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ABSTRACT

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[^{18}F]F_2 – New production methods and applications

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Fluorine-18 is a positron emitting radioisotope. It has a half-life of 109.8 min, a simple decay profile and low positron energy as a result of which properties fluorine-18 is an excellent candidate for use in the production of tracers for positron emission tomography (PET). Radiochemistry with fluorine-18 starts from the production of the radioactive isotope, which is then used for the labelling of bioactive molecules. The labelling can be done by nucleophilic or electrophilic methods. Nucleophilic ^{18}F-fluorination, using [^{18}F]F^-, is the most popular approach due to the effective production method. Production of [^{18}F]F_2 is more challenging and is one of the limiting factors for the use of electrophilic ^{18}F-fluorination. Production of [^{18}F]F_2 requires the addition of carrier F_2, which reduces the molar activity of the product. The electrophilic labelling method that gives the highest molar activity utilizes a high voltage discharge in the production of [^{18}F]F_2.

In this study, the first of the methods developed for the production of [^{18}F]F_2 replaces the high voltage discharge with a milder, more reliable excitation source i.e., high energy photons. In a second method, the toxic, very reactive F_2 gas used as a carrier is replaced by the very inert SF_6 gas. In addition, new applications of [^{18}F]F_2 based labelling syntheses were developed. [^{18}F]F_2 and its derivatives were used for stereoselective ^{18}F-fluorination, for the production of [^{18}F]-4-fluorosydnone, a new reagent for click chemistry as well as, for the production of 6-[^{18}F]fluoro-marsanidine, a PET tracer candidate for brain α_{2A}-adrenoceptors imaging.

Both methods developed for the production of [^{18}F]F_2 resulted in the production of the desire product in low yield and with moderated molar activity (A_m). Stereoselective ^{18}F-fluorination resulted in high yield and products in high enantiomeric excess. [^{18}F]-4-fluorosydnone, was successfully used for a click reaction, resulting in rapid complete cycloaddition. 6-[^{18}F]fluoro-marsanidine was synthetized with a quality sufficient for preclinical evaluation. However, rapid *in vivo* metabolism limits its usefulness for brain α_{2A}-adrenoceptor imaging in rodents.

Keywords: PET, fluorine-18, [^{18}F]F_2, excimer laser, SF_6, electrophilic ^{18}F-fluorination, stereoselective ^{18}F-fluorination, click chemistry, α_{2A}-adrenoceptors

TIIVISTELMÄ

Anna Krzyczmonik

[^{18}F]F_2 – Uudet tuotantomenetelmät ja käyttötarkoitukset

Turun Yliopisto
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Fluori-18 on positronisäteilevä radionuklidi, joka sopii positroniemissiotomografiassa (PET) käytettävien radiolääkkeiden leimaukseen 109,8 min puoliintumisaikansa, yksinkertaisen hajoamistapansa ja matalan positronienergiansa vuoksi. Fluori-18 leimauskemia alkaa radionuklidin valmistuksesta ja jatkuu ^{18}F-nuklidin liittämisellä bioaktiivisiin molekyyleihin joko nukleofiilisellä tai elektrofiilisellä leimausmenetelmällä. Nukleofiilinen ^{18}F-fluoridilla tehty^{18}F-fluoraus on käytetyin menetelmä, koska ^{18}F-fluoridia voidaan tuottaa suuria määriä. Radioleimatun fluorikaasun, [^{18}F]F_2, tuotanto on haastavampaa, mikä rajoittaa elektrofiilisen leimauksen käyttöä. [^{18}F]F_2-kaasun tuotannossa on käytettävä fluorikaasua kantajana, mikä alentaa reagenssin molaarista aktiivisuutta. Menetelmä, jolla saadaan [^{18}F]F_2:lle korkein molaarinen aktiivisuus, vaatii korkeajännitteisen sähköpurkauksen käyttöä.

Tässä tutkimuksessa on kehitetty menetelmä, jossa [^{18}F]F_2:n tuotannon korkeajännitteinen sähköpurkaus on korvattu lempeämmällä korkeaenergisiä fotoneja käyttävällä viritysmenetelmällä. Työssä kehitettiin myös menetelmä, jolla myrkyllinen ja reaktiivinen kantajana käytetty fluorikaasu korvattiin inertillä SF_6-kaasulla. Molemmat kehitetyt menetelmät osoittautuivat toimiviksi ja näillä pystyttiin syntetisoimaan [^{18}F]F_2:a matalalla saannolla ja tyydyttävällä molaarisella aktiivisuudella.

Tutkimuksessa kehitettiin myös uusia elektrofiilisiä leimausmenetelmiä. [^{18}F]F_2-kaasua ja sen johdannaisia käytettiin stereoselektiivisessä ^{18}F-fluorauksessa ja uuden click-kemiassa käyttökelpoisen [^{18}F]-4-fluorisydnonin leimaussynteesissä. Stereoselektiivisen ^{18}F-fluorauksen saanto ja enantiomeerinen puhtaus olivat erinomaiset. [^{18}F]-4-fluorisydnonia käytettiin menestyksekkäästi myös sykloaddiitioreaktiossa.

Elektrofiilisellä ^{18}F-fluorausmenetelmällä leimattiin myös uusi α_{2A}-adrenerginen PET-merkkiaine, 6-[^{18}F]fluori-marsanidiini. 6-[^{18}F]fluoro-marsanidiini evaluoitiin prekliinisesti jyrsijöissä. Yhdisteen nopea *in vivo* -metabolia oletettavasti rajoittaa yhdisteen käyttöä tulevaisuudessa.

Avainsanat: PET, fluori-18, [^{18}F]F_2, SF_6, eksimeerilaseri, elektrofiilinen ^{18}F-fluoraus, stereoselektiivinen ^{18}F-fluoraus click-kemia, α_{2A}-adrenoceptorit

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ABBREVIATIONS

A_m	Molar activity
AcOH	Acetic acid
AcOF	Acetyl hypofluoride
AgOTf	Silver trifluoromethanesulfonate
α_2-AR	α_2-Adrenoceptor
BCN	*exo*-((*1R,8S*)-bicyclo[6.1.0]non-4-yn-9-yl)methanol
BDE	Bond dissociation energy
CF_3OF	Trifluoromethyl hypofluorite
CT	Computed tomography
CuAAC	Copper-catalyzed Alkyne-Azide Cycloadditions
CuSAC	Copper-catalyzed Sydnone-Alkyne Cycloadditions
$Cu(py)_4(OTf)_2$	Tetrakis(pyridine)copper(II) bis(trifluoromethanesulfonate)
DCA	Dichloroacetic acid
DCM	Dichloromethane
DMA	*N,N*-dimethyloacetamide
ee	Enantiomeric excess
[^{18}F]EF5	[^{18}F]-2-(2-nitroimidazol-1[*H*]-yl)-*N*-(2,2,3,3,3-pentafuoropropyl)-acetamide
EOB	End of bombardment
$FClO_3$	Perchloryl fluoride
[^{18}F]FDG	2-deoxy-2-[^{18}F]fluoro-*D*-glucose
6-[^{18}F]fluoro-*L*-DOPA	6-[^{18}F]fluoro-*L*-3,4-dihydroxyphenylalanine
[^{18}F]F-DPA	*N,N*-diethyl-2-(2-(4-fluorophenyl)-5,7-dimethylpyrazolo[1,5-α]pyrimidine-3-yl)acetamide
Freon-11	Trichlorofluoromethane
GC	Gas chromatography
HBr	Hydrobromic acid
HCl	Hydrochloric acid
HPLC	High performance liquid chromatography
K_{222}	4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane
KO mice	Knockout mice
LC	Locus coeruleus
LS	Lateral septum
Marsanidine	1-[(imidazolidine-2-yl)imino]-1*H*-indazole
MeCN	Acetonitrile

MeF	Fluoromethane
MeI	Iodomethane
MeOH	Methanol
MTBE	Methyl tert-buthyl ether
[^{18}F]NFSi	[^{18}F]-*N*-fluorobenzenesulfonimide
OB	Olfactory bulb
PET	Positron emission tomography
RCP	Radiochemical purity
RCY	Radiochemical yield
ROI	Region of interest
[^{18}F]Selectfluor *bis*(triflate)	[^{18}F]-*N*-fluoro-1,4-diazabicyclo[2.2.2]octane *bis*(triflate)
SF_6	Sulphur hexafluoride
S_N2	Aliphatic nucleophilic substitution
S_NAr	Aromatic nucleophilic substitution
SPAAC	Strain-Promoted Alkyne-Azide Cycloadditions
STR	Striatum
SUV	Standardised uptake values
$T_{1/2}$	Half-life
TAC	Time-activity curve
TEDA	Triethylenediamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
UV	Ultraviolet
VOI	Volume of interest
VUV	Vacuum ultraviolet

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals.

I. **Krzyczmonik A***, Keller T*, Kirjavainen AK, Forsback S, Solin O. Vacuum ultraviolet photon–mediated production of [^{18}F]F_2. J Label Compd Radiopharm. 2017;60:186–193. *Equal contribution

II. **Krzyczmonik A**, Keller T, Kirjavainen AK, Lahdenpohja S, Forsback S, Solin O. Use of SF_6 for the production of electrophilic ^{18}F-fluorination reagents. J Fluorine Chem. 2017;204:90–97.

III. Buckingham F, Kirjavainen AK, Forsback S, **Krzyczmonik A**, Keller T, Newington IM, Glaser M, Luthra SK, Solin O, Gouverneur V. Organomediated Enantioselective ^{18}F Fluorination for PET Applications. Angew Chem Int Ed. 2015;54:13366–13369.

IV. Liu H, Audisio D, Plougastel L, Decuypere E, Buisson D-A, Koniev O, Kolodych S, Wagner A, Elhabiri M, **Krzyczmonik A**, Forsback S, Solin O, Gouverneur V, Taran F. Ultrafast Click Chemistry with Fluorosydnones. Angew Chem Int Ed. 2016;55:12073 – 12077.

V. **Krzyczmonik A**, Keller T, Lopez-Picon F, Forsback S, Kirjavainen AK, Wasilewska A, Scheinin M, Haaparanta-Solin M, Sączewski F, Solin O. Radiosynthesis and Preclinical Evaluation of an α_{2A}-Adrenoceptor Tracer Candidate, 6-[^{18}F]Fluoro-marsanidine. Submitted.

*Equal contribution

1 INTRODUCTION

Fluorine is a chemical element which, under standard conditions, exists as a diatomic highly toxic and reactive gas. Fluorine is the lightest halogen with the highest electronegativity.

Fluorine, in contrast to carbon or nitrogen, does not occur in most natural compounds however, because of its unique properties, it is often used in medical chemistry. Fluorine has a small size and can often be used to replace hydrogen without incurring drastic changes to the biological activity of the modified molecule. Introducing fluorine into an organic structure can increase its lipophilicity, which can be beneficial, especially when the specific target is located in the brain and the designed molecule needs to penetrate the blood-brain barrier. Today more than 25% of the drugs which are in use contain fluorine in their structure.

Positron emission tomography (PET) is a diagnostic imaging technique which allows for the study of biological process on the molecular level in living organisms. This method is based on the use of positron emitting radionuclides which are used for the labelling of biologically active molecules. Such a "tracer" is injected into a living subject and binds to a specific target in the body. Positrons emitted by the radioactive radionuclide are annihilated with electrons and thereby generate two gamma quanta travelling in opposite directions, both with an energy of 511 keV. This energy quanta can be detected simultaneously by PET scanner to obtain the 3D image of the radioactivity distribution in the body.

While there are many radionuclides which are suitable for use as PET tracers such as, carbon-11, nitrogen-14, oxygen-15, gallium-68 or copper-64, the most commonly used is fluorine-18 (^{18}F). It has a convenient half-live of 109.8 min, low positron energy (β_{max} = 635 keV) and clean β^+ decay profile (97% of β^+ decay, 3% electron capture).

Fluorine can be introduced into the molecular structure in two ways: nucleophilically or electrophilically. In traditional organic chemistry fluorination, the method is chosen based on the reactivity profile of the precursor. In radiochemistry, nucleophilic ^{18}F-fluorination is the most popular method for ^{18}F-labelling. Its main advantages over the electrophilic fluorination is the easy access to a nucleophilic fluorination reagent, [^{18}F]fluoride, with high molar activity (A_m).

In this thesis I present new methods for the production of electrophilic ^{18}F-fluorinating reagents together with novel applications for them (Figure 1).

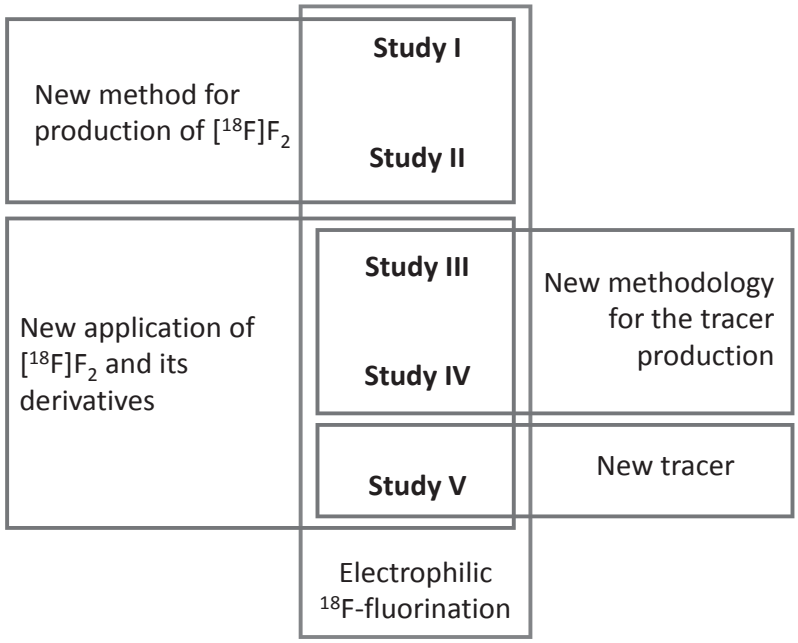


Figure 1 The relationship between studies I – V

2 REVIEW OF LITERATURE

2.1 Fluorine

Fluorine is a chemical element with interesting properties. This lightest halogen is known to have the highest electronegativity and is also the most reactive element in its pure form as fluorine gas. Elemental fluorine was first prepared in 1886 by Henri Moissan (Moissan 1886, Banks 1986, Flahaut and Viel 1986). He performed the electrolysis of anhydrous hydrogen fluoride and potassium fluoride. Since then other methods for the production of elemental fluorine have also been developed (Christe 1986, Wang et al. 1988, Bezmelnitsyn et al. 1996).

While there are not many natural compounds containing carbon–fluorine bonds, there is a high interest in fluorine-containing pharmaceuticals. The small size of the fluorine often allows one to replace a hydrogen in the structure without changing the geometry of the molecule although it has a profound effect on the chemical, physical and biological properties (Shah and Westwell 2007, Wang et al. 2014).

In radiochemistry, nucleophilic ^{18}F-fluorination is the most common method used for the production of ^{18}F-labelled PET tracers. Electrophilic ^{18}F-fluorination methods are limited in use mostly because of the low A_m of $[^{18}F]F_2$. For this reason, nucleophilic methods are often preferable, regardless of the reactivity profile of the labelled molecule.

Despite this, electrophilic synthesis remains the easiest means of ^{18}F-labelling of electron rich structures such as activated aromatic rings or alkenes. What is more, the electrophilic reactions are usually fast and easy to automate; the reaction is made by the bubbling of $[^{18}F]F_2$ in noble gas through a precursor solution. The selectivity of electrophilic ^{18}F-fluorination has been improved by the development of more selective $[^{18}F]F_2$ derivatives (Lerman et al. 1981, Sood et al. 1983, Ehrenkaufer and MacGregor 1983, Umemoto and Tomita 1986, Oberdorfer et al. 1988a, Oberdorfer et al. 1988b, Satyamurthy et al. 1990, Teare et al. 2007, Teare et al. 2010).

2.2 Production of fluorine-18

2.2.1 Production of [^{18}F]fluoride

Fluorine-18 can be produced using particle accelerators, especially cyclotrons (Table 1). Nowadays, the most common way to produce fluoride-18 is via the ^{18}O(p,n)^{18}F nuclear

reaction which leads to high A_m [^{18}F]fluoride (Nickles et al. 1983, Kilbourn et al. 1984, Kilbourn et al. 1985). This reaction is carried out on oxygen-18 enriched water which is placed in a target and irradiated with low energy protons (~18 MeV). This well optimized and effective nuclear reaction can be easily performed in small, on-site cyclotrons (Snyder and Kilbourn 2002).

2.2.2 Production of [^{18}F]fluorine with in-target method: ^{20}Ne(d,α)^{18}F

The ^{20}Ne(d,α)^{18}F nuclear reaction was first reported in 1937 (Snell 1937) and resulted in the first reported production of fluorine-18. Although the nuclear reaction was known, the process which allowed the recovery of [^{18}F]F_2 from the target was not published until 1978 (Lambrecht et al. 1978, Casella et al. 1980, Blessing et al. 1986). To be able to recover [^{18}F]F_2, a nickel target is first passivated with F_2 at 300–600 °C and a thin layer of NiF_2 is formed on the surface of the target. The target is filled with pressurized neon gas containing a small amount of non-radioactive F_2 and irradiated with a deuteron beam.

Extensive studies were performed to establish the parameters which influence the recovery of the activity from the target chamber (Lambrecht et al. 1978, Casella et al. 1980). The amount of [^{18}F]F_2 which is recovered from the target is a function of the target pressure and the concentration of the carrier fluorine and also depends on the current dose to the target.

2.2.3 Production of [^{18}F]fluorine with in-target method: ^{18}O(p,n)^{18}F

Another method requires the use of the ^{18}O(p,n)^{18}F nuclear reaction for the production of [^{18}F]F_2. The nuclear reaction carried out on an oxygen target is much more efficient (Ruth and Wolf 1979) than that carried out on a neon target. Also, the reaction does not require the use of a deuteron beam which has only half of the energy of the proton beam.

This reaction utilized oxygen-18 enriched O_2 as a target gas (Nickles et al. 1984, Chirakal et al. 1995, Roberts et al. 1995, Bishop et al. 1996, Hess et al. 2000). After the irradiation of the target with a proton beam, the produced ^{18}F is trapped on the target walls. For the recovery of [^{18}F]F_2, the target is filled with a mixture of non-radioactive F_2 in noble gas (max 1% F_2 in neon or krypton) and re-irradiated with a proton beam.

The first method reported for the production of [^{18}F]F_2 via a ^{18}O(p,n)^{18}F nuclear reaction used a nickel target chamber (Nickles et al. 1984). This method required long and difficult passivation and re-passivation procedures to form a thin layer of NiF_2 on the target wall which furthermore needed to be repeated before each irradiation. Changing the target

chamber material to aluminium resulted in a simplification of the process. Aluminium fluoride is not hygroscopic in contrast to nickel fluoride and requires only a short re-passivation procedure before irradiation (Chirakal et al. 1995, Bishop et al. 1996, Hess et al. 2000).

2.2.4 Production of [^{18}F]fluorine with post-target method

An alternative to these traditional in-target approaches is the post-target method for the production of [^{18}F]F_2 (Bergman and Solin 1997). This method starts from the production of high A_m [^{18}F]fluoride via the ^{18}O(p,n)^{18}F nuclear reaction which is then transformed into [^{18}F]F_2. Thus no additional gas target is needed and [^{18}F]fluoride can be used for both the nucleophilic reaction and production of [^{18}F]F_2 for electrophilic fluorination.

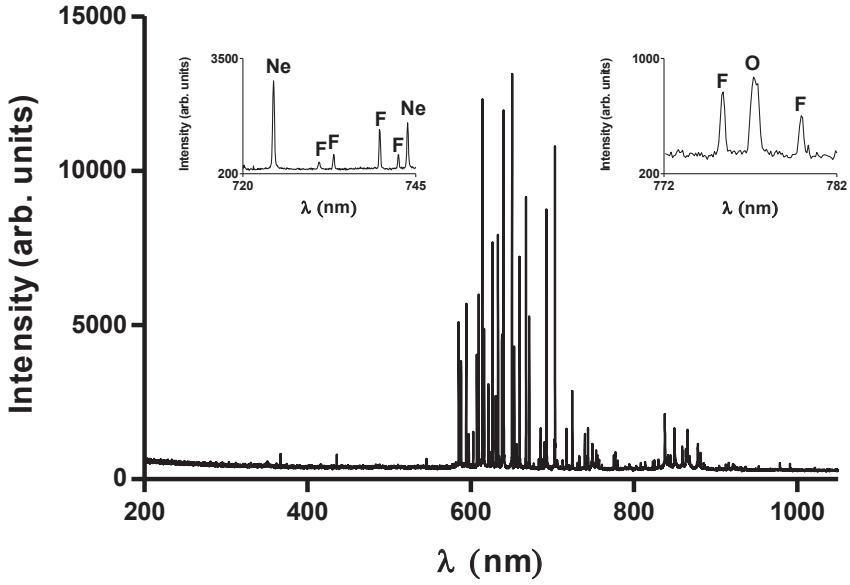


Figure 2 Optical emission spectrum of light emitted during high voltage discharge excitation of F_2/Ne gas mixture obtained according to the procedure reported by Bergman and Solin (Bergman and Solin 1997). Atomic emission lines characteristic of fluorine and neon atoms are observed

In this method, target water is first removed by azeotropic distillation with acetonitrile (MeCN) and the dry [^{18}F]fluoride is then converted into [^{18}F]MeF. After gas chromatography (GC) purification [^{18}F]MeF is mixed with a small amount of carrier F_2 in neon. The gas mixture is excited with a high voltage electrical discharge which promotes the ^{19}F/^{18}F isotopic exchange (Figure 3). During discharge, molecular and atomic bonds in [^{18}F]MeF

and the carrier F_2 are dissociated and rearranged into $[^{18}F]F_2$ and different ^{18}F-labelled C–F species. Atomization of the $[^{18}F]$MeF and carrier F_2 can be confirmed by optical emission spectrometry (Figure 2).

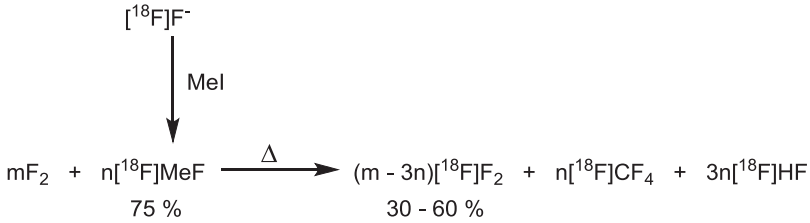


Figure 3 Post-target production of $[^{18}F]F_2$ with the respective yields for the synthesis of $[^{18}F]$MeF and isotopic exchange reaction (Bergman and Solin 1997). Overall yield for the $[^{18}F]F_2$ synthesis from $[^{18}F]F^-$ varies from 23–45% depending on the amount of carrier F_2 used for the reaction

This method provides electrophilic reagents with a much higher A_m than any previously reported in-target production method.

Table 1 Different approaches for production of fluorine-18. ^{18}F Recovery yield, for in-target methods, defined as percentage of ^{18}F-activity transferred from the target to reaction vessel or, for post-target method, activity of $[^{18}F]F_2$ available for the labelling after synthesis

Nuclear reaction	Target material	^{18}F Recovery yield (%)	A_m (GBq/µmol)	Product	Reference
Nucleophilic $[^{18}F]$fluoride					
$^{18}O(p,n)^{18}F$	$[^{18}O]H_2O$	> 90”	>5200§	$[^{18}F]F^-$	(Solin et al. 1988)
Electrophilic $[^{18}F]$fluorine					
In-target methods					
$^{18}O(p,n)^{18}F$	$[^{18}O]O_2$ + F_2/noble gas	~ 43#	0.6*	$[^{18}F]F_2$	(Hess et al. 2000)
$^{20}Ne(d,\alpha)^{18}F$	$^{nat}Ne+F_2$	~ 40”	0.13	$[^{18}F]F_2$	(Blessing et al. 1986)
Post-target method					
$^{18}O(p,n)^{18}F$	$[^{18}O]H_2O$	23 – 45’	55	$[^{18}F]F_2$	(Bergman and Solin 1997)

*Highest reported A_m = 1.3 GBq/µmol (Chirakal et al. 1995).
”^{18}F-fluorination reagent available at end of bombardment (EOB).
#$[^{18}F]F_2$ available after recovery irradiation 15–30 min after EOB.
’$[^{18}F]F_2$ available after $[^{18}F]F^-$ to $[^{18}F]F_2$ transformation 20 min after EOB.
§Highest reported A_m = 43 TBq/µmol (Füchtner et al. 2008).

2.3 Excimer laser

Excimer lasers are a group of gas lasers which operate in the ultraviolet (UV) region and generate nanosecond pulses. The name of the laser comes from the term "excited dimer" which refers to excited diatomic molecules e.g., Xe_2 which were used in the first excimer lasers. Since modern excimer lasers also use excited complexes, the more precise name would be exciplex laser, although usually the name "excimer" laser is used for both types.

The gain medium for the excimer laser usually consists of a mixture of a noble gas and a halogen (or only halogen in the case of an F_2 excimer laser) in a buffer gas (helium or neon). The gas mixture is excited with a high voltage electrical discharge delivered in short, nanosecond pulses in order to produce ions and metastable products of both the halogen and noble gas, which then create excimers. These unstable molecules immediately decay to their ground states. Since most of the excimers used in this technology do not exist in their ground state, the decay happens together with the rapid dissociation of the excimer.

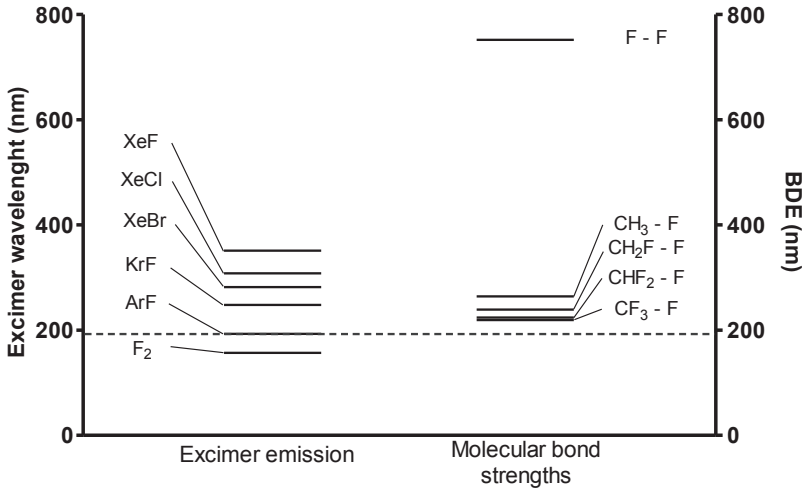


Figure 4 Examples of the excimer laser energies and bond dissociation energies (BDE) for simple C–F compound. Dashed line marks the energy of ArF laser which is higher than any BDEs of simple C–F compounds and F_2

$$E = \frac{hc}{\lambda}$$

Equation 1 Correlation between energy and wavelength of a photon, demonstrating that the energy is inversely proportional to the wavelength. While h – Planck constant and c – speed of light are constant, the wavelength of the photon can be given as a value of the energy which is a common practice in the case of lasers. E – energy, h – Planck constant, c – speed of light, λ – wavelength

An argon fluoride excimer laser is commonly used in eye surgery for laser-assisted in situ keratomileusis (LASIK) (Vogel and Venugopalan 2003, Blumenkranz 2014). It is a reliable device which generates a laser beam with photons having an energy of 193 nm (Equation 1). While bond dissociation energies (BDE) for the simplest C–F compounds (CH_3F, CH_2F_2, CHF_3, CF_4) are in range of 453–546 kJ/mol and the BDE for F_2 is 159 kJ/mol (Dolbier 2005), The ArF excimer laser provides enough energy to dissociate these molecules (Figure 4). The photons generated by this laser are in the range of vacuum UV light (VUV), which means that they are absorbed by the oxygen molecules in the air. To prevent this the laser beam is propagated through helium.

2.4 Sulphur hexafluoride (SF_6)

SF_6 is an inert, non-toxic, non-flammable, colourless gas. It is widely used as an isolator in gas insulated switchgear, gas insulated transmission lines and electrostatic accelerators. Despite its industrial uses, its applications in chemistry are rather limited. SF_6 as a source of fluorine for the C–F bond formation usually requires a high temperature and high pressure (Batt and Cruickshank 1966, Hagen and Callaway 1975). Only recently the first practical application of SF_6 in organic synthesis has been reported (McTeague and Jamison 2016) (Figure 5). Photoredox activation of SF_6 has been used for deoxyfluorination of allylic alcohols, proving that SF_6 can be used as a source of fluorine atoms.

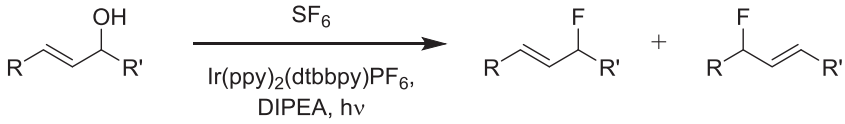


Figure 5 Photoredox deoxyfluorination of allylic alcohols with SF_6

It has been demonstrated that SF_6 is decomposed under electrical stress conditions and creates reactive fluorine species (Dibeler and Mohler 1948, Beyer et al. 2000, Liu et al. 2015). This finding suggests that SF_6 could be an alternative source of carrier fluorine for

reactions promoted by high voltage discharge. Its inert and non-toxic properties make it safe and easy to work with, thus it would be beneficial to use SF_6 instead of the fluorine gas which has so far been used in radiochemistry as a source of carrier fluorine.

2.5 Molar activity (A_m)

Molar activity (A_m) is defined as the measured radioactivity per mole of compound (Coenen et al. 2017).

$$\text{Maximum theoretical } A_m = N_A \frac{\ln 2}{T_{1/2}} \; [\, \text{Bq}/\mu\text{mol} \,]$$

Equation 2 Equation for calculating the maximum A_m. N_A = Avogadro's constant, $T_{1/2}$ = half-life

The maximum theoretical A_m for radionuclides depends only on their half-lives ($T_{1/2}$) (Equation 2). For fluorine-18, the maximum A_m is $6.34 \cdot 10^4$ GBq/μmol; however, this value is never achieved due to the presence of the stable isotope fluorine-19 (Phelps 2001). In practice it has been demonstrated that, for fluorine-18 production, with proper target handling and the use of fluorine-free materials, an A_m of $4.3 \cdot 10^4$ GBq/μmol (about 75% of maximum theoretical A_m) can be achieved (Füchtner et al. 2008, Lapi and Welch 2013).

The A_m is especially important in the case of PET tracers for which the amount of activity which is injected into a study subject needs to be sufficient to obtain good quality PET images. At the same time, the injected mass needs to be low enough to avoid pharmacological or potentially toxic effects. Depending on the study target, a low A_m might be sufficient (for example in cancer studies) but in some cases, especially in neurological studies, a very high A_m is required. For the receptors or transporters studies the saturation of the target should be kept below 5 to 10 % (Passchier et al. 2002). In this case, it is important to keep the A_m very high so that the target is not saturated with the high amount of nonradioactive compound. Also, the ratio of bound (B) to free (F) tracer, which can be approximated by the ratio of binding site concentration and equilibrium dissociation constant (B_{max}/K_d), should be ≥ 10 to obtain a good quality image (Eckelman 1998). For low abundant targets it is important to use high affinity tracer to get a high-quality image and also high A_m to keep the target saturation on the low level.

Due to the activity decay (the amount of non-radioactive compound stays the same while the radioactive component is continuously decreasing) the time at which the value of the A_m was measured needs to be stated.

2.6 Nucleophilic ^{18}F-fluorination

Nowadays, most of the ^{18}F-labelled PET tracers are made by nucleophilic synthesis routes because of the high availability of high A_m [^{18}F]fluoride.

The aqueous [^{18}F]fluoride produced during the nuclear reaction suffers from low reactivity because of hydrogen bonding between water and fluoride molecules. The reactivity of the [^{18}F]fluoride can be enhanced by the placing of counter ions or by azeotropic distillation with MeCN or the combination of both methods. The most popular counter ions are alkali metal cations, especially potassium, introduced as carbonate or oxalate. The crown ethers (18-crown-6) or cryptands (polyaminoethers; Kryptofix 222) are added to increase the solubility of the [^{18}F]fluoride in organic solvents (Spitznagle and Marino 1977, Block et al. 1986, Hamacher et al. 1986, Miller et al. 2008, Cai et al. 2008, Ametamey et al. 2008). The target water is removed by azeotropic distillation with MeCN. Other groups of counter ions which can be used are soft metal cations with large radii such as; Cs^+, Rb^+ or tert-alkylammonium salts (e.g., tBu$_4$N$^+$, Et$_4$N$^+$) which do not require the addition of cryptands (Jewett et al. 1988, Schirrmacher et al. 2007, Cai et al. 2008, Ametamey et al. 2008).

[^{18}F]Fluoride is mostly used for aliphatic nucleophilic substitution (S_N2) and aromatic nucleophilic substitution (S_NAr).

For S_N2 reactions, precursors containing halides or alkyl sulfonate esters (e.g., triflates, tosylates, mesylates, nosylates) as leaving groups are most often used (Miller et al. 2008). This reaction starts from a nucleophilic attack on the sp^3 hybridized carbon centre with the leaving group attached to it. The formation of the new C-[^{18}F]F bond and the breaking of the C-leaving group bond occur simultaneously. These reactions leads to inversion of the configuration on the stereogenic carbon centre.

Aromatic nucleophilic substitution with [^{18}F]fluoride is more challenging because of the high density of negative charge in the aromatic ring. The traditional approach requires the precursor not only to contain a good leaving group but also a strong electron withdrawing group in *ortho* or *para* position (Miller et al. 2008, Cai et al. 2008, Preshlock et al. 2016b).

Since the structure of the tracer is mostly defined by its biological activity, there has been a great deal of interest in developing leaving groups which allow nucleophilic ^{18}F-fluorination of non-activated or electron-rich aromatic systems.

Recently, a new generation of precursors (Figure 6) such as: aryl(2-thienyl)iodonium salts (Ross et al. 2007), triarylsulfonium salts (Mu et al. 2012) or spirocyclic iodonium ylides (Rotstein et al. 2014) has been developed for ^{18}F-fluorinating of non-activated or even electron-rich aromatic systems.

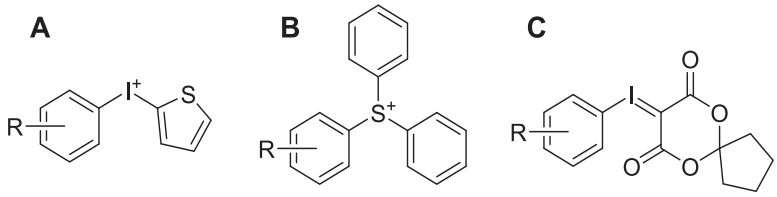


Figure 6 Examples of novel precursors for nucleophilic ^{18}F-fluorination: **A** aryl(2-thienyl)iodonium salts **B** triarylsulfonium salts **C** spirocyclic iodonium ylides

Also, there has been a growing interest in copper-mediated nucleophilic ^{18}F-fluorination. Use of arylboronate esters (Tredwell et al. 2014, Preshlock et al. 2016a) or aryl stannanes (Gamache et al. 2016) in reactions catalyzed by copper complexes allows for the ^{18}F-fluorination of non-activated or even electron-rich aromatic systems (Figure 7).

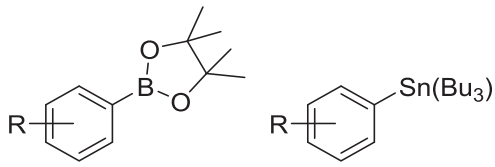


Figure 7 Precursors for copper-mediated nucleophilic ^{18}F-fluorination

2.7 Electrophilic ^{18}F-fluorination

Electrophilic ^{18}F-fluorination is used for fluorinating electron-rich structures such as aromatic rings or alkenes. In an electrophilic substitution reaction, only one atom from [^{18}F]F_2 is attached to the molecule and while [^{18}F]F_2 produced from an isotopic ^{18}F/^{19}F reaction contains only one ^{18}F atom, statistically, only 50% radiochemical yield (RCY) can be achieved for this reaction. For the addition reaction to alkenes the theoretical RCY is 100%.

Historically, the most important electrophilic reaction is the first synthesis of 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG). In 1978, Ido et al. reported the production of [^{18}F]FDG by addition of [^{18}F]F_2 to triacetoxy glucal (Ido et al. 1978). This reaction resulted in a mixture of [^{18}F]FDG and 2-deoxy-2-[^{18}F]fluoro-D-mannose (Figure 8).

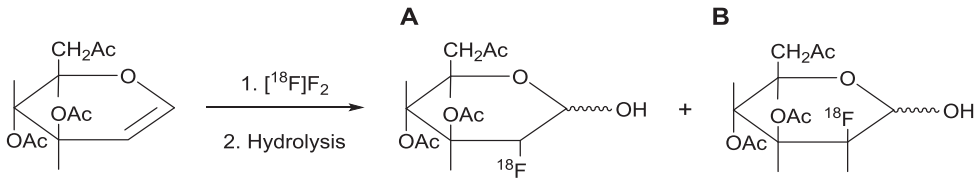


Figure 8 Electrophilic radiosynthesis of: **A** [^{18}F]FDG and **B** 2-Deoxy 2-[^{18}F]fluoro-D-mannose

Selective aromatic electrophilic substitution requires the use of a precursor containing a good leaving group. Organometallic groups, such as alkylated tin, germanium or mercury (Coenen and Moerlein 1987, Namavari et al. 1995, Forsback et al. 2008, Eskola et al. 2012b), have been successfully used, however due to their toxicity, boronic acids and esters have been developed as alternative, less toxic leaving groups for electrophilic ^{18}F-fluorination (Furuya et al. 2008, Stenhagen et al. 2013) (Figure 9).

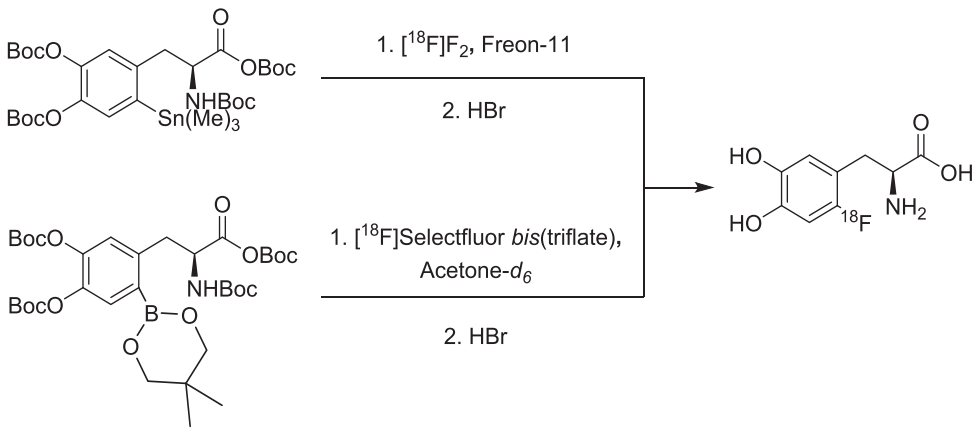
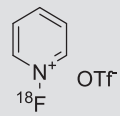
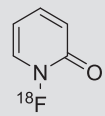
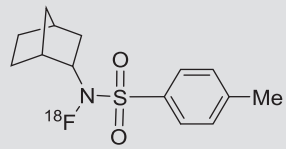
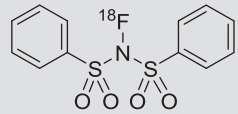
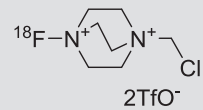


Figure 9 Synthesis of 6-[^{18}F]fluoro-*L*-DOPA from a precursor containing trimethyl tin group and arylboronic ester group (Forsback et al. 2008, Stenhagen et al. 2013)

Table 2 Electrophilic ^{18}F-fluorinating reagents: $[^{18}F]F_2$ and its derivatives (references are given in respective subchapters)

Group of electrophilic reagents	**Electrophilic ^{18}F-fluorinating reagent**
	[^{18}F]fluorine
	$[^{18}F]F_2$
	[^{18}F]xenon difluoride
	$[^{18}F]XeF_2$
-[^{18}F]OF	[^{18}F]trifluoromethyl hypofluorite
	$[^{18}F]CF_3OF$
	[^{18}F]acetyl hypofluoride
	$[^{18}F]CH_3COOF$
	[^{18}F]perchloryl fluoride
	$[^{18}F]FClO_3$
-[^{18}F]NF	*N*-[^{18}F]fluoropyridinium triflate 
	1-[^{18}F]fluoro-2-pyridone 
	N-[^{18}F]fluoro-*N*-alkylsulfonamides 
	[^{18}F]NFSi 
	[^{18}F]Selectfluor *bis*(triflate) 

2.7.1 [^{18}F]F_2

[^{18}F]F_2 is the simplest reagent for electrophilic fluorination (Casella et al. 1980). Direct ^{18}F-fluorination with [^{18}F]F_2 is fast and straightforward. The labelling procedure normally requires only the bubbling of freshly produced [^{18}F]F_2 gas through the precursor solution and the labelling is completed within 0.5 to 1 min.

Unfortunately, due to the high reactivity of [^{18}F]F_2, direct labelling often leads to production of different side products, which not only decrease the RCY but also may lead to problematic and time-consuming purification.

What is more, for some compounds, [^{18}F]F_2, instead of substituting the leaving group, the direct fluorination leads to products which can still contain the leaving group and have been labelled at different positions (Keller et al. 2017). This problem can be solved by the use of different, milder and more selective electrophilic reagents which can be produced from [^{18}F]F_2 (Table 2).

[^{18}F]F_2 can be also used for the electrophilic addition reaction. In 2001, synthesis of [^{18}F]-2-(2-nitroimidazol-1[*H*]-yl)-*N*-(2,2,3,3,3-pentafuoropropyl)-acetamide ([^{18}F]EF5), a hypoxia tracer, was reported (Dolbier et al. 2001, Komar et al. 2008, Eskola et al. 2012a). It is produced by the addition of [^{18}F]F_2 (Figure 10) to an allyl precursor and is the only known method for the labelling of the –C_2F_5 group.

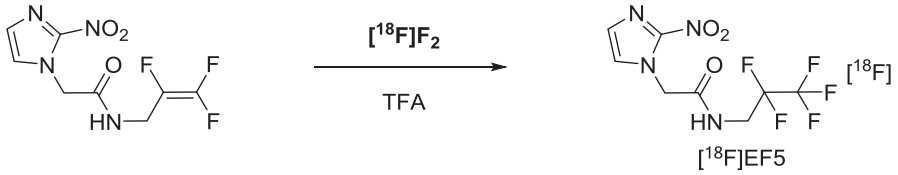


Figure 10 Synthesis of [^{18}F]EF5

2.7.2 [^{18}F]XeF_2

XeF_2 is a relatively mild electrophilic fluorinating reagent which can be widely used for the fluorination of different organic structures (Firnau et al. 1980, Tius 1995, Smith 1999, Tramsek and Zemva 2000, Ramsden 2014, Chatalova-Sazepin et al. 2016). The production of XeF_2 was first reported in 1962 and was achieved by irradiating the Xe/F_2 mixture with UV photons (250–350 nm), heating the same mixture at 400 °C or by excitation with electrical discharge (Chernick et al. 1962, Weeks et al. 1962, Claassen et al. 1962, Smith 1963). XeF_2 is a solid compound which can be easily dissolved and stored in different

organic solvents such as, Freon-11, MeCN or DCM (Dukat et al. 1993). Aqueous solutions of XeF_2 have a weak absorbance at λ_{max} 242 nm, which makes it possible to detect with UV detectors and it can be analysed by HPLC (Smith 1999, Shaw et al. 2011).

[^{18}F]XeF_2 can be produced from [^{18}F]F_2 by heating it with Xe in a closed vessel at 390 °C for 30−40 min (Sood et al. 1983, Chirakal et al. 1984b). It can also be synthesized by isotopic exchange (Schrobilgen et al. 1981, Constantinou et al. 2001, Lu and Pike 2010). Like [^{18}F]acetyl hypofluoride, [^{18}F]XeF_2 can be steroselectively added across the double bond in the production of [^{18}F]FDG with exclusive syn addition (Sood et al. 1983). [^{18}F]XeF_2 can be used for ^{18}F-fluorination of both aliphatic (Figure 11**A**) and aromatic (Figure 11**B**) compounds (Lu and Pike 2010).

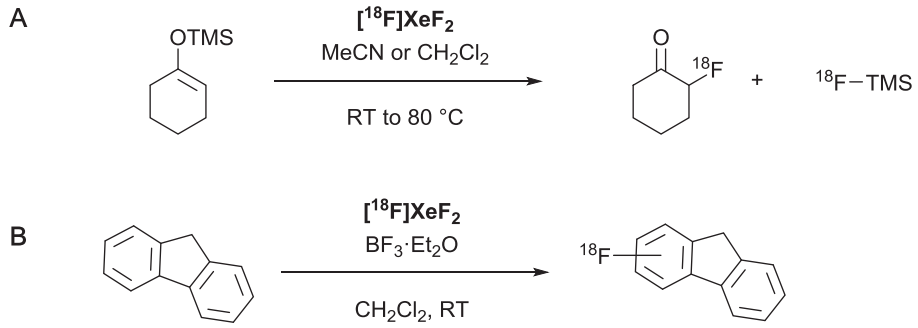


Figure 11 Examples of the use of [^{18}F]XeF_2 for **A** aliphatic and **B** aromatic ^{18}F-fluorination

2.7.3 -[^{18}F]OF reagents

A group of -[^{18}F]OF reagents has been developed as alternative reagents for electrophilic ^{18}F-fluorination. The first -[^{18}F]OF reagent [^{18}F]trifluoromethyl hypofluorite ([^{18}F]CF_3OF) was synthesized in 1978 (Neirinckx et al. 1978) but did not at that time find any practical application for tracer production. Later, [^{18}F]acetyl hypofluoride and [^{18}F]perchloryl fluoride were produced and were demonstrated to be more selective alternatives to [^{18}F]F_2 (Shiue et al. 1982, Ehrenkaufer and MacGregor 1983).

[^{18}F]Acetyl hypofluoride

In 1981, the new electrophilic reagent – acetyl hypofluoride (CH_3COOF) − was introduced for the fluorination of activated aromatic systems (Lerman et al. 1981, Rozen et al. 1981).

In 1982 the first labelling of acetyl hypofluoride with fluorine-18 was reported. It was produced by bubbling the freshly produced $[^{18}F]F_2$ gas through a solution of ammonium acetate in AcOH (Figure 12**A**) (Shiue et al. 1982). The reagent produced was used for the synthesis of $[^{18}F]$FDG. The results of this experiment showed that $[^{18}F]$AcOF is more selective than $[^{18}F]F_2$ and is stereoselective for syn addition to a double bond. $[^{18}F]$acetyl hypofluoride was also successfully used for regioselective synthesis of 6-$[^{18}F]$fluoro-*L*-DOPA (Chirakal et al. 1984a, Adam et al. 1986). Further studies resulted in the development of a new, more convenient gas−solid phase production method (Jewett et al. 1984) (Figure 12**B**).

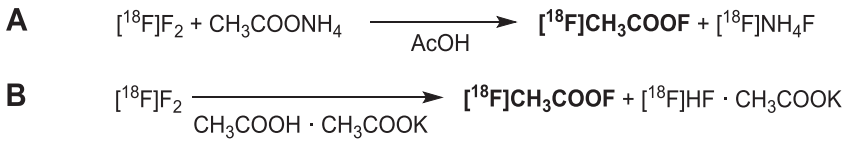


Figure 12 Two approaches to the synthesis of $[^{18}F]$acetyl hypofluoride. **A** gas−liquid and **B** gas−solid production methods

[^{18}F]Perchloryl fluoride

$[^{18}F]$Perchloryl fluoride ($[^{18}F]FClO_3$) can be prepared by passing the freshly produced $[^{18}F]F_2$ gas through a column containing $KClO_3$ at 90 °C (Figure 13). The resulting gas mixture is passed through NaOH and $Na_2S_2O_3$ to remove any unreacted $[^{18}F]F_2$ as well as any potential chlorine oxides formed during the reaction. $[^{18}F]$Perchloryl fluoride was further used for reaction with aryl lithiums, which resulted in the formation of a product with acceptable RCY. Analogous reactions carried out with $[^{18}F]F_2$ directly resulted in poor RCY and the formation of unidentified by-products (Ehrenkaufer and MacGregor 1983).

Figure 13 Radiosynthesis of $[^{18}F]$perchloryl fluoride

Due to its strong oxidizing potential, perchloryl fluoride is a potentially explosive compound and needs to be handled with care.

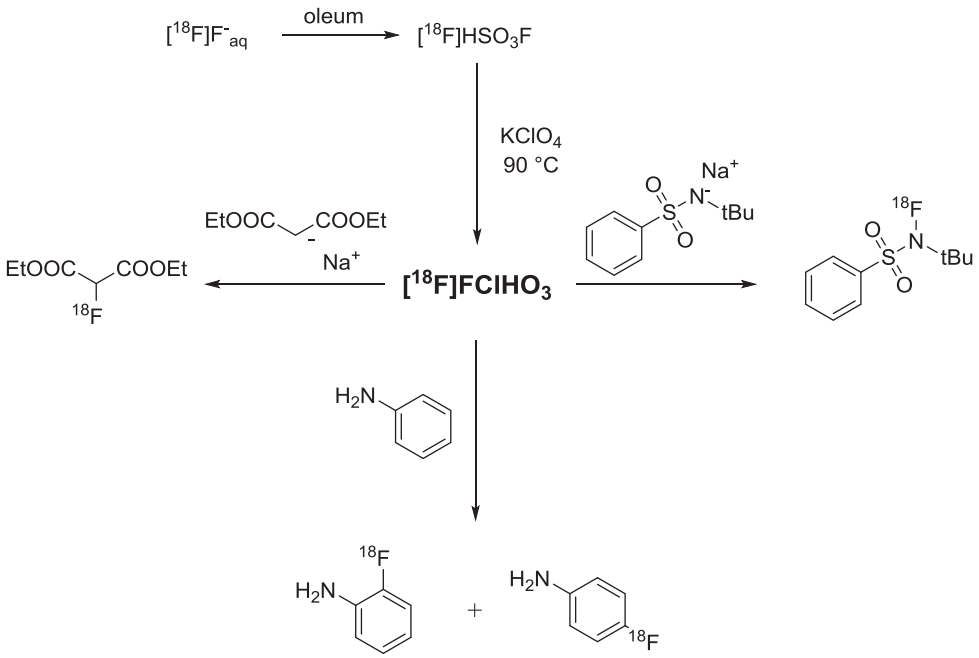


Figure 14 Non-carrier-added production of $[^{18}F]FClO_3$ and its applications (Hiller et al. 2008)

In 2008, Hiller et al. (Hiller et al. 2008) reported on the non-carrier-added production of $[^{18}F]FClO_3$ (Figure 14). The method presented resulted in a low yield (1–6%) and with low reproducibility – most experiments failed. The A_m achieved with this method was 5 GBq/µmol (determined only for *o*-[^{18}F]fluoro-aniline).

2.7.4 -[^{18}F]NF reagents

The group of -NF reagents has been developed to constitute mild and easy to handle electrophilic fluorinating reagents. There are two types of these compounds; neutral (R_2NF) or quaternary ammonium salts ($R_3NF^+A^-$), the latter containing a non-nucleophilic anion. Most of the -NF fluorinating regents can be produced in a straightforward reaction with elemental fluorine which makes it possible for them to be labelled with $[^{18}F]F_2$ and used in the production of PET tracers.

From the rather large variety of -NF compounds, only a few have been labelled with fluorine-18: *N*-[^{18}F]fluoropyridinium triflate (Oberdorfer et al. 1988a), 1-[^{18}F]fluoro-2-pyridone (Oberdorfer et al. 1988b), [^{18}F]-*N*-fluorobenzenesulfonimide ([^{18}F]NSFi) (Teare

et al. 2007) and [^{18}F]-*N*-fluoro-1,4-diazabicyclo[2.2.2]octane derivatives (Teare et al. 2010).

N-[^{18}F]fluoropyridinium triflate

N-[^{18}F]fluoropyridinium triflate can be produce by passing [^{18}F]F_2 through the *N*-trimethylsilylpyridinium solution at −42 ˚C. It was demonstrated that the reagent produced reacts with Grignard reagents, carbanions or enolates under rather mild conditions and leads to corresponding ^{18}F-labelled products (Figure 15) (Umemoto et al. 1986, Umemoto and Tomita 1986, Oberdorfer et al. 1988a).

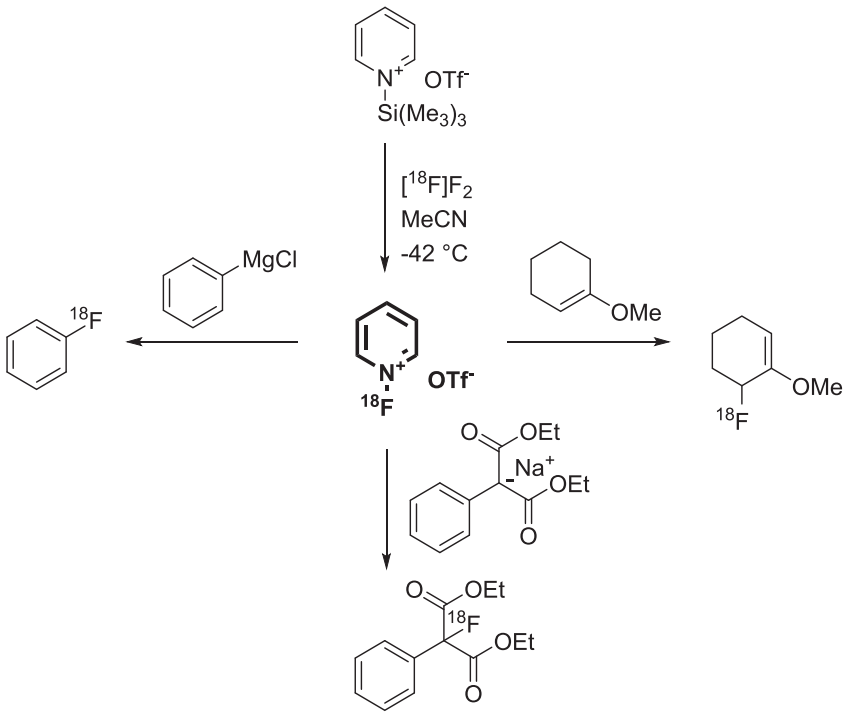


Figure 15 Production and applications of *N*-[^{18}F]fluoropyridinium triflate

1-[^{18}F]fluoro-2-pyridone

1-[^{18}F]fluoro-2-pyridone was prepared by passing [^{18}F]F_2 through a solution of 2-(trimethylsiloxy)pyridine in $CFCl_3$ (Figure 16**A**). The reactivity of the labelling reagent towards organometallic compounds was demonstrated by the reaction with methyl lithium (Figure 16**B**) (Oberdorfer et al. 1988b).

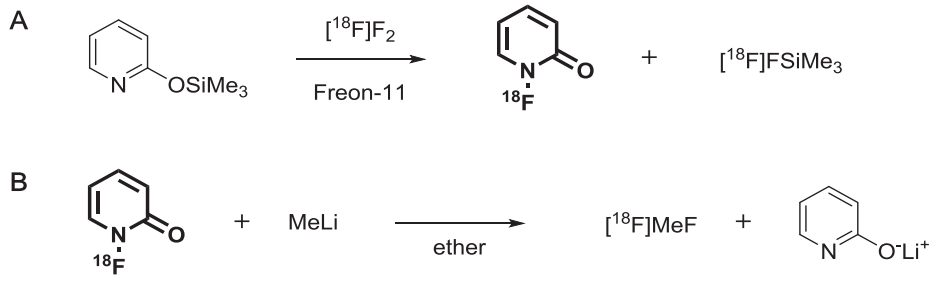


Figure 16 **A** Preparation and **B** application of 1-[^{18}F]fluoro-2-pyridone

N-[^{18}F]fluoro-N-alkylsulfonamides

The group of *N*-[^{18}F]fluoro-*N*-alkylsulfonamides was presented in 1990 by Satyamurthy et al. (Satyamurthy et al. 1990) as reagents for mild and regioselective ^{18}F-fluorination (Figure 17**A**). A simple synthesis procedure (Figure 17) was tested on 8 different sulfonamides, resulting in the formation of products with an RCY of 13–45% (max. theoretical RCY is 50%). Reactivates of the reagents synthesized were demonstrated in reactions with different organometallic compounds (Figure 17**B**).

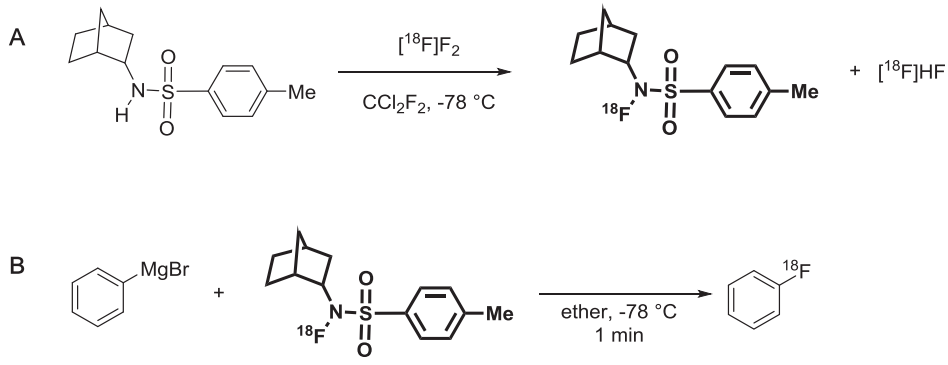


Figure 17 **A** Preparation and **B** an example of application of N-[^{18}F]fluoro-N-alkylsulfonamides

[^{18}F]NFSi

NFSi is a solid compound which is stable in room temperature and is soluble in common organic solvents such as: tetrahydrofuran (THF), DCM, MeCN or acetone (Differding and Ofner 1991). NFSi has been used for the fluorination of organometallic compounds as well as slightly activated aromatics (Davis et al. 1995, Rostami 2007, Liang et al.

2013). It has also been used for enantioselective organocatalyzed fluorination of α-aldehydes (Steiner et al. 2005, Beeson and MacMillan 2005, Franzen et al. 2005). [^{18}F]NFSi can be easily prepared from [^{18}F]F_2 gas (Figure 18**A**) and used in solution for electrophilic ^{18}F-fluorination (Figure 18**B**) (Teare et al. 2007).

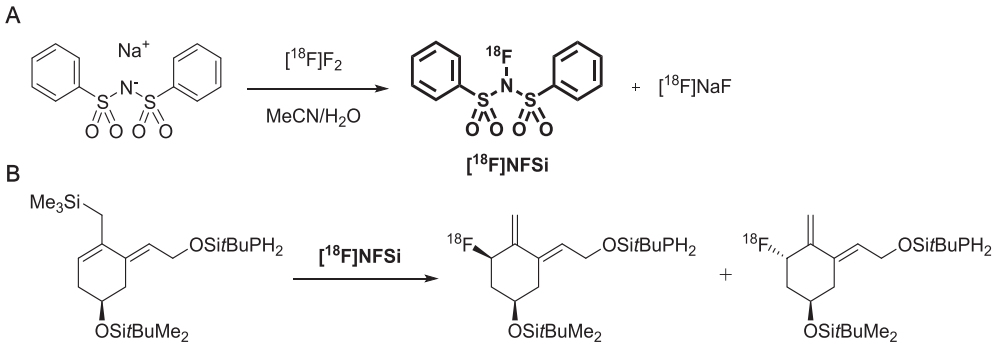


Figure 18 **A** Radiosynthesis and **B** application of [^{18}F]NFSi

F-TEDA-X reagents and [^{18}F]Selectfluor bis(triflate)

In 1988, *N*-fluoroquinuclidinium salts were reported as a new group of fluorinating N-F reagents (Banks et al. 1988, Banks and Sharif 1988). The reagent presented was a stable white solid compound which could be easily synthetized with good yield. The use of triethylenediamine (TEDA) moiety as a base for the molecule resulted in the discovery of the group of 1-alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts (F-TEDA-X, Selectfluor^{TM}) (Figure 19), which have the same non-toxic, easy to handle characteristics as *N*-fluoroquinuclidinium salts but are more powerful fluorinating reagents (Banks 1992).

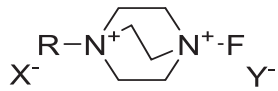


Figure 19 General structure of Selectfluor^{TM} reagents

The Selectfluor^{TM} family consist of reagents with different peripheral alkyl groups and different counter ions. The choice of the alkyl group can change the reactivity of the F-TEDA-X reagent but even the least reactive derivatives, such as methyl, ethyl or octane, are powerful enough to fluorinate pyridine and quinuclidine. The most popular alkyl group is chloromethyl because it is one of the most reactive and easy to synthetize derivatives. The commercial available Selectfluor also contains a tetrafluoroborate group as a

counter ion, however the studies of the influence of the counter ion showed that triflate salts were more reactive and led to fewer side products than tetrafluoroborate (Vincent et al. 1999). Selectfluor can be used for the fluorination of aliphatic chains, alkenes and aromatic rings (Banks et al. 1992, Vincent et al. 1999, Nyffeler et al. 2004, Singh and Shreeve 2004).

Selectfluor was also studied as a fluorinating reagent for metal-mediated or metal catalyzed fluorination (Furuya and Ritter 2008, Furuya and Ritter 2009, Furuya et al. 2009, Tang et al. 2010, Tang and Ritter 2011). In 2010, Teare et al. reported the synthesis of [^{18}F]Selectfluor *bis*(triflate) from [^{18}F]F_2 and its application in the labelling of a small number of model molecules (Teare et al. 2010). Since this time, [^{18}F]Selectfluor *bis*(triflate) has been used for the production of different PET tracers (Stenhagen et al. 2013, Keller et al. 2017). It can be used for fluorination of stannylated precursors, as can boronic esters, which do not contain toxic tin. [^{18}F]Selectfluor *bis*(triflate) has also been used for ^{18}F-fluorination of the tri- and difluoromethy groups (Mizuta et al. 2013) (Figure 20) which are commonly used in medicinal compounds (Müller et al. 2007, Hagmann 2008).

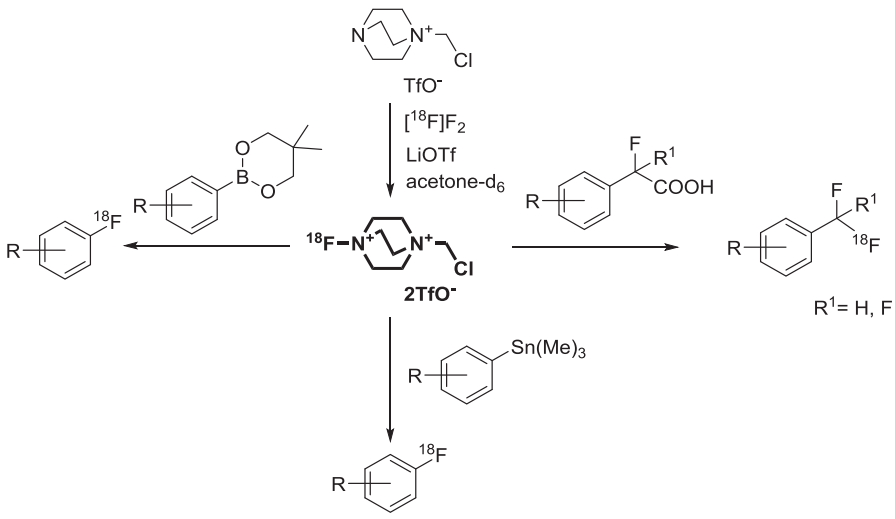


Figure 20 Radiosynthesis of [^{18}F]Selectfluor *bis*(triflate) and its applications

2.8 ^{18}F-Fluorination with transition metal complexes

All previously described electrophilic reagents for ^{18}F-fluorination suffer from a low A_m since they all require the addition of a carrier fluorine for their production.

In 2011, Ritter's group reported a non-carrier-added electrophilic method for ^{18}F-fluorination of aromatics (Lee et al. 2011). Pd-complexes can be produced directly from [^{18}F]fluoride and used for the labelling of aromatic systems (Figure 21).

This two-step method starts from the production of a ^{18}F-fluorinated Pd(IV) complex from dried [^{18}F]fluoride. This complex acts as a source of electrophilic ^{18}F-fluorine in oxidative fluorine transfer to the Pd(II) complex. The high valency Pd(IV) complex created undergoes carbon-fluorine reductive elimination to form ^{18}F-labelled products.

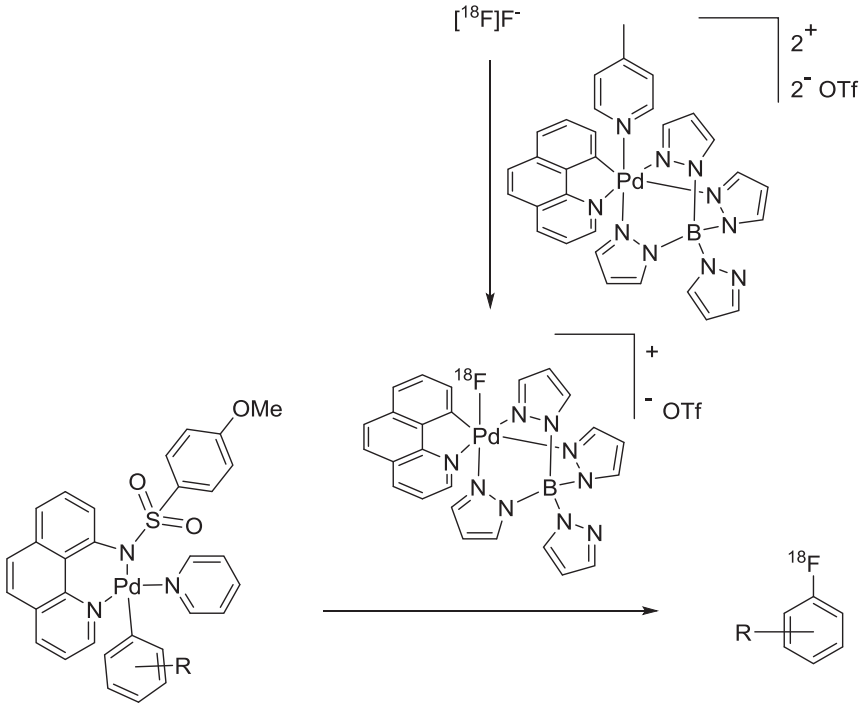


Figure 21 Late-stage electrophilic ^{18}F-fluorination with Pd complexes

Later, the same group presented a new method for direct oxidative ^{18}F-fluorination from [^{18}F]fluoride (Lee et al. 2012). The use of Ni complexes in the reaction mediated by hypervalent iodine oxidant can be performed in one step directly from an aqueous solution of [^{18}F]fluoride (Figure 22).

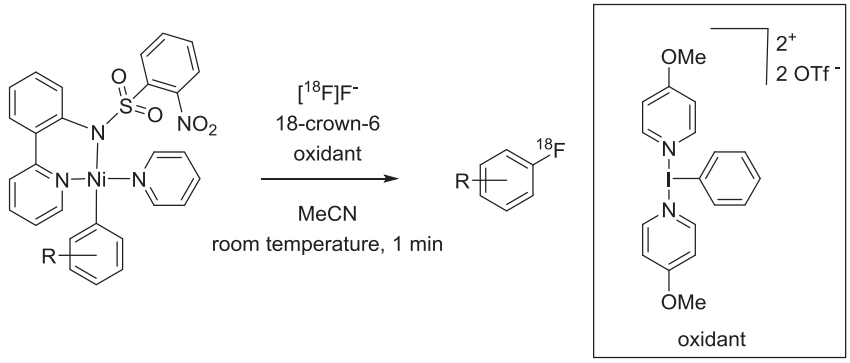


Figure 22 Direct reductive elimination of Ni complexes

The practicality of these methodologies is limited by the difficulty in the synthesis of the precursors, which are not commercially available (Kamlet et al. 2013) and also by the sensitive nature of the oxidant (Figure 22) which is very difficult to handle and can easily be destroyed during the reaction. Despite these problems the first automated Ni-mediated ^{18}F-fluorination has been reported (Ren et al. 2014, Hoover et al. 2016).

2.9 Click Chemistry for ^{18}F-fluorination

Click chemistry refers to the group of very fast and efficient reactions. The concept of click chemistry was first introduced by Sharpless in 2001 (Kolb et al. 2001). According to this idea, the reaction type needs to fulfil a number of requirements to be classified as a click reaction. Click chemistry describes the type of syntheses which results in high yield, is wide in scope and leads to one product or generates inoffensive by-products which can be easily removed without chromatography. Click reactions are carried out under simple reaction conditions and in benign solvents, or absent a solvent, and are stereoselective.

In radiochemistry it is an important method of introducing the fluorine-18 to more complex molecules under mild conditions, which is especially important for large biomolecules which are not stable at high temperatures. This technique starts from the labelling of a small molecule which is then selectively clicked with a larger substrate to give a designed ^{18}F-labelled product.

The first reaction recognized as a click reaction was copper-catalyzed 1,3-dipolar Huisgen cycloaddition (Copper-catalyzed Alkyne-Azide Cycloadditions – CuAAC) (Huisgen 1963). This reaction resulted in the formation of a 1,2,3-triazole ring at room temperature and in the presence of copper(I) (Figure 23). This approach was later used for the labelling

of different types of molecules such as peptides, glucose derivatives or nanoparticles which can be used in PET (Marik and Sutcliffe 2006, Glaser and Arstad 2007, Devaraj et al. 2009, Pretze et al. 2013).

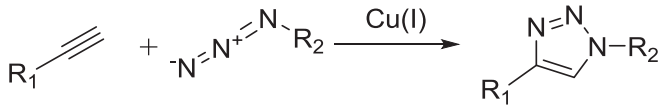


Figure 23 General reaction of the Copper-catalyzed Alkyne-Azide Cycloadditions

Strain-Promoted Alkyne-Azide Cycloaddition (SPAAC) (Figure 24) is the metal-free click reaction which was developed for *in vivo* application to avoid the use of toxic copper (Baskin et al. 2007). In this reaction, cyclooctynes are used instead of terminal alkynes. Because of the decreased activation energy of cyclooctynes in contrast to terminal alkynes, this reaction does not require a copper catalyst. Additionally, reaction kinetics can be changed by using different cyclooctyne derivatives.

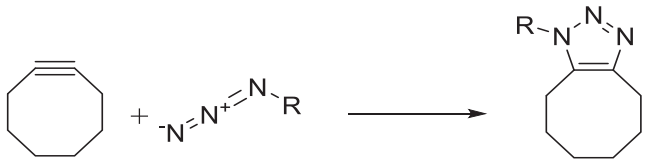


Figure 24 General reaction of the Strain-Promoted Alkyne-Azide Cycloadditions

The use of sydnones for click chemistry, as an alternative class of dipoles to azides, was first reported by Kolodych and co-workers in the modification of the CuAAC reaction (Kolodych et al. 2013) (Figure 25**A**). This Cu-catalyzed sydnone-alkyne cycloaddition (CuSAC) reaction was demonstrated to be applicable for wide scope terminal alkynes.

Due to copper cytotoxicity this method is not suitable for bioorthogonal reactions. Wallace and Chin presented a strain-promoted sydnone with bicycle-[6.1.0.]-nonyne (BCN) cycloaddition (Wallace and Chin 2014) (Figure 25**B**). Based on these findings, a new group of dipolarophiles – the dibenzocyclooctynes − has been discovered (Narayanam et al. 2016) (Figure 25**C**).

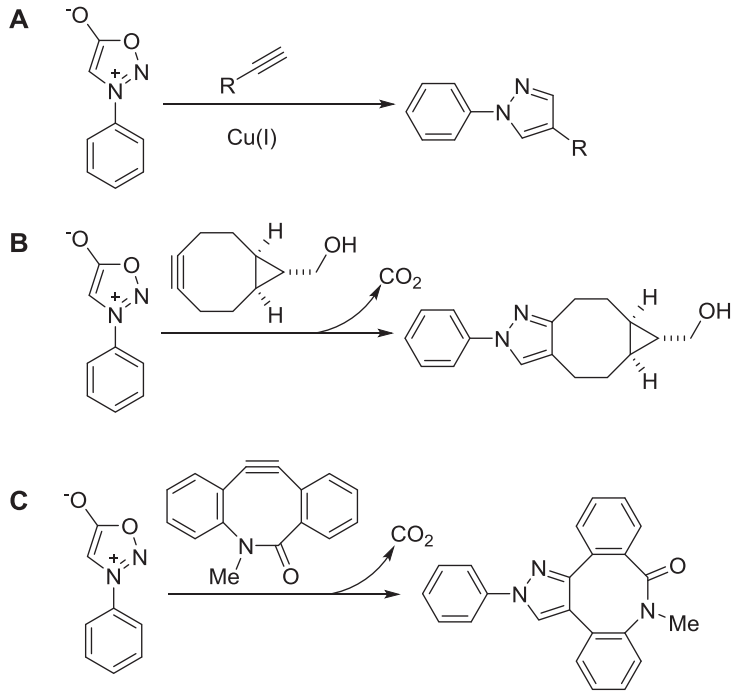


Figure 25 Use of sydnones in click chemistry **A** Cu-catalyzed sydnone-alkyne cycloaddition, **B** strain-promoted sydnone bicycle-[6.1.0.]-nonyne cycloaddition, **C** strain-promoted sydnone dibenzocyclooctyne cycloaddition

2.10 Enantioselectvie ^{18}F-fluorination

Chirality is a structural property of some molecules. Chiral compounds have two enantiomers, optical isomers which have the same chemical structure but are mirror imagines of each other and are non-superimposable. These geometrical properties are especially important for biomolecules since it has been demonstrated that two enantiomers can have significant differences in their biological activity. Thus, chirality is a highly important topic in pharmacology. In the context of drug development, enantiomeric purity plays a key role in reducing the possible toxic effects of the other enantiomer and decreasing the overall dose of the drug.

The use of racemic compounds in the pharmaceutical industry is constantly decreasing and today, more than half of the drugs which are in use contain at least one stereogenic centre, from which approximately half is reported to be enantiomerically pure or enriched (Caldwell et al. 2002, Nguyen et al. 2006).

A similar phenomenon has been noticed in the case of PET tracers. The use of a single enantiomer in PET, instead of a racemic mixture, can improve the quality of the image by eliminating the unspecific binding caused by the other enantiomer. Because of this, there is a growing interest in developing stereoselective radiosynthesis methods.

Current strategies for stereoselective ^{18}F-fluorination are rather limited (Buckingham and Gouverneur 2016).

2.10.1 S_N2 stereoselective ^{18}F-fluorination

^{18}F-Fluorination by aliphatic nucleophilic substitution is a selective process which results in the conversion of the configuration on the stereogenic centre. The most commonly employed S_N2 radiosynthesis method is via the production of [^{18}F]FDG (Hamacher et al. 1986, Fowler and Ido 2002). This synthesis is carried out on optically pure precursor containing triflate as a leaving group (Figure 26).

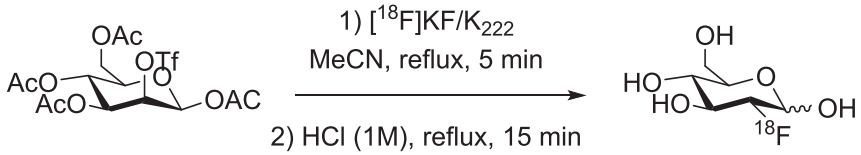


Figure 26 Radiosynthesis of [^{18}F]FDG S_N2 radiofluorination methods often require high temperatures which, in the case of stereoselective synthesis, means that not only the product but also the precursor needs to be resistant to racemization.

An example for the limitation of this method is the synthesis of 4-[^{18}F]fluoroglutamine and 4-[^{18}F]fluoroglutamic acid, potential metabolic imaging agents for tumours (Krasikova et al. 2011, Lieberman et al. 2011). While these molecules have two stereogenic centres they can form 4 diastereoisomers with different biological activity (Qu et al. 2011). To test the differences between all isomers Qu et al. developed the synthesis strategy for the production of all isomers based on stereoselective S_N2 ^{18}F-fluorination.

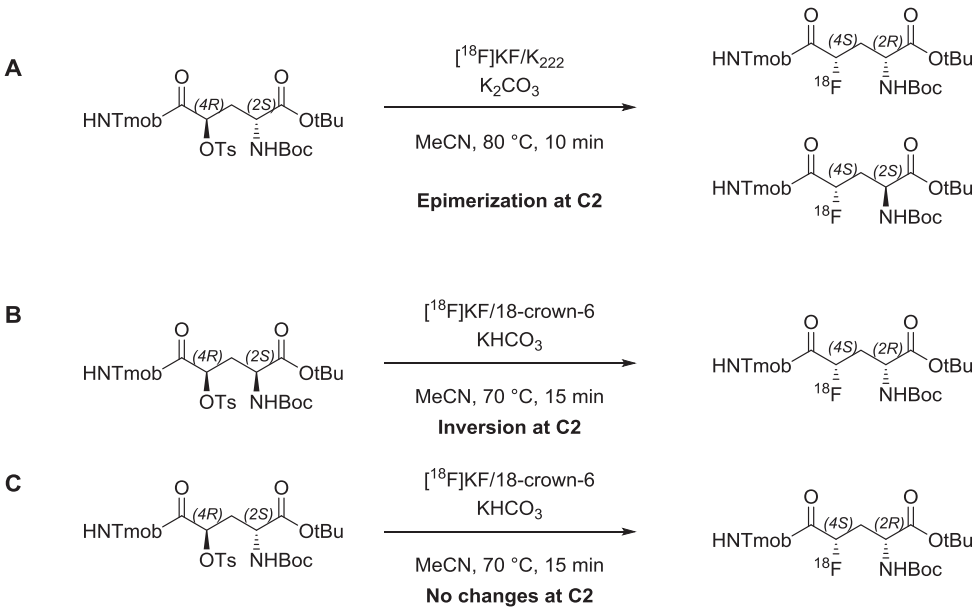


Figure 27 Synthesis of different diastereoisomers of 4-[^{18}F]fluoroglutamine and 4-[^{18}F]fluoroglutamic acid (Qu et al. 2011) **A** Reaction carried out with K_{222} and K_2CO_3 on (*2S, 4R*)-precursor leads to racemic mixture of (*2R, 4S*) and (*2S, 4S)* isomers **B** Reaction carried out with 18-crown-6 and $KHCO_3$ on (*2S, 4R*)-precursor results in inversion of the configuration at C2 position and production of isomer (*2R, 4S*) **C** Appling the same conditions on the (*2S, 4R*)-precursor does not result in any changes in the configuration at C2 position and leads to (*2R, 4S*) isomer

An initial attempt for the stereoselective synthesis of isomer (*2R, 4S*) with S_N2 ^{18}F-fluorination carried out on optically pure (*2S, 4R*)-precursor with K_{222} and K_2CO_3 leaded to the epimerisation at the C2 position (Figure 27A). This problem has been solved by using milder reagents such as: potassium bicarbonate and 18-crown-6 (Figure 27C). When a similar strategy was applied for the synthesis of the isomer (*2S, 4S*), complete inversion of the configuration at C2 position (double inversion) has been observed (Figure 27B). For further studies isomer (*2S, 4S*) has been separated by chiral HPLC from a (*2R, 4S*) and (*2S, 4S*) mixture (Qu et al. 2011, Buckingham and Gouverneur 2016).

In human studies with 4-[^{18}F]fluoroglutamic acid it showed fast defluorination of the tracer which makes it impractical for routine imaging (Smolarz et al. 2013). Defluorination of 4-(*2S,4R*)-[^{18}F]fluoroglutamine is slower and this tracer has recently been tested as feasible and safe for human use (Dunphy et al. 2018).

Apart from their clinical application, unusual behaviour of 4-[^{18}F]fluoroglutamine and 4-[^{18}F]fluoroglutamic acid under typical S_N2 ^{18}F-fluorination conditions make them highly interesting molecules for studying the stereoselective radiofluorination methods.

2.10.2 Metal-mediated stereoselective ^{18}F-fluorination

It has been reported that optically pure salen complexes with different transition metals can be used in stereoselective fluorination reactions (Kalow and Doyle 2010, Kalow and Doyle 2011). Contrary to the S_N2 approaches, this method does not require the use of optically pure precursors and the stereochemistry is set by enantioselective synthesis.

In 2014 enantioselective, metal-mediated stereoselective ^{18}F-fluorination, was reported (Graham et al. 2014). This method employed (*R,R*)-Co(salen) complexes for the selective ring opening of epoxides. The method presented started from the preparation of [^{18}F](*R,R*)-(salen)CoF complex from tosylate precursor. The synthetized complex was tested for the labelling of different [^{18}F]fluorohydrines, resulting in good RCY and enantiomeric excess (*ee*) of over 90% in all cases (Figure 28).

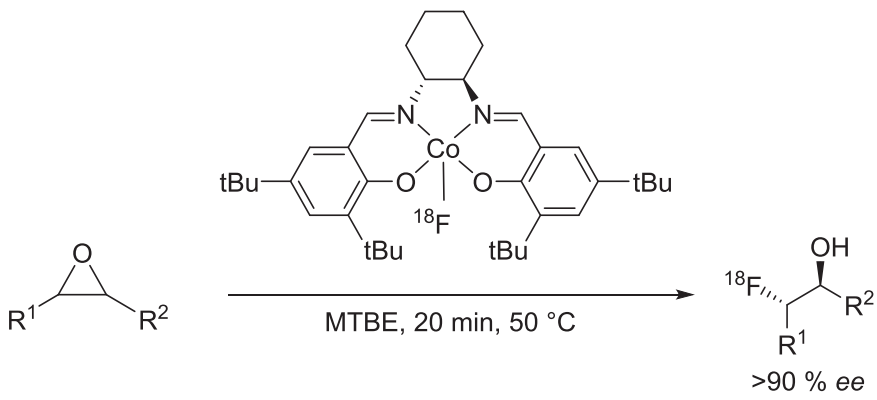


Figure 28 General procedure for enantioselective radiosynthesis of [^{18}F]fluorohydrines

The method presented has also been applied for the enatioselective synthesis of [^{18}F]F-MISO, tracer clinically used for hypoxia imaging (Revunov and Zhuravlev 2013, Revunov et al. 2015). The first attempt, with racemic precursor, resulted in *ee* of 55 % (Revunov and Zhuravlev 2013). Use of optically pure precursors increased the *ee* to over 99 %. Furthermore this method allows for the synthesis of both *S* and *R* enantiomers with the same *ee* by using opposite enantiomer of the salen complex (Figure 29) (Revunov et al. 2015). This study allowed Revunov et al. to determine the affinity of each enantiomer towards the target separately and decide if there is any benefit to the use of optically pure

tracer. Studies of optically pure [^{18}F]F-MISO, presented similar behaviour of both enantiomers and therefore there is no need for the use of the optically pure tracer in this case (Revunov et al. 2015).

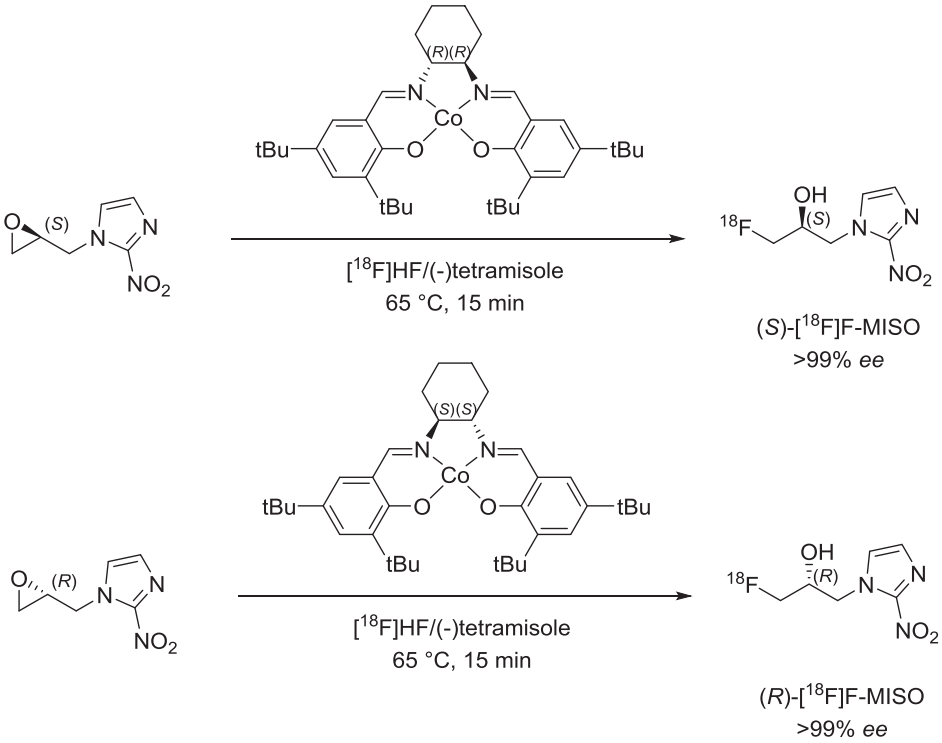


Figure 29 Stereoselective radiosynthesis of both enantiomers of [^{18}F]F-MISO

[^{18}F](*R,R*)-(salen)MnF has also been tested for enantioselective ^{18}F-fluorination (Huang et al. 2014). In 2014, Huang and co-workers reported on the direct stereoselective replacement a benzylic hydrogen with [^{18}F]fluorine. In this case, the [^{18}F](*R,R*)-(salen)MnF complex was oxidized in the presence of iodosobenzene. This method was demonstrated to be rather efficient for ^{18}F-fluorination on PET tracers (10 examples with RCY of 22–72%). The enantioselectivity of this process was tested in a single experiment – labelling of celestolide − and resulted in a low *ee* of 25% (Figure 30).

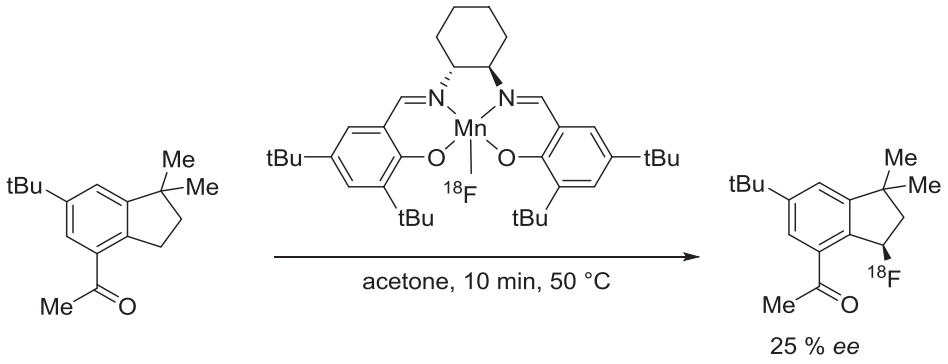


Figure 30 Enantioselective labelling of celestolide

2.11 PET imaging of α_2-adrenoceptors

α_2-Adrenoceprtors (α_2-ARs) are a group of G-coupled receptors located in the central and peripheral nervous systems. They mediate the biological actions of the endogenous catecholamines, norepinephrine and epinephrine. In humans and mammals they are divided into 3 subtypes: α_{2A}-, α_{2B}- and α_{2C}-ARs (Chabre et al. 1994, Saunders and Limbird 1999).

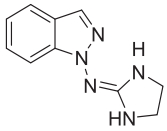
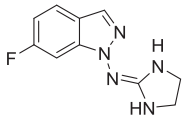
Among the subtype α_{2A}-, α_{2C}-ARs are located in central nervous system while α_{2B}-AR is mostly expressed in peripheral tissues and, compared to the other subtypes, its expression in the brain is weak and its role in CNS has not been clearly defined (Cottingham and Wang 2012).

The specific functions and location of the ARs subtypes in the central nervous system have been extensively studied in mice and rats (Scheinin et al. 1994, MacDonald and Scheinin 1995, Hein 2001). In such models, α_{2A}-AR is the most abundant subtype in the prefrontal cortex, hypothalamus and septum but it is poorly expressed in the striatum and thalamus (Wang et al. 1996). α_{2A}-AR is the main presynaptic inhibitory feedback receptor which controls exocytosis from adrenergic neurons. It is involved in the regulation of sympathetic nervous system activity, insulin secretion, arterial blood pressure, gastrointestinal functioning, body temperature and seizure threshold (Aoki et al. 1994, Scheinin et al. 1994, Aoki et al. 1994, Scheinin et al. 1994, Nicholas et al. 1996, Wang et al. 1996, Wang et al. 1996, Aoki et al. 1998, Aoki et al. 1998, Altman et al. 1999). α_{2C}-AR is located mostly in the olfactory tubercles, striatum and hippocampus (Scheinin et al. 1994, Wang et al. 1996). It has been suggested that it regulates cognition, sensory processes and mood (Scheinin et al. 2001, Sallinen et al. 2007, Knaus et al. 2007).

It has been reported that the functioning of the α_2-ARs may be interrupted in different neurological disorders such as Alzheimer's disease, depression, chronic stress and anxiety disorders (Sevy et al. 1989, Kalaria and Andorn 1991, Meana et al. 1992, Flugge et al. 1992, Flugge 1996, Flugge et al. 2003, Cottingham and Wang 2012, Langer 2015). This makes α_2-ARs a potential target for therapeutic drugs and highly interesting targets for PET imaging studies. So far, only few tracers have been chosen for either preclinical ([O-methyl-^{11}C]RS-15385-197 (Hume et al. 2000), [^{11}C]R107474 (Van der Mey et al. 2006)) or clinical ([^{11}C]yohimbine (Nahimi et al. 2015, Phan et al. 2017)) imaging of α_2-AR. In 2014, the first labelling synthesis for a α_{2C}-AR subtype selective PET tracer, [^{11}C]ORM-13070, was reported. It was originally evaluated in mice and its high selectivity for α_{2C}-AR was demonstrated in α_{2A} and α_{2AC} knockout (KO) mice (Arponen et al. 2014). This tracer was evaluated also in primates (Finnema et al. 2015) and has been used for selective imaging of α_{2C}-AR in humans (Luoto et al. 2014, Lehto et al. 2015). In 2010, [^{11}C]MPTQ was reported as a potential α_{2A}-AR PET tracer. However, its selectivity on α_{2A}-AR has not been demonstrated (Prabhakaran et al. 2010). So far no other tracer candidate for the α_{2A}-AR subtype has been reported.

1-[(imidazolidine-2-yl)imino]-1H-indazole (marsanidine) and its derivatives have been reported to be a selective α_{2A}-AR ligands (Saczewski et al. 2008, Sączewski et al. 2011). Introduction of a fluorine atom onto the aromatic ring in the marsanidine structure increases the affinity for α_{2A}-AR over α_{2C}-AR subtype (Table 3) (Wasilewska et al. 2014). It also makes it a promising molecule for labelling with fluorine-18 and use in PET imaging studies. It has also been suggested that this molecule can be labelled electrophilically with [^{18}F]Selectfluor *bis*(triflate) (Wasilewska et al. 2014).

Table 3 Binding affinities of marsanidine and 6-fluoro-marsanidine obtained with [^{3}H]RS-79948-197 to human α_2-AR subtypes expressed in CHO cell membranes (Wasilewska et al. 2014)

	K_i(nM)		
	α_{2A}-AR	α_{2B}-AR	α_{2C}-AR
 marsanidine	52	79	640
 6-fluoro-marsanidine	33	72	600

3 AIMS OF THE STUDY

The aim of this study was to develop novel methods for the production of $[^{18}F]F_2$ and its novel application.

The specific aims of each study were as follows:

1. To develop production methods for $[^{18}F]F_2$:
    - by using VUV photons as an excitation source for isotopic exchange reaction.
    - by using a source of carrier fluorine other than F_2.
2. To develop new applications for electrophilic fluorination with $[^{18}F]F_2$ derivatives.
3. To synthesize an α_{2A}-AR subtype selective PET tracer 6-$[^{18}F]$fluoro-marsanidine, and to evaluate this in a preclinical setting.

4 MATERIALS AND METHODS

4.1 Production of [^{18}F]fluoride and [^{18}F]MeF

[^{18}F]Fluoride was produced via the ^{18}O(p,n)^{18}F nuclear reaction with either MGC-20 cyclotron (Efremov Scientific Research Institute for Electrophysical Apparatuses (NIIEFA), Leningrad, USSR) by irradiating [^{18}O]H_2O (800 µL) with a 17 MeV proton beam (studies **I,V**), TR-19 cyclotron (Advanced Cyclotron Systems Inc. Richmond, British Columbia, Canada) by irradiating [^{18}O]H_2O (3.6 mL) with a 19 MeV proton beam (study **I**, high activity runs) or CC-18/9 cyclotron (Efremov Scientific Institute of Electrophysical Apparatus, St. Petersburg, Russia) by irradiating [^{18}O]H_2O (2.3 mL) with an 18 MeV proton beam (studies **II, III, IV**).

Irradiated water containing [^{18}F]fluoride was transferred directly into the reaction vessel (MGC-20 cyclotron) or passed through the anion exchange cartridge (QMA Sep Pak, Waters Corporation, Milford, MA, USA) and trapped [^{18}F]fluoride was eluted to the reaction vessel with K_{222}/K_2CO_3 solution (TR-19 cyclotron and CC-18/9 cyclotron).

The K_{222}/[^{18}F]KF complex was formed by azeotropic distillation with MeCN in the presence of K_{222} and K_2CO_3 while the reaction vessel was heated to 100 °C. MeI in MeCN (90 µL/mL) was added and the formation of [^{18}F]MeF was carried out at 100 °C for 40–90 s. Produced gas was purified by gas chromatography and trapped in a stainless steel loop submerged in liquid N_2. Purified [^{18}F]MeF was transferred to discharge or the illumination chamber together with the carrier gas.

4.2 Production of [^{18}F]F_2 (III, IV, V)

[^{18}F]F_2 was produced by a previously published method (Bergman and Solin 1997). Purified [^{18}F]MeF was transferred into the discharge chamber together with carrier F_2 (0.5% F_2 in Ne). ^{19}F/^{18}F isotopic exchange was promoted with a high voltage electrical discharge (25–30 kV) which was carried out for 10 s.

4.3 Production of [^{18}F]NFSi (I, III)

[^{18}F]F_2 was bubbled through the [^{18}F]NFSi precursor in MeCN/H_2O (9:1 vol/vol). The crude solution of [^{18}F]NFSi was analysed with radio HPLC.

4.4 Production of [^{18}F]Selectfluor *bis*(triflate) (II, IV, V)

[^{18}F]F_2 was bubbled through the solution of Selectfluor precursor and LiOTf in acetone–d_6. [^{18}F]Selectfluor *bis*(triflate) was used for further synthesis without any purification.

4.5 Production of [^{18}F]F_2 with VUV laser (I)

Purified [^{18}F]MeF was mixed with different amounts of carrier F_2 gas (0.5% F_2 in Ne) in the illumination chamber. The gas mixture was irradiated with VUV-photons generated by the ArF ExciStar XS laser (Coherent, Gottingen, Germany) with a repetition rate of 200 Hz and an energy of 11−12 mJ/pulse (Figure 31). Produced gas was used for the production of [^{18}F]NFSi. [^{18}F]NFSi was used as a model molecule to demonstrate the presence of [^{18}F]F_2 and to facilitate radio HPLC analysis.

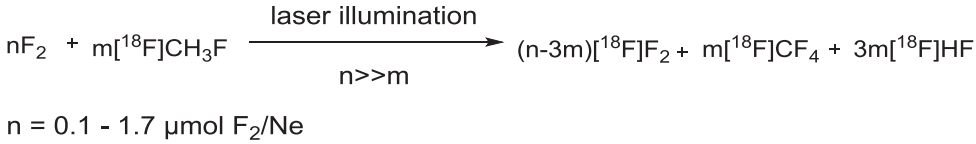


Figure 31 Synthesis scheme of laser-mediated production of [^{18}F]F_2

Three different illumination chambers (Table 4) were tested for the isotopic exchange reaction. The chamber which gave the best results for [^{18}F]NFSi labelling was used for test reactions with a different number of laser pulses (1500, 3000 or 6000) and with different amounts of carrier F_2 (95, 190, 380, 1180 or 1720 nmols). Conditions which gave the best results for [^{18}F]NFSi labelling were used for reaction with high starting activity.

Table 4 Different illumination chambers and chamber coatings used for laser-promoted production of $[^{18}F]F_2$

Chamber	Chamber material	Chamber shape and dimensions	Volume (cm^3)	Chamber coating
A	Glass with quartz windows on ends	Cylinder: 10 mm (diameter) x 110 mm	10.3	TiO_2
B	Quartz	Sphere: 30 mm diameter	9.8	Al
C	Quartz	Sphere: 30 mm diameter	9.8	TiO_2
D	Quartz	Sphere: 20 mm diameter	4.1	Al

4.6 Production of electrophilic ^{18}F-fluorination reagent with SF_6 (II)

Purified $[^{18}F]$MeF was transferred to the discharge chamber together with SF_6 in either Ne or Xe (1% SF_6 in Xe or Ne). The gas mixture was excited with a high voltage electrical discharge (32–36 kV, 400 µA) for 10, 50, 100 or 150 seconds (Figure 32). To confirm the presence of ^{18}F-labelled electrophilic species, produced gas was used for labelling of 6-$[^{18}F]$fluoro-*L*-DOPA.

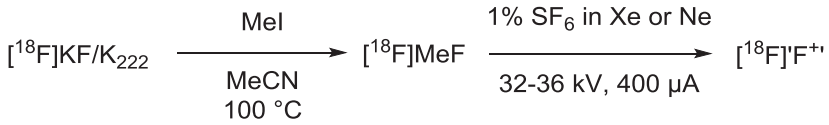


Figure 32 Synthesis scheme for the production of electrophilic ^{18}F-fluorinating reagent from SF_6

4.6.1 Production of 6-[^{18}F]fluoro-L-DOPA (II)

The $[^{18}F]F_2$ gas was bubbled into the reaction vessel containing 6-fluoro-*L*-DOPA precursor in Freon-11 with the addition of AcOH. Freon-11 was evaporated under the Ne flow. For deprotection, HBr was added to the reaction mixture and heated for 5 min at 130 °C (Figure 33). The final product was analysed by radio HPLC.

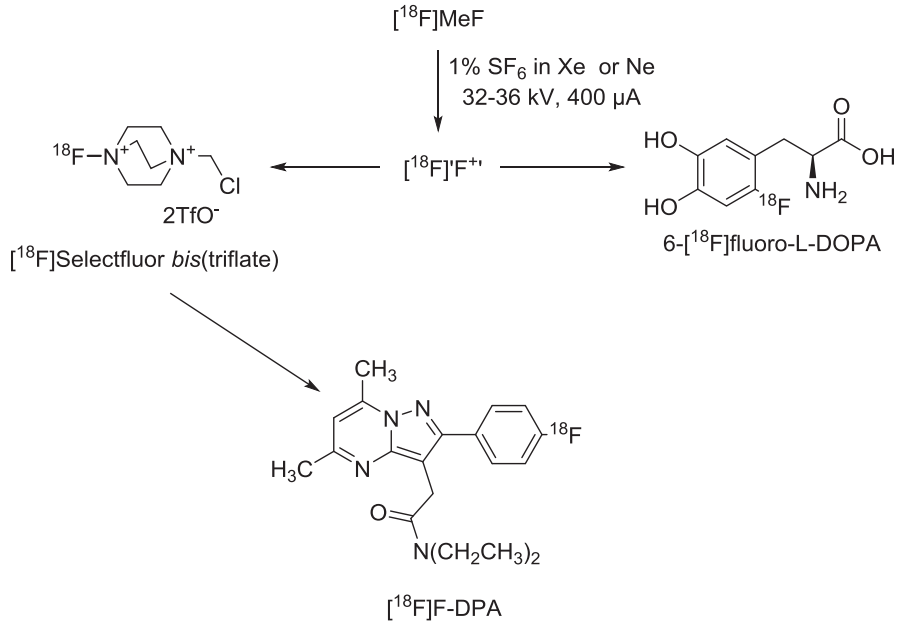


Figure 33 Synthesis of 6-[^{18}F]fluoro-*L*-DOPA, [^{18}F]Selectfluor and [^{18}F]F-DPA with electrophilic ^{18}F-fluorinating reagent produced with SF_6

4.6.2 Synthesis of [^{18}F]F-DPA with [^{18}F]Selectfluor bis(triflate) (II)

[^{18}F]Selectfluor *bis*(triflate) was synthesized from the gas mixture produced by the method described above, produced from SF_6 in Xe with 100 seconds discharge.

[^{18}F]Selectfluor *bis*(triflate) was added to the reaction vessel containing F-DPA precursor and silver trifluoromethanesulfonate (AgOTf). Approximately half of the solvent was evaporated under the He flow and the reaction was stirred for 15 min at 45 °C (Figure 33). The final product was analysed by radio HPLC.

4.6.3 Analysis of [^{18}F]XeF_2 (II)

The gas mixture produced by applying a high voltage discharge to a [^{18}F]MeF/SF_6/Xe mixture for 100 s, which was dissolved in MeCN containing XeF_2 reference. The solution was analysed by radio HPLC.

4.6.4 Emission spectrometry (II)

Light emitted from the discharge chamber when the high voltage electrical discharge was carried to a mixture of SF_6 and Xe or Ne was analysed by a Mechelle 7500 simultaneously recording optical spectrograph (Multichannel Instruments AB, Skarpnäck, Sweden) covering the spectral range from 185–1160 nm and with an exposure time of 1 s.

4.7 Enantioselective fluorination (III)

4.7.1 Labelling of α-[^{18}F]fluoro-aldehydes and its transformation to ^{18}F-labelled hydrazides

Labelling of α-[^{18}F]fluoro-aldehydes was carried out with freshly prepared [^{18}F]NFSi solution. First, the solvent was evaporated under a stream of He while the reaction vessel was heated to 60 °C. MeCN was added to the reaction vessel and the drying step was repeated. Dry [^{18}F]NFSi was dissolved in MTBE.

Solution of aldehyde in MTBE was added to the reaction vessel containing (*S*)-2,2,3-trimethyl-5-benzyl-4-imidazolidinone dichloroacetic acid ((*S*)-A, Figure 34). The reaction mixture was stirred for 10 min at room temperature. An aliquot of [^{18}F]NFSi in MTBE was added and the reaction was stirred for another 20 min (Figure 35). Formation of α-[^{18}F]fluoro-aldehydes was followed by the addition of benzhydrazide in methanol (MeOH) and the reaction was stirred in room temperature for 20 min (Figure 35**A**).

Alternatively, [^{18}F]Selectfluor *bis*(triflate) was tested as a ^{18}F-fluorinating reagent for this synthesis. (*S*)-pyrrolidine ((*S*)-B Figure 34) was used as a catalyst and THF/isopropanol was used as a solvent.

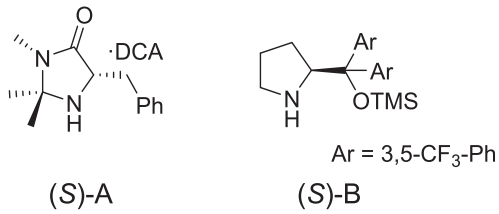


Figure 34 Structures of different catalysts tested for enantioselective ^{18}F-fluorination. DCA = dichloroacetic acid

The first conditions were applied for the production of different ^{18}F-labelled hydrazides (Figure 35**B**). The final product was separated by radio HPLC and the product peak was collected and re-injected onto chiral radio HPLC to determine *ee*.

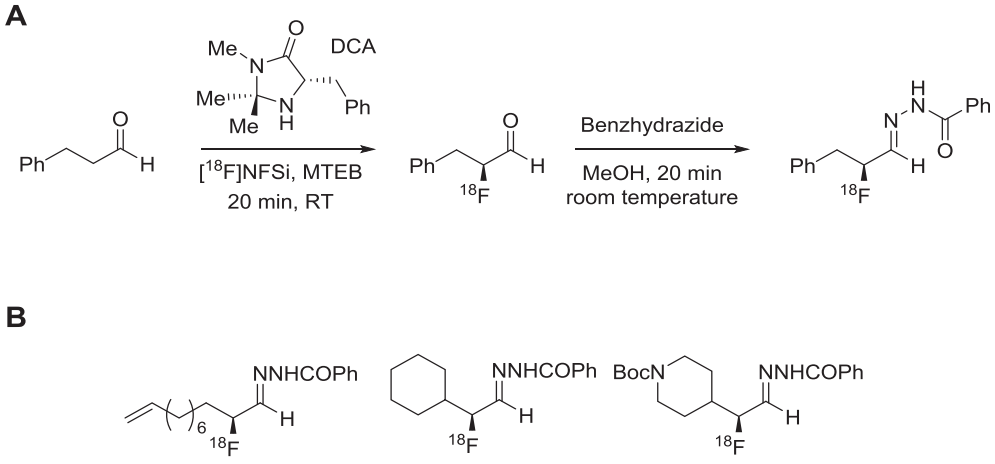


Figure 35 **A** General procedure for synthesis of α-[^{18}F]fluoro-aldehydes, **B** different ^{18}F-labelled hydrazides produced synthetized with the same method

4.7.2 Application of α-[^{18}F]fluoro-aldehydes

α-[^{18}F]fluoro-aldehydes were transformed into different compounds: carboxylic acid, primary and secondary amides and secondary amine (Figure 36). All of the reactions were performed in a one-pot process.

Synthesis of all the compounds started from the production of (*S*)-2-[^{18}F]fluoro-3-phenylpropanal according to the procedure described above which was used without any purification.

(*S*)-2-[^{18}F]fluoro-3-phenylpropanoic acid (Figure 36**A**): A solution of 2-methyl-but-2-ene in MeCN and $NaClO_2$ in H_2O was added to the crude α-[^{18}F]fluoro-aldehyde solution. The reaction was carried out in room temperature for 30 min.

(*S*)-[^{18}F]*N*-benzyl-2-fluoro-3-phenylpropanamide (Figure 36**B**): A solution of benzylamine and 2-methyl-but-2-ene in toluene was added to the crude α-[^{18}F]fluoro-aldehyde solution and stirred for 5 min. Next, $NaClO_2$ and NaH_2PO4 in H_2O was added and the reaction mixture was stirred for further 30 min in room temperature.

(*S*)-2-[^{18}F]fluoro-3-phenylpropanamide (Figure 36**C**): A solution of *bis*(4-metoxyphenyl)methanamine and 2-methyl-but-2-ene in toluene was added to the crude α-[^{18}F]fluoro-aldehyde solution and the reaction was carried out for 30 min at room temperature. Approximately half of the solvent volume was evaporated at 60 °C under a helium flow. Anisole in TFA was added to the solution and the reaction mixture was heated at 60 °C for 10 min.

(*S*)-[^{18}F]*N*-benzyl-2-fluoro-3-phenylpropan-1-amine (Figure 36**D**): A solution of benzylamine in dichloroethane was added to the crude α-[^{18}F]fluoro-aldehyde solution and stirred for 5 min at room temperature. Next, a solution of triacetoxyborohydride in dichloroethan was added and the reaction mixture was stirred for 30 min in room temperature.

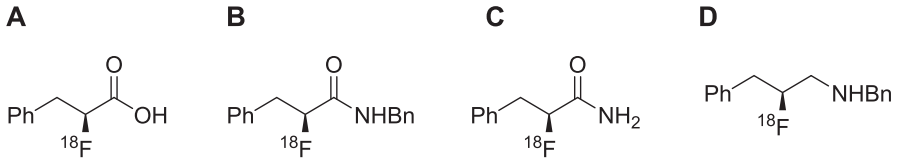


Figure 36 Different compounds **A** carbolic acid, **B** secondary amide, **C** primary amide and **D** secondary amine prepared from enantioselectively labelled α-[^{18}F]fluoro-aldehydes

4.7.3 Labelling of (2S,4S)-4-[^{18}F]fluoroglutamic acid

(*S*)-1-Tertbutyl-2-[bis-(tert-butoxycarbonyl)amino]-5-oxopentanoate was labelled with [^{18}F]NFSi according to the procedure described above.

Oxidation was performed by adding a solution of 2-methyl-2-butene in MeCN, $NaClO_2$ (80%) and NaH_2PO_4 in H_2O to the crude reaction mixture. The reaction was stirred for 30 min.

Before deprotection, the reaction mixture was heated to 60 °C under a flow of He to remove the solvents. Then, a mixture of anisole and TFA was added and the reaction was heated at 60 °C for 10 min and dried under a He flow. MeOH/H_2O (1:1) was added to the crude residue. Determination of enantiomeric excess (*ee*) was done by radio HPLC.

4.8 Click chemistry with [^{18}F]fluorosydnone

4.8.1 Synthesis and use of [^{18}F]-4-fluorosydnone

Aliquots (0.2 or 0.3 mL) of crude [^{18}F]Selectfluor *bis*(triflate) solution were added to a reaction vessel containing palladium complex. The reaction mixture was stirred for 5 min at 50 °C and allowed to cool to room temperature (Figure 37). Crude reaction mixture was analysed by radio HPLC.

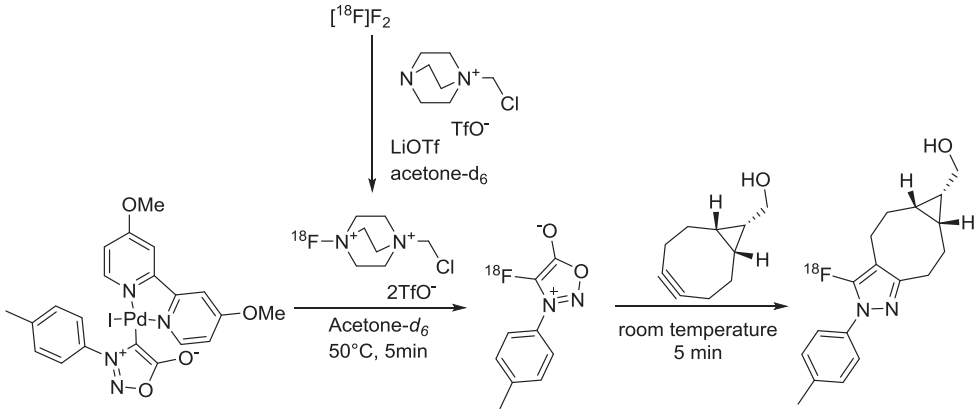


Figure 37 Synthesis of [^{18}F]-4-fluorosydnone and cycloaddition to BCN

Crude solution containing [^{18}F]-4-fluorosydnone was added to BCN and stirred at room temperature for 5 min. The [^{18}F]-4-fluorosydnone was analysed by the same radioHPLC system as the crude product.

4.9 Synthesis of 6-[^{18}F]fluoro-marsanidine

4.9.1 Electrophilic synthesis of 6-[^{18}F]fluoro-marsanidine

Stock solution of [^{18}F]Selectfluor *bis*(triflate) was added to a reaction vessel containing marsanidine precursor ((1-{[1,3-di(tert-butoxycarbonyl)imidazolidin-2-yl]imino}-6-(tributylstannyl)indazole)) and AgOTf. Approximately half of the solvent was evaporated under a Ne flow and the reaction was carried out for 10 min at 50 °C. Next, the rest of the solvent was evaporated and TFA was added. Deprotection was carried out for 5 min at 60 °C (Figure 38). The reaction mixture was diluted with 2 M NaOH and MeOH. The product was purified by radio HPLC.

Product was collected, diluted with water and concentrated on a Waters Sep-Pak C18 PLUS cartridge (Waters Corporation, Milford, MA, USA). Trapped product was eluted from the cartridge with ethanol and diluted with saline. The final product was analysed by radio HPLC.

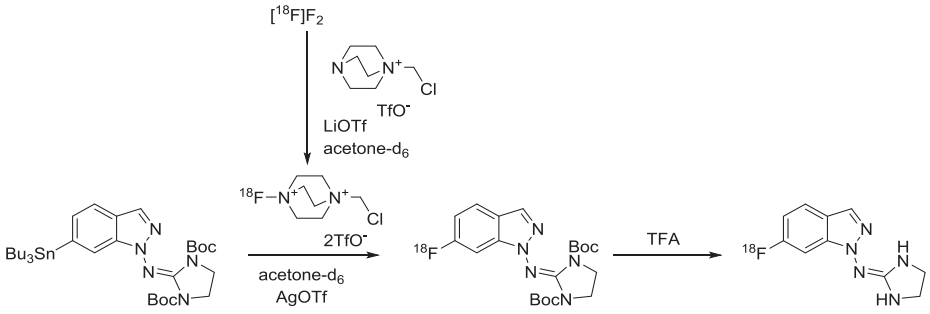


Figure 38 Electrophilic synthesis of 6-[^{18}F]fluoro-marsanidine

4.9.2 Nucleophilic synthesis of 6-[^{18}F]fluoro-marsanidine

Nucleophilic synthesis was carried out on the same precursor as electrophilic synthesis according to the procedure published by Gamache et al. in 2016.

[^{18}F]Fluoride was added to a reaction vessel containing K_{222} in MeCN and 0.25 M stock solution of K_2CO_3. Azeotropic distillation was carried out 3 times, each time MeCN was added to the reaction vessel and the reaction mixture was heated at 100 °C for 8 min. $Cu(py)_4(OTf)_2$ was premixed with MeCN at room temperature for 10 min before it was added to the dry K_{222}/[^{18}F]KF complex and the solvent was evaporated under a He flow. The marsanidine precursor in DMA was added to the reaction vessel and the reaction mixture was heated at 125 °C for 20 min. The crude reaction mixture sample was taken for radio HPLC analysis.

4.10 Evaluation of 6-[^{18}F]fluoro-marsanidine in rats and mice

Animal studies were performed on male Sprague Dawley rats, wild-type (WT) and α_{2A}-knockout (KO) mice (Table 5). For blocking studies, two rats were pretreated with medetomidine, a subtype-nonselective agonist of α_2-ARs, before tracer administration.

For *in vivo* study, animals were imaged with an Inveon multimodality PET/computed tomography (CT) scanner (Siemens Medical Solutions, Knoxville, TN, USA) first for 10 min with CT for attenuation correction and then, after tracer injection, with PET. Four rats and the mice were scanned with PET for 60 min and the medetomidine pretreated

rats were scanned for 15 min. PET images were co-registered with an averaged rat MRI brain template. Volumes of interest (VOIs) were drawn on the whole brain (WB), hippocampus (HIPP), hypothalamus (HYP) and striatum (STR) using the Inveon Research Workplace 4.2 (Siemens Medical Solution) analysis program, and reported as standardized uptake values (SUVs).

Table 5 Animals used for preclinical evaluation of 6-[^{18}F]fluoro-marsanidine. SD = Sprague Dawley, WT = wild-type, KO = knockout

Animals	Time	Blocking with medetomidine	Injected dose (µg/kg)	Injected dose (MBq)	N
SD rat	15 min		2.8 ± 3.0	18.0 ± 12.0	4
SD rat	15 min	0.5 mg/kg	1.5 0.5	31.4 10.7	2
SD rat	60 min		2.9 ± 3.3	20.3 ± 9.4	4
WT mice	60 min		28.3 5.8 5.6	6.5 3.1 3.2	3
α_{2A}-KO mouse	60 min		25.1	6.6	1

Organs of interest were collected, weighed and measured for radioactivity with a gamma counter. After this, the brains were frozen in isopentane cooled with dry ice and sliced to obtain cryosectiones of 20 µm. Slices were exposed on imaging plates (Imaging Plate BAS-TR2025; Fuji Photo Film Co.) for 4 h and then the imaging plates were scanned with a Fuji BAS-5000 Analyzer (Fuji, Japan). Autoradiography images were analysed with AIDA Image Analyzer 4.5 software (Raytest, Isotopenmessgeräte, Straubenhardt, Germany). Regions of interest (ROIs) were drawn over striatum (STR), lateral septum (LS), olfactory bulb (OB) and in rats also locus coeruleus (LC), calculated as photostimulated intensity/area - background (PSL/mm^2) and reported as ROI to STR ratio.

Samples of cortex and plasma were collected and the radioactive metabolites were analysed with thin-layer chromatography combined with autoradiography (radioTLC). Plasma proteins were precipitated with MeOH, centrifuged and the supernatant was spotted onto aluminium-based TLC silica gel 60 RP–18 $F_{254}S$ plate (EMD Millipore 1.05559.0001, Merck Millipore, Darmstadt, Germany). Brain samples were homogenized and metabolites were extracted with MeOH. Samples were spotted on the TLC plate together with plasma samples. TLC plates were developed with DCM:MeOH (9:1, vol/vol), and exposed on the imaging plate.

5 RESULTS

5.1 Production of $[^{18}F]F_2$ (I, II)

5.1.1 Laser method (I)

$[^{18}F]F_2$ was successfully synthetized and used for the synthesis of $[^{18}F]$NFSi where an excimer laser was used to promote the isotopic exchange reaction.

The best results were obtained when chamber A (Table 4) was used for the reaction. Spherical quartz chambers gave much lower RCYs for labelling of the $[^{18}F]$NFSi. The reactions carried out with different numbers of pulses showed that 30000 pulses gave significantly higher results for the A_m and RCY values than 15000 pulses, however, increasing the number of pulses further to 60000 did not make any significant difference. The highest A_m was obtained with chamber A, 30000 pulses and 190 nmol of carrier F_2 (Table 6).

Table 6 Results for production of $[^{18}F]F_2$ and labelling of $[^{18}F]$NFSi. A_m = molar activity, RCY = radiochemical yield

Chamber	Pulses	nF_2 (nmol)	$A_{[^{18}F]F^-}$ (GBq)	A_{crude} (MBq)	A_m (GBq/µmol)	$[^{18}F]$NFSi HPLC Yield (%)	N
A	30000	1260	3.15 3.15	142 360	0.04 0.15	36 34	2
B	30000	1280	3.75 2.76	352 608	0.04 0.12	15 15	2
C	30000	1280	3.26 ± 0.36	522 ± 86	0.07 ± 0.03	6 ± 1	3
D	30000	1090	3.06 3.12	393 333	0.05 0.04	13 9	2
A	15000	380	3.2 ± 0.5	420 ± 100	0.19 ± 0.12	10 ± 5	4
A	30000	380	3.6 ± 0.5	640 ± 330	0.66 ± 0.41	23 ± 5	4
A	60000	380	3.0 ± 0.2	260 ± 24	0.40 ± 0.08	17 ± 1	3
A	30000	1720	3.0 ± 0.5	380 ± 160	0.07 ± 0.05	29 ± 2	5
A	30000	1180	3.5 ± 0.6	570 ± 230	0.16 ± 0.07	31 ± 3	4
A	30000	380	3.6 ± 0.5	640 ± 330	0.66 ± 0.41	23 ± 5	4
A	30000	190	2.9 ± 0.4	500 ± 180	0.93 ± 0.43	13 ± 6	4
A	30000	95	3.1 ± 0.5	430 ± 78	0.57 ± 0.37	5 ± 2	3
A	30000	190	35.8 ± 1.9	4100 ± 2400	10.3 ± 0.9	13 ± 3	3

The values presented are corrected to end of synthesis (EOS), except for the $A_{[^{18}F]F-}$, which was measured at the start of synthesis.

For reactions carried out with high starting activity (35.8 ± 1.9 GBq) [^{18}F]NSFi with A_m = 10.3 ± 0.9 GBq/μmol was produced.

5.1.2 Production of [^{18}F]F_2 with SF_6 (II)

[^{18}F]F_2 was successfully produced when SF_6 in Xe was used as a source of carrier fluorine in a high voltage discharge reaction (Figure 39). The resulting gas mixture was immediately used for the labelling of 6-[^{18}F]fluoro-*L*-DOPA in order to confirm the presence of electrophilic ^{18}F-fluorination reagents. When discharge was carried out for 10 s, only a small amount of final product was produced. When the discharge time was increased to 50−150 seconds, 6-[^{18}F]fluoro-*L*-DOPA was synthesized with good RCY and A_m (Table 7).

Table 7 Results of the synthesis of 6-[^{18}F]fluoro-*L*-DOPA synthetized from [^{18}F]F_2 produced with SF_6/Xe mixture. For entry 4, a four times higher starting activity was used. Molar activity (A_m) and radiochemical yield (RCY) were determine based on the radio HPLC chromatogram of the crude reaction mixture

	Discharge time (s)	Activity of the crude product solution (MBq)	A_m (GBq/μmol)	RCY (%)
1	50	144 ± 7	0.8 ± 0.1	11 ± 1
2	100	178 ± 22	0.9 ± 0.1	13 ± 1
3	150	132 ± 20	0.8 ± 0.1	8 ± 2
4	100	297 ± 94	2.2 ± 0.5	23 ± 9

When the same reaction was carried out with SF_6 in Ne, only traces of 6-[^{18}F]fluoro-*L*-DOPA could be detected.

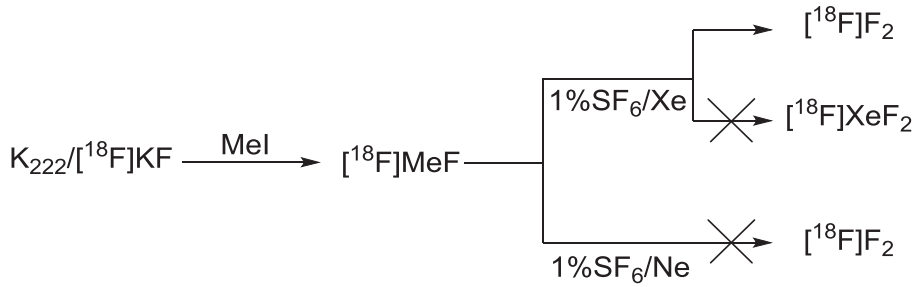


Figure 39 Results for the production of electrophilic ^{18}F-fluorinating reagents with SF_6

Synthesis of [^{18}F]F-DPA with [^{18}F]Selectfluor bis(triflate)

Electrophilic ^{18}F-fluorination reagent produced via a discharge reaction with SF_6 in Xe was used for production of [^{18}F]Selectfluor *bis*(triflate) which was subsequently used for the labelling of [^{18}F]F-DPA, resulting in 2% RCY and an A_m of 1.3 GBq/µmol.

Analysis of [^{18}F]XeF_2

The gas mixture produced during the discharge-promoted reaction with SF_6 was dissolved in MeCN and analysed by radio HPLC, showing that only negligible amounts of [^{18}F]XeF_2 were produced during this process.

Emission spectrometry

The analysis of the light emitted during the discharge carried out on SF_6 in Ne showed that SF_6 is atomized and the characteristic emission lines for both atomic fluorine and atomic sulphur were observed (Figure 40**A**). On the other hand, when discharge was carried out on an SF_6/Xe mixture, no characteristic lines from atomic fluorine were observed while clear emission lines from sulphur were detected (Figure 40**B**).

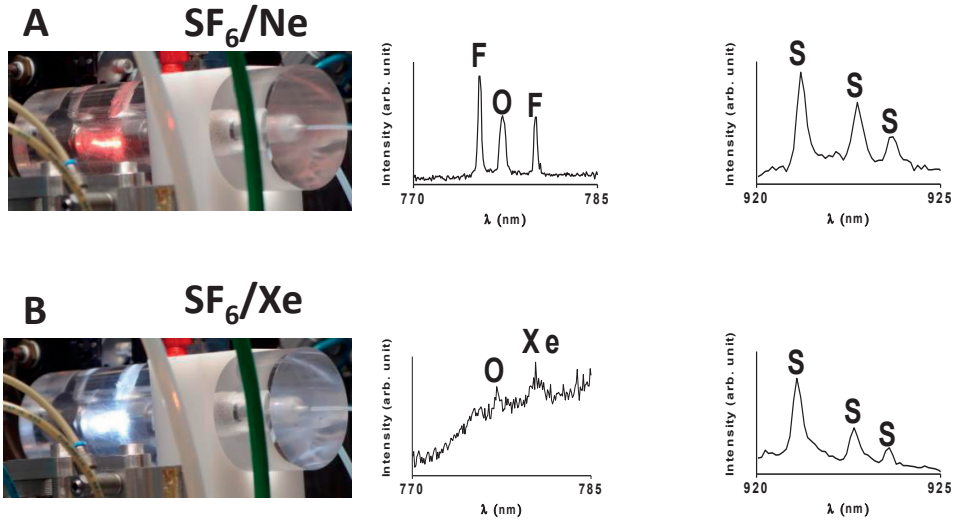


Figure 40 Photographs of discharges carried out in **A** SF_6/Xe or **B** SF_6/Ne and wavelength range in which strong emission lines from atomic fluorine and from sulphur are expected

In the spectrum taken on the SF_6/Xe, mixture weak emission lines at 260, 350, 460 nm, corresponding to XeF* emission (Brau and Ewing 1975, Ault and Andrews 1976, Kono and Shobatake 1995), were detected (Figure 41). Also, emission lines from both atomic and ionic Xe and atomic Ne were detected (Figure 41).

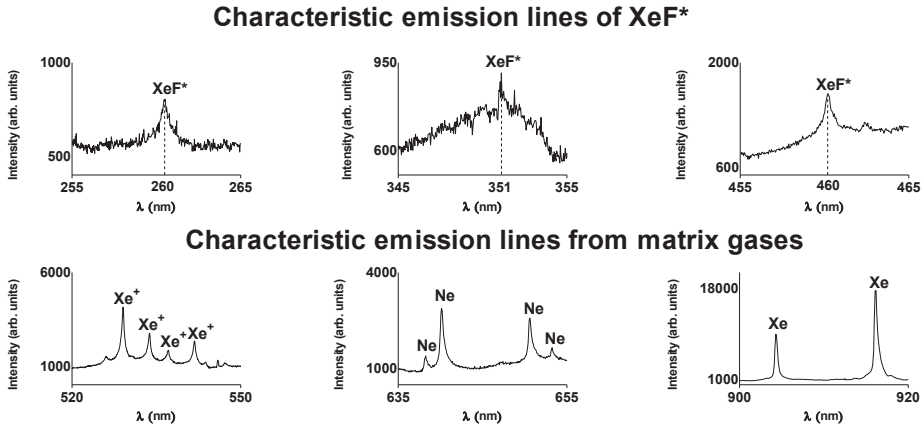


Figure 41 Wavelength ranges with emission lines putatively assigned to XeF*excimer. Wavelength ranges where characteristic emission from matrix gases are expected. Note that in Xe both atomic (neutral) and ionic emission are seen, as well as weaker Ne emission, which is a carrier gas for the purification of [^{18}F]MeF

5.2 Enantioselective electrophilic ^{18}F-fluorination

5.2.1 Synthesis of α-[^{18}F]fluoro-aldehydes and hydrazones

When [^{18}F]NFSi and (*S*)-imidazolidinone were used for the reaction carried out in MTBE, (*S*)-2-[^{18}F]fluoro-3-phenylpropanaldehyde was successfully synthetized with good RCY (62%) and an excellent *ee* of 92%.

Reaction catalysed with (*S*)-pyrrolidine resulted in an equally good *ee* but lower RCY of 45%. When a mixture of THF and IPA was used for as reaction solvent, this resulted in a better RCY (71%) but the *ee* was significantly lower (64%). No product was formed when [^{18}F]Selectfluor *bis*(triflate) was used as a fluorinating reagent.

[^{18}F]NFSi, (*S*)-imidazolidinone and MTBE were used for the synthesis of other ^{18}F-labelled hydrazones (Figure 42). All products were synthesized with a good RCY of 36–54% and an *ee* value of 92% in all cases.

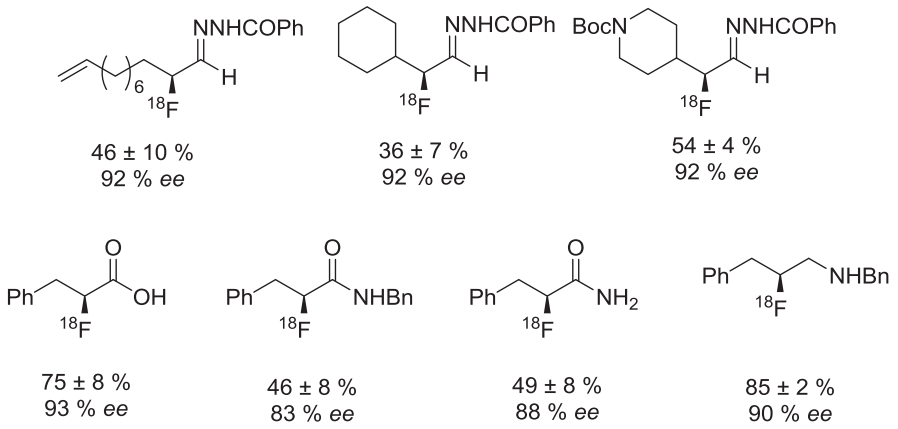


Figure 42 Results for the enantioselective synthesis of different ^{18}F-labelled hydrazides and different functionalized molecules synthetized from α-[^{18}F]fluoro-aldehydes

5.2.2 Applications of α-[^{18}F]fluoro-aldehydes

(*S*)-2-[^{18}F]Fluoro-3-phenylpropanaldehyde was successfully used for the production of corresponding ^{18}F-labelled carboxylic acid, primary and secondary amide and secondary amine. All products were obtained with an RCY of over 45% and an *ee* of over 80% (Figure 42).

5.2.3 Labelling of (2S,4S)-4-[^{18}F]fluoroglutamic acid

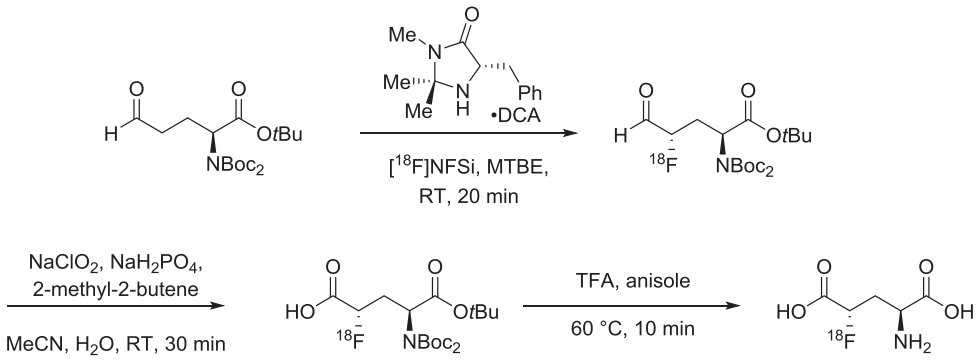


Figure 43 Labelling of (*2S,4S*)-4-[^{18}F]fluoroglutamic acid

The method developed was used for the synthesis of (*2S,4S*)-4-[^{18}F]fluoroglutamic acid (Figure 43). This reaction resulted in a final product with an RCY of 61% and *ee* of 99%.

5.3 Click chemistry

5.3.1 Results of non-radioactive experiment

Non-radioactive experiments were carried out by the group of Prof. Taran from Université Paris-Saclay in France.

4-fluorosydnone has been synthetized by reductive elimination from high-valent Pd^{IV} complex. To achieve that, stable sydnone-palladium complexes were fluorinated by using electrophilic fluorination with Selectfluor.

Crude reaction mixture containing freshly made 4-fluorosydnone was used for CuSAC. For that, 20 different alkynes have been tested as a substrate for cycloaddition. All attempts resulted in the formation of desire 5-fluoro-1,4-pyrazoles with yields between 35 and 73 %.

Possibilities for strain-promoted alkyne-sydnone cycloaddition has also been tested. An initial reaction carried out with BCN resulted in the quantitative formation of fluorinated cycloadduct. The reaction rate constant for the [3+2] cycloaddition has been measured to be $42 \pm 4\ M^{-1}s^{-1}$ what is higher than for non-fluorinated sydnone or azides. Further studies showed that the reaction rate constant is even higher when more strained alkynes are used or when 4-fluorosydnone contains electron-withdrawing group on its aryl ring.

5.3.2 Labelling of [^{18}F]-4-fluorosydnone and strain-promoted alkyne-sydnone cycloaddition

[^{18}F]-4-fluorosydnone was synthetized via electrophilic ^{18}F-fluorination. The reaction between [^{18}F]Selectfluor *bis*(triflate) and Pd^{II} complex resulted in the formation of [^{18}F]-4-fluorosydnone with an RCY of 7.5 ± 1.7%.

strain-promoted alkyne-sydnone cycloadditionReaction of the product with BCN resulted in nearly complete conversion to the desired product (Figure 44).

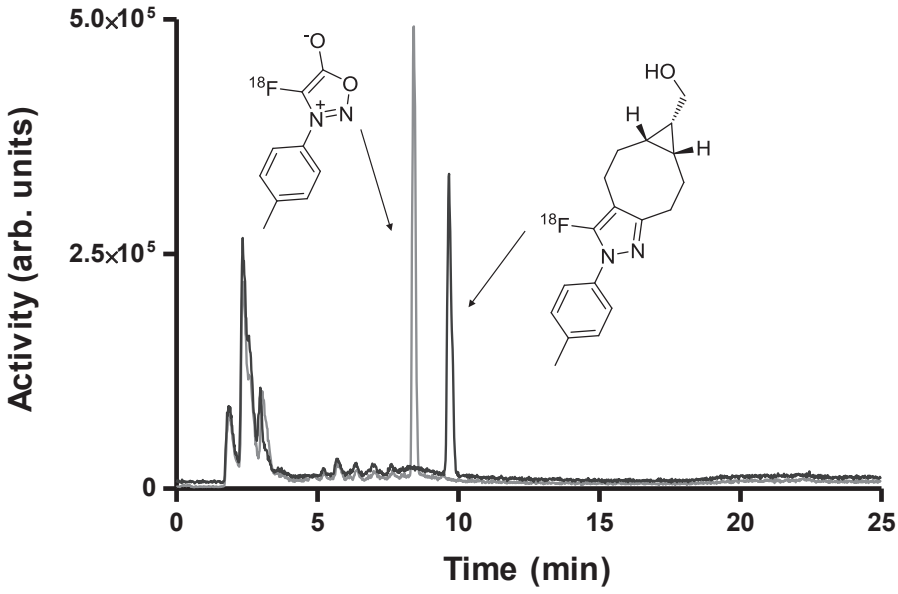


Figure 44 Radio HPLC analysis of the crude reaction mixture for the production of [^{18}F]-4-fluorosydnone and its full conversion into cycloaddition product after the addition of BCN

5.4 Synthesis of 6-[^{18}F]fluoro-marsanidine and evaluation in rodents

6-[^{18}F]Fluoro-marsanidine was successfully synthetized using [^{18}F]Selectfluor *bis*(triflate) with an RCY of 6.4 ± 1.7%. A_m decay corrected to end of bombardment (EOB) was in range 6.1–51.6 GBq/µmol depending on the amount of starting activity used for the synthesis. Radiochemical purity (RCP) exceeded 99% in all syntheses. Nucleophilic reaction did not resulted in the formation of 6-[^{18}F]fluoro-marsanidine.

Ex vivo autoradiography results of rat brains showed lower uptake ratios in LS, OB and LC in rats which were pretreated with medetomidine compared to the non-pretreated group (Figure 45). In mice LS/STR and OR/STR ratios for WT mice were higher than those for the α_{2A}-KO mouse (Figure 46**A**).

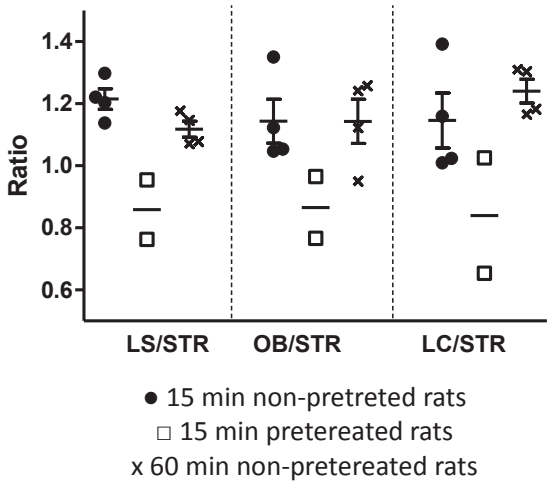


Figure 45 *Ex vivo* evaluation of 6-[^{18}F]fluoro-marsanidine in medetomidine pretreated and non-pretreated rats presented as lateral septum (LS), olfactory bulb (OB) and locus coeruleus (LC) to striatum (STR) ratios. Values are mean ± SD

In vivo time activity curves (TACs) in mice show that the initial uptake peak was higher for WT mice than for the α_{2A}-KO mouse (Figure 46**B**).

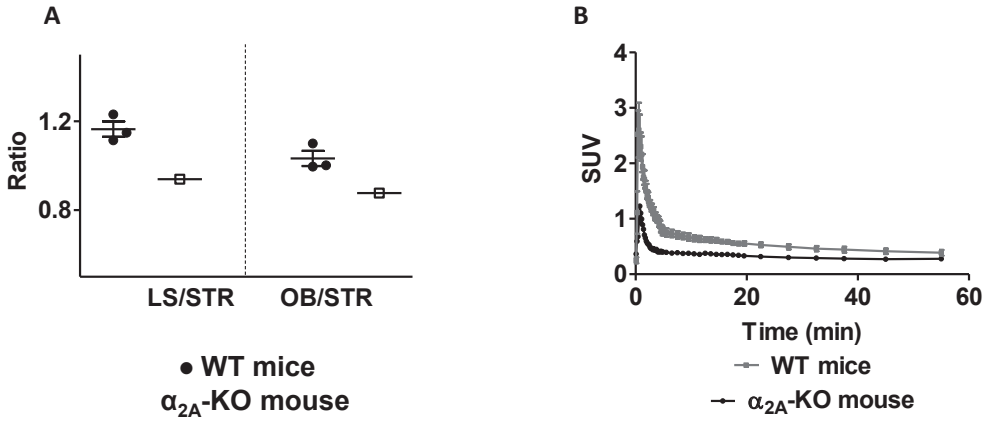


Figure 46 *Ex vivo* and *in vivo* evaluation of 6-[^{18}F]fluoro-marsanidine in wild type (WT) mice (n = 3) and α_{2A}-knockout (KO) mouse presented **A** as lateral septum (LS) and olfactory bulb (OB) to striatum (SRT) ratio and **B** as time-activity curves illustrating higher ^{18}F-activity in WT mice than in KO mouse. Values are mean ± SD

The highest ^{18}F-radioactivity for both rats and mice as a standardized uptake values (SUVs) was measured in the stomach and small intestine (SI), which increased with time. High levels of activity was also detected in the liver and kidneys but these levels stayed the same or decreased over time. In mice, high radioactivity was also found in the eyes and gallbladder. In both rats and mice, the high uptake in the urine showed that the urinary tract together with the gastrointestinal track are the main excretion routes for the tracer and its metabolites. The uptake in bone was low.

In both strains, the radioTLC analysis of radioactive metabolites showed fast metabolism of the tracer in both plasma and brain homogenate. Radiometabolites with the same retention factors were observed in both mice and rats. In the plasma, five different metabolites were detected. In rats, already 15 min after injection only 19.2 ± 8.9% of activity in the plasma corresponded to the unchanged tracer and this value decreased to 11.1 ± 0.9% after 60 min. In mice, the concentration of unchanged tracer in plasma was 28.9 ± 9.3% 60 min after injection. In the brain, only three metabolites were detected. In the rat brain, after 15 min, 43.2 ± 12.1% of the radioactivity detected corresponded to 6-[^{18}F]fluoromarsanidine and this decreased to 16.8 ± 3.9% after 60 min. In the mouse brain, 60 min after tracer injection, 32.5 ± 6.7% of radioactivity originated from unchanged tracer.

6 DISCUSSION

6.1 Production of [^{18}F]F_2

6.1.1 Laser method

The results showed that when a long, cylindrical chamber (Table 4) was used, the isotopic exchange was more efficient and gave a much higher RCY for the labelling of the [^{18}F]NFSi than either of the spherical chambers. This indicates that the non-reflected photons in the long chamber are more efficient in promoting the isotopic exchange in the gas than the reflected photons which are mainly present in the spherical chambers. As assumed, A_m increased proportionally to a certain point when lower amounts of carrier F_2 were used (Figure 47). The highest A_m was obtained when 190 nmol of F_2 was used. When less than 190 nmol of carrier was used there was no improvement of the A_m (□ point Figure 47). This suggested that some highly reactive fluorine is consumed by reacting with the chamber walls or by different side reactions. This suggests that there is a constant amount of fluorine which is consumed during the process independently of the amount of carrier F_2 added. Scaling on the starting activity to approximately 10 times higher, resulted in similar increase in A_m.

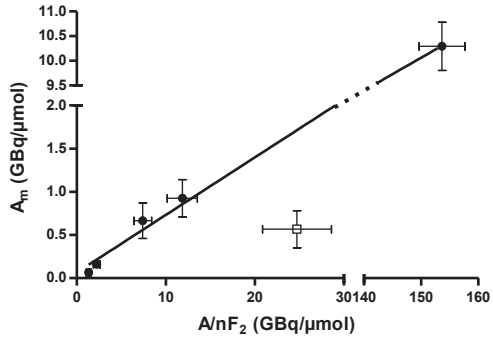


Figure 47 Linear correlation between A_m achieved in experiments carried out with different amounts of carrier F_2 and the maximum theoretical A_m which is calculated by dividing starting activity (A) by carrier amount. Data point corresponding to results obtained with the lowest amount of carrier F_2 (□) where the behaviour deviates from that of the others and was excluded when determining the trendline

6.1.2 SF_6 method

6-[^{18}F]Fluoro-*L*-DOPA was successfully synthesized when SF_6/Xe mixture was used in discharge reaction and the discharge was carried out for 50 second or more. When the same procedure was used on the SF_6/Ne mixture, only traces of the product were detected. Production of [^{18}F]Selectfluor *bis*(triflate) and the subsequent production of [^{18}F]F-DPA showed that the method presented can also be used for the production of milder electrophilic ^{18}F-fluorination reagents.

Synthesis of the 6-[^{18}F]fluoro-*L*-DOPA using a high starting activity demonstrated that the presented method can be used for the production of clinical tracers.

Since the discharge was carried out in Xe, it may be possible to achieve [^{18}F]XeF_2. Applying a high voltage discharge to the mixture of Xe and F_2 is one of the methods for the production of XeF_2 (Hoppe et al. 1962, Hoppe et al. 1963). However, only small amounts of [^{18}F]XeF_2 were detected in the crude reaction mixture. This suggests that the electrophilic ^{18}F-fluorination reagent produced by this method is [^{18}F]F_2. The mechanism could be explained by the formation of the intermediate XeF* excited species. Emission spectrometry did not confirm formation of atomic fluorine during the discharge carried out in SF_6/Xe. However, the presence of atomic sulphur suggests that SF_6 is decomposed during the discharge but fluorine is immediately involved in different interactions. Detection of the emission lines with the same wavelength as the XeF* emission lines supported this hypothesis.

This hypothesis also explains the negative results obtained with the SF_6/Ne mixture. Emission spectrometry showed the formation of atomic fluorine during the discharge carried out in Ne. However, only traces of the product were detected after the synthesis. This suggests that, since there are no interactions between neon and fluorine, SF_6 is atomized during the discharge and reorganized into different S-F species.

6.1.3 Utility of the new methods for the production of [^{18}F]F_2

These presented proof-of-concept experiments present a solution to the main disadvantages of the currently use discharge method which are: a use of high voltage discharge and non-radioactive fluorine gas. Currently, the methods presented result in lower A_m and RCY than the previously reported discharge method. Despite that, the laser method could be applied for the production of the PET tracers, but it would require high starting activity. The use of laser allows for the precise and repeatable delivery of the energy into the gas

mixture which is more difficult when the high voltage discharge is used. Further optimization of shape, material and reflective coating of the illumination chamber could improve both A_m and RCY of the product.

The SF_6 method results in very low RCY, what make it impractical for the use on clinical level. Further studies on high voltage discharge conditions, such as: used voltage or current and gas matrix are still needed.

6.2 New applications of electrophilic ^{18}F-fluorination

Electrophilic ^{18}F-fluorination was successfully applied for enantioselective fluorination. The reaction was carried out with [^{18}F]NFSi, which can be easily produced from [^{18}F]F_2 and can be used for further fluorination without any purification. In this method, in contrast to the most commonly used S_N2 nucleophilic substitution strategy for stereoselective ^{18}F-fluorination, simple non-chiral aldehydes are used as precursors. In this case, the asymmetric centre is created in the molecule stereoselectivly during the fluorination. Therefore, this method allows for the production of enantiomerically pure products without the need for optically pure precursors that are complicated to synthetize. Additionally, the synthesis is carried out at room temperature, which can prevent the eventual racemization of the product which sometimes can be promoted by high temperature. This method was originally used for the stereoselective production of α-[^{18}F]fluoro-aldehydes which were then transformed into [^{18}F]hydrazides, resulting in a product with very good enantiomeric enrichment. It has been demonstrated that the method also opens doors to the possibility of further transformations of the functional group, such as carboxylic acids, primary and secondary amides and secondary amines. These transformations can be done in a relatively simple one-pot synthesis approach and lead to products with high enantiomeric enrichment. In this work, a metal-free approach was used for the production of (*2S,4S*)-4-[^{18}F]fluoroglutamic acid, which has not been synthetized selectively with other methods, to demonstrate the utility of this method for the production of PET tracers.

The second application of electrophilic ^{18}F-fluorination which is presented uses [^{18}F]Selectfluor *bis*(triflate) for the production of a new reagent for a click reaction. The 4-Fluorosydnones have been identified to be the fastest reagents for the strained promoted click reaction. The kinetic studies of the reaction rate proved that the reactions carried out with 4-fluorosydnones are much faster than those with azides and non-fluorinated sydnones. [^{18}F]-4-fluorosydnone was successfully produced with an electrophilic reagent [^{18}F]Selectfluor *bis*(triflate) which can be easily produced from [^{18}F]F_2. Addition of [^{18}F]-4-fluorosydnone to BCN resulted in complete conversion in only 5 min at room temperature. This method is not only remarkably fast but also applies very mild conditions and could potentially be applied to the production of temperature-sensitive compounds. This

suggests that [^{18}F]-4-fluorosydnone can be used as a new prosthetic group for the production of ^{18}F-labelled biomolecules.

6.3 6-[^{18}F]fluoro-marsanidine

6-[^{18}F]Fluoro-marsanidine was successfully synthetized with [^{18}F]Selectfluor *bis*(triflate) and with a relatively high A_m for electrophilic synthesis. Nucleophilic reactions carried out on the stannylated precursor did not result in the formation of the desired product. It has been suggested that nitrogen-rich compounds can coordinate with the copper catalyst and cause its deactivation (Taylor et al. 2017). This suggests that copper-mediated ^{18}F-fluorination is not suitable for the synthesis of 6-[^{18}F]fluoro-marsanidine.

Preclinical evaluation in both rats and mice demonstrated good blood-brain barrier penetration of 6-[^{18}F]fluoro-marsanidine. *Ex vivo* results obtained from rats showed lower uptake of the tracer in α_{2A}-AR-rich brain regions of pretreated rats compared to the non-pretreated group (Figure 45). This confirmed the α_2-AR specificity of 6-[^{18}F]fluoro-marsanidine.

The 6-[^{18}F]fluoro-marsanidine α_{2A}-subtype selectivity was demonstrated as the LS/STR and OB/STR ratios from the α2A-KO mouse were lower than the ratios for the WT group (Figure 43A). Furthermore, the TACs showed lower uptake in the WB of the α_{2A}-KO mouse than for that of the WT mice, due to a lack of the target in KO brain.

Thus, data obtained from both rats and mice confirmed the specificity and subtype selectivity of 6-[^{18}F]fluoro-marsanidine towards α_{2A}-AR.

However, the low A_m achieved with electrophilic fluorination increased the injected masses to an undesirable level (Scheinin et al. 1994, Wang et al. 1996, Eckelman 1998, Passchier et al. 2002). Rapid metabolism of the tracer in the brain caused a high unspecific signal from brain tissue in both rats and mice brain making this tracer unsuitable for the imaging of α_{2A}-adrenoceptor in rodents.

7 CONCLUSIONS

1. **Two novel methods for the production of [^{18}F]F_2 were developed**

In the first method for the production of [^{18}F]F_2, VUV photons were used as a source of excitation instead of a high voltage discharge for the ^{18}F/^{19}F isotopic exchange reaction between [^{18}F]MeF and nonradioactive F_2. The second method used SF_6 as a source of carrier fluorine for the discharge-promoted reaction with [^{18}F]MeF instead of highly toxic F_2. Both proof-of-concept experiments provided good A_m values for the final product, which could be increased by further optimization. These methods could be utilized in clinical production.

2. **Two new applications of electrophilic ^{18}F-fluorination were developed**

In my work, I also focused on the new applications of two electrophilic ^{18}F-fluorinating reagents, [^{18}F]Selectfluor *bis*(triflate) and [^{18}F]NFSi. [^{18}F]Selectfluor *bis*(triflate) was used for the production of [^{18}F]-4-fluorosydnone for the strain-promoted-sydnone bicycle-[6.1.0.]-nonyne cycloaddition. This method provides a fast and effective means for ^{18}F-fluorination, which can be used for the labelling of biomolecules. [^{18}F]NFSi allows the enantioselective labelling of molecules without the need for an optically pure precursor or metal-containing catalyst. Both methods proved to be useful, new applications of electrophilic ^{18}F-fluorination.

3. **An α_{2A}-AR selective PET tracer candidate was synthetized and evaluated in a preclinical setting**

A new α_{2A}-AR tracer candidate, 6-[^{18}F]fluoro-marsanidine, was successfully synthetized. Preclinical evaluation showed the specificity and subtype selectivity of the tracer. Radioactive metabolites found in the brain increase the nonspecific binding and complicate the use of 6-[^{18}F]fluoro-marsanidine in rodents.

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