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Fluorine-18 Labelled Building Blocks for PET Tracer Synthesis

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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 $[^{18}\text{F}]$ 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:

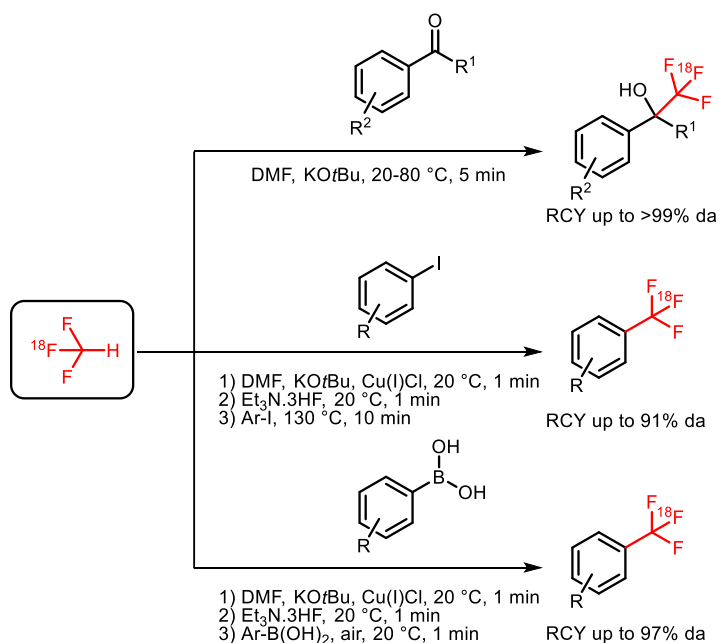
- Low radiochemical yields in the synthesis of structural complex PET tracers due to harsh reaction conditions.
- Challenging precursor synthesis and/or availability.
- Low specific activities of the synthesised PET tracers.
- Moderate applicability as only specific structures can be synthesised (e.g. 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 ($[^{18}\text{F}]\text{HCF}_3$) as a building block.

In **Chapter 3**, the synthesis of $[^{18}\text{F}]\text{HCF}_3$ is described. It is shown that $[^{18}\text{F}]\text{HCF}_3$ can be synthesised by mild nucleophilic substitution of difluoroiodomethane (HCF_2I) with $[^{18}\text{F}]\text{fluoride}$. Because $[^{18}\text{F}]\text{HCF}_3$ is volatile (boiling point = $-82\text{ }^\circ\text{C}$), it could be simply purified by distilling it out of the reaction mixture using a flow of Helium, followed by trapping the $[^{18}\text{F}]\text{HCF}_3$ in a second reaction vessel in a solvent of choice at $-60\text{ }^\circ\text{C}$. Using this method, pure $[^{18}\text{F}]\text{HCF}_3$ could be obtained in a good radiochemical yield of $60 \pm 15\%$ (decay corrected).

The electron withdrawing nature of fluorine atoms results in a rather acidic hydrogen atom in $[^{18}\text{F}]\text{HCF}_3$ that can be deprotonated by strong bases such as potassium *tert*-butoxide (KOtBu). The formed trifluoromethyl anion $[^{18}\text{F}]\text{CF}_3^-$ is a good nucleophile that readily reacts with various ketones and aldehydes towards $[^{18}\text{F}]\text{trifluoromethylcarbinols}$ (Scheme 1). Especially in DMF, excellent radiochemical yields were obtained.



Scheme 1 Application of $[^{18}\text{F}]\text{HCF}_3$ in the synthesis of $[^{18}\text{F}]\text{trifluoromethylcarbinols}$ and $[^{18}\text{F}]\text{trifluoromethyl arenes}$.

Furthermore, we showed that without DMF, the $[^{18}\text{F}]\text{CF}_3^-$ 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 $[^{18}\text{F}]$ trifluoromethylcarbinols.

These results show that $[^{18}\text{F}]\text{HCF}_3$ is indeed a useful building block for the synthesis of compounds bearing the $[^{18}\text{F}]\text{CF}_3$ group. In this particular case, the application is however limited to the synthesis of $[^{18}\text{F}]$ 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 $[^{18}\text{F}]$ trifluoromethylation of aryl iodides by *in situ* formation of $[^{18}\text{F}]\text{CuCF}_3$ using $\text{KO}t\text{Bu}$ as a strong base, Cu(I)Cl as a copper(I) source and $\text{Et}_3\text{N.HF}$ to stabilise the $[^{18}\text{F}]\text{CuCF}_3$ by precipitation of K^+ ions as KF(s) .

High yields were obtained within 10 minutes at 130 °C. Using this method various $[^{18}\text{F}]$ trifluoromethyl arenes were successfully synthesised including $[^{18}\text{F}]$ trifluoromethyl derivatives of estrone and phenyl alanine (Scheme 1).

To further extend the application of $[^{18}\text{F}]\text{HCF}_3$, the oxidative $[^{18}\text{F}]$ trifluoromethylation of boronic acids was investigated. $[^{18}\text{F}]$ Trifluoromethyl arenes could be synthesised from their corresponding boronic acid precursors by reaction with $[^{18}\text{F}]\text{CuCF}_3$ at room temperature and after 1 minute reaction time (Scheme 1). The $[^{18}\text{F}]\text{CuCF}_3$ reaction mixture had to be purged with air in the presence of the boronic acid precursor in order to obtain the $[^{18}\text{F}]$ trifluoromethyl arenes in decent yields and short reaction times. In comparison to the $[^{18}\text{F}]$ trifluoromethylation of iodoarenes, this reaction gives the $[^{18}\text{F}]$ 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 $[^{18}\text{F}]\text{HCF}_3$ was made via the procedure described in **Chapter 3**, the specific activity of the final $[^{18}\text{F}]$ trifluoromethylated products was $\sim 1 \text{ GBq}/\mu\text{mol}$. However, for a PET tracer to be useful for imaging low abundance targets, in general a specific activity of at least 18 $\text{GBq}/\mu\text{mol}$ is required. Efforts to increase the specific activity were successful. By decreasing the amount of difluoroiodomethane (HCF_2I) and base in the synthesis of $[^{18}\text{F}]\text{HCF}_3$, the specific activity of this building block, and thus of the PET tracers made by this building block, could be increased to $28 \pm 5 \text{ GBq}/\mu\text{mol}$.

Overall, it was shown that $[^{18}\text{F}]\text{HCF}_3$ is a useful building block for the synthesis of PET tracers with the fluorine-18 labelled trifluoromethyl functional group.