^{18}F-Labelling innovations and their potential for clinical application

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Abstract

An impressive variety of new methodologies for the preparation of ^{18}F-labelled tracers and ligands has appeared over the last decade. Most strategies of the newly developed radiofluorination methods predominantly aim at products of high molar activity by 'late-stage' labelling of small (hetero)aromatic molecules and the use of transition metals. This is accompanied by the improvement of technical procedures, like preparation of reactive [^{18}F]fluoride and automated syntheses. The newly introduced procedures reflect a high innovative level and creativity in radio(pharmaceutical) chemistry at present, which are based on modern chemical methods and deep mechanistic insights. Taking also automation and quality control into consideration, major recently developed radiofluorination methods, most of those still under development, are compiled here in view of their potential for clinical PET imaging and thus the ability to advance molecular imaging.

Introduction

Given the very advantageous nuclear decay properties of fluorine-18, i.e. a half-life of 109.7 min and almost the smallest positron emission energy of 635 keV maximum, ensuring a high imaging resolution, this radionuclide rapidly became the 'workhorse' of positron emission tomography (PET) and has remained so now for more than 30 years. Especially its favourable half-life allows, besides multi-step radiosyntheses, the supply of PET centres without a cyclotron by industrial production and the logistics of ^{18}F-labelled radiopharmaceuticals. This creates a concomitant desire for even better production of ^{18}F-labelled tracers and ligands. In fact, an impressive variety of new methodologies for radiofluorination has evolved over the last decade, extending considerably the possibilities of no-carrier-added (n.c.a.) radiosyntheses with fluorine-18.

A plethora of recent reviews already summarizes the major progress achieved, e.g. for the late-stage ^{18}F-fluorination of aromatic and heteroaromatic compounds [1, 2], the use of prosthetic groups and building blocks [3-5], asymmetric ^{18}F-fluorination [6], bond formation of fluorine-18 with group 13 and 14 elements [7-10], as well as general and technical aspects [11, 12]. Since n.c.a. [^{18}F]fluoride is presently the most practical reagent to achieve ^{18}F-radiopharmaceuticals of high molar activity (A_m), the majority of labelling strategies are based on this initial reagent. Thus, special attention is given here to its isolation and activation in predominantly nucleophilic substitution reactions. Many of the described new labelling methodologies appear quite promising, like the silicon-fluoride acceptor labelling methodology or the application of organo-[^{18}F]trifluoroborates [9]. However, these inorganic ^{18}F-acceptors are still at an experimental stage, and difficulties in routine production hampered their widespread application. So far, only the [^{18}F]fluoroaluminium complex of a RGD peptide ([^{18}F]alfatide) has successfully been used in human clinical trials for PET imaging [13]. Regarding the clinical aspect, labelling by formation of Al-F [7] and Si-F [9] bonds is therefore not considered here in more detail, although it has been examined for quite some time. Further on, the review only covers the radiosynthesis of mono-fluorinated compounds, and it does not address poly-fluorinated ones, like two- and tri-fluoromethylated derivatives, which were recently discussed in detail [1, 14].

In this review, rather than the labelling of novel PET imaging probes, major newer radiosynthetic developments are regarded, which already have, or will probably have, an impact on the routine production on ^{18}F-radiopharmaceuticals, in order to meet the increasing clinical demands. This includes general basic methods of radiofluorination, the synthesis of established ^{18}F-labelled radiopharmaceuticals, as well as indispensable techniques for automation to enable their routine preparation and supply in high amounts of activity, using cassette kit-systems and microfluidics. Besides efficiency, i.e. radiochemical yield (RCY), this rather concerns their suitability for practice, i.e. ease and reliability of routine application. Furthermore, the procedures have to fulfil the criteria of radiopharmaceutical production under conditions of good manufacturing practice (GMP) [15]. A comparative evaluation will require including all those aspects. However, a comparison of different reports is often hampered, since uniform definitions for the RCY as for other technical terms and units [16] is missing. In addition, RCYs are often only analytically determined from small samples of the reaction solution, and refer to a single conversion step of build-up syntheses only. Thus, for an objective comparison of different methods only the RCY of the final isolated radiotracer is meaningful reflecting the whole production process.

Two special criteria of the synthesis of radiopharmaceuticals labelled with fluorine-18 have principally to be considered. Their use requires high amounts of starting activity, due to its rather rapid decay. Therefore, labelling can only be performed by synthesis devices, which are placed in shielded “hot-cells”. Additionally, simple synthetic procedures with as few reaction steps as possible are required, allowing their straightforward, remote-controlled implementation and execution. The other aspect concerns the fulfilment of the GMP regulatory, i.e. production processes must comply with the requirements that will assure product quality, patient safety, traceability of the process, and reliability and robustness of the performance. Along with the introduction of more efficient and flexible ^{18}F-labelling methods, also many novel technological approaches emerged. Consequently, concepts of reliable ^{18}F-labelling techniques, amenable to automation on synthesis modules as well as fulfilling GMP-requirements, have to be realised as major prerequisites of the routine production of ^{18}F-labelled radiopharmaceuticals for PET imaging.

Electrophilic ^{18}F-fluorination

Due to the technological simplicity of labelling with elemental [^{18}F]fluorine gas, which is directly usable as received from the target, electrophilic ^{18}F-fluorination was earlier the method of choice for the routine production of especially electron-rich, ring-labelled aromatic [^{18}F]fluoroamino acids, like 6-[^{18}F]fluoro-L-DOPA (6-[^{18}F]FDOPA) [17]. However, since only a low A_m of ca. 100 MBq/µmol was obtainable by this procedure, it was limited to non-toxic compounds, which still achieve the criteria of the tracer principle, when administered in micromole (up to ca. 0.5 mg) amounts, as shown for labelled fatty acids, amino acids, or sugars.
Given the gaseous fluorination reagent [^{18}F]F_2 for labelling, two-step syntheses for 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG), in the beginning of its production [18, 19], and for 6-[^{18}F]FDOPA (first step ^{18}F-labelling, second step deprotection) could be easily established in an automatic synthesis device with one reactor [20], which is now commercially available [21, 22]. This has been achieved despite the need of hazardous elemental fluorine and, in the case of 6-[^{18}F]FDOPA, of corrosive acids (HCl, HBr, HI) for the hydrolysis were challenges for the stability of valves and tubing within the synthesis device. Earlier, those electrophilic ^{18}F-fluorination reactions were performed in Freon® ($CClF_3$) as solvent, but this is now commercially unavailable due to its environmental problem of ozone depletion. However, several studies have shown that $CDCl_3$ could replace $CClF_3$ without significant loss of RCY [22-24].

Besides that only a rather limited activity of elemental [^{18}F]F_2 can be produced and that only half of it can be consumed, the low A_m achievable by the traditional methods of its production [25, 26] has been the major limitation of its use for electrophilic radiofluorination of radiopharmaceuticals. Therefore, a post-target production method was developed, where highest molar activities of about 50 GBq/µmol for [^{18}F]F_2 have been achieved so far, using electrical discharge in a mixture of F_2 gas with n.c.a. [^{18}F]CH_3F [27-29]. In a recent technical attempt still under study, [^{18}F]F_2 was produced by illuminating a gas mixture of neon/F_2/[^{18}F]CH_3F with vacuum ultraviolet photons generated by an excimer-laser [30]. Both procedures to convert n.c.a. [^{18}F]fluoride into [^{18}F]F_2 are technically demanding, hardly cost-effective, and only result so far in limited molar activities and low radiochemical yields of below 10 %. At least the radiochemical yield, e.g. of 6-[^{18}F]FDOPA, could be improved to about 19 %, by converting [^{18}F]F_2 into [^{18}F]selectfluor bis(triflate) and using an arylboronic ester precursor [31]. A broader application of this approach in a clinical setting, however, remains questionable, considering the above properties and its exclusion for synthesising ^{18}F-ligands, which require generally a high A_m.

In early radiofluorination studies, elemental fluorine-18 was technically the easiest to obtain, and consequently unsaturated hydrocarbons were used for the preparation of radiofluorinated alkanes and alkenes [32, 33]. However, besides the disadvantages already described above for electrophilic radiofluorination of arenes, the formation of neither enantioselective nor position-selective products became an almost exclusive criterion for the electrophilic preparation of [^{18}F]fluoroalkanes. Here, the history of the radiosynthesis of [^{18}F]FDG serves as best documented example of such problems [19].

Thus, the main technical restrictions of electrophilic methods are besides the limited amounts of activity, which can be produced cost-effectively, the constraint of the achievable A_m, even with the approach via n.c.a. [^{18}F]CH_3F, and the need of special target equipment, withstanding the use of corrosive F_2 gas. In a clinical setting therefore, methods using electrophilic reagents are only rarely used today.

Nucleophilic ^{18}F-fluorination

In contrast to elemental [^{18}F]fluorine, production of [^{18}F]fluoride by the ^{18}O(p,n)^{18}F nuclear reaction is nowadays a mature technical procedure, delivering the radionuclide in amounts up to about 300 GBq from an [^{18}O]water target and with a very high specific activity [34, 35]. This relies to a large extent on improved target systems [36]. Further efforts on processing dedicated cyclotrons for smaller clinical settings are also of interest to mention in this context [37-39]. Thus to date, nucleophilic ^{18}F-fluorination is the only practical approach that enables the syntheses of ^{18}F-labelled radiotracers without addition of carrier. The activation of [^{18}F]fluoride generally includes the addition of an anion activator system, followed by an azeotropic drying step. For a long time, the phase transfer catalysts (PTC) tetraalkylammonium bicarbonates [40], or even more frequently the amino polyether Kryptofix®2.2.2. (crypt-222) in combination with K_2CO_3 [41] serve generally as anion activation system in preferably dipolar aprotic solvents. At present, this method is well established for the majority of routine ^{18}F-radiotracer productions and is employed in most commercially available synthesis devices.

The well established steps of a, now standard, automated nucleophilic ^{18}F-fluorination process generally include:

1. Separation of [^{18}F]fluoride by an anion exchange cartridge and removal of target [^{18}O]water (if this is not sacrificed, due to its low costs nowadays).
2. Transfer of [^{18}F]fluoride into a chemical reactor and azeotropic drying.
3. Addition of the labelling precursor in a suitable solvent and heating.
4. Hydrolyses of protecting groups, if necessary.

5. Separation of the final product by various chromatographic methods.
6. Formulation and sterilization of the final ^{18}F-product.

This sequence is based on the nucleophilic synthesis of [^{18}F]FDG [42], still the most applied PET-radiopharmaceutical worldwide [43]. Due to the importance of [^{18}F]FDG, the application of crypt-222/K_2CO_3 for [^{18}F]fluoride activation, initially developed and optimised for aliphatic nucleophilic substitution on fatty acid esters [41], found immediate world-wide acceptance. Further on, this concept of radiosynthesis led to the development of many novel synthesis devices for remote-controlled preparation of ^{18}F-radiopharmaceuticals [44]. Because of its importance, all of the production steps have been intensively optimized. Today, the synthesis is mainly performed via disposable and commercially available cassettes, which enable a fast, repeatable, easy to perform and GMP-conform routine production of [^{18}F]FDG on a commercial scale [45].

Novel methods for separation and activation of [^{18}F]fluoride

Activation of [^{18}F]fluoride for nucleophilic substitution

Even more than under ‘macroscopic’ conditions, so-called ‘naked’ fluoride is desirable, in order to ensure its high nucleophilic reactivity under no-carrier-added conditions. This is optimally achieved in form of a weak ion pair (salt or complex) of n.c.a. [^{18}F]fluoride with soft cations in preferably aprotic solvents. It must be kept in mind that fluoride in this state exhibits also a very high basicity. Thus, in order to obtain such conditions, it is mandatory that there is no chance of complexation with ‘hard’ Lewis acids, especially protons or small cations, forming tight ion pairs, strong hydrogen bonds or even hydrogen [^{18}F]fluoride, respectively. The readily polarizable cations of the above mentioned phase transfer catalysts, i.e. cryptand or tetraalkylammonium salts, together with basic, non-nucleophilic anions (e.g. CO_3^{2-} or HCO_3^-) in dipolar, aprotic solvents, fulfil the requirements rather ideally and have widely become the standard conditions for nucleophilic radiofluorination [25, 46, 47].

With highly reactive precursors, however, caesium and rubidium carbonates are already sufficient to achieve nucleophilic radiofluorination on an n.c.a. level [48]. As further discussed below, newer studies even proved that the presence of phase transfer catalysts can be avoided by using the ability of special labelling precursors to induce activation of [^{18}F]fluoride. In one case, arylsulfonates, as aliphatic leaving groups carry polyether moieties, which take the function of chelating the cation [49]. Another, a “minimalist” approach takes advantage of aromatic precursors, which are onium compounds, like iodonium and ammonium (not yet sulfonium) salts, playing the role of soft cations themselves [50, 51].

Surprisingly, it turned out during the last ten years or so, that nucleophilic substitution with n.c.a. [^{18}F]fluoride proceeds occasionally better in mixtures of acetonitrile and *tert*-butanol as solvents [52]. Here, obviously the interaction of [^{18}F]fluoride in those “protic” solutions with hydrogen is weak enough to fulfil the above mentioned criteria.

In part this can be attributed to the higher basicity of *tert*-butanolate, for example, than of fluoride, but a beneficiary supporting effect of those solvent mixtures on the nucleofugality of leaving groups was also discussed [53]. Furthermore, to an increasing degree there are studies, demonstrating that even in presence of traces of water effective nucleophilic exchange with n.c.a. [^{18}F]fluoride occurs, as shown with various examples below. Indeed, weak interaction with hydrogen (cages) can even replace other soft cations for nucleophilic activation of fluoride of increased selectivity as recently systematically examined with the stable isotope [54]. All of these latter findings will potentially expand the radiofluorination possibilities tremendously and also offer potential for considerable facilitation of quality control procedures, when compared with the former methods, where the more difficult to analyse aliphatic phase transfer catalysts were used for activation of [^{18}F]fluoride.

[^{18}F]Fluoride drying with thermal evaporation

So far, the first key step in nucleophilic ^{18}F-fluorination is generally the separation of [^{18}F]fluoride from the [^{18}O]water, which is today probably the exclusive target for its production by proton bombardment. The classical approach is a thermal evaporation step of [^{18}F]fluoride in presence of a base to avoid the loss as [^{18}F]hydrogen fluoride. Before that, the [^{18}F]fluoride is usually trapped on an anion exchange cartridge for removing (and recovering) the [^{18}O]water, and then eluted with a solution of potassium carbonate and the activating cryptand or a tetraalkylammonium salt. The following drying is performed azeotropically using acetonitrile. Today, this time-consuming and multi-step procedure is established in most commercial synthesizers [45, 55].

Multiple methods were examined over the years in order to optimize this procedure, especially simplifying it. The implementation on a microchip device necessitates a concentration of the [^{18}F]fluoride activity solution even more. Typical target volumes of [^{18}F]fluoride production are between 0.7 and 7 mL which are mostly reduced to a volume of < 500 µL for this purpose [56, 57]. Thus, the thermal evaporation step is far from convenient for an application in a microscale device.

Another aspect is the use of a base for eluting the [^{18}F]fluoride. This may cause side reactions like elimination in the following ^{18}F-fluorination reaction. In order to minimize the amount of the base, alternative anions of low basicity like potassium phosphate, potassium mesylate and potassium triflate, or in the case of copper-mediated ^{18}F-fluorination, the use of 4-dimethylaminopyridine were successfully applied for the elution of [^{18}F]fluoride from an anion exchange cartridge [58-60]. A methanolic instead of an aqueous solution of crypt-222/K_2CO_3 reduced significantly the time of the subsequent thermal evaporation [59, 61].

Methanol as solvent for [^{18}F]fluoride elution was also applied in the already mentioned efficient and time-saving “minimalist” approach [50]. The smart idea behind this is the use of onium compounds as precursors for labelling, serving itself as cation without addition of a phase transfer catalyst to obtain highly reactive n.c.a.

fluoride. After washing the ^{18}F-loaded anion exchange cartridge with dry methanol for removing water, [^{18}F]fluoride is eluted in this case together with the onium precursor dissolved in methanol. This is subsequently evaporated, and a desired organic solvent is added to the dry mixture to perform the nucleophilic exchange reaction.

[^{18}F]Fluoride drying without thermal evaporation

Several methods have been examined to avoid the thermal azeotropic drying by trapping [^{18}F]fluoride on a solid phase followed by removal of the water with dry solvents. Subsequently, the ^{18}F-fluorination could be performed either on the resin itself or after elution of fluoride from the stationary phase. The first study of ^{18}F-fluorination on the resin led only to poor RCY compared to a substitution in solution, presumably due to a slower reaction of [^{18}F]fluoride with the labelling precursor [62]. However, an enormous improvement could be made by using phosphazene bases fixed on a polymer support, which allowed nearly quantitative trapping and drying of [^{18}F]fluoride with dry organic solvents and subsequent radiofluorination on the solid phase [63].

An interesting alternative to the radiofluorination on a solid phase without a need of azeotropic drying is the use of titanium oxide nanoparticles. Here, the labelling precursor, containing a tosylate leaving group, is pre-incubated with TiO_2 nanoparticles in an acetonitrile / hexyl alcohol mixture and tetra-*n*-butylammonium bicarbonate for anion activation, and then it is directly reacted with [^{18}F]fluoride in [^{18}O]H_2O. This rapid and efficient nucleophilic reaction tolerates a water content of up to 25 vol %, and ^{18}F-fluorination of several aliphatic and even aromatic compounds was successfully performed without a drying step, using the corresponding tosylated precursors [64].

In contrast, to perform the drying process of [^{18}F]fluoride on an anion exchange cartridge, it is required to find an eluting system which does not necessitate the addition of water. In fact, the classical approach, using the crypt-222/K_2CO_3 system, proved unsuccessful for this purpose. Applying an anhydrous solution of crypt-222/KOH in CH_3CN, however, enabled the quantitative elution of [^{18}F]fluoride under water-free conditions which was directly suitable for nucleophilic fluorination reactions [65, 66].

A complete methodological alternative to avoid drying on a stationary phase is the conversion of [^{18}F]fluoride into gaseous [^{18}F]HF by acidification of the target water with H_2SO_4 in a glassy carbon/polyethylene vial which proceeds nearly quantitatively [67]. Here, the gaseous [^{18}F]HF is subsequently trapped on solid bound phosphazene bases, forming phosphazenium [^{18}F]hydrofluorides which activate the [^{18}F]fluoride for nucleophilic substitution reactions [67]. This method, however, appears technologically rather demanding for automation.

Phosphazene bases, especially 1-*tert*-octyl-4,4,4-tris(dimethylamino)-2,2-bis-[tris(di-methylamino)phosphoranylidenamino]-2λ5,4λ5-catenadi(phosphazene) (P_4tBu), if dissolved in acetonitrile, can also be used for elution of [^{18}F]fluoride from an anion exchange cartridge [68]. Water, added into the strong base, is converted to the hydroxide anion, which leads to the replacement of [^{18}F]fluoride on the cartridge. Residual water on the cartridge will also be converted, and thus, it does not disturb the subsequent ^{18}F-reaction. However, the strong basicity of the solution rather limits its application, especially with base-sensitive precursors. In another report, when water was not completely absent upon elution, it was successfully removed by rinsing the eluate of [^{18}F]fluoride over a cartridge containing Na_2SO_4 as drying agent [69]. However, in following studies it was shown again, that a certain amount of water does not always disturb a nucleophilic n.c.a. ^{18}F-substitution reaction.

In another approach, [^{18}F]fluoride was trapped on a solid phase of water-wettable macroporous copolymer coated with a quaternary long chain alkylammonium carbonate. After purging the cartridge with nitrogen gas, the [^{18}F]fluoride was eluted with acetonitrile. The received solution proved directly useful for nucleophilic aliphatic and aromatic ^{18}F-fluorination reactions without further azeotropic drying [70]. A further study made use of tetraethylammonium hydrogen carbonate, dissolved in a dipolar aprotic solvent, like acetonitrile, DMSO or DMF, with a content of 5 % water, enabling the quantitative elution of [^{18}F]fluoride from an anion exchange cartridge. This solution was also suitable for performing the ^{18}F-fluorination of several aliphatic and aromatic compounds, tolerating a low amount of water [71].

In addition, ionic liquids enabled the n.c.a. ^{18}F-substitution reaction on aliphatic compounds in the presence of water. However, a severe disadvantage of this approach is the high viscosity of these solvents, hindering its wider application [72]. Another drying method with a cartridge used the sequence of flushing it with air and then removing residual water with anhydrous acetonitrile. Upon elution with a combination of a cryptate, a potassium salt and an appropriate solvent containing 1 % water, [^{18}F]fluoride could directly be employed for the labelling reaction. This procedure was also successfully integrated into a “lab-on-chip” synthesis platform [73].

Quite recently it turned out in case of the important ^{18}F-fluoroethylation reaction, that [^{18}F]fluoride eluted from an anion exchange column formed the desired labelling agent 2-[^{18}F]fluoroethyl tosylate in up to 96 % RCY, which was directly ready for further coupling reactions. Here, the K_2CO_3/crypt-222/acetonitrile solution, containing 2–3% (v/v) water, was directly given to the 1,2-ethylene glycol-bis-tosylate precursor. When compared to the conventional approach, this so-called “hydrous ^{18}F-fluoroethylation” seems very promising. It improved considerably the radiochemical yield of isolated radiotracers by shortened overall reaction times and minimum loss of [^{18}F]fluoride [74].

Generally, nucleophilic aromatic ^{18}F-substitution reactions are sensitive to moisture. However, it could again be shown that in special cases the reaction is tolerant to water. For example, some diaryliodonium tosylates, $XArI^+Ar'Y\ TsO^-$ (X = H or p-MeO), could be converted to the desired [^{18}F]fluoroarene in moderate radiochemical yields notwithstanding a water content of up to 28 % [75]. A further special case was demonstrated with the use of rhenium(I) complexes of 2-chloro-1,10-phenanthroline for radiofluorination. With Re-complexes present, it surprisingly proved to be tolerant to some content of water, while the ^{18}F-fluorination with non-Re-complexed 2-chloro-1,10-phenanthroline could only be performed in absence of water [76].

Very benefitting, the novel Cu-mediated ^{18}F-fluorination methods, using (hetero)-arylboronic acids, pinacolyl boronates, or trialkylstannanes as precursors, enabled the rapid ^{18}F-fluorination without azeotropic drying steps, when using alcohols as co-solvents. This technique allowed "late-stage" ^{18}F-fluorination of indoles, phenols, and anilines starting from unprotected precursors, and led to a RCY in the range of 80–99 % for many radiofluorinated aromatic compounds [77].

Separation of [^{18}F]fluoride via electrochemistry

In principal, a very elegant method to isolate and concentrate n.c.a. [^{18}F]fluoride, upon production in enriched [^{18}O]water, would be its anodic deposition and release. This technology would also offer and facilitate possibilities of on-line integration with micro synthesis devices, e.g. lab-chips, microfluidics etc., for subsequent n.c.a. nucleophilic ^{18}F-fluorination. Based on previous experiences, an electrochemical cell was already designed, allowing to recover the deposited [^{18}F]fluoride in presence of an aprotic solvent, containing a phase-transfer catalyst. The radionuclide, electro-chemically adsorbed at the cylindrical surface of a glassy carbon electrode, could easily be dried by washing the cell with dry aprotic solvents while maintaining a low electric field, which made an azeotropic drying process obsolete [78].

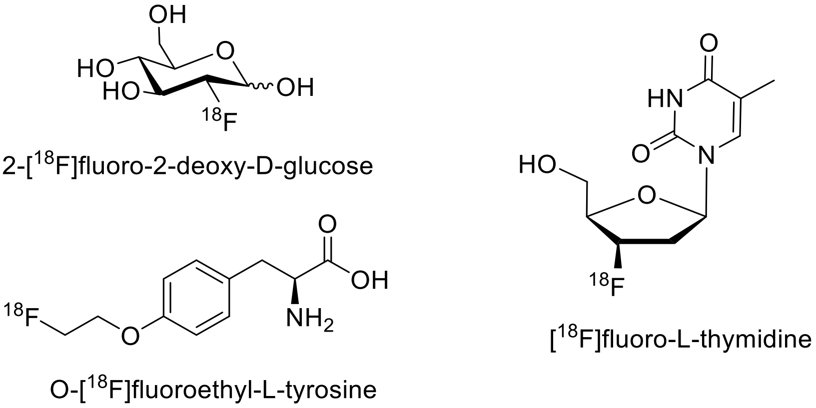
In order to optimize the release of n.c.a. [^{18}F]fluoride from the electrode, various structural modifications of carbon anodes, ranging from thin layers of crystalline boron-doped diamond up to highly graphitic bulk materials, were systematically examined. From those, pyrolysed carbon, i.e. “glassy carbon” (Sigradur®G), proved the most effective material for deposition and release, providing an overall radiochemical yield of about 60 % for fixation and release of [^{18}F]fluoride into DMSO / ionic additive as organic solution [79].

A further approach employed brass–platinum as electrodes, which proved the best material from a range of metals in an electrochemical micro-flow cell, to extract [^{18}F]fluoride from water and to release it into an organic solution in a fast and reliable manner. This cell proved not to suffer electrode erosion, to be reusable, and enabling application of increased voltages, so that it could be operated faster. Optimizing temperature, trapping and release potentials, flow rates, and electrode materials, an overall trapping and release efficiency of about 85 % was achieved [80].

Also using brass as anode material, the electrochemical method was already earlier realized for a microfluidic radiosynthesis by concentrating and transferring n.c.a. [^{18}F]fluoride into an aprotic solvent in a disposable microfluidic cell. For this, a flow of aqueous [^{18}F]fluoride was introduced into the cell under an electric potential, followed by anhydrous MeCN. The trapped [^{18}F]fluoride was released into the MeCN, containing crypt-222/$KHCO_3$, under heat and a reversed potential. An automated module provided the [^{18}F]fluoride ready for subsequent microfluidic radiosynthesis, claiming an overall radiochemical yield of 60 % for its isolation, albeit with a bigger volume of accompanying solvent [81].

Progress in aliphatic nucleophilic ^{18}F-fluorination

Aliphatic nucleophilic ^{18}F-fluorination is today the most frequently employed method for routine production of radiopharmaceuticals, because the majority of those are ^{18}F-labelled in aliphatic position. Most prominent examples are of course [^{18}F]FDG, [^{18}F]fluoro-L-thymidine ([^{18}F]FLT), and *O*-[^{18}F]fluoroethyl-L-tyrosine ([^{18}F]FET) (see Fig. 1). Newer improvements in the reliable preparation of the latter two are briefly summarized here. The methods for radiosyntheses can generally be divided into direct methods, i.e. “late-stage” ^{18}F-fluorination, or in indirect methods via ^{18}F-labelled building blocks [3, 5].



2-[^{18}F]fluoro-2-deoxy-D-glucose

[^{18}F]fluoro-L-thymidine

O-[^{18}F]fluoroethyl-L-tyrosine

Figure 1: Examples of established radiopharmaceuticals, subjected to continuous improvements in nucleophilic aliphatic ^{18}F-fluorination

[^{18}F]FET

The original synthesis of the indicator of amino acid transport [^{18}F]FET was performed by a build-up synthesis, coupling 2-[^{18}F]fluoroethyltosylate, at first prepared by ^{18}F-fluorination of 1,2-bis(tosyloxy)ethane, with the sodium salt of tyrosine [82]. This procedure was optimized with regard to purification and automation [83, 84]. Alternatively, an improved one-pot procedure, starting from a protected tyrosine derivative and thus allowing direct substitution, simplified the automation process [85] and was also further considerably optimized [86].

An improved yield of [^{18}F]FET was achieved by another direct nucleophilic synthesis, using an earlier developed chiral precursor, i.e. the Ni(II) complex of an alkylated (S)-tyrosine Schiff base, Ni-(S)-BPB-(S)-Tyr-OCH_2-CH_2OTs. A solid phase extraction for purification omitted a cumbersome high-performance-liquid-chromatography (HPLC) purification, when using a combination of reverse phase and strong cation exchange cartridges for solid phase extraction. The method was successfully automated on a commercially available synthesis module, and it provided [^{18}F]FET in high chemical, radiochemical and chiral purity and in 35 % radiochemical yield within 45 min of synthesis time [87].

Also, a resin-linker-vector strategy was recently described for ^{18}F-labelling of such tracer molecules, which releases the labelled vector from the solid phase into solution upon nucleophilic substitution of a polystyrene-bound arylsulfonate leaving group with the [^{18}F]fluoride ion [88]. In such cases, the efforts of synthesis and quality assurance for the solid-linked precursor must be taken into consideration.

[^{18}F]FLT

3′-Deoxy-3′-[^{18}F]fluoro-L-thymidine is an established PET tracer applied to study cell-proliferation rates in tumours [89]. The original syntheses are characterised by low activity yield and uncertain, time-consuming HPLC purification [90, 91], which were the main obstacles for routine clinical use of [^{18}F]FLT [92, 93]. To alleviate these difficulties several improvements were made for the synthesis of [^{18}F]FLT. The focus was on the design of better-suited labelling precursors with respect to protection and leaving group [94-100]. The best RCY was received, using 5’-*O*-(4,4’-dimethoxytriphenylmethyl)-2,3’-anhydrothymidine (DMTThy) as labelling precursor [98, 99, 101-103].

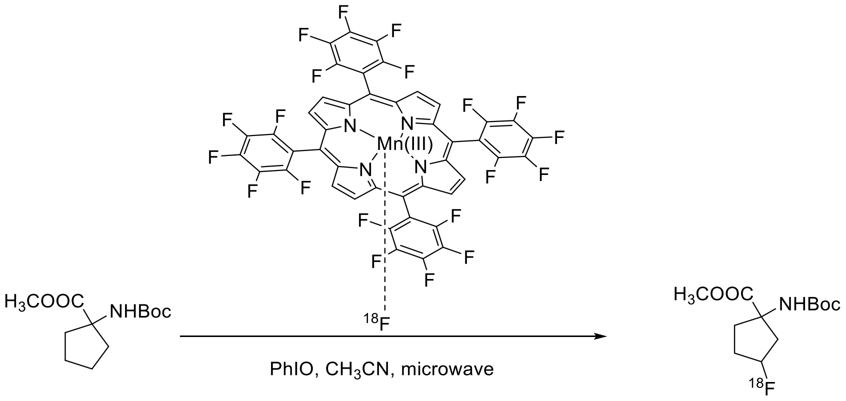
Yet, another publication reports on a reliable, simple and efficient preparation of [^{18}F]FLT, which provides an ethanol-free solution of the tracer without need for any HPLC purification. Due to the similarity with the [^{18}F]FDG synthesis, the method can principally be implemented on all commercial modules available for this common radiotracer [104]. Correspondingly, a further report also describes a high-yielding, automated production of this tracer, using a modified [^{18}F]FDG reaction module [105].

And last, not least, [^{18}F]FLT was also synthesized with a remarkably improved radiochemical yield (85 ± 4% analytically and 60 ± 5 % upon automated production) by nucleophilic substitution, when catalysed by a protic solvent under mild reaction conditions in a short preparation time [106]. This seems to be a very attractive method.

General improvements

Besides the newer developments concerning the routine production of established radiopharmaceuticals, general improvements of aliphatic radiofluorination with high potential for a broad application in PET-imaging are also to be mentioned. A recent publication summarises various newer nucleophilic methods, employing transition metal complexes or organocatalysis for asymmetric ^{18}F-fluorination of alkanes, thus widely overcoming the problems of regioselectivity and enantioselectivity encountered with addition reactions of elemental fluorine-18 [6].

Another promising development of aliphatic ^{18}F-labelling makes use of arylsulfonate as nucleophile assisting leaving groups (NALGs). There, a metal chelating unit is attached to the aryl ring by an ether linker. A series of NALGs prepared exhibited significant rate enhancements in halogenation reactions, using metal halides. Studies with an NALG, containing a macrocyclic ether unit, suggest that rate enhancements of these nucleophilic halogenation reactions are facilitated by a stabilization of charge in the transition state rather than through strong pre-complexation with the metal cation [49].



Scheme 1: ^{18}F-Fluorination of non-activated C-H bonds exemplified for Boc-protected 1-amino-cyclopentanecarboxylic acid methyl ester; adapted from [107]

Remarkable novel developments enable even the direct ^{18}F-fluorination on non-activated aliphatic C-H bonds, by using a manganese porphyrin/iodosylbenzene system with n.c.a. [^{18}F]fluoride (see Scheme 1) [107], and further, a higher selectivity favouring substitution vs. elimination was achieved by organocatalysis through hydrogen bonding of fluoride, however, so far only demonstrated on the carrier-added level [54]. These new approaches hold very great promise as powerful alternatives for aliphatic ^{18}F-fluorination in the future.

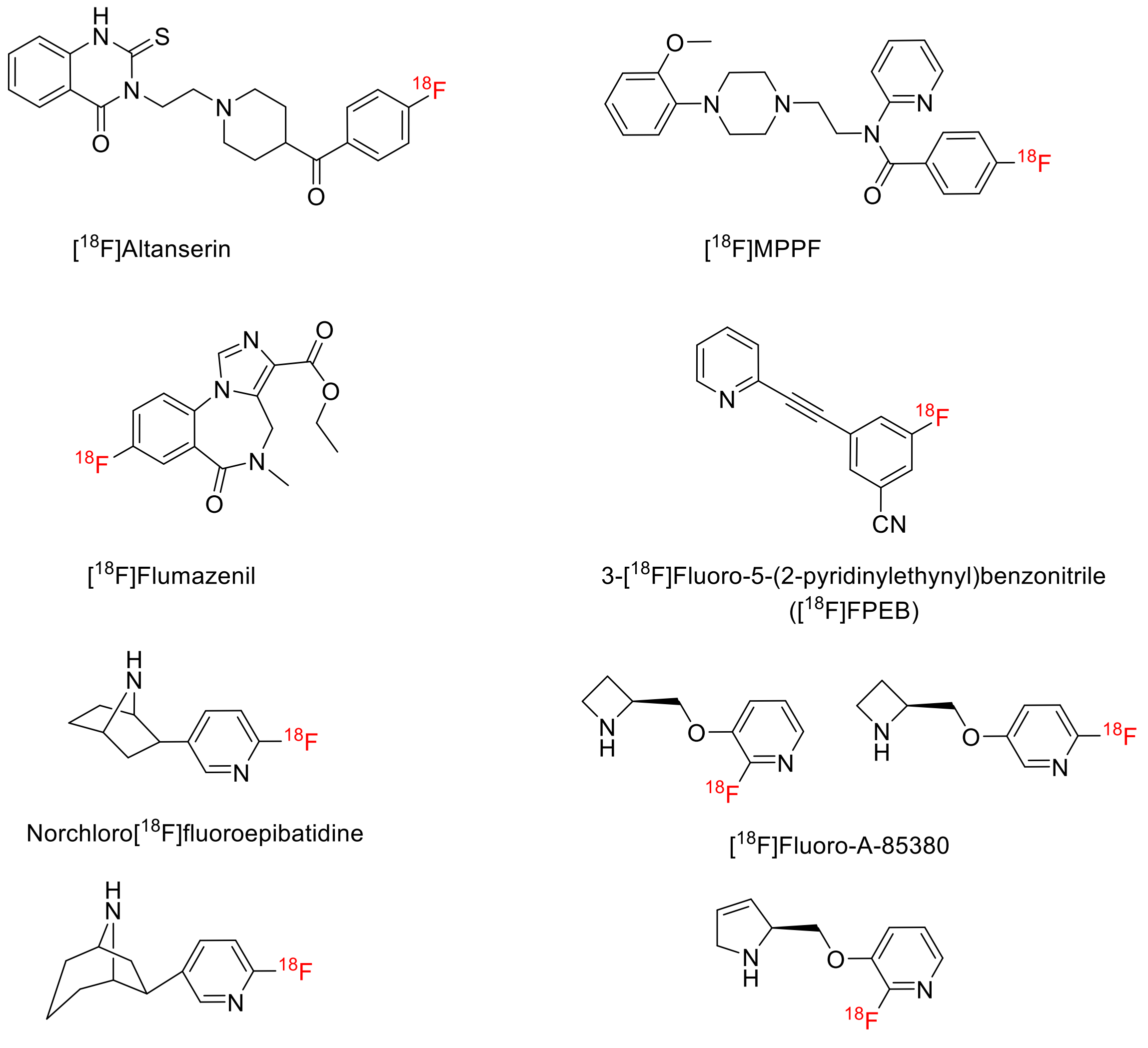
Progress in aromatic nucleophilic ^{18}F-fluorination

The first pathway to introduce n.c.a. [^{18}F]fluoride into arenes for routine synthesis of radiopharmaceuticals was the classical S_NAr method. Since it necessitates the presence of a leaving group and an electron-withdrawing group, preferably in ortho- or para-position, this approach was completely limited to electron deficient arenes [1, 11, 12, 25, 26], exhibiting a major challenge [108].

The first molecule that was ^{18}F-labelled via this approach for clinical application and is in use still today [109, 110] has been the serotonergic 5-HT_{2A} receptor ligand [^{18}F]altanserin [111, 112]. Like in many other complex molecules with activated carbocyclic aromatic positions [113], the keto group in para-position activates the ^{18}F-for-NO_2 exchange employed here, and the one-step synthesis is performed without the need of a protecting group. However, the reaction leads to a side product, which necessitates an extensive HPLC purification [114].

The same classical S_NAr strategy was used for the synthesis of 4-(2′-methoxyphenyl)-1-[2′-(N-2″-pyridinyl)-4-[^{18}F]fluorobenzamido]ethylpiperazine ([^{18}F]MPPF), a fluoro-analogue of the 5-HT_{1A} receptor ligand WAY-100635 [115, 116]. The benzodiazepine antagonist [^{18}F]flumazenil [117, 118] and the metabotropic glutamate receptor subtype-5 ligand, 3-[^{18}F]fluoro-5-(2-pyridinylethynyl)benzonitrile [119], were also efficiently ^{18}F-labelled via the S_NAr method, notwithstanding that the activating and leaving groups are in weaker activated meta-position of the benzene ring, which necessitates harsher labelling conditions (see Fig. 2).

An S_NAr reaction can of course directly be performed on sites of heteroarenes as in the ortho-position of pyridine or 2-positon of 1,3-thiazoles, which are activated for an ^{18}F-for-X exchange (X= NO_2, $^+N(CH_3)_3$, halide) [1, 120, 121]. This approach was, for example, realized in the direct synthesis of derivatives of nicotinic ligands, like norchloro-[^{18}F]fluoroepibatidine [122], ([^{18}F]fluoro-3-(2(S)-azetidinylmethoxy)pyridine ([^{18}F]fluoro-A-85380) [123, 124], (-)-[^{18}F]flubatidine [125], and 2-[^{18}F]fluoro-3-[2-((S)-3-pyrrolinyl)-methoxy]pyridine ([^{18}F]nifene) (see Fig. 2) [126, 127]. Also, small radiofluorinated heteroarenes proved very useful as prosthetic groups for labelling of macromolecules, such as proteins and oligonucleotides [121].


[^{18}F]Altanserin

[^{18}F]MPPF

[^{18}F]Flumazenil

3-[^{18}F]Fluoro-5-(2-pyridinylethynyl)benzonitrile ([^{18}F]FPEB)

Norchloro[^{18}F]fluoroepibatidine

[^{18}F]Fluoro-A-85380

(-)-[^{18}F]Flubatidine

[^{18}F]Nifene

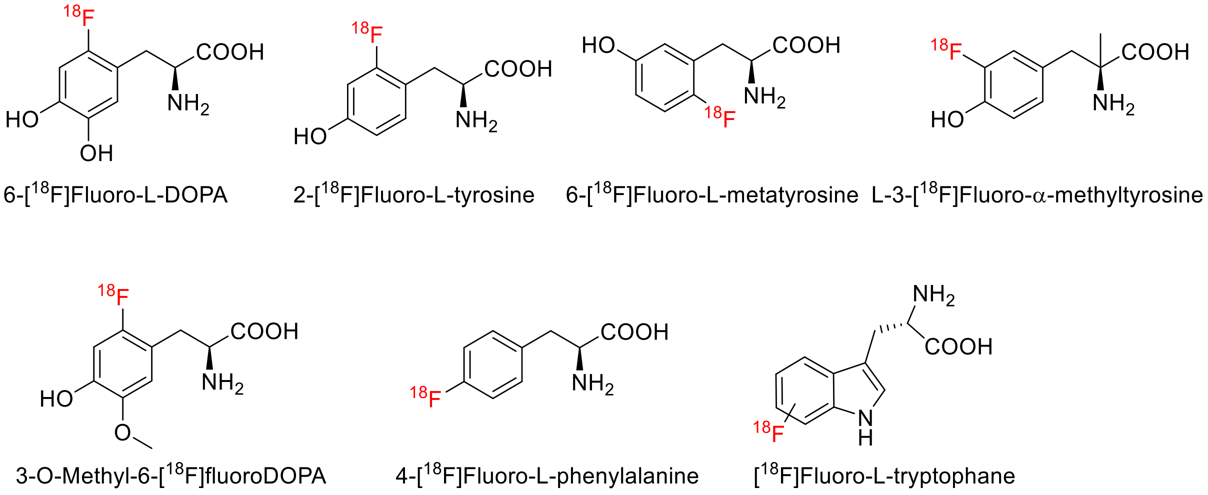
Figure 2: Prominent examples of ^{18}F-radiopharmaceuticals labelled via S_NAr reaction

During the last decade, three strategies were established for ^{18}F-fluorination of non-activated or even electron rich arenes, the most challenging compounds for nucleophilic substitution with n.c.a. [^{18}F]fluoride [108]. The three methodologies were elaborated for nucleophilic ^{18}F-synthesis of these kinds of compounds and have the ability to replace the electrophilic ^{18}F-fluorination of electron rich arenes. These are: i) three-step reactions, consisting of an ^{18}F-displacement reaction, removal of an activating group and hydrolysis of protecting groups, and one- or two-step reactions, ii) employing ”onium” compounds as precursors and most recently iii) by transition metal-mediated radiofluorination. In most cases of the latter two methods, the radiofluorination step is again followed by hydrolysis of protection groups.

Formerly, for radiofluorination of non-activated arenes methods via build-up syntheses, using ^{18}F-labelled building blocks like [^{18}F]fluorobenzaldehyde or [^{18}F]fluoronitrobenzene [3, 128], have been prevalently the method of choice (method i). Their disadvantage, however, is the difficulty of automation, since several reaction steps, often including separation und purification of intermediates, are necessary. Nevertheless, an originally five-step nucleophilic build-up synthesis of 6-[^{18}F]fluoro-L-DOPA succeeded for example, starting from [^{18}F]fluorobenzaldehyde derivatives [129, 130]. This approach was improved over a long period [131] and is now established in commercially available synthesis devices [132].

An alternative carbonyl-activated, three-step ^{18}F-fluorination was realized for the syntheses of the aromatic ^{18}F-labelled amino acids 6-[^{18}F]FDOPA [133], 2-[^{18}F]fluoro-L-tyrosine [134] and L- and D-3-[^{18}F]fluoro-α-methyltyrosine [135] (see Fig. 3). Here, the ^{18}F-displacement reaction is activated by a carbonyl function in ortho- or para-position, which is subsequently transformed either by Baeyer-Villiger oxidation to a hydroxyl group, or completely removed using the Wilkinson catalyst. This concept offers the possibility of a one-pot synthesis, as was established, for example, in a synthesis device with a modified precursor for the synthesis of n.c.a. 6-[^{18}F]FDOPA [136]. On the other hand, this procedure is sensitive to the basic conditions of the ^{18}F-fluorination reaction, which can lead to an epimerization of the amino acid.

In a recently published study on the nucleophilic synthesis of 6-[^{18}F]FDOPA both methods of carbonyl activated ^{18}F-exchange were compared, using the 3- and 5-step procedure [137]. It was convincingly shown that the three-step process was much easier and reliable to be automated, providing a RCY of 20 ± 1% within 114 min.



6-[^{18}F]Fluoro-L-DOPA
2-[^{18}F]Fluoro-L-tyrosine
6-[^{18}F]Fluoro-L-metatyrosine
L-3-[^{18}F]Fluoro-α-methyltyrosine
3-O-Methyl-6-[^{18}F]fluoroDOPA
4-[^{18}F]Fluoro-L-phenylalanine
[^{18}F]Fluoro-L-tryptophane

Figure 3: Structures of [^{18}F]fluorophenylamino acids of clinical interest

The iodonium strategy (method ii), which was for the first time introduced into ^{18}F-radiochemistry in 1995 [108, 138, 139], and the use of triarylsulfonium salts [140] were initially limited to the synthesis of small molecules, like 1-bromo-4-[^{18}F]fluorobenzene [141] and 1-[^{18}F]fluoro-4-iodobenzene [142, 143]. The latter served especially as building blocks in transition metal-mediated reactions for the synthesis of ^{18}F-radiotracers [128, 144]. This type of reaction has been well established in commercially available synthesis devices [145]. For the last decade then, the challenges for late-stage ^{18}F-fluorination of complex molecules, using iodonium compounds, were solved more and more, and a new review extensively discusses in detail their utility for small molecules, including mechanistic as well as application aspects [142].

Improvements included novel methods for the synthesis of iodonium salts [146], like methoxyaryl [147-149] or arylthionyl [150] precursors, the introduction of iodonium ylides [151-153], and the use of mesitylaryliodonium salts for a copper-mediated ^{18}F-fluorination [154] (see Fig. 4). The limited use of mesitylaryliodonium salts of electron rich arenes, which is due to their poor long-term stability, was overcome by the in-situ formation of these iodonium salts during the nucleophilic ^{18}F-fluorination [155]. The use of iodonium ylides enabled an efficient and automated synthesis of 3-[^{18}F]fluoro-5-[(pyridin-3-yl)ethynyl]benzonitrile ([^{18}F]FPEB) in >20 % RCY [156]. Combining iodonium precursors with the above mentioned “minimalist” method, the Cu-mediated nucleophilic radiofluorination, enabled the direct introduction of [^{18}F]fluoride into electron rich arenes with very high radiochemical yields and its implementation on a commercially available synthesis module [51, 157]. Additionally, two studies describe a reliable automated GMP production of the radioligands [^{18}F]flumazenil and [^{18}F]UCB from iodonium salts with a RCY of about 55 % and 35 %, respectively [158, 159].

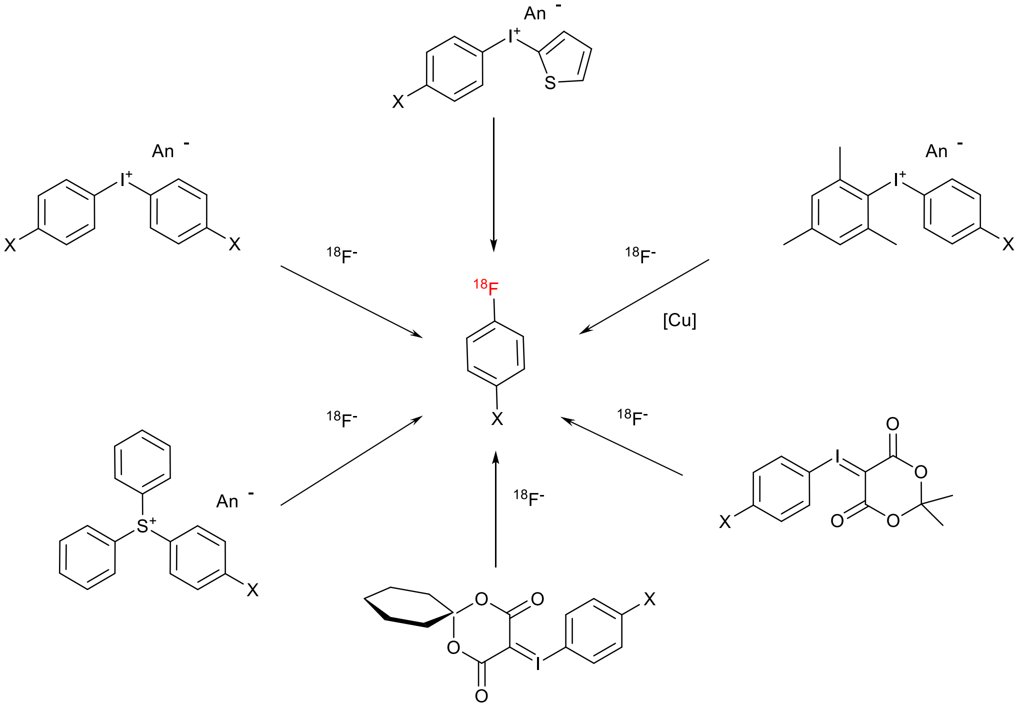
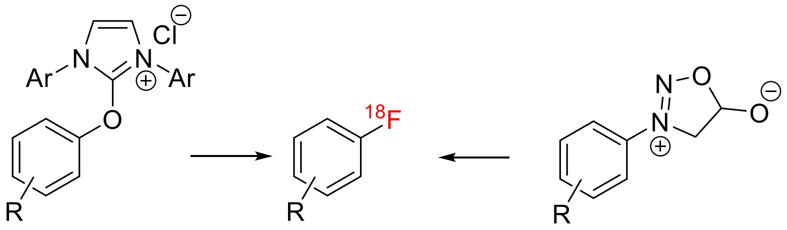


Figure 4: Methods of nucleophilic ^{18}F-substitution of non-activated arenes via “onium” compounds (method ii)

Besides the use of “onium” salt moieties as leaving group, phenols and anilines can also act as such, but they have to be pre-modified. The ^{18}F-deoxyfluorination of phenols became feasible by a transition-metal assistance, as recently reported for the first time [160]. This ruthenium-mediated reaction will probably offer a valuable addition to radiofluorination techniques. The transformation was claimed to benefit, besides the readily available phenols as starting materials, from tolerance of moisture and ambient atmosphere, accessing a large scope of compounds, and proved the ability to generate activity doses of products, like for [^{18}F]bavarostat, appropriate for PET imaging [161]. The nucleophilic radiofluorination of anilines with [^{18}F]fluoride was achieved by the initial modification of ArNH$_2$ to an *N*-arylsydnone precursor via a two-step process. However, the *N*-arylsydnone is only replaced by [^{18}F]fluoride, when activated by an electron withdrawing group (see Scheme 2) [162].



Scheme 2: ^{18}F-Deoxyfluorination [160] and ^{18}F-fluorination using N-arylsydnones (R = electron withdrawing group) [162]

The novel transition metal-mediated ^{18}F-labelling strategies (method iii) have a major potential to revolutionize ^{18}F-labelling of even electron rich arenes. Operationally simple under relatively mild reaction conditions, they can be performed at the n.c.a. level, the required precursors are mostly stable at room temperature, and they can be applied to a wide range of compounds (see Fig. 5).

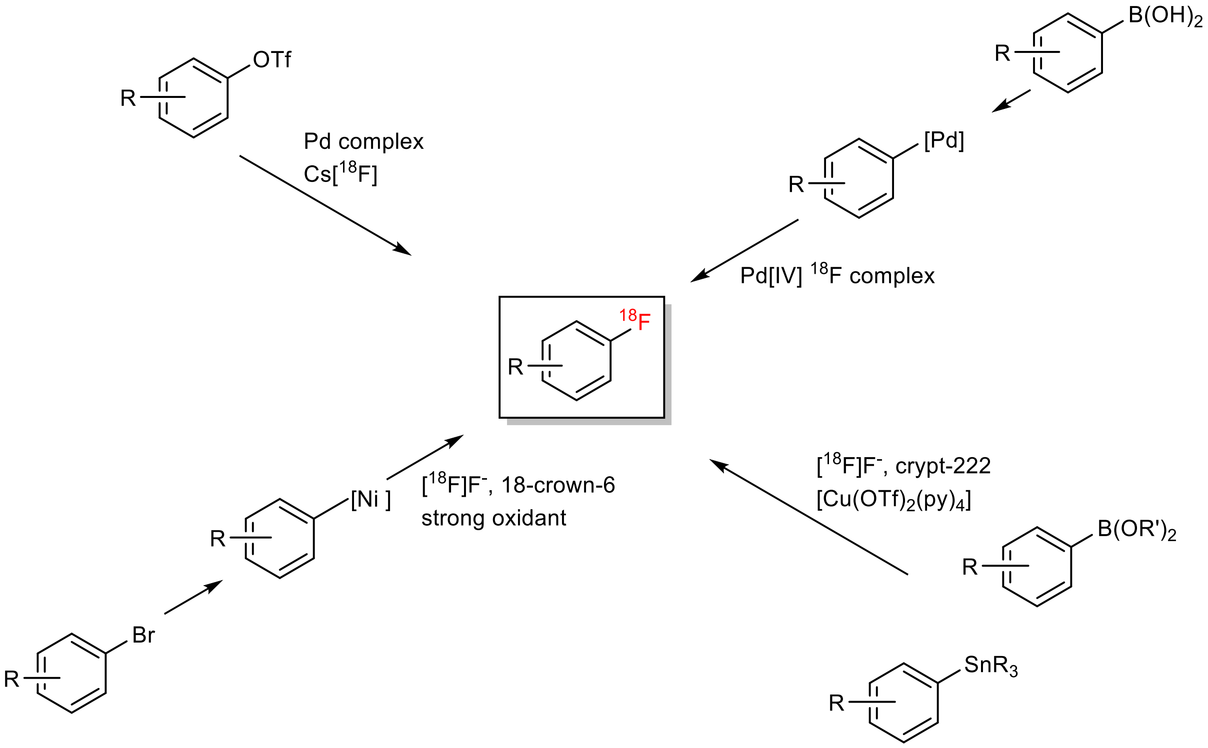


Figure 5: Novel transition metal catalysed radiofluorination methods for non-activated and electron-rich arenes (method iii)

The first attempts were performed by palladium-mediated radiofluorination [163] of Pd(V) complexes as precursors [164], or by nickel-catalysed ^{18}F-reactions [165-167] (see Fig. 5). However, those first attempts did not fulfil the desired, afore mentioned properties. The breakthrough was the introduction of copper-mediated ^{18}F-displacement reactions, using arylboron [168, 169] and arylstannanes [170] as precursors. The latter ones, which were earlier synthesised for electrophilic ^{18}F-fluorination, offer here a convenient possibility to use these precursors also for the copper-mediated nucleophilic substitution, as shown for the syntheses of [^{18}F]DAA1106, [^{18}F]MFBG, [^{18}F]FDOPA, 6-[^{18}F]fluoro-L-*meta*-tyrosine and [^{18}F]fluorodopamine ([^{18}F]FDA) [171] (see Fig. 6). The copper-mediated ^{18}F-fluorination method enabled the efficient synthesis of the EP4 receptor antagonist CJ-042794 [172] and different [^{18}F]fluoro-L-tryptophan derivatives [173-175]. The addition of small amounts of pyridine to the reaction medium of Cs_2CO_3 or crypt-222 as a solubilizing agent for [^{18}F]fluoride and $Cu(OTf)_2(py)_4$ as catalyst showed a significant improvement of the RCY as demonstrated for different [^{18}F]fluoroanisole derivatives and 4-[^{18}F]fluoro-L-phenylalanine [176].

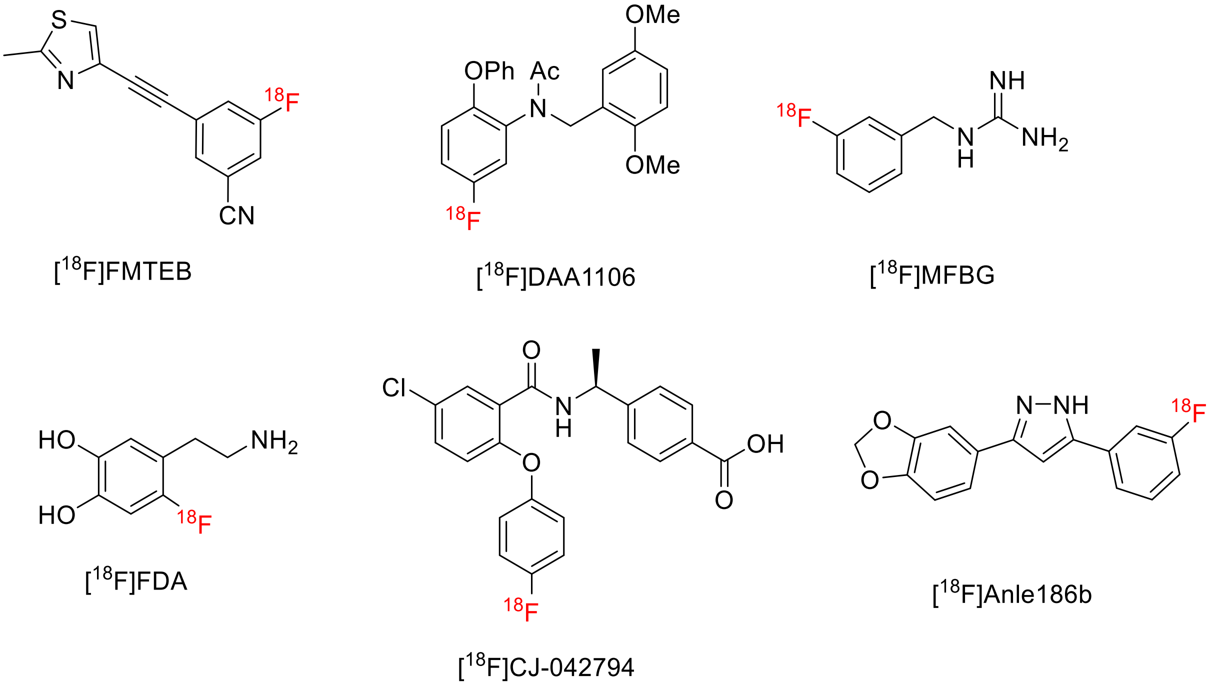


Figure 6: Examples of ^{18}F-radiopharmaceuticals labelled by Cu-mediated radiofluorination

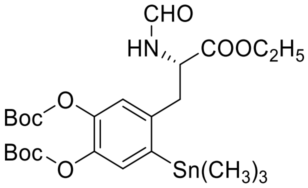
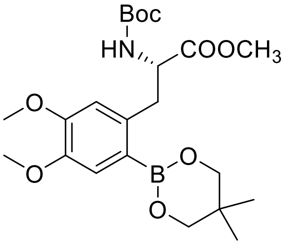
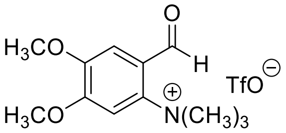
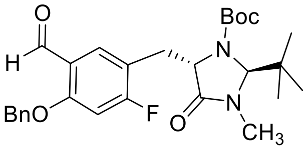
So far, however, the process of adapting these new transition-metal assisted reactions for automated production of radiopharmaceuticals has revealed limitations in fitting them into the confines of traditional radiochemistry systems. In particular, the presence of bases (e.g. K_2CO_3) and/or phase transfer catalysts (e.g. crypt-222) associated with ^{18}F-preparation was even found to be detrimental here to reaction yields. These limitations could be addressed by the development of alternative techniques for isolation of [^{18}F]fluoride from the target, providing the possibility to tailor an eluent individually which meets the specific needs of a metal-catalysed reaction of interest. It was demonstrated that various solutions of copper salts, bases, and ancillary ligands can be utilized for these reactions to elute [^{18}F]fluoride from ion exchange cartridges (see above). For proof of concept, the efficiency of the new procedure has been demonstrated by optimizing the radiosynthesis of [^{18}F]fluoro-acetophenone [60].

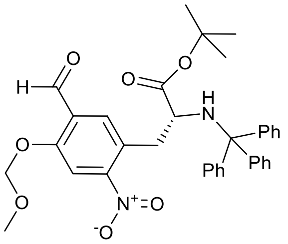
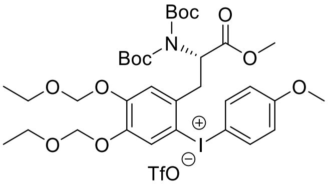
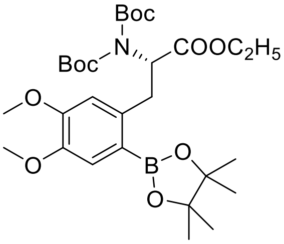
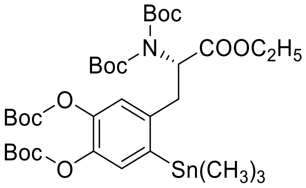
In the case of the Cu-mediated ^{18}F-labelling, even a beneficial effect of primary and secondary alcohols was reported. This observation contradicts the earlier assumption that such alcohols are inappropriate solvents for aromatic fluorination (see discussion above). Indeed, a protocol has been developed for rapid radiolabelling of an extraordinary broad scope of boronic esters and stannylated precursors, and radiofluorinated indoles, phenols, and anilines were synthesized directly from the corresponding, unprotected precursors [77]. This novel method enabled the facilitated preparation of [^{18}F]anle186b and of the [^{18}F]fluorophenylamino acids 6-

[^{18}F]FMT, 2-[^{18}F]fluoro-L-tyrosine, 6-[^{18}F]FDOPA, and 3-*O*-methyl-6-[^{18}F]FDOPA [177], as well as different [^{18}F]fluoro-L-tryptophan derivatives [178].

Especially, 6-[^{18}F]FDOPA exhibits a great importance in PET-imaging for more than 30 years with the focus on neurological diseases [179] and later on of neuroendocrine tumours [180]. As mentioned, many methods have been developed, using electrophilic as well as nucleophilic approaches [21, 181, 182], in order to improve the synthesis of 6-[^{18}F]FDOPA. These are summarized in Table 1 for comparison and to exemplify the tremendous efforts invested to optimally meet routine clinical supply.

Table 1: Methods for the radiosyntheses of 6-[^{18}F]FDOPA

<table>
<tr><td colspan="5"><i>Electrophilic methods</i></td></tr>
<tr><td>Precursor</td><td>^{18}F-reagent</td><td>Pros</td><td>Cons</td><td>Ref.</td></tr>
<tr><td rowspan="2"> </td><td>[^{18}F]F_2</td><td>easy to automate;
synthesis devices commercially available
RCY 33 ± 4%</td><td>c.a. synthesis;
corrosive F2</td><td>[20]</td></tr>
<tr><td>[^{18}F]F_2 via electrical discharge of $CH_3[^{18}F]F$</td><td>higher A_m compared to the classical electrophilic method
RCY 6.4±1.7%</td><td>no commercially available synthesis device; only remotely controlled handling</td><td>[183]</td></tr>
<tr><td> </td><td>[^{18}F]selectfluor bis(triflate) via electrical discharge of $CH_3[^{18}F]F$</td><td>higher A_m and better RCY compared to the classical electrophilic method
RCY 19±12%</td><td></td><td>[31]</td></tr>
<tr><td colspan="5"><i>Nucleophilic methods</i></td></tr>
<tr><td>Precursor</td><td>^{18}F-reagent</td><td>Pros</td><td>Cons</td><td>Ref.</td></tr>
<tr><td> </td><td>[^{18}F]F$^-$</td><td>n.c.a. synthesis;
synthesis devices commercially available;
RCY 36 ± 3%</td><td>five-step procedure;
corrosive reagents;
difficult to automate using common ^{18}F-synthesis devices</td><td>[131, 132, 137]</td></tr>
<tr><td> </td><td>[^{18}F]F$^-$</td><td>three-step procedure;
RCY 22 %</td><td>c.a. synthesis;
corrosive reagents;
difficult to automate using common ^{18}F-synthesis devices</td><td>[133]</td></tr>
</table>

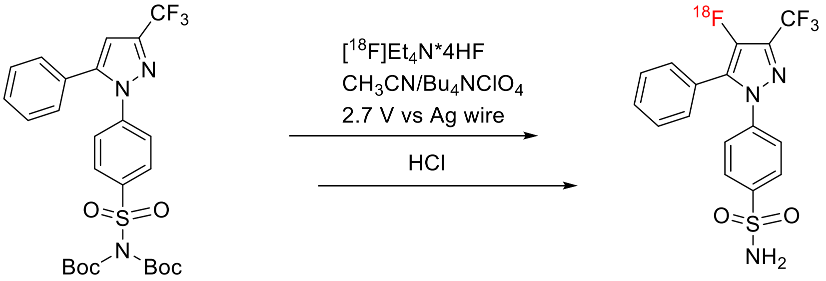
	[^{18}F]F$^-$	three-step procedure; n.c.a. synthesis; easy established on standard synthesis devices RCY 20 ± 1%		[136, 137]
	[^{18}F]F$^-$	two-step procedure; n.c.a. synthesis; RCY 33 ± 4%		[184]
	[^{18}F]F$^-$	two-step procedure; n.c.a. synthesis; RCY 22 ± 5%		[171]
	[^{18}F]F$^-$	two-step procedure; n.c.a. synthesis; RCY 54 ± 5%		[177]

Electrochemically supported ^{18}F-labelling

Based on the previous experiences with anodic deposition of no-carrier-added [^{18}F]fluoride (see above), a new type of an electrochemical cell and variable reaction volume has been developed. The reactor was designed for a small reaction volume and non-thermal drying of [^{18}F]fluoride. The implementation of this device for a completely remote-controlled synthesis was described for the routine production of [^{18}F]altanserin. By cryp-222 mediated nucleophilic ^{18}F-fluorination a radiochemical yield of about 24% was obtained with batches of up to 6 GBq of [^{18}F]altanserin and an A_m of 4,500 GBq/mmol within 75 min, suitable for human application [112].

Furthermore, the electrochemical method proved ability to label aromatic rings through direct nucleophilic ^{18}F-fluorination of cationic intermediates. At first, this was successfully shown for the carrier-added synthesis of a [^{18}F]fluorophenylalanine derivative using galvanostatic conditions [185]. Also, a direct nucleophilic radiosynthesis of di-*tert*-butyl-(4-[^{18}F]fluoro-1,2-phenylene)-dicarbonate was achieved by a no-carrier-added electrochemical reaction under potentiostatic conditions, using di-*tert*-butyl-(4-(*tert*-butyl)-1,2-phenylene)dicarbonate as precursor, however, with less than 2% radiochemical yield only. In this case, a 10 mM solution of triethylamonium acetate (Et_3NAc) in acetonitrile was used to release the [^{18}F]fluoride ions trapped on a quaternary ammonium anion exchange resin [186, 187].

Further on, the synthesis of the COX-2 inhibitor 4-(4-([^{18}F]fluoro)-5-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzenesulfonamide, directly radiolabelled on the heteroaromatic ring, could not be achieved by traditional means. However, with the corresponding hydrocarbon as precursor, an automated electrochemical radiosynthesis platform allowed to synthesize up to 200 MBq of radiochemically pure [^{18}F]fluoro-COX-2ib within 4 hours (see Scheme 3) [188].



Scheme 3: Synthesis of 4-(4-([^{18}F]fluoro)-5-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzenesulfonamide; adapted from [188].

Automation of nucleophilic ^{18}F-fluorination

The automation of ^{18}F-syntheses is an indispensable prerequisite for clinical application of PET-tracers. It enables fast and reliable syntheses, the use of high amounts of radioactivity, and it simplifies the fulfilment of regulatory compliances (GMP-requirements), including the sterility of the radiopharmaceuticals routinely prepared [189, 190]. Many principally different automated synthesis modules and platforms have been designed and implemented to produce ^{18}F-probes in an efficient, reproducible and safe manner, which allow carrying out repetitive synthetic steps and production cycles and which are commercially available [191] for electrophilic and nucleophilic ^{18}F-fluorination reactions [20, 45]. However, as discussed above, the nucleophilic approach is by far the dominating method for the synthesis of ^{18}F-labelled radiotracers and radioligands. Novel nucleophilic radiofluorination methods have the potential to replace all electrophilic methods, aiming to achieve n.c.a products and to minimise the chemical burden to patients.

The first commercial available synthesis devices were designed for the implementation of the [^{18}F]FDG synthesis, which only required the use of one reactor, where the radiofluorination step and the hydrolysis step was performed [44, 62, 192, 193]. The subsequent purification procedure was performed by solid phase extraction, leading to a high quality of the final product. However, other nucleophilic ^{18}F-labelling pathways often necessitate the use of a two-reactor system and/or HPLC purification after labelling and deprotection. Most of the commercial available automated devices are stationary, fixed-tubing systems. There, purification has to be performed after each run, and the hardware (tube, valves, plumbing) cannot be exchanged in day-to-day operation.

Alternatively, to get more flexible systems, modular subunit systems were developed [194]. As an example, a plug-and-play radiosynthesis platform accompanied by computer software based on modular subunits can easily and flexibly be configured to implement a diverse range of radiosynthesis protocols [194]. Using such systems, the standard procedures (^{18}F-labelling, hydrolysis and purification) have been implemented for many clinically relevant ^{18}F-tracers [103, 105, 191, 195-197] or ^{18}F-labelled building blocks for labelling of macromolecules [198-200] and build-up syntheses [145].

A special type of synthesis device is the hardware kit system, also called "cassette system" [201]. All reagents, which are needed thereby for radiofluorination, are prefabricated and enclosed in disposable cassettes, which are easily switched on the synthesis device. This enables multiple runs of ^{18}F-syntheses in short intervals on the same production day, because the exhausted and contaminated cassettes can quickly be removed into lead shielded waste boxes. Furthermore, these cassette systems reduce the time and effort of validation and cleaning processes, and thereby the risk of cross-contamination, what again facilitates the fulfilment of the GMP-requirements. Thus, the implementation of a radiofluorination process into a cassette system is the aim of many new developments. However, a drawback of these kit systems might be high costs and possible difficulties with the supply of hardware kits.

In an early stage of an automation process, however, conventional fixed-tubing systems offer more flexibility for establishing an ^{18}F-fluorination process. As alternative therefore, a novel fully automated 3-reactor radiosynthesiser was developed, which combines the advantages of both systems [202].

Several radiotracers have been implemented on standard synthesis devices fulfilling the GMP requirements for clinical trials as mentioned above for [^{18}F]flumazenil [158] and [^{18}F]UCB [159]. Those include the syntheses of [^{18}F]AV-45 ([^{18}F]florbetapir) [203, 204], [^{18}F]florbetaben [205], [^{18}F]flortanidazole ([^{18}F]HX4) [206], [^{18}F]MK-9470 [207], and [^{18}F]PSMA-1007 [208].

Microfluidic technology

Microfluidic devices appear as an attractive technology for the preparation of labelled radiotracers. The extremely low amounts of n.c.a. [^{18}F]fluoride offer the possibility to improve the efficiency of radiolabelling, using microfluidics [56, 209-214]. Compared to the "vessel" chemistry, where the radiofluorination is performed in vials of 5-20 mL size, the volume of microfluidics "vessels" are on the microliter scale. Therefore, the amount of chemicals, especially of rather expensive labelling precursors, can be tremendously reduced. This also leads to an improvement of the A_m, minimizing the contamination by the non-radioactive isotope [212], and the reaction time can significantly be shortened [215]. The microfluidic approach offers the implementation of a single-use system, enabling a dose-on-demand approach, which provides the synthesis of the desired radiotracer in proximity to the PET scanner [210].

Several challenges can be defined for the implementation of microfluidic technology in ^{18}F-chemistry, which are partly solved today. The whole process, including the pre-concentration of [^{18}F]fluoride, the synthesis steps (radiofluorination and deprotection), and the purification and formulation of the final product have to be miniaturized.
In this context, the concentration of [^{18}F]fluoride from millilitre target volumes to microliter reaction volumes is of great importance. Several concepts were studied to minimize the volume obtained from target (compare above). The common one is the use of anion exchange cartridges with low internal volume to reduce the complete volume of the eluate [57, 216, 217]. The usefulness of electrochemical methods for the concentration of [^{18}F]fluoride suitable for microfluidic devices was successfully demonstrated by nucleophilic ^{18}F-substitution of several radiotracers [80, 218]. In a novel development [^{18}F]fluoride is captured on QMA-tagged magnetic particles in a solution and subsequently released by ion-exchange with a K_2CO_3 solution [219].

As mentioned above, a crucial step in most nucleophilic ^{18}F-syntheses is the removal of target water from [^{18}F]fluoride. Possibilities to realize this for microfluidic systems are the use of a gas stream conveyed through the capillaries [57, 220], or the above-mentioned electrochemical methods. On the other hand, since several studies show that some nucleophilic radiofluorination methods are tolerant to protic solvents and even tolerate a small content of water, this helps to simplify the automation of the drying step [73, 221].

Further, the in-flow purification is a major challenge in microfluidic radiochemistry. Therefore, the use of microanalytic flow separations [222] might be advantageous. A final concentration of the product solution could be performed by solid-phase [223] and also by on-chip solid phase extraction [224]. A novel method reported the use of sweeping gas membrane distillation, in order to rapidly perform the concentration and formulation process in a fully automated microfluidic system [225].

In order to realize all necessary conditions for radiofluorination by microfluidic devices, two main constructions were designed [209, 211], the continuous-flow [226, 227] and the stop-flow (batch mode, also called “micro-vessel”) [228] microfluidics. A challenge of both systems is the necessity to connect the microfluidic devices to classical lab ware and to combine it with sensors and heating systems [210]. Furthermore, the material of the microfluidics devices has to be resistant against organic solvents and heating [229]. In spite of all those difficulties, several syntheses of clinically relevant ^{18}F-radiotracers were successfully implemented on microfluidic devices, including [^{18}F]FDG [73, 223, 224, 226, 230-233], [^{18}F]fallypride [216, 234], [^{18}F]altanserin [235], [^{18}F]FLT [236, 237], [^{18}F]FMISO [238, 239], and 7-(6-fluoropyridin-3-yl)-5*H*-pyrido[4,3-b]indole ([^{18}F]T807) [240].

Last not least, another serious demand with regard to the production by microfluidics is the fulfilment of pharmaceutical regulations [241]. This includes the qualification of starting materials, the in-process control and particularly the quality control of single batch (dose-on-demand) productions [210, 242, 243].

Advances in quality control procedures

As pointed out already in the context of automatized production methods, old and new procedures and materials must comply with the requirements of a GMP-conform preparation of radiopharmaceuticals and consider their facilitation, including the quality control methods themselves.

Regarding the short half-life of fluorine-18, quality control methods have to be fast and reliable. On the other hand, high-end equipment is not available in many clinics. Therefore, it is desirable that the analytical methods have to be on an easy level. As [^{18}F]FDG is the most used radiopharmaceutical for clinical PET examinations, it also played a leading role in the development of quality control methods. Several studies focused on the improvement or facilitating these techniques, including the TLC or HPLC analysis of possible radiochemical impurities like [^{18}F]fluoride, [^{18}F]fluorodeoxymannose ([^{18}F]FDM), partially or fully acetylated [^{18}F]FDG and chlorodeoxyglucose, besides other non-radioactive auxiliaries [190, 244-246]. For radiopharmaceuticals, which have no UV activity, capillary electrophoresis offers itself as an alternative, as well as for the detection of non-radioactive impurities [247].

The requirements for the quality control of [^{18}F]FDG are set out in the monographs of various pharmacopoeias, like the European or the United States Pharmacopeia, including the appearance of the product solution, radiochemical purity, chemical purity, pH, residual solvent, sterility and bacterial endotoxin levels. The Japanese Pharmacopeia further requires testing the concentration of Al^{3+}, which should be limited to 10 ppm per batch. For example, the [^{18}F]FDG cassettes for the most used synthesis devices, namely the GE FASTlab, are available with phosphate or citrate buffer. In a two-centre study it was found out that the phosphate cassettes often show precipitates of aluminium phosphates, formed by the interaction of phosphate buffer with Al^{3+} ions eluted from the alumina cartridge, what does not fulfil the requirement of the Japanese Pharmacopeia and also not the requirements for product solution appearance of the other pharmacopoeias [248].
Noteworthy is also the great effort invested to prove the absence of crypt-222 in the final solution of ^{18}F-radiopharmaceuticals, which is another important quality control criterion. The techniques used include simple TLC [249-252], GC [253], HPLC [245, 252], and capillary electrophoresis [247], but also highly-sophisticated LC-MS analytics [254]. A novel and simple method makes use of the colour change of I_2/I^- solutions [255].

Closing remarks

The large number of publications on the development of radiofluorination in recent years, concerning all areas of radiopharmaceutical production for PET-imaging, reflects, exemplarily for this field, the innovative level and creativity of radiopharmaceutical sciences. Much success and progress were achieved, providing many improved, modified or even completely new radiofluorination methods, which are considered with respect to their suitability for the clinical supply with ^{18}F-radiopharmaceuticals. As mentioned above, important aspects comprise, besides effectivity, i.e. activity yield and costs, especially the ease (practicality) of performance (automation) and the reliability of routine application, as well as the compliance of radiopharmaceutical production with GMP requirements. Thus, also compiled here were advances, concerning the automation of radiosyntheses on dedicated cassette and kit systems, or by microfluidics, in order to facilitate safe routine production, as well as those improving quality control procedures. The impact and requirements of GMP are often underestimated, or even ignored; not only considering routine production, but also during the design and realisation of radiopharmaceuticals. Since radiopharmaceutical chemistry is a very multidisciplinary field, generally performed by radiochemists, the essential pharmaceutical knowledge must be provided by pharmacists or appropriate education, and must also be mentioned here as a concern, as was recently discussed for other possible 'gaps in the pipeline of ^{18}F-tracer development for PET' [256].

The limitation to [^{18}F]fluoride as the only practical source for ^{18}F-labelling with a high molar activity causes a concentration on nucleophilic reactions with this single reagent for the synthesis of ^{18}F-probes. Although electrophilic processes are often easily applicable with tracers not demanding a very high A_m, there is still the issue of an avoidable chemical burden to patients. Thus, a wider part of this review deals with the isolation and activation of n.c.a. [^{18}F]fluoride. Although there are a few novel substitution reactions reported for aliphatic model compounds, bearing a high potential, a rather standardised level of routine syntheses of aliphatic ^{18}F-compounds is reached, as exemplified for the established tracers [^{18}F]FDG, [^{18}F]FLT, and [^{18}F]FET.

The nucleophilic ^{18}F-labelling of non-activated and especially electron-rich aromatic molecules, in contrast, poses still major challenges. Therefore, a great part of research has recently concentrated on these issues, and very interesting modern fluorination methods have been or are being adapted to the synthesis of n.c.a. [^{18}F]fluoroarenes. Here, some novel approaches with a great potential, facilitating and achieving the production of a still wider variety of ^{18}F-radiopharmaceuticals, may particularly be pointed out, besides several others. These are all copper-catalysed ^{18}F-radiofluorinations applicable for electron-rich arenes, using either aryliodonium or stannylated aryl precursors [154, 170], or aryl boronic esters [171], whereby both methods find already rapid introduction into the routine production of radiotracers. Furthermore, the very recent, still experimental, but extraordinary "C–H ^{18}F-fluorination" of (hetero)-arenes is to be mentioned [154, 155, 171].

The general goal of nearly all novel radiofluorination methods is to save reaction steps, in order to attain short synthesis times and to facilitate automation. This, however, is often only achieved at the expense of the necessity to synthesise specific precursors and/or that of using different mediating or activating additives. Many of the discussed helpful improvements benefit from modern, potentially toxic metal-compounds and -catalysts. For that, attention must be paid to the additional complexity to fulfil the requirements of GMP. Quarantine, fast and simple methods for quality control and testing of identity, etc., must be established for each further substance used in the production process. Examples like the aforementioned toxicity of crypt-222 or of transition metals and the, in part difficult to achieve, set-up of simple but reliable analytical procedures speak here for themselves.

From the many developments listed in this review, some are still from basic studies and concern principal n.c.a. reactions with simple test compounds, but not yet, or only to a limited extent, their application for production of established or new PET-probes. Some published novel methods hold great promise so far, to facilitate production in the future. Others have already proven their advantage and suitability for an automated routine production, while with some such experience does not yet exist, or is only limited to one laboratory. Unfortunately, many studies were performed isolated from each other and thus, are not directly comparable to similar approaches, which often depend on specific local resources (conditions and equipment) and clinical demands.

In fact, there are rarely cases, where different methods were compared in one laboratory, like for [^{18}F]FLT [103, 105] and 6-[^{18}F]FDOPA [137]. The latter is one of the few examples, where several labelling strategies were pursued with much effort and realised over the last three decades. Indeed, many more comparative evaluations under practical conditions of routine production and with comparable efforts are desirable, preferentially confirmed, or in collaboration, by various centres.
As the example of 6-[^{18}F]FDOPA shows, there might be various options to select from established or rather new procedures in the literature, when newly setting up a synthetic procedure of an established radiopharmaceutical. However, if an existing process is supposed to be changed to a newer one, the additional value has to justify the operating expenses under ecological and technological aspects, including all steps of production, from nuclide production and required reagents, via automated synthesis to formulation and quality control. All this must fit to the general conditions, including clinical demands, e.g. frequency of production, and the philosophy of the laboratory.

Given the multitude of present approaches and their developmental stages, reflecting in part also different strategies, it seems presently too early for final judgements or recommendations on the clinical usefulness of all these methods. Considering, however, the very many promising developments going on and the obvious high potential of radiopharmaceutical scientists, there is great confidence in further inventions and the establishment of a standardised methodology for reliable routine production. For example, the use of modern, high-resolution mass spectrometry in combination with minute amounts of fluorine-19 reagents, as recently realised [257], bears the potential to considerably accelerate studies on n.c.a. ^{18}F-fluorination reactions without application of the radioactive isotope. Thus, improved radiofluorination and production processes, together with advancing smart and specific ^{18}F-radiopharmaceuticals, will ensure the extension of *in vivo* molecular imaging with positron emission tomography and serve in a symbiotic collaboration with nuclear medicine to promote research on diseases and to improve diagnostics of patients.

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References

1. Preshlock S, Tredwell M, Gouverneur V (2016) ^{18}F-Labeling of Arenes and Heteroarenes for Applications in Positron Emission Tomography. Chem Rev 116:719-766.
2. Cole EL, Stewart MN, Littich R, Hoareau R, Scott PJH (2014) Radiosyntheses using fluorine-18: The art and science of late stage fluorination. Curr Top Med Chem 14:875-900.
3. van der Born D, Pees A, Poot AJ, Orru RVA, Windhorst AD, Vugts DJ (2017) Fluorine-18 labelled building blocks for PET tracer synthesis. Chem Soc Rev 46:4709-4773.
4. Schirrmacher R, Wängler B, Bailey J, Bernard-Gauthier V, Schirrmacher E, Wängler C (2017) Small Prosthetic Groups in ^{18}F-Radiochemistry: Useful Auxiliaries for the Design of ^{18}F-PET Tracers. Semin Nucl Med 47:474-492.
5. Kniess T, Laube M, Brust P, Steinbach J (2015) 2-[^{18}F]Fluoroethyl tosylate - a versatile tool for building ^{18}F-based radiotracers for positron emission tomography. MedChemComm 6:1714-1754.
6. Buckingham F, Gouverneur V (2016) Asymmetric ^{18}F-fluorination for applications in positron emission tomography. Chem Sci 7:1645-1652.
7. Laverman P, McBride WJ, Sharkey RM, Goldenberg DM, Boerman OC (2014) Al^{18}F labeling of peptides and proteins. J Labelled Compd Radiopharm 57:219–223.
8. Burke BP, Clemente GS, Archibald SJ (2015) Boron-^{18}F containing positron emission tomography radiotracers: advances and opportunities. Contrast Media & Molecular Imaging 10:96-110.
9. Bernard-Gauthier V, Bailey JJ, Liu Z, Wängler B, Wängler C, Jurkschat K, Perrin DM, Schirrmacher R (2016) From Unorthodox to Established: The Current Status of ^{18}F-Trifluoroborate- and ^{18}F-SiFA-Based Radiopharmaceuticals in PET Nuclear Imaging. Bioconjugate Chem 27:267-279.
10. Chansaenpak K, Wang M, Wang H, Giglio BC, Gabbai FP, Wu Z, Li Z (2017) Preparation of [^{18}F]-NHC-BF3 conjugates and their applications in PET imaging. RSC Adv 7:17748-17751.
11. Roeda D, Dolle F (2015) Recent developments in the chemistry of [^{18}F]fluoride for PET. Chemistry of Molecular Imaging, ed. Long N, Wong W T. Hoboken: John Wiley & Sons Inc. 55-77.
12. Jacobson O, Kiesewetter DO, Chen X (2015) Fluorine-18 Radiochemistry, Labeling Strategies and Synthetic Routes. Bioconjugate Chem 26:1-18.
13. Wan WX, Guo N, Pan DH, Yu CJ, Weng Y, Luo SN, Ding H, Xu YP, Wang LZ, Lang LX, Xie QG, Yang M, Chen XY (2013) First Experience of ^{18}F-Alfatide in Lung Cancer Patients Using a New Lyophilized Kit for Rapid Radiofluorination. J Nucl Med 54:691-698.
14. Lien VT, Riss PJ (2014) Radiosynthesis of [^{18}F]Trifluoroalkyl Groups: Scope and Limitations. BioMed Res Int.
15. Honer M, Gobbi L, Martarello L, Comley RA (2014) Radioligand development for molecular imaging of the central nervous system with positron emission tomography. Drug Discovery Today 19:1936-1944.

16. Coenen HH, Gee AD, Adam M, Antoni G, Cutler CS, Fujibayashi Y, Jeong JM, Mach RH, Mindt TL, Pike VW, Windhorst AD (2017) Consensus nomenclature rules for radiopharmaceutical chemistry — Setting the record straight. Nucl Med Biol 55:v-xi.
17. Firnau G, Chirakal R, Garnett ES (1984) Aromatic Radiofluorination with [^{18}F]Fluorine Gas: 6-[^{18}F]Fluoro-L-Dopa. J Nucl Med 25:1228-1233.
18. Ido T, Wan CN, Casella V, Fowler JS, Wolf AP, Reivich M, Kuhl DE (1978) Labeled 2-deoxy-D-glucose analogs. ^{18}F-labeled 2-deoxy-2-fluoro-D-glucose, 2-deoxy-2-fluoro-D-mannose and ^{14}C-2-deoxy-2-fluoro-D-glucose. J Labelled Compd Radiopharm 14:175-183.
19. Fowler JS, Ido T (2002) Initial and subsequent approach for the synthesis of ^{18}FDG. Semin Nucl Med 32:6-12.
20. de Vries EFJ, Luurtsema G, Brüssermann M, Elsinga PH, Vaalburg W (1999) Fully automated synthesis module for the high yield one-pot preparation of 6-[^{18}F]fluoro-l-DOPA. Appl Rad Isot 51:389-394.
21. Pretze M, Wängler C, Wängler B (2014) 6-[^{18}F]fluoro-L-DOPA: A well-established neurotracer with expanding application spectrum and strongly improved radiosyntheses. BioMed Res Int 2014.
22. Antuganov DO, Zykov MP, Ryzhkova DV, Zykova TA, Vinal'ev AA, Antuganova YO, Samburov OP (2016) Synthesis of [^{18}F]-L-DOPA radiopharmaceutical on a modified GE TracerLAB Fx F-E platform. Radiochemistry 58:649-653.
23. Füchtner F, Zessin J, Mäding P, Wüst F (2008) Aspects of 6-[^{18}F]fluoro-L-DOPA preparation: Deuterochloroform as a substitute solvent for Freon 11. NuklearMedizin 47:62-64.
24. Forsback S, Eskola O, Bergman J, Haaparanta M, Solin O (2009) Alternative solvents for electrophilic synthesis of 6-[^{18}F]fluoro-L-DOPA. J Labelled Compd Radiopharm 52:286-288.
25. Coenen HH (2007) Fluorine-18 Labeling Methods: Features and Possibilities of Basic Reactions In: Schubiger P A, Lehmann L, Friebe M (ed) PET Chemistry: The Driving Force in Molecular Imaging. Ernst Schering Research Foundation Workshop 62 Springer-Verlag, Berlin Heidelberg pp 15-50.
26. Miller PW, Long NJ, Vilar R, Gee AD (2008) Synthesis of ^{11}C, ^{18}F, ^{15}O, and ^{13}N Radiolabels for Positron Emission Tomography. Ang Chem Int Ed 47:8998-9033.
27. Bergman J, Johnström P, Haaparanta M, Solin O, Duelfer T, Stone-Elander S (1995) Radiolabelling of 2-oxoquazepam with electrophilic ^{18}F prepared from [^{18}F]fluoride. Appl Rad Isot 46:1027-1034.
28. Bergman J, Solin O (1997) Fluorine-18-labeled fluorine gas for synthesis of tracer molecules. Nucl Med Biol 24:677-683.
29. Forsback S, Solin O (2015) Post-target produced [^{18}F]F_2 in the production of PET radiopharmaceuticals. Radiochim Acta 103:219-226.
30. Krzyczmonik A, Keller T, Kirjavainen AK, Forsback S, Solin O (2017) Vacuum ultraviolet photon–mediated production of [^{18}F]$_2$ J Labelled Compd Radiopharm 60:186-193.
31. Stenhagen ISR, Kirjavainen AK, Forsback SJ, Jørgensen CG, Robins EG, Luthra SK, Solin O, Gouverneur V (2013) Fluorination of an arylboronic ester using [^{18}F]selectfluor bis(triflate): Application to 6-[^{18}F]fluoro-L-DOPA. Chem Comm 49:1386-1388.
32. Kilbourn MR (1990) Fluorine-18 Labeling of Radiopharmaceuticals. Nuclear Science Series. National Academy Press. 149.
33. Coenen HH (1986) New radiohalogenation methods: An overview In: Cox P H, et al. (ed) Progress in Radiopharmacy Springer pp 196–220.
34. Guillaume M, Luxen A, Nebeling B, Argentini M, Clark JC, Pike VW (1991) Recommendations for fluorine-18 production. Int J Appl Radiat Isot 42:749-762.
35. Stöcklin G, Qaim SM, Rösch F (1995) The impact of radioactivity on medicine. Radiochim Acta 70-1:249-272.
36. Awasthi V, Watson J, Gali H, Matlock G, McFarland A, Bailey J, Anzellotti A (2014) A "dose on demand" Biomarker Generator for automated production of [^{18}F]F^- and [^{18}F]FDG. Appl Rad Isot 89:167-175.
37. Siikanen J, Ohlsson T, Medema J, Van-Essen J, Sandell A (2013) A niobium water target for routine production of [^{18}F]Fluoride with a MC 17 cyclotron. Appl Rad Isot 72:133-136.
38. Berridge MS, Voelker KW, Bennington B (2002) High-yield, low-pressure [^{18}O]water targets of titanium and niobium for F-18 production on MC-17 cyclotrons. Appl Rad Isot 57:303-308.

39. Satyamurthy N, Amarasekera B, Alvord CW, Barrio JR, Phelps ME (2002) Tantalum [^{18}O]water target for the production of [^{18}F]Fluoride with high reactivity for the preparation of 2-deoxy-2-[^{18}F]Fluoro-d-glucose. Mol Imaging Biol 4:65–70.
40. Gatley JS, Shaughnessy WJ (1982) Production of ^{18}F-labeled compounds with ^{18}F− produced with a 1-MW Research reactor. Int J Appl Rad Isot 33:1325–1330.
41. Coenen HH, Klatte B, Knöchel A (1986) Preparation of n.c.a. [17-^{18}F]-fluoroheptadecanoic acid in high yields via aminopolyether supported, nucleophilic fluorination. J Labelled Compd Radiopharm 23:455-466.
42. Hamacher K, Coenen HH, Stöcklin G (1986) Efficient stereospecific synthesis of no-carrier-added 2-[^{18}F]fluoro-2-deoxy-D-glucose using aminopolyether supported nucleophilic substitution. J Nucl Med 27:235-238.
43. De Ruysscher D, Haustermans K, Thorwarth D (2016) FDG and Beyond In: Baumann M, Krause M, Cordes N (ed) Molecular Radio-Oncology Springer Berlin Heidelberg: Berlin, Heidelberg pp 163-173.
44. Hamacher K, Blessing G, Nebeling B (1990) Computer-aided synthesis (CAS) of no-carrier-added 2-[^{18}F]Fluoro-2-deoxy-D-glucose: an efficient automated system for the aminopolyether-supported nucleophilic fluorination. Appl Rad Isot 41:49-55.
45. Krasikova R (2007) Synthesis modules and automation in F-18 labeling In: Schubiger P A, Lehmann L, Friebe M (ed) PET Chemistry: The Driving Force in Molecular Imaging. Ernst Schering Research Foundation Workshop 62 pp 289-316.
46. Cai L, Lu S, Pike VW (2008) Chemistry with [^{18}F]fluoride ion. Eur J Org Chem:2853-2873.
47. Roeda D, Dollé F (2010) Aliphatic nucleophilic radiofluorination. Curr Radiopharm 3:81-108.
48. Attiná M, Cacace F, Wolf AP (1983) Displacement of a nitro-group by [^{18}F]fluoride ion. A new route to aryl fluorides of high specific activity. J Chem Soc Chem Commun:108-109.
49. Lu S, Lepore SD, Song YL, Mondal D, Cohn PC, Bhunia AK, Pike VW (2009) Nucleophile assisting leaving groups: A strategy for aliphatic ^{18}F-fluorination. J Org Chem 74:5290-5296.
50. Richarz R, Krapf P, Zarrad F, Urusova EA, Neumaier B, Zlatopolskiy BD (2014) Neither azeotropic drying, nor base nor other additives: a minimalist approach to ^{18}F-labeling. Org Biomol Chem 12:8094-8099.
51. Zischler J, Krapf P, Richarz R, Zlatopolskiy BD, Neumaier B (2016) Automated synthesis of 4-[^{18}F]fluoroanisole, [^{18}F]DAA1106 and 4-[^{18}F]FPhe using Cu-mediated radiofluorination under “minimalist” conditions. Appl Rad Isot 115:133-137.
52. Kim DW, Ahn D-S, Oh Y-H, Lee S, Kil HS, Oh SJ, Lee SJ, Kim JS, Ryu JS, Moon DH, Chi DY (2006) A New Class of SN2 Reactions Catalyzed by Protic Solvents: Facile Fluorination for Isotopic Labeling of Diagnostic Molecules. J Am Chem Soc 128:16394-16397.
53. Kim DW, Jeong, Lim ST, Sohn M-H, Katzenellenbogen JA, Chi DY (2008) Facile Nucleophilic Fluorination Reactions Using tert-Alcohols as a Reaction Medium: Significantly Enhanced Reactivity of Alkali Metal Fluorides and Improved Selectivity. J Org Chem 73:957-962.
54. Pfeifer L, Engle KM, Pidgeon GW, Sparkes HA, Thompson AL, Brown JM, Gouverneur V (2016) Hydrogen-Bonded Homoleptic Fluoride–Diarylurea Complexes: Structure, Reactivity, and Coordinating Power. J Am Chem Soc 138:13314-13325.
55. He P, Haswell SJ, Pamme N, Archibald SJ (2014) Advances in processes for PET radiotracer synthesis: Separation of [^{18}F]fluoride from enriched [^{18}O]water. Appl Rad Isot 91:64-70.
56. Pascali G, Matesic L, Collier TL, Wyatt N, Fraser BH, Pham TQ, Salvadori PA, Greguric I (2014) Optimization of nucleophilic ^{18}F radiofluorinations using a microfluidic reaction approach. Nat Protoc 9:2017-2029.
57. De Leonardis F, Pascali G, Salvadori PA, Watts P, Pamme N (2011) On-chip pre-concentration and complexation of [^{18}F]fluoride ions via regenerable anion exchange particles for radiochemical synthesis of Positron Emission Tomography tracers. J Chromatogr A 1218:4714-4719.
58. Lee SJ, Oh SJ, Chi DY, Moon DH, Ryu JS (2012) High yielding [^{18}F]fluorination method by fine control of the base. Bull Korean Chem Soc 33:2177-2180.
59. Seo JW, Lee BS, Lee SJ, Oh SJ, Chi DY (2011) Fast and easy drying method for the preparation of activated [^{18}F]fluoride using polymer cartridge. Bull Korean Chem Soc 32:71-76.
60. Mossine AV, Brooks AF, Ichiishi N, Makaravage KJ, Sanford MS, Scott PJH (2017) Development of Customized [^{18}F]Fluoride Elution Techniques for the Enhancement of Copper-Mediated Late-Stage Radiofluorination. Sci Rep 7.

61. Iwata R, Pascali C, Terasaki K, Ishikawa Y, Furumoto S, Yanai K (2017) Minimization of the amount of Kryptofix 222 - $KHCO_3$ for applications to microscale ^{18}F-radiolabeling. Appl Rad Isot 125:113-118.

62. Toorongian SA, Mulholland GK, Jewett DM, Bachelor MA, Kilbourn MR (1990) Routine production of 2-deoxy-2-[^{18}F]fluoro-d-glucose by direct nucleophilic exchange on a quaternary 4-aminopyridinium resin. Nucl Med Biol 17:273-279.

63. Mathiessen B, Zhuravlev F (2013) Automated Solid-Phase Radiofluorination Using Polymer-Supported Phosphazenes. Molecules 18:10531-10547.

64. Sergeev ME, Morgia F, Lazari M, Wang C, van Dam RM (2015) Titania-Catalyzed Radiofluorination of Tosylated Precursors in Highly Aqueous Medium. J Am Chem Soc 137:5686-5694.

65. Wessmann SH, Henriksen G, Wester HJ (2012) Cryptate mediated nucleophilic ^{18}F-fluorination without azeotropic drying. NuklearMedizin 51:1-8.

66. Kostikov AP, Chin J, Orchowski K, Niedermoser S, Kovacevic MM, Aliaga A, Jurkschat K, Wängler B, Wängler C, Wester HJ, Schirrmacher R (2012) Oxalic Acid Supported Si-^{18}F-Radiofluorination: One-Step Radiosynthesis of N-Succinimidyl 3-(Di-tert-butyl [^{18}F]fluorosilyl) benzoate ([^{18}F]SiFB) for Protein Labeling. Bioconjugate Chem 23:106-114.

67. Mathiessen B, Jensen M, Zhuravlev F (2011) [^{18}F]Fluoride recovery via gaseous [^{18}F]HF. J Labelled Compd Radiopharm 54:816-818.

68. Lemaire CF, Aerts JJ, Voccia S, Libert LC, Mercier F, Goblet D, Plenevaux AR, Luxen AJ (2010) Fast Production of Highly Reactive No-Carrier-Added [^{18}F]Fluoride for the Labeling of Radiopharmaceuticals. Ang Chem Int Ed 49:3161-3164.

69. Friebe M, Graham K, Berndt M, Schmitt-Willich H (2010) Process for production of radiopharmaceuticals. Patent WO2010/003548 A1.

70. Aerts J, Voccia S, Lemaire C, Giacomelli F, Goblet D, Thonon D, Plenevaux A, Warnock G, Luxen A (2010) Fast production of highly concentrated reactive [^{18}F]fluoride for aliphatic and aromatic nucleophilic radiolabelling. Tetrahedron Lett 51:64-66.

71. Brichard L, Aigbirhio F (2014) An Efficient Method for Enhancing the Reactivity and Flexibility of [^{18}F]Fluoride Towards Nucleophilic Substitution Using Tetraethylammonium Bicarbonate. Eur J Org Chem 2014:6145-6149.

72. Kim DW, Choe YS, Chi DY (2003) A new nucleophilic fluorine-18 labeling method for aliphatic mesylates: reaction in ionic liquids shows tolerance for water. Nucl Med Biol 30:345-350.

73. Lindner S, Rensch C, Neubaur S, Neumeier M, Salvamoser R, Samper V, Bartenstein P (2016) Azeotropic drying free [^{18}F]FDG synthesis and its application to a lab-on-chip platform. Chem Comm 52:729-732.

74. Kniess T, Laube M, Steinbach J (2017) “Hydrous ^{18}F-fluoroethylation” – Leaving off the azeotropic drying. Appl Rad Isot 127:260-268.

75. Chun J-H, Telu S, Lu S, Pike VW (2013) Radiofluorination of diaryliodonium tosylates under aqueous-organic and cryptand-free conditions. Org Biomol Chem 11:5094-5099.

76. Klenner MA, Pascali G, Zhang B, Sia TR, Spare LK, Krause-Heuer AM, Aldrich-Wright JR, Greguric I, Guastella AJ, Massi M, Fraser BH (2017) A Fluorine-18 Radiolabeling Method Enabled by Rhenium(I) Complexation Circumvents the Requirement of Anhydrous Conditions. Chem Eur J 23:6499-6503.

77. Zischler J, Kolks N, Modemann D, Neumaier B, Zlatopolskiy BD (2017) Alcohol-Enhanced Cu-Mediated Radiofluorination. Chem Eur J 23:3251-3256.

78. Hamacher K, Hirschfelder T, Coenen HH (2002) Electrochemical cell for separation of [^{18}F]fluoride from irradiated ^{18}O-water and subsequent no carrier added nucleophilic fluorination. Appl Rad Isot 56:519-523.

79. Kügler F, Roehrens D, Stumpf M, Drerup C, Ermert J, Hamacher K, Coenen HH (2014) Optimizing the transfer of [^{18}F]fluoride from aqueous to organic solvents by electrodeposition using carbon electrodes. Appl Rad Isot 91:1-7.

80. Sadeghi S, Liang V, Cheung S, Woo S, Wu C, Ly J, Deng Y, Eddings M, van Dam RM (2013) Reusable electrochemical cell for rapid separation of [^{18}F]fluoride from [^{18}O]water for flow-through synthesis of ^{18}F-labeled tracers. Appl Rad Isot 75:85-94.

81. Saiki H, Iwata R, Nakanishi H, Wong R, Ishikawa Y, Furumoto S, Yamahara R, Sakamoto K, Ozeki E (2010) Electrochemical concentration of no-carrier-added [^{18}F]fluoride from [^{18}O]water in a disposable microfluidic cell for radiosynthesis of ^{18}F-labeled radiopharmaceuticals. Appl Rad Isot 68:1703-1708.

82. Wester HJ, Herz M, Weber W, Heiss P, Senekowitsch-Schmidtke R, Schwaiger M, Stöcklin G (1999) Synthesis and radiopharmacology of O-(2-[^{18}F]fluoroethyl)-L-tyrosine for tumor imaging. J Nucl Med 40:205-212.
83. Zuhayra M, Alfteimi A, Forstner CV, Lützen U, Meller B, Henze E (2009) New approach for the synthesis of [^{18}F]fluoroethyltyrosine for cancer imaging: Simple, fast, and high yielding automated synthesis. Bioorg Med Chem 17:7441-7448.
84. Mueller D, Klette I, Kalb F, Baum RP (2011) Synthesis of O-(2-[^{18}F]fluoroethyl)-L-tyrosine based on a cartridge purification method. Nucl Med Biol 38:653-658.
85. Langen K-J, Hamacher K, Weckesser M, Floeth F, Stoffels G, Bauer D, Coenen HH, Pauleit D (2006) O-(2-[^{18}F]fluoroethyl)-l-tyrosine: uptake mechanisms and clinical applications. Nucl Med Biol 33:287-294.
86. Bourdier T, Greguric I, Roselt P, Jackson T, Faragalla J, Katsifis A (2011) Fully automated one-pot radiosynthesis of O-(2-[^{18}F]fluoroethyl)-L-tyrosine on the TracerLab FXFN module. Nucl Med Biol 38:645-651.
87. Fedorova O, Kuznetsova O, Stepanova M, Maleev V, Belokon Y, Wester H-J, Krasikova R (2014) A facile direct nucleophilic synthesis of O-(2-[^{18}F]fluoroethyl)-l-tyrosine ([^{18}F]FET) without HPLC purification. J Radioanal Nucl Chem 301:505-512.
88. Topley AC, Isoni V, Logothetis TA, Wynn D, Wadsworth H, Gibson AMR, Khan I, Wells NJ, Perrio C, Brown RCD (2013) A Resin-Linker-Vector Approach to Radiopharmaceuticals Containing ^{18}F: Application in the Synthesis of O-(2-[^{18}F]Fluoroethyl)-L-tyrosine. Chem Eur J 19:1720-1725.
89. Been LB, Suurmeijer AJH, Cobben DCP, Jager PL, Hoekstra HJ, Elsinga PH (2004) [^{18}F]FLT-PET in oncology: current status and opportunities. Eur J Nucl Med Mol Imaging 31:1659-1672.
90. Wilson IK, Chatterjee S, Wolf W (1991) Synthesis of 3′-fluoro-3′-deoxythymidine and studies of its ^{18}F-radiolabeling, as a tracer for the noninvasive monitoring of the biodistribution of drugs against AIDS. J Fluor Chem 55:283-289.
91. Grierson JR, Shields AF, Eary JF (1997) Development of a radiosynthesis for 3′-[^{18}F]fluoro-3′-deoxy-nucleosides. J Labelled Compd Radiopharm 40:60-62.
92. Alauddin MM (2013) Nucleoside-based probes for imaging tumor proliferation using positron emission tomography. J Labelled Compd Radiopharm 56:237-243.
93. Meyer J-P, Probst KC, Westwell AD (2014) Radiochemical synthesis of 2′-[^{18}F]-labelled and 3′-[^{18}F]-labelled nucleosides for positron emission tomography imaging. J Labelled Compd Radiopharm 57:333-337.
94. Machulla H-J, Blocher A, Kuntzsch M, Piert M, Wei R, Grierson JR (2000) Simplified Labeling Approach for Synthesizing 3′-Deoxy-3′-[^{18}F]fluorothymidine ([^{18}F]FLT). J Radioanal Nucl Chem 243:843-846.
95. Wodarski C, Eisenbarth J, Weber K, Henze M, Haberkorn U, Eisenhut M (2000) Synthesis of 3′-deoxy-3′-[^{18}F]fluoro-thymidine with 2,3′-anhydro-5′-O-(4,4′-dimethoxytrityl)-thymidine. J Labelled Compd Radiopharm 43:1211-1218.
96. Grierson JR, Shields AF (2000) Radiosynthesis of 3′-deoxy-3′-[^{18}F]fluorothymidine: [^{18}F]FLT for imaging of cellular proliferation in vivo. Nucl Med Biol 27:143-156.
97. Reischl G, Blocher A, Wei RQ, Ehrlichmann W, Kuntzch M, Solbach C, Dohmen BM, Machulla HJ (2006) Simplified, automated synthesis of 3'[^{18}F]fluoro-3'-deoxy-thymidine ([^{18}F]FLT) and simple method for a metabolite analysis in plasma. Radiochim Acta 94:447-451.
98. Yun M, Oh SJ, Ha H-J, Ryu JS, Moon DH (2003) High radiochemical yield synthesis of 3′-deoxy-3′-[^{18}F]fluorothymidine using (5′-O-dimethoxytrityl-2′-deoxy-3′-O-nosyl-β-D-threo pentofuranosyl)thymine and its 3-N-BOC-protected analogue as a labeling precursor. Nucl Med Biol 30:151-157.
99. Martin SJ, Eisenbarth JA, Wagner-Utermann U, Mier W, Henze M, Pritzkow H, Haberkorn U, Eisenhut M (2002) A new precursor for the radiosynthesis of [^{18}F]FLT. Nucl Med Biol 29:263-273.
100. Oh SJ, Mosdzianowski C, Chi DY, Kim JY, Kang SH, Ryu JS, Yeo JS, Moon DH (2004) Fully automated synthesis system of 3′-deoxy-3′-[^{18}F]fluorothymidine. Nucl Med Biol 31:803-809.
101. Teng B, Wang S, Fu Z, Dang Y, Wu Z, Liu L (2006) Semiautomatic synthesis of 3′-deoxy-3′-[^{18}F]fluorothymidine using three precursors. Appl Rad Isot 64:187-193.
102. Suehiro M, Vallabhajosula S, Goldsmith SJ, Ballon DJ (2007) Investigation of the role of the base in the synthesis of [^{18}F]FLT. Appl Rad Isot 65:1350-1358.

103. Marchand P, Ouadi A, Pellicioli M, Schuler J, Laquerriere P, Boisson F, Brasse D (2016) Automated and efficient radiosynthesis of [^{18}F]FLT using a low amount of precursor. Nucl Med Biol 43:520-527.

104. Pascali C, Bogni A, Fugazza L, Cucchi C, Crispu O, Laera L, Iwata R, Maiocchi G, Crippa F, Bombardieri E (2012) Simple preparation and purification of ethanol-free solutions of 3′-deoxy-3′-[^{18}F]fluorothymidine by means of disposable solid-phase extraction cartridges. Nucl Med Biol 39:540-550.

105. Cheung Y-Y, Nickels ML, McKinley ET, Buck JR, Manning HC (2015) High-yielding, automated production of 3′-deoxy-3′-[^{18}F]fluorothymidine using a modified Bioscan Coincidence FDG reaction module. Appl Rad Isot 97:47-51.

106. Lee SJ, Oh SJ, Chi DY, Kil HS, Kim EN, Ryu JS, Moon DH (2007) Simple and highly efficient synthesis of 3'-deoxy-3'-[^{18}F]fluorothymidine using nucleophilic fluorination catalyzed by protic solvent. Eur J Nucl Med Mol Imaging 34:1406-1409.

107. Liu W, Huang X, Placzek MS, Krska SW, McQuade P, Hooker JM, Groves JT (2018) Site-selective ^{18}F fluorination of unactivated C-H bonds mediated by a manganese porphyrin. Chem Sci 9:1168-1172.

108. Coenen HH, Ermert J (2010) Direct nucleophilic ^{18}F-fluorination of electron rich arenes: Present limits of no-carrier-added reactions. Curr Radiopharm 3:163-173.

109. Elmenhorst D, Kroll T, Matusch A, Bauer A (2012) Sleep Deprivation Increases Cerebral Serotonin 2A Receptor Binding in Humans. Sleep 35:1615-1623.

110. Quednow BB, Treyer V, Hasler F, Dörig N, Wyss MT, Burger C, Rentsch KM, Westera G, Schubiger PA, Buck A, Vollenweider FX (2012) Assessment of serotonin release capacity in the human brain using dexfenfluramine challenge and [^{18}F]altanserin positron emission tomography. NeuroImage 59:3922-3932.

111. Lemaire C, Cantineau R, Guillaume M, Plenevaux A, Christiaens L (1991) Fluorine-18-altanserin: A radioligand for the study of serotonin receptors with PET: Radiolabeling and in vivo biologic behavior in rats. J Nucl Med 32:2266-2272.

112. Hamacher K, Coenen HH (2006) No-carrier-added nucleophilic ^{18}F-labelling in an electrochemical cell exemplified by the routine production of [^{18}F]altanserin. Appl Rad Isot 64:989-994.

113. Ermert J, Coenen HH (2010) Nucleophilic ^{18}F-fluorination of complex molecules in activated carbocyclic aromatic position. Curr Radiopharm 3:109-126.

114. Hasler F, Kuznetsova OF, Krasikova RN, Cservenyak T, Quednow BB, Vollenweider FX, Ametamey SM, Westera G (2009) GMP-compliant radiosynthesis of [^{18}F]altanserin and human plasma metabolite studies. Appl Rad Isot 67:598-601.

115. Hayashi K, Furutsuka K, Ito T, Muto M, Aki H, Fukumura T, Suzuki K (2012) Fully automated synthesis and purification of 4-(2′-methoxyphenyl)-1-[2′-(N-2″-pyridinyl)-p-[^{18}F]fluorobenzamido]ethylpiperazine. J Labelled Compd Radiopharm 55:120-124.

116. Le Bars D, Lemaire C, Ginovart N, Plenevaux A, Aerts J, Brihaye C, Hassoun W, Leviel V, Mekhsian P, Weissmann D, Pujol JF, Luxen A, Comar D (1998) High-yield radiosynthesis and preliminary in vivo evaluation of p-[^{18}F]MPPF, a fluoro analog of WAY-100635. Nucl Med Biol 25:343-350.

117. Broggini G, Orlandi M, Turconi A, Zoni C (2003) A new synthesis of flumazenil suitable for fluorine-18 labeling. Organic Preparations and Procedures International 35:609-613.

118. Nasirzadeh M, Vaulina DD, Kuznetsova OF, Gomzina NA (2016) A novel approach to the synthesis of [^{18}F]flumazenil, a radioligand for PET imaging of central benzodiazepine receptors. Russian Chemical Bulletin 65:794-800.

119. Ryzhikov NN, Seneca N, Krasikova RN, Gomzina NA, Shchukin E, Fedorova OS, Vassiliev DA, Gulyás B, Hall H, Savic I, Halldin C (2005) Preparation of highly specific radioactivity [^{18}F]flumazenil and its evaluation in cynomolgus monkey by positron emission tomography. Nucl Med Biol 32:109-116.

120. Dollé F (2005) Fluorine-18-labelled fluoropyridines: Advances in radiopharmaceutical design. Curr Pharm Des 11:3221-3235.

121. Dollé F (2007) [^{18}F]Fluoropyridines: From conventional radiotracers to the labeling of macromolecules such as proteins and oligonucleotides In: Schubiger P A, Lehmann L, Friebe M (ed) PET Chemistry: The Driving Force in Molecular Imaging. Ernst Schering Research Foundation Workshop 62 pp 113-157.

122. Ding YS, Liang F, Fowler JS, Kuhar MJ, Carroll FI (1997) Synthesis of [^{18}F]norchlorofluoroepibatidine and its N-methyl derivative: New PET ligands for mapping nicotinic acetylcholine receptors. J Labelled Compd Radiopharm 39:827-832.
123. Dollé F, Valette H, Bottlaender M, Hinnen F, Vaufrey F, Guenther I, Crouzel C (1998) Synthesis of 2-[^{18}F]fluoro-3-[2(S)-2-azetidinylmethoxy]pyridine, a highly potent radioligand for in vivo imaging central nicotinic acetylcholine receptors. J Labelled Compd Radiopharm 41:451-463.
124. Ding YS, Liu N, Wang T, Marecek J, Garza V, Ojima I, Fowler JS (2000) Synthesis and evaluation of 6-[^{18}F]fluoro-3-(2(S)-azetidinylmethoxy)pyridine as a PET tracer for nicotinic acetylcholine receptors. Nucl Med Biol 27:381-389.
125. Brust P, Patt JT, Deuther-Conrad W, Becker G, Patt M, Schildan A, Sorger D, Kendziorra K, Meyer P, Steinbach J, Sabri O (2008) In vivo measurement of nicotinic acetylcholine receptors with [^{18}F]norchloro-fluoro-homoepibatidine. Synapse 62:205-218.
126. Easwaramoortry B, Pichika R, Collins D, Potkin SG, Leslie FM, Mukherjee J (2007) Effect of acetylcholinesterase inhibitors on the binding of nicotinic α4β2 receptor PET radiotracer, ^{18}F-nifene: A measure of acetylcholine competition. Synapse 61:29-36.
127. Pichika R, Easwaramoorthy B, Collins D, Christian BT, Shi B, Narayanan TK, Potkin SG, Mukherjee J (2006) Nicotinic $\alpha_4\beta_2$ receptor imaging agents: Part II. Synthesis and biological evaluation of 2-[^{18}F]fluoro-3-[2-((S)-3-pyrrolinyl)methoxy]pyridine (^{18}F-nifene) in rodents and imaging by PET in nonhuman primate. Nucl Med Biol 33:295-304.
128. Ermert J, Coenen HH (2010) No-carrier-added [^{18}F]fluorobenzene derivatives as intermediates for built-up radiosyntheses. Curr Radiopharm 3:127-160.
129. Lemaire C, Guillaume M, Cantineau R, Christiaens L (1990) No-Carrier-Added Regioselective Preparation of 6-[^{18}F]Fluoro-L-Dopa. J Nucl Med 31:1247-1251.
130. Lemaire C, Damhaut P, Plenevaux A, Comar D (1994) Enantioselective synthesis of 6-[fluorine-18]-fluoro-L-dopa from no- carrier-added fluorine-18-fluoride. J Nucl Med 35:1996-2002.
131. Lemaire C, Gillet S, Guillouet S, Plenevaux A, Aerts J, Luxen A (2004) Highly enantioselective synthesis of no-carrier-added 6-[^{18}F]fluoro-L-dopa by chiral phase-transfer alkylation. Eur J Org Chem:2899-2904.
132. Libert LC, Franci X, Plenevaux AR, Ooi T, Maruoka K, Luxen AJ, Lemaire CF (2013) Production at the curie level of no-carrier-added 6-^{18}F-fluoro- l-dopa. J Nucl Med 54:1154-1161.
133. Wagner FM, Ermert J, Coenen HH (2009) Three-Step, "One-Pot" Radiosynthesis of 6-Fluoro-3,4-Dihydroxy-L-Phenylalanine by Isotopic Exchange. J Nucl Med 50:1724-1729.
134. Castillo Meleán J, Ermert J, Coenen HH (2011) Enantiospecific synthesis of 2-[^{18}F]fluoro-L-phenylalanine and 2-[^{18}F]fluoro-L-tyrosine by isotopic exchange. Org Biomol Chem 9:765-769.
135. Castillo Meleán J, Humpert S, Ermert J, Coenen HH (2015) Stereoselective radiosynthesis of L- and D-3-[^{18}F]fluoro-α-methyltyrosine. J Fluor Chem 178:202-207.
136. Martin R, Baumgart D, Hubner S, Juttler S, Saul S, Clausnitzer A, Mollitor J, Smits R, Höpping A, Müller M (2013) Automated nucleophilic one-pot synthesis of ^{18}F-L-DOPA with high specific activity using the GE TRACERlab MXFDG. J Labelled Compd Radiopharm 56:S126-S126.
137. Pretze M, Franck D, Kunkel F, Foßhag E, Wängler C, Wängler B (2017) Evaluation of two nucleophilic syntheses routes for the automated synthesis of 6-[^{18}F]fluoro-L-DOPA. Nucl Med Biol 45:35-42.
138. Pike VW, Aigbirhio FI (1995) Reactions of cyclotron-produced [^{18}F]fluoride with diaryliodonium salts - A novel single-step route to no-carrier-added [^{18}]fluoroarenes. J Chem Soc Chem Commun:2215-2216.
139. Pike VW (2018) Hypervalent aryliodine compounds as precursors for radiofluorination. J Labelled Compd Radiopharm 61:196– 227.
140. Mu L, Fischer CR, Holland JP, Becaud J, Schubiger PA, Schibli R, Ametamey SM, Graham K, Stellfeld T, Dinkelborg LM, Lehmann L (2012) ^{18}F-radiolabeling of aromatic compounds using triarylsulfonium salts. Eur J Org Chem:889-892.
141. Ermert J, Hocke C, Ludwig T, Gail R, Coenen H (2004) Comparison of pathways to the versatile synthon of no-carrier-added 1-bromo-4-[^{18}F]fluorobenzene. J Labelled Compd Radiopharm 47:429-441.
142. Wüst FR, Kniess T (2003) Synthesis of 4-[^{18}F]fluoroiodobenzene and its application in Sonogashira cross-coupling reactions. J Labelled Compd Radiopharm 46:699-713.

143. Ross TL, Ermert J, Hocke C, Coenen HH (2007) Nucleophilic ^{18}F-Fluorination of heteroaromatic iodonium salts with no-carrier-added [^{18}F]Fluoride. J Am Chem Soc 129:8018-8025.
144. Way J, Bouvet V, Wuest F (2013) Synthesis of 4-[^{18}F]fluorohalobenzenes and Palladium-mediated Cross-coupling Reactions for the Synthesis of ^{18}F-labeled Radiotracers. Curr Org Chem 17:2138-2152.
145. Way JD, Wuest F (2014) Automated radiosynthesis of no-carrier-added 4-[^{18}F]fluoroiodobenzene: a versatile building block in ^{18}F radiochemistry. J Labelled Compd Radiopharm 57:104-109.
146. Yoshimura A, Zhdankin VV (2016) Advances in Synthetic Applications of Hypervalent Iodine Compounds. Chem Rev 116:3328-3435.
147. Wang B, Qin L, Neumann KD, Uppaluri S, Cerny RL, DiMagno SG (2010) Improved Arene Fluorination Methodology for I(III) Salts. Org Lett 12:3352-3355.
148. Hu B, Vāvere AL, Neumann KD, Shulkin BL, DiMagno SG, Snyder SE (2015) A Practical, Automated Synthesis of meta-[^{18}F]Fluorobenzylguanidine for Clinical Use. ACS Chem Neurosci 6:1870-1879.
149. Linstad EJ, Vavere AL, Hu B, Kempinger JJ, Snyder SE, DiMagno SG (2017) Thermolysis and radiofluorination of diaryliodonium salts derived from anilines. Org Biomol Chem 15:2246-2252.
150. Petersen IN, Villadsen J, Hansen HD, Madsen J, Jensen AA, Gillings N, Lehel S, Herth MM, Knudsen GM, Kristensen JL (2017) ^{18}F-Labelling of electron rich iodonium ylides: application to the radiosynthesis of potential 5-HT$_{2A}$ receptor PET ligands. Org Biomol Chem 15:4351-4358.
151. Cardinale J, Ermert J, Humpert S, Coenen HH (2014) Iodonium ylides for one-step, no-carrier-added radiofluorination of electron rich arenes, exemplified with 4-(([^{18}F]fluorophenoxy)-phenylmethyl) piperidine NET and SERT ligands. RSC Adv 4:17293-17299.
152. Rotstein BH, Stephenson NA, Vasdev N, Liang SH (2014) Spirocyclic hypervalent iodine(III)-mediated radiofluorination of non-activated and hindered aromatics. Nat Commun 5:4365.
153. Rotstein BH, Wang L, Liu RY, Patteson J, Kwan EE, Vasdev N, Liang SH (2016) Mechanistic studies and radiofluorination of structurally diverse pharmaceuticals with spirocyclic iodonium(III) ylides. Chem Sci 7:4407-4417.
154. Ichiishi N, Brooks AF, Topczewski JJ, Rodnick ME, Sanford MS, Scott PJH (2014) Copper-catalyzed [^{18}F]fluorination of (Mesityl)(aryl)iodonium salts. Org Lett 16:3224-3227.
155. McCammant MS, Thompson S, Brooks AF, Krska SW, Scott PJH, Sanford MS (2017) Cu-Mediated C–H ^{18}F-Fluorination of Electron-Rich (Hetero)arenes. Org Lett 19:3939-3942.
156. Stephenson NA, Holland JP, Kassenbrock A, Yokell DL, Livni E, Liang SH, Vasdev N (2015) Iodonium Ylide-Mediated Radiofluorination of ^{18}F-FPEB and Validation for Human Use. J Nucl Med 56:489-492.
157. Zlatopolskiy BD, Zischler J, Krapf P, Zarrad F, Urusova EA, Kordys E, Endepols H, Neumaier B (2015) Copper-Mediated Aromatic Radiofluorination Revisited: Efficient Production of PET Tracers on a Preparative Scale. Chem Eur J 21:5972-5979.
158. Moon B, Park J, Lee H, Lee B, Kim S (2014) Routine Production of [^{18}F]Flumazenil from Iodonium Tosylate Using a Sample Pretreatment Method: a 2.5-Year Production Report. Mol Imaging Biol 16:619-625.
159. Warnier C, Lemaire C, Becker G, Zaragoza G, Giacomelli F, Aerts J, Otabashi M, Bahri MA, Mercier J, Plenevaux A, Luxen A (2016) Enabling Efficient Positron Emission Tomography (PET) Imaging of Synaptic Vesicle Glycoprotein 2A (SV2A) with a Robust and One-Step Radiosynthesis of a Highly Potent 18F-Labeled Ligand ([18F]UCB-H). J Med Chem 59:8955-8966.
160. Beyzavi MH, Mandal D, Strebl MG, Neumann CN, D'Amato EM, Chen J, Hooker JM, Ritter T (2017) ^{18}F-Deoxyfluorination of Phenols via Ru π-Complexes. ACS Cent Sci 3:944-948.
161. Strebl MG, Campbell AJ, Zhao W-N, Schroeder FA, Riley MM, Chindavong PS, Morin TM, Haggarty SJ, Wagner FF, Ritter T, Hooker JM (2017) HDAC6 Brain Mapping with [^{18}F]Bavarostat Enabled by a Ru-Mediated Deoxyfluorination. ACS Cent Sci 3:1006-1014.
162. Narayanam MK, Ma G, Champagne PA, Houk KN, Murphy JM (2017) Synthesis of [^{18}F]Fluoroarenes by Nucleophilic Radiofluorination of N-Arylsydnones. Ang Chem Int Ed 56:13006-13010.

163. Cardinale J, Ermert J, Kuegler F, Helfer A, Brandt MR, Coenen HH (2012) Carrier-effect on palladium-catalyzed, nucleophilic ^{18}F-fluorination of aryl triflates. J Labelled Compd Radiopharm 55:450-453.
164. Lee E, Kamlet AS, Powers DC, Neumann CN, Boursalian GB, Furuya T, Choi DC, Hooker JM, Ritter T (2011) A fluoride-derived electrophilic late-stage fluorination reagent for PET imaging. Science 334:639-642.
165. Lee E, Hooker JM, Ritter T (2012) Nickel-Mediated Oxidative Fluorination for PET with Aqueous [^{18}F]Fluoride. J Am Chem Soc 134:17456-17458.
166. Zlatopolskiy BD, Zischler J, Urusova EA, Endepols H, Kordys E, Frauendorf H, Mottaghy FM, Neumaier B (2015) A Practical One-Pot Synthesis of Positron Emission Tomography (PET) Tracers via Nickel-Mediated Radiofluorination. ChemistryOpen 4:457-462.
167. Hoover AJ, Lazari M, Ren H, Narayanam MK, Murphy JM, van Dam RM, Hooker JM, Ritter T (2016) A Transmetalation Reaction Enables the Synthesis of [^{18}F]5-Fluorouracil from [^{18}F]Fluoride for Human PET Imaging. Organometallics 35:1008-1014.
168. Tredwell M, Preshlock SM, Taylor NJ, Gruber S, Huiban M, Passchier J, Mercier J, Génicot C, Gouverneur V (2014) A General Copper-Mediated Nucleophilic ^{18}F Fluorination of Arenes. Ang Chem Int Ed 53:7751-7755.
169. Mossine AV, Brooks AF, Makaravage KJ, Miller JM, Ichiishi N, Sanford MS, Scott PJH (2015) Synthesis of [^{18}F]Arenes via the Copper-Mediated [^{18}F]Fluorination of Boronic Acids. Org Lett 17:5780-5783.
170. Makaravage KJ, Brooks AF, Mossine AV, Sanford MS, Scott PJH (2016) Copper-Mediated Radiofluorination of Arylstannanes with [^{18}F]KF. Org Lett 18:5440-5443.
171. Preshlock S, Calderwood S, Verhoog S, Tredwell M, Huiban M, Hienzsch A, Gruber S, Wilson TC, Taylor NJ, Cailly T, Schedler M, Collier TL, Passchier J, Smits R, Mollitor J, Hoepping A, Mueller M, Genicot C, Mercier J, Gouverneur V (2016) Enhanced copper-mediated ^{18}F-fluorination of aryl boronic esters provides eight radiotracers for PET applications. Chem Comm 52:8361-8364.
172. Zhang Z, Lau J, Kuo H-T, Zhang C, Colpo N, Bénard F, Lin K-S (2017) Synthesis and evaluation of ^{18}F-labeled CJ-042794 for imaging prostanoid EP4 receptor expression in cancer with positron emission tomography. Bioorg Med Chem Lett 27:2094-2098.
173. Tang T, Gill HS, Ogasawara A, Tinianow JN, Vanderbilt AN, Williams S-P, Hatzivassiliou G, White S, Sandoval W, DeMent K, Wong M, Marik J (2017) Preparation and evaluation of L- and D-5-[^{18}F]fluorotryptophan as PET imaging probes for indoleamine and tryptophan 2,3-dioxygenases. Nucl Med Biol 51:10-17.
174. Giglio BC, Fei H, Wang M, Wang H, He L, Feng H, Wu Z, Lu H, Z. L (2017) Synthesis of 5-[^{18}F]Fluoro-α-methyl Tryptophan: New Trp Based PET Agents. Theranostics 7:1524-1530.
175. Schäfer D, Weiß P, Ermert J, Castillo Meleán J, Zarrad F, Neumaier B (2016) Preparation of No-Carrier-Added 6-[^{18}F]Fluoro-L-tryptophan via Cu-Mediated Radiofluorination. Eur J Org Chem 2016:4621-4628.
176. Antuganov D, Zykov M, Timofeeva K, Antuganova Y, Orlovskaya V, Krasikova R (2017) Effect of Pyridine Addition on the Efficiency of Copper-Mediated Radiofluorination of Aryl Pinacol Boronates. ChemistrySelect 2:7909-7912.
177. Zarrad F, Zlatopolskiy B, Krapf P, Zischler J, Neumaier B (2017) A Practical Method for the Preparation of ^{18}F-Labeled Aromatic Amino Acids from Nucleophilic [^{18}F]Fluoride and Stannyl Precursors for Electrophilic Radiohalogenation. Molecules 22:2231.
178. Zlatopolskiy BD, Zischler J, Schäfer D, Urusova EA, Guliyev M, Bannykh O, Endepols H, Neumaier B (2018) Discovery of 7-[^{18}F]Fluorotryptophan as a Novel Positron Emission Tomography (PET) Probe for the Visualization of Tryptophan Metabolism in Vivo. J Med Chem 61:189-206.
179. Politis M (2014) Neuroimaging in Parkinson disease: from research setting to clinical practice. Nat Rev Neurol 10:708-722.
180. Lussey-Lepoutre C, Hindié E, Montravers F, Detour J, Ribeiro MJS, Taïeb D, Imperiale A (2016) The current role of ^{18}F-FDOPA PET for neuroendocrine tumor imaging. Med Nucl 40:20-30.
181. Ermert J, Coenen HH (2013) Methods for ^{11}C- and ^{18}F-labelling of amino acids and derivatives for positron emission tomography imaging. J Labelled Compd Radiopharm 56:225-236.
182. Edwards R, Wirth T (2015) [^{18}F]6-fluoro-3,4-dihydroxy- l-phenylalanine – recent modern syntheses for an elusive radiotracer. J Labelled Compd Radiopharm 58:183-187.

183. Forsback S, Eskola O, Haaparanta M, Bergmann J, Solin O (2008) Electrophilic synthesis of 6-[^{18}F]fluoro-L-DOPA using post-target produced [^{18}F]F_2. Radiochim Acta 96:845-848.
184. Kuik WJ, Kema IP, Brouwers AH, Zijlma R, Neumann KD, Dierckx RAJO, DiMagno SG, Elsinga PH (2015) In vivo biodistribution of no-carrier-added 6-^{18}F-fluoro-3, 4-dihydroxy-L-phenylalanine (^{18}F-DOPA), produced by a new nucleophilic substitution approach, compared with carrier-added ^{18}F-DOPA, prepared by conventional electrophilic substitution. J Nucl Med 56:106-112.
185. Kienzle GJ, Reischl G, Machulla HJ (2005) Electrochemical radiofluorination. 3. Direct labeling of phenylalanine derivatives with [^{18}F]fluoride after anodic oxidation. J Labelled Compd Radiopharm 48:259-273.
186. He Q, Wang Y, Alfeazi I, Sadeghi S (2014) Electrochemical nucleophilic synthesis of di-tert-butyl-(4-[^{18}F]fluoro-1,2-phenylene)-dicarbonate. Appl Rad Isot 92:52-57.
187. He Q, Alfeazi I, Sadeghi S (2014) No-carrier-added electrochemical nucleophilic radiofluorination of aromatics. J Radioanal Nucl Chem 303.
188. Lebedev A, Jiao J, Lee JS, Yang F, Allison N, Herschman H, Sadeghi S (2017) Radiochemistry on electrodes: Synthesis of an ^{18}F-labelled and in vivo stable COX-2 inhibitor. Plos One 12:18.
189. Krasikova R (2013) PET Radiochemistry Automation: State of the Art and Future Trends in ^{18}F-nucleophilic Fluorination. Curr Org Chem 17:2097-2107.
190. Anzellotti A, McFarland A, Ferguson D, Olson K (2013) Towards the Full Automation of QC Release Tests for [^{18}F]fluoride-labeled Radiotracers. Curr Org Chem 17:2153-2158.
191. Shao X, Hoareau R, Hockley BG, Tluczek LJM, Henderson BD, Padgett HC, Scott PJH (2011) Highlighting the versatility of the tracerlab synthesis modules. Part 1: fully automated production of ^{18}F-labelled radiopharmaceuticals using a Tracerlab FX_{FN}. J Labelled Compd Radiopharm 54:292-307.
192. Iwata R, Ido T, Takahashi T, Monma M (1984) Automated synthesis system for production of 2-deoxy-2-[^{18}F]fluoro-D-glucose with computer control. Int J Appl Rad Isot 35:445-454.
193. Padgett HC, Schmidt DG, Luxen A, Bida GT, Satyamurthy N, Barrio JR (1989) Computer-controlled radiochemical synthesis: A chemistry process control unit for the automated production of radiochemicals. Int J Appl Radiat Isot 40:433-445.
194. Herman H, Flores G, Quinn K, Eddings M, Olma S, Moore MD, Ding H, Bobinski KP, Wang M, Williams D, Wiliams D, Shen CK-F, Phelps ME, van Dam RM (2013) Plug-and-play modules for flexible radiosynthesis. Appl Rad Isot 78:113-124.
195. Blom E, Koziorowski J (2014) Automated synthesis of [^{18}F]FMISO on IBA Synthera((R)). J Radioanal Nucl Chem 299:265-270.
196. Lee SJ, Hyun JS, Oh SJ, Yu KH, Ryu JS (2013) Development of a new precursor-minimizing base control method and its application for the automated synthesis and SPE purification of ^{18}F-fluoromisonidazole (^{18}F-FMISO). J Labelled Compd Radiopharm 56:731-735.
197. Collins J, Waldmann CM, Drake C, Slavik R, Ha NS, Sergeev M, Lazari M, Shen B, Chin FT, Moore M, Sadeghi S, Phelps ME, Murphy JM, van Dam RM (2017) Production of diverse PET probes with limited resources: 24 ^{18}F-labeled compounds prepared with a single radiosynthesizer. Proc Natl Acad Sci 114:11309-11314.
198. von Guggenberg E, Sader JA, Wilson JS, Shahhosseini S, Koslowsky I, Wuest F, Mercer JR (2009) Automated synthesis of an ^{18}F-labelled pyridine-based alkylating agent for high yield oligonucleotide conjugation. Appl Rad Isot 67:1670-1675.
199. Allott L, Da Pieve C, Turton DR, Smith G (2017) A general [^{18}F]AlF radiochemistry procedure on two automated synthesis platforms. Reaction Chemistry & Engineering 2:68-74.
200. Ackermann U, Yeoh SD, Sachinidis JI, Poniger SS, Scott AM, Tochon-Danguy HJ (2011) A simplified protocol for the automated production of succinimidyl 4-[^{18}F]fluorobenzoate on an IBA Synthera module. J Labelled Compd Radiopharm 54:671-673.
201. Sachinidis J, I. , Poniger S, Tochon-Danguy H, J. (2010) Automation for Optimised Production of Fluorine-18-Labelled Radiopharmaceuticals. Curr Radiopharm 3:248-253.
202. Lazari M, Collins J, Shen B, Farhoud M, Yeh D, Maraglia B, Chin FT, Nathanson DA, Moore M, van Dam RM (2014) Fully Automated Production of Diverse ^{18}F-Labeled PET Tracers on the ELIXYS Multireactor Radiosynthesizer Without Hardware Modification. J Nucl Med Technol 42:203-210.

203. Yao CH, Lin KJ, Weng CC, Hsiao IT, Ting YS, Yen TC, Jan TR, Skovronsky D, Kung MP, Wey SP (2010) GMP-compliant automated synthesis of [^{18}F]AV-45 (Florbetapir F 18) for imaging beta-amyloid plaques in human brain. Appl Rad Isot 68:2293-2297.
204. Liu YJ, Zhu L, Plossl K, Choi SR, Qiao HW, Sun XT, Li S, Zha ZH, Kung HF (2010) Optimization of automated radiosynthesis of [^{18}F]AV-45: a new PET imaging agent for Alzheimer's disease. Nucl Med Biol 37:917-925.
205. Wang HL, Guo XY, Jiang SD, Tang GH (2013) Automated synthesis of [^{18}F]Florbetaben as Alzheimer's disease imaging agent based on a synthesis module system. Appl Rad Isot 71:41-46.
206. Turton DR, Betts HM, Dutton D, Perkins AC (2015) Automated radiosynthesis of GMP quality [^{18}F]HX4 for PET imaging of hypoxia. Nucl Med Biol 42:494-498.
207. Thomae D, Morley TJ, Hamill T, Carroll VM, Papin C, Twardy NM, Lee HS, Hargreaves R, Baldwin RM, Tamagnan G, Alagille D (2014) Automated one-step radiosynthesis of the CB1 receptor imaging agent [^{18}F]MK-9470. J Labelled Compd Radiopharm 57:611-614.
208. Cardinale J, Martin R, Remde Y, Schäfer M, Hienzsch A, Hübner S, Zerges A-M, Marx H, Hesse R, Weber K, Smits R, Hoepping A, Müller M, Neels O, Kopka K (2017) Procedures for the GMP-Compliant Production and Quality Control of [18F]PSMA-1007: A Next Generation Radiofluorinated Tracer for the Detection of Prostate Cancer. Pharmaceuticals 10:77.
209. Rensch C, Jackson A, Lindner S, Salvamoser R, Samper V, Riese S, Bartenstein P, Wängler C, Wängler B (2013) Microfluidics: A groundbreaking technology for PET tracer production? Molecules 18:7930-7956.
210. Pascali G, Salvadori PA (2016) Opportunities and challenges in the utilization of microfluidic technologies to the production of radiopharmaceuticals. Chimica Oggi-Chemistry Today 34:28-32.
211. Elizarov AM (2009) Microreactors for radiopharmaceutical synthesis. Lab Chip 9:1326-1333.
212. Keng PY, van Dam RM (2015) Digital Microfluidics: A New Paradigm for Radiochemistry. Mol Imaging 14:7290.2015.00030.
213. Miller PW, deMello AJ, Gee AD (2010) Application of microfluidics to the ultra-rapid preparation of fluorine-18 labelled compounds. Curr Radiopharm 3:254-262.
214. Wang MW, Lin WY, Liu K, Masterman-Smith M, Shen CKF (2010) Microfluidics for Positron Emission Tomography Probe Development. Mol Imaging 9:175-191.
215. Hargrove K, Jones GB (2014) Accelerated labeling methods and syntheses of radiotracers utilizing microfluidic technology. Curr Radiopharm 7:36-48.
216. Lebedev A, Miraghaie R, Kotta K, Ball CE, Zhang J, Buchsbaum MS, Kolb HC, Elizarov A (2013) Batch-reactor microfluidic device: first human use of a microfluidically produced PET radiotracer. Lab Chip 13:136-145.
217. Lee C-C, Sui G, Elizarov A, Shu CJ, Shin Y-S, Dooley AN, Huang J, Daridon A, Wyatt P, Stout D, Kolb HC, Witte ON, Satyamurthy N, Heath JR, Phelps ME, Quake SR, Tseng H-R (2005) Multistep Synthesis of a Radiolabeled Imaging Probe Using Integrated Microfluidics. Science 310:1793-1796.
218. Wong R, Iwata R, Saiki H, Furumoto S, Ishikawa Y, Ozeki E (2012) Reactivity of electrochemically concentrated anhydrous [^{18}F]fluoride for microfluidic radiosynthesis of ^{18}F-labeled compounds. Appl Rad Isot 70:193-199.
219. Fiel SA, Yang H, Schaffer P, Weng S, Inkster JAH, Wong MCK, Li PCH (2015) Magnetic Droplet Microfluidics as a Platform for the Concentration of [^{18}F]Fluoride and Radiosynthesis of Sulfonyl [^{18}F]Fluoride. Acs Applied Materials & Interfaces 7:12923-12929.
220. Cvetkovic BZ, Lade O, Marra L, Arima V, Rinaldi R, Dittrich PS (2012) Nitrogen supported solvent evaporation using continuous-flow microfluidics. RSC Adv 2:11117-11122.
221. Pascali G, De Simone M, Matesic L, Greguric I, Salvadori PA (2014) Tolerance of Water in Microfluidic Radiofluorinations: A Potential Methodological Shift? J Flow Chem 4:86-91.
222. Pamme N (2007) Continuous flow separations in microfluidic devices. Lab Chip 7:1644-1659.
223. Pascali G, Mazzone G, Saccomanni G, Manera C, Salvadori PA (2010) Microfluidic approach for fast labeling optimization and dose-on-demand implementation. Nucl Med Biol 37:547-555.
224. Tarn MD, Pascali G, De Leonardis F, Watts P, Salvadori PA, Pamme N (2013) Purification of 2-[^{18}F]fluoro-2-deoxy-d-glucose by on-chip solid-phase extraction. J Chromatogr A 1280:117-121.

225. Chao PH, Collins J, Argus JP, Tseng WY, Lee JT, van Dam RM (2017) Automatic concentration and reformulation of PET tracers via microfluidic membrane distillation. Lab Chip 17:1802-1816.
226. Wester HJ, Schoultz BW, Hultsch C, Henriksen G (2009) Fast and repetitive in-capillary production of [^{18}F]FDG. Eur J Nucl Med Mol Imaging 36:653-658.
227. Kimura H, Tomatsu K, Saiki H, Arimitsu K, Ono M, Kawashima H, Iwata R, Nakanishi H, Ozeki E, Kuge Y, Saji H (2016) Continuous-Flow Synthesis of N-Succinimidyl 4-[^{18}F]fluorobenzoate Using a Single Microfluidic Chip. PLOS ONE 11:e0159303.
228. Pascali G, Watts P, Salvadori PA (2013) Microfluidics in radiopharmaceutical chemistry. Nucl Med Biol 40:776-787.
229. Rensch C, Lindner S, Salvamoser R, Leidner S, Bold C, Samper V, Taylor D, Baller M, Riese S, Bartenstein P, Wangler C, Wangler B (2014) A solvent resistant lab-on-chip platform for radiochemistry applications. Lab Chip 14:2556-2564.
230. Koag MC, Kim H-K, Kim AS (2014) Efficient microscale synthesis of [^{18}F]-2-fluoro-2-deoxy-d-glucose. Chem Eng J 258:62-68.
231. Gillies JM, Prenant C, Chimon GN, Smethurst GJ, Perrie W, Hamblett I, Dekker B, Zweit J (2006) Microfluidic reactor for the radiosynthesis of PET radiotracers. Appl Rad Isot 64:325-332.
232. Arima V, Pascali G, Lade O, Kretschmer HR, Bernsdorf I, Hammond V, Watts P, De Leonardis F, Tarn MD, Pamme N, Cvetkovic BZ, Dittrich PS, Vasovic N, Duane R, Jaksic A, Zacheo A, Zizzari A, Marra L, Perrone E, Salvadori PA, Rinaldi R (2013) Radiochemistry on chip: towards dose-on-demand synthesis of PET radiopharmaceuticals. Lab Chip 13:2328-2336.
233. Keng PY, Chen SP, Ding HJ, Sadeghi S, Shah GJ, Dooraghi A, Phelps ME, Satyamurthy N, Chatziioannou AF, Kim CJ, van Dama RM (2012) Micro-chemical synthesis of molecular probes on an electronic microfluidic device. Proc Natl Acad Sci USA 109:690-695.
234. Javed MR, Chen S, Lei J, Collins J, Sergeev M, Kim H-K, Kim C-J, van Dam RM, Keng PY (2014) High yield and high specific activity synthesis of [^{18}F]fallypride in a batch microfluidic reactor for micro-PET imaging. Chem Comm 50:1192-1194.
235. Ungersboeck J, Richter S, Collier L, Mitterhauser M, Karanikas G, Lanzenberger R, Dudczak R, Wadsak W (2012) Radiolabeling of [^{18}F]altanserin — a microfluidic approach. Nucl Med Biol 39:1087-1092.
236. Javed MR, Chen S, Kim HK, Wei L, Czernin J, Kim CJ, van Dam RM, Keng PY (2014) Efficient Radiosynthesis of 3 '-Deoxy-3 '-^{18}F-Fluorothymidine Using Electrowetting-on-Dielectric Digital Microfluidic Chip. J Nucl Med 55:321-328.
237. Koag MC, Kim H-K, Kim AS (2014) Fast and efficient microscale radiosynthesis of 3′-deoxy-3′-[^{18}F]fluorothymidine. J Fluor Chem 166:104-109.
238. Yokell DL, Leece AK, Lebedev A, Miraghaie R, Ball CE, Zhang J, Kolb H, Elizarov A, Mahmood U (2012) Microfluidic single vessel production of hypoxia tracer 1H-1-(3-[^{18}F]-fluoro-2-hydroxy-propyl)-2-nitro-imidazole ([^{18}F]-FMISO). Appl Rad Isot 70:2313-2316.
239. Zheng M-Q, Collier L, Bois F, Kelada OJ, Hammond K, Ropchan J, Akula MR, Carlson DJ, Kabalka GW, Huang Y (2015) Synthesis of [^{18}F]FMISO in a flow-through microfluidic reactor: Development and clinical application. Nucl Med Biol 42:578-584.
240. Liang SH, Yokell DL, Normandin MD, Rice PA, Jackson RN, Shoup TM, Brady TJ, Fakhri GE, Collier TL, Vasdev N (2014) First Human Use of a Radiopharmaceutical Prepared by Continuous-Flow Microfluidic Radiofluorination: Proof of Concept with the Tau Imaging Agent [^{18}F]T807. Mol Imaging 13:7290.2014.00025.
241. Salvadori AP (2008) Radiopharmaceuticals, Drug Development and Pharmaceutical Regulations in Europe. Curr Radiopharm 1:7-11.
242. Ha NS, Sadeghi S, van Dam RM (2017) Recent Progress toward Microfluidic Quality Control Testing of Radiopharmaceuticals. Micromachines 8.
243. Taggart MP, Tarn MD, Esfahani MMN, Schofield DM, Brown NJ, Archibald SJ, Deakin T, Pamme N, Thompson LF (2016) Development of radiodetection systems towards miniaturised quality control of PET and SPECT radiopharmaceuticals. Lab Chip 16:1605-1616.
244. Koziorowski J (2010) A simple method for the quality control of [^{18}F]FDG. Appl Rad Isot 68:1740-1742.
245. Nakao R, Ito T, Yamaguchi M, Suzuki K (2008) Simultaneous analysis of FDG, ClDG and Kryptofix 2.2.2 in [^{18}F]FDG preparation by high-performance liquid chromatography with UV detection. Nucl Med Biol 35:239-244.

246. Mihon M, Tuta CS, Ion AC, Koziorowski J, Niculae D, Lavric V, Draganescu D (2017) INFLUENCE OF THE SEPARATION PARAMETERS APPLIED FOR DETERMINATION OF IMPURITIES FDG AND CLDG. Farmacia 65:153-158.
247. Cheung S, Ly J, Lazari M, Sadeghi S, Keng PY, van Dam RM (2014) The separation and detection of PET tracers via capillary electrophoresis for chemical identity and purity analysis. J Pharm Biomed Anal 94:12-18.
248. Huang Y-Y, Taylor S, Koziorowski J, Chang Y-N, Kao W-H, Tzen K-Y, Shiue C-Y (2016) A two- center study for the quality control of [^{18}F]FDG using FASTlab phosphate cassettes. Ann Nucl Med 30:563-571.
249. Chaly T, Dahl JR (1989) Thin layer chromatographic detection of Kryptofix 2.2.2 in the routine synthesis of [^{18}F]2-fluoro-2-deoxy-d-glucose. Nucl Med Biol 16:385-387.
250. Mock BH, Winkle W, Vavrek MT (1997) A color spot test for the detection of Kryptofix 2.2.2 in [^{18}F]FDG preparations. Nucl Med Biol 24:193-195.
251. Scott PJH, Kilbourn MR (2007) Determination of residual Kryptofix 2.2.2 levels in [^{18}F]-labeled radiopharmaceuticals for human use. Appl Rad Isot 65:1359-1362.
252. Rokka J, Grönroos TJ, Viljanen T, Solin O, Haaparanta-Solin M (2017) HPLC and TLC methods for analysis of [^{18}F]FDG and its metabolites from biological samples. J Chromatogr B 1048:140-149.
253. Ferrieri RA, Schlyer DJ, Alexoff DL, Fowler JS, Wolf AP (1993) Direct analysis of Kryptofix 2.2.2 in ^{18}FDG by gas chromatography using a nitrogen-selective detector. Nucl Med Biol 20:367-369.
254. Ma Y, Huang BX, Channing MA, Eckelman WC (2002) Quantification of Kryptofix 2.2.2 in 2-[^{18}F]FDG and other radiopharmaceuticals by LC/MS/MS. Nucl Med Biol 29:125-129.
255. Anzellotti AI, McFarland AR, Olson KF (2013) A rapid and simple colorimetric test for 2,2,2-cryptand (Kryptofix 2.2.2.) in solution. Anal Methods 5:4317-4320.
256. Campbell MG, Mercier J, Genicot C, Gouverneur V, Hooker JM, Ritter T (2017) Bridging the gaps in F-18 PET tracer development. Nat Chem 9:1-3.
257. Zhang X, Dunlow R, Blackman BN, Swenson RE (2018) Optimization of ^{18}F-Syntheses using ^{19}F-Reagents at Tracer-level Concentrations and LC-MS/MS Analysis: Improved Synthesis of [^{18}F]MDL100907. J Labelled Compd Radiopharm:doi: 10.1002/jlcr.3606.