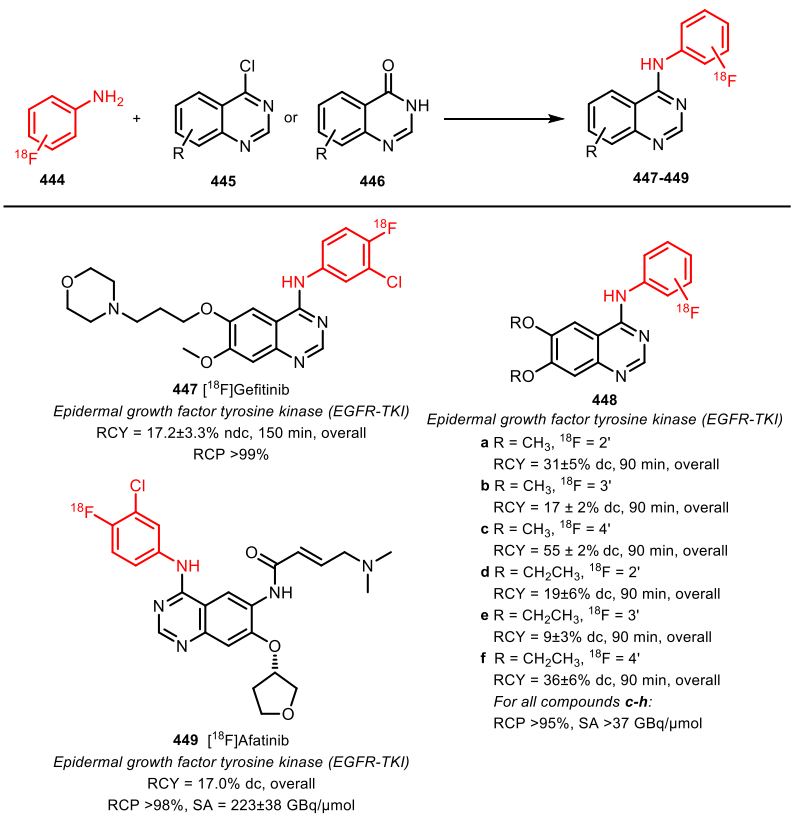
444a 4-18F
RCY = 94% dc from **443a**
444b 3-18F
RCY = 80% dc from **443b**
444c 2-18F
RCY = 84% dc from **443c**

Scheme 94 Preparation of [18F]fluoroanilines in a two-step fluorine-18 labelling and nitro reduction procedure.[191,282–286]

Radiofluorination of 1,3-dinitrobenzene gives 3-[18F]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 trimethyl-ammonium precursor **441** is used as a precursor, because the trimethylammonium group is a better leaving group then the nitro group (Scheme 94).[284,287,288]

One group of compounds in which [18F]fluoroanilines as reagents for PET tracers have proven to be useful are the epidermal growth factor receptor (EGFR) kinase inhibitors (Scheme 95).[284,287,288] The anilinoquinazoline structure can be built-up by the

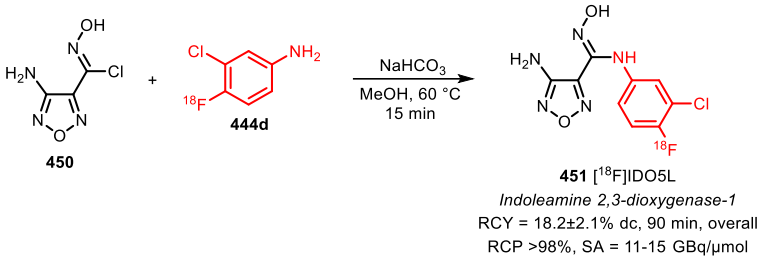
reaction of 4-[^{18}F]fluoroanilines with chloroquinazoline **445** or cyclic amide **446**, in which, for the latter, a strong base (1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)) and a coupling reagent (*O*-benzo-triazole-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (BOP)) are required. Using 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).[287,288] 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).[284]



Scheme 95 Synthesis of PET tracers for the EGFR-TKI by reaction of chloroquinazolines or cyclic amides with [^{18}F]fluoroanilines.[284,287,288]

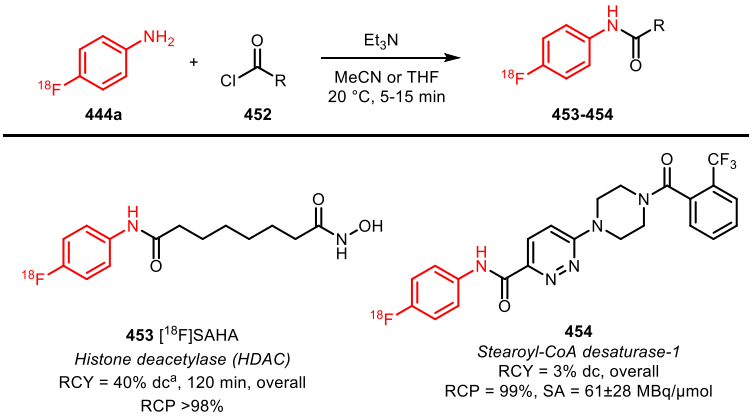
In a similar approach, Huang *et al*. synthesised the potential indoleamine 2,3-dioxygenase-1 tracer [^{18}F]IDO5L **451** in a radiochemical yield comparable to the EGFR inhibitors (Scheme 96).[286] A direct ^{18}F-radiolabelling towards **451** using the corresponding trimethylammonium precursor did 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 96 Synthesis of indolamine 2,3-dioxygenase-1 tracer [^{18}F]IDO5L using 3-chloro-4-[^{18}F]fluoroaniline.[286]

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).[285] 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 4-step synthesis, the question arises whether other strategies are actually needed at all.



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.[191,285]

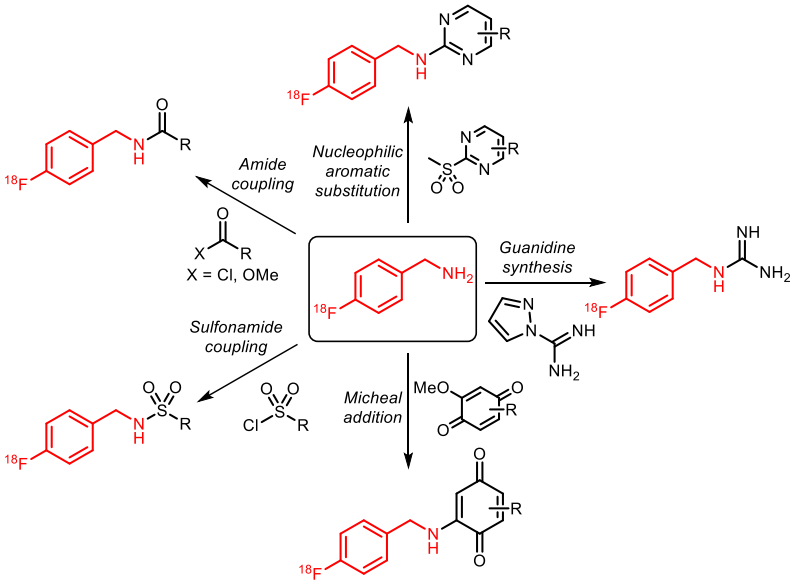
Stearoyl-CoA tracer **454** was also synthesised by reaction of 4-[^{18}F]fluoroaniline with an acid chloride.[191] However, this time only an overall radiochemical yield of 3% (dc) was obtained. The low yield was attributed by the authors to the poor reactivity of

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.

2.3.3.2 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 2.3.3.2.2), Michael addition (Section 2.3.3.2.3) nucleophilic substitution on (methylsulfonyl)-pyrimidines (Section 2.3.3.2.4) and guanidine synthesis (Section 2.3.3.2.5).[289–294]

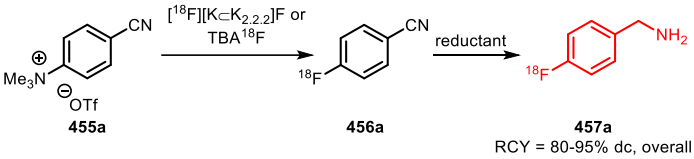


Scheme 98 Recent examples of reactions with [^{18}F]fluorobenzylamines.

2.3.3.2.1 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).[289–293,295,296] After formation of [^{18}F]fluoro-

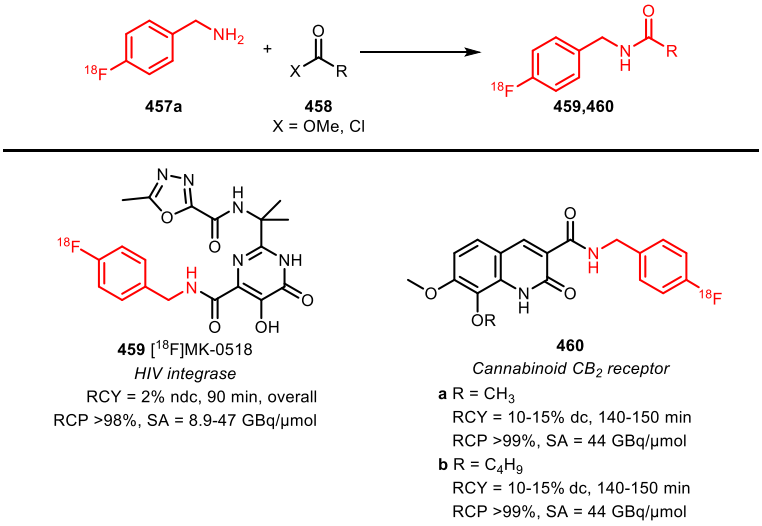
benzonitrile, the cyano group is reduced to an amine. Using this synthetic pathway, 4-[^{18}F]fluorobenzylamine **457a** can be obtained in a radiochemical yield of 80–95%.



Scheme 99 General synthesis route towards [^{18}F]fluorobenzylamines.[289–293,295,296]

For the reduction, various reducing agents have been used including $LiAlH_4$, borane dimethyl sulfide and mixtures of sodium borohydride with transition metal salts.[289–293,296] 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 LiAlH4, 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.[292,296]

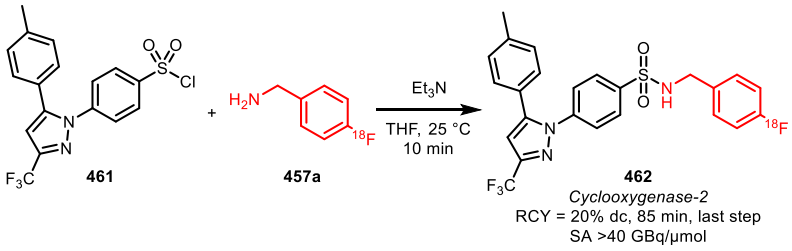


Scheme 100 Amide coupling reactions with [^{18}F]fluorobenzylamine.[289,291]

2.3.3.2.2 Application of [^{18}F]fluorobenzylamine in (sulfon)amide coupling reactions

Both human immunodeficiency virus 1 integrase (HIV-1 IN) inhibitor **459** and CB2 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).[289,291] 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.

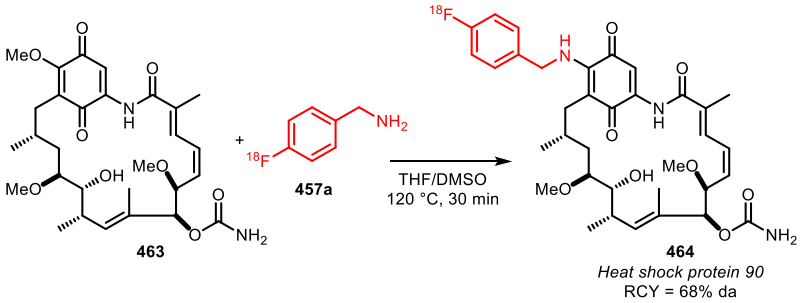
4-[^{18}F]Fluorobenzylamine was used for the synthesis of a sulfonamide, *via* a reaction with sulfonyl chloride **461**, to obtain COX-2 tracer **462** in a radiochemical yield of 20% (dc) in 85 min, calculated from 4-[^{18}F]fluorobenzylamine (Scheme 101).[294]



Scheme 101 Coupling of [^{18}F]fluorobenzylamine with sulfonyl chloride **461**.[294]

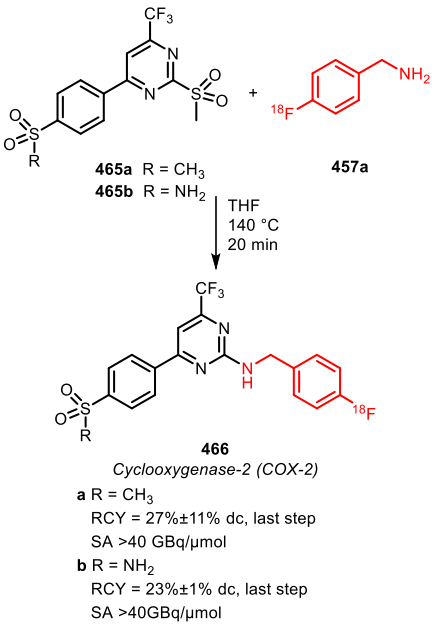
2.3.3.2.3 Application of [^{18}F]fluorobenzylamine in Michael addition reactions

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 102 Synthesis of [^{18}F]geldanamycin via Michael addition using [^{18}F]4-fluorobenzylamine.[292]

The coupling of 4-[^{18}F]fluorobenzylamine with geldanamycin **463** was investigated by Way *et al.*[292] 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.



Scheme 103 Synthesis of COX-2 inhibitors by nucleophilic aromatic substitution with 4-[^{18}F]fluorobenzylamine.[290]

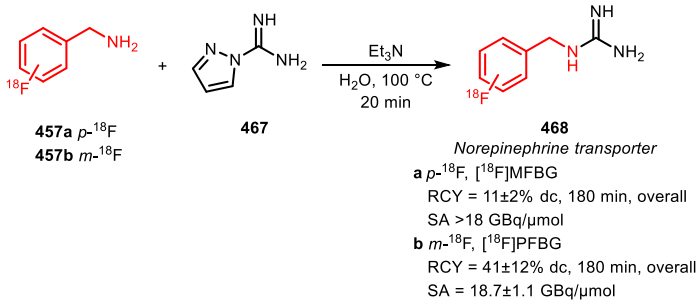
2.3.3.2.4 Application of [^{18}F]fluorobenzylamine in nucleophilic aromatic substitution on (methylsulfonyl)-pyrimidines

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).[290] Radiochemical yields of the coupling reactions were moderate, 27 ± 11% (dc) for product **466a** and 23 ± 1% for product **466b**.

2.3.3.2.5 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.[295] Following this publication, two articles were published in

1996 and 2002 in which [^{18}F]PFBG was investigated in rat and dog.[297,298] It took until 2014, when Zhang *et al*. showed a renewed interest in [^{18}F]MFBG and [^{18}F]PFBG.[293] 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.



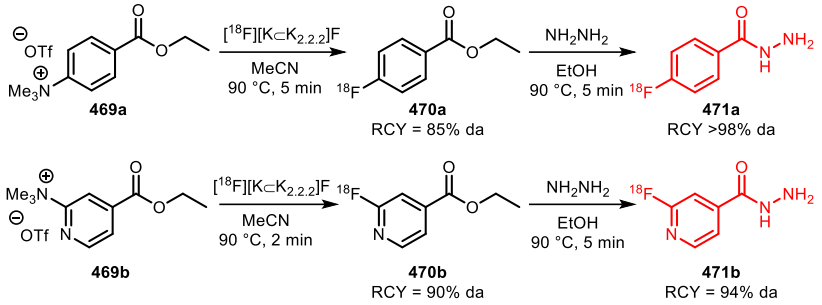
Scheme 104 Synthesis of [^{18}F]MFBG and [^{18}F]PFBG.[293]

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 2.3.3.2.2 to 2.3.3.2.5, [^{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.

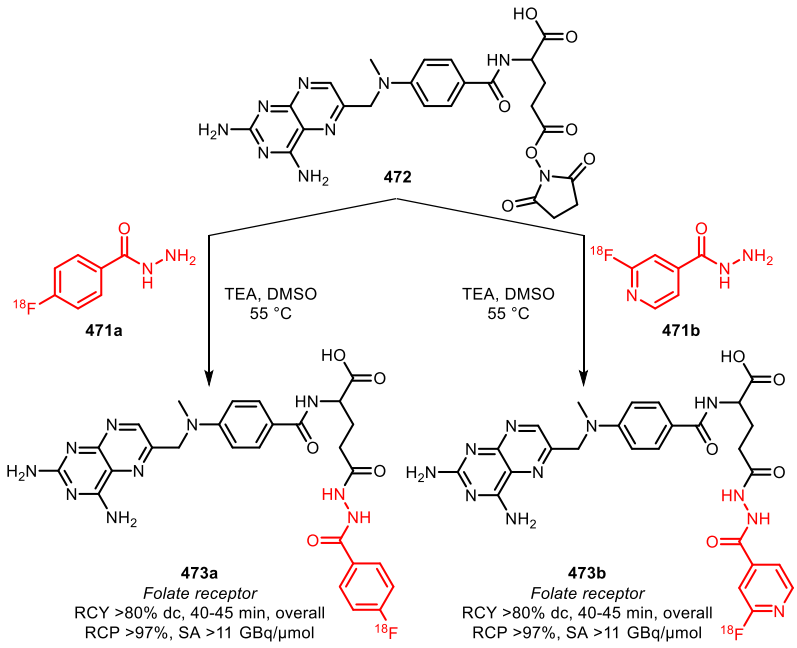
2.3.3.3 Synthesis and application of [^{18}F]fluorobenzohydrazides

The [^{18}F]fluorobenzohydrazide building blocks **471a** and **471b** have been developed by Al Jammaz *et al*. (Scheme 105).[294] 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 [^{18}F]fluoro-benzohydrazides **471a** and **471b** by reacting with hydrazine hydrate.[299,300]



Scheme 105 Synthesis of [^{18}F]fluorobenzohydrazide building blocks.[299]

These building blocks have recently been applied in the synthesis of fluorine-18 labelled derivatives of methotrexate (Scheme 106).[300] In this synthesis, the activated *N*-succinimidylmethotrexate 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 without the need of a HPLC purification.



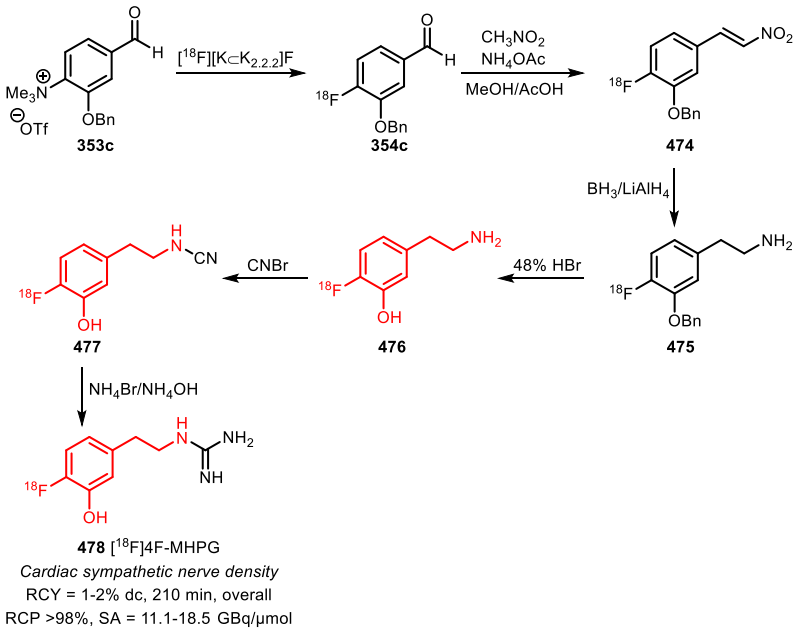
Scheme 106 Fluorine-18 labelling of methotrexate using [^{18}F]fluorobenzohydrazide building blocks.[300]

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%.[301,302]

2.3.3.4 Synthesis and application of [^{18}F]fluorophenethylamines

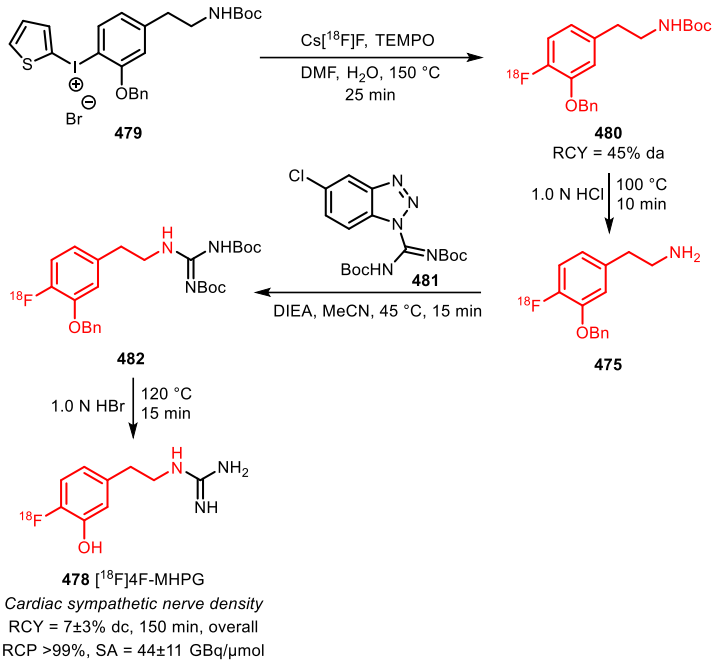
Since 2010, there have been two PET tracers published containing the fluorophenethyl moiety.[303–305] In the synthesis of the guanidine PET tracer **478**, described by Jang *et al.*, a three-step procedure for the synthesis of [^{18}F]fluorophenethylamine building block **476** has been reported (Scheme 107).[303]

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.[303]

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).[304]

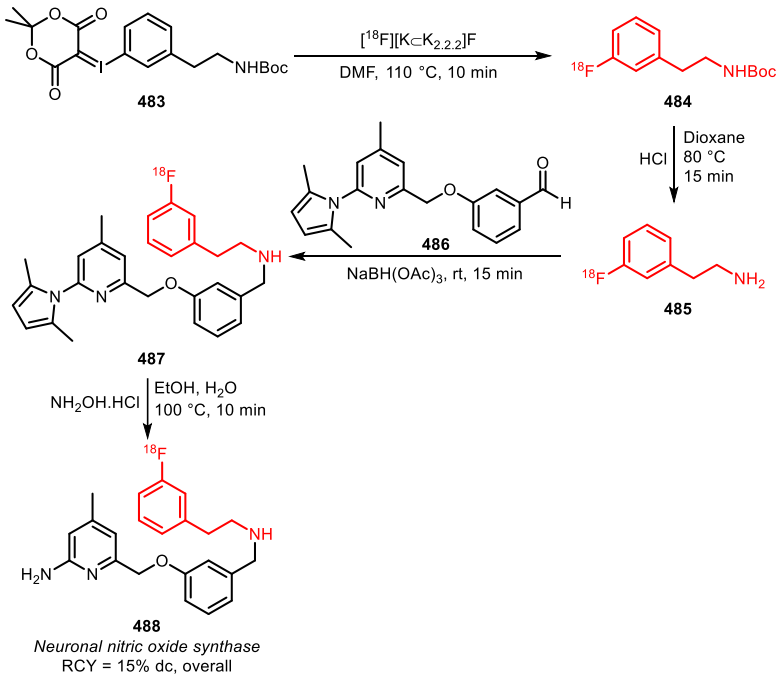


Scheme 108 Synthesis of 4-[^{18}F]fluoro-3-hydroxyphenylethylguaninidine in four steps.[304]

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 ± 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),[305] 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 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).

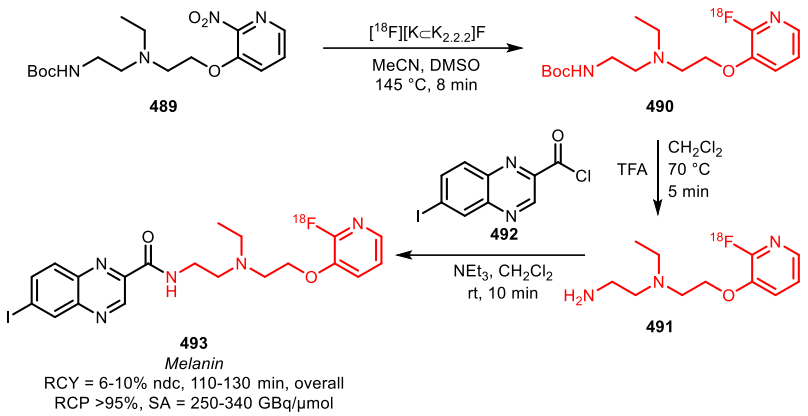
This procedure was not further optimised due to issues with reproducibility of the reductive amination step and because promising results were obtained with the novel late-stage radiofluorination of boronic acid pinacol esters (Table 1, entry 9).



Scheme 109 Building block approach towards neuronal nitric oxide synthase tracer **488**.[305]

2.3.3.5 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).[306] 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 types 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.



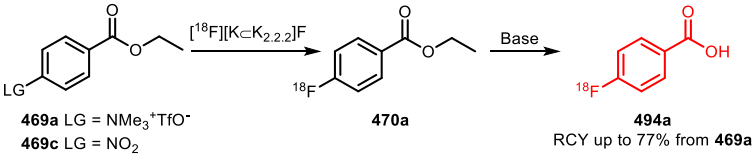
Scheme 110 Multistep radiosynthesis of fluorine-18 labelled melanoma PET tracer **493**.[306]

2.3.4 [^{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 formamides. Activated esters are either formed *in situ* from [^{18}F]fluorobenzoic acid (Section 2.3.4.1), or the active esters are isolated before use, as is the case with [^{18}F]SFB (Section 2.3.4.2) and [^{18}F]6-fluoronicotinic acid 2,3,5,6-tetrafluorophenyl ester ([^{18}F]FPy-TFP, Section 2.3.4.3).

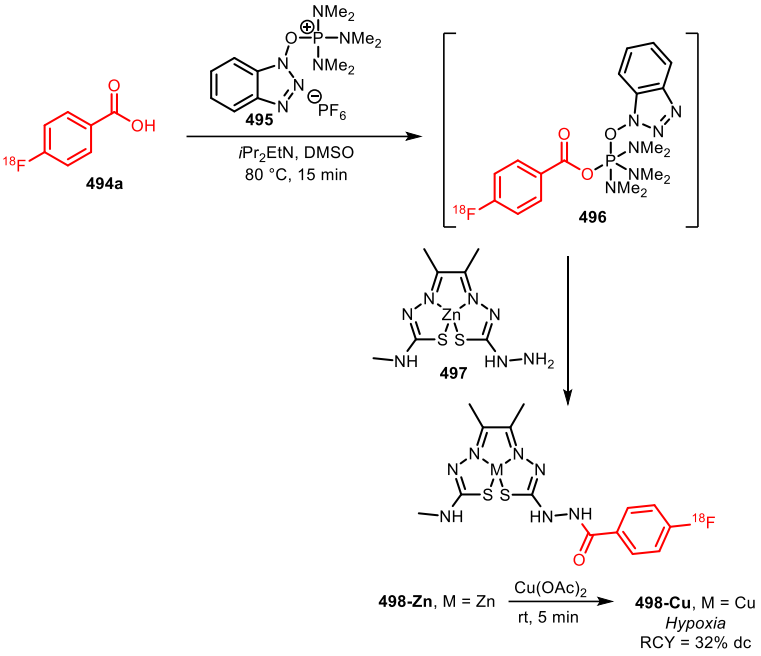
2.3.4.1 Synthesis and application of 4-[^{18}F]fluorobenzoic acid

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).[152,307,308]



Scheme 111 Synthesis of 4-[^{18}F]fluorobenzoic acid.[152,307,308]

In these recent articles, no radiochemical yields of the obtained 4-[^{18}F]fluoro-benzoic acid are mentioned, however, in publications from before 2010, radiochemical yields up to 77% are described when started from trimethylammonium triflate precursor **469a**.[309]

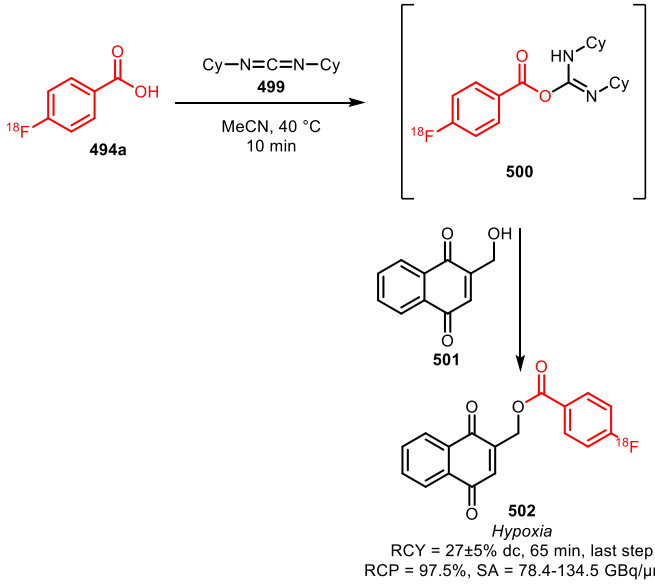


Scheme 112 Activation of 4-[^{18}F]fluorobenzoic acid and coupling to hydrazine derivative **497**.[152]

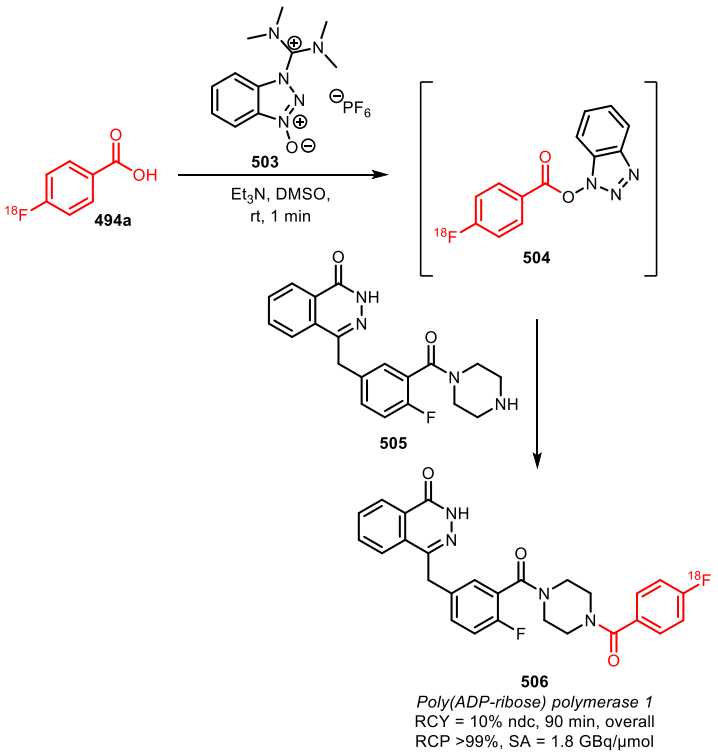
Various coupling reagents can be used to activate benzoic acid for nucleophilic substitution. Caroll *et al*. used BOP **495** together with *N*,*N*-diisopropylethylamine as a base to couple [^{18}F]4-fluorobenzoic acid to hydrazine derivative **497**, followed by a Cu for Zn exchange resulting in hypoxia tracer bis(thiosemicarbazonate) complex **498-Cu** in 32% radiochemical yield, starting from 4-[^{18}F]fluorobenzoic acid (Scheme 112).[152]

Another coupling agent to activate 4-[^{18}F]fluorobenzoic acid, *N*,*N'*-dicyclohexyl-carbodiimide (DCC) **499**, is applied by Ackermann *et al*. for the synthesis of fluorine-18 labelled naphthoquinone as a PET tracer for hypoxia (Scheme 113).[307] 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).[308] This is a low but acceptable radiochemical yield, considering the 4-[^{18}F]fluoro-benzoic acid is reacted with a bulky secondary amine.



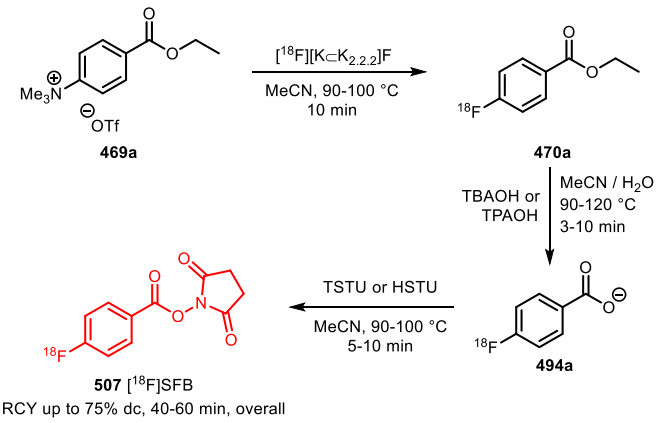
Scheme 113 Activation of 4-[^{18}F]fluorobenzoic acid with DCC and coupling to alcohol **501**.[307]



Scheme 114 Activation of 4-[^{18}F]fluorobenzoic acid with HBTU and coupling to secondary amine **505**.[308]

2.3.4.2 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.[310] 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.[73,82,311–325] 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.



Scheme 115 One pot, three step synthesis of [^{18}F]SFB.[73,82,311–315]

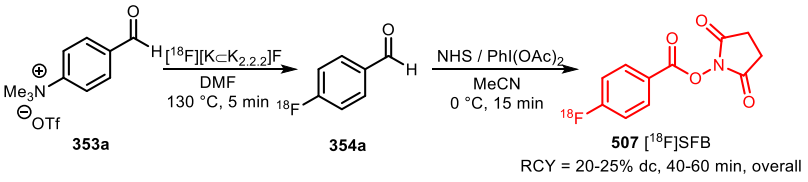
Currently, there are three methods in use for the synthesis of [^{18}F]SFB. The most convenient and commonly used method is the synthesis of [^{18}F]SFB *via* a one-pot, three-step procedure (Scheme 115).[73,82,311–315] This approach was first published by Tang *et al*. and starts with the radiofluorination 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]fluoro-benzoate **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 hydrolysis of ethyl 4-[^{18}F]fluorobenzoate **470a** with NaOH or HCl, which is subsequently purified by SPE before formation of [^{18}F]SFB.[316–318] 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).[319,320] 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.



Scheme 116 Two-step synthesis of [^{18}F]SFB.[319,320]

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.[73,82,311–328,320–325]

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.

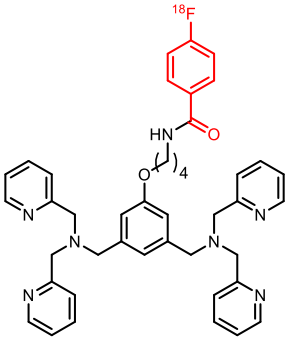
Table 2 Functional groups tolerated in acylation of amines with [^{18}F]SFB.

Functional group	**Compounds (Scheme 117)**
Carboxylic acid	**514**,[313] **515**,[13] **522**,[318] **523**,[312] **520a**,[324] **520b**,[320] **520c**,[324] **518a**,[325] **518b**,[325] **519a**,[325] **519b**[325]
Guanidine	**516**,[315] **524**,[317] **517**[314]
Alcohol	**517**[314]
Hydroxamide	**521**[316]

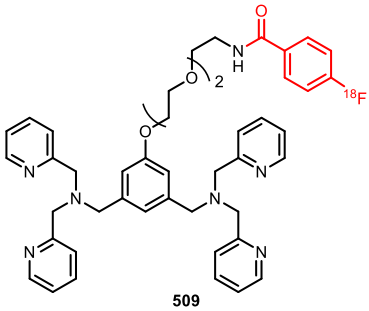
Typically, reaction of primary amines with [^{18}F]SFB are performed under basic conditions. Interestingly, for this reaction not just one type of base, but a wide range of bases in various solvents are reported. Two categories for the solvents and bases can be identified:

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.[82,312,314,316–318,320,324]
2) Reactions in organic solvents (DMSO, DMF, MeCN), using bases which readily dissolve in these solvents (DIPEA, NEt3). These conditions are used when the precursor is insoluble in water.[73,311,315,321,325]

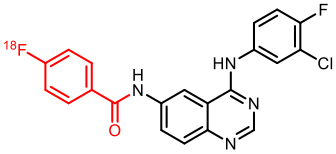
507 **508-524**



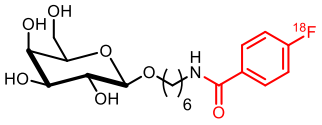
508
Cell death
RCY = 71±11% dc, 75 min, overall
RCP >99.5%, SA = 31.5 GBq/μmol



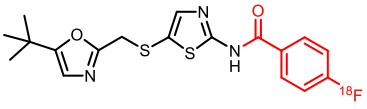
509
Cell death
RCY = 13±2% ndc, 100 min, overall
RCP >95%, SA = 28-35 GBq/μmol



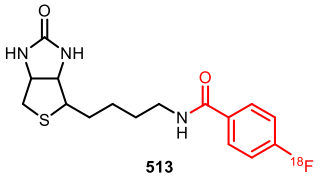
510
Epidermal growth factor receptor tyrosine kinase
RCY = 0% dc



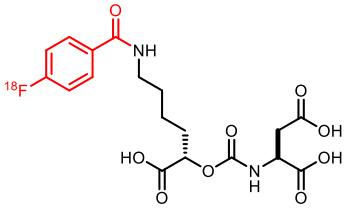
511 [^{18}F]FBHGal
Asialoglycoprotein receptor
RCY = 20-25% dc, overall[a]
RCP >98%, SA = 0.23 GBq/μmol



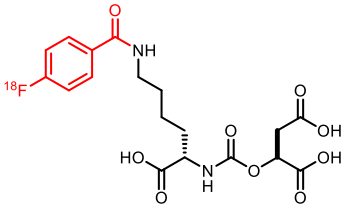
512
Cyclin-dependent kinase-2
RCY = 36-43% dc, 75 min, last step
RCP >95%, SA >20 GBq/μmol



513
Hypoxia-inducible factor 1
RCY = 38% ndc, 70-100 min, last step
RCP >95%, SA >97 GBq/μmol

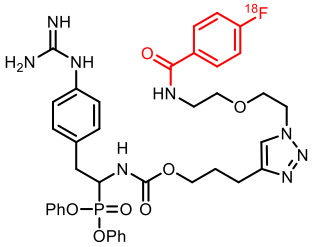


514
Prostate-specific membrane antigen
RCY = 27-28% ndc, last step
SA = 107-144 GBq/μmol

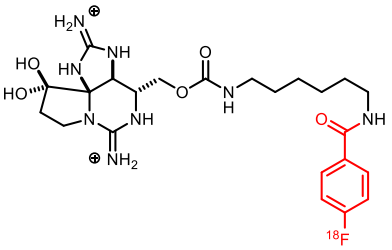


515
Prostate-specific membrane antigen
RCY = 5% ndc, last step

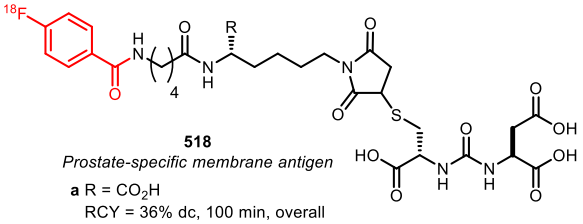
Scheme 117 PET tracers synthesised by amide formation using [^{18}F]SFB. [a]Includes removal of acetyl protecting groups.[73,82,311–318,320–325]



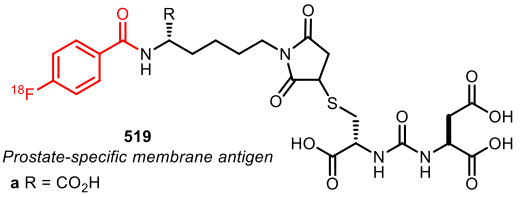
516
Urokinase plasminogen activator
RCY = 7±1% dc, 90 min, overall
RCP >95%, SA = 11 - 45 GBq/μmol



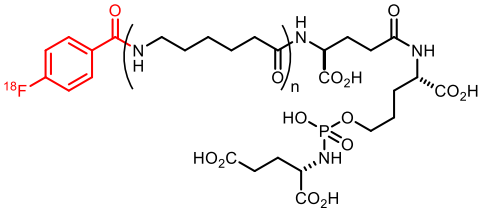
517 [^{18}F]STX
Voltage-gated sodium ion channel
RCY = 16.4±9.5% dc, 180-210 min, last step
RCP > 93%, SA = 60.3±42.2 GBq/μmol



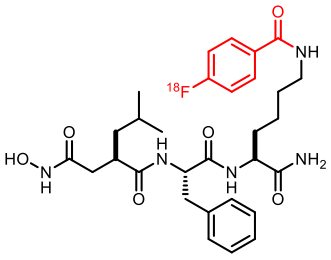
518
Prostate-specific membrane antigen
a R = CO_2H
RCY = 36% dc, 100 min, overall
RCP >95%
b R = H
RCY = 50% dc, 100 min, overall
RCP >95%



519
Prostate-specific membrane antigen
a R = CO_2H
RCY = 30% dc, 100 min, overall
RCP >95%
b R = H
RCY = 35% dc, 100 min, overall
RCP >95%

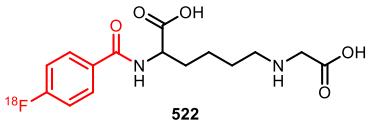


520
Prostate-specific membrane antigen
a n = o, **b** n = 1, **c** n = 2
RCY = 50-60% dc, last step
RCP >95%



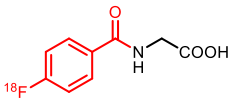
521
Metalloproteinase
RCY = 13-16% dc, last step
RCP >95%, SA = 41-66 GBq/μmol

Scheme 117 (Continued)



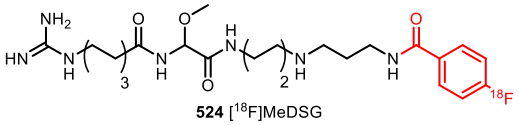
522

Distribution of advanced glycation end-products
RCY and synthesis time are not mentioned
RCP = 96%, SA = 3 GBq/μmol



523

Renal function
RCY = 91-95% dc, last step
RCP >99%

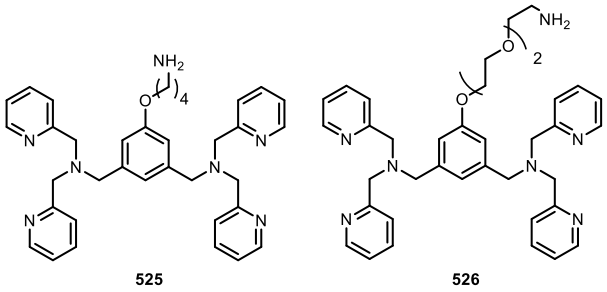


524 [^{18}F]MeDSG

Heat shock protein 70
RCY = 25-35%, 90 min, last step
RCP >95%, SA >74 GBq/μmol

Scheme 117 (Continued)

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).[73,82]



525 **526**

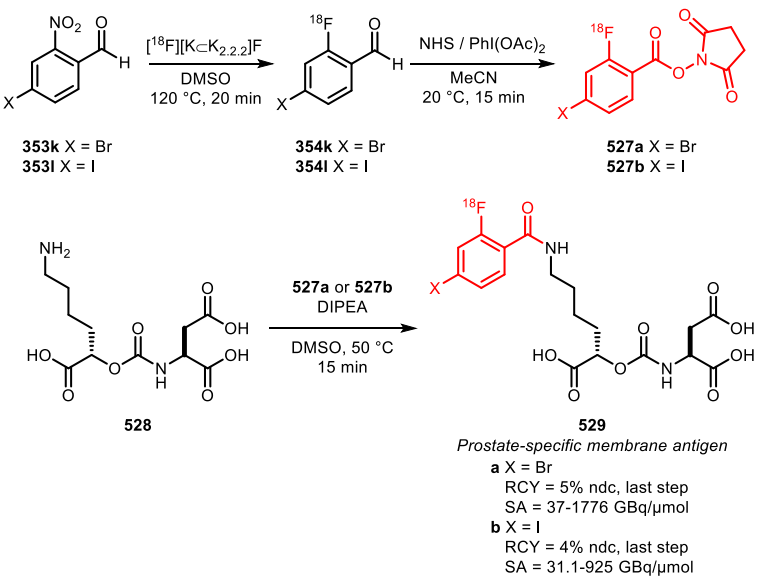
Figure 12 Alkylamine modified picolylamine derivatives.[73,82]

Table 3 Labeling of picolylamine precursors **525** and **526** with ^{18}F-labelled building blocks.[73,82]

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

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-nitrophenyl-propionate ([^{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).[322] 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).[323] 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.



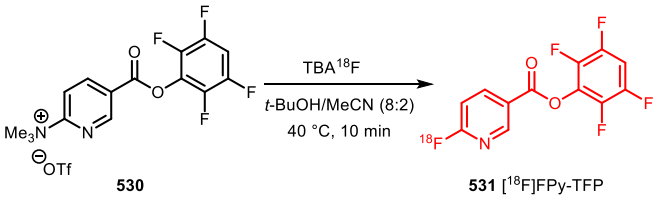
Scheme 118 PET tracers for imaging PSMA, labelled using [^{18}F]SFB derivatives.[313]

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**.[313] 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).

2.3.4.3 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).[326] [^{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.

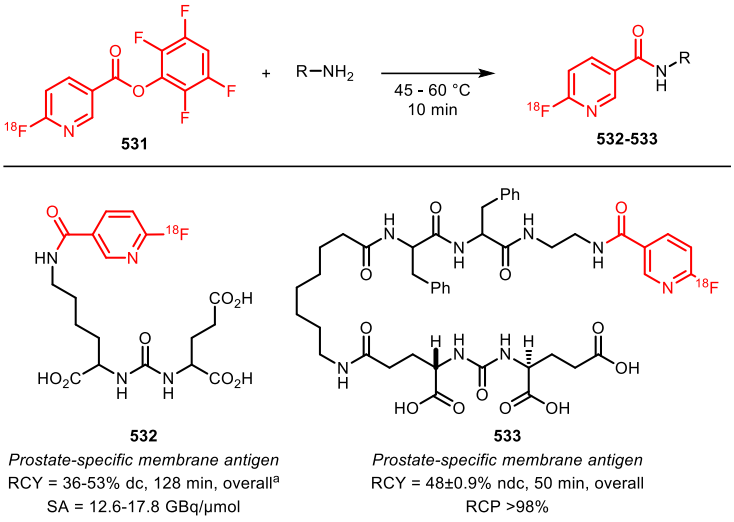
Besides labelling of large peptides, [^{18}F]FPy-TFP is also used for the labelling of small molecules, more specifically, in the labelling of PSMA targeting tracers (Scheme 120).[327,328] The carboxylic acids in the precursor were protected with 4-methoxybenzyl ether (PMB) protecting groups before reaction with [^{18}F]FPy-TFP in case of tracer **532**, therefore requiring an acidic deprotection after the coupling.[327]



Scheme 119 Synthesis of [^{18}F]FPy-TFP.[326]

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.[328] 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.

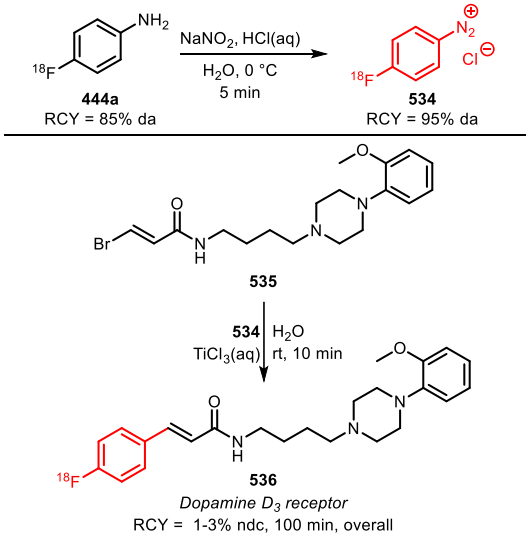


Scheme 120 Synthesis of PSMA targeting tracers using [^{18}F]FPy-TFP. [a]Includes deprotection of the PMB protected carboxylic acids using trifluoroacetic acid.[327,328]

2.3.5 Other fluorine-18 labelled aromatic building blocks

2.3.5.1 Synthesis and application of 4-[^{18}F]fluorophenyldiazonium ion

[^{18}F]Fluoroaniline **444a**, of which its synthesis and use has been described in Section 2.3.3.1, can be transformed to fluorine-18 labelled fluorophenyldiazonium ion **534**.

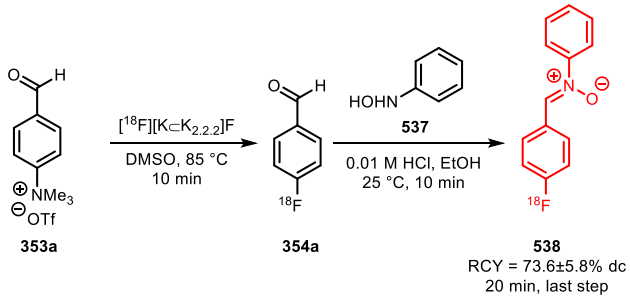


Scheme 121 Synthesis of dopamine D_3-selective ligand [^{18}F]SH317 using building block 4-[^{18}F]fluoro-phenyldiazonium chloride.[283]

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 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).[283] The overall radiochemical yield of [^{18}F]SH317 is 1–3% non-decay corrected with an overall synthesis time of 100 minutes.

2.3.5.2 Synthesis and application of *N*-phenyl-*C*-(4-[^{18}F]fluorophenyl)nitrone

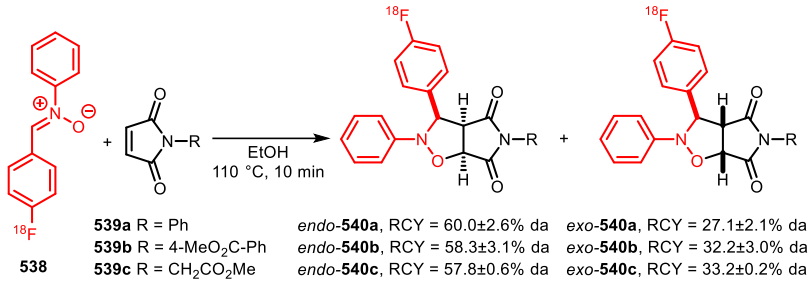
Zlatopolskiy *et al*. developed *N*-phenyl-*C*-(4-[^{18}F]fluorophenyl) nitrone **538**, a building block capable of undergoing [3+2]-dipolar cycloadditions with a variety of dipolarophiles.[329,320] 4-[^{18}F]Fluorobenzaldehyde **354a** is synthesised *via* nucleophilic substitution of trimethylammonium salt **353a** with [^{18}F]fluoride (Section 2.3.1.1), 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).



Scheme 122 Synthesis of *N*-phenyl-*C*-(4-[^{18}F]fluorophenyl) nitrone.[329,330]

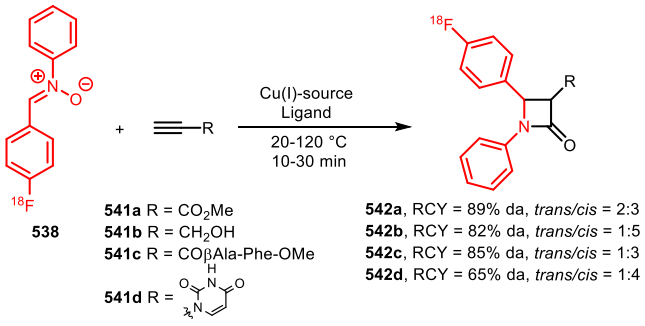
Zlatopolskiy *et al*. investigated the reaction of *N*-phenyl-*C*-(4-[^{18}F]fluorophenyl)-nitrone **538** with a variety of *N*-substituted maleimides, which can be easily introduced in peptides (Scheme 123).[329] The radiochemical yields towards the mixtures of *endo* and *exo* bicyclic isoxazolidines **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).[330] 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 123 Reaction of *N*-phenyl-*C*-(4-[^{18}F]fluorophenyl) nitrone with *N*-substituted maleimides.[329]

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.

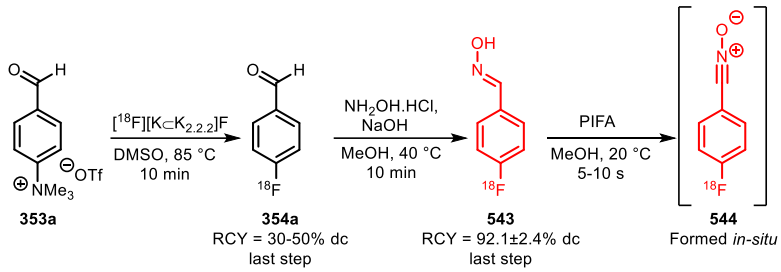


Scheme 124 Application of *N*-phenyl-*C*-(4-[^{18}F]fluorophenyl) nitrone in the synthesis of fluorine-18 labelled β-lactams.[330]

2.3.5.3 Synthesis and application of 4-[^{18}F]fluorophenyl nitrile oxide

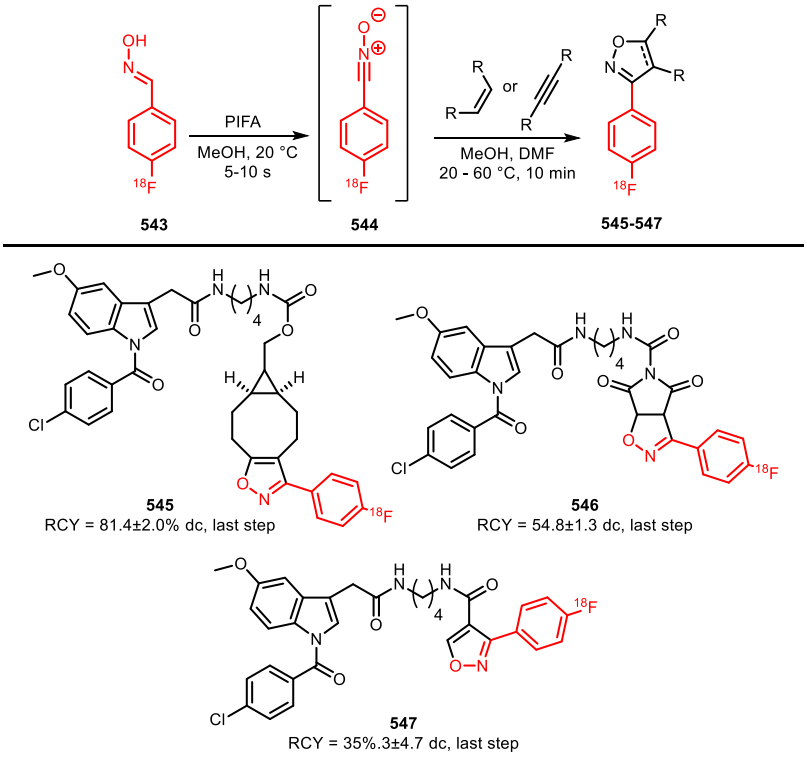
Next to the development of *N*-phenyl-*C*-(4-[^{18}F]fluorophenyl)nitrone **538** (Section 2.3.5.2), Zlatopolskiy *et al*. also developed 4-[^{18}F]fluorophenyl nitrile oxide **544** (Scheme 125), which can be used as building block for a copper free [2+3] cycloaddition alternative to the Huisgen 1,3-dipolar cycloaddition ('click'-reaction).[331]

4-[^{18}F]Fluorophenyl nitrile oxide **544** can be synthesised in three steps. Firstly, 4-[^{18}F]fluorobenzaldehyde is synthesised, (Section 2.3.1.1) 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.



Scheme 125 Three step synthesis of the building block 4-[^{18}F]fluorophenyl nitrile oxide.[331]

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).



Scheme 126 Application of 4-[^{18}F]fluorophenyl nitrile oxide **544** in the synthesis of fluorine-18 labelled indomethacin.[331]

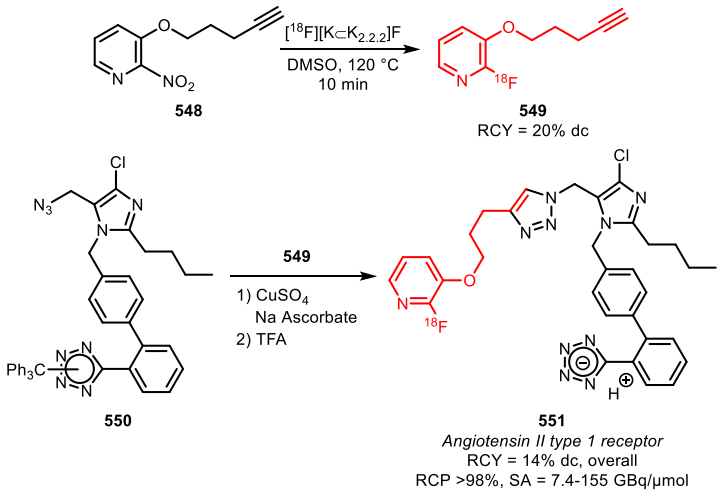
Fluorine-18 labelled indomethacin derivatives **545** and **546** could be isolated in 86% and 55% (ndc) radiochemical yield, starting from building block **543**. ^{18}F-Indomethacin derivative **547** was less easily formed and could initially only be obtained in a low radiochemical yield. However, 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, regio-specificity and good cycloaddition yields. Zlatapolsky *et al*. did however 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.

2.3.5.4 Synthesis and application of [^{18}F]fluorophenyl alkynes

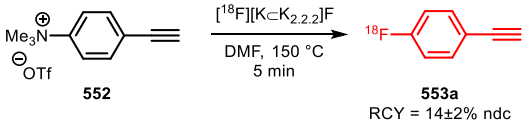
Despite the fact that the Huisgen 1,3-dipolar cycloaddition ('click'-reaction) is generally and widely applied in the synthesis of small molecule PET tracers, there are only three reports which describe 'click'-reactions with aromatic fluorine-18 labelled alkyne building blocks. The first report describes 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.[332]

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 AT1 inhibitor losartan (Scheme 127).[333] 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**.



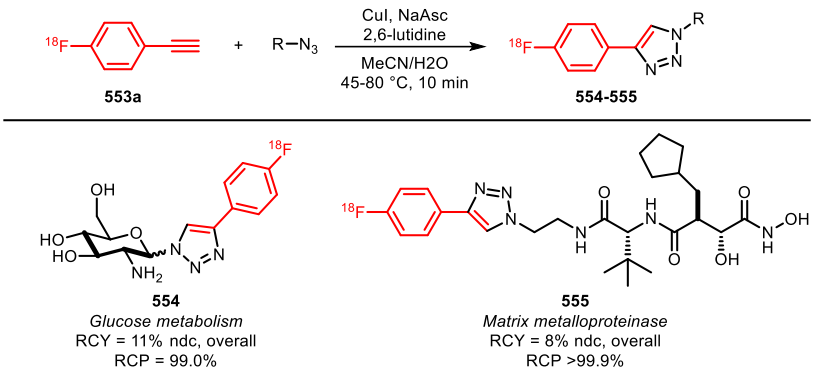
Scheme 127 Synthesis of a fluorine-18 labelled losartan derivative using [^{18}F]FPyKYNE as a building block.[332,333]

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).[334] 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.



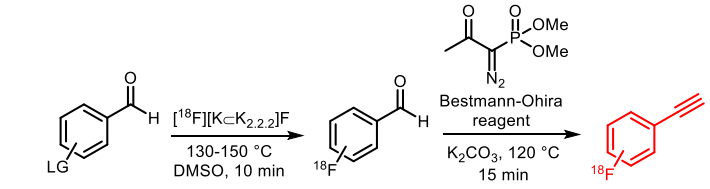
Scheme 128 Synthesis of (4-[^{18}F]fluorophenyl)acetylene by direct nucleophilic aromatic substitution with [^{18}F]fluoride.[334]

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).[334] 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**.



Scheme 129 'Click'-reaction with (4-[^{18}F]fluorophenyl)acetylene.[334]

A different approach towards the synthesis of ([^{18}F]fluorophenyl)acetylenes was recently published by Krapf *et al*. (Scheme 130).[335] 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).



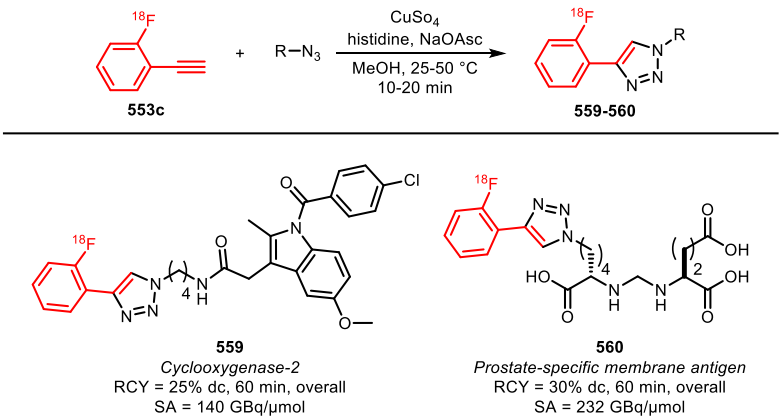
556 LG = *p*-($Me_3N^+ClO_4^-$) **363a** *p*-^{18}F, RCY = 65-75% ndc **553a** *p*-^{18}F, RCY = 40-60% ndc
557 LG = *m*-(4-$MeOC_6H_4$)I^+I **363k** *m*-^{18}F, RCY = 20-25% ndc **553b** *m*-^{18}F, RCY = 40-60% ndc
558 LG = *o*-($Me_3N^+ClO_4^-$) **363b** *o*-^{18}F, RCY = 50-65% ndc **553c** *o*-^{18}F, RCY = 40-60% ndc

Scheme 130 Synthesis of ([^{18}F]fluorophenyl)acetylenes by Seyferth–Gilbert homologation.[335]

The two step approach seems more promising than the direct approach employed by Roberts *et al*.,[334] 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.[335]

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).[335]



Scheme 131 Click reaction with (2-[^{18}F]fluorophenyl)acetylene.[335]

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.

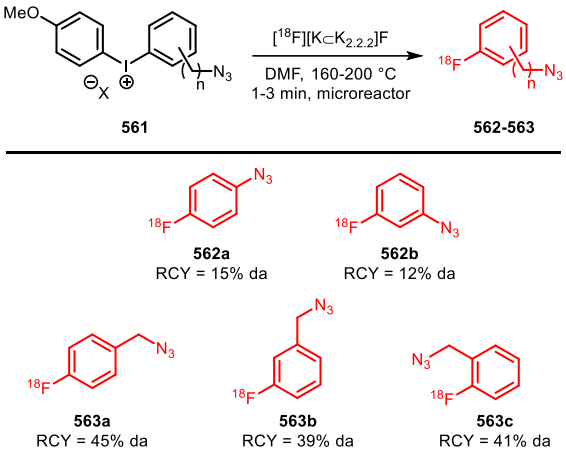
2.3.5.5 Synthesis and application of [^{18}F]fluorophenyl substituted azides

As is the case with [^{18}F]fluorophenyl alkynes (Section 2.3.5.4), [^{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 2.2.6.1).

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.[336] 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.

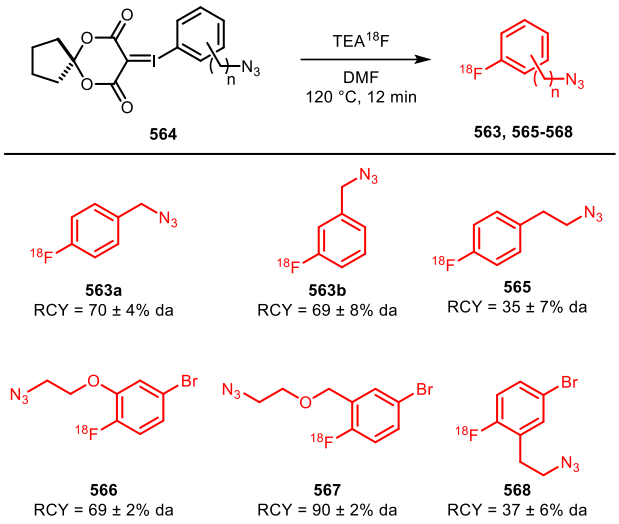
Chun *et al*. investigated the radiolabelling of diaryliodonium salt precursors towards [^{18}F]fluorophenyl azides and [^{18}F]fluorobenzyl azides (Scheme 132).[337] For the synthesis of [^{18}F]fluorophenyl azides **562a** and **562b**, the use of diaryliodonium salt precursors was unsuccessful, giving 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).



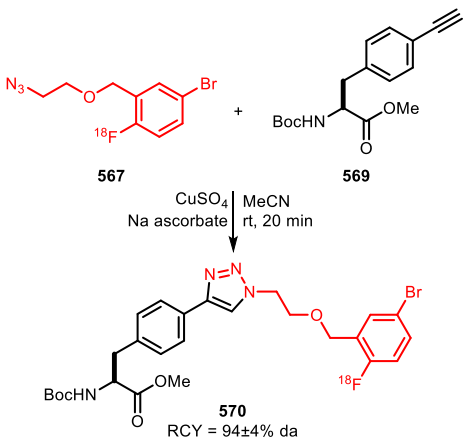
Scheme 132 Synthesis of [^{18}F]fluorophenyl azides and [^{18}F]fluorobenzyl azides from iodonium salt precursors.[337]

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).[5,338] 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).[333]

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.



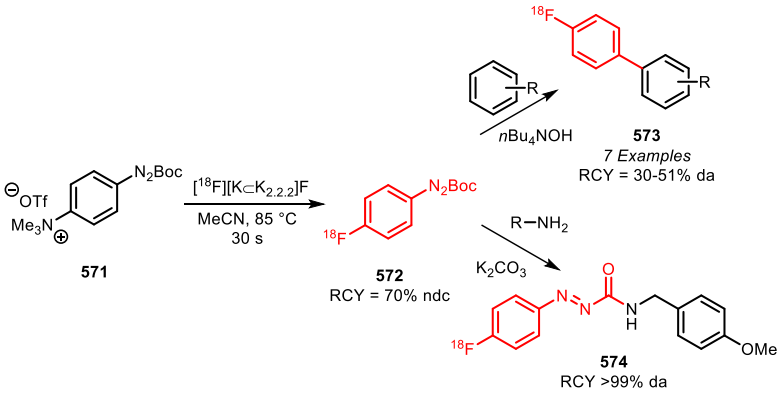
Scheme 133 Synthesis of various [^{18}F]fluorophenyl substituted azides from spirocyclic hypervalent iodine(III) precursors.[5,338]



Scheme 134 Synthesis of fluorine-18 labelled amino acid **570** using [^{18}F]fluorophenyl substituted azide building block **567**.[338]

2.2.5.6 Synthesis and application of tert-butyl 2-(4-[^{18}F]fluorophenyl)azocarboxylate

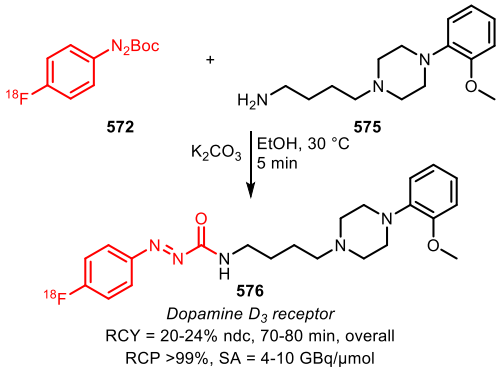
Fluorine-18 labelled azocarboxylic ester **572** is a novel building block developed by Fehler *et al.*[339] This building block can be synthesised in one step by nucleophilic aromatic substitution of trimethylammonium triflate **571** with [^{18}F]fluoride resulting in a radiochemical yield of 70%, because of the excellent electron withdrawing property of the azocarboxylic ester group at the *para*-position of the trimethylammonium leaving group (Scheme 135).



Scheme 135 Synthesis and application of [^{18}F]4-fluorophenylazocarboxylic *tert*-butyl ester.[339]

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 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).[339]

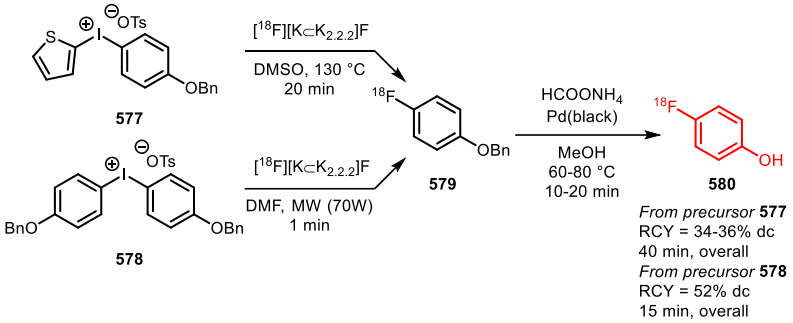
In conclusion, this building block is a good candidate for the synthesis of various PET tracers, as it is easy to synthesise and reacts in high yields. As it is a fairly new building block, its potential needs to be further explored.



Scheme 136 Application of [^{18}F]4-fluorophenylazocarboxylic *tert*-butyl ester in the synthesis of dopamine-D_3 ligand **576**.[339]

2.2.5.7 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.[340–344]

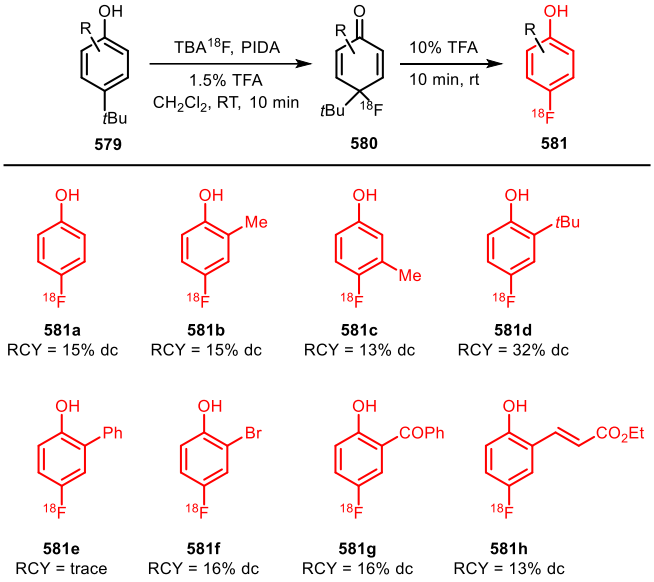


Scheme 137 Synthesis of 4-[^{18}F]fluorophenol from iodonium salt precursors.[345,346]

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).[345,346] 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**.[20] *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 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.

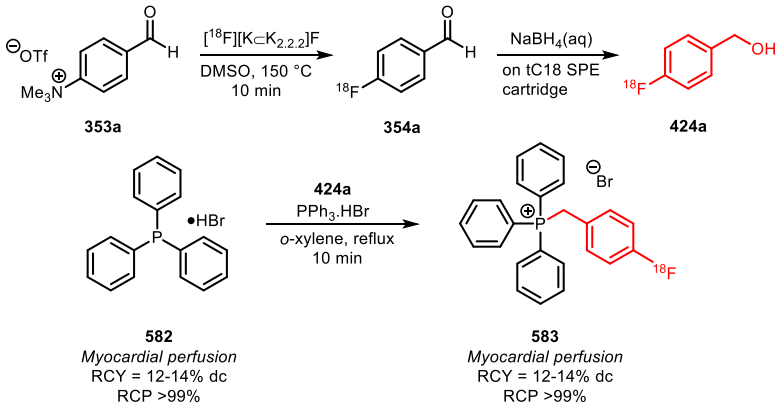
4-[^{18}F]Fluorophenol has not been applied in the synthesis of new PET tracers. However with these novel methods, 4-[^{18}F]fluorophenol becomes accessible as a fluorine-18 labelled building block and its application in the synthesis of PET tracers can therefore be expected in the future.



Scheme 138 Synthesis of 4-[^{18}F]fluorophenols by oxidative fluorination of 4-*tert*-butyl phenols.[20]

2.2.5.8 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 2.3.2.4). 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).[347] 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.[280]



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

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 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.

2.4 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 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.

2.5 References

1 S. Preshlock, M. Tredwell and V. Gouverneur, *Chem. Rev.*, 2016, **116**, 719–766.

2 A. F. Brooks, J. J. Topczewski, N. Ichiishi, M. S. Sanford and P. J. H. Scott, *Chem. Sci.*, 2014, **5**, 4545–4553.

3 T. L. Ross, J. Ermert, C. Hocke and H. H. Coenen, *J. Am. Chem. Soc.*, 2007, **129**, 8018–8025.

4 J. Cardinale, J. Ermert, S. Humpert and H. H. Coenen, *RSC Adv.*, 2014, **4**, 17293–17299.

5 B. H. Rotstein, N. A. Stephenson, N. Vasdev and S. H. Liang, *Nat. Commun.*, 2014, **5**, 4365.

6 M. B. Haskali, S. Telu, Y.-S. Lee, C. L. Morse, S. Lu and V. W. Pike, *J. Org. Chem.*, 2016, **81**, 297–302.

7 N. Ichiishi, A. F. Brooks, J. J. Topczewski, M. E. Rodnick, M. S. Sanford and P. J. H. Scott, *Org. Lett.*, 2014, **16**, 3224–3227.

8 N. Ichiishi, A. J. Canty, B. F. Yates and M. S. Sanford, *Org. Lett.*, 2013, **15**, 5134–5137.

9 L. Mu, C. R. Fischer, J. P. Holland, J. Becaud, P. A. Schubiger, R. Schibli, S. M. Ametamey, K. Graham, T. Stellfeld, L. M. Dinkelborg and L. Lehmann, *European J. Org. Chem.*, 2012, **2012**, 889–892.

10 K. Sander, T. Gendron, E. Yiannaki, K. Cybulska, T. L. Kalber, M. F. Lythgoe and E. Årstad, *Sci. Rep.*, 2015, **5**, 9941.

11 J.-H. Chun, C. L. Morse, F. T. Chin and V. W. Pike, *Chem. Commun.*, 2013, **49**, 2151–2153.

12 J. R. Brandt, E. Lee, G. B. Boursalian and T. Ritter, *Chem. Sci.*, 2014, **5**, 169–179.

13 A. S. Kamlet, C. N. Neumann, E. Lee, S. M. Carlin, C. K. Moseley, N. Stephenson, J. M. Hooker and T. Ritter, *PLoS One*, 2013, **8**, e59187.

14 E. Lee, A. S. Kamlet, D. C. Powers, C. N. Neumann, G. B. Boursalian, T. Furuya, D. C. Choi, J. M. Hooker and T. Ritter, *Science*, 2011, **334**, 639–642.

15 E. Lee, J. M. Hooker and T. Ritter, *J. Am. Chem. Soc.*, 2012, **134**, 17456–17458.

16 H. Ren, H.-Y. Wey, M. Strebl, R. Neelamegam, T. Ritter and J. M. Hooker, *ACS Chem. Neurosci.*, 2014, **5**, 611–615.

17 M. Tredwell, S. M. Preshlock, N. J. Taylor, S. Gruber, M. Huiban, J. Passchier, J. Mercier, C. Génicot and V. Gouverneur, *Angew. Chemie Int. Ed.*, 2014, **53**, 7751–7755.

18 A. V. Mossine, A. F. Brooks, K. J. Makaravage, J. M. Miller, N. Ichiishi, M. S. Sanford and P. J. H. Scott, *Org. Lett.*, 2015, **17**, 5780–5783.

19 K. J. Makaravage, A. F. Brooks, A. V. Mossine, M. S. Sanford and P. J. H. Scott, *Org. Lett.*, 2016, **18**, 5440–5443.

20 Z. Gao, Y. H. Lim, M. Tredwell, L. Li, S. Verhoog, M. Hopkinson, W. Kaluza, T. L. Collier, J. Passchier, M. Huiban and V. Gouverneur, *Angew. Chemie Int. Ed.*, 2012, **51**, 6733–6737.

21 C. N. Neumann, J. M. Hooker and T. Ritter, *Nature*, 2016, **534**, 369–373.

22 M. E. Sergeev, F. Morgia, M. Lazari, C. Wang and R. M. Van Dam, *J. Am. Chem. Soc.*, 2015, **137**, 5686–5694.

23 J.-H. Chun and V. W. Pike, *Org. Biomol. Chem.*, 2013, **11**, 6300–6306.

24 F. Basuli, H. Wu and G. L. Griffiths, *J. Label. Compd. Radiopharm.*, 2011, **54**, 224–228.

25 L. Hortala, J. Arnaud, P. Roux, D. Oustric, L. Boulu, F. Oury-Donat, P. Avenet, T. Rooney, D. Alagille, O. Barret, G. Tamagnan and F. Barth, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 283–287.

26 F. Beyerlein, M. Piel, S. Höhnemann and F. Rösch, *J. Label. Compd. Radiopharm.*, 2013, **56**, 360–363.

27 Y. H. Ryu, J.-S. Liow, S. Zoghbi, M. Fujita, J. Collins, D. Tipre, J. Sangare, J. Hong, V. W. Pike and R. B. Innis, *J. Nucl. Med.*, 2007, **48**, 1154–1161.

28 D. N. Tipre, S. S. Zoghbi, J. S. Liow, M. V Green, J. Seidel, M. Ichise, R. B. Innis and V. W. Pike, *J Nucl Med*, 2006, **47**, 345–353.

29 G. Smith, Y. Zhao, J. Leyton, B. Shan, Q.-D. Nguyen, M. Perumal, D. Turton, E. Årstad, S. K. Luthra, E. G. Robins and E. O. Aboagye, *Nucl. Med. Biol.*, 2011, **38**, 39–51.

30 X. Shao, B. G. Hockley, R. Hoareau, P. L. Schnau and P. J. H. Scott, *Appl. Radiat. Isot.*, 2011, **69**, 403–409.

31 C. Rami-Mark, M.-R. Zhang, M. Mitterhauser, R. Lanzenberger, M. Hacker and W. Wadsak, *Nucl. Med. Biol.*, 2013, **40**, 1049–1054.

32 P. J. Klein, J. A. M. Christiaans, A. Metaxas, R. C. Schuit, A. A. Lammertsma, B. N. M. van Berckel and A. D. Windhorst, *Bioorg. Med. Chem.*, 2015, **23**, 1189–1206.

33 N. J. Lodge, Y.-W. Li, F. T. Chin, D. D. Dischino, S. S. Zoghbi, J. a Deskus, R. J. Mattson, M. Imaizumi, R. Pieschl, T. F. Molski, M. Fujita, H. Dulac, R. Zaczek, J. J. Bronson, J. E. Macor, R. B. Innis and V. W. Pike, *Nucl. Med. Biol.*, 2014, **41**, 524–535.

34 R. Xu, J. Hong, C. L. Morse and V. W. Pike, *J. Med. Chem.*, 2010, **53**, 7035–7047.

35 J. Hu, B. Gao, L. Li, C. Ni and J. Hu, *Org. Lett.*, 2015, **17**, 3086–3089.

36 P. O. Miranda, R. M. Carballo, V. S. Martín and J. I. Padrón, *Org. Lett.*, 2009, **11**, 357–360.

37 T. R. Neal, S. Apana and M. S. Berridge, *J. Label. Compd. Radiopharm.*, 2005, **48**, 557–568.

38 G. Pascali, G. Nannavecchia, S. Pitzianti and P. A. Salvadori, *Nucl. Med. Biol.*, 2011, **38**, 637–644.

39 M. E. Rodnick, A. F. Brooks, B. G. Hockley, B. D. Henderson and P. J. H. Scott, *Appl. Radiat. Isot.*, 2013, **78**, 26–32.

40 H. Zeng, X. Wu, F. Song, C. Xu, H. Liu and W. Liu, *Eur. J. Med. Chem.*, 2016, **118**, 90–97.

41 H. Schieferstein, M. Piel, F. Beyerlein, H. Lüddens, N. Bausbacher, H.-G. Buchholz, T. L. Ross and F. Rösch, *Bioorg. Med. Chem.*, 2015, **23**, 612–623.

42 D. Thomae, T. J. Morley, H. S. Lee, O. Barret, C. Constantinescu, C. Papin, R. M. Baldwin, G. D. Tamagnan and D. Alagille, *J. Label. Compd. Radiopharm.*, 2016, **59**, 205–213.

43 E. G. Robins, Y. Zhao, I. Khan, A. Wilson, S. K. Luthra and E. Årstad, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 1749–1751.

44 L. Carroll, T. H. Witney and E. O. Aboagye, *MedChemCommun*, 2013, **4**, 653–656.

45 S. Merchant, L. Allott, L. Carroll, V. Tittrea, S. Kealey, T. H. Witney, P. W. Miller, G. Smith and E. O. Aboagye, *RSC Adv.*, 2016, **6**, 57569–57579.

46 P. J. Riss, S. Hoehnemann, M. Piel and F. Roesch, *J. Label. Compd. Radiopharm.*, 2013, **56**, 356–359.

47 M.-R. Zhang, A. Tsuchiyama, T. Haradahira, Y. Yoshida, K. Furutsuka and K. Suzuki, *Appl. Radiat. Isot.*, 2002, **57**, 335–342.

48 M.-R. Zhang, K. Furutsuka, Y. Yoshida and K. Suzuki, *J. Label. Compd. Radiopharm.*, 2003, **46**, 587–598.

49 D. Murali, T. E. Barnhart, N. T. Vandehey, B. T. Christian, R. J. Nickles, A. K. Converse, J. A. Larson, J. E. Holden, M. L. Schneider and O. T. Dejesus, *Appl. Radiat. Isot.*, 2013, **72**, 128–132.

50 H. Savolainen, M. Cantore, N. A. Colabufo, P. H. Elsinga, A. D. Windhorst and G. Luurtsema, *Mol. Pharm.*, 2015, **12**, 2265–2275.

51 Z.-F. Liu, G.-L. Wang, M.-J. Dong, J.-W. Jin, J.-J. Li, Q. Zhang, K. Zhao, S.-Y. Yang and X.-T. Lin, *J. Radioanal. Nucl. Chem.*, 2014, **299**, 1509–1515.

52 J. Schmaljohann, E. Schirrmacher, B. Wängler, C. Wängler, R. Schirrmacher and S. Guhlke, *Nucl. Med. Biol.*, 2011, **38**, 165–170.

53 J.-I. Andrés, M. De Angelis, J. Alcázar, L. Iturrino, X. Langlois, S. Dedeurwaerdere, I. Lenaerts, G. Vanhoof, S. Celen and G. Bormans, *J. Med. Chem.*, 2011, **54**, 5820–5835.

54 M. Ooms, S. Celen, M. Koole, X. Langlois, M. Schmidt, M. De Angelis, J. I. Andrés, A. Verbruggen, K. Van Laere and G. Bormans, *Nucl. Med. Biol.*, 2014, **41**, 695–704.

55 E. D. Hostetler, S. Sanabria-Bohórquez, W. Eng, A. D. Joshi, S. Patel, R. E. Gibson, S. O'Malley, S. M. Krause, C. Ryan, K. Riffel, S. Bi, O. Okamoto, H. Kawamoto, S. Ozaki, H. Ohta, T. de Groot, G. Bormans, M. Depré, J. de Hoon, I. De Lepeleire, T. Reynders, J. J. Cook, H. D. Burns, M. Egan, W. Cho, K. van Laere and R. J. Hargreaves, *Neuroimage*, 2013, **68**, 1–10.

56 K. Kawamura, Y. Shimoda, K. Kumata, M. Fujinaga, J. Yui, T. Yamasaki, L. Xie, A. Hatori, H. Wakizaka, Y. Kurihara, M. Ogawa, N. Nengaki and M. R. Zhang, *Nucl. Med. Biol.*, 2015, **42**, 406–412.

57 A. K. Tiwari, M. Fujinaga, J. Yui, T. Yamasaki, L. Xie, K. Kumata, A. K. Mishra, Y. Shimoda, A. Hatori, B. Ji, M. Ogawa, K. Kawamura, F. Wang and M.-R. Zhang, *Org. Biomol. Chem.*, 2014, **12**, 9621–9630.

58 M. Fujinaga, T. Yamasaki, J. Yui, A. Hatori, L. Xie, K. Kawamura, C. Asagawa, K. Kumata, Y. Yoshida, M. Ogawa, N. Nengaki, T. Fukumura and M.-R. Zhang, *J. Med. Chem.*, 2012, **55**, 2342–2352.

59 N. Evens, C. Vandeputte, G. G. Muccioli, D. M. Lambert, V. Baekelandt, A. M. Verbruggen, Z. Debyser, K. Van Laere and G. M. Bormans, *Bioorg. Med. Chem.*, 2011, **19**, 4499–4505.

60 K. Kawamura, T. Yamasaki, F. Konno, J. Yui, A. Hatori, K. Yanamoto, H. Wakizaka, M. Ogawa, Y. Yoshida, N. Nengaki, T. Fukumura and M.-R. Zhang, *Bioorg. Med. Chem.*, 2011, **19**, 861–870.

61 J. A. Deskus, D. D. Dischino, R. J. Mattson, J. L. Ditta, M. F. Parker, D. J. Denhart, D. Zuev, H. Huang, R. A. Hartz, V. T. Ahuja, H. Wong, G. K. Mattson, T. F. Molski, J. E. Grace, L. Zueva, J. M. Nielsen, H. Dulac, Y.-W. Li, M. Guaraldi, M. Azure, D. Onthank, M. Hayes, E. Wexler, J. McDonald, N. J. Lodge, J. J. Bronson and J. E. Macor, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 6651–6655.

62 M. Jahan, O. Eriksson, P. Johnström, O. Korsgren, A. Sundin, L. Johansson and C. Halldin, *EJNMMI Res.*, 2011, **1**, 33.

63 O. Gheysens, V. Akurathi, R. Chekol, T. Dresselaers, S. Celen, M. Koole, D. Dauwe, B. J. Cleynhens, P. Claus, S. Janssens, A. M. Verbruggen, J. Nuyts, U. Himmelreich and G. M. Bormans, *EJNMMI Res.*, 2013, **3**, 4.

64 C. Rami-Mark, B. Bornatowicz, C. Fink, P. Otter, J. Ungersboeck, C. Vraka, D. Haeusler, L. Nics, H. Spreitzer, M. Hacker, M. Mitterhauser and W. Wadsak, *Bioorg. Med. Chem.*, 2013, **21**, 7562–7569.

65 C. Philippe, J. Ungersboeck, E. Schirmer, M. Zdravkovic, L. Nics, M. Zeilinger, K. Shanab, R. Lanzenberger, G. Karanikas, H. Spreitzer, H. Viernstein, M. Mitterhauser and W. Wadsak, *Bioorg. Med. Chem.*, 2012, **20**, 5936–5940.

66 D. Block, H. H. Coenen and G. Stöcklin, *J. Label. Compd. Radiopharm.*, 1987, **24**, 1029–1042.

67 B. W. Schoultz, B. J. Reed, J. Marton, F. Willoch and G. Henriksen, *Molecules*, 2013, **18**, 7271–7278.

68 T. K. Heinrich, V. Gottumukkala, E. Snay, P. Dunning, F. H. Fahey, S. Ted Treves and A. B. Packard, *Appl. Radiat. Isot.*, 2010, **68**, 96–100.

69 S. Khanapur, S. Paul, A. Shah, S. Vatakuti, M. J. B. Koole, R. Zijlma, R. A. J. O. Dierckx, G. Luurtsema, P. Garg, A. van Waarde and P. H. Elsinga, *J. Med. Chem.*, 2014, **57**, 6765–6780.

70 V. J. Majo, V. Arango, N. R. Simpson, J. Prabhakaran, S. A. Kassir, M. D. Underwood, M. Bakalian, P. Canoll, J. John Mann and J. S. Dileep Kumar, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 4191–4194.

71 M. Asti, D. Farioli, M. Iori, C. Guidotti, A. Versari and D. Salvo, *Nucl. Med. Biol.*, 2010, **37**, 309–315.

72 H. J. Breyholz, S. Wagner, A. Faust, B. Riemann, C. Höltke, S. Hermann, O. Schober, M. Schäfers and K. Kopka, *ChemMedChem*, 2010, **5**, 777–789.

73 J. Li, B. D. Gray, K. Y. Pak and C. K. Ng, *J. Label. Compd. Radiopharm.*, 2012, **55**, 149–154.

74 J. Prabhakaran, V. Arango, V. J. Majo, N. R. Simpson, S. A. Kassir, M. D. Underwood, H. Polavarapu, J. N. Bruce, P. Canoll, J. John Mann and J. S. Dileep Kumar, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 5104–5107.

75 E. M. F. Billaud, L. Rbah-Vidal, A. Vidal, S. Besse, S. Tarrit, S. Askienazy, A. Maisonial, N. Moins, J. C. Madelmont, E. Miot-Noirault, J. M. Chezal and P. Auzeloux, *J. Med. Chem.*, 2013, **56**, 8455–8467.

76 E. Galante, T. Okamura, K. Sander, T. Kikuchi, M. Okada, M. Zhang, M. Robson, A. Badar, M. Lythgoe, M. Koepp and E. Årstad, *J. Med. Chem.*, 2014, **57**, 1023–1032.

77 A. Makino, T. Arai, M. Hirata, M. Ono, Y. Ohmomo and H. Saji, *Nucl. Med. Biol.*, 2016, **43**, 101–107.

78 F. Caillé, T. J. Morley, A. A. S. Tavares, C. Papin, N. M. Twardy, D. Alagille, H. S. Lee, R. M. Baldwin, J. P. Seibyl, O. Barret and G. D. Tamagnan, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 6243–6247.

79 D. O'Shea, R. Ahmad, E. Årstad, M. Avory, W. F. Chau, C. Durrant, E. Hirani, P. A. Jones, I. Khan, S. K. Luthra, D. Mantzilas, V. Morisson-Iveson, J. Passmore, E. G. Robins, B. Shan, H. Wadsworth, S. Walton, Y. Zhao and W. Trigg, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 2368–2372.

80 S. Rötering, M. Scheunemann, S. Fischer, A. Hiller, D. Peters, W. Deuther-Conrad and P. Brust, *Bioorg. Med. Chem.*, 2013, **21**, 2635–2642.

81 T. Sun, G. Tang, H. Tian, X. Wang, X. Chen, Z. Chen and S. Wang, *Appl. Radiat. Isot.*, 2012, **70**, 676–680.

82 H. Wang, X. Tang, G. Tang, T. Huang, X. Liang, K. Hu, H. Deng, C. Yi, X. Shi and K. Wu, *Apoptosis*, 2013, **18**, 1017–1027.

83 S. Perera, D. Piwnica-Worms and M. M. Alauddin, *J. Label. Compd. Radiopharm.*, 2016, **59**, 103–108.

84 J. Henrottin, C. Lemaire, D. Egrise, A. Zervosen, B. van Den Eynde, A. Plenevaux, X. Franci, S. Goldman and A. Luxen, *Nucl. Med. Biol.*, 2016, **43**, 379–389.

85 A. Bauman, M. Piel, R. Schirrmacher and F. Rösch, *Tetrahedron Lett.*, 2003, **44**, 9165–9167.

86 R. Li, S.-C. Wu, S.-C. Wang, Z. Fu, Y. Dang and L. Huo, *Appl. Radiat. Isot.*, 2010, **68**, 303–308.

87 A. Bauman, M. Piel, S. Höhnemann, A. Krauss, M. Jansen, C. Solbach, G. Dannhardt and F. Rösch, *J. Label. Compd. Radiopharm.*, 2011, **54**, 645–656.

88 H. S. Radeke, A. Purohit, T. D. Harris, K. Hanson, R. Jones, C. Hu, P. Yalamanchili, M. Hayes, M. Yu, M. Guaraldi, M. Kagan, M. Azure, M. Cdebaca, S. Robinson and D. Casebier, *ACS Med. Chem. Lett.*, 2011, **2**, 650–655.

89 V. Shalgunov, J.-P. van Wieringen, H. M. Janssen, P. M. Fransen, R. A. J. O. Dierckx, M. C. Michel, J. Booij and P. H. Elsinga, *EJNMMI Res.*, 2015, **5**, 41.

90 H. Ren, H. Ning, J. Chang, M. Zhao, Y. He, Y. Chong and C. Qi, *J. Radioanal. Nucl. Chem.*, 2016, 517–523.

91 U. Funke, W. Deuther-Conrad, G. Schwan, A. Maisonial, M. Scheunemann, S. Fischer, A. Hiller, D. Briel and P. Brust, *Pharmaceuticals*, 2012, **5**, 169–188.

92 Y. Chen, M. Feng, S. Li, J. Xu, H. Ning, Y. He, X. Wang, R. Ding and C. Qi, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 4745–4749.

93 B. H. Yousefi, A. Drzezga, B. Von Reutern, A. Manook, M. Schwaiger, H.-J. Wester and G. Henriksen, *ACS Med. Chem. Lett.*, 2011, **2**, 673–677.

94 H. Wadsworth, P. A. Jones, W. F. Chau, C. Durrant, V. Morisson-Iveson, J. Passmore, D. O'Shea, D. Wynn, I. Khan, A. Black, M. Avory and W. Trigg, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 5795–5800.

95 A. Jackson, B. B. Guilbert, S. D. Plant, J. Goggi, M. R. Battle, J. L. Woodcraft, A. Gaeta, C. L. Jones, D. R. Bouvet, P. a. Jones, D. M. O'Shea, P. H. Zheng, S. L. Brown, A. L. Ewan and W. Trigg, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 821–826.

96 R. Löser, R. Bergmann, M. Frizler, B. Mosch, L. Dombrowski, M. Kuchar, J. Steinbach, M. Gütschow and J. Pietzsch, *ChemMedChem*, 2013, **8**, 1330–1344.

97 P. J. Riss, L. Brichard, V. Ferrari, D. J. Williamson, T. D. Fryer, Y. T. Hong, J.-C. Baron and F. I. Aigbirhio, *MedChemCommun*, 2013, **4**, 852–855.

98 Z. Tu, X. Zhang, H. Jin, X. Yue, P. K. Padakanti, L. Yu, H. Liu, H. P. Flores, K. Kaneshige, S. M. Parsons and J. S. Perlmutter, *Bioorg. Med. Chem.*, 2015, **23**, 4699–4709.

99 X. Yue, C. Bognar, X. Zhang, G. G. Gaehle, S. M. Moerlein, J. S. Perlmutter and Z. Tu, *Appl. Radiat. Isot.*, 2016, **107**, 40–46.

100 F. Xie, R. Bergmann, T. Kniess, W. Deuther-Conrad, C. Mamat, C. Neuber, B. Liu, J. Steinbach, P. Brust, J. Pietzsch and H. Jia, *J. Med. Chem.*, 2015, **58**, 5395–5407.

101 F. Debus, M. M. Herth, M. Piel, H.-G. Buchholz, N. Bausbacher, V. Kramer, H. Lüddens and F. Rösch, *Nucl. Med. Biol.*, 2010, **37**, 487–495.

102 J. P. Van Wieringen, V. Shalgunov, H. M. Janssen, P. M. Fransen, A. G. M. Janssen, M. C. Michel, J. Booij and P. H. Elsinga, *J. Med. Chem.*, 2014, **57**, 391–410.

103 Y.-Y. Chen, X. Wang, J.-M. Zhang, W. Deuther-Conrad, X.-J. Zhang, Y. Huang, Y. Li, J.-J. Ye, M.-C. Cui, J. Steinbach, P. Brust, B.-L. Liu and H.-M. Jia, *Bioorganic Med. Chem.*, 2014, **22**, 5270–5278.

104 A. Chiotellis, A. Muller, L. Mu, C. Keller, R. Schibli, S. D. Kra and S. M. Ametamey, *Mol. Pharm.*, 2014, **11**, 3839–3851.

105 B. Neumaier, S. Deisenhofer, C. Sommer, C. Solbach, S. N. Reske and F. Mottaghy, *Appl. Radiat. Isot.*, 2010, **68**, 1066–1072.

106 E. Al-Momani, N. Malik, H.-J. Machulla, S. N. Reske and C. Solbach, *J. Radioanal. Nucl. Chem.*, 2013, **295**, 2289–2294.

107 V. Bernard-gauthier, A. Aliaga, A. Aliaga, M. Boudjemeline, R. Hopewell, A. Kostikov, P. Rosa-neto, A. Thiel and R. Schirrmacher, *ACS Chem. Neurosci.*, 2015, **6**, 260–276.

108 M. M. Herth, I. N. Petersen, H. D. Hansen, M. Hansen, A. Ettrup, A. A. Jensen, S. Lehel, A. Dyssegaard, N. Gillings, G. M. Knudsen and J. L. Kristensen, *Nucl. Med. Biol.*, 2016, **43**, 455–462.

109 P. Cumming, D. Skaper, T. Kuwert, S. Maschauer and O. Prante, *Synapse*, 2015, **69**, 57–59.

110 E. Blom, F. Karimi, O. Eriksson, H. Hall and B. Långström, *J. Label. Compd. Radiopharm.*, 2008, **51**, 277–282.

111 B. W. Schoultz, T. Hjørnevik, B. J. Reed, J. Marton, C. S. Coello, F. Willoch and G. Henriksen, *J. Med. Chem.*, 2014, **57**, 5464–5469.

112 S. L. James, S. K. Ahmed, S. Murphy, M. R. Braden, Y. Belabassi, H. F. VanBrocklin, C. M. Thompson and J. M. Gerdes, *ACS Chem. Neurosci.*, 2014, **5**, 519–524.

113 T. Peters, A. Vogg, I. M. Oppel and J. Schmaljohann, *Appl. Radiat. Isot.*, 2014, **94**, 141–146.

114 R. Chekol, O. Gheysens, J. Cleynhens, P. Pokreisz, G. Vanhoof, M. Ahamed, S. Janssens, A. Verbruggen and G. Bormans, *Nucl. Med. Biol.*, 2014, **41**, 155–162.

115 J. L. Musachio, J. Shah and V. W. Pike, *J. Label. Compd. Radiopharm.*, 2005, **48**, 735–747.

116 N. Jarkas, R. J. Voll and M. M. Goodman, *J. Label. Compd. Radiopharm.*, 2013, **56**, 539–543.

117 R. J. Voll, J. McConathy, M. S. Waldrep, R. J. Crowe and M. M. Goodman, *Appl. Radiat. Isot.*, 2005, **63**, 353–361.

118 A. L. Smith, S. M. Freeman, J. S. Stehouwer, K. Inoue, R. J. Voll, L. J. Young and M. M. Goodman, *Bioorg. Med. Chem.*, 2012, **20**, 2721–2738.

119 A. K. Bhattacharjee, L. Lang, O. Jacobson, B. Shinkre, Y. Ma, G. Niu, W. C. Trenkle, K. A. Jacobson, X. Chen and D. O. Kiesewetter, *Nucl. Med. Biol.*, 2011, **38**, 897–906.

120 D. van der Born, C. Sewing, J. D. M. Herscheid, A. D. Windhorst, R. V. A. Orru and D. J. Vugts, *Angew. Chemie Int. Ed.*, 2014, **53**, 11046–11050.

121 T. Rühl, W. Rafique, V. T. Lien and P. J. Riss, *Chem. Commun.*, 2014, **50**, 6056–6059.

122 P. Ivashkin, G. Lemonnier, J. Cousin, V. Grégoire, D. Labar, P. Jubault and X. Pannecoucke, *Chem. Eur. J.*, 2014, **20**, 9514–9518.

123 M. Suehiro, G. Yang, G. Torchon, E. Ackerstaff, J. Humm, J. Koutcher and O. Ouerfelli, *Bioorg. Med. Chem.*, 2011, **19**, 2287–2297.

124 P. J. Riss, V. Ferrari, L. Brichard, P. Burke, R. Smith and F. I. Aigbirhio, *Org. Biomol. Chem.*, 2012, **10**, 6980–6986.

125 P. J. Riss and F. I. Aigbirhio, *Chem. Commun.*, 2011, **47**, 11873–11875.

126 M. D. Bartholomä, V. Gottumukkala, S. Zhang, A. Baker, P. Dunning, F. H. Fahey, S. T. Treves and A. B. Packard, *J. Med. Chem.*, 2012, **55**, 11004–11012.

127 P. Cumming, S. Maschauer, P. J. Riss, N. Tschammer, S. K. Fehler, M. R. Heinrich, T. Kuwert and O. Prante, *J. Cereb. Blood Flow Metab.*, 2014, **34**, 1148–1156.

128 S. He, G. Tang, K. Hu, H. Wang, S. Wang, T. Huang, X. Liang and X. Tang, *Nucl. Med. Biol.*, 2013, **40**, 801–807.

129 L. Zhu, G. Li, S. R. Choi, K. Plössl, P. Chan, H. Qiao, Z. Zha and H. F. Kung, *Nucl. Med. Biol.*, 2013, **40**, 974–979.

130 J. S. Stehouwer, L. M. Daniel, P. Chen, R. J. Voll, L. Williams, S. J. Plott, J. R. Votaw, M. J. Owens, L. Howell and M. M. Goodman, *J. Med. Chem.*, 2010, **53**, 5549–5557.

131 D. Franck, T. Kniess, J. Steinbach, S. Zitzmann-Kolbe, M. Friebe, L. M. Dinkelborg and K. Graham, *Bioorg. Med. Chem.*, 2013, **21**, 643–652.

132 D.-Y. Kim, H.-J. Kim, K.-H. Yu and J.-J. Min, *Nucl. Med. Biol.*, 2012, **39**, 1093–1098.

133 D.-Y. Kim, H.-J. Kim, K.-H. Yu and J.-J. Min, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 319–322.

134 M. D. Bartholomä, S. Zhang, V. Akurathi, C. A. Pacak, P. Dunning, F. H. Fahey, D. B. Cowan, S. Ted Treves and A. B. Packard, *Nucl. Med. Biol.*, 2015, **42**, 796–803.

135 I. F. Antunes, H. J. Haisma, P. H. Elsinga, R. A. Dierckx and E. F. J. de Vries, *Bioconjug. Chem.*, 2010, **21**, 911–920.

136 Z. Zhao, Q. Yu, T. Mou, C. Liu, W. Yang, W. Fang, C. Peng, J. Lu, Y. Liu and X. Zhang, *Mol. Pharm.*, 2014, **11**, 3826–3831.

137 L. Frullano, C. Catana, T. Benner, A. D. Sherry and P. Caravan, *Angew. Chemie Int. Ed.*, 2010, **49**, 2382–2384.

138 D. Zhou, W. Chu, X. Peng, J. McConathy, R. H. Mach and J. A. Katzenellenbogen, *Tetrahedron Lett.*, 2015, **56**, 952–954.

139 L. Jia, Z. Cheng, L. Shi, J. Li, C. Wang, D. Jiang, W. Zhou, H. Meng, Y. Qi, D. Cheng and L. Zhang, *Appl. Radiat. Isot.*, 2013, **75**, 64–70.

140 R. Bejot, L. Carroll, K. Bhakoo, J. Declerck and V. Gouverneur, *Bioorg. Med. Chem.*, 2012, **20**, 324–329.

141 L. Carroll, S. Boldon, R. Bejot, J. E. Moore, J. Declerck and V. Gouverneur, *Org. Biomol. Chem.*, 2011, **9**, 136–140.

142 A. Gaeta, J. Woodcraft, S. Plant, J. Goggi, P. Jones, M. Battle, W. Trigg, S. K. Luthra and M. Glaser, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 4649–4652.

143 K. Nwe and M. W. Brechbiel, *Cancer Biother. Radiopharm.*, 2009, **24**, 289–302.

144 M. Glaser and E. Årstad, *Bioconjug. Chem.*, 2007, **18**, 989–993.

145 A. Monaco, O. Michelin, J. Prior, C. Rüegg, L. Scapozza and Y. Seimbille, *J. Label. Compd. Radiopharm.*, 2014, **57**, 365–370.

146 F. Pisaneschi, Q.-D. Nguyen, E. Shamsaei, M. Glaser, E. Robins, M. Kaliszczak, G. Smith, A. C. Spivey and E. O. Aboagye, *Bioorg. Med. Chem.*, 2010, **18**, 6634–6645.

147 E. Laurens, S. D. Yeoh, A. Rigopoulos, D. Cao, G. a Cartwright, G. J. O'Keefe, H. J. Tochon-Danguy, J. M. White, A. M. Scott and U. Ackermann, *Nucl. Med. Biol.*, 2014, **41**, 419–425.

148 W. Chu, A. Chepetan, D. Zhou, K. I. Shoghi, J. Xu, L. L. Dugan, R. J. Gropler, M. A. Mintun and R. H. Mach, *Org. Biomol. Chem.*, 2014, **12**, 4421–4431.

149 V. Hugenberg, H.-J. Breyholz, B. Riemann, S. Hermann, O. Schober, M. Schäfers, U. Gangadharmath, V. Mocharla, H. Kolb, J. Walsh, W. Zhang, K. Kopka and S. Wagner, *J. Med. Chem.*, 2012, **55**, 4714–4727.

150 J. Kelly, A. Amor-Coarasa, A. Nikolopoulou, D. Kim, C. Williams Jr, S. Ponnala and J. W. Babich, *Eur. J. Nucl. Med. Mol. Imaging*, 2016, **44**, 647-661.

151 D. Zhou, W. Chu, C. S. Dence, R. H. Mach and M. J. Welch, *Nucl. Med. Biol.*, 2012, **39**, 1175–1181.

152 L. Carroll, R. Bejot, R. Hueting, R. King, P. Bonnitcha, S. Bayly, M. Christlieb, J. R. Dilworth, A. D. Gee, J. Declerck and V. Gouverneur, *Chem. Commun.*, 2010, **46**, 4052–4054.

153 E. Galante, B. W. Schoultz, M. Koepp and E. Årstad, *Molecules*, 2013, **18**, 5335–5347.

154 Y. Chen, A. Lisok, S. Chatterjee, B. Wharram, M. Pullambhatla, Y. Wang, G. Sgouros, R. C. Mease and M. G. Pomper, *Bioconjug. Chem.*, 2016, **27**, 1655–1662.

155 U. Ackermann, L. Plougastel, Y. W. Goh, S. D. Yeoh and A. M. Scott, *Appl. Radiat. Isot.*, 2014, **94**, 72–76.

156 U. Ackermann, G. O'Keefe, S.-T. Lee, A. Rigopoulos, G. Cartwright, J. I. Sachinidis, a. M. Scott and H. J. Tochon-Danguy, *J. Label. Compd. Radiopharm.*, 2011, **54**, 260–266.

157 M. Glaser, J. Goggi, G. Smith, M. Morrison, S. K. Luthra, E. Robins and E. O. Aboagye, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 6945–6949.

158 R. Fortt, G. Smith, R. O. Awais, S. K. Luthra and E. O. Aboagye, *Nucl. Med. Biol.*, 2012, **39**, 1000–1005.

159 C. M. Waldmann, S. Hermann, A. Faust, B. Riemann, O. Schober, M. Schäfers, G. Haufe and K. Kopka, *Bioorg. Med. Chem.*, 2015, **23**, 5734–5739.

160 S. D. Boss, T. Betzel, C. Müller, C. R. Fischer, S. Haller, J. Reber, V. Groehn, R. Schibli and S. M. Ametamey, *Bioconjug. Chem.*, 2016, **27**, 74–86.

161 E. Laurens, S. D. Yeoh, A. Rigopoulos, D. Cao, G. A. Cartwright, G. J. O'Keefe, H. J. Tochon-Danguy, J. M. White, A. M. Scott and U. Ackermann, *Nucl. Med. Biol.*, 2012, **39**, 871–882.

162 D. Schrigten, H.-J. Breyholz, S. Wagner, S. Hermann, O. Schober, M. Schäfers, G. Haufe and K. Kopka, *J. Med. Chem.*, 2012, **55**, 223–232.

163 G. Smith, R. Sala, L. Carroll, K. Behan, M. Glaser, E. Robins, Q. D. Nguyen and E. O. Aboagye, *Nucl. Med. Biol.*, 2012, **39**, 652–665.

164 L. Jia, D. Jiang, P. Hu, X. Li, H. Shi, D. Cheng and L. Zhang, *Nucl. Med. Biol.*, 2014, **41**, 495–500.

165 V. Hugenberg, S. Hermann, F. Galla, M. Schäfers, B. Wünsch, H. C. Kolb, K. Szardenings, A. Lebedev, J. C. Walsh, V. P. Mocharla, U. B. Gangadharmath, K. Kopka and S. Wagner, *Nucl. Med. Biol.*, 2016, **43**, 424–437.

166 A. Udemba, G. Smith, Q.-D. Nguyen, M. Kaliszczak, L. Carroll, R. Fortt, M. J. Fuchter and E. O. Aboagye, *Org. Biomol. Chem.*, 2015, **13**, 5418–5423.

167 T. Läppchen, R. P. M. Dings, R. Rossin, J. F. Simon, T. J. Visser, M. Bakker, P. Walhe, T. van Mourik, K. Donato, J. R. van Beijnum, A. W. Griffioen, J. Lub, M. S. Robillard, K. H. Mayo and H. Grüll, *Eur. J. Med. Chem.*, 2015, **89**, 279–295.

168 A. Haslop, A. Gee, C. Plisson and N. Long, *J. Label. Compd. Radiopharm.*, 2013, **56**, 313–316.

169 A. Haslop, L. Wells, A. Gee, C. Plisson and N. Long, *Mol. Pharm.*, 2014, **11**, 3818–3822.

170 S. Maschauer, K. Michel, P. Tripal, K. Büther, T. Kuwert, O. Schober, K. Kopka, B. Riemann and O. Prante, *Am. J. Nucl. Med. Mol. Imaging*, 2013, **3**, 425–436.

171 S. Maschauer and O. Prante, *Carbohydr. Res.*, 2009, **344**, 753–761.

172 C. R. Fischer, C. Müller, J. Reber, A. Müller, S. D. Krämer, S. M. Ametamey and R. Schibli, *Bioconjug. Chem.*, 2012, **23**, 805–813.

173 S. Maschauer, C. Greff, J. Einsiedel, J. Ott, P. Tripal, H. Hübner, P. Gmeiner and O. Prante, *Bioorg. Med. Chem.*, 2015, **23**, 4026–4033.

174 F. Pisaneschi, R. L. Slade, L. Iddon, G. P. C. George, Q.-D. Nguyen, A. C. Spivey and E. O. Aboagye, *J. Label. Compd. Radiopharm.*, 2014, **57**, 92–96.

175 C. R. Fischer, V. Groehn, J. Reber, R. Schibli, S. M. Ametamey and C. Müller, *Mol. Imaging Biol.*, 2013, **15**, 649–654.

176 C. Lang, S. Maschauer, H. Hu, P. Gmeiner and O. Prante, *J. Med. Chem.*, 2013, **56**, 9361–9365.

177 S. Maschauer, J. Einsiedel, H. Hübner, P. Gmeiner, O. Prante, *J. Med. Chem.*, 2016, **59**, 6480-6492.

178 C.-M. Yook, S. J. Lee, S. J. Oh, H.-J. J. Ha and J. J. Lee, *J. Label. Compd. Radiopharm.*, 2015, **58**, 317–326.

179 V. Hugenberg, B. Riemann, S. Hermann, O. Schober, M. Schäfers, K. Szardenings, A. Lebedev, U. Gangadharmath, H. Kolb, J. Walsh, W. Zhang, K. Kopka and S. Wagner, *J. Med. Chem.*, 2013, **56**, 6858–6870.

180 H. Schieferstein, T. Betzel, C. R. Fischer and T. L. Ross, *EJNMMI Res.*, 2013, **3**, 68.

181 L. Mirfeizi, A. A. Rybczynska, A. van Waarde, L. Campbell-Verduyn, B. L. Feringa, R. A. J. O. Dierckx and P. H. Elsinga, *Nucl. Med. Biol.*, 2014, **41**, 203–209.

182 G. M. Entract, F. Bryden, J. Domarkas, H. Savoie, L. Allott, S. J. Archibald, C. Cawthorne and R. W. Boyle, *Mol. Pharm.*, 2015, **12**, 4414–4423.

183 M. Pretze and C. Mamat, *J. Fluor. Chem.*, 2013, **150**, 25–35.

184 H. Schieferstein and T. L. Ross, *Eur. J. Org. Chem.*, 2014, **17**, 3546–3550.

185 T. J. Tewson, *Nucl. Med. Biol.*, 1997, **24**, 755–760.

186 V. J. Majo, N. R. Simpson, J. Prabhakaran, J. J. Mann and J. S. D. Kumar, *J. Label. Compd. Radiopharm.*, 2014, **57**, 705–709.

187 Z. Zhang, J. Lau, H.-T. Kuo, C. Zhang, N. Hundal-Jabal, N. Colpo, F. Bénard and K.-S. Lin, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 584–588.

188 Y.-C. Huang, Y.-C. Chang, C.-N. Yeh and C.-S. Yu, *Molecules*, 2016, **21**, 387.

189 O. Sadovski, J. W. Hicks, J. Parkes, R. Raymond, J. Nobrega, S. Houle, M. Cipriano, C. J. Fowler, N. Vasdev and A. A. Wilson, *Bioorg. Med. Chem.*, 2013, **21**, 4351–4357.

190 T. M. Shoup, A. a. Bonab, A. a. Wilson and N. Vasdev, *Mol. Imaging Biol.*, 2015, **17**, 257–263.

191 W. C. Silvers, H. Cai, O. K. Öz and X. Sun, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 924–927.

192 M. B. Skaddan, L. Zhang, D. S. Johnson, A. Zhu, K. R. Zasadny, R. V Coelho, K. Kuszpit, G. Currier, K.-H. Fan, E. M. Beck, L. Chen, S. E. Drozda, G. Balan, M. Niphakis, B. F. Cravatt, K. Ahn, T. Bocan and A. Villalobos, *Nucl. Med. Biol.*, 2012, **39**, 1058–1067.

193 M. Glaser, E. Årstad, A. Gaeta, J. Nairne, W. Trigg, E. G. Robins, *J. Label. Compd. Radiopharm.*, 2012, **55**, 326-331.

194 B. H. Rotstein, H.-Y. Wey, T. M. Shoup, A. A. Wilson, S. H. Liang, J. M. Hooker and N. Vasdev, *Mol. Pharm.*, 2014, **11**, 3832–3838.

195 E. Sawatzky, E. Al-Momani, R. Kobayashi, T. Higuchi, S. Samnick and M. Decker, *ChemMedChem*, 2016, **11**, 1540–1550.

196 R. R. Flavell, C. Truillet, M. K. Regan, T. Ganguly, J. E. Blecha, J. Kurhanewicz, H. F. VanBrocklin, K. R. Keshari, C. J. Chang, M. J. Evans and D. M. Wilson, *Bioconjug. Chem.*, 2016, **27**, 170–178.

197 A. Baranwal, H. H. Patel and J. Mukherjee, *J. Label. Compd. Radiopharm.*, 2014, **57**, 86–91.

198 A. Baranwal and J. Mukherjee, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 2902–2906.

199 I. Al Jammaz, B. Al-Otaibi, S. Amer, N. Al-Hokbany and S. Okarvi, *Nucl. Med. Biol.*, 2012, **39**, 864–870.

200 M. Simpson, L. Trembleau, R. W. Cheyne and T. A. D. Smith, *Appl. Radiat. Isot.*, 2011, **69**, 418–422.

201 I. AlJammaz, B. Al-Otaibi, H. AlHindas and S. M. Okarvi, *Nucl. Med. Biol.*, 2015, **42**, 804–808.

202 M. Onega, J. Domarkas, H. Deng, L. F. Schweiger, T. A. D. Smith, A. E. Welch, C. Plisson, A. D. Gee and D. O'Hagan, *Chem. Commun.*, 2010, **46**, 139–141.

203 S. Dall'Angelo, N. Bandaranayaka, A. D. Windhorst, D. J. Vugts, D. van der Born, M. Onega, L. F. Schweiger, M. Zanda and D. O'Hagan, *Nucl. Med. Biol.*, 2013, **40**, 464–470.

204 X.-G. Li, S. Dall'Angelo, L. F. Schweiger, M. Zanda and D. O'Hagan, *Chem. Commun.*, 2012, **48**, 5247–5249.

205 O. Keinänen, X.-G. Li, N. K. Chenna, D. Lumen, J. Ott, C. F. M. Molthoff, M. Sarparanta, K. Helariutta, T. Vuorinen, A. D. Windhorst and A. J. Airaksinen, *ACS Med. Chem. Lett.*, 2016, **7**, 62–66.

206 M. Onega, J. Domarkas, H. Deng, L. F. Schweiger, T. A. D. Smith, A. E. Welch, C. Plisson, A. D. Gee and D. O'Hagan, *Chem. Commun.*, 2010, **46**, 139-141.

207 M. M. Alauddin, P. S. Conti and J. D. Fissekis, *J. Label. Compd. Radiopharm.*, 2002, **45**, 583–590.

208 Z. Li, H. Cai and P. S. Conti, *Nucl. Med. Biol.*, 2011, **38**, 201–206.

209 H. Anderson, N. Pillarsetty, M. Cantorias and J. S. Lewis, *Nucl. Med. Biol.*, 2010, **37**, 439–442.

210 B. S. Moon, N. H. Jo, K. C. Lee, M. I. El-Gamal, G. Il An, S. H. Hong, T. H. Choi, W. K. Choi, J.-H. Park, J.-H. Cho, G. J. Cheon and C.-H. Oh, *Bull. Korean Chem. Soc.*, 2010, **31**, 3309–3312.

211 H. Zhang, M. V Cantorias, N. Pillarsetty, E. M. Burnazi, S. Cai and J. S. Lewis, *Nucl. Med. Biol.*, 2012, **39**, 1182–1188.

212 H. Cai, Z. Li and P. S. Conti, *Nucl. Med. Biol.*, 2011, **38**, 659–666.

213 K. Chen, Z. Li and P. S. Conti, *Nucl. Med. Biol.*, 2012, **39**, 1019–1025.

214 V. Carroll, B. W. Michel, J. Blecha, H. Vanbrocklin, K. Keshari, D. Wilson and C. J. Chang, *J. Am. Chem. Soc.*, 2014, **136**, 14742–14745.

215 I. Lee, J. Yang, J. H. Lee and Y. S. Choe, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 5765–5769.

216 C. Besanceney-Webler, H. Jiang, T. Zheng, L. Feng, D. Soriano Del Amo, W. Wang, L. M. Klivansky, F. L. Marlow, Y. Liu and P. Wu, *Angew. Chemie Int. Ed.*, 2011, **50**, 8051–8056.

217 M. Pretze, F. Wuest, T. Peppel, M. Köckerling and C. Mamat, *Tetrahedron Lett.*, 2010, **51**, 6410–6414.

218 K.-Z. Hu, H. Wang, T. Huang, G. Tang, X. Liang, S. He and X. Tang, *Nucl. Med. Biol.*, 2013, **40**, 926–932.

219 H. Liu, S. Liu, Z. Miao, H. Jiang, Z. Deng, X. Hong and Z. Cheng, *Mol. Pharm.*, 2013, **10**, 3384–3391.

220 S. Gao, G. Tang, S. Zhu, K. Hu, S. Yao, C. Tang, C. Yang, Y. Wang, J. Li, X. Pan, J. Guo, Q. Wang, R. Gao, W. Zhang, J. Wang, J. Huang and L. Zang, *J. Radioanal. Nucl. Chem.*, 2016, **309**, 1257–1264.

221 Z. Li, H. Cai, M. Hassink, M. L. Blackman, R. C. D. Brown, P. S. Conti and J. M. Fox, *Chem. Commun.*, 2010, **46**, 8043–8045.

222 E. J. Keliher, T. Reiner, A. Turetsky, S. A. Hilderbrand and R. Weissleder, *ChemMedChem*, 2011, **6**, 424–427.

223 T. Reiner, E. J. Keliher, S. Earley, B. Marinelli and R. Weissleder, *Angew. Chemie Int. Ed.*, 2011, **50**, 1922–1925.

224 P. Carberry, B. P. Lieberman, K. Ploessl, S. R. Choi, D. N. Haase and H. F. Kung, *Bioconjug. Chem.*, 2011, **22**, 642–653.

225 H.-L. Huang, C.-N. Yeh, K.-W. Chang, J.-T. Chen, K.-J. Lin, L.-W. Chiang, K.-C. Jeng, W.-T. Wang, K.-H. Lim, C. G. Chen, K.-I. Lin, Y.-C. Huang, W.-J. Lin, T.-C. Yen and C.-S. Yu, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 3998–4003.

226 H.-L. Huang, Y.-C. Huang, W.-Y. Lee, C.-N. Yeh, K.-J. Lin and C.-S. Yu, *PLoS One*, 2014, **9**, e104118.

227 R. Hoareau, L. Gobbi, S. Grall-Ulsemer and L. Martarello, *J. Label. Compd. Radiopharm.*, 2014, **57**, 715–720.

228 Z. Li, L. Lang, Y. Ma and D. O. Kiesewetter, *J. Label. Compd. Radiopharm.*, 2008, **51**, 23–27.

229 R. Löser, S. Fischer, A. Hiller, M. Köckerling, U. Funke, A. Maisonial, P. Brust and J. Steinbach, *Beilstein J. Org. Chem.*, 2013, **9**, 1002–1011.

230 J. Pan, M. Pourghiasian, N. Hundal, J. Lau, F. Bénard, S. Dedhar and K.-S. Lin, *Nucl. Med. Biol.*, 2013, **40**, 850–857.

231 H. Doi, M. Goto and M. Suzuki, *Bull. Chem. Soc. Jpn.*, 2012, **85**, 1233–1238.

232 F. Kügler, J. Ermert and H. H. Coenen, *J. Label. Compd. Radiopharm.*, 2013, **56**, 609–618.

233 C. Lemaire, L. Libert, A. Plenevaux, J. Aerts, X. Franci and A. Luxen, *J. Fluor. Chem.*, 2012, **138**, 48–55.

234 C. Lemaire, P. Damhaut, A. Plenevaux, R. Cantineau, L. Christiaens and M. Guillaume, *Appl. Radiat. Isot.*, 1992, **43**, 485–494.

235 H. Suzuki, N. Yazawa, Y. Yoshida, O. Furusawa and Y. Kimura, *Bull. Chem. Soc. Jpn.*, 1990, 63, 2010–2017.

236 D. R. Hwang, C. S. Dence, Z. A. McKinnon, C. J. Mathias and M. J. Welch, *Nucl. Med. Biol.*, 1991, **18**, 247–252.

237 A. A. Wilson, R. F. Dannals, H. T. Ravert and H. N. Wagner, *J. Label. Compd. Radiopharm.*, 1990, **28**, 1189–1199.

238 F. Kügler, W. Sihver, J. Ermert, H. Hübner, P. Gmeiner, O. Prante and H. H. Coenen, *J. Med. Chem.*, 2011, **54**, 8343–8352.

239 K. Dahl, M. Schou and C. Halldin, *J. Label. Compd. Radiopharm.*, 2012, **55**, 455–459.

240 S. R. Taylor, M. P. Roberts, N. A. Wyatt, T. Q. Pham, D. Stark, T. Bourdier, P. Roselt, A. Katsifis and I. Greguric, *Aust. J. Chem.*, 2013, **66**, 491–499.

241 G.-C. Li, R. Zhang, L.-J. Li and K.-J. Jiang, *J. Radioanal. Nucl. Chem.*, 2013, **295**, 385–391.

242 V. Shalgunov, J.-P. van Wieringen, H. Janssen, P. M. Fransen, R. A. J. O. Dierckx, M. Michel, J. Booij and P. H. Elsinga, *J. Nucl. Med.*, 2015, **56**, 133–139.

243 G. I. Warnock, J. Aerts, M. A. Bahri, F. Bretin, C. Lemaire, F. Giacomelli, F. Mievis, N. Mestdagh, T. Buchanan, A. Valade, J. Mercier, M. Wood, M. Gillard, A. Seret, A. Luxen, E. Salmon and A. Plenevaux, *J. Nucl. Med.*, 2014, **55**, 1336–1341.

244 Z. Li, X. Zhang, X. Zhang, M. Cui, J. Lu, X. Pan and X. Zhang, *J. Med. Chem.*, 2016, **59**, 10577–10585.

245 I. N. Petersen, J. Villadsen, H. D. Hansen, A. A. Jensen, S. Lehel, N. Gillings, M. M. Herth, G. M. Knudsen and J. L. Kristensen, *Bioorg. Med. Chem.*, 2016, **24**, 5353–5356.

246 M. G. Strebl, C. Wang, F. A. Schroeder, M. S. Placzek, H.-Y. Wey, G. C. Van de Bittner, R. Neelamegam and J. M. Hooker, *ACS Chem. Neurosci.*, 2016, **7**, 528–533.

247 X.-G. Li, M. Haaparanta and O. Solin, *J. Fluor. Chem.*, 2012, **143**, 49–56.

248 R. J. Abdel-Jalil, M. Aqarbeh, D. Löffler, B. Shen, S. A. Orabi, W. Voelter and H.-J. Machulla, *J. Radioanal. Nucl. Chem.*, 2010, **283**, 239–243.

249 C. R. Conard and M. A. Dolliver, *Org. Synth.*, 1932, **12**, 22.

250 Z. Li, M. Cui, J. Zhang, J. Dai, X. Zhang, P. Chen, H. Jia and B. Liu, *Eur. J. Med. Chem.*, 2014, **84**, 628–638.

251 X. Cui, X. Zhang, C. Peng, J. Dai, B. Liu and M. Cui, *RSC Adv.*, 2016, **6**, 44646–44654.

252 L. Li, M. N. Hopkinson, R. L. Yona, R. Bejot, A. D. Gee and V. Gouverneur, *Chem. Sci.*, 2011, **2**, 123–131.

253 J. Way, V. Bouvet and F. Wuest, *Curr. Org. Chem.*, 2013, **17**, 2138–2152.

254 F. Kügler, J. Ermert, P. Kaufholz and H. H. Coenen, *Molecules*, 2015, **20**, 470–486.

255 J. D. Way, M. Wang, I. Hamann, M. Wuest and F. Wuest, *Nucl. Med. Biol.*, 2014, **41**, 660–669.

256 J. D. Way and F. Wuest, *J. Label. Compd. Radiopharm.*, 2014, **57**, 104–109.

257 Y. Yagi, H. Kimura, K. Arimitsu, M. Ono, K. Maeda, H. Kusuhara, T. Kajimoto, Y. Sugiyama and H. Saji, *Org. Biomol. Chem.*, 2015, **13**, 1113–1121.

258 G. Yuan, G. B. Jones, N. Vasdev and S. H. Liang, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 4857–4860.

259 M. Glaser, E. Årstad, A. Gaeta, J. Nairne, W. Trig, E. G. Robins, *J. Label. Compd. Radiopharm.*, 2012, **55**, 326-331.

260 H. M. Betts and E. G. Robins, *J. Label. Compd. Radiopharm.*, 2014, **57**, 215-218.

261 R. Iwata, C. Pascali, A. Bogni, G. Horvath, Z. Kovács, K. Yanai and T. Ido, *Appl. Radiat. Isot.*, 2000, **52**, 87–92.

262 P. A. Schubiger, L. Lehmann and M. Friebe, PET Chemistry - The Driving Force in Molecular Imaging, 2007.

263 C. Lemaire, M. Guillaume, R. Cantineau, A. Plenevaux and L. Christiaens, *Appl. Radiat. Isot.*, 1991, **42**, 629–635.

264 M. Namavari, A. Bishop, N. Satyamurthy, G. Bida and J. R. Barrio, *Int. J. Radiat. Appl. Instrumentation. Part A*, 1992, **43**, 989–996.

265 S. Forsback, O. Eskola, M. Haaparanta, J. Bergman and O. Solin, *Radiochim. Acta*, 2008, **96**, 845–848.

266 F. Dolle, S. Demphel, F. Hinnen, D. Fournier, F. Vaufrey and C. Crouzel, *J. Label. Compd. Radiopharm.*, 1997, **41**, 105–114.

267 C. H. K. Kao, W. L. Hsu, H. L. Xie, M. C. Lin, W. C. Lan and H. Y. Chao, *Ann. Nucl. Med.*, 2011, **25**, 309–316.

268 B. B. Azad, R. Chirakal and G. J. Schrobilgen, *J. Label. Compd. Radiopharm.*, 2007, **50**, 1236–1242.

269 C. Lemaire, S. Gillet, S. Guillouet, A. Plenevaux, J. Aerts and A. Luxen, *Eur. J. Org. Chem.*, 2004, **2004**, 2899–2904.

270 C. Lemaire, A. Plenevaux, R. Cantineau, L. Christiaens, M. Guillaume and D. Comar, *Appl. Radiat. Isot.*, 1993, **44**, 737–744.

271 C. Lemaire, P. Damhaut, A. Plenevaux and D. Comar, *J. Nucl. Med.*, 1994, **35**, 1996–2002.

272 D. Yin, L. Zhang, G. Tang, X. Tang and Y. Wang, *J. Radioanal. Nucl. Chem.*, 2003, **257**, 179–185.

273 R. N. Krasikova, V. V. Zaitsev, S. M. Ametamey, O. F. Kuznetsova, O. S. Fedorova, I. K. Mosevich, Y. N. Belokon, Š. Vyskočil, S. V. Shatik, M. Nader and P. A. Schubiger, *Nucl. Med. Biol.*, 2004, **31**, 597–603.

274 R. N. Krasikova, O. S. Fedorova, I. K. Mosevich, O. F. Kuznetsova, M. Korsakov, S. M. Ametamey and P. A. Schubiger, *J. Label. Compd. Radiopharm.*, 1999, **42**, S102–S104.

275 B. Shen, W. Ehrlichmann, M. Uebele, H. J. Machulla and G. Reischl, *Appl. Radiat. Isot.*, 2009, **67**, 1650–1653.

276 L. C. Libert, X. Franci, A. R. Plenevaux, T. Ooi, K. Maruoka, A. J. Luxen and C. F. Lemaire, *J. Nucl. Med.*, 2013, **54**, 1154–1161.

277 C. Lemaire, L. Libert, X. Franci, J.-L. Genon, S. Kuci, F. Giacomelli and A. Luxen, *J. Label. Compd. Radiopharm.*, 2015, **58**, 281–290.

278 M. Pretze, D. Franck, F. Kunkel, E. Foßhag, C. Wängler and B. Wängler, *Nucl. Med. Biol.*, 2017, **45**, 35–42.

279 F. Basuli, H. Wu, C. Li, Z.-D. Shi, A. Sulima and G. L. Griffiths, *J. Label. Compd. Radiopharm.*, 2011, **54**, 633–636.

280 H. T. Ravert, D. P. Holt and R. F. Dannals, *J. Label. Compd. Radiopharm.*, 2014, **57**, 695–698.

281 V. Bernard-Gauthier and R. Schirrmacher, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 4784–4790.

282 C.-Y. Shiue, M. Watanabe, A. P. Wolf, J. S. Fowler and P. Salvadori, *J. Label. Compd. Radiopharm.*, 1984, **21**, 533–547.

283 S. B. Höfling, S. Maschauer, H. Hübner, P. Gmeiner, H.-J. Wester, O. Prante and M. R. Heinrich, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 6933–6937.

284 N. Vasdev, P. N. Dorff, J. P. O'Neil, F. T. Chin, S. Hanrahan and H. F. VanBrocklin, *Bioorg. Med. Chem.*, 2011, **19**, 2959–2965.

285 J. A. Hendricks, E. J. Keliher, B. Marinelli, T. Reiner, R. Weissleder and R. Mazitschek, *J. Med. Chem.*, 2011, **54**, 5576–5582.

286 X. Huang, R. J. Gillies and H. Tian, *J. Label. Compd. Radiopharm.*, 2015, **58**, 156–162.

287 T. Läppchen, M. L. H. Vlaming, E. Custers, J. Lub, C. F. Sio, J. DeGroot and O. C. Steinbach, *Appl. Radiat. Isot.*, 2012, **70**, 205–209.

288 P. Slobbe, A. D. Windhorst, M. Stigter-van Walsum, R. C. Schuit, E. F. Smit, H. G. Niessen, F. Solca, G. Stehle, G. A. M. S. van Dongen and A. J. Poot, *Nucl. Med. Biol.*, 2014, **41**, 749–757.

289 W. Li, W. Thompson, T. Fisher, J. S. Wai, D. Hazuda, H. D. Burns and T. G. Hamill, *J. Label. Compd. Radiopharm.*, 2010, **53**, 517–520.

290 O. Tietz, S. K. Sharma, J. Kaur, J. Way, A. Marshall, M. Wuest and F. Wuest, *Org. Biomol. Chem.*, 2013, **11**, 8052–8064.

291 N. Turkman, A. Shavrin, V. Paolillo, H. H. Yeh, L. Flores, S. Soghomonian, B. Rabinovich, A. Volgin, J. Gelovani and M. Alauddin, *Nucl. Med. Biol.*, 2012, **39**, 593–600.

292 J. Way and F. Wuest, *Nucl. Med. Biol.*, 2013, **40**, 430–436.

293 H. Zhang, R. Huang, N. Pillarsetty, D. L. J. Thorek, G. Vaidyanathan, I. Serganova, R. G. Blasberg and J. S. Lewis, *Eur. J. Nucl. Med. Mol. Imaging*, 2014, **41**, 322–332.

294 J. Kaur, O. Tietz, A. Bhardwaj, A. Marshall, J. Way, M. Wuest and F. Wuest, *ChemMedChem*, 2015, **10**, 1635–1640.

295 P. K. Garg, S. Garg and M. R. Zalutsky, *Nucl. Med. Biol.*, 1994, **21**, 97–103.

296 I. Koslowsky, J. Mercer and F. Wuest, *Org. Biomol. Chem.*, 2010, **8**, 4730–4735.

297 C. R. Berry, P. K. Garg, M. R. Zalutsky, R. E. Coleman and T. R. DeGrado, *J. Nucl. Med.*, 1996, **37**, 2011–2016.

298 C. R. Berry, T. R. DeGrado, F. Nutter, P. K. Garg, E. B. Breischwerdt, K. Spaulding, K. D. Concannon, M. R. Zalutsky and E. Coleman, *Vet. Radiol. Ultrasound*, 2002, **43**, 183–186.

299 I. Al Jammaz, B. Al-Otaibi, S. Okarvi and J. Amartey, *J. Label. Compd. Radiopharm.*, 2006, **49**, 125–137.

300 I. Al Jammaz, B. Al-Otaibi, S. Amer and S. M. Okarvi, *Nucl. Med. Biol.*, 2011, **38**, 1019–1028.

301 T. L. Ross, M. Honer, C. Müller, V. Groehn, R. Schibli and S. M. Ametamey, *J. Nucl. Med.*, 2010, **51**, 1756–1762.

302 T. Betzel, C. Müller, V. Groehn, A. Müller, C. R. Fischer, S. D. Krämer, R. Schibli and S. M. Ametamey, *Bioconjug. Chem.*, 2013, **24**, 205–214.

303 K. S. Jang, Y. W. Jung, P. S. Sherman, C. A. Quesada, G. Gu and D. M. Raffel, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 1612–1616.

304 K. S. Jang, Y. Jung, G. Gu, R. A. Koeppe, P. S. Sherman, C. A. Quesada and D. M. Raffel, *J. Med. Chem.*, 2013, **56**, 7312–7323.

305 C. Drerup, J. Ermert and H. H. Coenen, *Molecules*, 2016, **21**, 1160.

306 A. Maisonial, B. Kuhnast, J. Papon, R. Boisgard, M. Bayle, A. Vidal, P. Auzeloux, L. Rbah, M. Bonnet-Duquennoy, E. Miot-Noirault, M.-J. Galmier, M. Borel, S. Askienazy, F. Dollé, B. Tavitian, J.-C. Madelmont, N. Moins and J.-M. Chezal, *J. Med. Chem.*, 2011, **54**, 2745–2766.

307 U. Ackermann, D. Sigmund, S. D. Yeoh, A. Rigopoulos, G. O'Keefe, G. Cartwright, J. White, A. M. Scott and H. J. Tochon-Danguy, *J. Label. Compd. Radiopharm.*, 2011, **54**, 788–794.

308 B. Carney, G. Carlucci, B. Salinas, V. Di Gialleonardo, S. Kossatz, A. Vansteene, V. A. Longo, A. Bolaender, G. Chiosis, K. R. Keshari, W. A. Weber and T. Reiner, *Mol. Imaging Biol.*, 2016, **18**, 386–392.

309 J. Marik and J. L. Sutcliffe, *Appl. Radiat. Isot.*, 2007, **65**, 199–203.

310 S. Richter and F. Wuest, *Molecules*, 2014, **19**, 20536–20556.

311 T. Kudo, M. Ueda, H. Konishi, H. Kawashima, Y. Kuge, T. Mukai, A. Miyano, S. Tanaka, S. Kizaka-Kondoh, M. Hiraoka and H. Saji, *Mol. Imaging Biol.*, 2011, **13**, 1003–1010.

312 V. Awasthi, G. Pathuri, H. B. Agashe and H. Gali, *J. Nucl. Med.*, 2011, **52**, 147–153.

313 X. Yang, R. C. Mease, M. Pullambhatla, A. Lisok, Y. Chen, C. A. Foss, Y. Wang, H. Shallal, H. Edelman, A. T. Hoye, G. Attardo, S. Nimmagadda and M. G. Pomper, *J. Med. Chem.*, 2016, **59**, 206–218.

314 A. Hoehne, D. Behera, W. H. Parsons, M. L. James, B. Shen, P. Borgohain, D. Bodapati, A. Prabhakar, S. S. Gambhir, D. C. Yeomans, S. Biswal, F. T. Chin and J. Du Bois, *J. Am. Chem. Soc.*, 2013, **135**, 18012–18015.

315 J. Ides, D. Thomae, L. Wyffels, C. Vangestel, J. Messagie, J. Joossens, F. Lardon, P. Van der Veken, K. Augustyns, S. Stroobants and S. Staelens, *Nucl. Med. Biol.*, 2014, **41**, 477–487.

316 N. Matusiak, R. Castelli, A. W. Tuin, H. S. Overkleeft, R. Wisastra, F. J. Dekker, L. M. Prély, R. P. M. Bischoff, A. van Waarde, R. A. J. O. Dierckx and P. H. Elsinga, *Bioorg. Med. Chem.*, 2015, **23**, 192–202.

317 P. Ghosh, K. C. Li and D. Y. Lee, *Appl. Radiat. Isot.*, 2011, **69**, 609–613.

318 H. Xu, Z. Wang, Y. Wang, S. Hu and N. Liu, *PLoS One*, 2013, **8**, e57897.

319 M. Glaser, E. Årstad, S. K. Luthra and E. G. Robins, *J. Label. Compd. Radiopharm.*, 2009, **52**, 327–330.

320 T. Ganguly, S. Dannoon, M. R. Hopkins, S. Murphy, H. Cahaya, J. E. Blecha, S. Jivan, C. R. Drake, C. Barinka, E. F. Jones, H. F. Vanbrocklin and C. E. Berkman, *Nucl. Med. Biol.*, 2015, **42**, 780–787.

321 H.-W. Kao, C.-L. Chen, W.-Y. Chang, J.-T. Chen, W.-J. Lin, R.-S. Liu and H.-E. Wang, *Bioorg. Med. Chem.*, 2013, **21**, 912–921.

322 C. Neto, C. Fernandes, M. C. Oliveira, L. Gano, F. Mendes, T. Kniess and I. Santos, *Nucl. Med. Biol.*, 2012, **39**, 247–260.

323 F. Svensson, T. Kniess, R. Bergmann, J. Pietzsch and F. Wuest, *J. Label. Compd. Radiopharm.*, 2011, **54**, 769–774.

324 S. Dannoon, T. Ganguly, H. Cahaya, J. J. Geruntho, M. S. Galliher, S. K. Beyer, C. J. Choy, M. R. Hopkins, M. Regan, J. E. Blecha, L. Skultetyova, C. R. Drake, S. Jivan, C. Barinka, E. F. Jones, C. E. Berkman and H. F. VanBrocklin, *J. Med. Chem.*, 2016, **59**, 5684–5694.

325 N. Harada, H. Kimura, S. Onoe, H. Watanabe, D. Matsuoka, K. Arimitsu, M. Ono and H. Saji, *J. Nucl. Med.*, 2016, **57**, 1978–1984.

326 D. E. Olberg, J. M. Arukwe, D. Grace, O. K. Hjelstuen, M. Solbakken, G. M. Kindberg and A. Cuthberson, *J. Med. Chem.*, 2010, **53**, 1732–1740.

327 Y. Chen, M. Pullambhatla, C. A. Foss, Y. Byun, S. Nimmagadda, S. Senthamizhchelvan, G. Sgouros, R. C. Mease and M. G. Pomper, *Clin. Cancer Res.*, 2011, **17**, 7645–7653.

328 N. Malik, H. J. Machulla, C. Solbach, G. Winter, S. N. Reske and B. Zlatopolskiy, *Appl. Radiat. Isot.*, 2011, **69**, 1014–1018.

329 B. D. Zlatopolskiy, R. Kandler, F. M. Mottaghy and B. Neumaier, *Appl. Radiat. Isot.*, 2012, **70**, 184–192.

330 B. D. Zlatopolskiy, P. Krapf, R. Richarz, H. Frauendorf, F. M. Mottaghy and B. Neumaier, *Chem. Eur. J.*, 2014, **20**, 4697–4703.

331 B. D. Zlatopolskiy, R. Kandler, D. Kobus, F. M. Mottaghy and B. Neumaier, *Chem. Commun.*, 2012, **48**, 7134–7136.

332 B. Kuhnast, F. Hinnen, B. Tavitian and F. Dollé, *J. Label. Compd. Radiopharm.*, 2008, **51**, 336–342.

333 N. Arksey, T. Hadizad, B. Ismail, M. Hachem, A. C. Valdivia, R. S. Beanlands, R. A. DeKemp and J. N. DaSilva, *Bioorg. Med. Chem.*, 2014, **22**, 3931–3937.

334 M. P. Roberts, T. Q. Pham, J. Doan, C. D. Jiang, T. W. Hambley, I. Greguric and B. H. Fraser, *J. Label. Compd. Radiopharm.*, 2015, **58**, 473–478.

335 P. Krapf, R. Richarz, E. A. Urusova, B. Neumaier and B. D. Zlatopolskiy, *Eur. J. Org. Chem.*, 2016, **2016**, 430–433.

336 K. Hashizume, N. Hashimoto and Y. Miyake, *J. Org. Chem.*, 1995, **60**, 6680–6681.

337 J.-H. Chun and V. W. Pike, *Eur. J. Org. Chem.*, 2012, **2012**, 4541–4547.

338 L. Wang, O. Jacobson, D. Avdic, B. H. Rotstein, I. D. Weiss, L. Collier, X. Chen, N. Vasdev and S. H. Liang, *Angew. Chemie Int. Ed.*, 2015, **54**, 12777–12781.

339 S. K. Fehler, S. Maschauer, S. B. Höfling, A. L. Bartuschat, N. Tschammer, H. Hübner, P. Gmeiner, O. Prante and M. R. Heinrich, *Chem. Eur. J.*, 2014, **20**, 370–375.

340 L. Barré, L. Barbier and M. Lasne, *J. Label. Compd. Radiopharm.*, 1993, **32**, 101–102.

341 I. Ekaeva, L. Barre, M.-C. Lasne and F. Gourand, *Appl. Radiat. Isot.*, 1995, **46**, 777–782.

342 T. Ludwig, J. Ermert and H. H. Coenen, *Nucl. Med. Biol.*, 2002, **29**, 255–262.

343 U. Mühlhausen, J. Ermert and H. H. Coenen, *J. Label. Compd. Radiopharm.*, 2009, **52**, 13–22.

344 T. Stoll, J. Ermert, S. Oya, H. F. Kung and H. H. Coenen, *J. Label. Compd. Radiopharm.*, 2004, **47**, 443–455.

345 A. Helfer, J. Castillo Meleán, J. Ermert, A. Infantino and H. H. Coenen, *Appl. Radiat. Isot.*, 2013, **82**, 264–267.

346 T. L. Ross, J. Ermert and H. H. Coenen, *Molecules*, 2011, **16**, 7621–7626.

347 T. Tominaga, H. Ito, Y. Ishikawa, R. Iwata, K. Ishiwata and S. Furumoto, *J. Label. Compd. Radiopharm.*, 2016, **59**, 117–123.

3

Efficient synthesis of [^{18}F]trifluoromethane and its application in the synthesis of PET tracers

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A new strategy towards [^{18}F]trifluoromethyl-containing compounds is developed. [^{18}F]trifluoromethane is synthesised in a fast and efficient manner and subsequently used in the reaction with aldehydes and ketones forming [^{18}F]trifluoromethyl carbinols in good yields.

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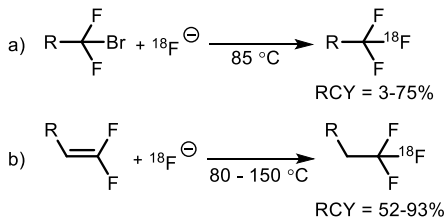
3.1 Introduction

Positron emission tomography (PET) is a powerful molecular imaging technique that can visualise biological processes *in vivo*.[1,2] Today, PET has proven to be a valuable tool for the detection, characterisation and monitoring of diseases and for the investigation of the efficacy of pharmaceuticals. Therefore, there is a continuous need for effective positron-emitting tracers that specifically interact in the biological processes of interest.[3-7]

The development of a PET-tracer usually starts from a known biologically active compound by replacing one of the carbon, nitrogen, oxygen or fluorine atoms by its radioactive isotope. Synthesis of such compounds is challenging due to the short physical half-life of these isotopes (^{11}C $t_{1/2}$ = 20 min, ^{13}N $t_{1/2}$ = 10 min, ^{15}O $t_{1/2}$ = 2 min, ^{18}F $t_{1/2}$ = 110 min). In general, the introduction of the isotope and subsequent purification and analysis of the tracer has to be finalised within 3 half-lives. Consequently, robust, reliable and rapid chemical procedures are essential for succes.[8-12]

Many pharmaceuticals contain a trifluoromethyl (CF_3) functional group. The CF_3 group is incorporated into drug candidates to improve their binding selectivity, lipophilicity, and metabolic stability.[13,14] [^{18}F]CF_3-containing compounds are however rare because only limited synthetic approaches are available. Of the various fluorine-18 sources, only [^{18}F]fluoride is available at most cyclotron sites, and therefore reactions using this fluorine-18 source are especially of interest. Albeit, only a handful of procedures using nucleophilic [^{18}F]fluoride to prepare [^{18}F]trifluoromethylated compounds have been reported.[15-21] Published methods employ the direct reaction of [^{18}F]fluoride with electrophiles, like difluorobromomethyl- or *gem*-difluoro-alkenyl containing compounds (Scheme 1).



Scheme 1 Reported reactions of [^{18}F]fluoride with: a) difluorobromomethyl[15-19] and b) gem-difluoroalkenyl[20,21] precursors.

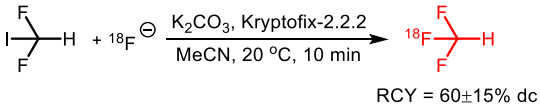
These methods do generate the [^{18}F]trifluoromethyl group in a single synthetic step, but with limited success. Simple substrates react in up to 93% yield, however, the labelling of more complex structures results in very low yields (<15%).[15-21] Moreover, precursors containing the difluorobromomethyl- or *gem*-difluoroalkenyl functional

group are hard to obtain by commercial sources or synthetic methods. A major limitation of the reaction with the *gem*-difluoroalkenyl group is that it actually yields a [^{18}F]2,2,2-trifluoroethyl group. Trifluoromethyl aryls, for example, can therefore not be obtained *via* this method.

In this chapter, we present a novel approach to synthesise radiopharmaceuticals containing a CF_3 group *via* nucleophilic trifluoromethylation using [^{18}F]trifluoromethane.

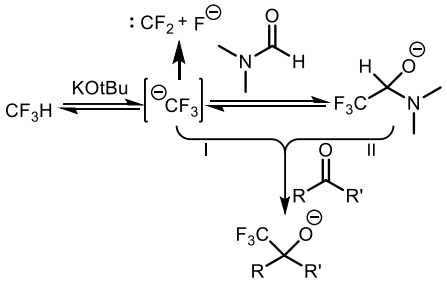
3.2 Results and discussion

During initial studies, we discovered that the reaction of difluoroiodomethane with [^{18}F]fluoride/kryptofix-2.2.2 in acetonitrile provided [^{18}F]trifluoromethane in a satisfactory 60 ± 15% yield in 10 minutes reaction time at room temperature (Scheme 2). [^{18}F]trifluoromethane could be easily isolated by purging it out of the reaction mixture using a flow of helium. The gaseous [^{18}F]trifluoromethane was separated from any gaseous difluoroiodomethane precursor by leading it through a silica column and trapping the product in either DMF at -60 °C with a 88 ± 8% efficiency or in THF at -100 °C with a 96 ± 3% efficiency in 3 minutes. HPLC analysis of the obtained [^{18}F]trifluoromethane solution showed no radioactive or UV-active impurities.



Scheme 2 Synthesis of [^{18}F]trifluoromethane.

The time needed for the synthesis of [^{18}F]trifluoromethane, which includes azeotropic drying of [^{18}F]fluoride/kryptofix-2.2.2 and subsequent reaction and purification, takes about 30 minutes. This leaves enough time for a follow up reaction, and therefore the applicability of [^{18}F]trifluoromethane was further investigated.



Scheme 3 Reaction pathways of the trifluoromethyl anion.

In order to use [^{18}F]trifluoromethane in nucleophilic trifluoromethylations, it needs to be deprotonated first. It is known that deprotonation of "cold" trifluoromethane in THF yields a trifluoromethyl anion that decomposes to difluorocarbene and fluoride (Scheme 3).[7] Deprotonation in DMF however, results in a trifluoromethyl anion stabilised as the corresponding *gem*-aminoalcoholate. Using this method, aldehydes and ketones undergo reactions with trifluoromethane to form the corresponding trifluoro-carbinols in high yields.[22,23] The trifluoromethylation of a carbonyl group may proceed *via* two distinct pathways (Scheme 3). Either the trifluoromethyl anion attacks directly the electrophilic carbonyl group, where the *gem*-aminoalcoholate only acts as a temporary reservoir of the trifluoromethyl anion, or the *gem*-aminoalcoholate formed in DMF reacts with the carbonyl group.

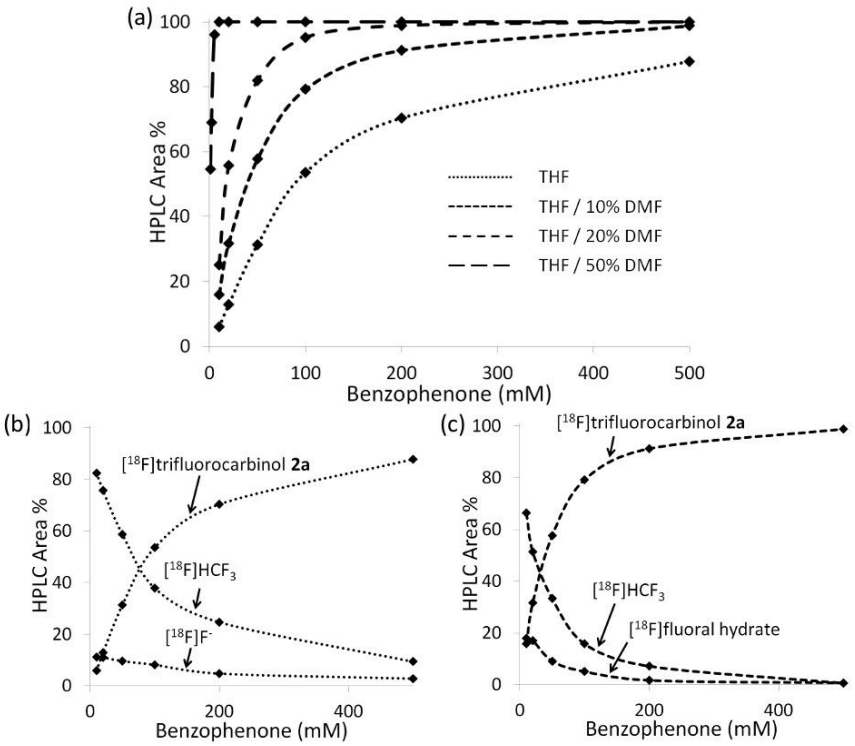
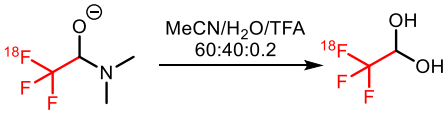


Figure 1 Analysis of the reaction of [^{18}F]HCF_3 with benzophenone by radio-HPLC. a) Investigation of the influence of the DMF concentration on the formation of [^{18}F]trifluorocarbinol **2a**; b) Determination of the reaction products in THF; c) Determination of the reaction products in THF with 10% DMF.

When fluorine-18 is used in a reaction the resulting products and reactants can easily be monitored with HPLC and a radioactivity detector. With such an analytical set-up, reaction progress is easily followed and we decided to investigate the mechanism of

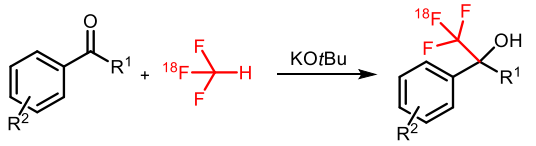
trifluoromethylation of carbonyls using [^{18}F]trifluoromethane in more detail. The reaction of [^{18}F]trifluoromethane and benzophenone was selected as a model reaction, because initial experiments showed that benzophenone reacts cleanly to the corresponding [^{18}F]trifluorocarbinol **2a**. First the trifluoromethylation reaction using [^{18}F]trifluoromethane and KO*t*Bu (100 mM) (5 min at 20 °C) at various concentrations of benzophenone was investigated in THF that contained various percentages of DMF (Figure 1a).

Surprisingly, the reaction in neat THF yielded the desired product **2a** in up to 86%. However, to achieve this, a high concentration of benzophenone (500 mM) was required. This demonstrates that the trifluoromethyl anion can react directly with benzophenone (pathway I). However, at low benzophenone concentrations, the yield of **2a** decreased and decomposition of the trifluoromethyl anion led to the formation of [^{18}F]fluoride. In this case, the presence of 50% of DMF led to a tremendous increase in product yield. Apparently, the direct reaction pathway I is very slow at these concentrations and pathway II *via* the *gem*-aminoalcoholate comes more into play at increasing DMF concentrations. In these reactions, [^{18}F]fluoride was also not found as a by-product, but [^{18}F]fluoral hydrate was detected instead. This can be attributed to protonation of the *gem*-aminoalcoholate intermediate in the acidic HPLC eluent (Scheme 4) and therefore can be used to quantify the amount of *gem*-aminoalcoholate present in the reaction mixture.



Scheme 4 Formation of [^{18}F]fluoral hydrate in the HPLC eluent.

The absence of [^{18}F]fluoride indicates that the *gem*-aminoalcoholate does not act as a trifluoromethyl anion reservoir, but reacts directly in a conserted reaction with the substrate. If the *gem*-aminoalcoholate is in equilibrium with the trifluoromethyl anion, at least some [^{18}F]fluoride should have been formed.



R^1 = Ph (**1a-f**,[^{18}F]**2a-f**); CH_3 (**3a-f**,[^{18}F]**4a-f**); H (**5a-f**,[^{18}F]**6a-f**)

Scheme 5 [^{18}F]trifluoromethylation using [^{18}F]HCF_3.

To investigate the scope of the [^{18}F]trifluoromethylation reaction discussed above, various benzaldehydes **1**, acetophenones **3** and benzophenones **5** (for R^2 see table 1-3) containing electron withdrawing and donating groups (Scheme 5) were selected as the electrophilic reaction partners.

Table 1 Trifluoromethylation of benzophenones **1**.[a]

Entry	R^2	Substrate (µmol)	KO*t*Bu (µmol)	Product	Radiochemical conversion (%)
1	H	10	20	[^{18}F]**2a**	>99
2	4-OMe	10	20	[^{18}F]**2b**	16
3	4-OMe	10	30	[^{18}F]**2b**	>99
4	4-CF_3	10	20	[^{18}F]**2c**	99
5	4-F	10	20	[^{18}F]**2d**	>99
6	4-NO_2	10	20	[^{18}F]**2e**	1
7	4-NO_2	10	50	[^{18}F]**2e**	96
8	3-NO_2	10	20	[^{18}F]**2f**	30
9	3-NO_2	10	50	[^{18}F]**2f**	74

[a] Reaction conditions: 1 mL DMF, 20 °C, 5 minutes.

Reaction with substituted benzophenones **1** provided the expected products in excellent yields (Table 1). The synthesis of [^{18}F]**2b** (R^2 = 4-OMe), [^{18}F]**2e** (R^2 = 4-NO_2) and [^{18}F]**2f** (R^2 = 3-NO_2) required although an increasing concentration of KO*t*Bu. Under the low yielding reaction conditions, unreacted [^{18}F]trifluoro-methane was still present, because the substrates had degraded (as shown by UV-HPLC analysis).

Table 2 Trifluoromethylation of acetophenones **3**.[a]

Entry	R^2	Substrate (µmol)	KO*t*Bu (µmol)	Product	Radiochemical conversion (%)
1	H	100	150	[^{18}F]**4a**	41
2	4-OMe	100	150	[^{18}F]**4b**	44
3	4-CF_3	100	150	[^{18}F]**4c**	22
4	4-F	100	150	[^{18}F]**4d**	36
5	4-NO_2	100	150	[^{18}F]**4e**	0
6	3-NO_2	100	150	[^{18}F]**4f**	0

[a] Reaction conditions: 1 mL DMF, 20 °C, 5 minutes.

High base concentrations probably led to faster deprotonation and reaction of [^{18}F]trifluoromethane with the substrates, before degradation of the substrate occurred.

In the case of acetophenones **3**, enolate formation was expected under the applied reaction conditions, which would lead to a decreased availability of reactive ketone. Indeed, higher base and precursor concentrations were required to obtain the products in satisfactory yields (Table 2).

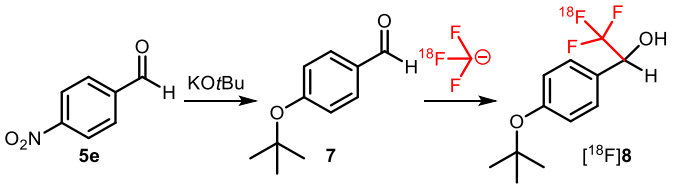
In these reactions, also no radioactive by-products were formed and in the synthesis of [^{18}F]**4e** (R^2 = 4-NO_2) and [^{18}F]**4f** (R^2 = 3-NO_2) only unreacted [^{18}F]trifluoromethane was observed. Substrate degradation, as was observed by UV-HPLC, caused by the strong basic conditions probably led to low yields.

Table 3 Trifluoromethylation of benzaldehydes **5**.[a]

Entry	R^2	Substrate (µmol)	KO*t*Bu (µmol)	Product	Radiochemical conversion (%)
1	H	100	150	[^{18}F]**4a**	41
2	4-OMe	100	150	[^{18}F]**4b**	44
3	4-CF_3	100	150	[^{18}F]**4c**	22
4	4-F	100	150	[^{18}F]**4d**	36
5	4-NO_2	100	150	[^{18}F]**4e**	0
6	3-NO_2	100	150	[^{18}F]**4f**	0

[a] Reaction conditions: 1 mL DMF, 20 °C, 5 minutes.

Benzaldehydes **5** reacted in a moderate to high yield with [^{18}F]trifluoromethane (Table 3). Also here a positive effect of an increasing KO*t*Bu concentration on the product yield was observed. Most reactions didn't yield by-products, except for the synthesis of [^{18}F]**6e**. In that case not [^{18}F]**6e**, but [^{18}F]**8** was formed (Scheme 6). This may be explained by nucleophilic attack of the *tert*-butoxide anion on the precursor 4-nitrobenzaldehyde **5e** (Scheme 6) resulting in 4-*t*-butoxy-benzaldehyde **7** which subsequently reacts with [^{18}F]trifluoromethane to form [^{18}F]1-(4-(*tert*-butoxy)phenyl)-2,2,2-trifluoroethanol **8**.



Scheme 6 Major by-product formation in the reaction of **5e** with [^{18}F]HCF_3^-.

3.3 Conclusions

In summary, [^{18}F]trifluoromethane can be prepared in high yield in a short synthesis time and undergoes smooth reaction with various aromatic aldehydes and ketones to give [^{18}F]trifluoromethylcarbinols in reasonable to good yields. Substrate stability seems to be the most important factor to obtain high product yields. We are currently investigating the use of [^{18}F]trifluoromethane towards other products (trifluoromethyl-thioethers, trifluoromethylarenes) and towards the synthesis of [^{18}F]TMSCF$_3$, a milder reagent for trifluoromethylation reactions.

3.4 Materials and methods

3.4.1 General

All chemicals, including reference compounds 2,2,2-trifluoro-1-diphenylethanol **2a**, 1,1,1-trifluoro-2-phenylpropan-2-ol **4b** and 2,2,2-trifluoro-1-phenylethanol and all precursors were obtained from commercial suppliers and were used without further purification, except for the precursors 4-nitrobenzaldehyde, 4-fluorobenzaldehyde and 4-(trifluoromethyl)-benzaldehyde, which were further purified by distillation or sublimation. THF was distilled from lithium aluminium hydride, all other solvents were dried on 3Å molecular sieves. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker Avance 250 (^{1}H = 250.13 MHz, ^{13}C = 60.90 MHz, ^{19}F = 235.33 MHz) instrument, where spectra were recorded at a temperature of 25 °C. Chemical shifts (δ) are given in ppm, internally referenced to residual solvent resonances (^{1}H: δ = 7.26 ppm, ^{13}C: δ = 77.0 ppm). Thin Layer Chromatography was performed using TLC plates from Merck (SiO_2, neutral kieselgel 60 on alumina with a 254 nm fluorescence indicator). Compounds on the TLC plate were visualised by 254 nm UV light. Flash column chromatography was performed with Screening Devices 60Å silica gel. Analytical HPLC was done on a HPLC system consisting of a Jasco PU-1580 pump, a Jasco UV-2075 Plus UV/Vis detector set at a wavelenght of 254 nm, a Scionex 51BP 51/2 NaI radioactivity detector, a Raytest Gina data acquisition and control interface and a Grace Alltima™ C18 5u 250mm x 4.6mm column using a 70:30:0.2 MeCN/H_2O/TFA eluent at a flow of 1 mL/min. Radioactivity was quantified with a Veenstra VDC-304 dose calibrator.

3.4.2 Synthesis of [^{18}F]trifluoromethane

[^{18}F]fluoride was produced by the ^{18}O(p,n)^{18}F nuclear reaction using an IBA 18/9 cyclotron. After irradiation, [^{18}F]fluoride was trapped on a Chromafix® 30-PS-HCO_3 ^{18}F separation cartridge and eluted to a reaction vessel using a solution of Kryptofix $K_{2.2.2}$ (13 mg) and K_2CO_3 (2 mg) in MeCN/H_2O (1 mL, ratio 9:1). The solution was dried under a stream of Helium and reduced pressure at 90 °C. Residual water was removed by

azeotropic co-evaporation using three portions of anhydrous MeCN (3 times 1 mL). Difluoroiodomethane (8 mg, 7.1 µmol) dissolved in MeCN (1 mL) was added to the dry [^{18}F]fluoride and was allowed to stand at room temperature for 10 minutes. Using a helium flow of 10 mL/min, the formed [^{18}F]trifluoromethane (60% ± 15% yield) was purged out of the reaction mixture, through a Waters Sep-Pak® Plus Silica cartridge and trapped in DMF (1 mL, -60 °C) or THF (1 mL, -100 °C) in an efficiency of 88 ± 8% and 96% ± 3% respectively in 3 minutes.

3.4.3 Detailed analysis of separation of [^{18}F]trifluoromethane from difluoroiodomethane

To purify gaseous [^{18}F]trifluoromethane from any gaseous difluoroiodomethane precursor, a stream of helium (10 mL/min) was led through a Waters Sep-Pak® Plus Silica cartridge as described in the previous section. The boiling points of [^{18}F]trifluoromethane (-82.1 °C) and difluoroiodomethane (21.6 °C) are far enough apart that the silica column can separate the gasses (silica column acts as a small room temperature gas chromatograph).

To demonstrate the efficiency of the Waters Sep-Pak® Plus Silica cartridge, Helium was bubbled (10 mL/min) through a vessel containing 1 mL of a 0.04M difluoroiodomethane solution in MeCN and trapped in a second vessel containing 1 mL THF at -60 °C for 3 minutes or for 6 minutes. For entry 1 (3 minutes from start) and 3 (6 minutes from start) of table 4, a Waters Sep-Pak® Plus Silica cartridge was placed before the second vessel and for entry 2 (3 minutes from start) and 4 (6 minutes from start) of table 4 no Waters Sep-Pak® Plus Silica cartridge was placed before the second vessel. The distillate was analysed using UV-HPLC, which can detect difluoroiodomethane at 250 nm with a detection limit of 10 µM. All experiments were performed in triplicate. The results are shown in Table 4.

Table 4 Efficacy of a Waters Sep-Pak® Plus Silica cartridge.

Entry	Time (min)	Silica Sep-Pak	CHF_2I (µM)	CHF_2I (%)
1	3.0	YES	<10	<0.03
2	3.0	NO	267 ± 42	0.67
3	6.0	YES	31 ± 20	0.08
4	6.0	NO	461 ± 215	1.15

The concentration of difluoroiodomethane, when using a Silica Sep-Pak, is under the HPLC detection limit of 10 µM for the 3.0 minutes distillation and is 31 µM for the 6.0 minutes distallation. Fortunately, 3.0 minutes is sufficient to transport al the

[^{18}F]trifluoromethane and therefore the [^{18}F]trifluoromethane stock solution will contain less than 10 nanomol of difluoroiodomethane using 1 mL THF to trap [^{18}F]trifluoromethane. These amounts will not interfere in the labelling reactions. When no Silica Sep-Pak is used (entry 2 & 4), the difluoroiodomethane concentration is 267 µM after 3.0 minutes and 461 µM 6.0 minutes of distillation, showing that the silica Sep-Pak is actually effectively separating [^{18}F]trifluoromethane from its precursor difluoroiodomethane.

3.4.4 General procedure for the synthesis of [^{18}F]trifluoromethylcarbinols

To a reaction vessel was added either benzophenone **1a-f**, acetophenone **3a-f**, or benzaldehyde **5a-f**, followed by DMF, [^{18}F]CHF$_3$ in DMF and 0.2M KO*t*Bu in DMF up to a total volume of 1 mL. The reaction was stirred for 5 minutes at 20 °C for benzophenones **1** and benzaldehydes **3**, or at 80 °C for acetophenones **5**. The reaction mixture was analysed by injecting 1 µL of it directly on analytical HPLC.

The HPLC chromatograph in Figure 2 shows the result of the reaction of [^{18}F]trifluoromethane with benzaldehyde. The radio chromatograph shows that the peak of [^{18}F]trifluoromethane at 4.23 min has disappeared and a new peak has formed at 6.27 min. To identify this peak as [^{18}F]2,2,2-trifluoro-1-phenylethanol, the cold reference compound was injected on HPLC under the same conditions.

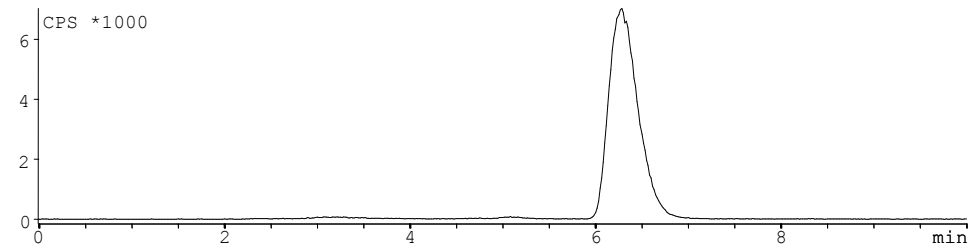


Figure 2 radioHPLC of the synthesis of [^{18}F]2,2,2-trifluoro-1-phenylethanol

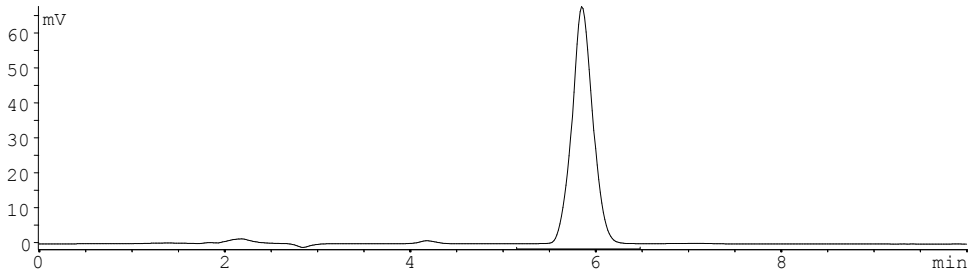


Figure 3 HPLC-UV (254 nm) chromatogram of cold reference 2,2,2-trifluoro-1-phenylethanol

Figure 3 shows that the reference compound forms a peak at 5.90 minutes. There is a time difference between detection on the UV detector and the radioactivity detector of 0.37 minutes. Therefore, the radioactive product has the same retention on the HPLC column as the 2,2,2-trifluoro-1-phenylethanol reference and can be positively identified to be [^{18}F]2,2,2-trifluoro-1-phenylethanol.

3.4.5 Formation and identification of [^{18}F]fluoral hydrate

After addition of KOtBu (100 µmol) to a solution of [^{18}F]CHF_3 in DMF (1 mL), HPLC analysis showed conversion of [^{18}F]CHF_3 (R_t: 4.27 min) towards a new radioactive peak (R_t: 3.38 min), most probably [^{18}F]fluoral hydrate, formed from the intermediate *gem*-aminoalcoholate II upon quenching in the HPLC eluent. To identify the radioactive peak as [^{18}F]fluoral hydrate, the reaction mixture was co-injected on HPLC with 30 µmol non-radioactive fluoral hydrate and the radioactive peak with Rt 3.38 min was collected. ^{19}F-NMR analysis of the collected peak positively identified the radioactive peak to be [^{18}F]fluoral hydrate.

3.4.6 Synthesis of the reference trifluoromethylcarbinols

All reference compounds were synthesised by following the method published by Prakash *et al.*[24] The TMS-ether trifluorocarbinol derivatives were synthesised first, followed by hydrolysis by either 1M TBAF in THF or 1M HCl in 1:1 H_2O / THF. Further experimental details for every reference compound are described on the following pages.

2,2,2-trifluoro-1-(4-methoxyphenyl)-1-phenylethanol (2b):

To a solution of 4-methoxybenzophenone (250 mg, 1.18 mmol) in DMF (3 mL) was added $TMSCF_3$ (517 µL, 3.50 mmol) and K_2CO_3 (50.0 mg, 0.36 mmol). After stirring at room temperature for 42 hours, H_2O was added (40 mL) and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude TMS ether was purified by flash column chromatography (silicagel, EtOAc / n-Hexane 1:99) and hydrolysed by adding THF (3 mL) and TBAF (3 mL, 1M in THF, 3 mmol). After stirring at room temperature for 3 hours, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / n-Hexane 1:9) to yield **2b** as a colourless oil (37 mg, 11%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.53 - 7.46 (m, 2H), 7.44 - 7.31 (m, 5H), 6.92 - 6.82 (m, 2H), 3.81 (s, 3H), 2.77 (s, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -74.5 (s, 3F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 159.8, 139.7, 131.7, 129.0, 128.7, 128.3, 127.6, 125.5 (q, $^1J_{CF}$ = 286.3 Hz), 113.7, 79.4 (q, $^1J_{CF}$ = 29.0 Hz), 55.4, HPLC retention time:

11.32 min. Synthesis and analysis of this compound is described previously by White et al.[25]

2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)-1-phenylethanol (2c):
To a solution of 4-(trifluoromethyl)benzophenone (212 mg, 0.85 mmol) in DMF (3 mL) was added $TMSCF_3$ (222 µL, 1.50 mmol) and K_2CO_3 (14 mg, 0.1 mmol). After stirring at room temperature for 72 hours, TBAF (3 mL, 1M in THF, 3 mmol) was added to hydrolyse the intermediate TMS ether. After stirring at room temperature for 3 hours, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / n-Hexane 1:9) to yield **2c** as a pale-yellow oil (171 mg, 63%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.63 (br. s, 4H), 7.54 - 7.43 (m, 2H), 7.43 - 7.34 (m, 3H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -62.8 (s, 3F), -74.3 (s, 3F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 143.1, 139.0, 131.0 (q, $^2J_{CF}$ = 32.6 Hz), 129.2, 128.8, 128.2, 127.4, 125.3 (q, $^3J_{CF}$ = 3.4 Hz), 125.2 (q, $^1J_{CF}$ = 286.3 Hz), 124.1 (q, $^1J_{CF}$ = 272.1 Hz), 79.5 (q, $^2J_{CF}$ = 29.0 Hz), HPLC retention time: 21.32 min. Synthesis of this compound is described previously by Liu et al.[26]

2,2,2-trifluoro-1-(4-fluorophenyl)-1-phenylethanol (2d):
To a solution of 4-fluorobenzophenone (212 mg, 1.00 mmol) in DMF (3 mL) was added $TMSCF_3$ (222 µL, 1.50 mmol) and K_2CO_3 (14 mg, 0.1 mmol). After stirring at room temperature for 96 hours, TBAF (3 mL, 1M in THF, 3 mmol) was added to hydrolyse the intermediate TMS ether. After stirring at room temperature for 3 hours, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / *n*-Hexane 1:9) to yield **2d** as a pale-yellow oil (134 mg, 50%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.55 - 7.42 (m, 4H), 7.41 - 7.32 (m, 3H), 7.11 - 6.97 (m, 2H), 2.83 (s, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -74.5 (s, 3F), -113.1 (s, 1F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 162.9 (d, $^1J_{CF}$ = 248.2 Hz), 139.4, 135.2 (d, $^4J_{CF}$ = 3.2 Hz), 129.7 (d, $^3J_{CF}$ = 7.4 Hz), 129.0, 128.6, 127.4, 125.4 (q, $^1J_{CF}$ = 286.8 Hz), 115.3 (d, $^2J_{CF}$ = 21.6 Hz), 79.3 (q, $^2J_{CF}$ = 29.0 Hz), HPLC retention time: 12.72 min. Synthesis of this compound and ^{19}F-NMR analysis is described previously by Dayal *et al*.[27]

2,2,2-trifluoro-1-(4-nitrophenyl)-1-phenylethanol (2e):
To a solution of 4-nitrobenzophenone (227 mg, 1.00 mmol) in DMF (3 mL) was added $TMSCF_3$ (222 µL, 1.50 mmol) and K_2CO_3 (14 mg, 0.1 mmol). After stirring at room temperature for 3 hours, TBAF (3 mL, 1M in THF, 3 mmol) was added to hydrolyse the

intermediate TMS ether. After stirring at room temperature for 15 minutes, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was two times purified by flash column chromatography (silicagel, EtOAc / n-Hexane 1:4) to yield **2e** as a pale-yellow crystals (99 mg, 33%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.28 - 8.14 (m, 2H), 7.70 (d, ^{3}J = 8.5 Hz, 2H), 7.53 - 7.35 (m, 5H), 2.98 (s, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -74.2 (s, 3F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 148.0, 145.9, 138.6, 129.4, 128.9, 128.8, 127.2, 123.4, 125.0 (q, $^1J_{CF}$ = 286.3 Hz), 79.4 (q, $^2J_{CF}$ = 29.0 Hz), HPLC retention time: 12.18 min. Synthesis and analysis of this compound is described previously by Prakash et al.[28]

2,2,2-trifluoro-1-(3-nitrophenyl)-1-phenylethanol (2f):

To a solution of 3-nitrobenzophenone (227 mg, 1.00 mmol) in DMF (3 mL) was added $TMSCF_3$ (222 µL, 1.50 mmol) and K_2CO_3 (14 mg, 0.1 mmol). After stirring at room temperature for 72 hours, TBAF (3 mL, 1M in THF, 3 mmol) was added to hydrolyse the intermediate TMS ether. After stirring at room temperature for 3 hours, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / n-Hexane 1:4) to yield **2f** as a pale-yellow crystals (196 mg, 66%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.43 (s, 1H), 8.25 - 8.20 (m, 1H), 7.84 - 7.76 (m, 1H), 7.54 (t, ^3J = 8.1 Hz, 1H), 7.50 - 7.37 (m, 5H), 3.00 (s, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -74.3 (s, 3F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 148.2, 141.3, 138.5, 133.8, 129.4, 129.3, 128.9, 127.2, 123.7, 122.7, 125.0 (q, $^1J_{CF}$ = 282.7 Hz), 79.1 (q, $^2J_{CF}$ = 29.4 Hz), HPLC retention time: 11.87 min.

1,1,1-trifluoro-2-(4-methoxyphenyl)propan-2-ol (4b):

To a solution of 4'-methoxyacetophenone (150 mg, 1.00 mmol) in DMF (3 mL) was added $TMSCF_3$ (500 µL, 3.38 mmol) and K_2CO_3 (50.0 mg, 0.36 mmol). After stirring at room temperature for 24 hours, H_2O was added (40 mL) and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude TMS ether was purified by flash column chromatography (silicagel, EtOAc / n-Hexane 1:99) and hydrolysed by adding TBAF (3 mL, 1M in THF, 3 mmol). After stirring at room temperature for 19 hours, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / n-Hexane 15:85) to yield **4b** as a yellow oil (20 mg,

9%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.55 - 7.44 (m, 2H), 6.96 - 6.87 (m, 2H), 3.82 (s, 3H), 2.41 (s, 1H), 1.77 (s, 3H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -81.2 (s, 3F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 159.9, 130.7, 127.6, 125.8 (q, $^{1}J_{CF}$ = 285.0 Hz), 113.8, 74.7 (q, $^{2}J_{CF}$ = 29.4 Hz), 55.4, 24.0, HPLC retention time: 6.32 min. Synthesis and analysis of this compound is described previously by Amyes et al.[29]

1,1,1-trifluoro-2-(4-(trifluoromethyl)phenyl)propan-2-ol (4c):
To a solution of 4'-(trifluoromethyl)acetophenone (564 mg, 3.00 mmol) in DMF (10 mL) was added $TMSCF_3$ (665 µL, 4.50 mmol) and K_2CO_3 (41 mg, 0.1 mmol). After stirring at room temperature for 22 hours, H_2O was added (40 mL) and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude TMS ether was hydrolysed by adding THF (10 mL) and 1M HCl (10 mL). After stirring at room temperature for 24 hours, H2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / n-Hexane 15:85) to yield **4c** as a yellow oil (312 mg, 40%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.83 - 7.57 (m, 4H), 2.43 (s, 1H), 1.81 (s, 3H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -62.8 (s, 3F), -80.9 (s, 3F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 142.6, 131.1 (q, $^{2}J_{CF}$ = 32.6 Hz), 126.9, 125.6 (q, $^{1}J_{CF}$ = 285.0 Hz), 125.4 (q, $^{3}J_{CF}$ = 3.7 Hz), 124.2 (q, $^{1}J_{CF}$ = 272.5 Hz), 75.0 (q, $^{2}J_{CF}$ = 29.4 Hz), 23.8, HPLC retention time: 11.07 min. Synthesis and analysis of this compound is described previously by Liu et al.[26]

1,1,1-trifluoro-2-(4-fluorophenyl)propan-2-ol (4d):
To a solution of 4'-fluoroacetophenone (414 mg, 3.00 mmol) in DMF (10 mL) was added $TMSCF_3$ (665 µL, 4.50 mmol) and K_2CO_3 (41 mg, 0.1 mmol). After stirring at room temperature for 96 hours, H_2O was added (40 mL) and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude TMS ether was hydrolysed by adding THF (10 mL) and 1M HCl (10 mL). After stirring at room temperature for 72 hours, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / n-Hexane 1:9) to yield **4d** as a yellow oil (122 mg, 20%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.61 - 7.51 (m, 2H), 7.14 - 7.01 (m, 2H), 2.38 (s, 1H), 1.78 (s, 3H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -81.2 (s, 3F), -113.7 (s, 1F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 162.9 (d, $^{1}J_{CF}$ = 248.2 Hz), 134.2 (d, $^{4}J_{CF}$ = 3.2 Hz), 128.1 (d, $^{3}J_{CF}$ = 7.8 Hz), 125.5 (q, $^{1}J_{CF}$ = 285.4 Hz), 115.2 (d, $^{2}J_{CF}$ = 22.1 Hz), 74.6 (q, $^{2}J_{CF}$ = 29.9 Hz),

23.9, HPLC retention time: 7.05 min. Synthesis and analysis of this compound is described previously by Mizuta et al.[30]

1,1,1-trifluoro-2-(4-nitrophenyl)propan-2-ol (4e):

To a solution of 4'-nitroacetophenone (165 mg, 1.00 mmol) in DMF (3 mL) was added $TMSCF_3$ (222 µL, 1.50 mmol) and K_2CO_3 (14 mg, 0.10 mmol). After stirring at room temperature for 17 hours, TBAF (3 mL, 1M in THF, 3 mmol) was added to hydrolyse the intermediate TMS ether. After stirring at room temperature for 4 hours, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / n-Hexane 1:4) to yield **4e** as white crystals (129 mg, 55%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.32 - 8.19 (m, 2H), 7.86 - 7.72 (m, 2H), 2.57 (s, 1H), 1.83 (s, 3H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -80.8 (s, 3F); ^{13}C NMR (63 MHz, CDCl3) δ (ppm): 148.1, 145.4, 127.6, 123.5, 125.2 (q, $^1J_{CF}$ = 285.4 Hz), 74.9 (q, $^2J_{CF}$ = 30.1 Hz), 24.1, HPLC retention time: 7.02 min. Synthesis and analysis of this compound is described previously by Song et al.[31]

1,1,1-trifluoro-2-(3- nitrophenyl)propan-2-ol (4f):

To a solution of 3'-nitroacetophenone (165 mg, 1.00 mmol) in DMF (3 mL) was added $TMSCF_3$ (443 µL, 3.00 mmol) and K_2CO_3 (28 mg, 0.20 mmol). After stirring at room temperature for 21 hours, TBAF (3 mL, 1M in THF, 3 mmol) was added to hydrolyse the intermediate TMS ether. After stirring at room temperature for 1 hour, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / n-Hexane 1:4) to yield **4f** as a yellow oil (138 mg, 59%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.49 (s, 1H), 8.34 - 8.19 (m, 1H), 8.03 - 7.87 (m, 1H), 7.60 (t, ^3J = 7.8 Hz), 2.53 (s, 1H), 1,85 (s, 3H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -81.0 (s, 3F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 148.3, 140.8, 132.6, 129.5, 123.7, 121.7, 125.2 (q, $^1J_{CF}$ = 285.9 Hz), 74.6 (q, $^1J_{CF}$ = 29.9 Hz), 23.9, HPLC retention time: 6.93 min. Synthesis and analysis of this compound is described previously by Mizuta et al.[30]

2,2,2-trifluoro-1-(4-methoxyphenyl)ethanol (6b):

To a solution of 4-methoxybenzaldehyde (136 mg, 1.00 mmol) in DMF (3 mL) was added $TMSCF_3$ (222 µL, 1.50 mmol) and K_2CO_3 (14 mg, 0.10 mmol). After stirring at room temperature for 1 hour, TBAF (3 mL, 1M in THF, 3 mmol) was added to hydrolyse the intermediate TMS ether. After stirring at room temperature for 16 hours, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic

layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / n-Hexane 1:4) to yield **6b** as a yellow oil (90 mg, 44%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.45 - 7.35 (m, 2H), 6.98 - 6.89 (m, 2H), 5.04 - 4.90 (m, 1H), 3.38 (s, 3H), 2.42 (d, ^3J = 4.5 Hz, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -78.5 (s, 3F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 160.6, 128.9, 126.4, 124.5 (q, $^1J_{CF}$ = 281.7 Hz), 114.2, 72.6 (q, $^2J_{CF}$ = 32.2 Hz), 55.4, HPLC retention time: 5.53 min. Synthesis and analysis of this compound is described previously by Shi et al.[32]

2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethanol (6c):

To a solution of 4-(trifluoromethyl)benzaldehyde (174 mg, 1.00 mmol) in DMF (10 mL) was added $TMSCF_3$ (222 µL, 1.50 mmol) and K_2CO_3 (14 mg, 0.1 mmol). After stirring at room temperature for 5 hours, H_2O was added (20 mL) and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 30 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude TMS ether was hydrolysed by adding THF (3 mL) and 1M HCl (3 mL). After stirring at room temperature for 21 hours, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / n-Hexane 15:85) to yield **6c** as a colourless oil (33 mg, 13%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.73 - 7.57 (m, 4H), 5.11 (q, J = 6.6 Hz, 1H), 2.79 (s, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -62.9 (s, 3F), -78.4 (d, J = 6.9 Hz, 3F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 137.6, 131.8 (q, $^2J_{CF}$ = 32.6 Hz), 127.9, 125.6 (q, $^3J_{CF}$ = 3.7 Hz), 123.9 (q, $^1J_{CF}$ = 282.2 Hz) 123.8 (q, $^1J_{CF}$ = 282.2 Hz), 72.2 (q, $^2J_{CF}$ = 32.2 Hz), HPLC retention time: 8.80 min. Synthesis and analysis of this compound is described previously by Miyake et al.[33]

2,2,2-trifluoro-1-(4-fluorophenyl)ethanol (6d):

To a solution of 4-fluorobenzaldehyde (745 mg, 6 mmol) in DMF (20 mL) was added $TMSCF_3$ (1330 µL, 9.00 mmol) and K_2CO_3 (83 mg, 0.6 mmol). After stirring at room temperature for 48 hours, H_2O was added (40 mL) and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude TMS ether was hydrolysed by adding THF (20 mL) and 1M HCl (20 mL). After stirring at room temperature for 18 hours, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / n-Hexane 15:85) to yield **6d** as a yellow oil (751 mg,

65%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.52 - 7.41 (m, 2H), 7.16 - 7.05 (m, 2H), 5.09 - 4.96 (m, 1H), 2.55 (d, ^{3}J = 4.0 Hz, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -78.6 (s, 3F), -111.8 (s, 1F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 163.6 (d, $^{1}J_{CF}$ = 248.2 Hz), 129.9, 129.5 (d, $^{3}J_{CF}$ = 8.3 Hz), 124.3 (q, $^{1}J_{CF}$ = 282.2 Hz), 115.8 (d, $^{2}J_{CF}$ = 21.6 Hz), 72.3 (q, $^{2}J_{CF}$ = 32.6 Hz), HPLC retention time: 6.02 min. Synthesis and analysis of this compound is described previously by Xu et al.[34]

2,2,2-trifluoro-1-(4-nitrophenyl)ethanol (6e):

To a solution of 4-nitrobenzaldehyde (453 mg, 3 mmol) in DMF (3 mL) was added $TMSCF_3$ (665 µL, 4.50 mmol) and K_2CO_3 (41 mg, 0.3 mmol). After stirring at room temperature for 4 hours, H_2O was added (40 mL) and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude TMS ether was hydrolysed by adding THF (3 mL) and 1M HCl (3 mL). After stirring at room temperature for 2 hours, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / n-Hexane 15:85) to yield **6e** as a yellow oil (313 mg, 47%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.38 - 8.27 (m, 2H), 7.75 (d, J = 8.8 Hz), 5.23 (q, J = 6.4 Hz); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -78.2 (s, 3F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 148.8, 140.5, 128.6, 123.9 (q, $^{1}J_{CF}$ = 282.2 Hz), 123.8, 72.0 (q, $^{2}J_{CF}$ = 32.6 Hz), HPLC retention time: 5.95 min. Synthesis and analysis of this compound is described previously by Xu et al.[34]

2,2,2-trifluoro-1-(3-nitrophenyl)ethanol (6f):

To a solution of 3-nitrobenzaldehyde (151 mg, 1.00 mmol) in DMF (3 mL) was added $TMSCF_3$ (222 µL, 1.50 mmol) and K_2CO_3 (14 mg, 0.10 mmol). After stirring at room temperature for 1 hour, TBAF (3 mL, 1M in THF, 3 mmol) was added to hydrolyse the intermediate TMS ether. After stirring at room temperature for 25 minutes, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / n-Hexane 1:4) to yield **6f** as a yellow oil (103 mg, 47%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.39 (s, 1H), 8.33 - 8.22 (m, 1H), 7.89 - 7.80 (m, 1H), 7.62 (t, J = 8.1 Hz, 1H), 5.19 (q, J = 6.4 Hz, 1H), 2.83 (s, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -78.4 (s, 3F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 148.4, 136.2, 133.7, 129.8, 124.5, 124.0 (q, $^{1}J_{CF}$ = 282.7 Hz), 122.7, 71.8 (q, $^{2}J_{CF}$ = 32.2 Hz), HPLC retention time: 6.02 min. Synthesis and analysis of this compound is described previously by Prakash et al.[35]

2,2,2-trifluoro-1-(4-(tert-butoxy)phenyl)ethanol (8):

To a solution of 4-(tert-butoxy)benzaldehyde (178 mg, 1 mmol) in DMF (3 mL) was added $TMSCF_3$ (443 µL, 3.00 mmol) and K_2CO_3 (28 mg, 0.2 mmol). After stirring at room temperature for 22 hours, H_2O was added (20 mL) and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 30 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude TMS ether was hydrolysed by adding THF (3 mL) and 1M HCl (3 mL). After stirring at room temperature for 18 hours, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / n-Hexane 1:9) to yield **8** as white crystals (75 mg, 30%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.40 - 7.31 (m, 2H), 7.10 - 6.92 (m, 2H), 5.04 - 4.91 (m, 1H), 2.57 (d, ^3J = 4.4 Hz, 1H), 1.36 (s, 9H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -78.4 (s, 3F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 156.3, 129.0, 128.2, 124.0, 124.4 (q, $^1J_{CF}$ = 281.7 Hz), 79.2, 72.5 (q, $^2J_{CF}$ = 31.7 Hz), 28.8, HPLC retention time: 8.73 min.

3.5 References

1 J. S. Fowler and A. P. Wolf, *Acc. Chem. Res.*, 1997, **30**, 181-188.

2 M. E. Phelps, *Proc. Natl. Acad. Sci. USA*, 2000, **97**, 9226-9233.

3 J. S. Fowler, Y. Ding and N. D. Volkow, *Semin. Nucl. Med.*, 2003, **33**, 14-27.

4 J. K. Willmann, N. van Bruggen, L. M. Dinkelborg and S. S. Gambhir, *Nat. Rev. Drug. Discov.*, 2008, **7**, 591-607.

5 M. P. S. Dunphy and J. S. Lewis, *J. Nucl. Med.*, 2009, **50**, 106S-121S.

6 S. Vallabhajosula, *Molecular Imaging: Radiopharmaceuticals for PET and SPECT*, Springer-Verlag, Berlin Heidelberg, 2009;

7 S. Vallabhajosula, L. Solnes and B. Vallabhajosula, *Semin. Nucl. Med.*, 2011, **41**, 246-264.

8 P. W. Miller, N. J. Long, R. Vilar and A. D. Gee, *Angew. Chem. Int. ed.*, 2008, **47**, 8998-9033.

9 S. M. Ametamey, M. Honer and P. A. Schubiger, *Chem. Rev.*, 2008, **108**, 1501-1516.

10 L. Cai, S. Lu and V. W. Pike, *Eur. J. Org. Chem.*, 2008, 2853-2873.

11 H. H. Coenen, P. H. Elsinga, R. Iwata, M. R. Kilbourn, M. R. A. Pillai, M. G. R. Rajan, H. N. Wagner Jr. and J. J. Zaknun, *Nucl. Med. Biol.*, 2010, **37**, 727-740.

12 R. Littich and P. J. H. Scott, *Angew. Chem. Int. Ed.*, 2012, **51**, 1106-1109.

13 H. L. Yale, *J. Med. Pharmaceut. Ch.*, 1959, **1**, 121-133.

14 S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.*, 2007, **37**, 320-330.

15 M. R. Kilbourn, M. R. Pavia and V. E. Gregor, *Appl. Radiat. Isot.*, 1990, **41**, 823-828.

16 M. K. Das and J. Mukherjee, *Appl. Radiat. Isot.*, 1993, **44**, 835-842.

17 P. Johnström and S. Stone-Elander, *J. Labelled Comp. Rad.*, 1995, **39**, 537-548.

18 J. Prabhakaran, M. D. Underwood, R. V. Parsey, V. Arango, V. J. Majo, N. R. Simpson, R. van Heertum, J. J. Mann and J. S. D. Kumar, *Bioorg. Med. Chem.*, 2007, **15**, 1802-1807.

19 M. Suehiro, G. Yang, G. Torchon, E. Ackerstaff, J. Humm, J. Koutcher and O. Ouerfelli, *Bioorg. Med. Chem.*, 2011, **19**, 2287-2297.

20 P. J. Riss and F. I. Aigbirhio, *Chem. Commun.*, 2011, **47**, 11873-11875.

21 P. J. Riss, V. Ferrari, L. Brichard, P. Burke, R. Smith, F. I. Aigbirhio, *Org. Biomol. Chem.*, 2012, **10**, 6980-6986.

22 J. Russel and N. Roques, *Tetrahedron*, 1998, **54**, 13771-13782.

23 B. Folléas, I. Marek, J-F. Normant and L. Saint-Jalmes, *Tetrahedron*, 2000, 56, 85 275-283.

24 G. K. S. Prakash, C. Panja, H. Vaghoo, V. Surampudi, R. Kultyshev, M. Mandal, G. Ra-sul, T. Mathew and G. A. Olah, *J. Org. Chem.*, 2006, **71**, 6806-6813.

25 J. R. White, G. J. Price, P. K. Plucinski and C. G. Frost, *Tetrahedron Lett.*, 2009, **50**, 7365-7368.

26 K. Liu and M. Kuo, *Tetrahedron Lett.*, 1985, **26**, 355-358.

27 S. K. Dayal, S. Ehrenson and R. W. Taft, *J. Am. Chem. Soc.*, 1972, **94**, 9113-9122.

28 G. K. S. Prakash, J. Hu and G. A. Olah, *Org. Lett.*, 2003, **5**, 3253-3256.

29 T. L. Amyes, I. W. Stevens and J. P. Richard, *J. Org. Chem.*, 1993, **58**, 6057-6066.

30 S. Mizuta, N. Shibata, S. Akiti, H. Fujimoto, S. Nakamura and T. Toru, *Org. Lett.*, 2007, **9**, 3707-3710.

31 J. J. Song, Z. Tan, J. T. Reeves, F. Gallou, N. K. Yee and C. H. Senanayake, *Org. Lett.*, 2005, **7**, 2193-2196.

32 M. Shi, X. Liu, Y. Guo and W. Zhang, *Tetrahedron*, 2007, **63**, 12731-12734.

33 N. Miyake and T. Kitazume, *J. Fluorine. Chem*, 2003, **122**, 243-246.

34 Q. Xu, H. Zhou, X. Geng and P. Chen, *Tetrahedron*, 2009, **65**, 2232-2238.

35 G. K. S. Prakash, F. Paknia, T. Mathew, G. Mlostoń, J. P. Joschek and G. A. Olah, *Org. Lett.*, 2011, **13**, 3-6.

4

A universal procedure for the [^{18}F]trifluoromethylation of aryl iodides and aryl boronic acids with highly improved specific activity

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Herein, we describe a valuable method for the introduction of the [^{18}F]CF_3 group into arenes with highly improved specific activity by the reaction of [^{18}F]trifluoromethane with aryl iodides or aryl boronic acids. This [^{18}F]trifluoromethylation reaction is the first to be described in which the [^{18}F]CF_3 products are generated in actual trace amounts and can therefore effectively be used as PET tracers. The method shows broad scope with respect to possible aryl iodide and aryl boronic acid substrates, as well as good to excellent conversion. In particular, the [^{18}F]trifluoromethylation of boronic acids was found to outperform [^{18}F]trifluoromethylation reactions of halogenated aryl precursors with regard to conversion, reaction conditions, and kinetics.

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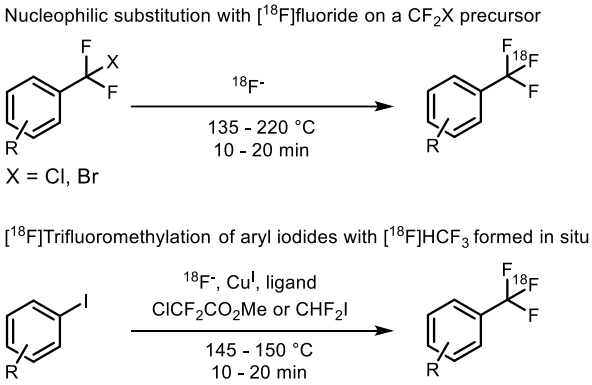
4.1 Introduction

Positron emission tomography (PET) is a non-invasive molecular-imaging technique for the visualization of human physiology by the use of biomarkers labelled with a positron emitting radionuclide.[1] As only trace amounts of a radiolabelled biomarker are required for the emission of enough positrons for a PET scan, PET is a very valuable technique for the imaging of low-density biological targets without inducing any biological effects. Therefore, PET has proven to be an excellent diagnostic tool in all areas of medicine and is frequently used to detect, characterise, and monitor cancer as well as neuro-degenerative and cardiovascular diseases; it can even lead to diagnosis well before structural changes or symptoms occur.[2-8] Furthermore, PET imaging is of added value in drug-discovery and drug-development programs.[9-11]

Among the various positron-emitting isotopes available, fluorine-18 is most commonly used. Fluorine-18 has a relatively low positron energy (E_{max} = 634 keV) and is readily produced with a low-energy cyclotron. This characteristic, in combination with a half-life of 110 min, makes fluorine-18 perfectly suited for introduction in small-molecule PET radiopharmaceuticals. Still, short synthesis times are required, and for optimal utilization, the introduction of fluorine-18 and subsequent purification, formulation, and quality control of the ^{18}F-labelled PET radiopharmaceutical has to be completed within 2 h. Consequently, there is an increasing demand for new robust, reliable, and rapid radiochemical synthetic methodology for the late-stage introduction of fluorine-18 into radiopharmaceuticals. Of particular interest are methods that utilise [^{18}F]fluoride, as this reagent is obtained by the ^{18}O(p,n)^{18}F nuclear reaction in high yields and is commercially available.[12-15]

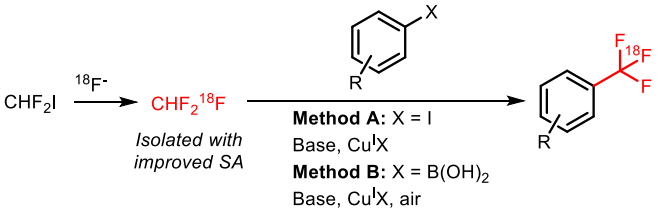
The CF_3 group is a popular functional group in many active pharmaceutical ingredients (APIs) and/or drug candidates, because it improves binding selectivity, lipophilicity, and metabolic stability.[16-18] Efficient methodology to introduce ^{18}F-labelled CF_3 groups into such compounds makes them useful as potential PET tracers. Today, only a few methods are available for the radiolabeling of trifluoromethyl arenes with [^{18}F]fluoride (Scheme 1). These methods can be divided into two categories: the direct treatment of [^{18}F]fluoride with a precursor of the type $ArCF_2X$,[19-22] and the introduction of a [^{18}F]CF_3 group by the treatment of an aryl iodide with [^{18}F]$CuCF_3$ formed *in situ*.[23-25] Both approaches require harsh reaction conditions and long reaction times. Furthermore, the labelled products are not suitable as PET tracers. Owing to degradation of the RCF_2X ($ArCF_2X$, HCF_2I, $COOMeCF_2I$) precursors, not only radioactive ^{18}F, but also mass amounts of ^{19}F are incorporated into the products. In radiochemistry, the ratio of ^{18}F over the total mass of the product is expressed as the specific activity (SA) in GBq/µmol. The reported specific activities of 100–139 MBq/µmol for methods based on

the use of [^{18}F]$CuCF_3$ make these products unsuitable for the imaging of low-density biological targets.[26]



Scheme 1 Reported methods for the synthesis of [^{18}F]trifluoromethyl arenes.

Recently, we reported the synthesis of [^{18}F]HCF_3 and its application as a labelling agent for the [^{18}F]trifluoromethylation of aldehydes and ketones.[27] To further extend the application of [^{18}F]HCF_3, we focused on broadening the scope of the reaction by exploring the labelling of aryl iodides and aryl boronic acids. To make the products useful for PET imaging, we also investigated the synthesis of [^{18}F]HCF_3 with an improved SA. We suspect that all [^{18}F]trifluoromethylation products derived from [^{18}F]HCF_3 with an improved SA will also be obtained with an improved SA. Herein we report the broad applicability of [^{18}F]HCF_3 as a labelling agent with improved SA for the aromatic [^{18}F]trifluoromethylation of aryl iodides and aryl boronic acids (Scheme 2).

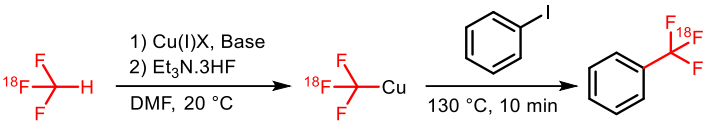


Scheme 2 Our strategy for [^{18}F]trifluoromethylation by the use of [^{18}F]HCF_3 with highly improved specific activity as a versatile labeling agent.

4.2 Results and discussion

First, we focused on the [^{18}F]trifluoromethylation of aryl iodides by using iodobenzene as a model substrate. Initial experiments with various strong bases and CuI sources did not lead to satisfactory yields of the desired [^{18}F](trifluoromethyl)benzene, and decomposition of [^{18}F]$CuCF_3$ to [^{18}F]fluoride was observed.[28] However, the addition of $Et_3N{\cdot}3HF$ to the solution was found to stabilise the $CuCF_3$ species owing to precipitation of the K^+ cation as KF(s), as was reported by Zanardi et al.[29] With this approach, we obtained [^{18}F]trifluoromethylbenzene in satisfactory yields (Table 1). The formation of [^{18}F]$CuCF_3$ and subsequent stabilization with $Et_3N{\cdot}3HF$ was completed in just 2 min at room temperature.

Table 1 Optimization of the [^{18}F]trifluoromethylation of iodobenzene.[a]



Entry	Base	Cu^I source	Cu^I [mM]	Ratio[b]	t [min]	Conversion [%] (*n* = 3)
1	KO*t*Bu	Cu^{I}Cl	20	1:3:1	10	48 ± 3
2	KO*t*Bu	Cu^{I}Br	20	1:3:1	10	56 ± 3
3	KO*t*Bu	Cu^{I}I	20	1:3:1	10	57 ± 3
4	NaO*t*Bu	Cu^{I}Br	20	1:3:1	10	3 ± 3
5	KHMDS	Cu^{I}Br	20	1:3:1	10	12 ± 5
6	KO*t*Bu	Cu^{I}Br	20	1:3:0.5	10	4 ± 2
7	KO*t*Bu	Cu^{I}Br	20	1:3:1.5	10	46 ± 3
8	KO*t*Bu	Cu^{I}Br	40	1:3:1	10	34 ± 2
9	KO*t*Bu	Cu^{I}Br	10	1:3:1	10	61 ± 2
10	KO*t*Bu	Cu^{I}Br	10	1:3:1	5	32 ± 5

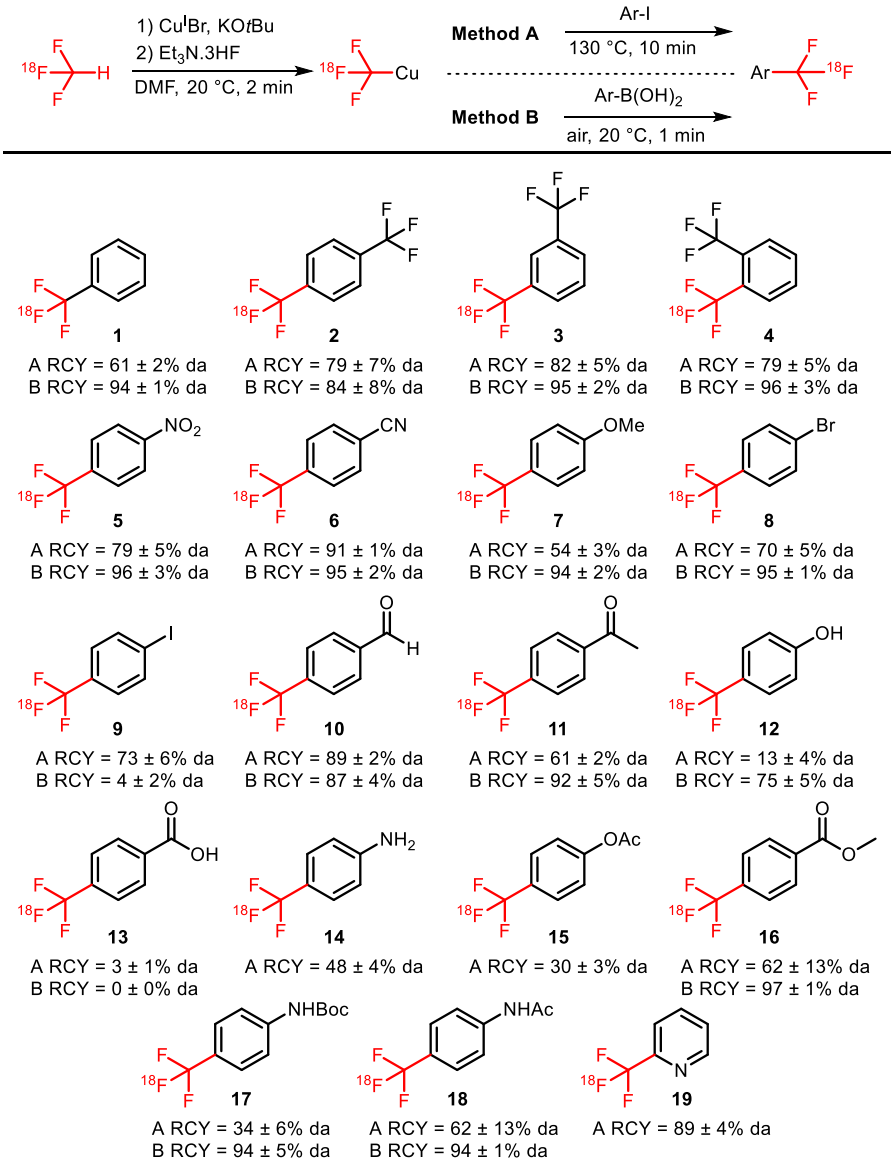
[a]Standard reaction conditions: [^{18}F]$CuCF_3$ formation at 20 °C for 1 min; $Et_3N{\cdot}3HF$ stabilization at 20 °C for 5 min; [^{18}F]trifluoromethylation at 130 °C; DMF (0.5 mL). [b]Cu^{I}X/base/$Et_3N{\cdot}3HF$ ratio. DMF = *N,N*-dimethylformamide, HMDS = hexamethyldisilazide.

Optimal [^{18}F]trifluoromethylation of iodobenzene proceeded at 130 °C in DMF in 10 min in the presence of Cu^{I}Br, KO*t*Bu, and $Et_3N{\cdot}3HF$ in a molar ratio of 1:3:1 and with a total Cu^{I}Br concentration of 10 mm. Various other CuI sources can also be used (Table 1, entries 1–3). Of the various bases, however, only KO*t*Bu led to good conversion (Table 1,

entries 4 and 5), when used in 3 molar excess relative to the amount of Cu^{I}Br. For the stabilization of the formed [^{18}F]CuCF$_3$, all K$^+$ ions had to react with Et$_3$N·3HF; thus, relative to KO*t*Bu, 1 equivalent of HF, which corresponds to 0.33 equivalents of Et$_3$N·3HF, had to be present in the reaction mixture. A decrease in the amount of Et$_3$N·3HF led to a drastic reduction in conversion into the product (Table 1, entry 6). We also found that the total concentration of the Cu^{I}Br, KO*t*Bu, and HF reagents is quite important. Higher concentrations of these reagents led to lower conversion (Table 1, entry 8).

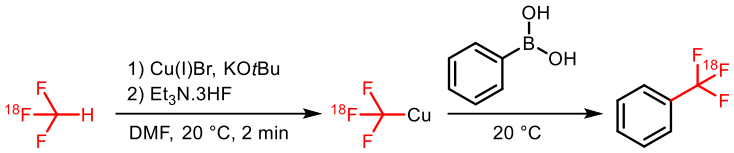
Having optimised the reaction conditions for the [^{18}F]trifluoromethylation of aryl iodides, we turned our attention to the scope of this reaction (Scheme 3). A broad range of aryl iodides could be converted successfully into the desired [^{18}F]trifluoromethyl arenes. From Scheme 3, it becomes clear that electronic effects do not have a large impact, and a wide array of functional groups in the precursor structure are compatible with the reaction. Even more interesting is that both 4-iodobenzaldehyde and 4-iodoacetophenone are exclusively converted into the [^{18}F]ArCF$_3$ products **10** and **11**, with no [^{18}F]trifluorocarbinol formation observed. Trifluorocarbinols are known to be formed by the reaction of the trifluoromethyl anion with aldehydes and ketones.[27,30-32] However, as we did not observe any [^{18}F]trifluorocarbinol side products, we can conclude that no sources of the [^{18}F]CF$_3$ anion were present in the reaction mixture. Unprotected alcohols and carboxylic acids were found to be incompatible with our method. The use of unprotected aniline, however, did lead to product formation with good conversion.

To further extend the application of [^{18}F]HCF$_3$ as a labelling agent, we investigated the oxidative [^{18}F]trifluoromethylation of boronic acids (Table 2).[33] The required [^{18}F]Cu^{I}CF$_3$ reagent was prepared as described for the [^{18}F]trifluoromethylation of aryl iodides. Next, [^{18}F]Cu^{I}CF$_3$ was oxidised to [^{18}F]Cu^{II}CF$_3$ in the presence of the boronic acid precursor by purging the reaction mixture with air during the first minute of the reaction. Oxidation with air is required, as only a low conversion was found when the reaction mixture was not purged with air (Table 2, entry 1). The preparation of [^{18}F]trifluoromethyl arenes by using boronic acid substrates led to some major improvements over the [^{18}F]trifluoromethylation of aryl iodides, thus making this method more appropriate for the synthesis of PET radiopharmaceuticals.



Scheme 3 Scope of the [^{18}F]trifluoromethylation of aryl iodides and aryl boronic acids. Standard reaction conditions: [^{18}F]$CuCF_3$ formation: 1) Cu^{I}Br (5 µmol), KO*t*Bu (15 µmol), DMF, 20 °C, 1 min; 2) $Et_3N{\cdot}3HF$ (5 µmol), 20 °C, 1 min; method A: aryl iodide (100 µmol), 130 °C, 10 min; method B: aryl boronic acid (50 µmol), air (10 mL), 20 °C, 10 min. Boc = *tert*-butoxycarbonyl. All radiochemical yields are determined by analytical HPLC (*n* = 3).

Table 2 Optimization of the [^{18}F]trifluoromethylation of phenylboronic acid.[a]

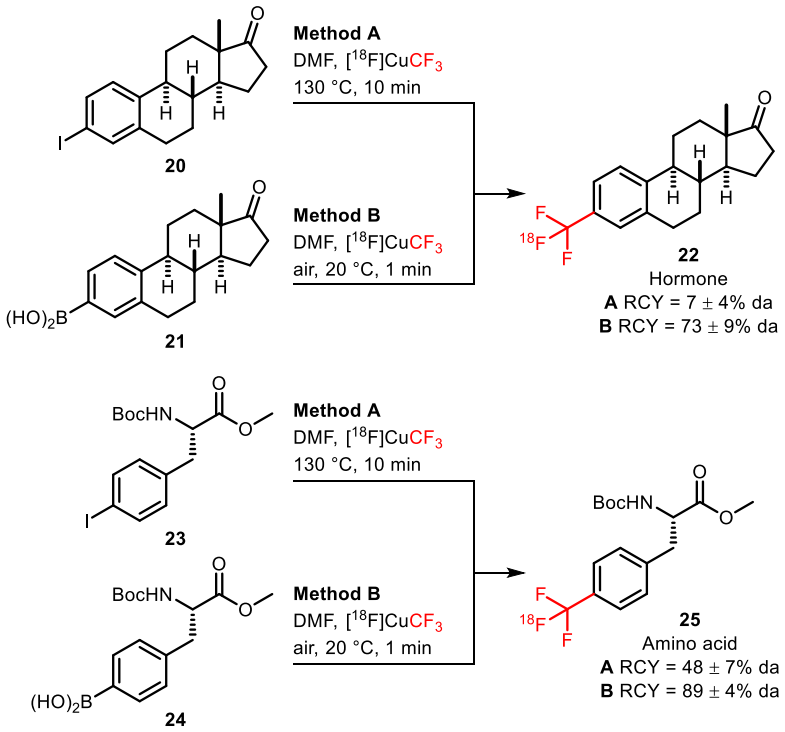


Entry	Phenylboronic acid [µmol]	Air [mL]	t [min]	Conversion [%] (*n* = 3)
1	100	0	10	19 ± 22
2	100	0.5	10	62 ± 19
3	100	5	10	87 ± 8
4	50	5	10	94 ± 1
5	20	5	10	55 ± 17
6	10	5	10	4 ± 5
7	50	5	1	85 ± 10
8	50	10	1	94 ± 1

[a]Standard reaction conditions: Cu^{I}Br (5 µmol), KO*t*Bu (15 µmol), $Et_3N{\cdot}3HF$ (5 µmol), DMF (0.5 mL); [^{18}F]$CuCF_3$ formation at 20 °C for 1 min; $Et_3N{\cdot}3HF$ stabilization at 20 °C for 1 min; [^{18}F]trifluoromethylation at 20 °C.

Significant advantages over the [^{18}F]trifluoromethylation of aryl iodides are the reduction in the amount of the precursor required from 100 to 50 µmol (Table 2, entries 3–6), the completion of the synthesis in just 1 min instead of 10 min (Table 2, entries 7 and 8), and a reaction temperature of 20 °C instead of 130 °C. All in all, these conditions result in less degradation of the precursor. In general, an improved substrate scope of the reaction and higher conversion were observed when boronic acids were used instead of aryl iodide precursors (Scheme 3). Again, electronic effects did not have a large impact on conversion into the product, and the reaction of boronic acids with an aldehyde or ketone functionality only led to the [^{18}F]$ArCF_3$ products **10** and **11**. From the boronic acid precursor, even the unprotected [^{18}F]trifluoromethylated phenol **12** could be formed; thus, acetyl protection of phenol groups is not required. The reaction to form aniline **14** could unfortunately not be investigated owing to the unsuccessful synthesis of the boronic acid precursor; however, the N-Boc-protected aniline **17** and phenylamide **18** were formed with excellent conversion. Carboxylic acid **13** could not be formed: Protection of the acid group was required. The low conversion in the formation of iodide **9** was attributed to the poor solubility of 4-iodophenylboronic acid in DMF.

To prove the applicability of this method for the synthesis of PET radiopharmaceuticals, we synthesised the [^{18}F]trifluoromethyl-substituted estrone derivative **22** as well as the Boc- and OMe-protected [^{18}F]4-trifluoromethylphenylalanine **25** (Scheme 4). Both products are radiopharmaceuticals of interest for PET. Estrone has a high binding affinity for the estrogen receptor, and this [^{18}F]trifluoromethylestrone derivative is therefore a potentially useful tracer for the imaging of overexpression of the estrogen receptor in breast cancer. This type of cancer relies on estrogen hormones for growth. If overexpression is found by the use of PET, a hormone-suppression treatment could be started.[34-35] Radiolabelled amino acids, including [^{18}F]4-fluorophenylalanine, have found their application in the imaging of upregulated amino acid incorporation by various types of cancer cells. Methods for the synthesis of [^{18}F]fluoro-substituted phenylalanine, however, are impractical, as they require multistep synthetic routes and/or electrophilic labelling methods.



Scheme 4 Synthesis of the [^{18}F]trifluoromethyl-substituted estrone derivative **22** and Boc/OMe-protected [^{18}F]4-trifluoromethylphenylalanine **25**.

For both estrone and phenylalanine, direct instalment of the fluorine-18 isotope at the aromatic ring by nucleophilic substitution with [^{18}F]fluoride is not possible owing to

the high electron density of the aromatic systems. However, as [^{18}F]trifluoromethylation is barely affected by electronic effects, we reasoned that it should be possible to install the [^{18}F]CF_3 group at the aromatic ring in these compounds. As anticipated, both the [^{18}F]trifluoromethylation of aryl iodides **20** and **23** and the oxidative [^{18}F]trifluoromethylation of boronic acids **21** and **24** led to the desired products. In particular when the boronic acids were used as the starting material, we observed excellent conversion in just 1 min at 20 °C.

Next, we investigated the specific activity (SA) of the products obtained by the method described herein. The initial measured SA of [^{18}F]1-trifluoromethyl-4-nitrobenzene, obtained by the [^{18}F]trifluoromethylation of 1-iodo-4-nitrobenzene, was approximately 1 GBq/µmol. As CHF_2I in the first step towards [^{18}F]HCF_3 is probably the major source of ^{19}F, we investigated the reduction of the amount of CHF_2I used. Indeed, a decrease in the CHF_2I amount from 40 to 1 µmol and an increase in the reaction temperature to 130 °C led to the formation of [^{18}F]1-trifluoromethyl-4-nitrobenzene with specific activities ranging from 22 to 32 GBq/µmol. This method did lead to the formation of less [^{18}F]HCF_3, but it was still obtained in an acceptable yield of 36 ± 7%.

The presence of $Et_3N{\cdot}3HF$ in the next reaction could theoretically reduce the SA of the obtained reaction product through ^{19}F/^{18}F isotopic exchange. We showed by the application of a single batch of [^{18}F]HCF_3 for three reactions with 1-iodo-4-nitrobenzene, 4-nitrophenylboronic acid, and benzophenone that the SA of all three obtained products was the same (see the Supporting Information for details). Since in the reaction of benzophenone with [^{18}F]HCF_3 no addition of $Et_3N{\cdot}3HF$ is required, we thus proved indirectly that no ^{19}F/^{18}F isotopic exchange occurs during the reaction of [^{18}F]HCF_3 with 1-iodo-4-nitrobenzene and 4-nitrophenylboronic acid. We can safely assume that the SA of the reaction products is determined by the SA of [^{18}F]HCF_3, and this reagent could be applied broadly to obtain [^{18}F]CF_3-labelled compounds with improved SA. From all combined experiments we found a SA of 27 ± 8 GBq/µmol for [^{18}F]HCF_3 and thus a SA of 25 ± 7 GBq/µmol for the reaction products after a reaction time of 15 min. We did observe a decrease in the yield of the reactions of [^{18}F]HCF_3 of improved SA with 1-iodo-4-nitrobenzene (60 ± 12% (n=6)) and 4-nitrophenylboronic acid (65 ± 4% (n=2)). This yield decrease might be caused by unfavourable reaction kinetics due to the lower amounts of HCF_3 present in the reaction mixture; however, more evidence is required to support this finding.

4.3 Conclusions

In summary, [^{18}F]HCF_3 was found to be an excellent labelling agent for the [^{18}F]trifluoromethylation of aryl iodides and aryl boronic acids with strongly improved specific activities under mild reaction conditions. As the -CF_3 group is a common moiety

in drug candidates and active pharmaceutical ingredients, we expect that this methodology will be widely applied in the synthesis of fluorine-18 labelled PET tracers.

4.4 Materials and methods

4.4.1 General

Chemicals were purchased from Sigma-Aldrich, Acros and ABCR and used as received. Solvents were purchased from Biosolve and Sigma-Aldrich and were dried on activated 3Å molecular sieves. NMR spectra were recorded on Bruker Avance 250, Bruker Avance 400 and Bruker Avance 500 spectrometers at a temperature of 20 °C. Chemical shifts (δ) are given in ppm, internally referenced to residual solvent resonances for ^{1}H and ^{13}C (^{1}H: δ = 7.26 ppm, ^{13}C: δ = 77.16 ppm) and referenced to $CFCl_3$ as internal standard for ^{19}F (δ = 0.00 ppm). Coupling constants (*J*) are reported in units of hertz (Hz). The following abbreviations are used to describe multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br. s (broad singlet). NMR spectra of boronic acids were taken in DMSO-δ6 with added D_2O to prevent the formation of boronic acid trimers. Electrospray Ionisation (ESI) high-resolution mass spectrometry was carried out using a Bruker micrOTOF-Q instrument in positive or negative ion mode (capillary potential of 4500 V). Thin Layer Chromatography was performed using TLC plates from Merck (SiO_2, neutral kieselgel 60 on alumina with a 254 nm fluorescence indicator). Compounds on the TLC plate were visualised by UV light at 254 nm. Flash column chromatography was performed on a Büchi Sepacore® X10 flash system using silica packed cartridges. Analytical HPLC was done on a HPLC system consisting of a Jasco PU-1580 pump, a Jasco UV-2075 Plus UV/Vis detector set at a wavelength of 254 nm, a Scionex 51BP 51/2 NaI radioactivity detector, Raytest Gina data acquisition and control interface and a Grace Alltima™ C18 5u 250mm x 4.6mm or Agilent Zorbax Bonus-RP 5u 250mm x 4.6 mm column. Radioactivity was quantified with a Veenstra VDC-304 dose calibrator.

4.4.2 Production of [^{18}F]fluoride

[^{18}F]fluoride was produced by the $^{18}O(p,n)^{18}F$ nuclear reaction on an IBA Cyclone® 18/9 cyclotron using a $H_2{}^{18}O$ liquid target. After irradiation, the target water was passed through a Chromafix® 30-PS-HCO_3 ^{18}F separation cartridge to trap the [^{18}F]fluoride.

4.4.3 Synthesis of [^{18}F]trifluoromethane

Herein, two methods are described for the synthesis of [^{18}F]trifluoromethane. Method I should be chosen if a high specific activity is not required, as it gives [^{18}F]trifluoro-methane in a yield of 60% ± 15%, however with a specific activity of ~1 GBq/µmol (starting from 10 GBq of [^{18}F]fluoride). If a high specific activity is required, one should

choose method II, as it gives [^{18}F]trifluoromethane with a specific activity of 32 ± 7 GBq/µmol (starting from 31 GBq of [^{18}F]fluoride), however [^{18}F]trifluoro-methane is obtained in a lower yield of 34% ± 8%. In addition, lower amounts of Kryptofix $K_{2.2.2}$ and K_2CO_3 are used, requiring a modified protocol for the elution of [^{18}F]fluoride from the Chromafix® 30-PS-HCO_3 ^{18}F separation cartridge.

Method I - Low specific activity, high yield

A Chromafix® 30-PS-HCO_3 ^{18}F separation cartridge loaded with [^{18}F]fluoride was eluted using a solution of Kryptofix $K_{2.2.2}$ (13 mg) and K_2CO_3 (2 mg) in MeCN/H_2O (1 mL, ratio 9:1). The solution was dried under a stream of Helium and reduced pressure at 90 °C for 10 minutes during which residual water was removed by azeotropic co-evaporation using three portions of anhydrous MeCN (1 mL). Difluoroiodomethane (7.1 mg, 40 µmol) dissolved in MeCN (1 mL) was added to the dry [^{18}F]fluoride and was reacted at room temperature for 10 minutes. After the reaction time was over, the formed [^{18}F]trifluoromethane was purged out of the reaction mixture by bubbling helium through it with a flow of 10 mL/min for 3 minutes. The gaseous [^{18}F]trifluoromethane was led through a Waters Sep-Pak® Plus Silica cartridge to remove any volatile difluoro-iodomethane and was trapped in DMF (1 mL, -65 °C) in 60% ± 15% yield with a specific activity of ~1 GBq/µmol (starting from 10 GBq of [^{18}F]fluoride).

Method II - Improved specific activity

A Chromafix® 30-PS-HCO_3 ^{18}F separation cartridge loaded with [^{18}F]fluoride was eluted in reverse order to a reaction vessel using a solution of K_2CO_3 (0.2 mg) in water (0.5 mL) followed by a solution of Kryptofix $K_{2.2.2}$ (1.3 mg) in MeCN (0.5 mL). The solution was dried under a stream of Helium and reduced pressure at 90 °C for 10 minutes during which residual water was removed by azeotropic co-evaporation using three portions of anhydrous MeCN (1 mL). Difluoroiodomethane (0.18 mg, 1 µmol) dissolved in MeCN (1 mL) was added to the dry [^{18}F]fluoride and was reacted at room temperature for 10 minutes. After the reaction time was over, the formed [^{18}F]trifluoromethane was purged out of the reaction mixture by bubbling helium through it with a flow of 10 mL/min for 3 minutes. The gaseous [^{18}F]trifluoromethane was led through a Waters Sep-Pak® Plus Silica cartridge to remove any volatile difluoroiodomethane and was trapped in DMF (1 mL, -65 °C) in 34% ± 8% yield with a specific activity of 32 ± 7 GBq/µmol (starting from 31 GBq of [^{18}F]fluoride).

4.4.4 General procedure for the [^{18}F]trifluoromethylation of aryl iodides

A reaction vessel loaded with Cu(I)Br (0.7 mg, 5 µmol) was closed with a septum and purged with argon. *Via* the septum were subsequently added DMF (200 µL), [^{18}F]HCF_3 in

DMF (100 µL) and 0.3M KO*t*Bu in DMF (50 µL, 15 µmol) and this reaction mixture was kept at room temperature for 1 minute to form [^{18}F]$CuCF_3$, which was then stabilised by the addition of $Et_3N.3HF$ (0.82 µL, 5 µmol) in 50 µL DMF. After 1 minute at room temperature, the aryl iodide (100 µmol) in 100 µL DMF was added to the reaction mixture. After 10 minutes at 130 °C, the reaction mixture was quenched by addition of 500 µL water and cooled to room temperature.

4.4.5 General procedure for the [^{18}F]trifluoromethylation of arylboronic acids

A reaction vessel loaded with Cu(I)Br (0.7 mg, 5 µmol) was closed with a septum and purged with argon. *Via* the septum were subsequently added DMF (200 µL), [^{18}F]HCF_3 in DMF (100 µL) and 0.3M KO*t*Bu in DMF (50 µL, 15 µmol) and this reaction mixture was kept at room temperature for 1 minute to form [^{18}F]$CuCF_3$, which was then stabilised by the addition of $Et_3N.3HF$ (0.82 µL, 5 µmol) in 50 µL DMF. After 1 minute at room temperature, the arylboronic acid (50 µmol) in 100 µL DMF was added to the reaction mixture. During 1 minute at room temperature, air was bubbled through the reaction mixture, after which it was quenched by addition of 500 µL water.

4.4.6 Analysis of the [^{18}F]trifluoromethylation reactions

All the reactions were analysed by HPLC chromatography using a Grace Alltima™ C18 5u 250mm x 4.6mm column with various ratios of MeCN/H_2O/TFA (Table 3). Radioactive products were identified by comparison of the retention times of the radioactivity peak with the UV peak of co-injected non-radioactive reference. Within the HPLC system, the eluent passes first through the UV detector followed by the radioactivity detector, causing a 0.15 - 0.17 min difference between the UV and the radioactivity peaks which should be taken in account. Conversions can be calculated from the HPLC chromatographs, as no radioactive compounds (for example [^{18}F]fluoride) are retained to the Grace Alltima™ C18 column.

The HPLC retention times of both the references and radiolabelled products are shown in the table 3.

Table 3 HPLC retention times of references and radiolabelled products.

Compound Name	**^{19}F-Reference R_t (min)**	**^{18}F- Product R_t (min)**	**HPLC Eluens**
Benzotrifluoride	7.12	7.27	70:30:0.2 MeCN/H_2O/TFA
1,4-bis(trifluoromethyl)benzene	9.00	9.17	70:30:0.2 MeCN/H_2O/TFA
1,3-bis(trifluoromethyl)benzene	8.90	9.05	70:30:0.2 MeCN/H_2O/TFA
1,2-bis(trifluoromethyl)benzene	8.27	8.42	70:30:0.2 MeCN/H_2O/TFA
1-nitro-4-(trifluoromethyl)-benzene	5.58	5.73	70:30:0.2 MeCN/H_2O/TFA
1-methoxy-4-(trifluoromethyl)benzene	7.17	7.33	70:30:0.2 MeCN/H_2O/TFA
1-bromo-4-(trifluoromethyl)benzene	9.85	10.00	70:30:0.2 MeCN/H_2O/TFA
4-iodobenzotrifluoride	11.18	11.33	70:30:0.2 MeCN/H_2O/TFA
4-(trifluoromethyl)-benzaldehyde	12.17	12.33	50:50:0.2 MeCN/H_2O/TFA
4'-(trifluoromethyl)-acetophenone	13.35	13.52	50:50:0.2 MeCN/H_2O/TFA
4-(trifluoromethyl)phenol	23.68	23.78	35:65:0.2 MeCN/H_2O/TFA
4-(trifluoromethyl)benzoic acid	8.35	8.52	35:65:0.2 MeCN/H_2O/TFA
4-(trifluoromethyl)benzonitrile	5.72	5.88	70:30:0.2 MeCN/H_2O/TFA
4-(trifluoromethyl)aniline	6.05	6.20	50:50:0.2 MeCN/H_2O/TFA
4-(trifluoromethyl)phenyl acetate	14.75	14.92	50:50:0.2 MeCN/H_2O/TFA
4-(trifluoromethyl)benzoate	7.13	7.30	70:30:0.2 MeCN/H_2O/TFA
N-Boc-4-(trifluoromethyl)aniline	9.10	9.23	70:30:0.2 MeCN/H_2O/TFA
N-(4-(trifluoromethyl)-phenyl)acetamide	7.95	8.10	50:50:0.2 MeCN/H_2O/TFA
2-(trifluoromethyl)pyridine	7.18	7.33	50:50:0.2 MeCN/H_2O/TFA
3-deoxy-3-(trifluoromethyl)estrone	6.52	6.68	90:10:0.2 MeCN/H_2O/TFA
N-(tert-butoxycarbonyl)-4-(trifluoro-methyl)-L-phenylalanine methyl ester	7.23	7.40	70:30:0.2 MeCN/H_2O/TFA

4.4.7 Measurement of specific radioactivity

To measure the specific radioactivity, [^{18}F]trifluoromethane, synthesised *via* either method I or method II (Section 4.4.3), was reacted with 1-iodo-4-nitrobenzene using the general procedure for the [^{18}F]trifluoromethylation of aryl iodides (Section 4.4.4). The specific radioactivity of the [^{18}F]1-(trifluoromethyl)-4-nitrobenzene product was determined by HPLC. The amount of non-radioactive 1-(trifluoromethyl)-4-nitrobenzene in the reaction mixture was determined using analytical HPLC by measuring the UV peak area. A calibration curve was made in duplo by measuring 1-(trifluoromethyl)-4-nitrobenzene stock solutions at a wavelength of 254 nm. The amount of activity of [^{18}F]1-(trifluoromethyl)-4-nitrobenze injected on the HPLC was determined by collection of the product peak and subsequent measurement using a dose calibrator. The specific activity can then be calculated by dividing the collected [^{18}F]1-(trifluoromethyl)-4-nitrobenze activity in GBq by the amount of 1-(trifluoromethyl)-4-nitrobenzene in μmol. The specific activity of [^{18}F]1-(trifluoromethyl)-4-nitrobenze obtained by method I was <1 GBq/μmol (starting from 10 GBq of [^{18}F]fluoride) and the specific activity obtained by method II was 32 ± 7 GBq/μmol (starting from 31 GBq of [^{18}F]fluoride). Examples of data from determination of the specific activity of [^{18}F]1-(trifluoromethyl)-4-nitrobenzene using [^{18}F]HCF_3 produced using method I and method II are shown in Table 4 and Table 5.

Table 4 Example of specific activity determination of [^{18}F]1-(trifluoromethyl)-4-nitrobenzene synthesized using [^{18}F]HCF_3 produced via method I.

HPLC System	Zorbax Bonus RP 5 µm 4.6 x 250 mm; 2 mL/min, 35:65:0.2 MeCN/H_2O/TFA
Starting amount of [^{18}F]fluoride	8696 MBq
UV peak area	1511 mV*min
1-(Trifluoromethyl-4-nitrobenzene Amount injected	6.35 nmol
[^{18}F]1-(Trifluoromethyl)-4-nitrobenzene Activity injected	2.970 MBq (dc, end of synthesis)
[^{18}F]1-(Trifluoromethyl)-4-nitrobenzene Specific Activity	0.47 GBq/µmol

HPLC Chromatogram

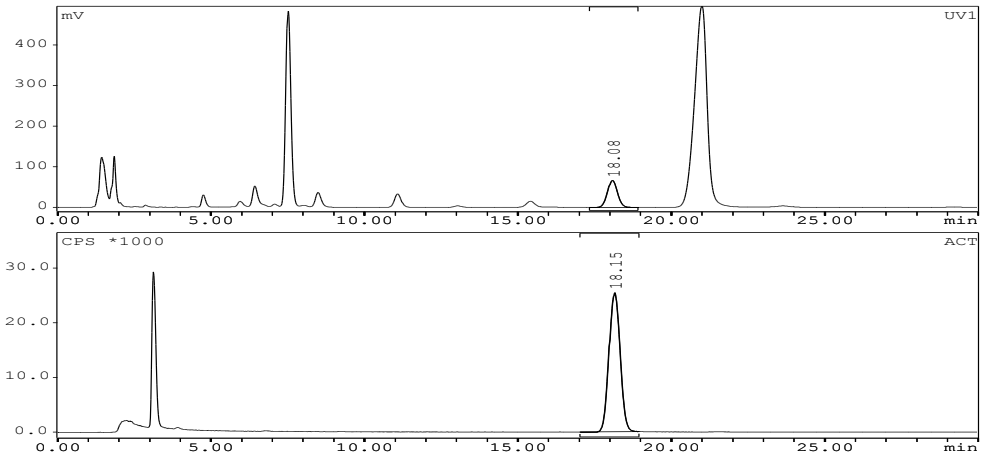
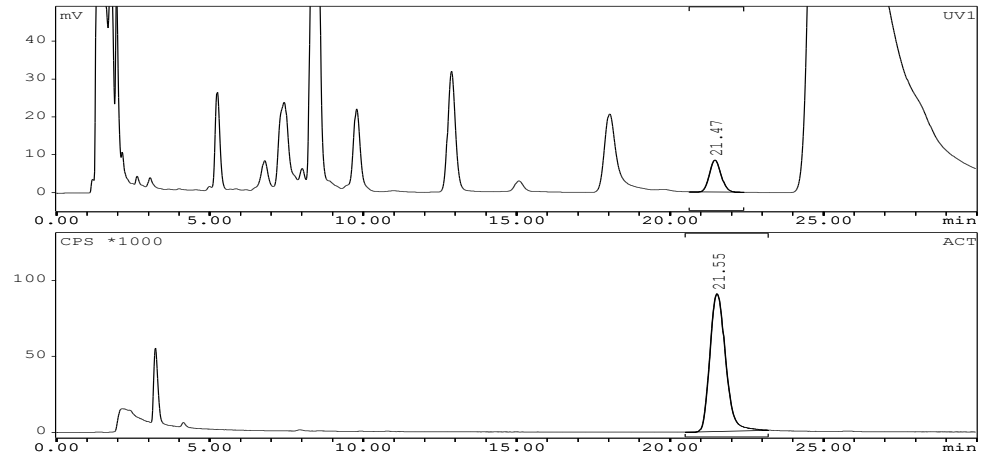


Table 5 Example of specific activity determination of [^{18}F]1-(trifluoromethyl)-4-nitrobenzene synthesized using [^{18}F]HCF_3 produced via method II.

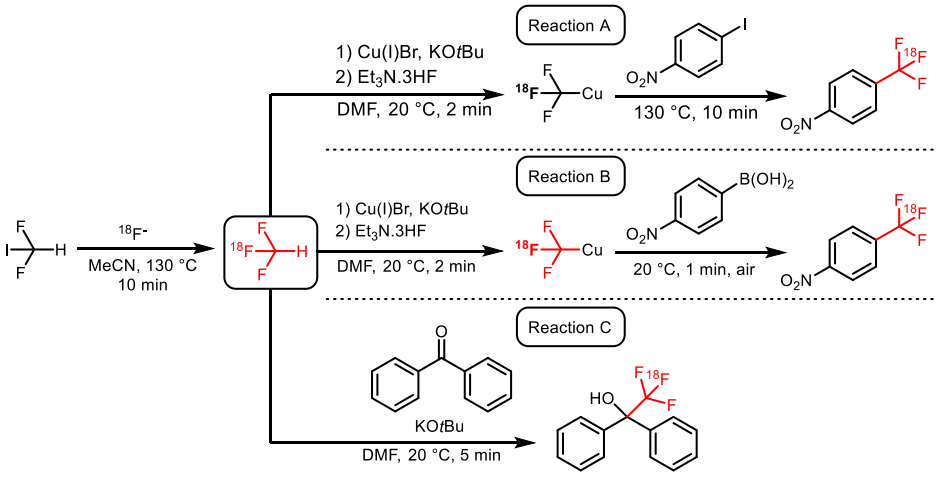
HPLC System	Zorbax Bonus RP 5 µm 4.6 x 250 mm; 2 mL/min, 35:65:0.2 MeCN/H_2O/TFA
Starting amount of [^{18}F]fluoride	31160 MBq
UV peak area	226.7 mV*min
1-(Trifluoromethyl-4-nitrobenzene Amount injected	0.95 nmol
[^{18}F]1-(Trifluoromethyl)-4-nitrobenzene Activity injected	29.33 MBq (dc, end of synthesis)
[^{18}F]1-(Trifluoromethyl)-4-nitrobenzene Specific Activity	28.0 GBq/µmol

HPLC Chromatogram



4.4.8 Reaction of [^{18}F]HCF$_3$ with 1-iodo-4-nitrobenzene, 4-nitrophenylboronic acid and benzophenone: comparison of specific activities

To show that after purification of [^{18}F]HCF$_3$ no ^{19}F is introduced in the subsequent trifluoromethylation reactions, we split up a single batch of [^{18}F]HCF$_3$ made *via* method II and let it react with 1-iodo-4-nitrobenzene (Reaction A), 4-nitrophenylboronic acid (Reaction B) and benzophenone (Reaction C)(Scheme 5). After the reactions, we measured the specific activities of the formed products (decay corrected to the end of synthesis of [^{18}F]HCF$_3$). The overall yield of [^{18}F]HCF$_3$, synthesised *via* method II, was 30%. The specific activity of [^{18}F]-trifluoromethyl-4-nitrobenzene was found to be 20.3 GBq/µmol when formed by reaction of [^{18}F]HCF$_3$ with 1-iodo-4-nitrobenzene (Reaction A) and 19.0 GBq/µmol when formed by reaction of [^{18}F]HCF$_3$ with 4-nitrophenylboronic acid (Reaction B). The reaction of [^{18}F]HCF$_3$ with benzophenone gave [^{18}F]2,2,2-trifluoro-1-diphenylethanol in a specific activity of 16.0 GBq/µmol (Reaction C).



Scheme 5 Reaction of [^{18}F]HCF$_3$; made via method II, with 1-iodo-4-nitrobenzene, 4-nitrophenylboronic acid and benzophenone for determination of the specific activity of the radiolaballed products.

The whole experiment was performed in duplicate. The data are shown in the Table 6. As can be seen in both experiments, the products of reaction A, B and C were formed with similar specific activity (corrected to the same time). In reaction C, the reaction with benzophenone, no sources of ^{19}F are present in the reaction mixture. In reactions A and B, Et$_3$N.3HF was added to stabilize the formed CuCF$_3$. This could lead to a reduction of the specific activity due to incorporation of ^{19}F originating from Et$_3$N.3HF. However, this did not occur since the specific activities of reaction A and B were not lower than the specific activity in reaction C. In the same way, the specific activities of all products

formed by the reaction of [^{18}F]HCF_3 with aryl iodides and arylboronic acids should reflect the specific activity of the synthesized [^{18}F]HCF_3.

Table 6 Specific activity determination of the reaction of [^{18}F]HCF_3 with 1-iodo-4-nitrobenzene, 4-nitrophenylboronic acid and benzophenone.

	Experiment I		Experiment II	
Synthesis of [^{18}F]HCF_3				
Amount of [^{18}F]fluoride	33 GBq	10:15	31 GBq	13:22
Amount of [^{18}F]HCF_3	9.8 GBq	10:57	6.2 GBq	14:10
Yield of [^{18}F]HCF_3	45%		30%	
Reaction A				
Amount of [^{18}F]HCF_3 used	1155 MBq	12:40	773 MBq	15:25
Reaction yield	58%		72%	
Specific activity reaction A	11.0 GBq/µmol	12:54	11.6 GBq/µmol	15:38
Specific activity at end of synthesis [^{18}F]HCF_3	23.0 GBq/µmol	10:57	20.3 GBq/µmol	14:10
Reaction B				
Amount of [^{18}F]HCF_3 used	2333 MBq	11:07	1584 MBq	14:14
Reaction yield	62%		68%	
Specific activity reaction B	20.5 GBq/µmol	11:00	17.9 GBq/µmol	14:19
Specific activity at end of synthesis [^{18}F]HCF_3	22.6 GBq/µmol	10:57	19.0 GBq/µmol	14:10
Reaction C				
Amount of [^{18}F]HCF_3 used	721 MBq	13:48	470 MBq	16:15
Reaction yield	99%		100%	
Specific activity reaction C	8.9 GBq/µmol	13:28	8.9 GBq/µmol	13:28
Specific activity at end of synthesis [^{18}F]HCF_3	23.0 GBq/µmol	10:57	16.0 GBq/µmol	10:57

4.4.9 Synthesis of precursors and reference compounds

1-Methoxy-4-(trifluoromethyl)benzene

To a solution of 4-(trifluoromethyl)phenol (595 mg, 3.67 mmol) in acetone (5 mL) was added K_2CO_3 (517 mg, 3.74 mmol) and CH_3I (0.32 mL, 5.14 mmol). The reaction mixture was stirred at room temperature for 24 hours, followed by concentration *in vacuo*. The residue was taken up in water (4 mL) and extracted with EtOAc (2 x 4 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (*n*-hexane) to afford 1-methoxy-4-(trifluoromethyl)benzene (585 mg, 3.32 mmol, 91% yield) as a colourless oil.

^{1}H NMR (500.23 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.5 Hz, 2H), 6.96 (d, *J* = 8.5 Hz, 2H), 3.85 (s, 3H); ^{13}C NMR (125.80 MHz, $CDCl_3$) δ 162.1, 127.0 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.6 (q, $J_{C\text{-}F}$ = 272.5 Hz), 123.0 (q, $J_{C\text{-}F}$ = 32.7 Hz), 114.1, 55.6; ^{19}F NMR (235.33 MHz, $CDCl_3$): δ = -62.0 (s, 3F). Spectral data match reported data in literature.[36,37]

***Tert*-butyl (4-iodophenyl)carbamate**

To a solution of 4-iodoaniline (5.00 g, 22.8 mmol) in THF was added di-tert-butyl dicarbonate (5.23 g, 24.0 mmol). Next, the reaction mixture was refluxed for 24 hours, subsequently cooled to room temperature and concentrated *in vacuo*. The residue was taken up in EtOAc (100 mL), washed with 0.5M aqueous citric acid (3 x 50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (gradient 100:0 - 95:5 *n*-hexane:EtOAc) to afford t-butyl(4-iodophenyl)carbamate (4.82 g, 15.1 mmol, 66% yield) as a white solid. ^{1}H NMR (500.23 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.9 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 6.45 (br. s, 1H), 1.51 (s, 9H); ^{13}C NMR (125.80 MHz, $CDCl_3$) δ 125.6, 138.3, 138.0, 120.5, 85.9, 81.1, 28.4; HRMS (ESI) calcd for $C_{11}H_{15}INO_2$ [M+H$^+$] 284.0887, found 284.0869.[38,39]

***Tert*-butyl (4-(trifluoromethyl)phenyl)carbamate**

To a reaction vessel were added 4-(trifluoromethyl)aniline (195 µL, 1.55 mmol), di-tert-butyl dicarbonate (356 mg, 1.63 mmol) and THF (5 mL). The reaction vessel was closed and stirred at 70 °C for 8 days. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The residue was taken up in EtOAc (5 mL), washed with 0.5M aqueous citric acid (3 x 5 mL) and brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (*n*-hexane, 0.1% Et_3N) to afford tert-butyl (4-(trifluoromethyl)phenyl)carbamate (349 mg, 1.34 mmol, 86%) as a white solid. ^{1}H NMR (500.23 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 6.64 (br. s, 1H), 1.53 (s, 9H); ^{13}C NMR (125.80 MHz, $CDCl_3$) δ 152.4, 141.6, 126.4 (q, $J_{C\text{-}F}$ = 3.6 Hz), 124.9 (q, $J_{C\text{-}F}$ = 32.7 Hz), 124.4 (q, $J_{C\text{-}F}$ = 271.6 Hz), 118.0, 81.4, 28.4; ^{19}F NMR (235.33 MHz, $CDCl_3$) δ -62.4 (s, 3F); HRMS (ESI) calcd for $C_{12}H_{14}F_3NNaO_2$ [M+H$^+$] 284.0869, found 284.0887. Spectral data match reported data in literature.[38,40]

4-Iodophenyl acetate

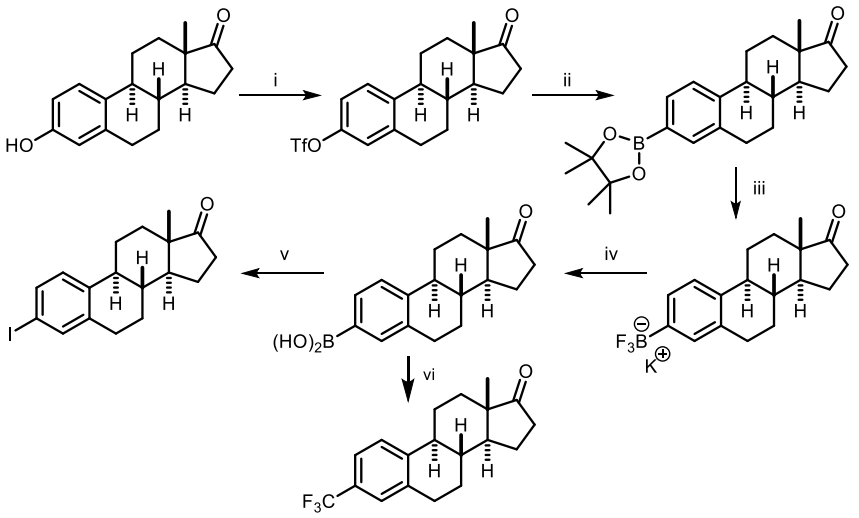
To a solution of 4-iodophenol (5 g, 22.7 mmol) in CH_2Cl_2 (100 mL) at 0 °C were added acetyl chloride (1.94 mL, 27.3 mmol) and Et_3N (4.75 mL, 34.1 mmol). The reaction mixture was stirred for 40 minutes at 0 °C, followed by 7 hours at room temperature and finally washed with water (100 mL). After drying of the organic layer over Na_2SO_4 and filtration, the solution was concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (gradient 100:0 – 96:4 *n*-hexane:EtOAc) to afford 4-

iodophenyl acetate (5.10 g, 19.5 mmol, 86% yield) as a white solid. ^{1}H NMR (500.23 MHz, $CDCl_3$) δ 7.68 (m, 2H), 6.86 (m, 2H), 2.29 (s, 3H); ^{13}C NMR (125.80 MHz, $CDCl_3$) δ 169.3, 150.6, 138.6, 123.9, 90.0, 21.3. Spectral data match reported data in literature.[41,42]

4-(Trifluoromethyl)phenyl acetate

To a solution of 4-(trifluoromethyl)phenol (150 mg, 0.93 mmol) in CH_2Cl_2 (5 mL) at 0 °C were added acetyl chloride (79 µL, 1.11 mmol) and Et_3N (387 µL, 2.78 mmol). The reaction mixture was stirred for 72 hours at 50 °C. After washing with water (5 mL), the solution was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (90:10 *n*-hexane:EtOAc) to afford 4-(trifluoromethyl)phenyl acetate (90 mg, 0.44 mmol, 48% yield) as a colorless oil. ^{1}H NMR (500.23 MHz, $CDCl_3$) δ 7.65 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 8.2 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (125.80 MHz, $CDCl_3$) δ 169.1, 153.2, 128.2 (q, $J_{C\text{-}F}$ = 32.7 Hz), 126.9 (q, $J_{C\text{-}F}$ = 3.6 Hz), 124.0 (q, $J_{C\text{-}F}$ = 272.5 Hz), 122.2, 21.3; ^{19}F NMR (235.33 MHz, $CDCl_3$) δ -62.8 (s, 3F). Spectral data match reported data in literature.[41,43]

Synthesis route towards 3-deoxyestrone-3-boronic acid, 3-deoxy-3-iodo-estrone and 3-deoxy-3-(trifluoromethyl)estrone



Scheme 6 Reagents (i) Tf_2O, Et_3N, CH_2Cl_2; (ii) $Pd(dppf)Cl_2$-CH_2Cl_2, HBPin, Et_3N, dioxane; (iii) KHF_2, H_2O, MeOH; (iv) TMSCl, H_2O, MeCN; (v) $Cu(NO_3)_2.2H_2O$, I_2, MeCN; (vi) CHF_3, Cu(I)Br, KO*t*Bu, $Et_3N.3HF$, air, DMF.

3-(Trifluoromethanesulfonyl)estrone

To a solution of estrone (2.00 g, 7.40 mmol) in CH_2Cl_2 (38 mL) were added triethylamine (2.06 mL, 14.8 mmol) and trifluoromethanesulfonic anhydride (1.38 mL, 8.14 mmol). The reaction mixture was stirred for 50 min at 0 °C, followed by the addition of aqueous sat. $NaHCO_3$ (40 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layers were washed with brine (80 mL) and dried over Na_2SO_4. After filtration and concentration *in vacuo*, the crude product was purified by silica gel column chromatography (gradient 100:0 - 25:75 *n*-hexane:EtOAc) to afford 3-(trifluoro-methanesulfonyl)estrone (2.85 g, 7.08 mmol, 96%) as a white solid. ^{1}H NMR (250.13 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.5 Hz, 1H), 7.07-6.97 (m, 2H), 2.98-2.89 (m, 2H), 2.60-1.91 (m, 7H), 1.70-1.38 (m, 6H), 0.92 (s, 3H). Spectral data match reported data in literature.[44]

3-Deoxyestrone-3-boronic acid pinacol ester

To a mixture of 3-(trifluoromethanesulfonyl)estrone (2.85 g, 7.08 mmol) and $Pd(dppf)Cl_2$-CH_2Cl_2 (0.29 g, 0.35 mmol) in dioxane (35 mL) under argon were added triethylamine (5.92 mL, 42.5 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.18 mL, 20.5 mmol). The reaction mixture was stirred at 100 °C for 24 hours, followed by cooling to room temperature and concentration *in vacuo*. The residue was purified by silica gel column chromatography (gradient 100:0 - 80:20 *n*-hexane:EtOAc) to afford 3-deoxyestrone-3-boronic acid pinacol ester (1.85 g, 4.86 mmol, 69%) as a white solid. ^{1}H NMR (250.13 MHz, $CDCl_3$) δ 7.63-7.55 (m, 2H), 7.32 (d, *J* = 7.6 Hz, 1H), 2.98-2.89 (m, 2H), 2.57-1.92 (m, 7H), 1.70-1.38 (m, 6H), 1.34 (s, 12H), 0.90 (s, 3H). Spectral data match reported data in literature.[45]

Potassium 3-deoxyestrone-3-trifluoroborate

To a solution of 3-deoxyestrone-3-boronic acid pinacol ester (1.85 g, 4.86 mmol) in methanol (40 mL) was added a solution of potassium hydrogen fluoride (2.12 g, 27.2 mmol) in water (20 mL). The reaction mixture was stirred at room temperature for 25 hours, followed by removal of most of the solvent by evaporation. The crude material was washed with hot acetone (50 °C, 3 x 50 mL). Drying under vacuum afforded potassium 3-deoxyestrone-3-trifluoroborate (1.19 g, 3.30 mmol, 97%) as a white solid, which was used without further purification. ^{1}H NMR (500.23 MHz, DMSO) δ 7.06 (d, *J* = 7.6 Hz, 1H), 7.01 (s, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 2.84-2.71 (m, 2H), 2.43 (dd, *J* = 18.9, 8.2 Hz, 1H), 2.38-2.30 (m, 1H), 2.24-2.14 (m, 1H), 2.13-2.02 (m, 1H), 2.00-1.90 (m, 2H), 1.80-1.71 (m, 1H), 1.62-1.44 (m, 3H), 1.43-1.28 (m, 3H), 0.83 (s, 3H); ^{13}C NMR (125.80 MHz, $CDCl_3$) δ 219.9, 135.7, 133.1, 132.2, 128.9, 122.9, 49.8, 47.4, 44.0, 38.1, 35.4, 31.5, 29.2, 26.5, 25.5, 21.2, 13.6, carbon directly bonded to boron was not observed, however with

$^{1}H,^{13}C$-HMBC NMR its resonance signal was found at 147.3 ppm; ^{19}F NMR (235.33 MHz, $CDCl_3$) δ -138.2 (s, 3F).[46]

3-Deoxyestrone-3-boronic acid

To a solution of potassium 3-deoxyestrone-3-trifluoroborate (1.15 g, 3.2 mmol) in acetonitrile (30 mL) were added water (173 µL, 9.59 mmol) and trimethylchlorosilane (1.23 mL, 9.59 mmol). After stirring for 1 hour at room temperature, the reaction was quenched by addition of sat. $NaHCO_3$ (5 mL). The excess water was removed by repeatedly drying over Na_2SO_4 and filtration. After the last filtration, the solution was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (75:25 *n*-hexane:acetone) to afford 3-deoxyestrone-3-boronic acid (677 mg, 2.27 mmol, 71%) as a white solid. ^{1}H NMR (500.23 MHz, DMSO + D_2O) δ 7.50 (d, *J* = 7.9 Hz, 1H), 7.47 (s, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 2.86-2.79 (m, 2H), 2.48-2.31 (m, 2H), 2.28-2.19 (m, 1H), 2.11-2.01 (m, 1H), 1.99-1.90 (m, 2H), 1.80-1.71 (m, 1H), 1.61-1.44 (m, 3H), 1.44-1.30 (m, 3H), 0.81 (s, 3H), $B(OH)_2$ not observed due to H-D exchange; ^{13}C NMR (125.80 MHz, $CDCl_3$) δ 220.6, 141.9, 135.3, 135.2, 131.8, 124.6, 50.0, 47.7, 44.3, 37.9, 35.7, 31.6, 29.2, 26.4, 25.5, 21.5, 13.8, carbon directly bonded to boron was not observed, however with $^{1}H,^{13}C$-HMBC NMR its resonance signal was found at 130.7 ppm; HRMS (ESI) calcd for $C_{18}H_{23}BNaO_3$ [M+Na$^+$] 321.1632, found 321.1641. Spectral data match reported data in literature.[45,46]

3-Deoxy-3-iodoestrone

To a reaction vial were added $Cu(NO_3)_2.2H_2O$ (32.4 mg, 0.134 mmol), iodine (170 mg, 0.671 mmol), 3-deoxyestrone-3-boronic acid (200 mg, 0.671 mmol) and acetonitrile (5 mL). The reaction vessel was stirred for 3 days at room temperature under an argon atmosphere. After addition of water (40 mL), the reaction was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were washed with 10% aqueous sodium hyposulfite (40 mL), distilled water (40 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (gradient 100:0 - 75:25 *n*-hexane:EtOAc) to afford 3-deoxy-3-iodoestrone (157 mg, 0.41 mmol, 62%) as a white solid. ^{1}H NMR (500.23 MHz, $CDCl_3$) δ 7.48-7.43 (m, 2H), 7.02 (d, *J* = 8.2 Hz, 1H), 2.90-2.84 (m, 2H), 2.51 (dd, *J* = 19.2, 8.8 Hz, 1H), 2.41-2.35 (m, 1H), 2.30-2.21 (m, 1H), 2.19-2.10 (m, 1H), 2.09-1.92 (m, 3H), 1.69-1.37 (m, 6H), 0.90 (s, 3H); ^{13}C NMR (125.80 MHz, $CDCl_3$) δ 220.8, 139.6, 139.3, 137.9, 134.8, 127.6, 91.3, 50.5, 48.1, 44.3, 38.0, 36.0, 31.6, 29.1, 26.4, 25.7, 21.7, 14.0.[47]

3-Deoxy-3-(trifluoromethyl)estrone

To a reaction vessel were added Cu(I)Br (48 mg, 0.33 mmol) and DMF (4 mL). After cooling to -65 °C under argon, 1M KOtBu in DMF (0.67 mL, 0.67 mmol) was added and

gaseous trifluoromethane (22.5 mL, 1.00 mmol) was bubbled through the reaction mixture. The vessel was warmed to room temperature and stirred for 30 minutes to form $CuCF_3$. The formed $CuCF_3$ was stabilised by addition of Et3N.3HF (36 µL, 0.22 mmol) and stirring for 30 minutes at room temperature. After addition of 3-deoxyestrone-3-boronic acid (50 mg, 0.168 mmol), the reaction was stirred for another 2.5 hours, followed by the addition of H_2O (30 mL) to quench the reaction. The mixture was extracted with Et_2O (3 x 10 mL). The combined Et_2O layers were washed with H_2O (3 x 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (gradient 100:0 - 75:25 *n*-hexane:EtOAc) to afford 3-deoxy-3-(trifluoromethyl)estrone (6 mg, 0.019 mmol, 11%) as a white solid. ^{1}H NMR (500.23 MHz, $CDCl_3$) δ 7.39 (s, 2H), 7.35 (s, 1H), 3.00-2.93 (m, 2H), 2.52 (dd, *J* = 19.1, 8.7 Hz, 1H), 2.48-2.42 (m, 1H), 2.38-2.30 (m, 1H), 2.21-1.96 (m, 4H), 1.70-1.41 (m, 6H), 0.92 (s, 3H); ^{13}C NMR (125.80 MHz, $CDCl_3$) δ 220.7, 143.8, 137.4, 128.2 (q, $J_{C\text{-}F}$ = 31.8 Hz), 125.92, 125.86 (q, $J_{C\text{-}F}$ = 3.6 Hz), 124.5 (q, $J_{C\text{-}F}$ = 271.6 Hz), 122.6 (q, $J_{C\text{-}F}$ = 3.6 Hz), 50.6, 48.0, 44.6, 37.9, 36.0, 31.6, 29.4, 26.3, 25.7, 21.7, 13.9; ^{19}F NMR (235.33 MHz, $CDCl_3$) δ -62.9 (s, 3F); HRMS (ESI) calcd for $C_{19}H_{21}F_3NaO_3$ [M+Na$^+$] 345.1449 found 345.1436. Spectral data match data reported in literature.[48]

_N_-(tert-butoxycarbonyl)-4-borono-L-phenylalanine methyl ester

To a solution of 4-borono-L-phenylalanine (250 mg, 1.20 mmol) in water (16.5 mL) and acetone (16.5 mL) were added Na_2CO_3 (139 mg, 1.32 mmol) and di-tert-butyl dicarbonate (287 mg, 1.32 mmol), after which the reaction mixture was stirred at room temperature for 24 hours. Next the reaction mixture was acidified with 10% aqueous citric acid (10 mL), followed by the removal of acetone by evaporation. The aqueous solution was extracted with EtOAc (3 x 65 mL), the combined extracts were washed with 10% citric acid (3 x 50 mL) and brine (3 x 50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford N-(tert-butoxycarbonyl)-4-borono-L-phenyalanine (265 mg, 72%) as a white solid which was used without further purification. To a solution of N-(tert-butoxycarbonyl)-4-borono-L-phenylalanine (260 mg, 0.84 mmol) in DMF (2.5 mL) were added $KHCO_3$ (168 mg, 1.68 mmol) and methyl iodide (105 µL, 1.68 mmol) and the mixture was stirred at room temperature for 7 days. The reaction mixture was concentrated *in vacuo* and the residue was suspended in EtOAc (12 mL). The mixture was washed with 10% citric acid (3 x 5 mL), saturated $NaHCO_3$ (3 x 5 mL) and brine (3 x 5 mL) and dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (gradient 100:0 - 95:5 CH_2Cl_2:MeOH) to afford N-(tert-butoxycarbonyl)-4-borono-L-phenylalanine methyl ester (191 mg, 0.59 mmol, 70%) as a white solid. ^{1}H NMR (500.23 MHz, DMSO + D_2O) δ 7.67 (d, *J* = 7.6 Hz, 2H), 7.17 (d, *J* = 7.6 Hz, 2H), 4.15 (dd, *J* = 9.8, 5.0 Hz, 1H), 3.59 (s, 3H), 2.98

(dd, *J* = 13.7, 5.0 Hz, 1H), 2.87-2.76 (m, 1H), 1.30 (s, 9H), $B(OH)_2$ and NH not observed due to H-D exchange, contains 16% of a Boc rotamer (Boc rotamer singlet at 1.23 ppm); ^{13}C NMR (125.80 MHz, $CDCl_3$) δ 173.0, 155.8, 139.9, 134.4, 128.5, 78.8, 55.3, 52.2, 36.7, 28.4, carbon directly bonded to boron was not observed, however with $^{1}H,^{13}C$-HMBC NMR its resonance signal was found at 132.0 ppm; HRMS (ESI) calcd for $C_{15}H_{22}BNNaO_6$ [M+Na^+] 346.1432, found 346.1436. Spectral data match data reported in literature.[49,50]

***N*-(tert-butoxycarbonyl)-4-iodo-L-phenylalanine methyl ester**

Thionyl chloride (1.00 mL, 13.7 mmol) and 4-iodo-L-phenylalanine (800 mg, 2.75 mmol) were added to methanol (10 mL) at 0 °C. After removal of the ice bath, the reaction mixture was refluxed for 2 hours, followed by rotary evaporation to dryness. The residue was washed with Et_2O on a sintered glass filter, to afford 4-iodo-L-phenylalanine methyl ester as a white solid which was used without further purification. To a solution of the 4-iodo-L-phenylalanine methyl ester in CH_2Cl_2 (4 mL) were added N-methylmorpholine (906 µL, 8.25 mmol) and di-tert-butyl dicarbonate (779 mg, 3.57 mmol). The reaction mixture was stirred for 16 hours under an argon atmosphere at room temperature, followed by evaporation of the solvent *in vacuo*. The residue was dissolved in EtOAc (100 mL) and washed with sat. $NaHCO_3$ (50 mL), 50 mM citric acid (50 mL), water (50 mL), brine (50 mL). After drying over Na_2SO_4, the organic layer was filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (90:10 *n*-hexane:EtOAc) to afford N-(tert-butoxycarbonyl)-4-iodo-L-phenylalanine methyl ester (712 mg, 1.76 mmol, 64%) as a white solid. ^{1}H NMR (500.23 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.9 Hz, 2H), 6.87 (d, *J* = 7.9 Hz, 2H), 4.97 (d, *J* = 7.3 Hz, 1H), 4.61-4.53 (m, 1H), 3.71 (s, 3H), 3.07 (dd, *J* = 13.9, 5.4 Hz, 1H), 2.98 (dd, *J* = 13.9, 5.4 Hz, 1H), 1.42 (s, 9H); ^{13}C NMR (125.80 MHz, $CDCl_3$) δ 172.2, 155.1, 137.7, 135.8, 131.5, 92.7, 80.2, 54.3, 52.5, 38.0, 28.4; HRMS (ESI) calcd for $C_{15}H_{20}INNaO_4$ [M+Na^+] 428.0329, found 428.0333. Spectral data match reported data in literature.[51]

***N*-(tert-butoxycarbonyl)-4-(trifluoromethyl)-L-phenylalanine methyl ester**

Thionyl chloride (175 µL, 2.14 mmol) and 4-(trifluoromethyl)-L-phenylalanine (100 mg, 0.43 mmol) were added to methanol (1.2 mL) at 0 °C. After removal of the ice bath, the reaction mixture was refluxed for 2 hours, followed by rotary evaporation to dryness. The residue was washed with Et_2O on a sintered glass filter, to afford 4-(trifluoromethyl)-L-phenylalanine methyl ester as a white solid which was used without further purification. To a solution of the 4-(trifluoromethyl)-L-phenylalanine methyl ester in CH_2Cl_2 (4 mL) were added N-methylmorpholine (141 µL, 1.29 mmol) and di-tert-butyl dicarbonate (122 mg, 0.56 mmol). The reaction mixture was stirred for 16 hours under inert atmosphere at room temperature, followed by evaporation of the solvent *in*

vacuo. The residue was dissolved in EtOAc (100 mL) and washed with sat. $NaHCO_3$ (50 mL), 50 mM citric acid (50 mL), water (50 mL), brine (50 mL). After drying over Na_2SO_4, the organic layer was filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (90:10 *n*-hexane:EtOAc) to afford N-(tert-butoxycarbonyl)-4-(trifluoromethyl)-L-phenylalanine methyl ester (90 mg, 0.26 mmol, 60%) as a white solid. ^{1}H NMR (500.23 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.6 Hz, 2H), 7.22-7.16 (m, 2H), 4.94 (d, *J* = 7.3 Hz, 1H), 4.60-4.52 (m, 1H), 3.66 (s, 3H), 3.14 (dd, *J* = 13.5, 5.4 Hz, 1H), 3.01 (dd, *J* = 13.5, 6.1 Hz, 1H), 1.34 (s, 9H); (^{13}C NMR, 125.80 MHz, $CDCl_3$): δ = 172.1, 155.1, 140.4, 129.8, 129.4 (q, $J_{C\text{-}F}$ = 32.7 Hz), 125.5 (q, $J_{C\text{-}F}$ = 3.6 Hz), 124.3 (q, $J_{C\text{-}F}$ = 271.6 Hz), 80.3, 54.3, 52.6, 38.4, 28.4; ^{19}F NMR (235.33 MHz, $CDCl_3$) δ -63.0 (s, 3F); HRMS (ESI) calcd for $C_{16}H_{20}F_3NNaO_4$ [M+Na$^+$] 370.1236, found 370.1244. Spectral data match reported data in literature.[51,52]

4.5 References

1 S. M. Ametamey, M. Honer and P. A. Schubiger, *Chem. Rev.*, 2008, **108**, 1501-1516.

2 M. Politis and P. Piccini, *J. Neurol.*, 2012, **259**, 1769-1780.

3 L. Zimmer and A. Luxen, *NeuroImage,* 2012, **61**, 363-370.

4 N. Adenaw and M. Salerno, *J. Nucl. Cardiol.*, 2013, **20**, 976-989.

5 L. W. Dobrucki and A. J. Sinusas, *Nat. Rev. Cardiol.*, 2010, **7**, 38-47.

6 G. Tomasi and L. Rosso, *Curr. Opin. Pharmacol.* 2012, **12**, 569-575.

7 T. Jones and P. Price, *Lancet Oncol.*, 2012, **13**, e116-e125.

8 S. L. Pimlott and A. Sutherland, Chem. Soc. Rev. 2011, **40**, 149-162.

9 P. M. Matthews, E. A. Rabiner, J. Passchier and R. N. Gunn, *Br. J. Clin. Pharmacol.*, 2012, **73**, 175-186.

10 N. Tamaki and Y. Kuge, Molecular Imaging for Integrated Medical Therapy and Drug Development, Springer, Heidelberg, 2010.

11 J. K. Willmann, N. van Bruggen, L. M. Dinkelborg and S. S. Gambhir, *Nat. Rev. Drug Discovery*, 2008, **7**, 591-607.

12 P. W. Miller, N. J. Long, R. Vilar and A. D. Gee, *Angew. Chem. Int. Ed.*, 2008, **47**, 8998-9033.

13 M. Tredwell and V. Gouverneur, *Angew. Chem. Int. Ed.*, 2012, **51**, 11426-11437.

14 L. Cai, S. Lu and V. W. Pike, *Eur. J. Org. Chem.,* 2008, 2853-2873.

15 T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem. Int. Ed.*, 2013, **52**, 8214-8264.

16 S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320-330.

17 J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432-2506.

18 W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359-4369.

19 J. Prabhakaran, M. D. Underwood, R. V. Parsey, V. Arango, V. J. Majo, N. R. Simpson, R. Van Heertum, J. J. Mann and J. S. D. Kumar, *Bioorg. Med. Chem.*, 2007, **15**, 1802-1807.

20 M. R. Kilbourn, M. R. Pavia and V. E. Gregor, *Int. J. Rad. Appl. Instrum. A.*, 1990, **41**, 823-828.

21 G. Angelini, M. Speranza, A. P. Wolf and C.-Y. Shiue, *J. Labelled Compd. Radiopharm.*, 1990, **28**, 1441-1448.

22 G. Angelini, M. Speranza, C.-Y. Shiue and A. P. Wolf, *J. Chem. Soc. Chem. Commun.*, 1986, 924-925.

23 M. Huiban, M. Tredwell, S. Mizuta, Z. Wan, X. Zhang, T. L. Collier, V. Gouverneur and J. Passchier, *Nat. Chem.*, 2013, **5**, 941-944.

24 T. Rühl, W. Rafique, V. T. Lien and P. J. Riss, *Chem. Commun.*, 2014, **50**, 6056-6059.

25 P. Ivashkin, G. Lemonnier, J. Cousin, V. Gr_goire, D. Labar, P. Jubault and X. Pannecoucke, *Chem. Eur. J.*, 2014, **20**, 9514-9518.

26 S. E. Lapi and M. J. Welch, *Nucl. Med. Biol.*, 2012, **39**, 601-608.

27 D. van der Born, J. D. M. Herscheid, R. V. A. Orru and D. J. Vugts, *Chem. Commun.*, 2013, **49**, 4018-4020.

28 D. van der Born, J. D. M. Herscheid and D. J. Vugts, *J. Labelled Compd. Radiopharm.*, 2013, **56**, S2.

29 A. Zanardi, M. Novikov, E. Martin, J. Benet-Buchholz and V. V. Grushin, *J. Am. Chem. Soc.*, 2011, **133**, 20901-20913.

30 J. Russell and N. Roques, *Tetrahedron*, 1998, **54**, 13771-13782.

31 B. Folléas, I. Marek, J.-F. Normant and L. Saint-Jalmes, *Tetrahedron Lett.*, 1998, **39**, 2973-2976.

32 B. Folléas, I. Marek and L. Saint-Jalmes, *Tetrahedron*, 2000, **56**, 275-283.

33 P. Novák, A. Lishchynskyi and V. V. Grushin, *Angew. Chem. Int. Ed.*, 2012, **51**, 7767-7770.

34 R. M. Blair, H. Fang, W. S. Branham, B. S. Hass, S. L. Dial, C. L. Moland, W. Tong, L. Shi, R. Perkins and D. M. Sheehan, *Toxicol. Sci.*, 2000, **54**, 138-153.

35 S.-I. Hayashi, H. Eguchi, K. Tanimoto, T. Yoshida, Y. Omoto, A. Inoue, N. Yoshida and Y. Yamaguchi, *Endocr.-Relat. Cancer*, 2003, **10**, 193-202.

36 K. R. Romines, G. A. Freeman, L. T. Schaller, J. R. Cowan, S. S. Gonzales, J. H. Tidwell, C. W. Andrews, D. K. Stammers, R. J. Hazen, R. G. Ferris, S. A. Short, J. H. Chan and L. R. Boone, *J. Med. Chem.*, 2006, **49**, 727-739.

37 S. Mizuta, I. S. R. Stenhagen, M. O'Duill, J. Wolstenhulme, A. K. Kirjavainen, S. J. Forsback, M. Tredwell, G. Sandford, P. R. Moore, M. Huiban, S. K. Luthra, J. Passchier, O. Solin and V. Gouverneur, *Org. Lett.*, 2013, **15**, 2648-2651.

38 A. Huang, A. Moretto, K. Janz, M. Lowe, P. W. Bedard, S. Tam, L. Di, V. Clerin, N. Sushkova, B. Tchernychev, D. H. H. Tsao, J. C. Keith Jr., G. D. Shaw, R. G. Schaub, Q. Wang and N. Kaila, *J. Med. Chem.*, 2010, **53**, 6003–6017.

39 D. K. Maiti and A. Banerjee, *Chem. Commun.*, 2013, **49**, 6909-6911.

40 P. C. Roosen, V. A. Kallepalli, B. Chattopadhyay, D. A. Singleton, R. E. Maleczka and M. R. Smith, *J. Am. Chem. Soc.*, 2012, **134**, 11350-11353.

41 D. Flaherty, T. Kiyota, Y. Dong, T. Ikezu and J. L. Vennerstrom, *J. Med. Chem.*, 2010, **53**, 7992-7999.

42 A. Escribano-Cuesta, P. Pérez-Galán, E. Herrero-Gómez, M. Sekine, A. a C. Braga, F. Maseras and A. M. Echavarren, *Org. Biomol. Chem.*, 2012, **10**, 6105-6111.

43 A. K. Cook, M. H. Emmert and M. S. Sanford, *Org. Lett.*, 2013, **15**, 5428-5431.

44 T. Furuya, A. E. Strom and T. Ritter, *J. Am. Chem. Soc.*, 2009, **131**, 1662-1663.

45 V. Ahmed, Y. Liu, C. Silvestro and S. D. Taylor, *Bioorg. Med. Chem.*, 2006, **14**, 8564-8573.

46 J. Messinger, B. Husen, U. Schoen, H. Thole, P. Koskimies and M. Unkila, *Substituted Estratrien Derivatives as 17Beta HSD Inhibitors*, 2008.

47 Y.-L. Ren, X.-Z. Tian, C. Dong, S. Zhao, J. Wang, M. Yan, X. Qi and G. Liu, *Catal. Commun.*, 2013, **32**, 15-17.

48 Y. Ye and M. S. Sanford, *J. Am. Chem. Soc.*, 2012, **134**, 9034-9037.

49 C. L. Kusturin, L. S. Liebeskind and W. L. Neumann, *Org. Lett.*, 2002, **4**, 983-985.

50 Y. Hattori, H. Yamamoto, H. Ando, H. Kondoh, T. Asano, M. Kirihata, Y. Yamaguchi and T. Wakamiya, *Bioorg. Med. Chem.*, 2007, **15**, 2198-2205.

51 H. Lei, M. S. Stoakes, P. B. Herath, Kamal, J. Lee and A. W. Schwabacher, *J. Org. Chem.*, 1994, **59**, 4206-4210.

52 A. J. Ross, F. Dreiocker, M. Schäfer, J. Oomens, A. J. H. M. Meijer, B. T. Pickup and R. F. W. Jackson, *J. Org. Chem.*, 2011, **76**, 1727-1734.

5

Summary and outlook

5.1 Summary

Positron Emission Tomography (PET) is a molecular imaging technique, which can visualise the distribution of biologically active compounds labelled with a positron emitting radionuclide, so called PET tracers. In the clinic, PET is used for the diagnosis of disease and monitoring of treatment by visualizing biological targets and processes involved with the disease. Besides being a clinical imaging tool, PET imaging is also of interest for drug development, since it can be used to investigate the interaction of a novel drug candidate with a biological target using a PET tracer, or by visualising the distribution and pharmacokinetics of the novel drug candidate by labelling the drug itself.

Of the available positron emitting radionuclides, fluorine-18 is most frequently used, because (i) PET tracers with this nuclide can be transported to other satellite PET scan facilities due to its 110 minute half-life, and (ii) high resolution PET images can be obtained due to its clean decay profile and low positron energy.

Two strategies can be identified to synthesise fluorine-18 labelled PET tracers: (1) late-stage radiofluorination, in which fluorine-18 is introduced in the last step of the PET tracer synthesis and (2) the building block approach, in which first a fluorine-18 labelled building block is synthesised in a fast and efficient manner, which is subsequently further transformed to the actual PET tracer.

The building block approach is the main focus of this thesis, as it describes both a comprehensive overview of ^{18}F-labelled building blocks applied since 2010 is given , as well as novel ^{18}F-labelling strategies towards ^{18}F-trifluoromethylations using [^{18}F]trifluoromethane as a building block.

In **Chapter 1**, an introduction is provided about the basic principles of Positron Emission Tomography and the general approaches towards the synthesis of fluorine-18 labelled PET tracers as well as a short introduction on the synthesis of PET tracers containing the fluorine-18 labelled trifluoromethyl moiety.

In **Chapter 2**, a comprehensive overview is presented that discusses the synthesis and application of fluorine-18 labelled building blocks in the synthesis of PET tracers in the period of 2010 - 2016. The syntheses of the building blocks as well as the chemical reactions that can be performed with these building blocks to arrive at the final PET tracers are discussed. Details are given on reaction conditions, purification methods, radiochemical yields, radiochemical purities and specific activities of the building blocks and the PET tracers made with these building blocks.

It is shown that some fluorine-18 labelled building blocks are frequently used, including:

- The alkylating building blocks [^{18}F]fluoroethyl bromide and [^{18}F]FETos and the "click"-reaction building block [^{18}F]fluoroethyl azide, due to their simple, easy to automate synthesis and efficient follow-up reaction with precursors.
- 4-[^{18}F]Fluorobenzaldehyde, due to its versatility. The compound has been applied in at least five different types of coupling reactions as well as in various multicomponent reactions.
- *N*-succinimidyl-4-[^{18}F]fluorobenzoate, due to its selectivity, as it almost exclusively reacts with primary amines.

Other building blocks are less widely applied, however still find use in the synthesis of PET tracers which cannot be synthesised easily via late-stage radiofluorination chemistry or for the fast and easy access to a series of PET tracers with the aim to select the PET tracer with the optimal biological characteristics.

In the discussion, it becomes clear that the current toolkit of fluorine-18 labelled building blocks still has various shortcomings, including the poor availability of good methods to synthesise PET tracers which contain a fluorine-18 labelled trifluoromethyl (CF_3) functional group. Novel methods to produce these PET tracers are desired, as many biologically active compounds contain a trifluoromethyl (CF_3) functional group, because it potentially improves their binding selectivity, lipophilicity and metabolic stability. There were limited methods available for the synthesis of PET tracers with the fluorine-18 labelled CF_3 functional group at the start of the work described in this thesis (2010). These all show one or more shortcomings including:

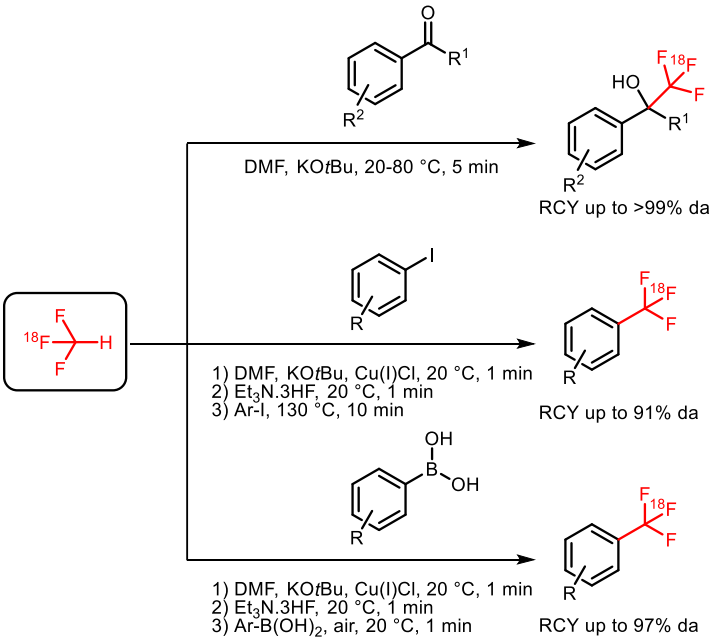
- Low radiochemical yields in the synthesis of structural complex PET tracers due to harsh reaction conditions.
- Challenging precursor synthesis and/or availability.
- Low specific activities of the synthesised PET tracers.
- Moderate applicability as only specific structures can be synthesised (e.g. synthesis of the 1,1,1-[^{18}F]trifluoroethyl group by ^{18}F-fluorination of 1,1-difluorovinyl precursors).

All in all, there is a demand for a universal method to synthesise PET tracers with the fluorine-18 labelled CF_3 functional group with good radiochemical yields and high specific activities, using bench-stable precursors and simple radiochemistry methodology. Therefore, the aim of the research, described in the following chapters, is to

develop such a universal method towards PET tracers with the fluorine-18 labelled CF_3 functional group using [^{18}F]trifluoromethane ([^{18}F]HCF_3) as a building block.

In **Chapter 3**, the synthesis of [^{18}F]HCF_3 is described. It is shown that [^{18}F]HCF_3 can be synthesised by mild nucleophilic substitution of difluoroiodomethane (HCF_2I) with [^{18}F]fluoride. Because [^{18}F]HCF_3 is volatile (boiling point = -82 °C), it could be simply purified by distilling it out of the reaction mixture using a flow of Helium, followed by trapping the [^{18}F]HCF_3 in a second reaction vessel in a solvent of choice at -60 °C. Using this method, pure [^{18}F]HCF_3 could be obtained in a good radiochemical yield of 60 ± 15% (decay corrected).

The electron withdrawing nature of fluorine atoms results in a rather acidic hydrogen atom in [^{18}F]HCF_3 that can be deprotonated by strong bases such as potassium *tert*-butoxide (KO*t*Bu). The formed trifluoromethyl anion [^{18}F]CF_3^- is a good nucleophile that readily reacts with various ketones and aldehydes towards [^{18}F]trifluoromethylcarbinols (Scheme 1). Especially in DMF, excellent radiochemical yields were obtained.



Scheme 1 Application of [^{18}F]HCF_3 in the synthesis of [^{18}F]trifluoromethylcarbinols and [^{18}F]trifluoromethyl arenes.

Furthermore, we showed that without DMF, the $[^{18}F]CF_3^-$ anion rapidly disintegrated to difluorocarbene and fluoride. In the presence of DMF, this anion reacts with DMF to form a *gem*-aminoalcoholate. This *gem*-aminoalcoholate is stable and reacts in a concerted fashion with aldehydes and ketones to form [^{18}F]trifluoromethylcarbinols.

These results show that $[^{18}F]HCF_3$ is indeed a useful building block for the synthesis of compounds bearing the $[^{18}F]CF_3$ group. In this particular case, the application is however limited to the synthesis of [^{18}F]trifluoromethylcarbinols.

In **Chapter 4**, we aimed at the development of a novel method towards the synthesis of PET tracers containing an ^{18}F-labelled aryl-CF_3 group, because the aryl-CF_3 group has found widespread application in biologically active compounds. First, we focussed on the [^{18}F]trifluoromethylation of aryl iodides by *in situ* formation of $[^{18}F]CuCF_3$ using KO*t*Bu as a strong base, Cu(I)Cl as a copper(I) source and $Et_3N.HF$ to stabilise the $[^{18}F]CuCF_3$ by precipitation of K^+ ions as KF(s).

High yields were obtained within 10 minutes at 130 °C. Using this method various [^{18}F]trifluoromethyl arenes were successfully synthesised including [^{18}F]trifluoromethyl derivatives of estrone and phenyl alanine (Scheme 1).

To further extend the application of $[^{18}F]HCF_3$, the oxidative [^{18}F]trifluoromethylation of boronic acids was investigated. [^{18}F]Trifluoromethyl arenes could be synthesised from their corresponding boronic acid precursors by reaction with $[^{18}F]CuCF_3$ at room temperature and after 1 minute reaction time (Scheme 1). The $[^{18}F]CuCF_3$ reaction mixture had to be purged with air in the presence of the boronic acid precursor in order to obtain the [^{18}F]trifluoromethyl arenes in decent yields and short reaction times. In comparison to the [^{18}F]trifluoromethylation of iodoarenes, this reaction gives the [^{18}F]trifluoromethyl arenes in higher radiochemical yields (determined analytically), at lower temperatures (20 °C vs 130 °C) and in shorter reaction times (1 minute vs 10 minutes).

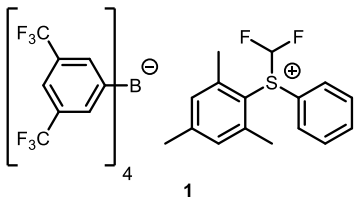
When $[^{18}F]HCF_3$ was made via the procedure described in **Chapter 3**, the specific activity of the final [^{18}F]trifluoromethylated products was ~1 GBq/µmol. However, for a PET tracer to be useful for imaging low abundance targets, in general a specific activity of at least 18 GBq/µmol is required. Efforts to increase the specific activity were successful. By decreasing the amount of difluoroiodomethane (HCF_2I) and base in the synthesis of $[^{18}F]HCF_3$, the specific activity of this building block, and thus of the PET tracers made by this building block, could be increased to 28 ± 5 GBq/µmol.

Overall, it was shown that $[^{18}F]HCF_3$ is a useful building block for the synthesis of PET tracers with the fluorine-18 labelled trifluoromethyl functional group.

5.2 Outlook

This work shows that [^{18}F]HCF_3 is a useful addition to the radiochemist's toolkit as this building block can be made in good yields using a relatively simple procedure and has already shown application in the synthesis of [^{18}F]trifluoromethylcarbinols (**Chapter 3**) and [^{18}F]trifluoromethyl arenes (**Chapter 4**). Furthermore, this is still the only available method which gives these compounds in good specific activities of >18 GBq/µmol. Therefore, it seems likely that [^{18}F]HCF_3 will be highly appreciated by other radiochemists as a novel fluorine-18 labelled building block. Consequently, we foresee the use of this building block in the synthesis of various PET tracers in the future.

Although we have demonstrated here a first proof of the applicability of [^{18}F]HCF_3, various improvements are still needed to show its overall potential. Concerning the synthesis of [^{18}F]HCF_3 itself, improvements that increase the radiochemical yield and the specific activity seem vital. One way in which this may be achieved is by the use of alternative methods to introduce fluorine-18. Especially novel "dry" radiofluorination methodology might be interesting to explore for the synthesis of [^{18}F]HCF_3. Such an approach should allow the use of lower amounts of HCF_2I precursor, which should lead to higher specific activities in combination with higher radiochemical yields. Because HCF_2I is very volatile and can therefore be challenging to handle, other difluoromethane HCF_2X precursors in which X represents a larger leaving group than iodine may be worthwhile to study in more detail. Such building blocks are better handled and should also lead to higher radiochemical yields and better specific activity. One recent example of such a new HCF_2X precursor is the (difluoromethyl)(mesityl)(phenyl) sulfonium salt depicted in Scheme 2. This material is reported as a novel precursor for the synthesis of [^{18}F]HCF_3 by the group of Phillipe Jubault and Xavier Pannecoucke.[1,2] This precursor is a bench stable, crystalline compound, and is therefore easier to handle. The radiochemical yield (29%) as well the specific activity (<1 GBq/µmol) were however still low.

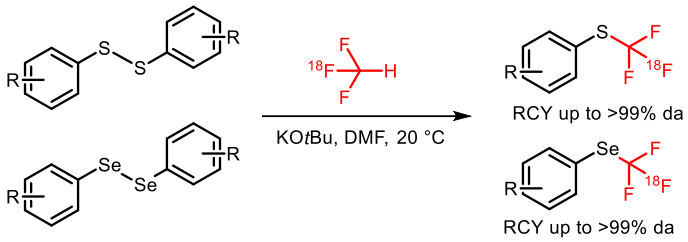


1

Scheme 2 (difluoromethyl)(mesity)(phenyl) sulfonium salt **1**.

In our work, we reported on the reaction of [^{18}F]HCF_3 with aldehydes and ketones via *in situ* formed [^{18}F]CF_3^- as a nucleophile and on the reaction of [^{18}F]HCF_3 with aryl iodides and aryl boronic acids via *in situ* formed [^{18}F]$CuCF_3$. Both intermediates, [^{18}F]CF_3^-

and [^{18}F]CuCF$_3$, have potential to be used in other types of reactions. A recent example, reported by Carbonnel *et al.* shows the reaction of [^{18}F]HCF$_3$ via *in situ* formed [^{18}F]CF$_3^-$ with disulfides and diselenides towards [^{18}F]R-SCF$_3$ derivatives (Scheme 3), providing these products in excellent radiochemical yields.[2]



Scheme 3 Reaction of [^{18}F]HCF$_3$ with disulfides and diselenides.

Other types of reactions which could be of interest, using the *in situ* formed [^{18}F]CF$_3^-$ anion as a nucleophile, include the reaction with esters and imines leading to [^{18}F]trifluoromethyl ketones and [^{18}F]α-trifluoromethyl amines.

Also *in situ* formed [^{18}F]CuCF$_3$ may be used for other types of cross-coupling chemistry such as the trifluoromethylation of terminal alkenes, benzyl halides and vinyl halides. Futhermore, beside [^{18}F]CuCF$_3$, other metal complexes containing the ^{18}F-labelled -CF$_3$ moiety, either with or without ligands, could be potentially useful intermediates for trifluoromethylation reactions in the future.

Besides the building block approach using [^{18}F]HCF$_3$, in which the building block is first synthesised by reaction of [^{18}F]fluoride with difluoroiodomethane, followed by isolation of the building block and subsequent trifluoromethylation towards the desired [^{18}F]CF$_3$-containing PET tracer, many effort has lately been put in the development of chemistry in which the [^{18}F]CF$_3$-containing PET tracer is made directly in one step. There are two ways in which this is performed: (1) [^{18}F]HCF$_3$, [^{18}F]CF$_3^-$, [^{18}F]CuCF$_3$ or other ^{18}F-labelled CF$_3$ intermediates are formed *in situ* from [^{18}F]fluoride, after which the intermediate reacts directly (without purification) with a precursor towards the desired PET tracer of interest;[3-6] (2) [^{18}F]fluoride is reacted directly with a precursor containing a -CF$_2$Br, -CF$_2$Cl, -CF$_2$H precursor moiety.[7-10] In both cases, the specific acitivity of the [^{18}F]CF$_3$-containing products was rather low: <10 GBq/µmol. This is caused by the presence of large amounts of non-radioactive ^{19}F in these reactions, originating from the precursor. In the method from this work, ^{19}F is also present in the HCF$_2$I precursor, however, after distillation of the formed [^{18}F]HCF$_3$, it is collected in a new reaction vessel, which does not contain any HCF$_2$I, which can lead to isotopic dilution. Isotopic dilution can only occur during the synthesis of [^{18}F]HCF$_3$ in the first reacton vessel, however, because the synthesis of [^{18}F]HCF$_3$ occurs very efficently, the amount of ^{19}F containing

HCF_2I precursor could be already reduced to 1 µmol and may be even further reduced in the future to deliver $[^{18}F]HCF_3$ in specific activites higher than 28 ± 5 GBq/µmol.

Very recently, M. Haskali *et al.* published a method which delivers PET tracers with the radioactive -CF_3 moiety in very high specific activites of 242 - 551 GBq/µmol by employing carbon-11 labelled $[^{11}C]HCF_3$.[11] They showed that $[^{11}C]HCF_3$ can be synthesised efficiently and in high specific activities by gas phase fluorination of $[^{11}C]CH_4$ using a high temperature $CoCF_3$ column. As $[^{11}C]HCF_3$ is chemically identical to $[^{18}F]HCF_3$, it can be used for exactly the same chemical reactions, giving the products in similar yields and this time also in high specific activities. Of course, although high specific activity PET tracers can be obtained via this methods, the application is limited due to the short half-life of carbon-11 (20 minutes). Therefore, high specific activity fluorine-18 labelled $[^{18}F]HCF_3$ is still a very valuable building block besides $[^{11}C]HCF_3$.

Interestingly, a similar approach was employed for the synthesis of $[^{18}F]HCF_3$.[12] First $[^{18}F]H_3CF$ was made by reaction of $[^{18}F]$fluoride with MeOMs. Subsequently, the $[^{18}F]$ H_3CF was reacted to $[^{18}F]HCF_3$ using the same high temperature $CoCF_3$ column. Unfortantely, oposed to the $[^{11}C]HCF_3$ synthesis, the specific activity of products made using $[^{18}F]HCF_3$ was measured to be only 14 GBq/µmol.

In conclusion, we have shown that $[^{18}F]HCF_3$ is a valuable building block with high potential to be commonly used in the future, mainly due to its versatility and its high specific activity which is expected to be even further improved. It is however of importance that its capability is shown soon by using this building block in the synthesis of structurally complex PET tracers, including purification, formulation and application of the PET tracers in preclinical and clinical imaging studies.

5.3 References

1 P. Ivashkin, G. Lemonnier, J. Cousin, V. Grégoire, D. Labar, P. Jubault and X. Pannecoucke, *Chem. Eur. J.*, 2014, **20**, 9514-9518.

2 E. Carbonnel, T. Besset, T. Poisson, D. Labar, X. Pannecoucke and P. Jubault, *Chem. Comm.*, 2017, **53**, 5706-5709.

3 M. Huiban, M. Tredwell, S. Mizuta, Z. Wan, X. Zhang, T. L. Collier, V. Gouverneur and J. Passchier, *Nat. Chem.*, 2013, **5**, 941-944.

4 T. Rühl, W. Rafique, V. T. Lien and P. J. Riss, *Chem. Comm.*, 2014, **50**, 6056-6059.

5 J. Zheng, L. Wang, J.-H. Lin, J.-C. Xiao and S. H. Liang, *Angew. Chem. Int. Ed.*, 2015, **54**, 13236-13240.

6 J. Zheng, R. Cheng, J.-H. Lin, D.-H. Yu, L. Ma, L. Jia, L. Zhang, L. Wang, J.-C. Xiao and S. H. Liang, *Angew. Chem. Int. Ed.*, 2017, **56**, 3196-3200.

7 T. Khotavivattana, S. Verhoog, M. Tredwell, L. Pfeifer, S. Calderwoord, K. Weelhouse, T. L. Collier and V. Gouverneur, *Angew. Chem. Int. Ed.*, 2015, **54**, 9991-9995.

8 L. Carroll, H. L. Evans, A. C. Spivey and E. O. Aboagye, *Chem. Comm.*, 2015, **51**, 8439-8441.

9 S. Verhoog, L. Pfeifer, T. Khotavivattana, S. Calderwood, T. L. Collier, K. Weelhouse, M. Tredwell and V. Gouverneur, *Synlett*, 2016, **27**, 25-28.

10 A. B. Gómez, M. A. Cortés González, M. Lübcke, M. J. Johansson, C. Halldin, K. J. Szabó and M. Schou, *Chem. Comm,* 2016, **52**, 13963-13966.

11 M. B. Haskali and V. W. Pike, *Chem. Eur. J.* 2017, **23**, Accepted.

12 B. Y. Yeung, S. Telu, M. B. Haskali and V. W. Pike, *J. Labelled. Compd. Radiopharm.*, 2017, **60**, S35.

Appendices

Curriculum vitae

List of publications

Dankwoord

Curriculum vitae

Dion van der Born was born on July 11, 1986 in Alphen aan den Rijn, the Netherlands. After finishing secondary school (HAVO) at the "Katholieke Scholengemeenschap Hoofddorp", he obtained his Bachelor of Applied Sciences in the field of Organic Chemistry at the University of Applied Sciences Leiden. At the VU University Medical Center Amsterdam, he gained his first experience in radiochemistry as a research technician under the supervision of dr. J. D. M. Herscheid. Because the field of radiochemistry spiked his interest, he started both the Master's programme in chemistry at the Vrije Universiteit Amsterdam and as well a PhD project at the VU University Medical Center Amsterdam under 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 trifluoromethyl group directly onto arenes. He received his MSc in chemistry in 2016 and following the completion of the practical part of his PhD work, he joined FutureChemistry as a radiochemist, where he is involved in the development and application of novel equipment for the synthesis of radiolabelled compounds.

List of publications

1 **Dion van der Born**, Anna Pees, Alex J. Poot, Romano V. A. Orru, Albert D. Windhorst, Danielle J. Vugts, "Fluorine-18 labelled building blocks for PET tracer synthesis", *Chemical Society Reviews*, **2017**, 46, 4709-4773.

2 Lorenzo Cavina, **Dion van der Born**, Peter H. M. Klaren, Martin C. Feiters, Otto C. Boerman, Floris P. J. T. Rutjes, "Design of Radioiodinated Pharmaceuticals: Structural Features Affecting Metabolic Stability towards in Vivo Deiodination", *European Journal of Organic Chemistry*, **2017**, 3387-3414.

3 **Dion van der Born**, Claudia Sewing, J. (Koos) D. M. Herscheid, Albert D. Windhorst, Romano V. A. Orru, Danielle J. Vugts, "A Universal Procedure for the [^{18}F]Trifluoromethylation of Aryl Iodides and Aryl Boronic Acids with Highly Improved Specific Activity, *Angewandte Chemie International Edition*, **2014**, 126, 11226-11230.

4 Sergio Dall'Angelo, Nouchali Bandaranayaka, Albert D. Windhorst, Danielle J. Vugts, **Dion van der Born**, Mayca Onega, Lutz F. Schweiger, Matteo Zanda, David O"Hagan, "Tumour imaging by Positron Emission Tomography using fluorinase generated 5-[^{18}F]fluoro-5-deoxyribose as a novel tracer", *Nuclear Medicine and Biology*, **2013**, 40, 464-470.

5 **Dion van der Born**, J. (Koos) D. M. Herscheid, Romano V. A. Orru, Danielle J. Vugts, "Efficient synthesis of [18F]trifluoromethane and its application in the synthesis of PET tracers", *Chemical Communications*, **2013**, 49, 4018-4020.

6 Rana Al Hussainy, Joost Verbeek, **Dion van der Born**, Carla Molthoff, Jan Booij, J. (Koos) D. M. Herscheid, "Synthesis, biodistribution and PET studies in rats of 18F-Labeled bridgehead fluoromethyl analogues of WAY-100635", *Nuclear Medicine and Biology*, **2012**, 39, 1068-1076.

7 Ranal Al Hussainy, Joost Verbeek, **Dion van der Born**, Jan Booij, J. (Koos) D. M. Herscheid, Design, synthesis and in vitro evaluation of bridgehead fluoromethyl analogs of "N-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}-N-(pyridin-2-yl)cyclohexanecarboxamide (WAY-100635) for the 5-HT1A receptor", *European Journal of Medicinal Chemistry*, **2011**, 46, 5728-5735.

8 Rana Al Hussainy, Joost Verbeek, **Dion van der Born**, Anton H. Braker, Josée E. Leysen, Remco J. Knol, J. (Koos) D. M. Herscheid, "Design, Synthesis, Radiolabeling, and in Vitro and in Vivo Evaluation of Bridgehead Iodinated Analogues of N-{2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl}-N-(pyridin-2-yl)cyclohexanecarboxamide (WAY-100635) as Potential SPECT Ligands for the 5-HT1A Receptor", *Journal of Medicinal Chemistry*, **2011**, 54, 3480-3491.

9 Niels Elders, **Dion van der Born**, Loes J. D. Hendrickx, Brian J. J. Timmer, Alrik Krause, Elwin Janssen, Frans J. J. de Kanter, Eelco Ruijter, Romano V. A. Orru, "The Efficient One-Pot Reaction of up to Eight Components by the Union of Multicomponent Reactions", *Angewandte Chemie International Edition*, **2009**, 48, 5856-5859.

Dankwoord

Eindelijk, het is af! Om tot dit resultaat te komen, ben ik de mensen om mij heen zeer dankbaar. Zonder hun hulp en steun was dit uiteraard niet gelukt! Daarom wil ik in dit dankwoord graag deze mensen bedanken voor hun bijdrage aan de totstandkoming van dit proefschrift. Hierbij streef ik ernaar om niemand te vergeten.

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grond heeft doen vallen (goede redding, Berend!). Ook werden er regelmatig virtuele apen in elkaar gemept op de computer van Paul of Berend (voor de kenners, Super Smash Bros. op de Nintendo 64) met het geluid hard aan. In ieder geval, even rustig werken was er niet altijd bij.

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