PET Chemistry: An Introduction

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5.1 Introduction

One major advantage of radioactivity is its extremely high sensitivity of detection. Regarding the medical applicability of radioactivity, it permits non-invasive in vivo detection of radiolabelled compounds at nano- to picomolar levels. The use of substances at such low concentrations usually precludes a physiological, toxic or immunologic response of the investigated biological system. Consequently, the considered physiological process or system is examined in an unswayed situation. Furthermore, a wide range of substances, even those which are toxic at higher concentrations, become considerable for the development of radiopharmaceuticals and use in nuclear medicine. In contrast to the wide range of employable bioactive molecules, the range of suitable radioactive nuclides is much more restricted by their nuclear physical and chemical properties. In particular, radionuclides for diagnostic applications should provide appropriate (short) half-lives and radiation properties for detection and imaging, but at the same time the radiation dose of patients and personnel have to be kept to minimum. Nonetheless, to date, a couple of radionuclides have proven suitable for both nuclear medical diagnostic applications, single photon emission computed tomography (SPECT), and positron emission tomography (PET).

As indicated by their names, SPECT is based on photon or γ-ray emitting nuclides while PET is derived from those nuclides which belong to the group of neutron-deficient nuclides and emit positrons (β^+-decay). Large scale production of positron emitting radionuclides became possible for the first time by the invention of the cyclotron by Ernest Orlando Lawrence in 1929 [1]. Since then, many (medical) cyclotrons have been built and have been in use at various nuclear medicine PET facilities. As a result, short-lived positron emitters such as most commonly employed fluorine-18 and carbon-11 are routinely produced at most nuclear medicine centres on a daily basis.

In the β^+-decay of a neutron-deficient nucleus, a positron (β^+) and a neutrino (ν) are synchronously emitted, while in the nucleus, a proton is converted into a neutron. Neutrinos show practically no interaction with matter and thus they are not detectable by PET cameras. In contrast, the emitted positron is able to interact with an electron, its anti-particle. As a result, both particles annihilate and give two γ-rays with a total energy of 1.022 MeV, the sum of the

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masses of positron and electron, 511 keV each. Both γ-rays show a nearly 180° distribution and each carries the characteristic energy of 511 keV. Accordingly, the decay of positron emitters which are used as label for PET radiopharmaceuticals results in two γ-rays and as these are body-penetrating photons, they can be detected by an appropriate PET camera. This physical phenomenon provides the base of PET imaging.

In PET scanners, a circular ring of detector pairs, which record only coincidence events, registers the in vivo generated pairs of γ-rays. An appropriate computer-aided data acquisition provides PET images with information about in vivo distribution and levels of accumulation of the radionuclide and the radiopharmaceutical, respectively. Consequently, biochemical processes can be visualised and a dynamic data acquisition further allows for registration of a temporal component such as pharmacokinetics of a certain drug. In combination with bio-mathematical models and individual corrections of attenuation, transmission and scatter effects, physiological and pharmacological processes can be precisely acquired and quantified [2].

The most important radionuclides for PET imaging are fluorine-18 and carbon-11. Particularly, the ^{18}F-labelled glucose derivative 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) represents the most widely used PET radiopharmaceutical which has contributed most to the worldwide success of clinical PET imaging. The combination of a highly efficient radiochemistry and a high yielding ^{18}O(p,n)^{18}F nuclear reaction makes [^{18}F]FDG available in large amounts and also enables shipment and distribution by commercial producers. Since its development in the 1970s [3], [^{18}F]FDG has been employed in many PET studies in oncology, neuroscience and cardiology [4–7]. However, further substances have followed and to date, several PET radiopharmaceuticals for specific targets have been developed and evaluated for a wide range of applications in clinical nuclear medicine as well as in preclinical research [8–11].

The following chapter deals with the development and the use of PET radiopharmaceuticals. Here a comprehensive overview of basic considerations and possibilities in development of PET radiopharmaceuticals is given. An outline of commonly employed clinically established PET radiopharmaceuticals, their most important production routes and clinical applications follows in the next chapter, in which also aspects of routine production and quality control of PET radiopharmaceuticals as well as their use in drug development are introduced and briefly summarised. Both chapters principally cover literature until the beginning of 2009.

5.2 Choice of the Radionuclide

There is a variety of basic functions and effects which can generally be followed and visualised by PET such as metabolism, pharmacokinetics, (patho)physiological and general biochemical functions; receptor-ligand biochemistry; enzyme functions and inhibition; immune reactions and response; pharmaceutical and toxicological effects. However, a close look into the designated processes and the related biochemistry is necessary to find a positron emitter with appropriate characteristics.

Although fluorine-18 is the most commonly preferred positron emitter for PET radiopharmaceuticals, monoclonal antibodies labelled with fluorine-18 for immuno-PET imaging are normally not useful because the physical half-life of 110 min does not fit to the slow accumulation (normally 2–4 days) of most monoclonal antibodies in solid tumours [12]. In such cases, longer-lived PET nuclides as iodine-124 ($T_{½}$ = 4.18 days) and zirconium-89 ($T_{½}$ = 3.27 days) are more suitable for this particular application. On the other hand, longer half-lives increase radiation doses to the patients and thoughtful considerations towards a health/risk–benefit analysis are mandatory.

As a basic principle, short-lived radionuclides should preferably be used if their suitability is similarly good with respect to a certain application. Blood flow tracers are a perfect example for the use of extremely short-lived radionuclides such as oxygen-15 ($T_{½}$ = 2 min), nitrogen-13 ($T_{½}$ = 10 min) and rubidium-82 ($T_{½}$ = 1.3 min). The scanning times of blood flow studies using PET are normally very short and not longer than 2–5 min. Hence, radiolabelled substances such as [^{15}O]water, [^{15}O]butanol, [^{13}N]ammonia and [^{82}Rb]RBCl are particularly suitable. However, the relatively short half-lives of the these radionuclides place some constraints on imaging procedure and execution.

Besides half-lives, there are further physical aspects to be considered. One is the β^+-energy ($E_{\beta+}$) of the emitted positrons. The $E_{\beta+}$ also clearly affects the radiation dose to the patients and thus the lower the $E_{\beta+}$ the better it is for the patients. Since the $E_{\beta+}$ is also

responsible for the positron range (travelling distance of the positron) and a short positron range enhances the spatial resolution in PET, a low $E_{\beta+}$ is also very favorable for high resolution PET imaging. However, in human PET scanners, the distance of the detectors to the object is long and the positron range is no longer significant for the absolute spatial resolution as demonstrated in comparable studies using different positron emitters in imaging phantoms [13, 14]. In contrast, high-resolution small animal PET scanners show dramatically degraded image quality by the use of positron emitters with high $E_{\beta+}$ or complex decay schemes [15].

In comparison with most of the available positron emitters for PET, it is already quite evident from the nuclear properties that fluorine-18 is the most preferred radionuclide for PET. The optimal half-life of fluorine-18 offers multi-step radiochemistry, extended PET studies of slower biochemistry as well as the shipment of the ^{18}F-labelled radiopharmaceuticals to clinics without an on-site cyclotron or a radiochemistry facility. Furthermore, it has one of the lowest $E_{\beta+}$ among the PET nuclides and provides high-resolution PET images. An overview of the nuclear data of important positron emitters for PET is given in Table 5.1.

In the same way as the radionuclide must fulfil the physical requirements of the PET imaging, it needs to exhibit suitable chemical properties with respect to available labelling techniques. Thereby, the labelling strategy depends on the initial situation and attendant restrictions. If a certain radionuclide is given by reasons such as availability or imaging characteristics, the target structure often needs to be modified towards its suitability for corresponding labelling methods. In contrast, if the structure of a biomolecule is stipulated, a combination of a radionuclide with an appropriate and efficient labelling procedure needs to be found. However, a restricted number of PET radionuclides and a limited selection of reactions for their introduction into biomolecules generally necessitate the approach of tailored structures. Noteworthy, those structural modifications of the parent biomolecule are mostly accompanied by changes in the pharmacological behaviour and usually a compromise covering pharmacological performance, radiochemistry, dosimetry and PET imaging requirements must be found.

In general, the choice for the right positron emitter for a new PET radiopharmaceutical can be described as the best match between efficient radiochemistry, acceptable dosimetry and favourable pharmacological and PET imaging properties.

Table 5.1 Important positron emitters used for PET and their nuclear data from [16, 17]

Nuclide	Half-life	Decay mode (%)	$E_{\beta+,max}$ [keV]
Organic			
^{11}C	20.4 min	β^+ (99.8) EC (0.2)	960
^{13}N	9.96 min	β^+ (100)	1,190
^{15}O	2.03 min	β^+ (99.9) EC (0.1)	1,720
^{30}P	2.5 min	β^+ (99.8) EC (0.2)	3,250
Analogue			
^{18}F	109.6 min	β^+ (97) EC (3)	635
^{73}Se	7.1 h	β^+ (65) EC (35)	1,320
^{75}Br	98 min	β^+ (75.5) EC (24.5)	1,740
^{76}Br	16.2 h	β^+ (57) EC (43)	3,900
^{77}Br	2.38 days	β^+ (0.7) EC (99.3)	343
^{120}I	81.1 min	β^+ (64) EC (36)	4,100
^{124}I	4.18 days	β^+ (25) EC (75)	2,140
Metallic			
^{38}K	7.6 min	β^+ (100)	2,680
^{45}Ti	3.09 h	β^+ (85) EC (15)	1,040
^{60}Cu	23.7 min	β^+ (93) EC (7)	3,772
^{61}Cu	3.33 h	β^+ (61) EC (39)	1,215
^{62}Cu	9.7 min	β^+ (98) EC (2)	2,930
^{64}Cu	12.7 h	β^+ (18) β^- (37) EC (45)	655
^{68}Ga	68.3 min	β^+ (90) EC (10)	1,900
^{72}As	26 h	β^+ (88) EC (12)	2,515
^{82}Rb	1.3 min	β^+ (96) EC (4)	3,350
^{86}Y	14.7 h	β^+ (34) EC (66)	1,300
^{89}Zr	3.27 days	β^+ (33) EC (77)	902
^{94m}Tc	52 min	β^+ (72) EC (28)	2,470

5.2.1 Labelling Methods – Introduction of the Radionuclide

Organic positron emitters: The introduction of the radionuclide into a biomolecule or a structure of (patho)physiological interest obviously is one of the

essential steps in the development of radiopharmaceuticals. Biomolecules and pharmaceuticals mainly consist of carbon, hydrogen, oxygen, nitrogen, sulphur and phosphorous due to that fact the so-called organic radionuclides (see Table 5.1), carbon-11, oxygen-15, ammonia-13 and phosphorous-30 allow the so-called authentic labelling without any changes in (bio)chemical and physiological behaviour of the radiolabelled molecule. However, these organic radionuclides are extremely short-lived isotopes with half-lives only from 2 to 20 min and that strongly limits their applicability. Only the half-life of 20 min of carbon-11 offers the possibility of radiosyntheses with more than one step and the detection of physiological processes with slower pharmacokinetics. Besides an unchanged pharmacology, the major advantage of such short half-lives is a low radiation dose to the patients and possible repeat studies within a short period.

Analogue positron emitters: Biomolecules and pharmaceuticals are generally relatively complex organic compounds and claim for multi-step radiosyntheses for their radiolabelled counterparts. In addition, many (patho)physiological processes are slower and thus not detectable with the extremely short-lived radionuclides. Alternatively, the so-called analogue radionuclides with longer half-lives from 80 min to 4 days are commonly introduced into biomolecules. The labelling with analogue radionuclides makes use of similarities in steric demand and/or in electronic character of the substituted atom or functional group. The steric demand of an atom or a functional group refers to the amount of space occupied by an atom or a functional group. Accordingly, selenium-73 can be used in the manner of sulphur. Selenium as the next homologue to sulphur has very similar steric and chemical properties. The analogue radiopharmaceuticals L-[^{73}Se]selenomethionine [18] and L-homocysteine[^{73,75}Se]selenolactone [19] are examples for such a selenium-sulphur-analogy. Similarly, ^{75,76,77}Br and ^{120,124}I can be regarded as structural analogues for methyl groups.

In the majority of cases, the analogue radionuclides evoke only small insignificant structural differences, but the arising electronic changes and those of chemical reactivity can be important. In each individual case, the pharmacological behaviour and properties of such analogue radiotracers have to be tested for changes in characteristics. In the last decades, the number of new pharmaceuticals has increased rapidly and more and more compounds have been identified as pharmacologically relevant substances which are originally carrying fluorine, bromine or iodine [20, 21]. Consequently, the advantages of authentic labelling and longer half-lives accrue and simplify the development of a corresponding radiopharmaceutical.

Metallic positron emitters: In a third group, there are also some metallic positron emitters which are suitable for PET imaging (see Table 5.1). The half-lives vary from minutes to days and offer a broad range of applicability. In contrast to organic or analogue PET nuclides, some of the metallic radionuclides are achievable from generator systems (e.g. ^{62}Zn/^{62}Cu, ^{68}Ge/^{68}Ga and ^{82}Sr/^{82}Rb) which make them available in places without an on-site cyclotron. Metallic PET nuclides can be used either directly in their free cationic forms or as complexes. Rubidium-82 has been evaluated as a myocardial perfusion PET tracer [22, 23]. In form of [^{82}Rb]RbCl, it is used as radiopharmaceutical for perfusion PET imaging on the market for almost 20 years (CardioGen-82©, approved by the FDA in 1989). The similarities of rubidium to the potassium cation lead to a rapid uptake of rubidium-82 into the myocardium and allow the identification of regions of insufficient perfusion by PET imaging [24, 25]. In complexes, the metallic radionuclides are usually incorporated into biomolecules which carry suitable chelators (i.e. Fig. 5.27 for the somatostatin receptor ligand [^{68}Ga-DOTA, Tyr^3]octreotide [26]).

In addition to differences in chemical, physical and nuclear properties of the radionuclides, the production routes or processes can also influence the labelling approach. The production route as well as the work-up provides the radionuclide in a certain chemical form which requires suitable (radio)chemistry in the following synthetic steps. From the production process, PET radionuclides are obtained only in a nano- to picomolar range while they are still very well detectable by their radioactive decay. As a result, the final PET radiopharmaceuticals are so attractive to medicinal purposes. In the body, they can be detected with non-invasive methods while the quantity of material is extremely small and generally toxic and pharmacological effects are negligible.

Specific activity: Owing to the desired insignificant quantities, a fundamental criterion of the quality of a radionuclide and the final radiopharmaceutical is its specific (radio)activity (SA) which depends on the amount of stable isotopes (carrier) present. Carrier can be divided into:

- *Isotopic carrier*: isotopes of the same element as the radionuclide and
- *Non-isotopic carrier*: isotopes of other elements mostly with very similar chemical and physical properties to the radionuclide

On this account, SA is defined as the mass-related radioactivity:

$$\mathrm{SA} = A/m[\mathrm{Bq/g}]$$

where A is the radioactivity in Becquerel and m is the mass of the radioactive material including all impurities and carrier, respectively. In (radio)chemistry such a specification related to the mass is inconvenient and thus SA is generally expressed on the molar basis as radioactivity related to the amount of substance:

$$\mathrm{SA} = A/n[\mathrm{Bq/mol}]$$

where m is replaced by n for the amount of substance in moles. In the absence of impurities or isotopic carrier, the theoretically attainable maximum molar SA equals to:

$$\mathrm{SA} = N_\mathrm{A}(\ln 2/T_{1/2})[\mathrm{Bq/mol}] \quad \text{or}$$
$$\mathrm{SA} = 1.16 \times 10^{20}/T_{1/2}[\mathrm{Bq/mol}]$$

where N_A is Avogadro's number (6.023×10^{23}) in atoms/mol and $T_{½}$ is the half-life of the radionuclide in hours. The general abundance of stable isotopes of the PET radionuclides smaller the theoretically attainable SA and the quantity of material become higher by natural isotopic carrier, but it is normally still at a nano- to picomolar level (6.3×10^4 versus 300–600 GBq/μmol for theoretical and practical SA, respectively, for fluoride-18 produced from $^{18}\mathrm{O(p,n)}^{18}\mathrm{F}$). Most applications in molecular imaging call for high (molar) specific activities and a lot of effort is put into this issue. Especially for brain receptor PET imaging, high specific activities are essential when receptor systems of low density can be saturated by radioligands with low SA. Besides poor PET imaging results, because of an unfavourable signal-to-noise ratio, pharmacological or toxic effects have also to be considered. In general, for radiochemical practice, the radionuclide situations can be classified as:

- Carrier-free (c.f.)
- No-carrier-added (n.c.a.)
- Carrier-added (c.a.)

Carrier free (c.f): Ideally carrier-free systems are not achievable with PET radionuclides as they all have naturally occurring stable isotopes. For example, carbon is the fourth most abundant element on earth and it is present in almost every kind of material. Thus, especially for carbon-11 high specific activities are an exceptional challenge. However, in radiochemistry of PET radionuclides, traces of stable isotopes are omnipresent and act as isotopic carrier. Sources of isotopic carrier are the air, target and vessel materials, transport lines and tubes, chemicals and solvents.

No carrier added (n.c.a): Contaminations in chemicals and solvents are below normal chemical purification limits, but they are still in the quantity of the radionuclide. Those conditions are referred to as no-carrier-added (n.c.a.) conditions and correspond to a state of practically highest SA attainable.

Carrier added (c.a): On the contrary, some circumstances require the addition of stable isotopes what is termed as carrier-added (c.a.). Predominantly, c.a. conditions are employed to achieve weighable quantities of a product for characterisation by non-radioactive analytical methods or to increase radiochemical yields. As a widely used c.a. procedure the production of electrophilic fluorine-18 is well known. The addition of the isotopic carrier fluorine-19 is necessary to mobilise n.c.a. $[^{18}\mathrm{F}]\mathrm{F}_2$ which is too reactive and adheres to the walls of targets and tubes.

Labelling reactions and radiosyntheses on the n.c.a. scale mean to work at a subnanomolar level regarding the amount of radioactive substance while all other reactants and solvents are still present at a macroscopic scale. Hence, the course of reaction may differ strongly from that of classical chemical reactions at balanced stoichiometric ratios, where all substrates and reagents are present in amounts in a similar or equal range. Such labelling reactions under non-equilibrium conditions generally proceed according to pseudo-first-order kinetics where the precursor amounts are in extreme excess to the radionuclide and can approximately be set as constant. On the other hand, the radionuclide and the labelled product exist on a n.c.a. scale and thus a consecutive labelling reaction or an interaction of two radioactive species can be statistically excluded.

In labelling procedures and radiosyntheses, obviously, the decay has to be taken into account and thus the half-life of the employed radionuclide. With respect to the PET imaging, the final radiopharmaceutical

must be obtained in reasonable amounts sufficient for the following PET procedures. As a rule of thumb, the radiosynthesis including purification, formulation and quality control of a PET radiopharmaceutical should not exceed three half-lives of the radionuclide. Consequently, the extremely short-lived PET radionuclides call for very fast chemistry and preclude multi-step procedures.

The efficacy of radiolabelling reactions is generally quantified by the radiochemical yield (RCY) which corresponds to the decay-corrected yield related to the starting activity. In contrast, the real yield reflects the amount of isolated radioactive material, but is not functional as an appraisal factor of the labelling procedure.

5.2.2 Labelling Methods for Fluorine-18

The indisputable importance of fluorine-18 in PET makes ^{18}F-labelled radiopharmaceuticals the most favoured ones; thus, especially procedures for the introduction of fluorine-18 are of great interest and several methods and strategies have been developed [27–31]. There are many established nuclear production pathways for fluorine-18; the most commonly used are listed in Table 5.2 [32, 33].

The main difference between various nuclear reactions is the target material which is either gas or liquid (water) and determines the final chemical form of fluorine-18. From gas targets, fluorine-18 is achieved as electrophilic c.a. [^{18}F]fluorine gas ([^{18}F]F_2) and from the water targets, nucleophilic n.c.a. [^{18}F]fluoride in aqueous solution is obtained. As mentioned before, in case of the electrophilic [^{18}F]F_2, adsorption of the produced n.c.a. fluorine-18 on the walls of the target requires the addition of non-radioactive F_2 (isotopic carrier) for an isotopic exchange and removal of the n.c.a. fluorine-18 out of the target. Due to this fact, the procedure dramatically lowers the obtainable specific activity which is one of the major disadvantages of these production routes.

Nonetheless, many compounds of (radio)pharmacological interest call for electrophilic labelling methods and thus necessitate c.a. [^{18}F]F_2 or its derived secondary labelling agents. The most popular PET radiopharmaceutical which is routinely produced via an electrophilic c.a. ^{18}F-labelling (^{18}F-fluorodestannylation) is 6-[^{18}F]fluoro-L-DOPA ([^{18}F]F-DOPA) (see Fig. 5.3) [34, 35]. So far, an efficient nucleophilic approach for a n.c.a. ^{18}F-fluorination of [^{18}F]F-DOPA is still lacking.

However, the nucleophilic production route using ^{18}O-enriched water as target material is the most efficient procedure and also provides the n.c.a. [^{18}F]fluoride in high specific activities. As a result, the ^{18}O(p,n)^{18}F reaction is the most widely used method to produce fluorine-18. The required proton energy of 16 → 3 MeV for the nuclear reaction is achievable without problems from small cyclotron, so-called medical cyclotrons. Normal batches of 50–100 GBq for the production of ^{18}F-labelled clinically utilised PET radiopharmaceuticals can be obtained within 30–60 min depending on the target construction and the corresponding beam current.

Regarding the chemical concepts for the introduction of fluorine-18 into organic molecules, the methods of the macroscopic organic chemistry could be principally transferred. In general chemistry, the commonly used fluorination procedures are based on the Wallach reaction [36] and the Balz–Schiemann reaction [37]. However, in n.c.a. ^{18}F-radiosyntheses, these procedures led only to very low radiochemical yields [38, 39]. Effects of the unusual stoichiometric ratios under n.c.a. conditions as well as principle aspects of

Table 5.2 Most common nuclear reactions for production of fluorine-18

Reaction	^{18}O(p,n)^{18}F	^{16}O(^{3}He,p)^{18}F	^{20}Ne(d,α)^{18}F	^{18}O(p,n)^{18}F
Target filling	$H_2{}^{18}O$	H_2O	Ne (200 μmol F_2)	$^{18}O_2$, Kr (50 μmol F_2)
Particle energy [MeV]	16 → 3	36 → 0	14 → 0	16 → 3
Chemical product form	[^{18}F]fluoride (aq)	[^{18}F]fluoride (aq)	[^{18}F]F_2	[^{18}F]F_2
Yield [GBq/μAh]	2.22	0.26	0.37–0.44	~0.35
Specific activity [GBq/μmol]	40 × 10^3	40 × 10^3	~0.04–0.40	~0.35–2.00

the reactions' mechanisms and reactants led to these results. Both reaction types revealed inappropriate for fluorine-18 chemistry under n.c.a. conditions.

Generally, radiofluorination methods can be divided into electrophilic and nucleophilic reactions (substitutions) according to the chemical form of fluorine-18 and thus the production route. Both methods represent direct ^{18}F-fluorinations and can be completed by two additionally indirect methods, the ^{18}F-fluorinations via prosthetic groups and the ^{18}F-fluorinations via built-up syntheses. In general, the indirect methods are based on direct methods for the ^{18}F-labelling of the required prosthetic group or synthon. Frequently, the nucleophilic ^{18}F-methods are employed here due to higher specific activities, higher radiochemical yields and a better availability of n.c.a. [^{18}F]fluoride.

5.2.2.1 Electrophilic Substitutions

Fluorine-18 for electrophilic substitution reactions is available as c.a. [^{18}F]F_2 directly from targets. ^{20}Ne and enriched [^{18}O]O_2 can be used as target materials (cf. Table 5.2). Both alternatives come along with an adsorption of the fluorine-18 on the target walls and entail an addition of [^{19}F]F_2 to mobilise the produced fluorine-18 by isotopic exchange. In the ^{18}O(p,n)^{18}F reaction, the enriched [^{18}O]O_2 target filling is removed after bombardment and the target is filled with 0.1% [^{19}F]F_2 in Kr and repeatedly irradiated for the [^{18}F]F_2 formation [40]. In comparison, the ^{20}Ne(d,α)^{18}F reaction is more practical as 0.1% [^{19}F]F_2 is directly added with the neon and an additional step for recovery of the enriched material and the consecutive irradiation is saved. Furthermore, the process does not require enriched material and is less expensive. Therefore, the ^{20}Ne(d,α)^{18}F reaction is the commonly employed process for electrophilic fluorine-18, although its production rates are lower [32, 33]. As all production processes for electrophilic fluorine-18 require carrier addition, c.a. [^{18}F]F_2 or milder reagents derived from it cannot be used in preparations of PET radiopharmaceuticals where high specific activities are mandatory [41, 42].

Generally, the methods of electrophilic fluorinations from organic chemistry can be directly transferred into c.a. fluorine-18 chemistry. Due to the fact that carrier is added here, the stoichiometric ratios are more balanced than under n.c.a. conditions and thus closer to macroscopic chemistry. In organic chemistry, elemental fluorine is known for its high reactivity and its poor selectivity. Therefore c.a. [^{18}F]F_2 is often transferred into less reactive and more selective electrophilic fluorination agents such as [^{18}F]acetyl hypofluoride ([^{18}F]CH_3COOF) [43], [^{18}F]xenon difluoride ([^{18}F]XeF_2) [44, 45] or [^{18}F]fluorosulfonamides [46]. The maximum radiochemical yield in electrophilic radiofluorinations is limited to 50% as only one fluorine in [^{18}F]F_2 is substituted by a ^{18}F atom. Consequently, that is also the situation for all secondary electrophilic radiofluorination agents derived from c.a. [^{18}F]F_2.

The most popular example of electrophilic radiofluorinations using c.a. [^{18}F]F_2 is the first method to produce 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) by Ido et al. in 1978 (see Fig. 5.1) [3]. [^{18}F]F_2 was used in an electrophilic addition to the double bond of triacetoxyglucal and gave [^{18}F]FDG in a radiochemical yield of 8%. As a radioactive side product 3% of the ^{18}F-labelled mannose derivative (2-deoxy-2-[^{18}F]fluoro-D-mannose, [^{18}F]FDM) was obtained. In 1982, a higher RCY of 20% and an improved product-to-byproduct-ratio of 7:1 were achieved in the approach of Shiue et al. using the milder radiofluorination agent [^{18}F]acetyl hypofluoride [47]. Many other approaches

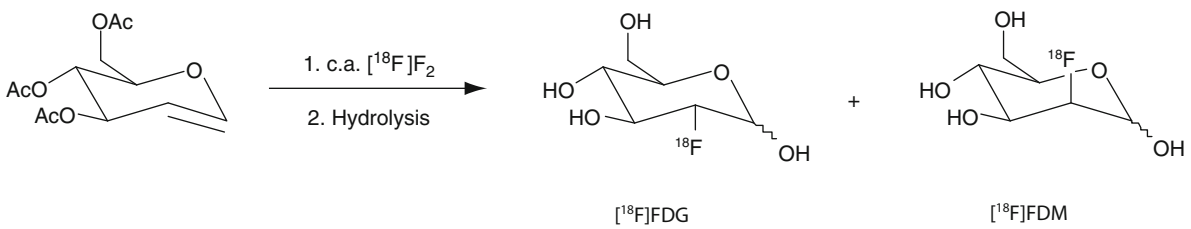


Fig. 5.1 Original radiosynthesis of [^{18}F]FDG (RCY = 8%) by Ido et al. using c.a. [^{18}F]F_2. As a side product, the ^{18}F-labelled mannose derivative ([^{18}F]FDM) was obtained in a RCY of 3%

were made to increase radiochemical yields of [^{18}F]FDG in electrophilic procedures [48–50], including also attempts with [^{18}F]XeF_2 [51–53].

Another example for a direct electrophilic ^{18}F-fluorination is 5-[^{18}F]fluorouracil which is the ^{18}F-labelled analogue of 5-fluorouracil. 5-Fluorouracil is a chemotherapeutic and thus its ^{18}F-labelled analogue can be used for therapy control, for visualisation of various tumours and for prediction of therapy response in liver metastases [54, 55]. 5-[^{18}F]fluorouracil can be prepared by direct ^{18}F-fluorination of uracil using c.a. [^{18}F]F_2 [56].

The most important PET radiopharmaceutical which is routinely produced via electrophilic ^{18}F-fluorination methods is 6-[^{18}F]fluoro-L-DOPA ([^{18}F]F-DOPA). After [^{18}F]FDG, [^{18}F]F-DOPA ranks second in its frequency of clinical use. The direct radiofluorination of 3,4-dihydroxyphenyl-L-alanine using [^{18}F]F_2 leads to three possible ^{18}F-labelled regioisomers namely 2-[^{18}F]F-DOPA (12%), 5-[^{18}F]F-DOPA (1.7%) and 6-[^{18}F]F-DOPA (21%) (see Fig. 5.2) and requires a complex HPLC purification to obtain the desired 6-[^{18}F]F-DOPA in only 3% RCY [57].

Several attempts have been made to improve radiochemical yields and regioselectivity in the direct radiofluorination of L-DOPA [58, 59]. So far, the most efficient procedures for 6-[^{18}F]F-DOPA which provide adequate RCY of up to 33% for clinical PET imaging are based on ^{18}F-fluorodemetallation reactions [60–62]. Among the ^{18}F-demetallation reactions, to date, the ^{18}F-fluorodestannylation is the most commonly used reaction for routinely produced 6-[^{18}F]F-DOPA (see Fig. 5.3) [34, 63]. An automation of this radiosynthesis and recently improved precursor synthesis and quality control allows reliable routine productions for clinical PET imaging using 6-[^{18}F]fluoro-L-DOPA [35, 64].

To date, the ^{18}F-fluorodestannylations are generally the preferred methods for electrophilic ^{18}F-labelling of complex molecules as they provided satisfactory radiochemical yields and high regioselectivity.

For higher specific activities in electrophilic ^{18}F-fluorinations, [^{18}F]F_2 can be obtained from n.c.a. [^{18}F]CH_3F via an electric gaseous discharge reaction in the presence of [^{19}F]F_2 (150 nmol) (see Fig. 5.4). This provides specific activities of up to 55 GBq/μmol

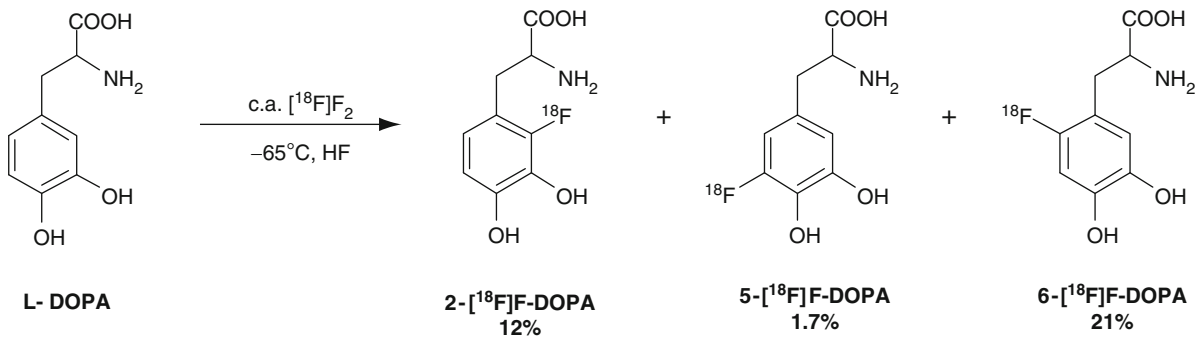
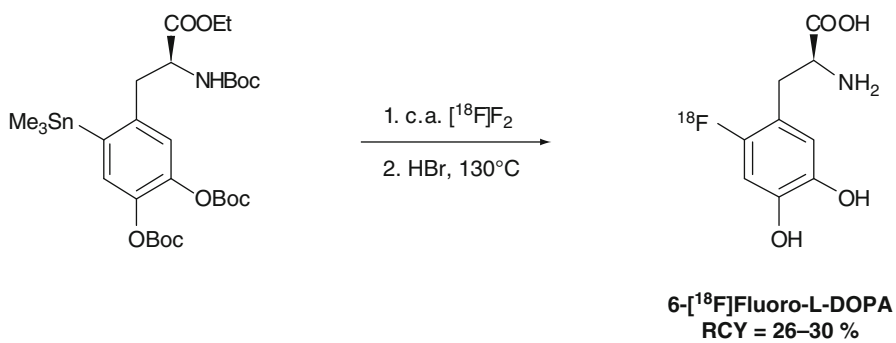


Fig. 5.2 Direct electrophilic radiofluorination of [^{18}F]F-DOPA using c.a. [^{18}F]F_2. The product mixture contains 21% of the desired ^{18}F-labelled regioisomer 6-[^{18}F]F-DOPA

Fig. 5.3 Electrophilic radiofluorination of 6-[^{18}F]F-DOPA by regioselective ^{18}F-fluorodestannylation. After 45–50 min 6-[^{18}F]F-DOPA is obtained in RCY of 26–33%



in case of the [^{18}F]F_2 which leads to SA of ~15 GBq/µmol of final ^{18}F-labelled products [65].

However, electrophilic substitution reactions using [^{18}F]F_2 and secondary milder fluorination agents derived from it can be used in clinically routine production of PET radiopharmaceuticals where low specific activities and moderate radiochemical yields are not essential. PET imaging of receptor systems and other PET imaging investigations which require high specific activities, still necessitate ^{18}F-radiopharmaceuticals produced under no-carrier-added conditions and thus derive from nucleophilic substitution using n.c.a. [^{18}F]fluoride.

5.2.2.2 Nucleophilic Substitutions

As mentioned earlier, the ^{18}O(p,n)^{18}F reaction using enriched [^{18}O]water as target material is the most efficient and most widely used production route for (nucleophilic) fluorine-18. The required proton energy of 16 MeV can be easily generated by medial cyclotrons and so 50–100 GBq of n.c.a. fluorine-18 can be produced within 30–60 min. The fluorine-18 is obtained directly from the target as nucleophilic n.c.a. [^{18}F]fluoride in aqueous solution without any carrier addition.

For saving the costly, enriched material, the first step after the irradiation is the separation of the [^{18}F]fluoride from the [^{18}O]water. Commonly, [^{18}F]fluoride is trapped on an anionic exchange resin (solid phase extraction cartridge systems) while the [^{18}O]water is recovered. [^{18}F]Fluoride in aqueous solution is strongly hydrated and inactivated for nucleophilic reactions. For an activation of the [^{18}F]fluoride, generally, the water is removed by azeotropic distillation with acetonitrile and the remaining dry [^{18}F]fluoride is available for nucleophilic substitution reaction as an activated nucleophile.

Due to the strong tendency of fluoride ions to form hydrogen fluoride, the ^{18}F-labelling reactions must be carried out under dry and aprotic conditions. Hence, nucleophilic ^{18}F-labelling is usually performed in dipolar aprotic organic solvents. For further activation and increased nucleophilicity of the [^{18}F]fluoride, it is used in combination with weak and soft cations, those of caesium or rubidium. As a result, a so-called 'naked' [^{18}F]fluoride of high nucleophilicity is produced. Similarly, phase transfer catalyst such as tetraalkylammonium salts, mainly as their carbonates, hydroxides or hydrogen carbonates, can be used. One of the most efficient and commonly applied system in radiofluorinations is the combination of a cryptand, the aminopolyether Kryptofix©2.2.2, and potassium carbonate (see Figs. 5.5 and 5.6) [66, 67]. In case of base-

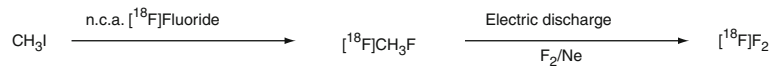


Fig. 5.4 Production of c.a. [^{18}F]F_2 of higher specific activities derived from electric gaseous discharge of n.c.a. [^{18}F]fluoromethane under carrier-added conditions. [^{18}F]F_2 is obtained with specific activities of 55 GBq/µmol

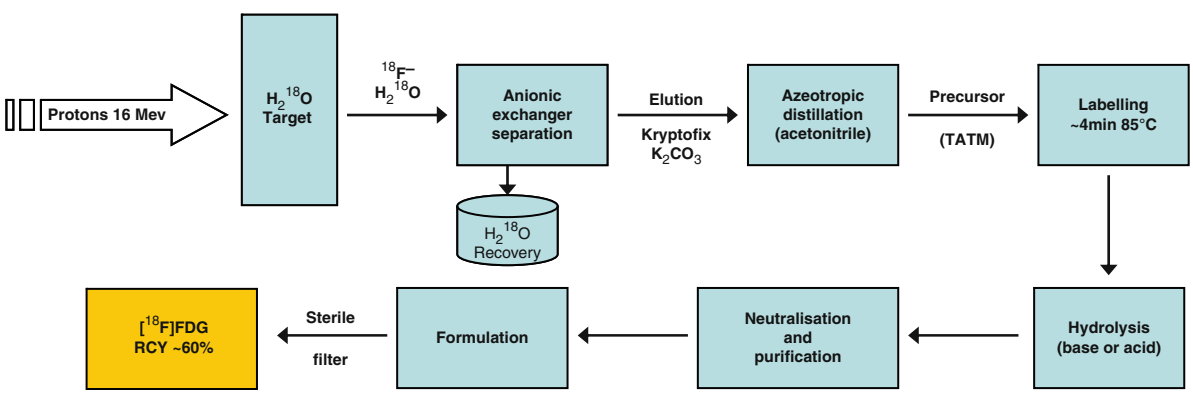


Fig. 5.5 Steps of the [^{18}F]FDG routine production. TATM = 1,3,4,6-tetra-*O*-acetyl-2-*O*-trifluoro-methanesulfonyl-beta-*D*-mannopyranose

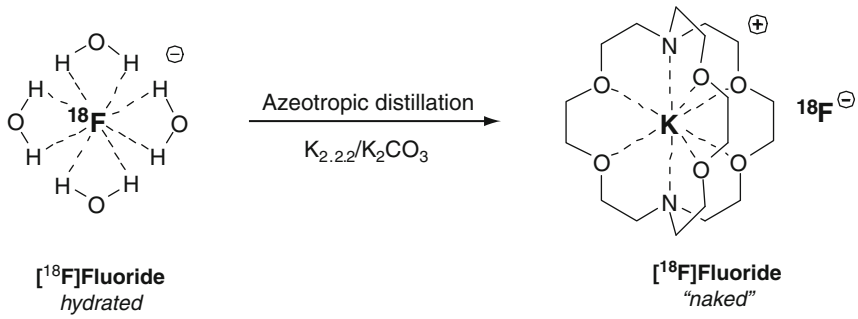


Fig. 5.6 Principle of [^{18}F]fluoride activation by removal of water in combination with the Kryptofix©2.2.2/potassium carbonate system

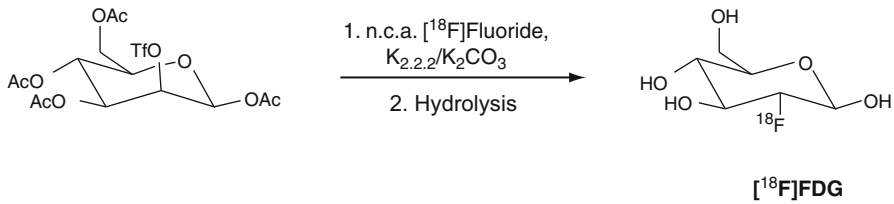


Fig. 5.7 Most commonly used radiosynthesis of n.c.a. [^{18}F]FDG (RCY = 50–70%) by Hamacher et al.

sensitive compounds the carbonate can be exchanged by oxalate which provides less basic conditions. In another method, the [^{18}F]fluoride is separated from [^{18}O]water by an electrochemical anodic adsorption [68]. For drying the cell is flushed two times with acetonitrile or dimethylamide. A polarity change of the electrical field provides a subsequent desorption and release of the [^{18}F]fluoride into a dipolar aprotic solvent containing a phase transfer catalyst system [69]. In recent studies, the use of ionic liquids showed very high ^{18}F-labelling efficiency of up to 90% RCY without previous drying procedures [70]. Small volumes of aqueous ^{18}F-solution are directly added to the reaction mixture containing a base, precursor and ionic liquid. The best results were obtained from the combination of caesium carbonate and the ionic liquid 1-butyl-3-methylimidazolium triflate ([bmim][OTf]). This method was also applied for [^{18}F]FDG productions and showed good RCY of 50–60%, but so far, it has been tested just with small amounts of [^{18}F]fluoride of less than 1 GBq [71].

Generally, the most important procedures to get ^{18}F-labelled radiopharmaceuticals are based on the nucleophilic substitution using n.c.a. [^{18}F]fluoride which is so far also the only way to get ^{18}F-radiopharmaceuticals of high specific activities. Nucleophilic substitution reactions can be divided into aliphatic and aromatic substitutions.

Aliphatic substitution: In case of aliphatic nucleophilic substitutions, the reactions follow the S_N2 mechanism and suitable leaving groups are required. The most efficient leaving groups are sulphonic acid esters such as the methane sulphonic acid ester (mesylate), the trifluoromethane sulphonic acid ester (triflate), the *para*-toluene sulphonic acid ester (tosylate) and the *para*-nitrobenzene sulphonic acid ester (nosylate). Further suitable leaving groups are halogens. The most important and prominent example of such an aliphatic nucleophilic substitution using n.c.a. [^{18}F]fluoride is the synthesis of [^{18}F]FDG using an acetyl-protected mannose precursor (1,3,4,6-tetra-*O*-acetyl-2-*O*-trifluoro-methanesulfonyl-beta-*D*-mannopyranose, TATM) carrying a triflate leaving group which was developed by Hamacher et al. in 1986 (see Fig. 5.7) [67]. This procedure provides [^{18}F]FDG after deprotection and purification in very high radiochemical yields of 50–70% with high specific activities of ~300–500 GBq/μmol. To date, this is the most widely used method for the production of [^{18}F]FDG towards preclinical and clinical applications.

Regarding the reaction conditions for aliphatic nucleophilic substitutions using n.c.a. [^{18}F]fluoride, best results are typically obtained from acetonitrile as solvent and the Kryptofix©2.2.2/potassium carbonate system. Applied reaction temperatures vary from 80°C to 110°C and depend on the individual precursor molecule. Due to the low boiling point of acetonitrile of 82–84°C, temperatures higher than 110°C are not practical. Further suitable solvents are dimethylformamide, dimethylsulfoxide and dimethylacetamide

which also allow higher temperatures up to 160–190°C. In recent studies, Kim et al. found increased radiochemical yields in aliphatic nucleophilic ^{18}F-labelling by the use of *tert*-alcohols (frequently *tert*-butanol) as co-solvents to acetonitrile. A beneficial effect was shown for a number of clinically important ^{18}F-labelled PET radiopharmaceuticals [72].

Generally, the aliphatic nucleophilic substitution is high yielding and does not take much longer than 10–15 min for completion. Often, a subsequent deprotection step is necessary, but can also be accomplished within short reaction times of 5–10 min. As a result, aliphatic nucleophilic substitution is widely applied in ^{18}F-labelling chemistry and several routinely produced ^{18}F-labelled PET radiopharmaceuticals are obtained from this reaction type. Besides [^{18}F]FDG, the most popular examples are 3-deoxy-3′-[^{18}F]fluoro-L-thymidine ([^{18}F]FLT) [73], [^{18}F]fluoromisonidazole ([^{18}F]FMISO) [74], O-(2-[^{18}F]fluoroethyl-L-tyrosine) ([^{18}F]FET) [75, 76] and [^{18}F]fluorocholine ([^{18}F]FCH) [77].

Aromatic substitution: The nucleophilic aromatic n.c.a. ^{18}F-fluorinations require an activated aromatic system, an electron deficient system. Otherwise, the desired target ring is not attractive for a nucleophilic attack by n.c.a. [^{18}F]fluoride. Such activation can be reached by strong electron-withdrawing groups (EWG) such as nitro, cyano, carbonyl functionalities and halogens in *ortho*- or *para*-position to the substitution (see Fig. 5.8).

Suitable leaving groups (LG) are nitro, halogens and especially trimethylammonium salts as their triflate, tosylate, perchlorate or iodide [30, 31, 78]. Generally, dimethylsulfoxide is the solvent of choice for the nucleophilic aromatic substitution, but also dimethylamide and dimethylacetamide or solvent mixtures have been found beneficial. The nucleophilic aromatic substitution usually requires higher energy than its aliphatic variant, especially in case of the fluoro-for-nitro exchange. Therefore, the dipolar aprotic solvents with higher boiling points are preferred and the use of acetonitrile is rare.

An example of a nucleophilic aromatic substitution is the direct ^{18}F-fluorination of the butyrophenone neuroleptic *N*-methyl-[^{18}F]fluorospiperone using the corresponding nitro-precursor which gave a RCY of ~20% (isolated product) after 70 min synthesis time (see Fig. 5.9) [79]. The aromatic system is activated by the electron-withdrawing effect of the *para*-ketone functionality. However, butyrophenones are base sensitive and the direct ^{18}F-labelling of *N*-methyl-[^{18}F]fluorospiperone could be realised only with the less basic Kryptofix©2.2.2/potassium carbonate/oxalate buffer system. In the same manner, [^{18}F]haloperidol [79, 80], [^{18}F]altanserin [81] and *p*-[^{18}F]MPPF (4-[^{18}F]fluoro-*N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]

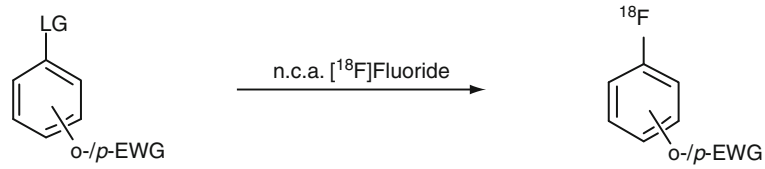


Fig. 5.8 Nucleophilic aromatic substitution using n.c.a. [^{18}F]fluoride

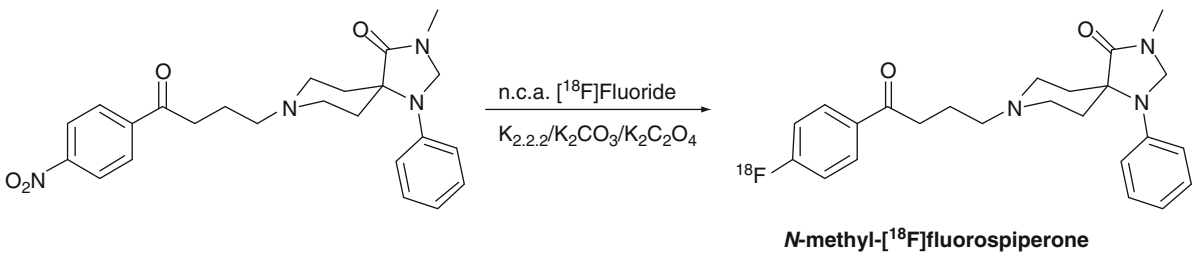


Fig. 5.9 Nucleophilic aromatic ^{18}F-fluorination of n.c.a. *N*-methyl-[^{18}F]fluorospiperone

ethyl]-*N*-2-pyridinyl-benzamide) [82, 83] have been successfully labelled with n.c.a. [^{18}F]fluoride by the fluoro-for-nitro exchange.

Another possibility for nucleophilic aromatic substitutions is given by electron-deficient heteroaromatic systems such as pyridines which do not need further activating electron-withdrawing groups [84–86]. ^{18}F-fluoroanalogues of epibatidine have been labelled via a nucleophilic (hetero)aromatic substitution in the *ortho*-position of the pyridinyl group (see Fig. 5.10) and gave radiochemical yields of 55–65% using the trimethylammonium triflate leaving group [87–89]. However, the ^{18}F-labelled epibatidines revealed very toxic [88, 90] and further less toxic ^{18}F-labelled ligands for the nicotine acetylcholine receptor system have been developed, again via the nucleophilic (hetero)aromatic substitution on the *ortho*-position of a pyridinyl group [91, 92]. In case of *meta*-substitutions, the activation of the pyridine is normally not efficient enough and additional activating groups are necessary to obtain sufficient ^{18}F-incorporation [86] as shown by the ^{18}F-labelling of a MAO-B inhibitor in the *meta*-position of the pyridinyl moiety using the fluoro-for-nitro exchange (see Fig. 5.11); 10% RCY after 120 min total synthesis time [93].

Using the direct nucleophilic aromatic substitution, several ^{18}F-labelled PET radiopharmaceuticals have been successfully synthesized including ^{18}F-labelled butyrophenone neuroleptics [79, 80], [^{18}F]altanserin [81], [^{18}F]methylbenperidol [94], *p*-[^{18}F]MPPF [82, 83], [^{18}F]flumazenil [95], ^{18}F-labelled MAO-B inhibitor [93], ^{18}F-labelled epibatidine analogues [87–89] and further ligands for the nicotine acetylcholine receptor system (nAChR) [91, 92].

In general, radiolabelling chemistry benefits from microwave heating which usually dramatically enhances reaction (labelling) kinetics and provides products within minutes and often with higher (radiochemical)yields [96]. However, the aromatic fluoro-for-nitro exchange, particularly, benefits usually from microwave heating and increased radiochemical yields within markedly reduced reaction times can be obtained [81, 97, 98].

If an aromatic system is somehow non-activated or even deactivated (electron-rich) for nucleophilic ^{18}F-fluorination, a possible strategy is the introduction of auxiliary activating groups transferring the deactivated arene into an activated system. Such supplementary groups or functions need to be removed or modified after the ^{18}F-labelling which implies a multistep radiosynthesis. Aldehydes and ketone functions are particularly suitable as activating groups as they can be removed by reductive decarbonylation [99–101]. This method has been applied for nucleophilic ^{18}F-labelling approaches towards n.c.a. 6-[^{18}F]FDOPA which resulted in only 3–5% RCY

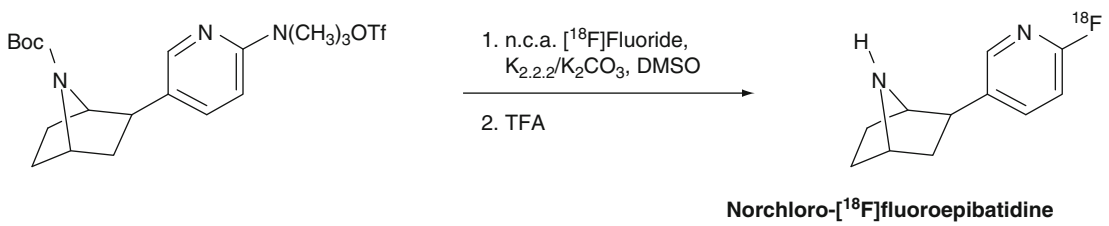


Fig. 5.10 ^{18}F-Fluoroanalogue of epibatidine. ^{18}F-labelling via nucleophilic (hetero)aromatic substitution

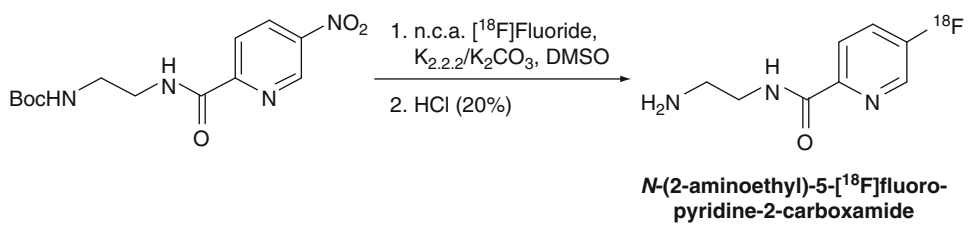


Fig. 5.11 ^{18}F-labelling of N-(2-aminoethyl)-5-[^{18}F]fluoropyridine-2-carboxamide, a MAO-B inhibitor, using nucleophilic (hetero) aromatic substitution in pyridine's *meta*-position

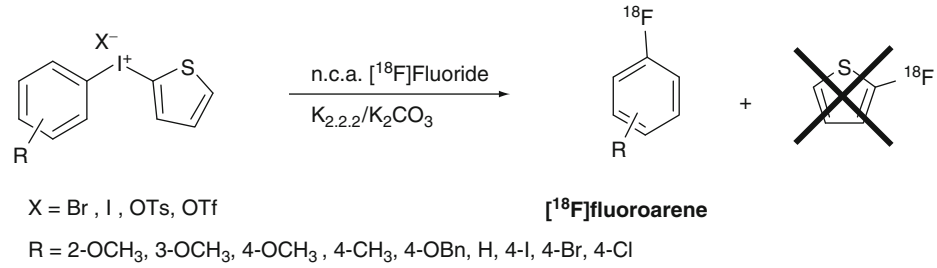


Fig. 5.12 Nucleophilic aromatic ^{18}F-labelling of various arenes including electron-rich systems using aryl(2-thienyl)iodonium salts as precursors

after a three-step radiosynthesis [102] and towards n.c.a. 2-[^{18}F]fluoroestradiol which could be achieved in 10–24% RCY [103].

Another method which allows a direct nucleophilic aromatic ^{18}F-labelling of deactivated systems is the use of diaryliodonium or aryl(heteroaryl)iodonium salts (see Fig. 5.12) [104, 105]. The resulting product distribution after the nucleophilic attack of the n.c.a. [^{18}F]fluoride strongly depends on the electronic and steric character of each aryl ring and its substituents, respectively. Generally, the more electron-deficient ring of the iodonium salt is preferred for the ^{18}F-introduction. Thus, the use of electron-rich heteroaryl systems as one iodonium moiety such as the 2-thienyl group leads to a regioselective ^{18}F-labelling on the counter ring [105]. So far, some attempts of using diaryliodonium salts as precursors for complex structures towards ^{18}F-labelled radiopharmaceuticals have been made, but the ^{18}F-labelling of complex structures via diaryliodonium salts still remains a challenge [103, 106]. One successful example is the PBR ligand [^{18}F]DAA1106 which was recently ^{18}F-labeled in radiochemical yields of 46% from a diaryliodonium precursor [107].

5.2.2.3 ^{18}F-Fluorinations Via Prosthetic Groups

^{18}F-labelling via prosthetic groups is based on small molecules which are first ^{18}F-labelled and then introduced into appropriate biomolecules [31, 108–110]. As mentioned before, the direct nucleophilic ^{18}F-labelling methods which usually provide the ^{18}F-labelled PET radiopharmaceutical fast and in high RCY are generally inappropriate for multifunctionalised structures such as peptides, oligonucleotides or antibodies. For that reason, small organic molecules are labelled with fluorine-18 using a direct method and subsequently, they are conjugated to the target structure forming the final ^{18}F-labelled PET radiopharmaceutical. Principally, both electrophilic and nucleophilic ^{18}F-labelling are suitable for the ^{18}F-introduction into prosthetic groups, but due to high specific activities, higher RCY and better availability of n.c.a. [^{18}F]fluoride, the nucleophilic methods clearly outperform the electrophilic procedures.

The prosthetic group: A variety of prosthetic groups have been developed so far, whereas only limited methods for their introduction into biomolecules are available: acylation [111–122], alkylation [123–125], amidation [126–130], imidation [125], thiol-coupling [131, 132], oxime-formation [133, 134] and photochemical conjugation [122, 135] (see Fig. 5.13).

Most of the procedures for preparation of prosthetic groups are multi-step radiosyntheses and with the final coupling step to bioactive molecules they end as 4–5 – step radiosynthesis. Furthermore, the methods for introduction of certain prosthetic groups require certain functionalities in the target structure and some suffer from low RCY or poor in vivo stability, but prosthetic groups are still indispensable, because of the limitations of direct nucleophilic ^{18}F-labelling.

[^{18}F]SFB: The most commonly applied ^{18}F-labelled prosthetic group is *N*-succinimidyl-4-[^{18}F]fluorobenzoate ([^{18}F]SFB) which cannot be obtained in a single step [116, 117]. Generally, [^{18}F]SFB derives from n.c.a. ^{18}F-labelling of the triflate salt of 4-trimethylammonium-ethylbenzoate yielding 4-[^{18}F]fluorobenzoic acid ([^{18}F]FBA) after basic hydrolysis; in the next step, [^{18}F]FBA is converted into activated succinimidyl esters using activating agents like *N*-hydroxysuccinimidine/1,3-dicyclohexalcarbodiimide (NHS/DCC) [118], *N*,*N*′-disuccinimidyl carbonate (DSC) [119] or *O*-(*N*-succinimidyl)-*N*-*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TSTU) [121] to give [^{18}F]SFB. To date, the TSTU-mediated procedure is the fastest and most

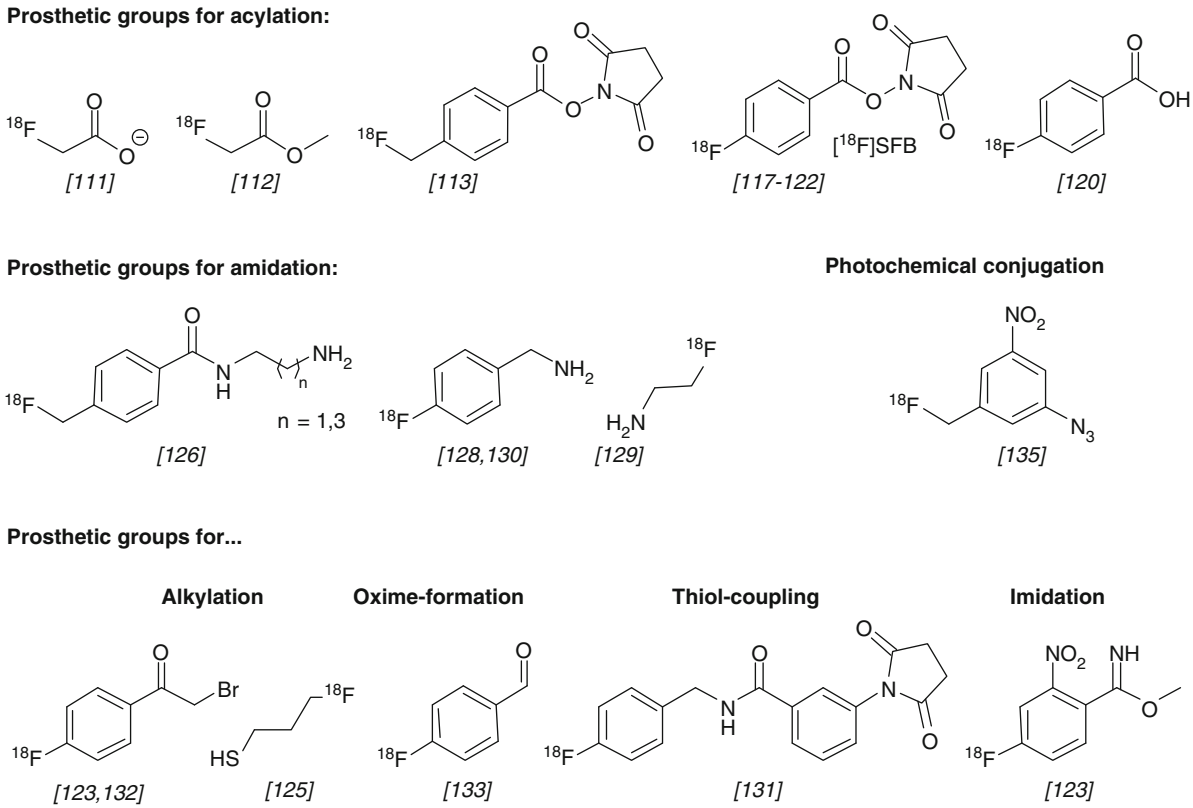


Fig. 5.13 Examples of prosthetic groups and their application in n.c.a. ^{18}F-labelling of biomolecules. References are given in brackets

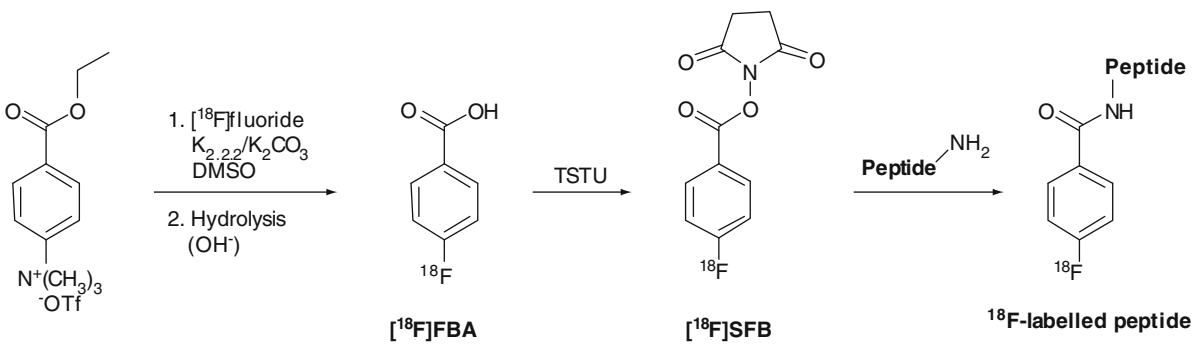


Fig. 5.14 Principle of prosthetic group ^{18}F-labelling of biomolecules using n.c.a. [^{18}F]SFB (TSTU mediated). TSTU: *O*-(*N*-succinimidyl)-*N*-*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate

convenient method to produce [^{18}F]SFB (see Fig. 5.14) [121]. [^{18}F]SFB can then be coupled to an amino function of the target structure.

Recently, the Cu(I)-catalysed 1,3-dipolar cycloaddition between alkynes and azides which is the most prominent representative of the so-called 'click chemistry' [136] has been applied to fluorine-18 chemistry [137–139]. Very mild reaction conditions accompanied by high efficiency, high selectivity and excellent yields make this click reaction particularly suitable for biological applications as well as for the synthesis of PET radiopharmaceuticals.

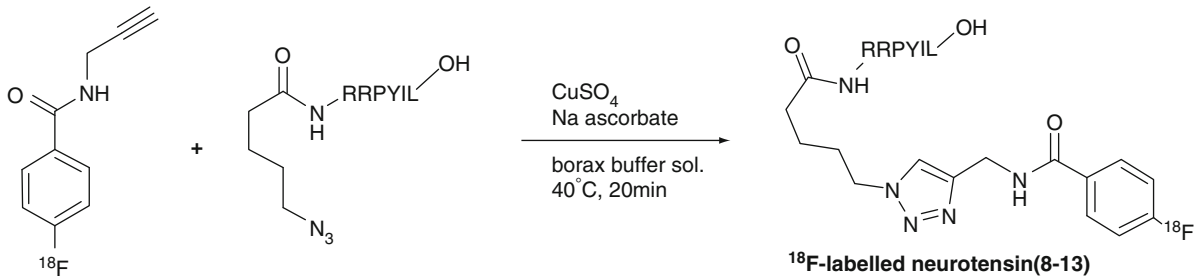


Fig. 5.15 N.c.a. ^{18}F-labelling of neurotensin(8-13) using click chemistry

As an example, the hexapeptide neurotensin(8–13) was successfully n.c.a. ^{18}F-labelled using the click reaction of the ^{18}F-alkyne n.c.a. 4-[^{18}F]fluoro-*N*-(prop-2-ynyl)benzamide and the azide-functionalised $N_3(CH_2)_4CO$-neurotensin(8–13) (see Fig. 5.15) [140]. Under very mild conditions of only 40°C reaction temperature and in borax buffer solution, radiochemical yields of 66% were achieved within 20 min.

In each individual case, the choice of the prosthetic group, and therewith the method of conjugation, depends on the chemical and pharmacological properties of the target structure. Furthermore, the in vivo stability of the prosthetic group and the influence on the pharmacological behaviour of the ^{18}F-labelled compound has to be considered. In terms of the most important requirements for prosthetic group ^{18}F-labelling, to date, the [^{18}F]SFB group seems to be the most suitable prosthetic group. However, the wide scope and the very mild conditions of the ^{18}F-click cycloaddition have added a new and wide flexibility to the ^{18}F-labelling prosthetic groups.

5.2.2.4 Direct ^{18}F-Labelling of Multifunctional Molecules

As mentioned above, the method of choice to introduce the ^{18}F-label into structures like peptides is the use of small ^{18}F-labelled prosthetic groups which are coupled to the biomolecule (see previous paragraph). Recently, the first successful approaches of direct nucleophilic ^{18}F-labelling were reported. Peptides can be selectively functionalised with a highly activated aromatic system bearing a trimethylammonium leaving group which enables a direct one-step nucleophilic aromatic n.c.a. ^{18}F-labelling under very mild conditions [141]. Another new strategy of direct ^{18}F-labelling is based on organoboron and organosilicon bioconjugates which can be labelled with n.c.a. [^{18}F]fluoride in one step under aqueous conditions with high RCY [142–144]. In a similar approach, organosilicon building blocks were introduced into a peptide structure and facilitated direct nucleophilic n.c.a. ^{18}F-labelling of peptides in one step under very mild aqueous and even slightly acidic conditions without the need for protection group chemistry (see Fig. 5.16) [145]. Depending on the type of precursor, either 45% RCY or 53% RCY is achieved after 15 min ^{18}F-labelling of the silane precursor or the silanol precursor, respectively.

5.2.2.5 ^{18}F-Labelled Synthons for Built-Up Radiosyntheses

The growing number of complex and multifunctional pharmaceuticals poses a particular challenge to radiolabelling methods. Frequently, the target structure is not suitable for direct ^{18}F-labelling and only an indirect ^{18}F-labelling method can be applied. Besides the prosthetic group ^{18}F-labelling, the ^{18}F-labelling via built-up radiosynthesis offers another indirect alternative [27–31, 86, 146]. Both methods are very similar as they are based on ^{18}F-labelled small organic molecules and indeed the lines between them are often blurred. Generally, the ^{18}F-labelling via built-up radiosyntheses using synthons are used in the direction of small monomeric radiotracers while the ^{18}F-labelled prosthetic groups are mostly applied towards ^{18}F-labelling of macromolecular structures such as peptides or antibody fragments. Obviously, the indirect ^{18}F-labelling methods imply multi-step radiosyntheses of minimum two steps.

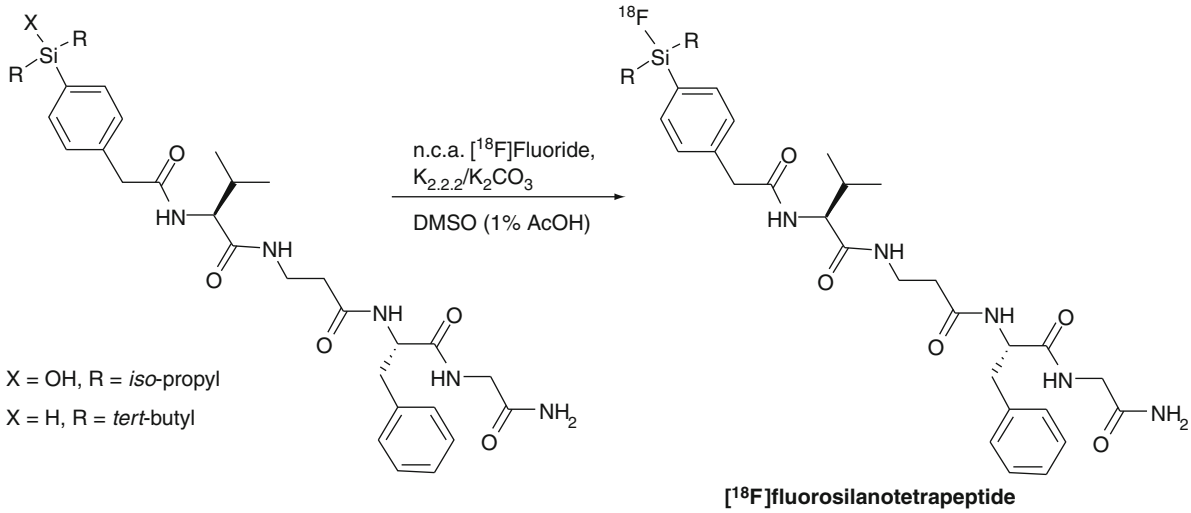


Fig. 5.16 Direct nucleophilic n.c.a. ^{18}F-labelling of a silicon tetrapeptide

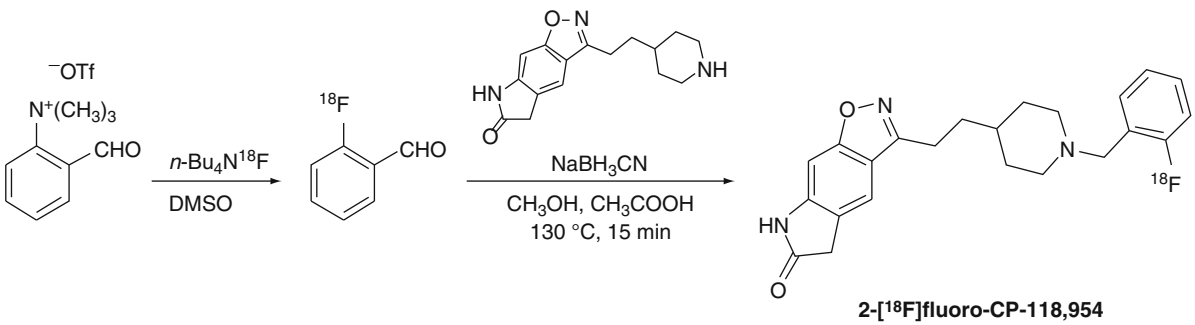


Fig. 5.17 Reductive amination with 2-[^{18}F]fluorobenzaldehyde forming the AChE inhibitor 2-[^{18}F]fluoro-CP-118,954

The Synthons: The built-up radiosynthesis approach is based on small activated organic molecules which are subsequent to the ^{18}F-fluorination used for a built-up synthesis of the final target compound. Such ^{18}F-labelled synthons are generally derivatives of [^{18}F]fluorobenzene or similar ^{18}F-labelled aryls. Regarding the ^{18}F-introduction they usually bear a leaving group and an activating group. In addition, they need to be functionalised towards further coupling or built-up reactions. Either the activation group is modified or the synthons bear additional substituents which provide further derivatisation and allow coupling reactions. Frequently, the activation group is modified for following coupling or built-up reaction steps.

[^{18}F]Fluorobenzaldehydes give several possibilities for built-up syntheses and represent the most versatile class of synthons. The aldehyde moiety can be easily transferred into other functionalities. Thus, [^{18}F]fluorobenzaldehydes can be reduced to their [^{18}F]fluorobenzamines or –amides and subsequently used in amination reactions towards *N*-[^{18}F]fluorobenzylamines [147–152]. Recently, the AChE inhibitor 5,7-Dihydro-3-[2-[1-(2-[^{18}F]fluorobenzyl)-4-piperidinyl]ethyl]-6H-pyrrolo[3,2,f]-1,2-benzisoxazol-6-one (2-[^{18}F]fluoro-CP-118,954) has been labelled with fluorine-18 via reductive amination using 2-[^{18}F]fluorobenzaldehyde (see Fig. 5.17) [152].

Additional useful derivatives from [^{18}F]fluorobenzaldehydes are the [^{18}F]fluorobenzyl halides which can be used as alkylation agents for amino [153–155], hydroxyl [156] or thiol [156] functions. 2-[^{18}F]fluoro-4,5-dimethoxybenzaldehyde was prepared from its trimethylammonium triflate precursor and used as synthon in a five-step enantioselective radiosynthesis

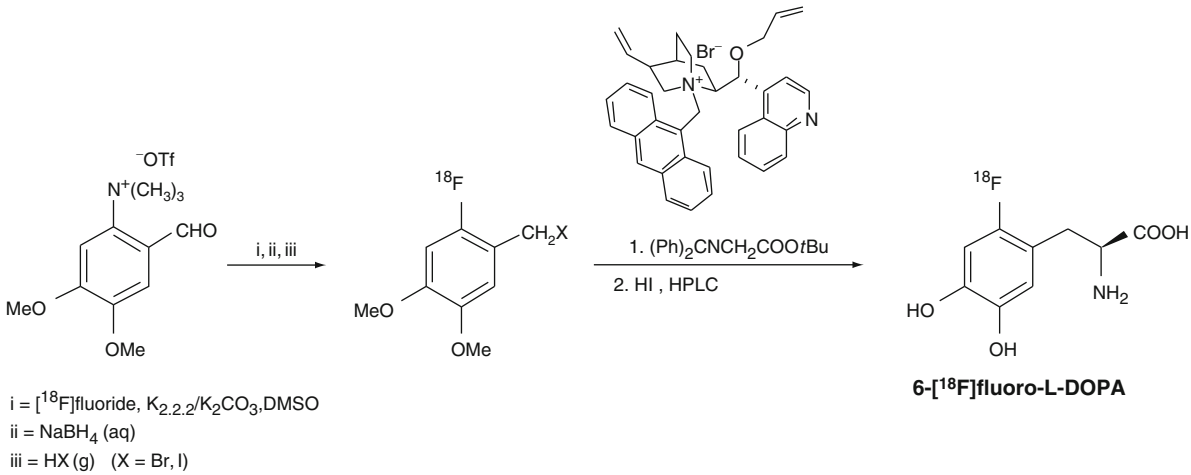


Fig. 5.18 2-[^{18}F]fluoro-4,5-dimethoxybenzyl halides as synthons for n.c.a. radiosynthesis of 6-[^{18}F]fluoro-L-DOPA

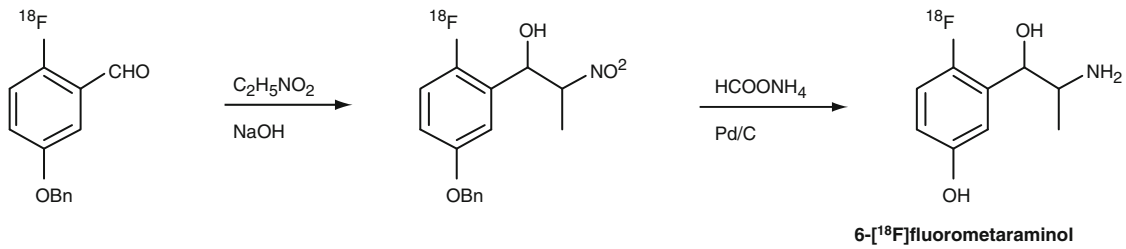


Fig. 5.19 N.c.a. radiosynthesis of 6-[^{18}F]fluorometaraminol via nucleophilic addition of nitroethane to 3-benzyloxy-6-[^{18}F] fluorobenzaldehyde

of n.c.a. 6-[^{18}F]fluoro-L-DOPA (see Fig. 5.18) [157, 158]. After reduction of the aldehyde group with sodium borhydride to the benzylalkohol function, the treatment with the corresponding hydrogen halide leads to the 2-[^{18}F]fluoro-4,5-dimethoxybenzyl halide. N.c.a. 6-[^{18}F]fluoro-L-DOPA was achieved from an enantioselective coupling with *N*-(diphenylmethylene) glycine *tert*-butyl ester, deprotection and semi-preparative HPLC in RCY of 25–30% with an enantiomeric excess of >95%.

Besides the conversion reactions of the aldehyde group, [^{18}F]fluorobenzaldehydes can also function as direct reaction partner according to organic carbonyl chemistry. Prominent representatives of such chemistry which have also been applied to ^{18}F-radiochemistry are the Wittig reaction [159], the Horner–Wadsworth–Emmons reaction [160] and the Knoevenagel condensation [161].

In addition, the electrophilic character of aldehydes also offers the possibility of nucleophilic additions. [^{18}F]Fluorobenzaldehydes have also been applied in nucleophilic additions [162, 163]. In this way, the nucleophilic addition of nitroethane to n.c.a 3-benzyloxy-6-[^{18}F]fluorobenzaldehyde and following reductive deprotection led to n.c.a. 6-[^{18}F]fluorometaraminol in a diastereomeric mixture from which the stereoisomers could be separately isolated by two subsequent semi-preparative HPLC purifications (see Fig. 5.19) [164]. In the same manner, also the n.c.a 4-[^{18}F]fluorometaraminol was synthesised.

Similar to the carbonyl chemistry of [^{18}F]fluorobenzaldehydes, [^{18}F]fluoroacetophenones offer a broad range of synthetic possibilities [164, 165]. Moreover, secondary derived synthon/prosthetic group 4-[^{18}F] fluorophenacylbromide can be conjugated to peptides and proteins via alkylation reaction or thiol-coupling reactions [125, 134].

Another group of versatile synthons derive from the [^{18}F]fluoro-4-haloarenes which can be used in palladium(0)-catalysed C–C-bond formation reactions

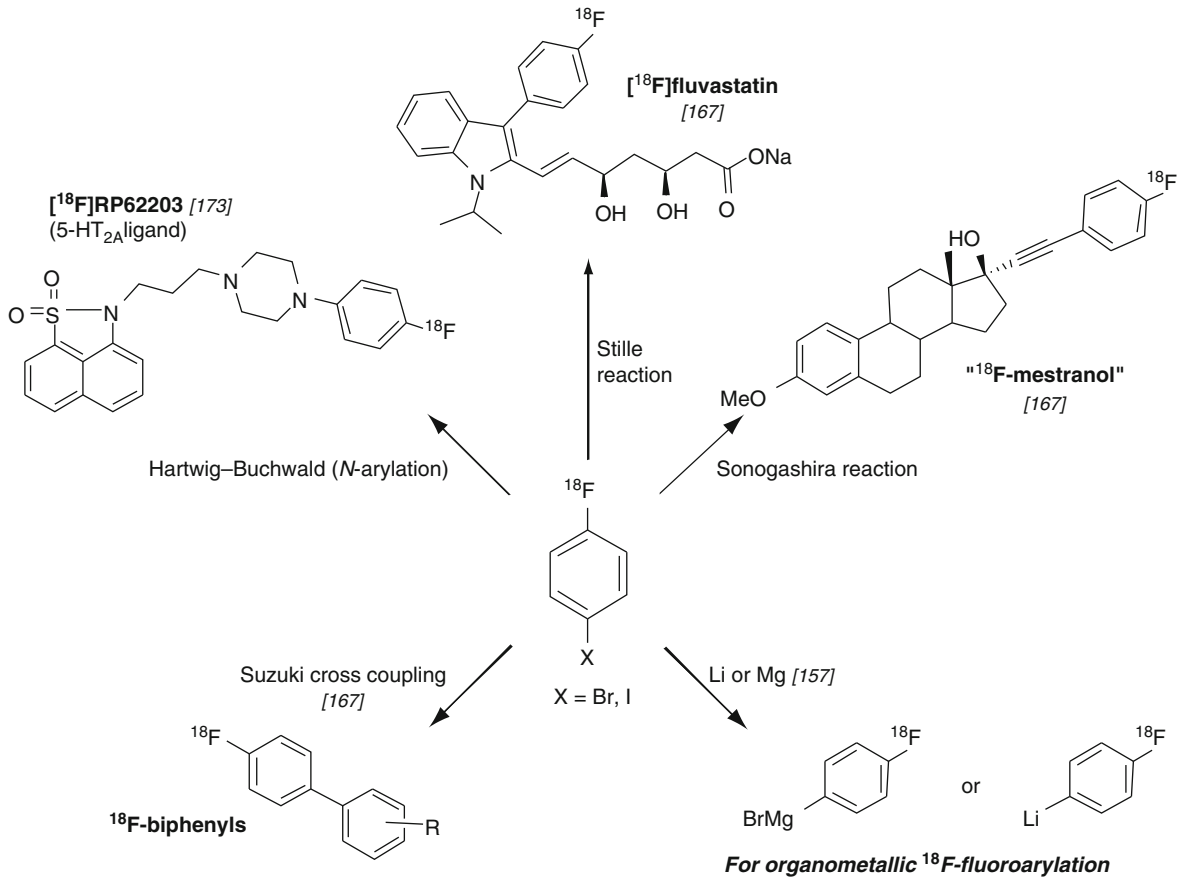


Fig. 5.20 N.c.a. 4-[^{18}F]fluorohalobenzenes as versatile synthons for palladium(0)-catalysed coupling reactions and their transformation into metalorganic reagents for ^{18}F-fluoroarylation reaction

such as the Stille reaction [166–170], the Sonogashira reaction [171] and Suzuki cross-coupling reactions [172] (see Fig. 5.20). Furthermore, 4-bromo and 4-iodo-[^{18}F]fluorobenzenes have been used in palladium-mediated *N*-arylation reactions, also referred to as Hartwig-Buchwald reactions [173, 174]. In addition, n.c.a. [^{18}F]fluoro-4-haloarenes can also be easily transferred into reactive species such as Grignard reagents or into 4-[^{18}F]fluorophenyl lithium which can be employed in various metalorganic coupling reactions [175].

Due to their broad applicability, [^{18}F]fluorohalobenzenes and their secondary derived ^{18}F-labelling synthons have become more and more attractive. In the past decade, several methods for an efficient preparation of [^{18}F]fluorohaloarenes have been developed and make this class of ^{18}F-labelled synthons readily available [105, 166, 176–179].

In addition to the most widely used ^{18}F-labelling synthons [^{18}F]fluorobenzaldehydes, [^{18}F]fluorobenzyl halides and [^{18}F]fluorohalobenzenes, further primary and secondary ^{18}F-aryls have been developed and proven to be useful for ^{18}F-labelling via built-up radiosynthesis. Accordingly, n.c.a. 4-cyano-1-[^{18}F]fluorobenzene or 4-[^{18}F]fluorobenzonitrile was employed for built-up radiosyntheses of several ^{18}F-butyrophenone neuroleptics [180]. On the other hand, it can also be transferred into the secondary ^{18}F-labelling synthon n.c.a. 4-[^{18}F]fluorobenzyl amine which can be used as prosthetic group [130, 132] or further converted into *N*-4-[^{18}F]fluorobenzyl-α-bromoacetamide as prosthetic group for the ^{18}F-labelling of oligonucleotides [129]. More in a sense of a prosthetic group n.c.a. 4-[^{18}F]fluorobenzyl amine was recently used for the ^{18}F-labelling of the first ^{18}F-labelled folic acid derivatives [132].

N.c.a. [^{18}F]fluoronitrobenzenes, which is available from high-yielding ^{18}F-labelling of the appropriate dinitrobenzene precursors, can be easily reduced to the corresponding [^{18}F]fluoroanilines by the use of common reducing agents such as $NaBH_4$, $SnCl_2$, N_2H_2/Pd, H_2/Pd-C, BH_3 or $LiAlH_4$ [181]. N.c.a. [^{18}F]fluoroanilines have been employed for the ^{18}F-labelling of several anilinoquinazolines as epidermal growth factor receptor (EGFR) ligands [183–185] as well as for fluorophenylureas [183]. A subsequent treatment of the 4-[^{18}F]fluoroaniline with nitrites leads to the 4-[^{18}F]fluorophenyldiazonium derivative which was used for the preparation of ^{18}F-labelled 5-HT_2 receptor ligands [182].

Since various biologically active compounds bear a 4-fluorophenoxy moiety [186], the secondary synthon n.c.a. 4-[^{18}F]fluorophenol is of great interest. The first radiosynthesis of this versatile synthon was based on a hydrolysis of the 4-[^{18}F]fluorophenyldiazonium salt [187]. In recent years, new synthetic strategies towards 4-[^{18}F]fluorophenol and several improvements of the radiosyntheses have made 4-[^{18}F]fluorophenol readily available for built-up radiosyntheses [188, 189]. Thus, it was applied for the radiosynthesis of a highly selective dopamine D_4 receptor ligand [190] as well as in a catalysed variant of the Ullmann ether coupling to provide 2-(4-[^{18}F]fluorophenoxy)-benzylamines (see Fig. 5.21) [190].

Finding the right ^{18}F-labelling strategies for new radiopharmaceuticals is generally limited by the target structures themselves. Although a variety of ^{18}F-fluorination methods have been developed, many of them still do not provide the desirable broad applicability and call for very special conditions. Thus, there is still room for improvement and new development of ^{18}F-labelling methods. However, many ^{18}F-labelled PET radiopharmaceuticals from various classes of compounds have been prepared and some are routinely produced and employed in nuclear medicine practice.

5.2.3 Labelling Methods for Carbon-11

Besides fluorine-18, carbon-11 is the most commonly used positron emitter for PET radiopharmaceuticals. Although the short half-life of only 20.4 min of carbon-11 does not allow time-consuming radiosyntheses or the shipment of produced ^{11}C-labelled radiopharmaceuticals, several important ^{11}C-radiopharmaceuticals are routinely employed in the clinics.

Similar to the requirements for fluorine-18 productions, the production of carbon-11 can be facilitated with small medical cyclotrons using protons in an energy range of 15 → 7 MeV. The ^{14}N(p,α)^{11}C nuclear reaction is applied as the general production method [191]. The reaction is carried out with ^{14}N-gas targets. Small portions of oxygen (≤2%) added to the target gas cause [^{11}C]CO_2 formation and in case of hydrogen (5–10%) addition, [^{11}C]CH_4 is the final product form [192, 193].

Several further production routes are known for carbon-11, but generally, they are of much less

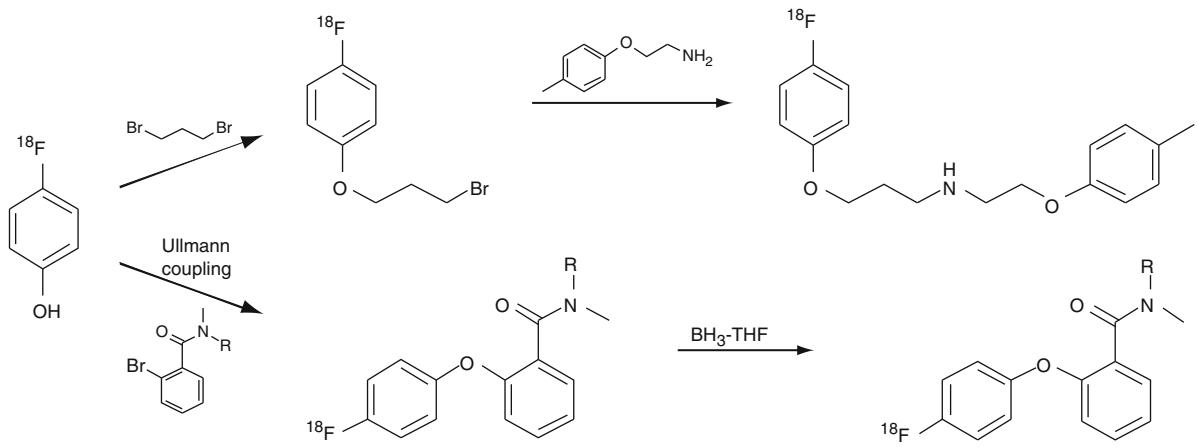


Fig. 5.21 N.c.a. 4-[^{18}F]fluorophenol as versatile synthon in built-up radiosyntheses

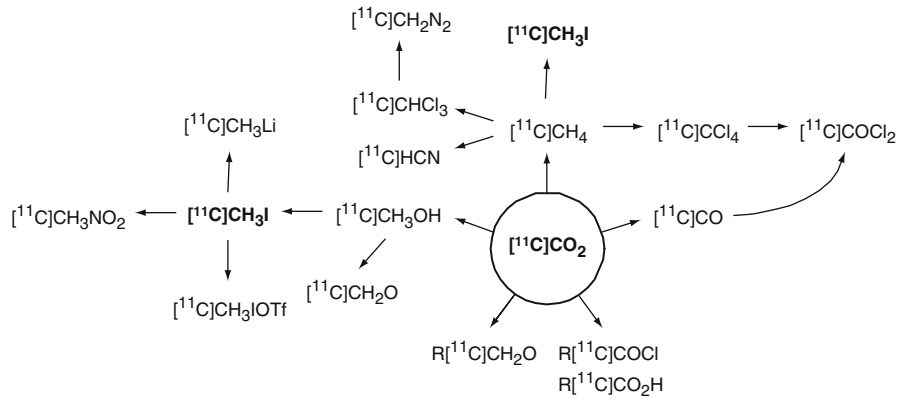


Fig. 5.22 Secondary and further ^{11}C-labelling synthons derived from the primary [^{11}C]CO_2

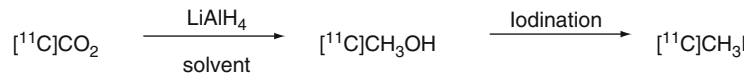


Fig. 5.23 Radiosynthesis of [^{11}C]CH_3I according to the 'wet' method starting from primary [^{11}C]CO_2

importance than the ^{14}N(p,α)^{11}C reaction [16, 32, 194, 195]. Furthermore, using the ^{14}N(p,α)^{11}C nuclear reaction, carbon-11 can be obtained in high radiochemical yields with high specific activities.

^{11}C precursors: Regarding the two product forms and thus the two primary ^{11}C-labelling synthons [^{11}C]CH_4 and [^{11}C]CO_2, the latter is the most preferred labelling precursor. [^{11}C]carbon dioxide offers the possibility of direct ^{11}C-introductions into organic molecules. Accordingly, [^{11}C]CO_2 reacts with primary amino functions to form [^{11}C]ureas and [^{11}C]isocyanates [196]. Another direct ^{11}C-labelling possibility is given by the reaction with organometallic systems. Thus, the treatment of the Grignard reagents CH_3MgBr or CH_3MGCl with [^{11}C]CO_2 gives [1-^{11}C]acetate which is the most important ^{11}C-labelled radiopharmaceutical derived from direct ^{11}C-carboxylation [197, 198].

Even though the half-life of 20.4 min of carbon-11 allows only reactions and conversions with fast kinetics, most ^{11}C-labelling methods are based on secondary ^{11}C-labelling synthons derived from [^{11}C]CO_2 (see Fig. 5.22) [199]. Along with all the possible pathways, the ones using [^{11}C]CH_3I are the preferred routes for ^{11}C-labelling. However, [^{11}C]HCN and [^{11}C]CO are also important ^{11}C-labelling synthons. Especially, [^{11}C]CO has been proven for its applicability in palladium- or selenium-catalysed reactions [200].

'Wet method': The first efficient radiosynthesis for [^{11}C]CH_3I was developed by Comar et al. in 1973 [201, 202]. This so-called 'wet' method is based on reduction of [^{11}C]CO_2 to [^{11}C]CH_3OH by means of lithium aluminium hydride ($LiAlH_4$) in solvents such as ethyleneglycol dimethylether, tetrahydrofuran or diethylether. [^{11}C]CH_3OH is then iodinated using hydroiodic acid or triphenylphosphite ethyliodide (see Fig. 5.23). Diphosphorous tetraiodide [203] and triphenylphosphine diiodide [204] can also be employed as iodination agents. Although the 'wet' method provides reliable and high radiochemical yields, it has one major drawback: the use of $LiAlH_4$. $LiAlH_4$ is a source of non-radioactive carbon dioxide which in turn brings in isotopic carrier carbon-12 and thus dramatically reduces the specific radioactivity of the [^{11}C]CH_3I and the following products.

Dry method: More recently, a new approach to [^{11}C]CH_3I, the so-called 'gas phase' or 'dry' method was developed [205, 206]. Starting from [^{11}C]CO_2, hydrogen reduction in presence of a nickel catalyst provides [^{11}C]CH_4 which is passed through a heated glass tube (~720°C) with iodine vapour for iodination (see Fig. 5.24). The product [^{11}C]CH_3I is trapped on a Porapak column and after completion of the iodination, [^{11}C]CH_3I is released by heating and a stream of helium. The iodination process can be performed in a single pass reaction where the [^{11}C]CH_4 slowly passes the heated glass tube for iodination only once

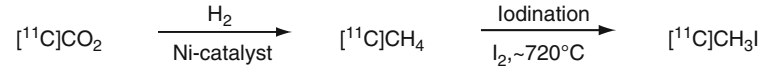


Fig. 5.24 Radiosynthesis of [^{11}C]CH_3I according to the 'dry' method starting from primary [^{11}C]CO_2

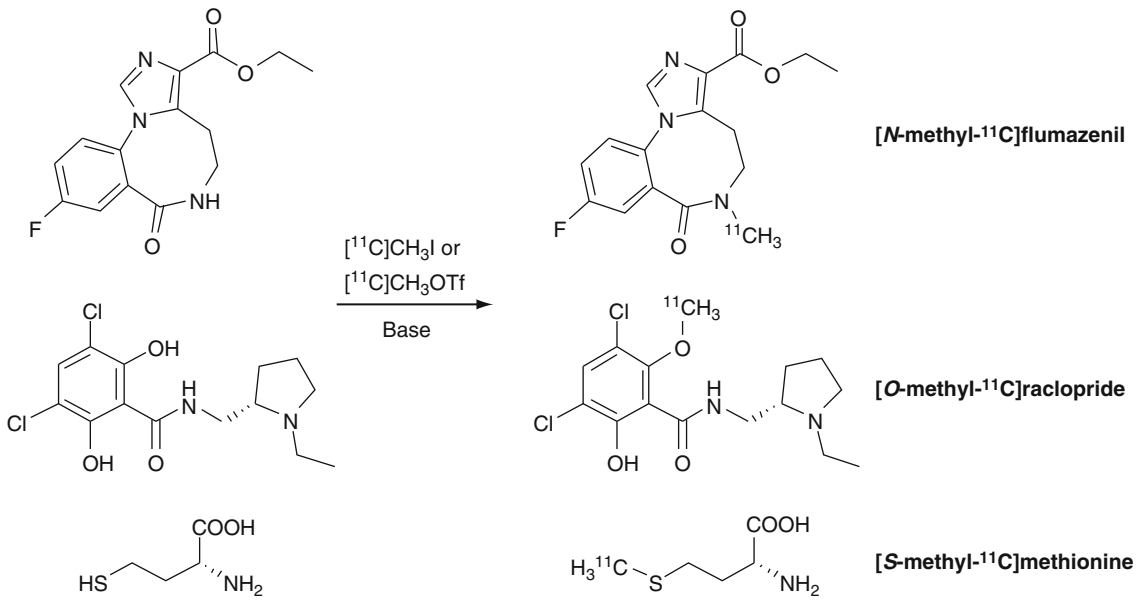


Fig. 5.25 N-, O- and S-heteroatom ^{11}C-methylation reactions based on [^{11}C]CH_3I and/or [^{11}C]CH_3OTf

[207] or in a circulation process where the [^{11}C]CH_4 is circularly pumped through the iodination system until complete iodination [208].

Alternatively, the [^{11}C]CH_4 can be produced in situ in the target and used directly for the iodination process. This variant saves one reaction step and thus time. Furthermore, the in situ production of [^{11}C]CH_4 in the target generally provides higher specific radioactivity. To date, the highest reported specific radioactivity of [^{11}C]CH_3I was 4,700 GBq/μmol and was obtained from iodination of in situ produced [^{11}C]CH_4 in a single pass reaction [209, 210]. Due to that fact, an easier automation of the process and more convenient ongoing maintenance of the synthesis system, the 'dry' method almost superseded the 'wet' alternative for [^{11}C]CH_3I productions. Particularly, when high specific radioactivity is required as for PET studies of receptor systems in the CNS, the 'dry' process is the method of choice for the [^{11}C]CH_3I production.

In some cases, [^{11}C]CH_3I is not reactive enough for sufficient ^{11}C-methylation and a more reactive ^{11}C-methylation agent is needed [211]. Hence, [^{11}C]CH_3I can be converted to the more reactive [^{11}C]CH_3OTf by means of silver triflate at elevated temperatures. The ^{11}C-methylation with [^{11}C]CH_3OTf generally offers higher RCY in reduced reaction times and at lower temperatures in comparison to the [^{11}C]CH_3I methylation as it has already been demonstrated for several important ^{11}C-labelled PET radiopharmaceuticals [212–215].

Generally, ^{11}C-labelling via methylation is performed as N-, O- or S-heteroatom ^{11}C-methylation using the desmethyl precursors. Accordingly, the routinely used ^{11}C-labelled PET radiopharmaceuticals [*N*-methyl-^{11}C]flumazenil [210, 216, 217], [*O*-methyl-^{11}C]raclopride [218, 219] or L-[*S*-methyl-^{11}C]methionine [203, 220] are prepared via N-, O- or S-^{11}C-methylation, respectively (see Fig. 5.25).

Heteroatom ^{11}C-methylation reactions are usually carried out in solvents such as dimethylformamide, dimethylsulfoxide or acetonitrile. The ^{11}C-methylation agents is directly transferred into the solution which contains the desmethyl precursor and mostly a base such as sodium hydroxide, sodium hydride, potassium carbonate or tetrabutylammonium hydroxide. ^{11}C-

Methylations are normally completed within 10 min under elevated temperatures.

Solid phase: Over the years, the basic reaction conditions have not been changed so much, but several interesting and innovative technical improvements have been developed. As a consequence, most of the radiosyntheses of the routinely employed ^{11}C-labelled PET radiopharmaceuticals can be performed on solid-phase. As resin or solid phase material, commercially available C-18 solid-phase-extraction (SPE) cartridges can be applied. The cartridges are loaded with precursor, base and small amounts of solvent and the ^{11}C-methylation agent is passed through the cartridge by a gentle stream of nitrogen or helium. The reactions are normally efficient at ambient temperature and completed after short reaction times. The ^{11}C-labelled product is eluted from the cartridge with an appropriate solvent and often it is directly eluted into a loop of the HPLC system for the subsequent purification. For example, the 5-HT_{1A} antagonist [^{11}C]WAY 100635 have been prepared and isolated within 25 min synthesis time in good yields of ~40% (related to [^{11}C]CH_3I, not decay corrected) [221]. Several important ^{11}C-labelled PET radiopharmaceuticals have also shown applicability for solid-phase-supported radiosynthesis [222–224].

Loop method: A further development of the solid-phase supported radiosyntheses is the so-called loop method. A conventional HPLC loop is coated with a film of the precursor solution and the ^{11}C-methylation agent is passed through by a gentle stream of nitrogen or helium. Subsequently, the loop content is washed out and simultaneously injected into the HPLC system. The method saves reaction time and reduces the technical assembly to a bare minimum. A variety of ^{11}C-labelled radiopharmaceuticals can be prepared by this convenient and fast method [225–229].

Another technical advancement which has recently entered the PET radiochemistry field is the microfluidic radiosyntheses systems. The systems are based on continuous-flow microreactors and use only micro- or nanolitre volumes. Some systems have been developed so far (see Sect. 5.2) and have already been successfully applied for ^{11}C-labelling of several carboxylic acid esters [230].

^{11}C–C bond reactions: [^{11}C]CH_3I can also be applied in ^{11}C–C bond formation reactions. Due to the short half-life, the most limiting factor is the reaction/synthesis time of such ^{11}C–C bond formations. Nonetheless, there are several examples of C–C bond formations applied in ^{11}C-labelling using [^{11}C]CH_3I. Some examples can be found for the use of [^{11}C]CH_3I in Wittig reactions as its corresponding triphenylphosphorane [^{11}C]CH_2PPh_3 [231] or triphenylarsonium [^{11}C]CH_2ArPh_3 [232]. Most examples of various ^{11}C–C bond formation reactions can be found for ^{11}C-labelled amino acids using methods like enzymatic ^{11}C–C bond formations [233, 234] or enantioselective ^{11}C–C bond formations based on Schiff-base Ni-complexes as chiral auxiliaries [235, 236]. Furthermore, such multi-step radiosyntheses of ^{11}C–C bond formations towards ^{11}C-labelled amino acids have been shown to be transferable into automated synthesis systems [237]. However, besides amino acids, also several other pharmacologically relevant substances have been ^{11}C-labelled by C–C bond formations [238–243].

Other approaches for ^{11}C–C bond formations are palladium-supported cross-coupling reactions which have been developed for various ^{11}C-labelled radiopharmaceuticals. The most prominent representatives of these reaction type are the Stille reaction [244–247], the Suzuki cross coupling reaction [245, 247, 248] and the Sonogashira reaction [248, 249]. The Stille reaction is the most intensively employed variant of palladium-catalysed ^{11}C–C bond formations (see Fig. 5.26)

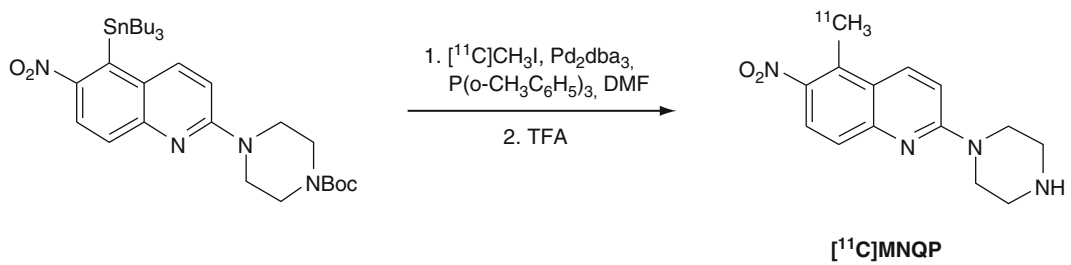


Fig. 5.26 Radiosynthesis of the serotonin transporter ligand 5-[^{11}C]methyl-6-nitroquipazine ([^{11}C]MNQP) using [^{11}C]CH_3I in a palladium-catalysed Stille reaction

and has proven its applicability for many ^{11}C-labelled PET radiopharmaceuticals [245–248, 250–254].

Most ^{11}C-labelling procedures are clearly based on [^{11}C]CH_3I as the most versatile ^{11}C-labelling synthon or precursor. The most convenient methods are the very fast N-, O- and S-heteroatom ^{11}C-methylation reactions which can be accomplished even with simple technical equipment such as a conventional HPLC loop in case of a [^{11}C]CH_3I loop reaction. Furthermore, also multi-step radiosyntheses like ^{11}C–C bond formations have been proven as useful ^{11}C-labelling strategy. Particularly, the palladium-promoted ^{11}C–C bond formations have broadened the applicability of ^{11}C-labelling towards PET radiopharmaceuticals.

5.2.4 Fast Reactions for Oxygen-15 and Nitrogen-13

The half-lives of 2 and 10 min of the extremely short-lived positron emitter oxygen-15 and nitrogen-13, respectively, allow only very fast conversions without time-consuming labelling procedures. Moreover, in PET imaging using ^{15}O- or ^{13}N-labelled radiopharmaceuticals, only simple physiological processes with very fast kinetics such as perfusion or blood flow can be studied.

The extremely short half-life of oxygen-15 allows only very fast online reactions in terms of radiochemistry. A number of nuclear reactions exist for the production of oxygen-15, but the most commonly used method is the ^{14}N(d,n)^{15}O nuclear reaction [255]. The target material is aluminium and the target content is a mixture of nitrogen and 0.2–1.0% of oxygen. An example for such an online reaction is the preparation of the perfusion tracer [^{15}O]water. The target release is mixed with hydrogen and passed over a palladium/activated charcoal catalyst at 200°C to give [^{15}O]water [256, 257]. Another ^{15}O-labelled perfusion and blood flow tracer is n-[^{15}O]butanol [258]. In this case, a solid phase-supported (cartridge extraction) reaction of tri-n-butylborane and the target released c.a. [^{15}O]O_2 furnishes the n-[^{15}O]butanol. The radiosyntheses of ^{15}O-labelled PET radiopharmaceuticals are restricted to such fast online processes and the application of ^{15}O-tracers in PET imaging is limited to perfusion or blood flow studies.

The general production route to nitrogen-13 is the ^{16}O(p,α)^{13}N nuclear reaction [259]. The nitrogen-13 is obtained in the form of ^{13}N-labelled nitrites and nitrates, which are subsequently reduced to [^{13}N] ammonia by titanium(III)chloride or Devarda's alloy in alkaline medium [260]. Another method uses additional ethanol in the target gas as radical scavenger to avoid nitrite and nitrate formation [261]. This method leads directly to [^{13}N]ammonia.

[^{13}N]NH_3 is a perfusion tracer and the most commonly used ^{13}N-labelled PET radiopharmaceutical in PET imaging. In addition to the direct clinical applications of [^{13}N]NH_3, there are a few examples of ^{13}N-labelled compounds which derive from [^{13}N]NH_3, but generally without clinical relevance. The L-[^{13}N] amino acids L-[^{13}N]LEU, L-[^{13}N]VAL and L-[^{13}N] GLU were ^{13}N-labelled via an enzyme-supported amino acid synthesis and used for investigations of their pharmacokinetics in the myocardium [262]. The half-life of 10 min of nitrogen-13 offers a little bit more flexibility than does oxygen-15, but its half-life is still unsuitable for extensive radiosyntheses.

5.2.5 Non-standard Positron Emitters

5.2.5.1 Labelling Using Radioiodine

From more than 30 radioactive isotopes of iodine, only iodine-120 and iodine-124 have suitable properties for use as PET radionuclides. However, the low abundance of positron emission (56% for ^{120}I and 22% for ^{124}I), their high positron energies (4.1 MeV for ^{120}I and 2.1 MeV for ^{124}I) and an extensive production route make them less attractive for routine PET imaging. Significantly more importance in nuclear medicine and general life science have iodine-123 (100% EC, 159 keV γ-line [main]) as SPECT nuclide, iodine-125 (100% EC, 35 keV γ-line [main]) for long-term in vitro studies and radioimmunoassays and the β^--emitter iodine-131 as nuclide in radiotherapy of thyroid gland and tumours. Because of the convenient longer half-life ($T_{½}$ = 8.02 days), the well-detectable γ-line of 364 keV (85.5%) and the good availability, ^{131}I lends itself as model isotope for radiotracer development.

The main pathways for radioiodine labelling can be classified into four general procedures [10, 263–264]:

- Direct electrophilic radioiodination
- Electrophilic demetallation

- Non-isotopic exchange (nucleophilic labelling)
- Prosthetic group labelling (indirect method)

5.2.5.2 Direct Electrophilic Radioiodination

The direct electrophilic substitution is the most commonly used radioiodination method. A lot of various techniques are available, which lead to high RCY in uncomplicated labelling reactions and which can be often carried out at room temperature. Due to its high volatility, low reactivity and the need for carrier addition, molecular iodine (I_2) is excluded for the n.c.a. scale. These problems to achieve reactive electrophilic species are easily circumvented by an in situ oxidation of iodide, which is obtained straight from the target. The generally used oxidants are Chloramine-T (CAT; *para*-tosylchloramide sodium), Iodogen™ (1,3,4,6-tetrachloro-3α,6α-diphenylglycouril) and *N*-halogen-succinimides.

The exact chemical nature and oxidation state of the iodinating species are not fully clarified so far. In case of aqueous solutions with strong acidic conditions, a hypoiodite, and for neutral and alkaline conditions, an iodine-analogue of, for example, CAT are postulated [265]. Due to the insignificant differences in their redox potentials, the choice of the proper oxidant is depended on the reaction conditions and the character of the iodine substrate. CAT allows oxidations in homogeneous aqueous solutions, whereas Iodogen™ is insoluble in water and thus it is the proper substance for a heterogenic reaction route, which is advantageous for oxidation-sensitive precursors. In the group of *N*-halogensuccinimides *N*-chlorotetrafluorosuccinimide (NCTFS), *N*-chlorosuccinimide (NCS) and rarely *N*-bromosuccinimide (NBS) are applied for in situ oxidation [266, 267]. When using NCS in trifluoromethane sulphonic acid, even deactivated aromatic compounds can be labelled with radioiodine in acceptable RCY [268]. Besides these oxidants, conventional oxidising reagents are in use, such as hydrogen peroxide, respectively, peracids [269] and metal cations (Ag^+, Tl^{3+}, Pb^{4+} and Ce^{4+}) [270]. Rather unconventional, but also useful are enzymatic [271] or electrochemical [272] methods for oxidation. As a disadvantage, the electrophilic radioiodination may raise the problem of a regio-unselective attack, as a result of which isomeric derivatives may occur.

5.2.5.3 Electrophilic Demetallation

Contrary to the direct electrophilic procedure, the electrophilic demetallation provides an almost regiospecific radioiodination. Especially for automated syntheses, it offers simple purification and isolation of the radiotracer and is therefore the first choice. Nonetheless, the syntheses of the organometallic precursors may become complex and extensive [273]. Suitable precursors for demetallation radioiodine-labelling are organometallic compounds of thallium [274], boron [275], mercury [276] and particularly, the organometallics of the elements of the group IVb. Of these, an exceptional position is taken by the organotins, which show, many times, excellent RCY in very short reaction time (few minutes); generally the RCY increases with Si < Ge < Sn [277]. Currently, the radioiodo-destannylation is the most suitable radioiodination procedure and thus is the most commonly employed method.

5.2.5.4 Non-isotopic Exchange (Nucleophilic Labelling)

Another labelling procedure for regiospecific radioiodine introduction is the non-isotopic exchange. Non-isotopic exchange is generally Cu(I)-catalysed and is suitable for electron-rich as well as for electron-deficient aromatic molecules [278]. In case of iodine-for-bromine exchange, high specific activities are available. In Cu(I)-promoted reactions, the readiness of the displacement follows the nucleofugality of the halogens ($I^- > Br^- > Cl^-$). In the Cu(I)-mediated substitution mechanism, a quadratic-planar complex was suggested, including Cu(I) as coordinated central atom, whereby the activation energy for the substitution process is reduced and the iodine can be introduced [279]. In variations, the Cu(I)-salts are in situ synthesised by a mild reduction of Cu(II)-salts (reducing agent: ascorbic acid, bisulphite or Sn(II)-compounds). Hereby, Cu_2SO_4 is more applicable than the use of copper halides, because the formation of halogenated side products is excluded. One of the important advantages is the much easier precursor preparation and their high stability. Moreover, it is again a highly regiospecific labelling route for radioiodine. In comparison to the electrophilic radioiodination, disadvantages are relatively high reaction temperatures of up to 180°C and vastly longer reaction

times up to hours. In given cases, the separation and isolation of the radiotracer provokes difficulties due to its chemical and physical similarities to the bromine precursor.

5.2.5.5 Prosthetic Group Labelling

If molecules are sensitive to oxidative reagents or functional groups for iodination are lacking, the above-mentioned direct radioiodination methods fail. As an alternative, small molecules can be radioiodinated as labelling synthons and subsequently coupled with the desired compound. This is principally the same procedure as for the ^{18}F-labelling via prosthetic groups (cf. Sect. 5.4.3.1).

The first approach on prosthetic groups for radioiodination was the so-called Bolton–Hunter reagent, *N*-succinimidyl-3-(4-hydroxyphenyl)propionate (SHPP), an activated ester as labelling synthon for proteins via coupling with a free amino function, normally of the amino acid lysine [280, 281]. It is still widely used for radioiodination of proteins and macromolecules; thus a ^{124}I-labelled VEGF antibody (VEGF = vascular endothelial growth factor) for measuring angiogenesis was recently radioiodinated via a derivative of the Bolton–Hunter reagent [282]. The Bolton–Hunter principle for radioiodination of proteins led to further developments of prosthetic groups such as methyl-*p*-hydroxybenzimidate (Wood reagent) which is an activated imidate ester and also a versatile and convenient radioiodination synthon [283]. In addition, aldehydes, isothiocyanates [284] and activated α-carbonyl halides [285] are further prosthetic groups for labelling via free amino functions.

In case of aldehydes, the radioiodo-tyramine-cellobiose is an important compound which, for example, was used for labelling monoclonal antibodies [286]. Several other coupling methods of prosthetic groups with functional groups of proteins or complex molecules are known. Another common example for suitable functions is the thiol group of cysteine, where appropriate prosthetic groups are malimide derivatives [287].

5.2.5.6 Labelling Using Radiobromine

In case of positron emitting radioisotopes of bromine, three nuclides are suitable for PET imaging, ^{75}Br ($T_{½}$ = 98 min, 75% β^+), ^{76}Br ($T_{½}$ = 16.2 h, 57% β^+) and ^{77}Br ($T_{½}$ = 57 h, 0.7% β^+). Among these nuclides, the most preferred one is bromine-76. It has a longer and more convenient half-life than bromine-75 and a much higher β^+-abundance than bromine-77. Bromine-77 is more attractive for radiotherapy than for PET imaging as it decays also by Auger electron-emission [288–291]. It has been demonstrated that bromine-77 is highly lethal when it is incorporated into DNA of mammalian cells [289].

In small medical cyclotrons, bromine-76 can be produced via the ^{76}Se(p,n)^{76}Br nuclear reaction using a Cu_2Se target. The bromine-76 is isolated from the target by a dry distillation process and usually trapped in alkaline solution [292]. In the same way as radioiodine, for electrophilic demetallation reactions (mostly destannylations), radiobromine can be easily oxidised in situ using oxidants such as CAT, NCS or simply hydrogen peroxide in combination with acetic acid. As an example, the proliferation marker [^{76}Br]bromofluorodeoxyuridine has been radiobrominated via in situ oxidation by CAT and electrophilic destannylation of the corresponding trimethyltin precursor [293–295]. An alternative radiobromination method is the nucleophilic non-isotopic exchange. Again the conditions of nucleophilic radioiodination reactions are transferable, thus Cu(II)-mediated exchange reactions are particularly suitable. According to this, a ^{76}Br-labelled derivative of epibatidine was synthesised for PET imaging studies of the nicotinic acetylcholine receptor system [296].

In general, radiobromine is less available than radioiodine, due to more complicated target work-up and isolation procedures. In the radiochemistry of radiobromine, methods from radioiodine labelling can often be directly adopted and the radiochemistry is more convenient to accomplish than fluorine-18 labelling. Predominantly, the electrophilic destannylation reactions are employed for radiobromination chemistry. However, a few ^{76}Br-labelled radiopharmaceuticals have been developed to date [294–301], but they have only little relevance in clinical PET imaging.

5.2.5.7 Complexes for Labelling with Metallic PET Radionuclides

Among the metallic positron emitters which are suitable for PET imaging, the production routes can be

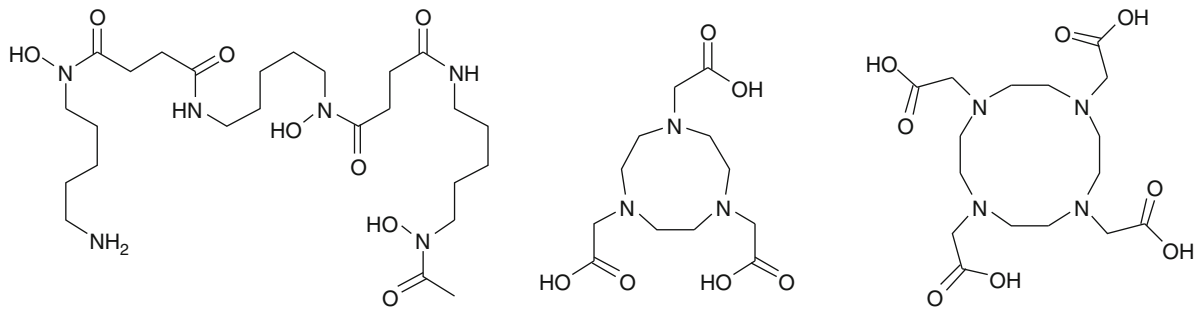


Fig. 5.27 Chelator systems for labelling with metallic nuclides such as gallium-68

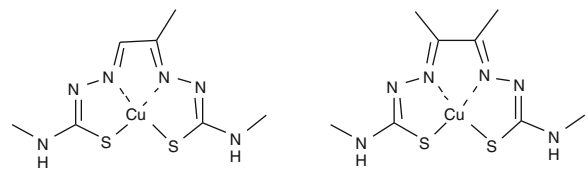


Fig. 5.28 Chelator systems for (radio)copper

divided into cyclotron-produced nuclides such as copper-64, titanium-45, yttrium-86 or zirconium-89 and generator-produced nuclides such as gallium-68, rubidium-82, or copper-62. The main advantage of the latter is clearly their availability which is not limited to facilities with an on-site cyclotron. Gallium-68 ($T_{½}$ = 68 min) is available from the ^{68}Ge-^{68}Ga generator. In a similar manner, rubidium-82 ($T_{½}$ = 1.3 min) can be obtained from the ^{82}Sr-^{82}Rb generator and copper-62 ($T_{½}$ = 10 min) from the ^{62}Zn-^{62}Cu generator. Especially, gallium-68 has more and more drawn the attention of radiopharmaceutical research, due to its favourable nuclear characteristics.

In terms of radiochemistry, labelling with metallic nuclides is based on chelatoring systems which are coupled to biomolecules or which have interesting biological properties themselves. Prominent examples of chelating systems for gallium-68 are DOTA (1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid), NOTA (1,4,7-triazacyclononane-*N*,*N*′,*N*″-triacetic acid) and DFO (desferrioxamine-B) (see Fig. 5.27). The latter was used as an octreotide conjugate forming a ^{68}Ga-labelled octreotide derivative for tumour imaging of somatostatin receptor-positive tumours [302]. Octreotide was also ^{68}Ga-labelled using the DOTA and the NOTA system; however, of these, the most promising candidate is the DOTA conjugate [^{68}Ga-DOTA, Tyr^3]octreotide ([^{68}Ga]DOTA-TOC) [26, 303–305].

In a similar manner, radiocopper forms complexes such as Cu-PTSM (pyruvaldehyde-bis(N^4-methythiosemicarbazone)) or Cu-ATSM (diacetyl-bis(N^4-methylthiosemicarbazone)) (see Fig. 5.28) [306–309]. These Cu-complexes are both employed in the clinics. ^{62}Cu-labelled PTSM is used as perfusion and blood flow agent for heart and brain, whereas ^{62}Cu-labelled ATSM has been shown to accumulate in hypoxic tumour cells.

5.3 Conclusions

A variety of labelling methods has already been developed, but some methods are only suitable for certain radionuclides and they are often limited in their applicability. On the other hand, more and more molecules of biological or pharmacological interest are discovered and pose new challenges to radiolabelling and radiochemistry. Consequently, the development and

improvement of new labelling strategies and methods for PET radiopharmaceuticals are of paramount interest. In particular, the expansion of the labelling methods for fluorine-18 as the most commonly used and preferred radionuclide in PET imaging are of great importance.

However, many PET radiopharmaceuticals have been developed and a few of them found the way into clinical routine. PET chemistry forms the basis of PET radiopharmaceuticals and PET imaging and will always be a major contributor to the success of the growing field of this molecular imaging modality.

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