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Radiosyntheses using Fluorine-18: the Art and Science of Late Stage Fluorination

Erin L. Cole[†], **Megan N. Stewart**[‡], **Ryan Littich**[†], **Raphael Hoareau**[†], and **Peter J. H. Scott**[*,†,‡]

[†]Department of Radiology, University of Michigan Medical School, Ann Arbor, MI, USA

[‡]The Interdepartmental Program in Medicinal Chemistry, The University of Michigan, Ann Arbor, MI, USA

Abstract

Positron (β^+) emission tomography (PE) is a powerful, noninvasive tool for the in vivo, three-dimensional imaging of physiological structures and biochemical pathways. The continued growth of PET imaging relies on a corresponding increase in access to radiopharmaceuticals (biologically active molecules labeled with short-lived radionuclides such as fluorine-18). This unique need to incorporate the short-lived fluorine-18 atom ($t_{1/2}$ = 109.77 min) as late in the synthetic pathway as possible has made development of methodologies that enable rapid and efficient late stage fluorination an area of research within its own right. In this review we describe strategies for radiolabeling with fluorine-18, including classical fluorine-18 radiochemistry and emerging techniques for late stage fluorination reactions, as well as labeling technologies such as microfluidics and solid-phase radiochemistry. The utility of fluorine-18 labeled radiopharmaceuticals is showcased through recent applications of PET imaging in the healthcare, personalized medicine and drug discovery settings.

Keywords

fluorine-18; radiochemistry; radiopharmaceutical synthesis; PET imaging; positron emission tomography

1. Introduction

1.1 General Introduction

With the discovery of X-rays in 1895 by Wilhelm Röntgen, the field of diagnostic radiology emerged. Today medical professionals still utilize X-rays in addition to modern computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US) to yield structural information and diagnose various medical conditions. However, whilst these techniques provide valuable anatomical information, they provide little functional information about complex biological systems. In order to visualize a particular biological

[*]pjhscott@umich.edu, tel. +1(734)615-1756, fax +1(734)615-2557.

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structure or metabolic process, targeted probes consisting of a receptor ligand attached to a reporter group provide more detail. Fluorescent reporter groups are utilized best for cellular and small animal imaging due to poor tissue depth penetration [1, 2], while radioactive tracers for positron (β^+) emission tomography (PET) and single-photon emission computed tomography (SPECT) have achieved routine clinical usage [3]. Development of new imaging probes is not trivial and a rapidly expanding area of research. Application of PET tracers for use in oncology, neurology, psychiatry, and cardiology continues to expand and is moving us to an age of truly personalized medicine (recent reviews: [4, 5]). More recently, in the pharmaceutical industry setting, PET has been used to provide a wealth of information for drug development including data on target engagement, as well as pharmacokinetic and pharmacodynamic properties of drug candidates (recent reviews: [6]).

PET has many advantages in that of sensitivity by approximately two to three order of magnitude over that of SPECT [7]. Also PET imaging allows one to obtain quantitative 2D and 3D biochemical and physiological information through the use of positron emitting radioelements such as ^{11}C, ^{13}N, ^{15}O, and ^{18}F (Table 1). Each have relative low molecular weights and can label molecules of interest with little or no change in biological activity from their non-labeled counterparts. PET radionuclides decay by positron emission, and in the case of fluorine-18, it decays to oxygen-18 releasing a neutrino (ν) and a positron (β^+). Each positron then travels through surrounding tissue up to 1 mm, where it can encounter its antiparticle, the electron (e^-), thus causing an annihilation event. The event produces two gamma ray photons (γ) of 511 keV each, which progress away from the annihilation at 180° in opposite directions (Figure 1). PET scanners have detectors that are set in rings that encircle the patient and can identify the photon pair simultaneously in a coincidence event. Allowing for the location of the radiopharmaceutical to be accurately determined. PET scanners can also be coupled with CT to provide additional structural detail. Moreover, the usefulness of PET expands well beyond disease monitoring for early detection and can be applied to the development of personalized medicine, drug discovery, in addition to allowing for a large population of clinical trials, and easy monitoring of patient response to therapy.

The isotopes ^{13}N and ^{15}O have very short half-lives of 9.96 and 2.04 min, respectively, and therefore are predominantly used as $[^{15}O]H_2O$, $[^{15}O]CO_2$, and $[^{13}N]NH_3$. These products can be acquired directly from the cyclotron and readily used, but require an on site radiochemistry facility. The half-life of ^{11}C is longer at 20.3 min, which allows for the synthesis of a wide variety of compounds by the addition of an $[^{11}C]CH_3$ in place of a methyl group. Substitution does not change the carbon skeleton and thus many chemical and biological properties of the probe remain the same, which is extremely desirable. Yet synthesis of ^{11}C-containing molecules is hindered by the half-life being too short to allow for the multi-step synthesis of complex products. Miller and colleagues have comprehensively reviewed the chemistry of carbon-11, nitrogen-13 and oxygen-15 in their review of strategies for radiopharmaceutical synthesis [8].

The most predominate isotope for PET imaging is undoubtedly ^{18}F with a half-life of 109.77 min that allows for complex multi-step synthesis of one to three half-lives that is not possible with ^{11}C, ^{13}N, and ^{15}O. Another distinct advantage of ^{18}F-labeled compounds is

their ability to be transported off-site to facilities or used in studies of slow physiological processes, which can require scanning times of up to half a day [9]. Additionally, fluorine-18 has low positron energy corresponding to the average distance the positron travels before the annihilation - whereby the lower the energy, the lower the travel distance and thus a better spatial resolution for imaging physical characteristics. [^{18}F]Sodium fluoride can be used directly for bone imaging (particularly during recent shortages of technetium-99m, the more traditional isotope for bone scans) [10], but it is much more common to tag bioactive molecules with fluorine-18. The resulting radiopharmaceuticals are then used in PET imaging studies. Though it is not generally associated with bioactive molecules, fluorine is often the choice substitute in place of a hydrogen atom or hydroxyl group because F-for-H substitutions are often well tolerated (F and H share similar van der Waal's radii and steric perturbations are of minimal concern) [11]. The unique need to incorporate the short-lived fluorine-18 atom as late in the synthetic pathway as possible has made development of methodologies that enable rapid and efficient late stage fluorination an area of research within its own right (recent reviews: [8, 12-17]). It is not our intent to duplicate these reviews. Rather, herein we provide an overview of fluorine-18 radiochemistry and highlight classical approaches, but focus primarily upon newly developed methodologies and technologies that have been reported in recent years. An overview of some of the newer applications of PET imaging beyond traditional diagnostic imaging is also provided.

1.2 Production of Fluorine-18

Fluorine-18 generation can be accomplished using charged particle accelerators, both cyclotron and linear, in addition to nuclear reactors. A list of nuclear reactions for the production of fluorine-18 is given in Table 2. The majority of PET facilities obtain fluorine-18 via cyclotron irradiation of target molecules. Gaseous [^{18}F]F_2 for direct electrophilic labeling is generated by bombardment of neon-20 with deuterons via the nuclear reaction ^{20}Ne(d,α)^{18}F . While proton bombardment of oxygen-18 enriched water by the nuclear reaction ^{18}O(p,n)^{18}F, followed by trapping of newly generated [^{18}F]F^- in an ion-exchange chromatography with potassium carbonate, or another base, to afford [^{18}F]KF. Unfortunately aqueous fluoride is a poor nucleophile and must be desolvated and activated by treatment with a chelator such as Kryptofix 2.2.2 (K222) to bind up the potassium and release free [^{18}F]fluoride ions for direct nucleophilic labeling reactions [18, 19]. Electrophilic and nucleophilic reactions are explored in more detail in each of their respective sections of this review.

1.3 Synthesis Considerations with Fluorine-18

With radiochemical reactions, there are many considerations with specific activity and radiochemical yield being the most essential. Radiochemical yield deals with the radioactivity of the purified fluorine-18 labeled compound in comparison to its initial radioactivity. Radioactivity for PET is given in the SI unit Becquerel (Bq) or the older non-SI unit of Curie (Ci); for reference, 1 Ci is equal to 37 GBq. It is important to consider both the overall radioactive dose a subject receives in addition to possible toxic effects of radiochemical byproducts and overall probe concentration of “hot” and “cold” probe. For this reason, yields are reported as radiochemical yields rather than overall chemical reaction

yields. In literature, radiochemical yields are derived by several different methods: they may be corrected or uncorrected for radioactive decay, in addition to being calculated based upon the amount of radioactivity in the final product, in relation to the initial amount of radiation produced in the cyclotron target, or the reactivity of a given intermediate. Due to these inconsistences in radiochemical yields, this review will not focus on yields unless to demonstrate a particular advantage or disadvantage of a given synthetic route when there are large differences noted. Specific activity is a measure of the amount of "hot" fluorine-18 in relation to "cold" fluorine-19 in the final radiopharmaceutical to be administered, and is also inconsistently estimated or measured in literature. Fluorine-18 chemicals are primarily analyzed by high-performance liquid chromatography (HPLC) or gas chromatography (GC) with the addition of a standard of known mass. Due to instrumentation and operator differences resulting data can vary. Most fluorine-18 radiopharmaceuticals are optimally prepared by a no-carrier-added (N.C.A.) method in which no carrier fluorine-19 has been added during the generation of the radionuclide or radiochemical synthesis. This does not mean that there is no cold fluorine in the system, just that none was added deliberately. There are a few methods that use carrier-added fluorine-18 radiochemical syntheses, but they are increasingly rare in modern literature.

2. [^{18}F]Fludeoxyglucose ([^{18}F]FDG): the Workhorse of PET Imaging

The most ubiquitous PET tracer is the glucose analogue 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG) with multiple modalities for application. Glucose is the predominant biological energy source for many biological systems ranging from bacterial to human cells. Glucose transporters (GluT) traffic glucose into cells and across the blood brain barrier (BBB) where it is phosphorylated by the enzyme hexokinase utilizing adenosine-5′-triphosphate (ATP) as a phosphate source. These same GluT also bring [^{18}F]FDG into cells with high metabolic activity to be phosphorylated, but the product [^{18}F]FDG-6-phosphalate is not a substrate for the enzyme that metabolizes glucose, glucose-6-phosphate isomerase, and thus becomes metabolically trapped in the cell. Radioactive decay of fluorine-18 into oxygen-18 produces 2-[^{18}O]-deoxyglucose-6-phosphate, which can then reenter the metabolic pathway while [^{18}F]FDG that is not phosphorylated is excreted [21]. There are many applications of [^{18}F]FDG in cardiology, neurology, and oncology [22].

2.1 Electrophilic Syntheses of [^{18}F]FDG

Though laboratory synthesis of [^{18}F]FDG had been accomplished in the late 1960s [23], it was not until 1976 when Wolf *et al.*, in a collaboration between the National Institutes of Health, Brookhaven National Laboratory, and the University of Pennsylvania, produced the first [^{18}F]FDG for human study [24, 25]. It was designed specifically for investigating glucose metabolism in a living human brain [26]. Their synthesis utilized direct electrophilic substitution of the precursor 3,4,6-tri-*O*-acetyl-D-glucal **1** with [^{18}F]F_2. This reaction produced a 3:1 ratio of the desired difluoro-glucose and difluoro-mannose isomers that could be separated by preparative gas chromatography. Then proceeding to hydrolysis for the production of [^{18}F]FDG with low specific activity and low radiochemical yield of around 8% (Scheme 1a). The next decade provided great advancements of both diagnostic and synthetic strategies for [^{18}F]FDG. Replacement of [^{18}F]F_2 with [^{18}F]acetyl hypofluorite

([^{18}F]AcOF) more than doubled the radiochemical yield to around 40% [27-29], in addition to eliminating the need for protection of the hydroxyl groups of the precursor **2** (Scheme 1b) [30, 31]. It was observed that the stereoselectivity of the fluorination reaction by [^{18}F]F_2 and [^{18}F]AcOF was highly solvent dependent [32-35]. Another approach utilized [^{18}F]xenon difluoride ([^{18}F]XeF_2) as an electrophilic fluorinating reagent [36, 37]. Unfortunately all electrophilic synthetic routes produced varying amounts of labeled and unlabeled mannose isomers [32], which resulted in underestimation of glucose metabolic rates in kinetic studies [38], causing in this route to be abandoned by radiochemical facilities in favor of nucleophilic aliphatic substitution with substantially higher radiochemical yields and specific activity [19].

2.2 Nucleophilic Syntheses of [^{18}F]FDG

Several nucleophilic fluorination methods have been published making use of Cs[^{18}F] [39, 40], Et_4N[^{18}F] [41, 42] and KH[^{18}F]F_2 [43, 44], in the production of [^{18}F]FDG. The most significant advancement in nucleophilic production was the reaction of [^{18}F]KF·K222 with 1,3,4,6-tetra-*O*-acetyl-2-*O*-triflate-*β*-D-mannose **3** published in 1986 [19]. With the reaction proceeding by nucleophilic fluorine displacing the 2-triflate leaving group, creating an inversion of stereochemistry at the C-2 carbon center of the acetyl-protected mannose precursor forming the glucose derivative (Scheme 1c). This reaction is then followed by base-catalyzed hydrolysis of acetyl protecting groups with controlled to conditions to reduce epimerization, which is faster and milder than acid hydrolysis [45]. Currently [^{18}F]FDG production is an everyday routine synthesis involving computer-controlled production instruments with radiochemical yields greater than 60% (corrected for radioactive decay) and an overall synthesis time of less than 26 minutes, from cyclotron product to final radiopharmaceutical. It is by far the most refined and efficient radiochemical synthesis of any fluorine-18 probe to date [46].

3. Strategies for Direct Electrophilic Fluorination

3.1 General Considerations

Many historically relevant radiopharmaceuticals were prepared by electrophilic fluorination reactions, and whilst such reactions have predominantly been replaced by newer nucleophilic fluorination reactions over time, certain radiopharmaceuticals are still best prepared (or can only be prepared) by using electrophilic techniques. The simplest fluorination reagent is fluorine gas ([^{18}F]F_2), although it can be problematic to handle due to its high reactivity, resulting in reduced radiochemical yields and selectivity. It can be obtained from the nuclear reaction ^{20}Ne(d,α)^{18}F, that facilitates the exchange of fluorine-18 and fluorine-19 atoms resulting in carrier-added [^{18}F]F_2 production. Conditions were developed to counter the reactivity issues resulting from dilution of [^{18}F]F_2 in an inert gas at low temperature, such as 0.1 to 2% [^{18}F]F_2 in Ne [47, 48]. A second production method involves a sequential two-step procedure by the irradiation of oxygen-18 (^{18}O(p,n)^{18}F) followed by a second irradiation in a gaseous mixture of carrier fluorine gas to produce [^{18}F]F_2 [49, 50]. Due to carrier-added production, radiochemical products have low specific-activity in addition to complicated purification conditions to isolate the desired radiopharmaceutical.

Production of intermediate electrophilic fluorination reagents derived from $[^{18}F]F_2$ have been used to increase yield and selectivity. They include $[^{18}F]XeF_2$ [51, 52], and $[^{18}F]$AcOF [31, 53, 54], discussed prior for the synthesis of [^{18}F]FDG. While these reagents they have a theoretical maximum radiochemical yield of 50% and actual yields that are often much lower, they remain an important synthetic tool and have been used to prepare fluorine-18 labeled radiopharmaceuticals. Other fluorinated intermediates are: [^{18}F]*N*-fluorobenzenesulfonamide ([^{18}F]NFSi) [55], for producing fluorinated ketones and allylic fluorides (Scheme 2); [^{18}F]*N*-fluoro-*N*-alkylsulfonamides (e.g. [^{18}F]**4**) [56, 57], used in the labeling of aryl compounds (Scheme 3); [^{18}F]*N*-fluoropyridinium triflate [58-60], a fluoride transfer agent; in addition to [^{18}F]perchloryl fluoride ([^{18}F]$FClO_3$),[61, 62] [^{18}F]diethylaminosulfur trifluoride ([^{18}F]DAST) [63], [^{18}F]nitrosyl fluoride [64], and [^{18}F]*N*-fluoro-pyridone ([^{18}F]**5**, Scheme 4) [59].

A mild fluorinating compound Selectfluor [65], has been adapted by Gouverneur and co-workers for radiochemistry as [^{18}F]Selectfluor bis(triflate) [66]. The reagent is prepared by chlormethylation of diazabicyclo[2.2.2]octane **6**, anion exchange, and lastly fluorination by F_2 or $[^{18}F]F_2$ to provide the bis(triflate) products **7** and [^{18}F]**7**, respectively. Bis(triflate) **7** has been demonstrated to be more selective than $[^{18}F]F_2$ and successful when other fluorinating agents were not, and has been used to prepare a variety of fluoroaromatic and difluoromethyl arenes (Scheme 5). Recently the first electrophilic fluorination reagent derived from [^{18}F]fluoride ion has been created by Ritter and co-workers, (Scheme 6) [67]. The [^{18}F]fluoride-derived palladium (IV) reagent [^{18}F]**9** is produced by [^{18}F]KF treatment of its Pd(IV) precursor **8** with benzo[h]quinolyl and tetrapyrazole borate ligands. The newly formed [^{18}F]**9** can react with palladium(II) aryl compounds to form Pd(IV) aryl fluoride complexes, that can then undergo C–F reductive elimination to yield fluorine-18 aryl products.

However, use of the [^{18}F]fluoride-derived palladium (IV) electrophilic fluorinating reagent [^{18}F]**9** has been limited, likely due to the two-step sequence involved, as well as the need for dry fluoride and potentially sensitive organometallic reagents. To address these issues, the same group has subsequently developed a one-step oxidative fluorination of aromatic rings using nickel complexes (Scheme 7) [68]. For radiofluorination, aqueous [^{18}F]fluoride was combined with 18-crown-6, the nickel complex **10** (which contains the aryl substrate) and the hypervalent iodine oxidant **11** at room temperature and under ambient atmosphere. Analysis of the reactions after 1 minute revealed rapid formation of the desired aryl fluoride products **12** (13 – 58% RCY).

3.1.2 Direct electrophilic fluorination of alkenes—The most studied electrophilic addition to an alkene is undoubtedly the addition of $[^{18}F]F_2$ or [^{18}F]AcOF to yield [^{18}F]FDG, as previously described. Nucleic acids and nucleosides have also been labeled with high regioselectivity for the 5-position using this approach [69-73], with the 6-fluoro or 6-acetoxy then preferentially eliminated (Scheme 8a). Radiolabeled versions of bioactive molecules have been prepared by similar reactions (e.g. [^{18}F]**15**), such as quinones [74], the prescription drug diazepam [75], and hypoxia biomarker 2-(2-nitro-1*H*-imidazol-1-yl)-*N*-(2,2,3,3,3-pentafluoropropyl)acetamide (EF5) [76]. A substituent class of alkenes, vinyl

[^{18}F]fluorides, can be fabricated from the corresponding vinyl silanes. An example of this is the synthesis of 4-[^{18}F]fluoroantipyrine **17** from 4-(trimethylsilyl)-antipyrine **16** (Scheme 8b) [77].

3.1.3 Direct electrophilic fluorination and demetallation of aromatic rings—

Fluorination of aromatic rings can be accomplished with [^{18}F]F_2, [^{18}F]AcOF, and [^{18}F]XeF_2, usually exhibiting poor regioselectivity requiring complicated HPLC separation conditions [78]. Several aromatic amino acids, phenylalanine, tyrosine, and their derivatives have been successfully radiolabeled by various electrophilic methods. Similarly to [^{18}F]FDG, regioselectivity in the synthesis of 3-[^{18}F]fluorotyrosine has been shown to be highly solvent and fluorination reagent dependent [79]. Fluorination of tyrosine in hydrogen fluoride by [^{18}F]F_2 yields 3-[^{18}F]fluorotyrosine exclusively (Scheme 9). Yet the fluorination of *O*-acetyltyrosine with [^{18}F]AcOF gives a mixture of 2- and 3-[^{18}F]fluorotyrosine with a ratio of 83 to 17. When the *O*,*N*-diacetylated methyl ester protected tyrosine was reacted with [^{18}F]F_2 in CF_3COOH, the ratio shifted in favor of 3-[^{18}F]fluorotyrosine, with a ratio of 40 to 60. Even with the regioselectivity limitations this methodology has been utilized to label integrin receptor peptide cyclic Arg-Gly-Asp (cRGD) for imaging of tumors [80]. The cyclic peptide contains a phenylalanine that can undergo direct electrophilic fluorination with [^{18}F]AcOF in trifluoroacetic acid to yield mono- and difluorinated products.

To improve regioselectivity of electrophilic addition to aromatic rings, regioselective fluordemetallation reactions have proven successful. The aryl organometallic compounds have been prepared with a variety of metals: silicon [81-84], tin [85, 86], germanium [81], and mercury [87-89]. An L-tyrosine biological derivative, L-3,4-dihydroxyphenylalanine (L-DOPA), is a precursor to the neurotransmitters: dopamine, norepinephrine, and epinephrine. The radiopharmaceutical L-3,4-dihydroxy-6-[^{18}F]fluorophenylalanine (6-[^{18}F]fluoroDOPA, [^{18}F]FDOPA) is taken up by dopaminergic neurons in the brain and decarboxylated to 6-[^{18}F]fluorodopamine along with endogenous l-DOPA. Synthesis of [^{18}F]FDOPA has been done by the unselective direct electrophilic fluorination of DOPA [90], and more efficiently from organomercuric, organostannane, and organosilver precursors (Scheme 10) [87, 91-94]. Similar reaction conditions have been utilized for the synthesis of 4-[^{18}F]fluoro-m-tyrosine by fluorodemercuration[95] and 2-[^{18}F]fluoro-L-tyrosine from an organostannane [96].

Metaraminol, a sympathomimetic amine, has been adapted for use as a cardiac sympathetic innervation tracer for PET imaging. Preparation of 6-[^{18}F]fluorometaraminol by demercuration with [^{18}F]AcOF, without need to protect the phenol or benzylic alcohol for either the mercuration or fluorination steps.[88] The derivative (1*R*,2*S*)-4-[^{18}F]fluorometaraminol has been produced with higher specific activity from the organostannane precursor[97] and [^{18}F]F_2 produced by a “post-target” methodology previously published by Bergman and Solin.[98] Overall, fluorinated aryl compounds from demetallation reactions suffer from low specific activity like other electrophilic fluorinations, but are generally enantiomerically pure after synthesis. Their largest downfall is that each compound must undergo stringent purification and quality control measures to eliminate any metals from the final radiopharmaceutical.

3.1.4 Direct electrophilic fluorination of carbanions—A very different and rarely used fluorination approach is the fluordemetallation of aryl Grignard or aryl lithium reagents with a positive fluoride source. Aryl [^{18}F]fluorides can be prepared by treatment of the corresponding aryl-lithium precursors with [^{18}F]$FClO_3$, producing very low overall yields of 2 to 34% (Scheme 11) [62, 99]. Fluorination with *N*-[^{18}F]fluoro-*N*-alkysulfonamides derived from [^{18}F]F_2 and *N*-endo-norbonyl(*p*-tolyl)sulfonamide improves yields drastically to 60 to 70% (Scheme 11) [57, 100]. The reaction of *N*-trimethylsilylpyridinium triflate with [^{18}F]F_2 generates the fluorination reagent from [^{18}F]*N*-fluoropyridinium triflate that can be used to produce [^{18}F]fluorobenzene with similar high yields [59].

4. Strategies for Direct Nucleophilic Fluorination

4.1 General Considerations

Nucleophilic [^{18}F]fluoride is produced by ^{18}O(*p*,*n*) ^{18}F from enriched [^{18}O]H_2O. However, the resultant $^{18}F^-$ is poorly nucleophilic fluoride due to solvation, and typically requires extensive preparation before it can be used as an effective nucleophile. First it must be subjected to dehydration then loaded onto an ion-exchange column. From there, a cryptand source, most often the aminopolyether K222 is used with potassium carbonate to activate the ^{18}F-fluoride [5, 12, 18]. Alternatives to [^{18}F]KF·K222 include [^{18}F]cesium fluoride, [^{18}F]tetrabutylammonium fluoride ([^{18}F]TBAF) and tetraethylammonium fluoride, prepared by eluting [^{18}F]fluoride from the ion exchange column with cesium carbonate, tetrabutylammonium bicarbonate, or tetraethylammonium bicarbonate, respectively [8, 101]. Using any of these reagents, a reactive [^{18}F]fluoride nucleophile source is produced. While the [^{18}F]fluoride nucleophile requires activation, the radiotracer precursor must have an appropriate leaving group. Nucleophilic reactions using [^{18}F]fluoride can be readily divided into two main categories: aromatic and aliphatic fluorinations.

4.2 Nucleophilic Aliphatic Fluorination Reactions

Aliphatic reactions are perhaps the classical method of radiolabeling with fluorine-18. Such reactions have been used to label a variety of molecules in one step, where no protecting groups are necessary, and frequently proceed via displacement of standard leaving groups in organic chemistry such as triflates, tosylates, mesylates etc. The chemistry therefore mandates synthesis of, for example, the corresponding alkyl tosylate precursors (e.g. **18**). Examples include [^{18}F]fluoroethoxybenzovesamicol ([^{18}F]FEOBV), a radioligand for the vesicular acetylcholine transporter (Scheme 12a) [102], and [^{18}F]fallypride for imaging the D2/D3 receptors [103]. However, many precursors do contain functional groups that require protection, typically using standard protecting groups from the organic chemistry literature (Boc, Fmoc etc.). The radiosynthesis then is a two-step process, in which there a deprotection step follows the initial fluorination [104]. This can generate radiotracers functionalized with fluoroalkyl groups as described above, but when issues of chemical or metabolic stability present, tosyl-PEG precursors (e.g. **19**) can be employed, such as in the synthesis of [^{18}F]Amyvid, a radiopharmaceutical for quantifying amyloid plaque burden being developed by Avid Radiopharmaceuticals and Eli Lilly (Scheme 12b) [105].

In addition to the synthesis of simple primary alkyl fluorides, synthesis of secondary alkyl fluorides is also desirable, and has been discussed above in the context of the synthesis of [^{18}F]FDG [19]. Though [^{18}F]FDG is the most widely used fluorine-18 labeled PET radiotracer, typically for detecting cancer, it does have limited sensitivity for some cancer types such as androgen-dependent prostate cancer [106]. Moreover, in brain, there is low tumor-to-background resolution with [^{18}F]FDG due to the high levels of glucose uptake in the normal cortex, thus making the delineation of the extent of these lesions difficult [107]. As a result, the search for non-FDG radiotracers continues, and many typify fluorine-18 radiosyntheses for nucleophilic substitution reactions. For example, 3′-deoxy-3′[^{18}F]fluorothymidine ([^{18}F]FLT) is a radiolabeled analog of the DNA base that can be used to evaluate cell proliferation and tumor growth. It can be synthesized from a cyclic precursor **20**, which ring-opens to yield [^{18}F]FLT on treatment with [^{18}F]fluoride (Scheme 13a). This reaction however suffers from low radiochemical yields, and so alternative precursors (e.g. Boc-Boc-Nosyl **21**) have been designed, which contain a secondary nosylate leaving group, rather than the cyclic precursor, and provide higher yields of [^{18}F]FLT (Scheme 13b) [102]. A range of other radiopharmaceuticals for oncological imaging have been developed including [^{18}F]fluoroethyl tyrosine ([^{18}F]FET), and 2-nitroimidazoles such as [^{18}F]fluoroazomycin arabinoside ([^{18}F]FAZA), [^{18}F]fluoromisonidazole ([^{18}F]FMISO) and [^{18}F]flortanidazole ([^{18}F]HX4) for imaging of tumor hypoxia that are all prepared using similar chemistry. A discussion of each of these is beyond the scope of this article, but many are highlighted in a recent review article by Gulyás and co-workers [108].

Beyond these classical fluorination reactions, a number of reports describing improved methods and substrates for nucleophilic fluorination have recently appeared in the literature. Examples that represent well the integration of modern synthetic organic chemistry technology with that of radiochemistry include metal-catalyzed allylic fluorination reactions. A preliminary indication of iridium-mediated allylic fluorination of trichloroacetimidate derivatives of activated alcohols was reported by Tewson [109], whilst Gouverneur and co-workers have described a protocol for palladium-catalyzed allylic fluorination (Scheme 14) [110]. Allyl 4-nitrophenyl carbonates were smoothly converted to the corresponding allylic fluorides by treating with TBAF·(tBuOH)$_4$ in the presence of catalytic Pd(dba)$_2$ (dba = dibenzylideneacetone). The method was then evaluated for compatibility with short-lived fluorine-18. Nitrophenyl cinnamyl carbonate **22** gave cinnamyl fluoride **23** in 7% RCY; higher conversions (10–52% RCY) were obtained when methyl cinnamyl carbonate was subjected to prolonged reaction times (30 min). Satisfactory yields were also obtained comparing the protocol to direct S_N2 ^{18}F fluorination. Subjecting cinnamyl bromide to the system for 5 min at room temperature gave 20% RCY of the corresponding fluoride. Forcing conditions (110 °C, 20 min) generated cinnamyl fluoride in 40 and 42% RCY from cinnamyl chloride and bromide, respectively.

4.3 Nucleophilic Aromatic Fluorination Reactions

Nucleophilic aromatic substitution with [^{18}F]fluoride can be used to prepare radiolabeled arenes. As the reactions are frequently quite sluggish; however, a combination precursor design, activated substrates (typically aromatic rings bearing electron withdrawing groups) and harsh reaction conditions (such as elevated reaction temperatures) are often required and

can limit the synthetic utility of such reactions. Early examples capitalized on the electronegativity of fluorine and involved isotopic exchange reactions with the corresponding fluorine-19 species, such as in the first reported synthesis of [^{18}F]flumazenil [111]. The drawback of such reactions is of course the inevitable poor specific activity of the radiotracer that results from the inability to separate the two isotopic products. Therefore, alternative precursors are used whenever possible, and the corresponding nitro-aromatic precursors, as well as trialkylammonium arene precursors originally reported by Haka and co-workers, have been the state of the art for over 20 years [112]. For example, *p*-MPPF is a high affinity *in vivo* antagonist of serotonin-1A (5-HT1A) receptors in the central nervous system, and because the 5-HT1A receptor has been implicated in anxiety, depression, dementia, schizophrenia, the modulation of emotion and hypothalamus function [113], it has since been developed as a PET radiotracer, [^{18}F]MPPF (4-(2′-methoxyphenyl)-1-[2′-(*N*-2″pyridinyl)-*p*-[^{18}F]fluorobenzamido]ethylpiperazine) [113, 114]. Radiosynthesis of [^{18}F]MPPF involves a direct nucleophilic substitution of the nitro-precursor **24** with [^{18}F]fluoride (Scheme 15) [102, 113].

Difficulties with such nucleophilic aromatic substitution reactions; however, have made development of new aromatic fluorination reactions an area of research in its own right, particularly with the aim of synthesizing radiopharmaceuticals containing unactivated or even electron rich rings. Certain ingenious solutions have been reported involving protecting group manipulations. At its simplest, this involves transforming an electron-donating group into an electron-withdrawing group through use of appropriate protecting groups. For example, in the synthesis of [^{18}F]flutemetamol, it would be impossible to radiolabel the *ortho*-nitroaniline directly. However, protecting the aniline as the corresponding formamide **25** enables displacement of the nitro group with [^{18}F]fluoride to give **26**, and subsequent deprotection of the protecting group yields [^{18}F]flutemetamol (Scheme 16) [115].

Similar issues are encountered when radiolabeling phenols. To circumvent the issue, fluorination of the corresponding aldehyde (or ketone) has been reported. Subsequent Bayer-Villiger oxidation favors migration of the electron rich aromatic ring to generate the ester, and final saponification with sodium hydroxide generates the radiolabeled phenolic species (Scheme 17) [116].

Whilst such approaches are elegant in their theory and design, from a practical perspective in a radiochemistry laboratory, they are often times messy and difficult to accomplish successfully. Therefore, precursors permitting direct fluorination of electron rich aromatics remain high on the wish list of all fluorine-18 radiochemists, and a major development occurred with the introduction of diaryliodonium salt precursors [117-122]. Symmetric and asymmetric diaryliodonium salts of target precursors, in particular, have received attention owing to their ease of preparation and compatibility with moderately electronic-rich arene systems (Scheme 18). For example, the Carroll[123] and Coenen[124] groups have independently explored the use aryl(2-thienyl)iodonium salts as substrates of ^{18}F for S_NAr, showing enhanced reactivity at electron-rich homoarenes (Scheme 18a). More recently, Pike and colleagues have employed diaryliodonium tosylates in the synthesis of metabotropic glutamate receptor 5 (mGluR5) PET radioligands (Scheme 18b) [125]. Advances in this area

have significantly expanded the scope of classical S_NAr beyond electron-deficient arenes, to the benefit of ^{18}F radiochemistry.

Ametamey *et al.* disclosed a method for the ^{18}F-radiolabelling of aromatic substrates via S_NAr employing precursor triarylsulfonium salts and K[^{18}F]F or Cs[^{18}F]F as the nucleophilic fluoride-18 source. A variety of sulfonium species derived from haloarenes **31**, benzamide **32** and an oligopeptide (not shown) were prepared and successfully fluorinated (Scheme 19) [126, 127]. Generally, moderate to nearly quantitative ^{18}F incorporation was observed after 15 min under reaction temperatures ranging from 80 to 110 °C. Optimal substrate-solvent combinations were noted, and electron-rich aromatic systems were observed to provide fluorobenzene alone.

Concurrently, the preparation of [^{18}F]fluoroarenes from diarylsulfoxides was described by Pike and co-workers [128]. In a microfluidic reactor system, a range of electron-deficient, symmetrical and non-symmetrical diarylsulfoxides were submitted to S_NAr. At elevated temperatures, in the presence of N.C.A [^{18}F]fluoride ion and Kryptofix 2.2.2, moderate to good yields of *p*-fluoroarenes were obtained (Scheme 20). Fluorination occurred selectively toward substrates bearing a para electron-withdrawing group, even in instances where electron-donating substituents were present on the same arene.

Beyond classical arenes, the diversity of biological molecules also makes the ability to synthesize other ^{18}F heterocyclic compounds of significant importance. For example, fluorination of pyridines is a widely used strategy, because they are found in a number of compounds of interest, and similar precursors (nitro, trialkylammonium, halo) to those described above for standard arenes are readily fluorinated (typically in the 2 position). A number of pyridine derivatives are ligands for the α4β2-subtype of the nicotinic acetylcholine receptor (NaChR), imaging of which is interesting because it is associated with an assortment of disorders, including Alzheimer's disease, Parkinson's disease, and others (for a review see: [129]), and fluorine-18 labeled versions have been prepared using S_NAr reactions. For example, the radiotracer 2-([^{18}F]Fluoro)-3-[(2*S*)-2-azetidinylmethoxy]pyridine ([^{18}F]2FA) is an analog of an Abbott Laboratories compound A-85380, which is a known nicotinic acetylcholine receptor agonist, and has been successfully used in imaging NaChRs in a clinical setting [130-133]. The synthesis of [^{18}F]2FA utilizes a Boc-protected iodo or trimethylammonium precursor that, via an S_NAr reaction with $^{18}F^-$ in the presence of Kryptofix 2.2.2, is then deprotected to give the final product (Scheme 21a) [134]. One drawback of [^{18}F]2FA, is its comparatively slow *in vivo* kinetics that requires over 5 hours of imaging assay acquisition, and limits its utility for imaging cogtively impaired patients 129. o compensate for the extended acquisition time of [^{18}F]2FA, the development of new radioligands for α4β2 NaChRs receives continuing attention. One of the most promising is [^{18}F]flubatine, a high affinity and selective PET radiotracer for NAChRs with improved kinetics over the earlier developed ligands [135, 136]. The first reported radiosynthesis of [^{18}F]flubatine, a derivative of epibatidine, utilized the norchloro-bromo-homo-epibatidine (NCBrHEB) precursor that underwent a nucleophilic substitution with the bromine leaving group, then the enantiomers separated and the product purified appropriately via HPLC [136-138]. However, due to low radiochemical yields, other candidate precursors were explored for radiolabeling and the BOC-protected

trimethylammonium iodide precursor (BOC-trimethylammoniumhomo-epibatidine, BTHEB) was shown to give the best yields of approximately 60% and adapted for fully automated synthesis [135]. This precursor has since become commercially available, making it more accessible for clinicians, and a validated production method suitable for clinical application has been reported by our group (Scheme 21b) [139].

5. Other Strategies for Radiolabeling with Fluorine-18

5.1 Prosthetic Groups

One of the greatest synthetic challenges chemists face is that of functional group compatibility. There is a large arsenal of protecting groups and multi-step synthetic techniques for overcoming hurdles in making pharmaceutical compounds. Many radiopharmaceuticals, including [^{18}F]FDG, utilize a two step procedure of direct fluorination followed by deprotection of functional groups. However, for more complicated molecules it is often ideal to directly label a prosthetic group that can then be added to a wide variety of compounds that are not well suited for direct fluorination. A wide number of strategies have been developed that are highlighting in this section.

5.1.1 Radiolabeled Alkylating Agents—The simplest approach to preparing prosthetic groups is to prepare radiolabeled alkylating agents. This is commonplace in carbon-11 radiochemistry, where many [^{11}C]radiopharmaceuticals are prepared through *O*-, *S*- or *N*-alkylation with [^{11}C]methyl iodide or [^{11}C]methyl triflate. This same approach is viable using fluorine-18, although it is much less common. Such chemistry has been most widely explored to prepare [^{18}F]fluorocholine ([^{18}F]FCH) [140], a fluorine-18 labeled analog of [^{11}C]choline which is a successful tracer for tumors in a variety of tissue, including prostate, brain and lung [141, 142]. In the most widely used method, dibromomethane **35** undergoes direct nucleophilic fluorination to yield [^{18}F]fluorobromomethane **36**. A second S_N2 reaction with dimethylamino ethanol (DMAE) generates [^{18}F]FCH (Scheme 22a). Alternatively, [^{18}F]FCH can be synthesized by alkylation of dimethylamino ethanol with [^{18}F]fluoromethyl tosylate, such as in a recent report by Scott and colleagues [143]. Other sequential S_N2 reactions are used for the production of: *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine ([^{18}F]FET, Scheme 22b) [101, 144-147], [^{18}F]substance-p antagonist-receptor quantifier ([^{18}F]SPA-RQ) [148, 149], 8-((*E*)-4-fluoro-but-2-enyl)-3β-*p*-tolyl-8-aza-bicyclo[3.2.1]octane-2β-carboxylic acid methyl ester ([^{18}F]LBT-999) [150-153], and [^{18}F]fluoropropyl carbomethoxy iodophenyl nortropane ([^{18}F]FP-CIT) [154-157].

Other innovative [^{18}F]fluorine-containing reagents for radiopharmaceutical preparation have recently been disclosed. Cognizant that the trifluoromethyl is a privileged motif in small molecule drugs, Riss and Aigbirhio reported the synthesis of 1-[^{18}F]fluoro-1,1-difluoromethyl groups [158, 159]. A simple and efficient procedure for the preparation of 2-[^{18}F]fluoro-2,2-difluoroethyltosylate **41** was outlined, beginning from the difluorovinylsulfonate **40** (Scheme 23). The resulting [^{18}F]fluoroethylating agent proved effective for *N*- and *O*-alkylation, giving rise to tropane derivative **[^{18}F]42** and the neurofibrillary tangle imaging agent **[^{18}F]43**, respectively. Scott and colleagues have applied related chemistry to the radiosynthesis of [^{18}F]lansoprazole **44**, also a radiopharmaceutical for imaging of tau neurofibrillary tangles [160].

5.1.2 Amide Bond and reactive amines—Peptide chemists have refined the art of amide bond formation by using coupling agents and protecting groups strategically [161-163]. Adding a fluorine-18 labeled prosthetic group is an ideal choice for synthesis of large peptides and proteins, such as the RGD peptide analogue, [^{18}F]FPPRGD2 (Scheme 24a) [164]. A popular prosthetic group for radiolabeling of peptides [165], proteins [166], and antibodies [167-169] is *N*-succinimidyl 4-[^{18}F]fluorobenzoate ([^{18}F]SFB) as it can be easily conjugated to a peptide through a simple acylation reaction (Scheme 24b) [170-173]. There are many other amine-reactive prosthetic groups including: *N*-succinimidyl 4-([^{18}F]fluoromethyl)benzoate [174], 4-[^{18}F]fluorobenzoic acid [175], 4-([^{18}F]fluoromethyl)-phenyl isothiocyanate [176], and methyl 3-[^{18}F]fluoro-5-nitrobenzimidate [177]. Amidation has been used to create a fluorine-18 labeled insulin through prosthetic group addition [170].

5.1.3 Thiol Functionalization—Peptides and proteins containing cysteine are known to form disulfide bonds, but also yield an additional site for fluorine-18 labeling. Thiol reactive [^{18}F]maleimide prosthetic groups proved quite useful for labeling peptides and other biomolecules (Scheme 25a) [178-182]. Several thiol reactive groups are: [^{18}F]fluorophenacyl bromide ([^{18}F]FPB) [183], *N*-(2-(4-[^{18}F]fluorobenzamido)ethyl)maleimide ([^{18}F]FBEM) [181, 184], *N*-(4-[^{18}F]fluorophenyl)maleimide ([^{18}F]FPM) [185], 1-(3-(2-[^{18}F]fluoropyridin-3-yloxy)propyl)pyrrole-2,5-dione ([^{18}F]FpyMe) [182], and *N*-(6-(4-[^{18}F]fluorobenzylidene)aminooxyhexyl)maleimide ([^{18}F]FBAM).[178, 180] Formation of oxime [186], hydrazone [187, 188], and thiourea (Scheme 25b) [176] bonds are additional methodologies, including an interesting synthesis by Wuest and co-workers that details the direct peptide labeling of [^{18}F]FDG, through an acyclic form of [^{18}F]FDG via an oxime bond (Scheme 25c) [189, 190].

5.1.4 Radio-Click Chemistry—Azide-alkyne 1,3-dipolar (Huisgen) cycloaddition reactions, or more commonly known as “click” reactions, have become more prevalent in literature for labeling of biological molecules due to the ease of formation and stability of the triazole [191, 192]. The transformation's broad substrate scope, mild reaction conditions, short reaction times, high chemical yield, chemoselectivity and regioselectivity have led to its significant use in PET radiochemistry research (recent reviews: [192, 193]). Fluorine-18 labeling of peptides with the radiolabeled prosthetic group bearing either an alkyne[194] or azide[195] have been reported. Advances in the Huisgen cycloaddition for PET increasingly have had to take into account considerations of intellectual property and the potential for cytotoxic transition-metal contamination in clinic-bound radiotracers. To circumvent such complications, newer developments in catalyst-free click chemistry have been developed for non-radiolabeling of molecules in biological systems, where metals are not ideal [196]. This methodology has also been adapted to the radiochemistry setting, and have proven useful to radiochemists wanting to eliminate metals from their synthetic labeling techniques for peptides (Scheme 26) [197-199].

5.1.5 Transition-metal Catalyzed Cross-coupling Reactions—The Nobel Prize in Chemistry 2010 was awarded to Richard F. Heck, Ei-ichi Negishi, and Akira Suzuki for palladium-catalyzed cross-couplings in organic synthesis. Organic chemists readily utilize

cross-coupling reactions in their synthetic toolkits, while medicinal chemists often avoid synthetic procedures that require metals due to stringent FDA regulations. Nevertheless they are important synthetic option for radiochemists developing new methodology for the formation of the elusive carbon-carbon bond. Synthesis of fluorine-18 labeled compounds by palladium-catalyzed cross-couplings primarily have incorporated 1-[^{18}F]fluoro-4-iodobenzene and derivatives. Preparation of 4-[^{18}F]fluoroiodobenzene can be achieved by reacting [^{18}F]KF·K222 with dihomoaryliodonium or aryl(2-thienyl)iodonium salts, radio chemical yield is sensitive to changes in solvent, temperature, counterion, and ring substitution [200]. Sonogashira cross-coupling brings together a terminal alkyne with an aryl or vinyl halide. Cross-coupling of 4-[^{18}F]fluoroiodobenzene with 1-ethynylcyclopentan-1-ol **48** with $Pd(PPh_3)_4$ and CuI as catalysts with triethylamine in THF produced the desired fluorine-18 labeled compound **49** as reported by Wüst and Kniess in 2003 (Scheme 27a) [201]. These conditions were also successful for labeling 17α-ethynyl-3,17β-estradiol and 17α-ethynyl-3,17β-estradiol-3-methylether.

Suzuki-Miyaura cross-coupling joins an aryl- or vinyl-halide with an aryl- or vinyl-boronic acid. Steiniger and Wuest coupled 4-[^{18}F]fluoroiodobenzene and 4-tolylboronic acid **50** with a variety of Pd(0) and Pd(II) catalysts, bases, and solvent conditions (Scheme 27b) [202]. They determined that $Pd_2(dba)_3$ with Cs_2CO_3 in MeCN were the ideal conditions to further investigate the cross-coupling of 4-[^{18}F]fluoroiodobenzene with various aryl boronic acids. An interesting observation they noted was that of the 4-phenyl halogen-substituted boronic acids. Both fluorine- and chlorine boronic acids had high radiochemical yields of 82 and 77% respectively while 4-bromophenylboronic acid was significantly lower at 30% after 5 min and 34% after 20 min. It was hypothesized this lower yield might be due to competitive homo-coupling reaction of 4-bromophenylboronic acid. Recently Davis and co-workers published an enhanced aqueous Suzuki-Miyaura cross-coupling for labeling of small molecules, peptides, and proteins (Scheme 27c) [203]. They reacted 4-[^{18}F]fluoroiodobenzene with $B_2(OH)_4$, $Pd(dppf)Cl_2$, and KOAc in DMSO to produce 4-[^{18}F]fluoroboronic acid, which was coupled with a range of substrates (**52**) ranging from small molecules to proteins. Several Pd(0) catalysts with water-soluble ligands were evaluated with 1,1-dimethylguanidine (DMG) performing the best. This publication is the first Pd-catalyzed direct incorporation of fluorine-18 with a protein (**53**).

Stille coupling consists of joining an aryl- or vinyl-halide with an organostannane by use of a Pd(0) catalyst. An early example employing fluorine-18 in Stille chemistry was reported by Forngren and Långström in 1998. They synthesized 4-[^{18}F]fluorophenyltributyltin for Stille cross-coupling to several aryl-bromides **54** (Scheme 27d) [204]. Lasne and co-workers developed fluorine-18 analogues of (–)-cytisine for imaging studies of nicotinic receptors as alternatives to [^{18}F]fluoroepibatidine and *N*-[^{11}C]methylcytisine [205]. Several cold analogues were initially synthesized followed by fluorine-18 labeling with 4-[^{18}F]fluorobromobenzene to produce 9-(4′-[^{18}F]fluorophenyl)cytisine. Wüst and Kniess developed methodology for labeling nucleosides with 4-[^{18}F]fluoroiodobenzene, specifically 5-(4′-[^{18}F]fluorophenyl)-uridine and 5-(4′[^{18}F]fluorophenyl)-2′-deoxy-uridine **57** (Scheme 27e) [206]. Metz and co-workers produced fluorine-18 labeled cyclooxygenase-2 (COX-2) inhibitors labeled with 4-[^{18}F]fluoroiodobenzene [207]. A final example of a Pd-mediated

reaction is that of *N*-arylation of indoles with 4-[^{18}F]fluoroiodobenzene as σ_2 receptor ligands [208].

5.2 Photochemical Reactions

Keeping with the trend to eliminate metals and other non-biologically compatible reagents, photochemical conjugations are an alternative method of prosthetic group labeling. Irradiating 4-azidophenacyl-[^{18}F]fluoride ([^{18}F]APF) at 366 nm creates a singlet arylnitrene **59**, which can undergo rearrangement to azacycloheptatetraene **60** (in resonance with **61**). Azacycloheptatetraene **60** will react with the free amine of a protein to give **62** initially and, following rearomatization, 2-substitutued-3*H*-acepines **63** (Scheme 28) [166]. Human serum albumin (HAS), Avidin, and IgG have each been successfully labeled by this reaction. Similarly, the addition of oligonucleotides to 3-azido-5-nitrobenzyl-[^{18}F]fluoride ([^{18}F]ANBF) has been published [209].

5.3 Multicomponent Reactions

Gouverneur and co-workers recently showed that 4-[^{18}F]fluorobenzaldehydes are efficient vehicles for ^{18}F delivery in classical multicomponent reactions [210]. Overcoming sub-stoichiometric quantities of 4-[^{18}F]fluorobenzaldehyde versus other reaction participants and prolonged reaction times witnessed in “cold” studies, radio-Groebke–Bienaymø–Blackburn reactions were successfully executed to yield [^{18}F]**64** (Scheme 29). Not illustrated here for the sake of brevity, Ugi, Passerini, and Biginelli reactions were also accomplished in good to excellent radiochemical yields. Notably, the 3,4-dihydropyrimidin-2-(1H)-ones, imidazo[1,2-a]pyridines and α-acyloxyamides obtained by these methods feature ^{18}F substituents not readily accessible by conventional direct S_NAr techniques.

5.4 Enzymatic Reactions

Organofluorine (C–F) bond formation is a rare in biological systems. In the bacterium *Streptomyces cattleya*, an enzymatic reaction forms C–F bonds by use of fluorinase enzyme. Lehel *et al.* first published the synthesis of 5′-[^{18}F]fluoro-5′deoxyadenosine ([^{18}F]-5′-FDA), in 2000 from either the bromo, chloro, or iodo precursor by traditional nucleophilic substitution [211]. However, using this method produced very low radiochemical yields of around 1% and they determined that synthesis from the adenosine precursor was not ideal [212]. Building upon this work O'Hagen and co-workers first published the utilization of the fluorinase enzyme, 5′-fluoro-5′-deoxyadenosine synthase (5′-FDAS, E.C. 2.5.1.63), for fluorine-18 labeling a decade ago [213-215]. Originally they focused on the conversion of *S*-adenosyl-L-methionine (SAM) into [^{18}F]-5′-FDA, through incubation of protein extract from *S. cattleya* with [^{18}F]HF and SAM. The major disadvantage of this reaction was that using the wild-type enzyme required reaction conditions of 5 hours with radiochemical yield of 1% being obtained.

Significant improvements were found with the isolation, cloning, and overexpression of fluorinase enzyme in *E. coli* and a multistep synthesis, resulting in radiochemical yields of around 45% after 4 hours [216]. The fluorinase catalyzed reaction of SAM into [^{18}F]-5′-FDA and L-methionine is in an equilibrium which can be shifted to produce higher yields of [^{18}F]-5′-FDA through the removal of L-methionine by enzyme conversion or further

coupled enzyme reactions of [^{18}F]-5′-FDA. A variety of coupled enzyme reactions generated radiochemicals including: 5′-deoxy-5′-[^{18}F]fluoroinosine (5′-[^{18}F]FDI), 5-deoxy-5-[^{18}F]fluoro-D-ribose (5-[^{18}F]FDR), 5′-deoxy-5′-[^{18}F]-fluorouridine (5′-[^{18}F]FDU), and others as detailed by O'Hagan and co-workers in their mini-review [217]. A more recent publication refined the synthesis of 5-[^{18}F]FDR by a two-step biotransformation of SAM with 5′-FDAS followed by conversion of [^{18}F]-5′-FDA into [^{18}F]-5′-FDA with the nucleoside hydrolase isolated from *Trypanosoma vivax* (*Tv*NH) [218]. Their one-pot reaction biotransformation produced radiochemical yields of around 80%, a significant improvement of the enzyme-catalyzed addition of fluorine-18.

5.5 Beyond the C–F Bond

The last few years have seen radiochemists begin to move beyond the standard C–F associated with fluorine-18 chemistry, and a number of attractive examples that exploit the mild conditions associated with fluorine-acceptor chemistry have been reported. Fluorine-acceptor chemistry takes advantage of stable fluorine bonds to aluminum, boron and silicon. These bonds have strong Lewis acid character and, like its fluorine-19 counterpart, fluorine-18 can be introduced under mild ion-exchange or chelation conditions. For example, the [^{18}F]fluoroorganosilanes: [^{18}F]fluorotriphenylsilane, [^{18}F]fluoro-*t*butyldiphenylsilane, and [^{18}F]fluorodi-*t*butylphenylsilane **65**, were evaluated by Schirmacher and colleagues [219]. They determined that di-*tert*-butyl substituted peptides gave the greatest *in vivo* stability in addition to ease of labeling with fluorine-18 to yield **[^{18}F]66** (Scheme 31a). Development of a one-step kit-like labeling of boronic acid ester peptides **67** with fluorine-18 has to give **[^{18}F]68** been reported by Perrin and colleagues. This chemistry is rare in that it does not require drying of fluorine, and thus can be carried out under aqueous conditions (Scheme 31b) [220]. A final kit-like preparation for radiolabeling includes, 1,4,7-triazacyclononane-triacetic acid (NOTA) peptides with Al^{3+} pre-chelated **69** [221]. Fluorine-18 can then form a complex creating a stable aluminum-fluorine bond **70** (Scheme 31c).

Inkster and co-workers have developed syntheses of sulfonyl fluoride-based prosthetic groups [222]. For example, [^{18}F]3-formyl-2,4,6-trimethylbenzenesulfonyl fluoride **71** could be prepared from the corresponding sulfonyl chloride, and was then used to radiolabel a bombesin analog (BBN-ONH_2) through imine formation to provide **[^{18}F]72** (Scheme 32).

6. Technologies for Enhancing Fluorine-18 Radiochemistry

6.1 Solid-phase Radiochemistry

Solid-phase organic radiosynthesis (SPOR) is a relatively new area of research and only a few peer-reviewed articles and patents have been published to date. The electrophilic, nucleophilic and prosthetic group chemistry described throughout this review have all been adapted for SPOR, and are highlighted below as well as in recent review articles from our group [223, 224]. For example, the [^{18}F]fluoroDOPA **76** SPOR (Scheme 33), uses the same radiochemistry as employed in the corresponding solution-phase electrophilic radiosyntheses. [^{18}F]FluoroDOPA **76** is synthesized by treatment of the polymer-supported stannane precursor **74** with electrophilic fluorine [225]. Fluorination results in concomitant

cleavage of the protected intermediate **75**, and treatment with acid furnishes [^{18}F]fluoroDOPA **76**. All stannane by-products as well as unreacted precursor remain bound to the solid-support and can be removed by simple filtration.

Nucleophilic fluorination reactions have also been adapted to solid-phase conditions. As noted above, [^{18}F]FDG is the most widely used fluorine-18 labeled radiopharmaceutical to date, and so the synthesis has also been explored in the solid-phase setting. Strategies utilizing perfluorsulfonyl linker units have been reported by Wadsworth [225, 226] and Brady [227, 228], and illustrate proof-of-concept (Scheme 33). The cleavage step utilizes standard radiofluorination conditions employing potassium carbonate and Kryptofix 2.2.2 to generate the labeled fully-protected sugar **10**. Subsequent acidic deprotection provided [^{18}F]FDG (**11**) in 73% RCY (EOB) according to Wadsworth's strategy. The perfluorosulfonate linker has also been used to prepare other compounds, such as FACBC (and related analogs) [229] and NADH: ubiquinone oxydoreductase inhibitors [230]. However in certain cases, a simple sulfonate group has also been used to attached substrates to the resin, such as in the radiosynthesis of [^{18}F]FDDNP and fluorinated analogs of Pittsburgh Compound B [227, 228].

As highlighted in Section 4.3, diaryliodonium species are attractive precursors for radiolabeling inactivated aryl groups with electron-donating or no substituents. Brady and colleagues have developed aryliodonium-supported resins **80**, and utilized them in the solid-phase radiosynthesis of [^{18}F]fluorouracil **81** (Scheme 35) [227, 228, 231].

Finally, prosthetic groups labeled with fluorine-18 have also been adapted for use in SPOR. This can involve the solid-phase synthesis of prosthetic groups such as the synthesis of [^{18}F]fluorobromomethane reported by Brady and co-workers [227, 228]. Alternatively, peptide radiolabelling has been investigated by Sutcliffe using conjugation of a solution-phase prosthetic group (such as [^{18}F]4-fluorobenzoic acid **83**) with a resin-bound peptidic substrate **82** (Scheme 36) [232-235]. The strategy was straightforward, and the two-step conjugation yielded radiolabelled peptide **84** from 70% to 80% RCY at the end of the synthesis.

6.2 Microfluidics

The radiochemical reactions discussed herein are typically conducted in synthesis modules containing a reaction vessel. Subsequent purification is then achieved *via* semi-preparative HPLC or solid-phase extraction (SPE). However, the small scale of the radiochemical syntheses described herein has led many to explore whether microfluidic-assisted radiochemistry is more appropriate for synthesizing radiopharmaceuticals. There are three strategies typically employed: continuous-flow systems; batch-based reactor systems and, more recently, digital droplet approaches (recent reviews: [236-240]). Continuous-flow systems typically come to mind when discussing classical microfluidics and appear to be the most widely used, often for the synthesis of [^{18}F]FDG as proof-of-concept [241]. However, more adventurous chemistry is possible, highlighted by a recent adaption of the Hoffman rearrangement to a microfluidics system reported by Palmeiri and co-workers [242], and the range of other microfluidic-assisted syntheses of radiopharmaceuticals reported in recent years ([236-240] and references therein). In many cases microfluidic approaches offer

increased yields over their “macrofluidic” counterparts, but the field is still in its infancy and remains confined to those radiochemical laboratories willing to invest in specialized microfluidic equipment for exploratory and development purposes. Time will tell whether the benefits are sufficient for microfluidics to replace the classical approaches to fluorine-18 radiochemistry used daily in radiopharmaceutical manufacturing facilities around the world.

7. Applications of PET Imaging

The fluorine-18 labeled radiopharmaceuticals described herein, when combined with PET imaging, offer a powerful technology that finds utility in personalized medicine within a healthcare setting, as well as drug discovery within the pharmaceutical industry.

7.1 Applications of PET Imaging in a Healthcare Setting

In a healthcare setting, PET imaging is routinely used for the non-invasive diagnosis and staging of diseases, such as cancer or dementia, that previously would have required invasive biopsy or even post-mortem evaluation. For example, neurologists in the United States estimate that dementia affects 14,000 / 100,000 of the population, including 24% of people over the age of 80 [243]. However, the symptoms associated with dementia can result from any number of clinically overlapping conditions, and current clinical diagnostic accuracy is only ∼60–80%. This lack of appropriate tools makes diagnosis and management of patients difficult. To address this issue, significant work has been undertaken to develop radiopharmaceuticals that allow non-invasive imaging of dementias by PET imaging. As Alzheimer's disease (AD) is the most common, accounting for 50% of dementia cases, and is a fatal disease with no treatment, significant work has focused on this condition. The most commonly explored strategy to date involves imaging of amyloid plaques, because for decades the presence of amyloid plaques, traditionally identified during post-mortem by a pathological stain, has been the definitive diagnosis of AD. Thus, [^{11}C]PiB (University of Pittsburgh) [244], [^{18}F]flutemetamol (GE Healthcare) [245], [^{18}F]amyvid ([^{18}F]florbetapir, Avid Radiopharmaceuticals / Eli Lilly) [246], and [^{18}F]florbetaben (Bayer Healthcare / Piramal Healthcare)[247] have all been extensively developed. These compounds all show high cortical uptake in amyloid-positive patients [248], and proof-of-mechanism has been confirmed by pivotal autopsy studies [249, 250]. [^{18}F]Amyvid was the first of these to garner marketing approval from the U.S. FDA, in April 2012, as a radioactive diagnostic agent for PET imaging of the brain to estimate β-amyloid neuritic plaque density in adults. These agents are expected to be crucial, if an anti-amyloid therapeutic strategy is identified.

The functional information obtained from one or more PET scans can enable differentiation of clinically overlapping conditions that would be difficult or impossible by other means. For example, patients in one study at the University of Michigan received an amyloid PET scan ([^{11}C]PiB) and a VMAT2 PET scan ([^{11}C]DTBZ), and combining the findings from both scans allowed accurate differentiation of patients with Alzheimer's disease, frontotemporal dementia and dementia with Lewy bodies (Figure 2).

In the oncology arena, PET imaging can be used to garner a wealth of information. For example, at its simplest FDG-PET can be used identify and stage cancer (for a recent review see: [251]), but it is increasingly finding more sophisticated applications such as prediction

of patient response to therapy and then monitoring for that expected response. In an example that employs PET at the interface between healthcare and drug discovery, and clearly shows our advance towards personalized medicine, PET can be used to predict whether or not a patient is likely respond to a proposed treatment regimen. Van der Veldt and co-workers employed [^{11}C]docetaxel to evaluate pharmacokinetics on a case by case basis for patients being considered for docetaxel chemotherapy [252]. Patients received a [^{11}C]docetaxel baseline PET scan, followed by a therapeutic scan ([^{11}C]docetaxel + 75 mg·m^{-2}), and the [^{11}C]docetaxel K*i* derived from the baseline PET scan was found to correlate with the area under the curve for the tumor of docetaxel during the therapeutic scan (Spearman $\rho = 0.715$; $P = 0.004$), and with tumor response to docetaxel chemotherapy (Spearman $\rho = -0.800$; $P = 0.010$). In this study, [^{11}C]docetaxel-PET was therefore able to predict tumor uptake of docetaxel, and predict the likelihood of a patient responding favorably to a docetaxel chemotherapy regimen. In addition to improving patient prognosis by tailoring chemotherapy to individual patients, predicting response to therapy prior to attempting costly treatment can be expected to lead to significant cost savings. In a final application in oncology, if patients receive multiple PET scans in series, then PET can also be used an accurate and convenient method of monitoring their response to treatment. Such an approach has been used to great effect by the Van den Abbeele group, who use [^{18}F]FDG PET to monitor patient response to treatment of gastrointestinal stromal tumors (GIST) with imatinib [253]. If a patient is responding, metabolic changes in the tumor can be seen in the PET scan weeks or even months before tumor shrinkage is apparent on the CT scan. Similarly, if a patient is not responding, this is also apparent by [^{18}F]FDG PET. For example, secondary c-kit mutations frequently lead to GIST with acquired resistance to imatinib. In such cases, patients can be switched to sunitinib, which has been shown to be effective, and using PET imaging to tailor treatment to an individual moves us ever closer to the age of personalized medicine.

7.2 Application of PET Imaging in a Drug Discovery Setting

PET Imaging is being used in the pharmaceutical industry to more rapidly and effectively answer questions that are central to the drug discovery process; an area recently reviewed by Matthews and co-workers [6]. For example, at its simplest, biodistribution studies with radiolabeled versions of drug candidates can be used to non-invasively determine whether or not a molecule reaches the target tissue *in vivo* in rodents and primates initially, and eventually in humans. For example, this approach can be used in the development of CNS drugs to evaluate whether or not a candidate molecule crosses the blood-brain-barrier [254]. Data obtained from such experiments can also provide a wealth of other important information, such as whether or not a drug candidate also accumulates at non-target sites with potential to cause side effects or dose-limiting toxicity at intended therapeutic doses. Beyond pharmacological and toxicological information, dynamic PET scans also provide data about pharmacokinetics and pharmacodynamics, including excretion pathways. If blood samples are drawn throughout a PET scan, analyzed via radio-TLC or radio-HPLC, and compared to authentic samples of the parent compound, then information is equally readily accessible on how a given compound is metabolized.

More sophisticated studies can also be designed to explore receptor occupancy and provide valuable information for guiding drug development decisions. A seminal paper in this area is the report by Bergström and co-workers investigating the substance P (neurokinin 1 (NK_1) receptor) antagonist aprepitant, which was being considered as both a treatment for chemotherapy-induced nausea and as an anti-depressant [255]. Using [^{18}F]SPA-RQC, an NK_1-selective PET radiotracer, imaging studies confirmed ≥90% NK1 receptor occupancy was achieved in patients receiving at least 100 mg/day (Figure 3). This finding is consistent with the effective antiemetic regimen (125 mg on day 1 of chemotherapy, followed by 80 mg on days 2 and 3), and indeed, aprepitant is still used in this capacity today. However, 300 mg / day was not effective in the treatment of depression during a Phase III clinical trial. The PET data with [^{18}F]SPA-RQC confirmed that this dose was more than suitable to achieve the targeted receptor occupancies, and so was critical in the decision to terminate the Phase III trial of aprepitant as an antidepressant and ultimately saved Merck millions of dollars. In addition, this *in vivo* biomarker could then be employed as a feedback biomarker within Merck's drug development program, feeding information back into the discovery pipeline. For example, using information from the PET studies would allow receptor occupancy above a certain level to be defined as a success criterion for backup drug candidates also targeting the NK1 receptor for treatment of depression.

A finally valuable application of PET is selection of appropriate patients for a clinical trial. For example, when Eisai was conducting a clinical trial to evaluate E2609, a BACE (beta-site amyloid precursor protein-cleaving enzyme) inhibitor for the potential treatment of Alzheimer's disease, they recognized the importance of populating the clinical trial with cognitively impaired patients positive for amyloid pathology [256]. Inclusion of amyloid-negative cognitively impaired patients would lead to incorrect efficacy outcomes. Therefore patients would only be enrolled in the clinical trial following an amyloid-positive [^{18}F]flutemetamol PET scan, as [^{18}F]flutemetamol PET can stratify patients based upon presence or absence of amyloid pathology (Figure 4) [257]. Identifying the right patients for participation in clinical trials can be expected to facilitate market entry of important new therapeutics, and reduce time to market going forward.

8. Conclusions

In response to the increasing demand for novel radiopharmaceuticals labeled with fluorine-18, a number of research groups have initiated programs directed toward the development of new methodology for late stage fluorination. This global effort has brought to bear an impressive range of methods and reactions for fluorine-18 radiochemistry, including adaptation of many state-of-the-art reactions from mainstream synthetic organic and fluorine chemistry. The articles highlighted herein demonstrate significant advances pertinent not only to radiolabeling with fluorine-18, but electrophilic and nucleophilic fluorination in general. The application of these methods together with solid-phase synthesis and microfluidic technologies is enabling access to increasingly complex radiopharmaceuticals previously difficult to obtain.

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Abbreviations

β^+	positron
$\mathbf{e}^-$	electron
ν	neutrino
γ	gamma ray photon
5-HT1A	serotonin-1A receptor
5′-FDAS	5′-fluoro-5′-deoxyadenosine synthase
9-BBN	9-borabicyclo[3.3.1]nonane
AD	Alzheimer's disease
ATP	adenosine-5′-triphosphate
BACE	beta-site amyloid precursor protein-cleaving enzyme
BBB	blood brain barrier
Boc	di-*t*-butyl dicarbonate
Bq	Becquerel
BTHEB	Boc-trimethylammoniumhomo-epibatidine
Bz	benzyl
CT	computed tomography
Ci	Curie
CNS	central nervous system
COX-2	cyclooxygenase-2
cRGD	integrin receptor peptide cyclic Arg-Gly-Asp
CuAAC	copper-catalyzed azide-alkyne 1,3-dipolar cycloaddition
DIPEA	*N*,*N*-diisopropylethylamine
DMT	dimethoxytrityl

EC	electron capture
EF5	2-(2-nitro-1*H*-imidazol-1-yl)-*N*-(2,2,3,3,3-pentafluoropropyl)acetamide
EOB	end of bombardment
EOS	end of synthesis
Fmoc	fluorenylmethyloxycarbonyl chloride
GIST	gastrointestinal stromal tumors
GluT	glucose transporters
HATU	(1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate)
HPLC	high-performance liquid chromatography
K222	Kryptofix® 2.2.2
L-DOPA	L-3,4-dihydroxyphenylalanine
MOE	methoxyethyl
MRI	magnetic resonance imaging
mGluR5	metabotropic glutamate receptor 5
NaChR	α4β2-subtype of the nicotinic acetylcholine receptor
NADH	nicotinamide adenine dinucleotide
N.C.A	no-carrier-added
NCBrHEB	norchloro-bromo-homo-epibatidine
Nos	nosyl
NOTA	1,4,7-triazacyclononane-triacetic acid
Oligo	oligonucleotide
PET	positron emission tomography
RCY	radio chemical yield
SAM	*S*-adenosyl-L-methionine
SPE	solid-phase extraction
SPECT	single-photon emission computed tomography
SPOR	solid-phase organic radiosynthesis
substance-P	neurokinin 1 (NK_1) receptor
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
TIPS	triisopropylsilane

***Tv*NH**	*Trypanosoma vivax*
US	ultrasound
[^{18}F	
[^{18}F]2FA	2-([^{18}F]fluoro)-3-[(2*S*)-2- azetidinylmethoxy]pyridine
[^{18}F]-5′-FDA	5′-[^{18}F]fluoro-5′deoxyadenosine
[^{18}F]-5′-FDI	5′-deoxy-5′-[^{18}F]fluoroinosine
[^{18}F]-5′-FDU	5′-deoxy-5′-[^{18}F]-fluorouridine
[^{18}F]AcOF	[^{18}F]acetyl hypofluorite
[^{18}F]ANBF	3-azido-5-nitrobenzyl-[^{18}F]fluoride
[^{18}F]APF	4-azidophenacyl-[^{18}F]fluoride
[^{18}F]FClO3	[^{18}F]perchloryl fluoride
[^{18}F]FDOPA	L-3,4-dihydroxy-6-[^{18}F]fluorophenylalanine
[^{18}F]DAST	[^{18}F]diethylaminosulfur trifluoride
[^{18}F]FAZA	[^{18}F]fluoroazomycin arabinoside
[^{18}F]FBAM	*N*-(6-(4-[^{18}F]fluorobenzylidene)aminooxyhexyl)maleimide
[^{18}F]FBEM	*N*-(2-(4-[^{18}F]fluorobenzamido)ethyl)maleimide
[^{18}F]FCH	[^{18}F]fluorocholine
[^{18}F]FDDNP	2-(1-(6-[(2-[^{18}F]fluoroethyl)(methyl)amino]-2-naphthyl)-ethylidene)malononitrile
[^{18}F]FDG	2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG)
[^{18}F]FEOBV	[^{18}F]fluoroethoxybenzovesamicol
[^{18}F]FET	*O*-(2-[^{18}F]fluoroethyl)-L-tyrosine
[^{18}F]FLT	3′-deoxy-3′-[^{18}F]fluorothymidine
[^{18}F]FMISO	[^{18}F]fluoromisonidazole
[^{18}F]FPB	[^{18}F]fluorophenacyl bromide
[^{18}F]FP-CIT	[^{18}F]fluoropropyl carbomethoxy iodophenyl nortropane
[^{18}F]FPM	*N*-(4-[^{18}F]fluorophenyl)maleimide
[^{18}F]FpyMe	1-(3-(2-[^{18}F]fluoropyridin-3-yloxy)propyl)pyrrole-2,5-dione
[^{18}F]HX4	[^{18}F]flortanidazole
[^{18}F]LBT-999	8-((*E*)-4-fluoro-but-2-enyl)-3β-*p*-tolyl-8-aza-bicyclo[3.2.1]octane-2β-carboxylic acid methyl ester
[^{18}F]MPPF	4-(2′-methoxyphenyl)-1-[2′-(*N*-2″pyridinyl)-*p*-[^{18}F]fluorobenzamido]ethylpiperazine

[^{18}F]NFSi	[18F]*N*-fluorobenzenesulfonamide
[^{18}F]SFB	*N*-succinimidyl-4-[^{18}F]fluorobenzoate
[^{18}F]SPA-RQ	[^{18}F]substance-P antagonist-receptor quantifier
[^{18}F]TBAF	[^{18}F]tetrabutylammonium fluoride
[^{18}F]XeF_2	[^{18}F]xenon difluoride
[^{11}C	
[^{11}C]DTBZ	(+)-α-[^{11}C]dihydrotetrabenazine
[^{11}C]PiB	2-(4-*N*-[^{11}C]methylaminophenyl)-6-hydroxybenzothiazole

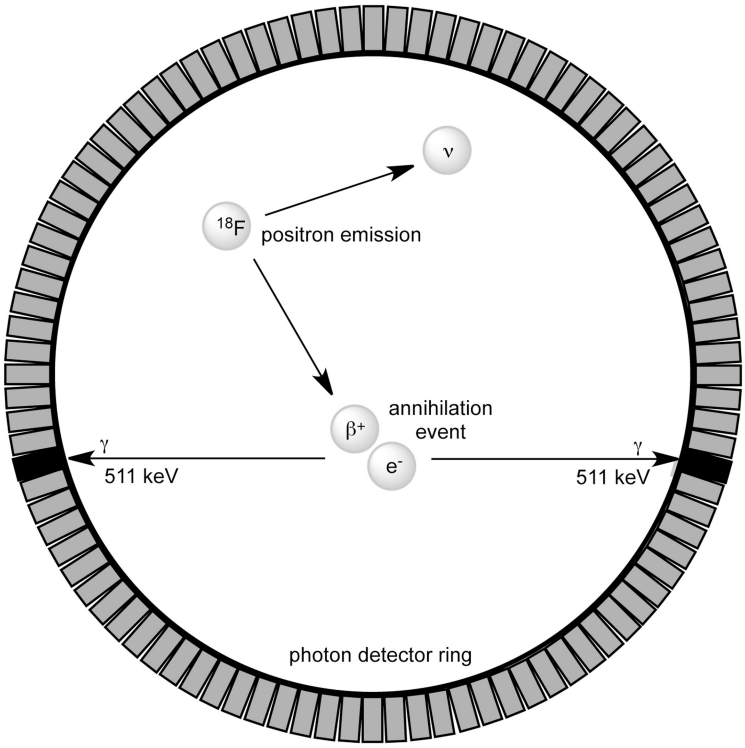


Figure 1.
PET imaging detector. Positron emission followed by an annihilation event and detection of photons.

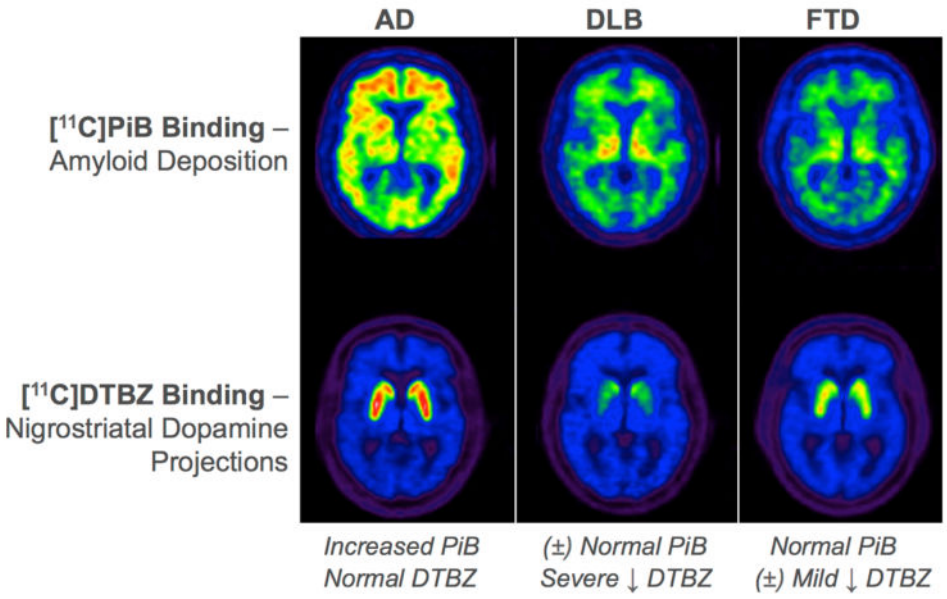


Figure 2.

Differentiation of Dementia Subtypes using PET Imaging (adapted from Burke, J. F. *et al.* Assessment of mild dementia with amyloid and dopamine terminal positron emission tomography, *Brain*, **2011**, *134 (Pt. 6)*, 1647-57; by permission of Oxford University Press)

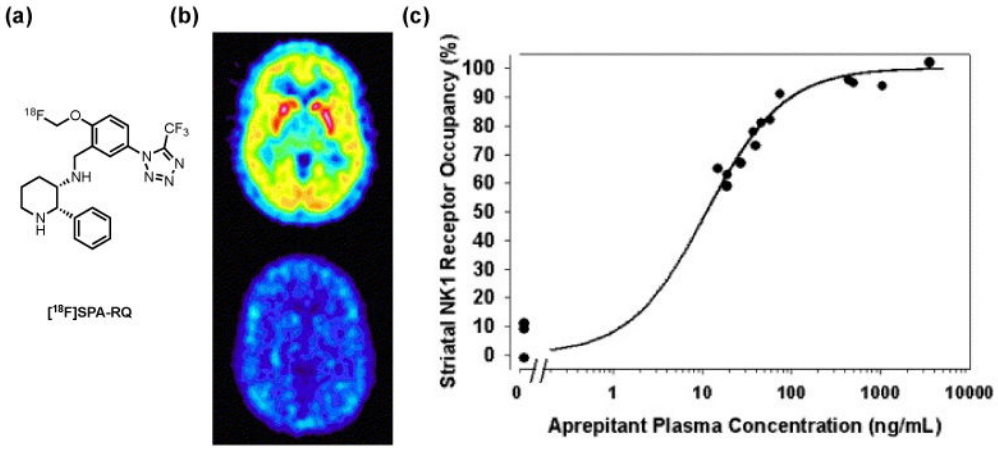


Figure 3.

(a) [^{18}F]SPA-RQ; (b) Positron emission tomography (PET) image from the striatum of a subject who received aprepitant 100 mg. Predose (top) and postdose (bottom). Subject number 01, estimated occupancy = 94%; (c) estimated relationship between plasma concentration of aprepitant and occupancy of striatal NK_1 receptors. Curve depicted is based on fit of the data to the Hill equation (slope = 1) ((b) and (c) reprinted from M. Bergström *et al.*, Human positron emission tomography studies of brain neurokinin 1 receptor occupancy by aprepitant, *Biol. Psychiatry*, **2004**, *55*, 1007-1012, Copyright (2004), with permission from Elsevier).

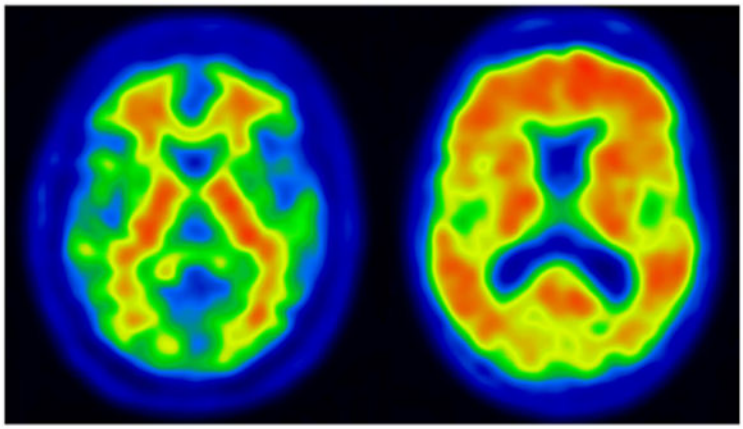
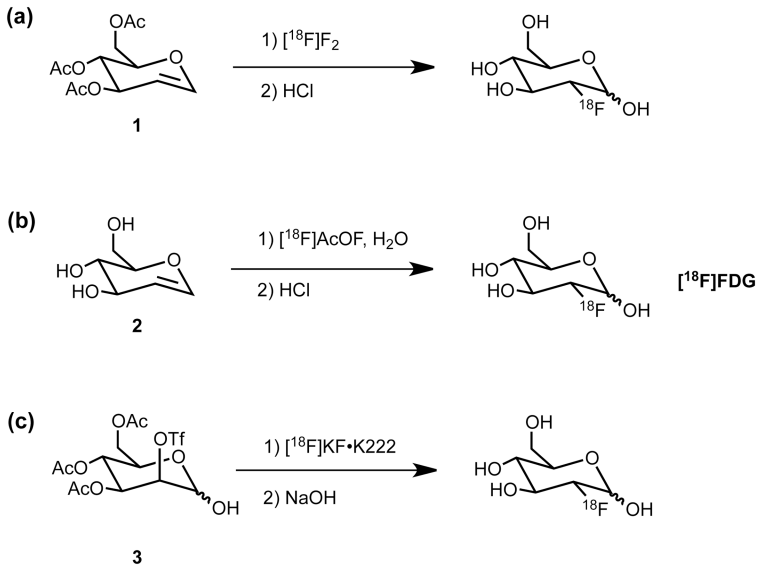


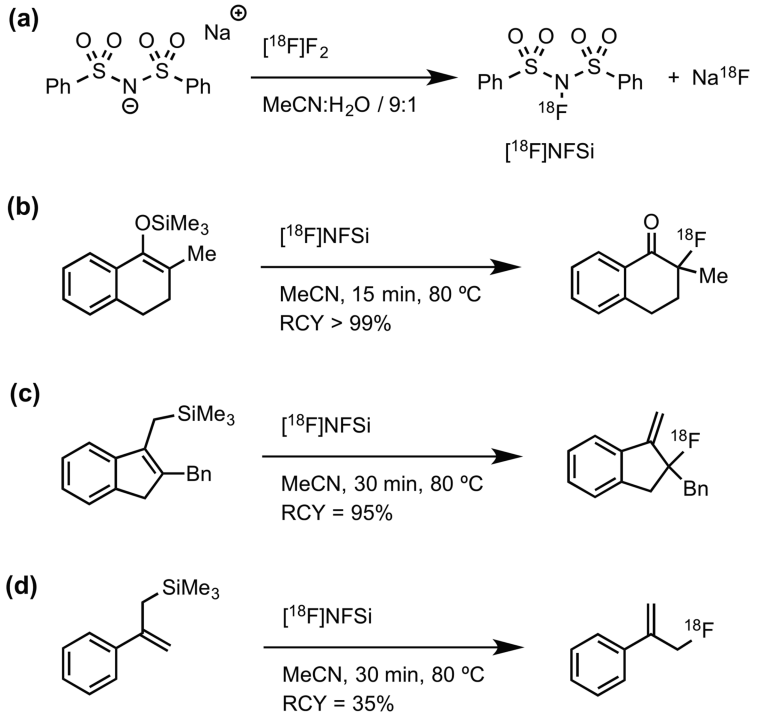
Figure 4.

Typical patterns of ^{18}F-flutemetamol uptake in negative scan (left) and positive scan (right). White matter uptake is similar in both scans, but there is considerably more uptake in gray matter in the positive scan (this research was originally published in JNM: R. Lundqvist *et al.* Implementation and Validation of an Adaptive Template Registration Method for ^{18}F-Flutemetamol Imaging Data. *J. Nucl. Med.* **2013**, *54*, 1472-1478. © by the Society of Nuclear Medicine and Molecular Imaging, Inc.



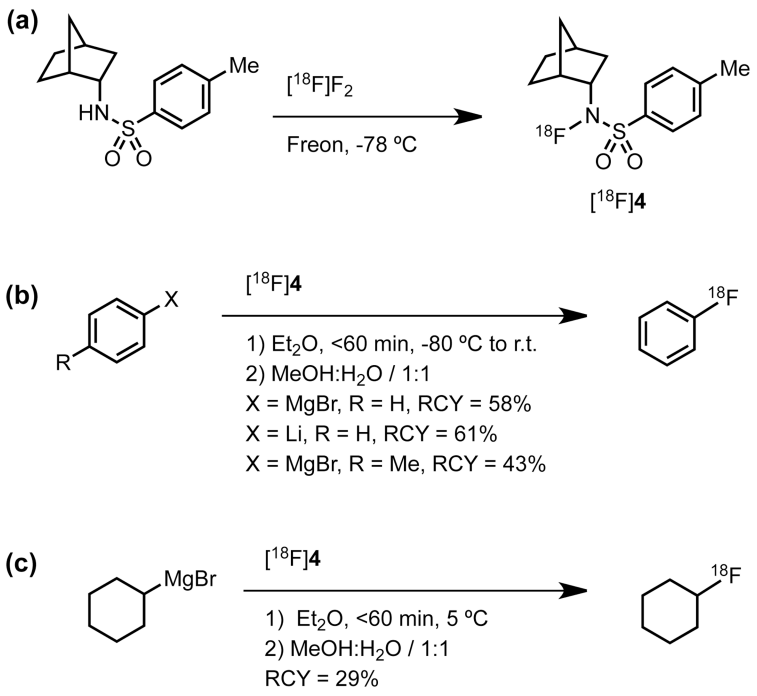
Scheme 1.

Synthesis of [^{18}F]FDG: (a) electrophilic fluorination of 3,4,6-tri-*O*-acetyl-D-glucal **1** by [^{18}F]F_2, (b) electrophilic fluorination of 3,4,6-trihydroxy-D-glucal **2** with [^{18}F]acetyl hypofluorite, and (c) nucleophilic aliphatic substation of 1,3,4,6-tetra-*O*-acetyl-2-*O*-triflate-*β*-D-mannose **3**.



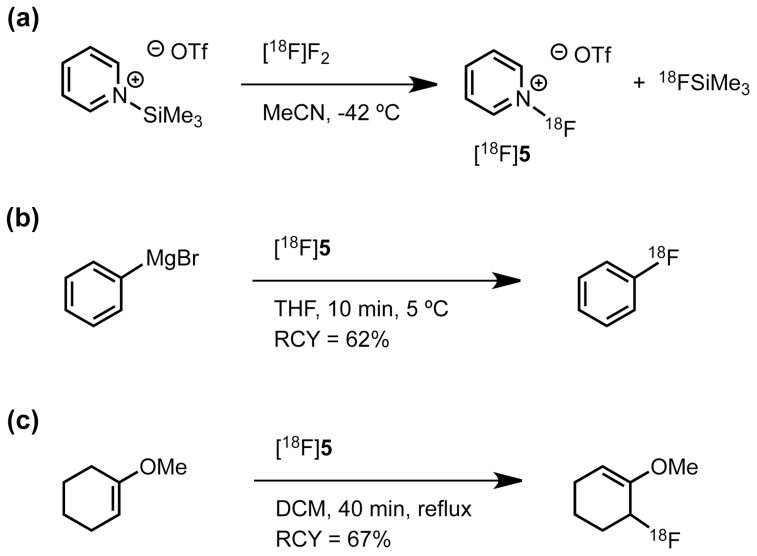
Scheme 2.

Synthesis (a) and synthetic applications (b,c,d) of [^{18}F]*N*-fluorobenzenesulfonamide.



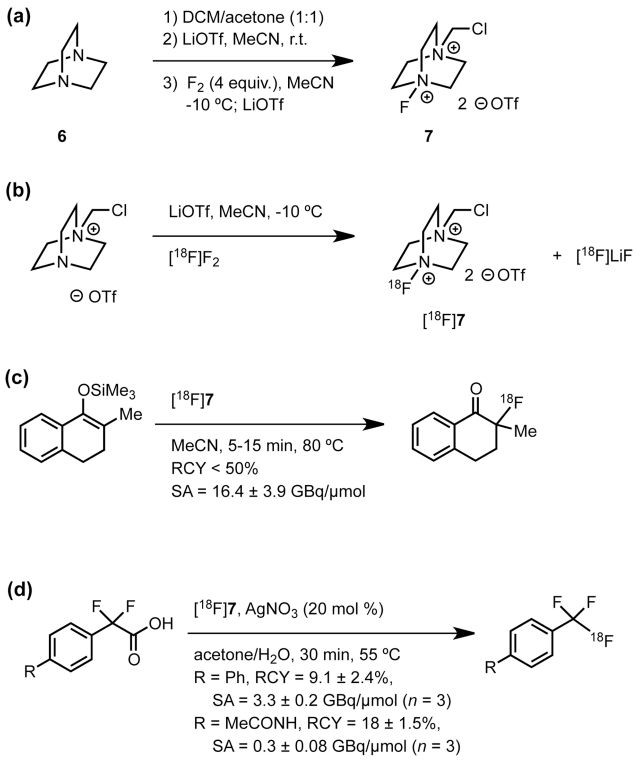
Scheme 3.

Synthesis (a) of [^{18}F]*N*-fluoro-*N*-alkylsulfonamide [^{18}F]**4**, and subsequent applications (b,c).



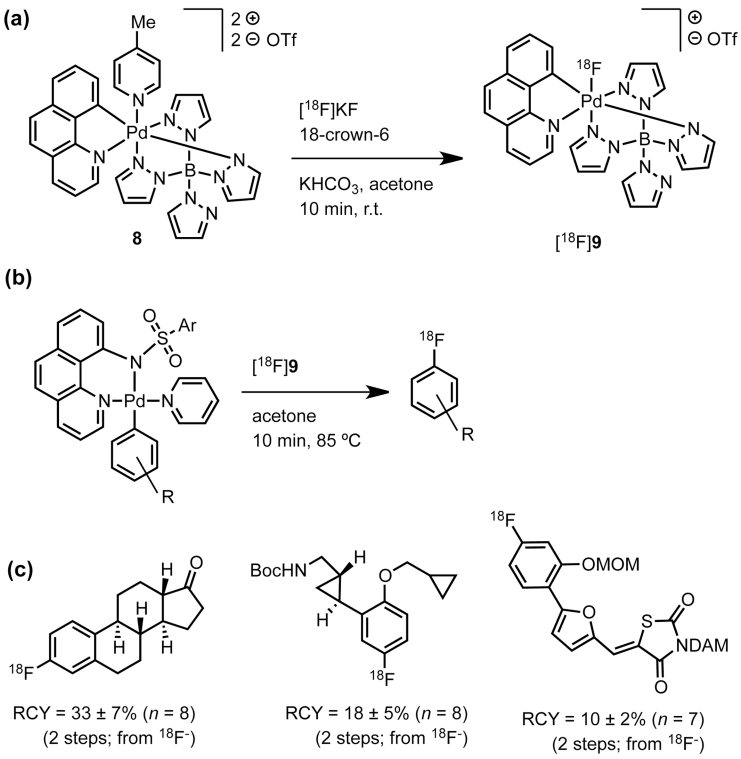
Scheme 4.

Synthesis of (a) [^{18}F]*N*-fluoropyridone [^{18}F]**5**, and (b,c) reactions.



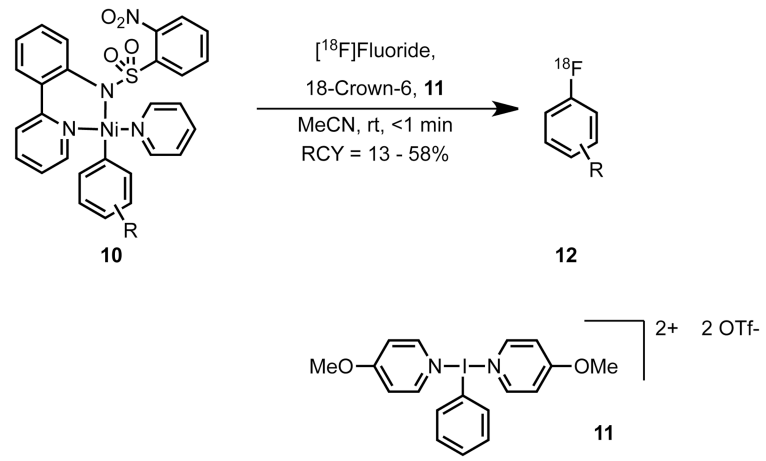
Scheme 5.

Synthesis (a,b) of [^{18}F]Selectfluor bis(triflate) ([^{18}F]**7**), (c,d) and synthetic applications.

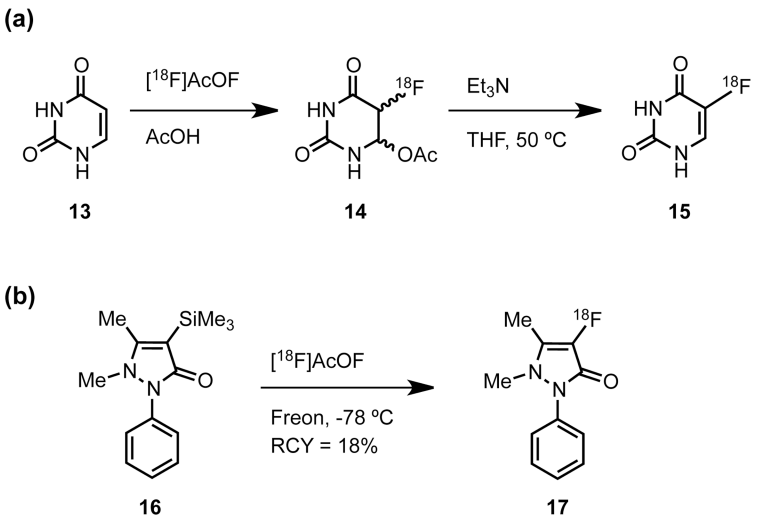


Scheme 6.

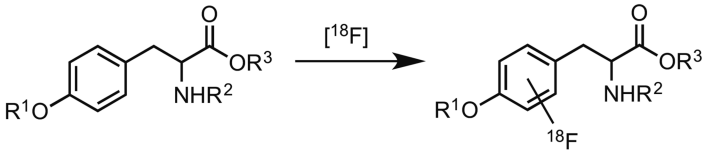
(a) [^{18}F]Fluoride-derived palladium (IV) electrophilic fluorinating reagent [^{18}F]**4**. (b) Palladium (II) aryl complex reaction with [^{18}F]**9**. (c) Fluorine-18 radiopharmaceuticals.



Scheme 7. Nickel-mediated oxidative fluorination with aqueous [^{18}F]fluoride



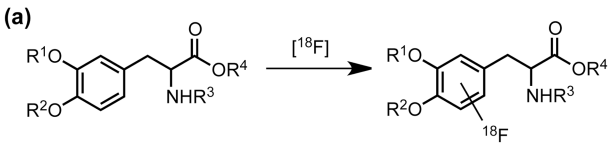
Scheme 8. Synthesis of (a) 5-[^{18}F]fluorouracil 15 and (b) 4-[^{18}F]fluoroantipyrine 17



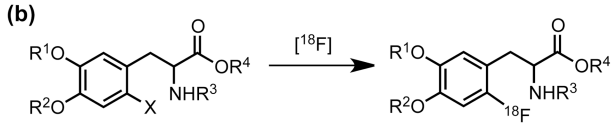
[^{18}F]	R	2- : 3-[^{18}F]fluorotyrosine
[^{18}F]F_2, HF	R^1, R^2, R^3 = H	0:100
[^{18}F]AcOF, AcOH	R^1 = Ac R^2, R^3 = H	83:17
[^{18}F]F_2, CF_3OOH	R^1, R^2 = Ac R^3 = Me	40:60

Scheme 9.

2-[^{18}F]fluorotyrosine and 3-[^{18}F]fluorotyrosine synthesis is highly reagent dependent.



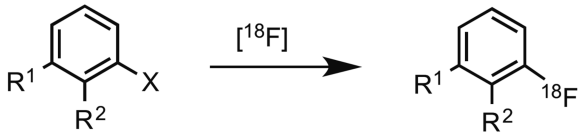
[18F]	R	2- : 5- : 6-[18F]FDOPA
[18F]F2, HF	R1, R2, R3, R4 = H	35:5:59
[18F]AcOF	R1, R4 = Me R2, R3 = Ac	50:0:50



[18F]	X	R	RCY / SA*
[18F]AcOF, $CHCl_3$	$HgOCOCF_3$	R1, R2, R4 = Me R3 = Ac	RCY < 12%
[18F]AcOF, Freon-11	$SnMe_3$	R1, R2 = Ac R3 = CHO, R4 = Et	RCY = 8%
[18F]**7**, acetone-d_6, AgOTf	$SnMe_3$	R1, R2 = Boc R3 = CHO, R4 = Et	RCY = 12.1 ± 3.7% SA = 3.4 ± 0.1 GBq/μmol
[18F]**7**, acetone-d_6, AgOTf	Ag	R1, R2, R4 = Me R3 = Boc	RCY = 19 ± 12% SA = 2.6 ± 0.3 GBq/μmol

Scheme 10.

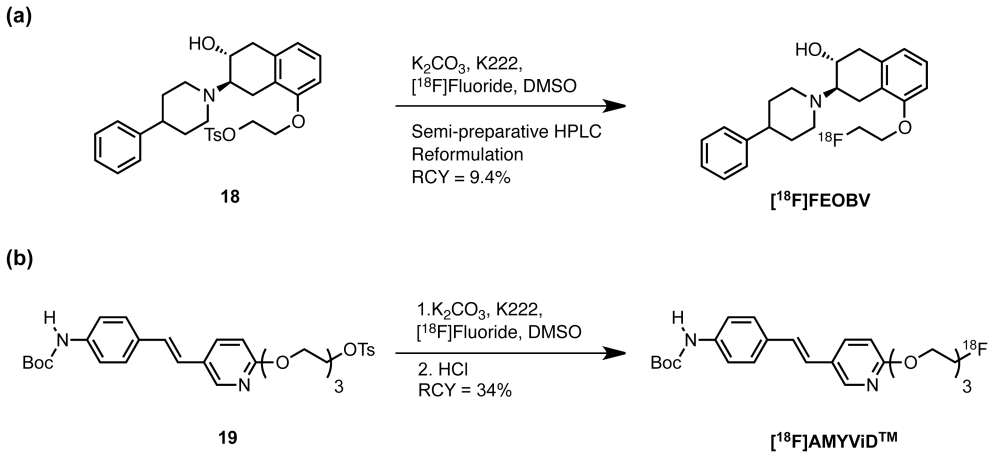
6-[18F]fluoroDOPA ([18F]FDOPA) synthesis by (a) unselective direct fluorination and (b) selective fluorination via organometallic precursors. *RCY and SA given for deprotected [18F]FDOPA.



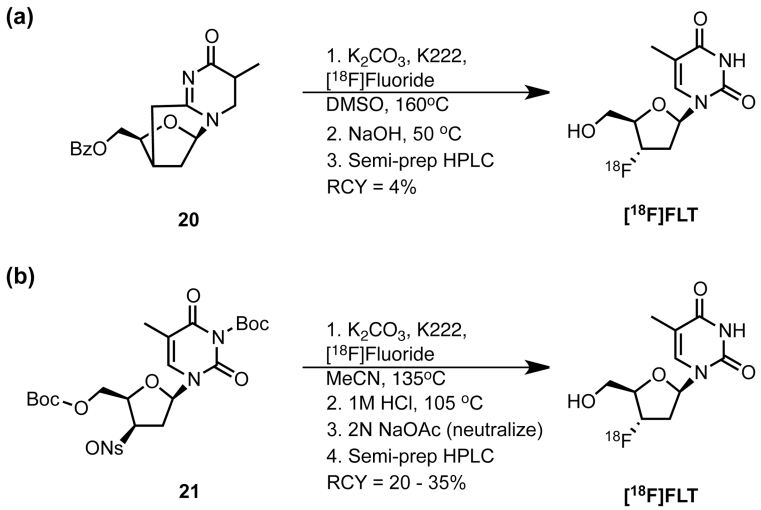
[18F]	X	R
[18F]FClO3	Li	R1 = H, R2 = OMe
[18F]FClO3	Li	R1, R2 = OMe
[18F]AcOF, Freon-11	Li, MgBr	R1, R2 = H

Scheme 11.

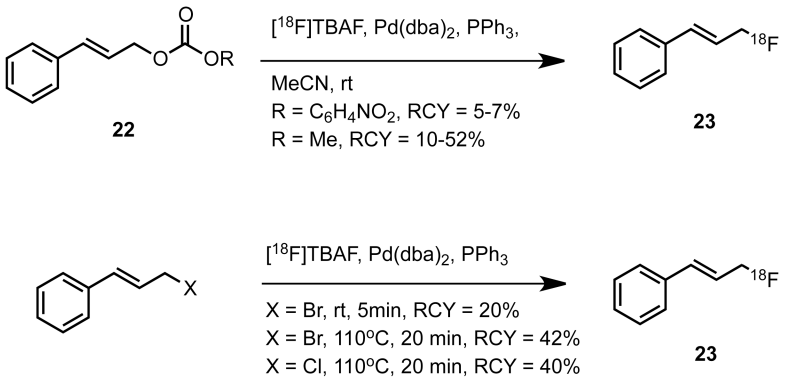
Electrophilic fluorination of aryl Grignard and aryl lithium compounds via carbanion intermediates.



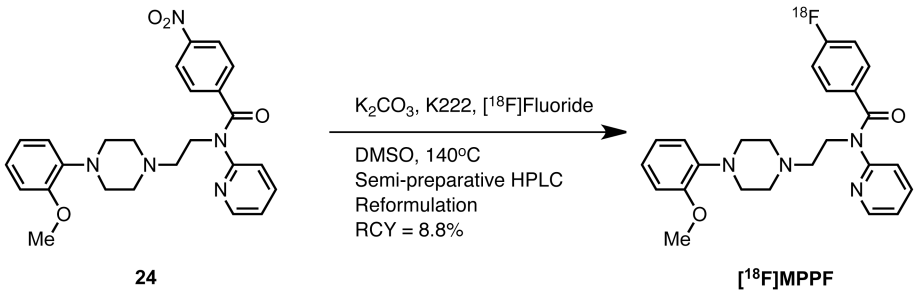
Scheme 12. Radiosynthesis of [^{18}F]FEOBV and [^{18}F]AMYViD™



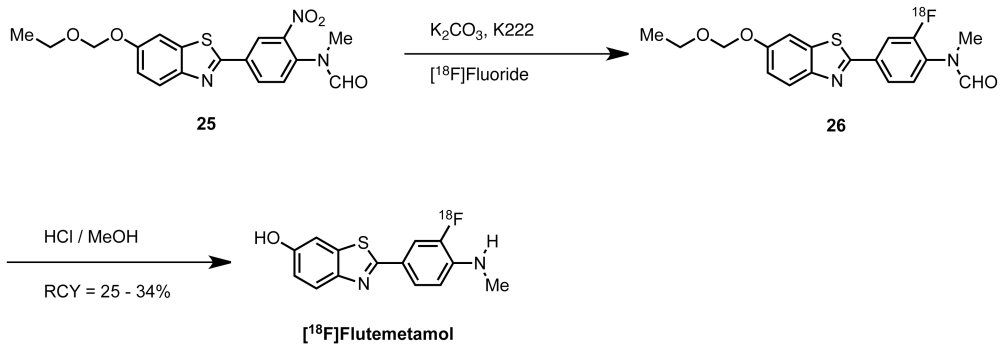
Scheme 13. Strategies for the Synthesis of [^{18}F]FLT



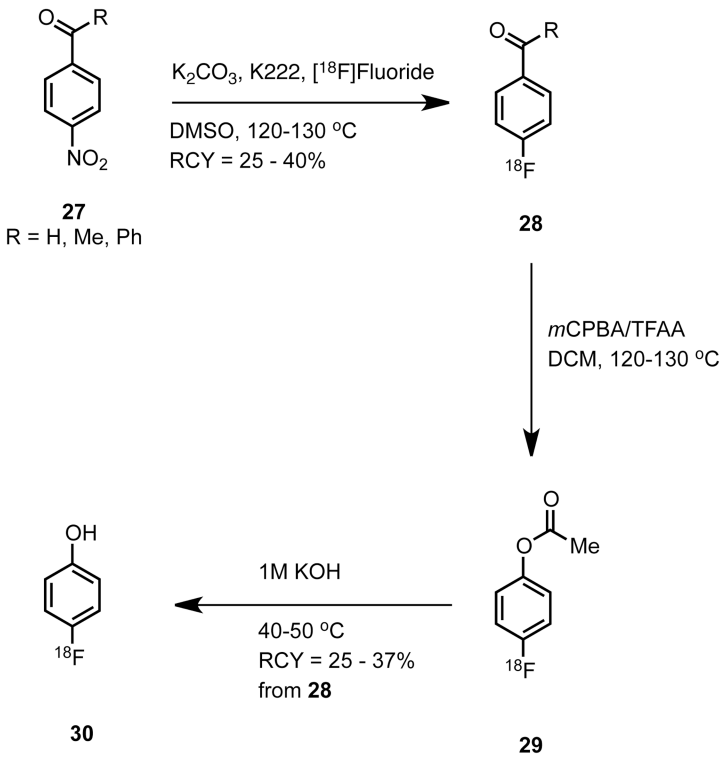
Scheme 14.
Pd-Catalyzed allylic [^{18}F]fluorination reactions.



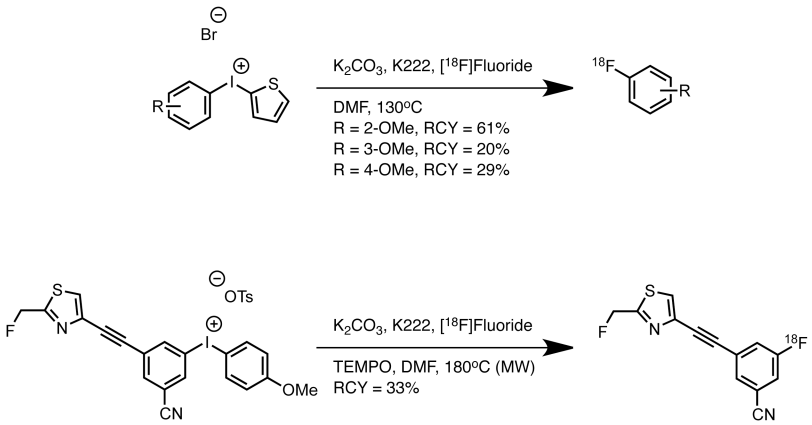
Scheme 15. Radiosynthesis of [^{18}F]MPPF



Scheme 16. Radiosynthesis of [^{18}F]Flutemetamol

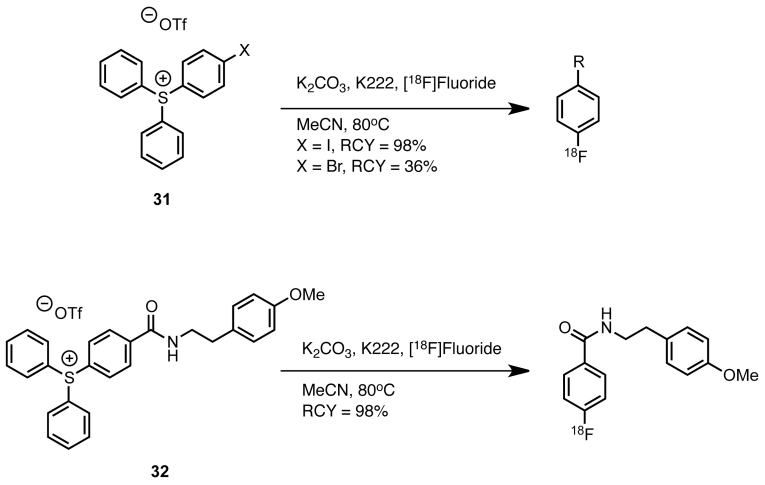


Scheme 17. Synthesis of Radiolabeled Phenols *via* Bayer-Villiger Chemistry

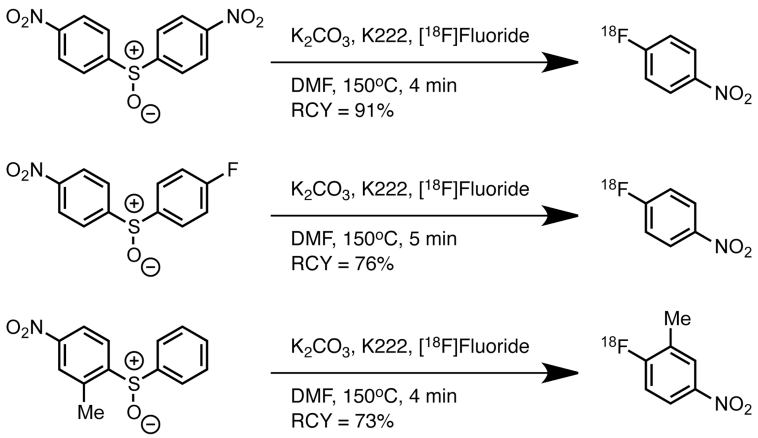


Scheme 18.

Diaryliodonium salts for the preparation of [^{18}F]fluoroarenes.

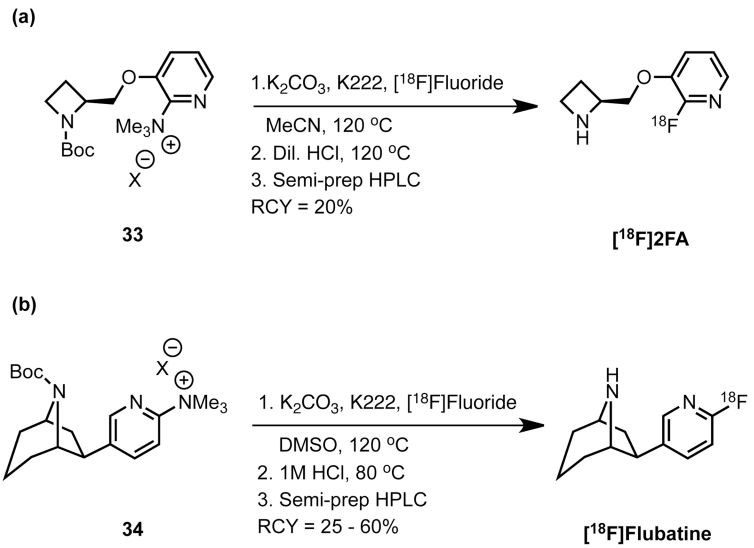


Scheme 19.
[^{18}F]Fluoroarenes from triarylsulfonium salts.

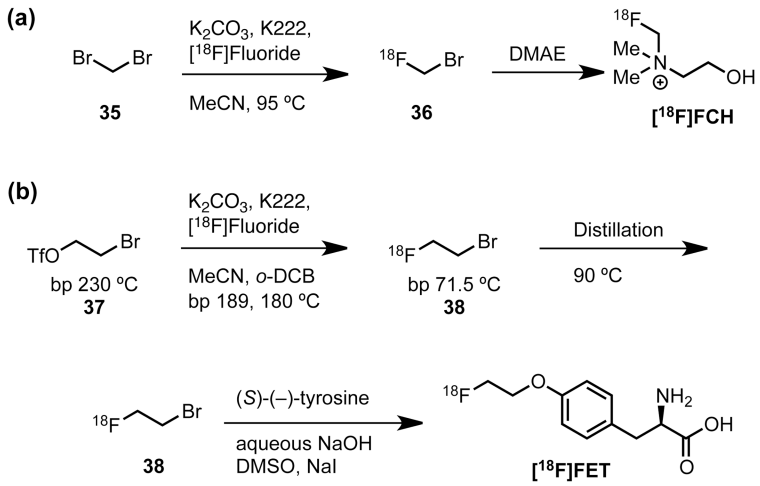


Scheme 20.

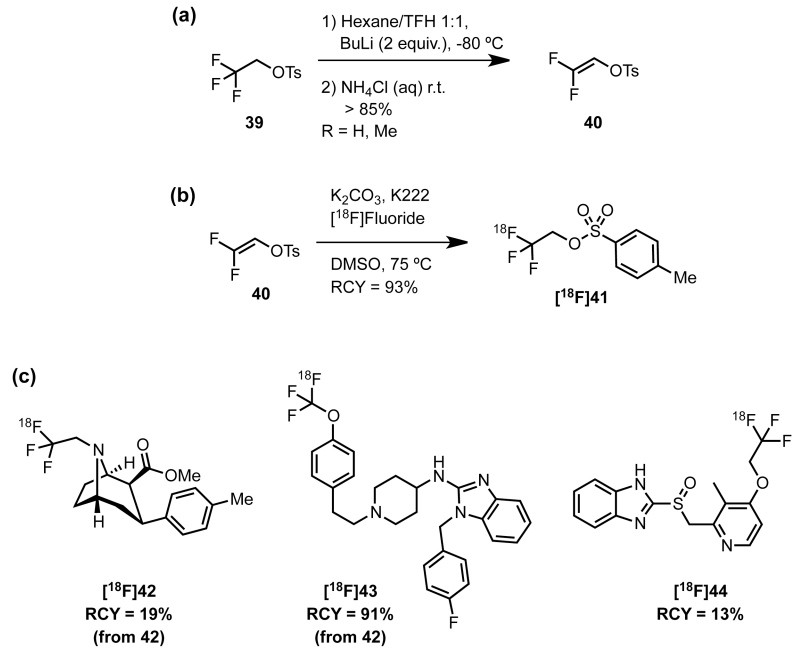
p-[^{18}F]Fluoroarenes from diarylsulfoxides.



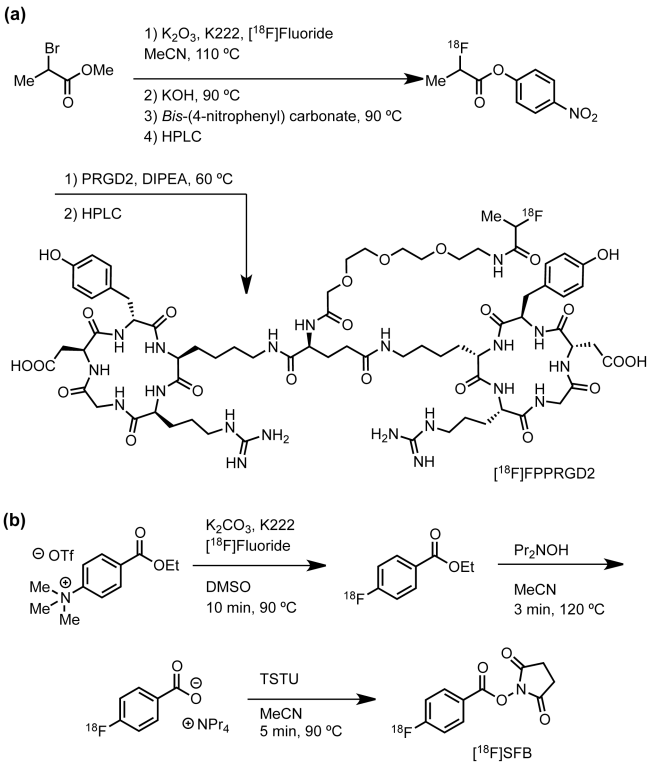
Scheme 21. Radiosynthesis of NAChR Radioligands (a) [^{18}F]2-FA and (b) [^{18}F]Flubatine



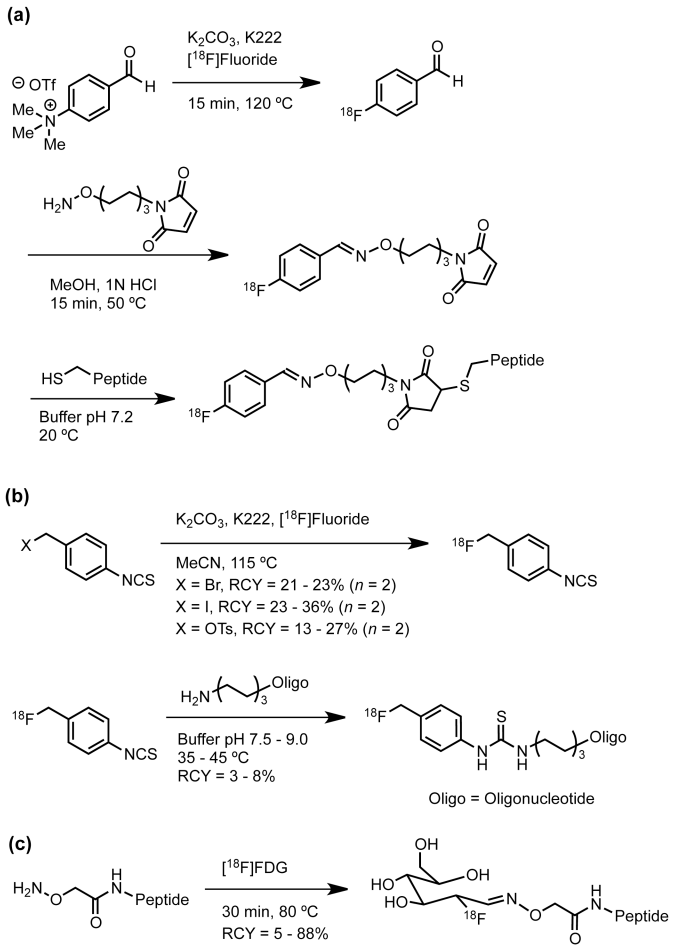
Scheme 22. Radiosynthesis of (a) [^{18}F]FCH and (b) [^{18}F]FET



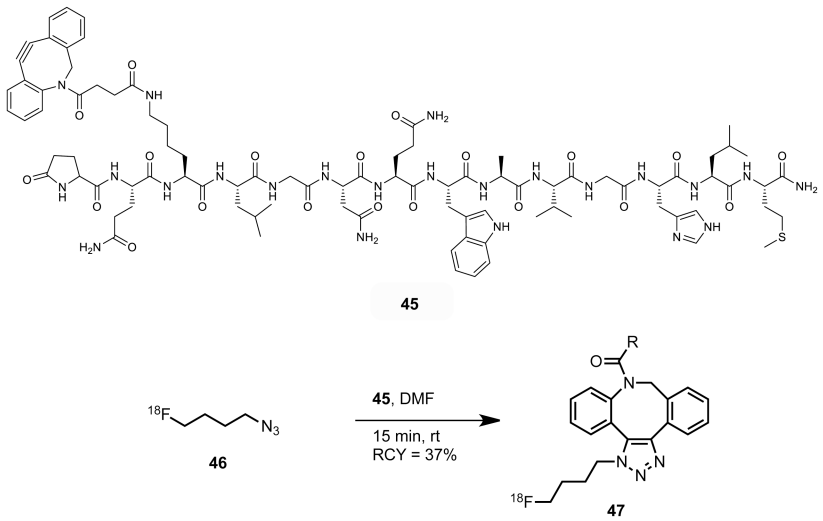
Scheme 23. Generation of [^{18}F]CF_3 Groups



Scheme 24. Radiosynthesis of [^{18}F]FPPRGD2 and [^{18}F]SFB

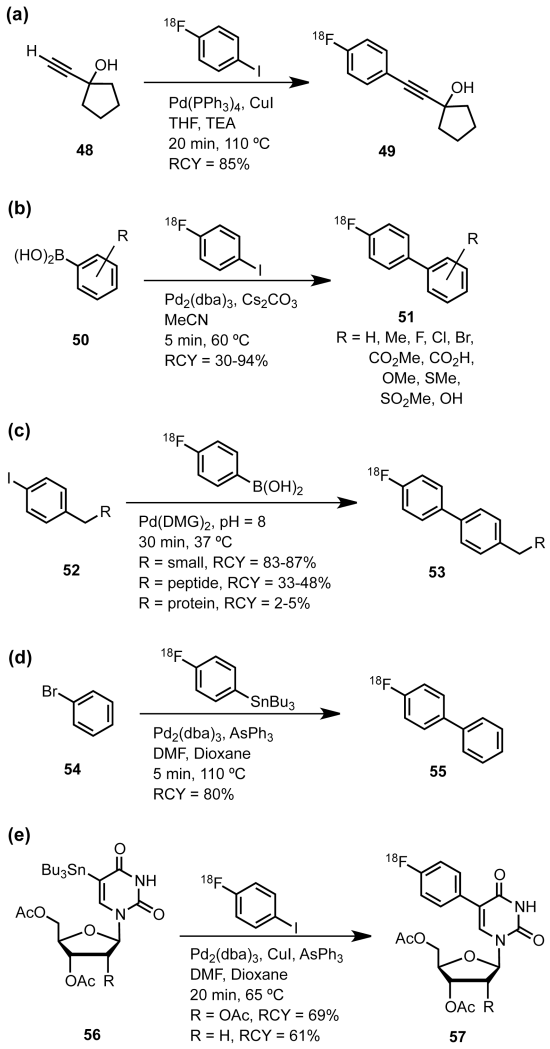


Scheme 25. Radiosyntheses via Thiol Functionalization

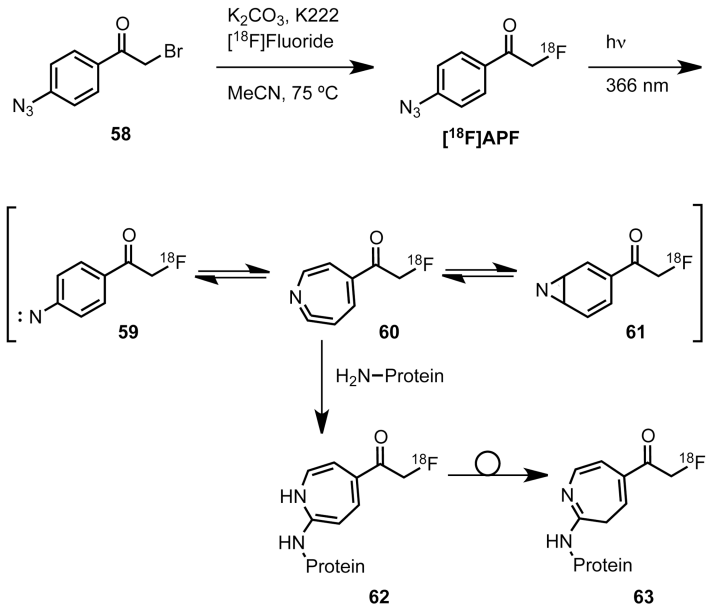


Scheme 26.

Representative example of strain relief-promoted, copper-free click chemistry for ^{18}F-radiolabeling. R = bombesin.

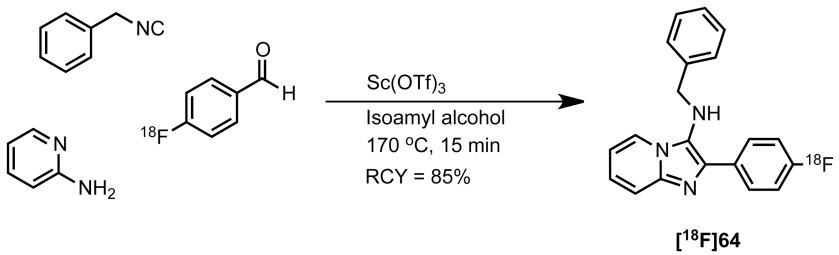


Scheme 27. Palladium-mediated Cross-coupling Reactions with Fluorine-18 including Sonogashira (a), Suzuki (b and C) and Stille (d and e) Reactions



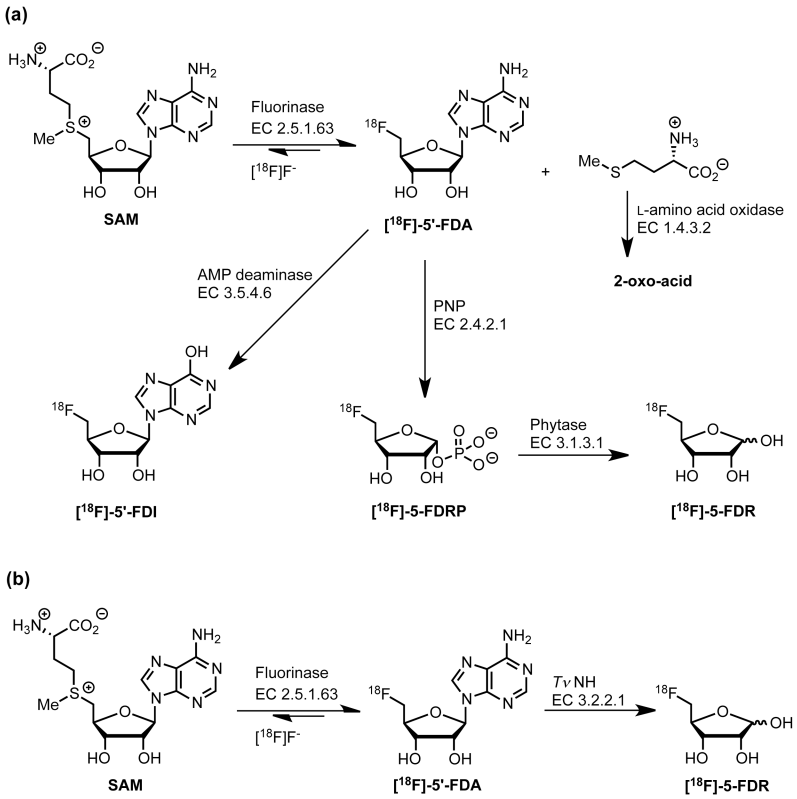
Protein	Protein Concentration (mg/100 μl)	RCY
HSA	1	25%
Avidin	1	15%
IgG	0.8	11%

Scheme 28. Photochemical Reactions with Fluorine-18

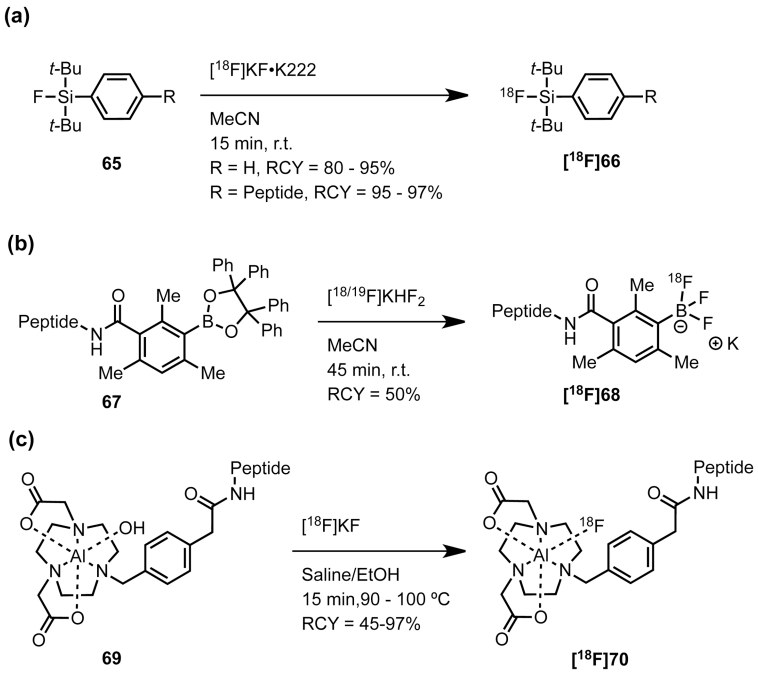


[^{18}F]64

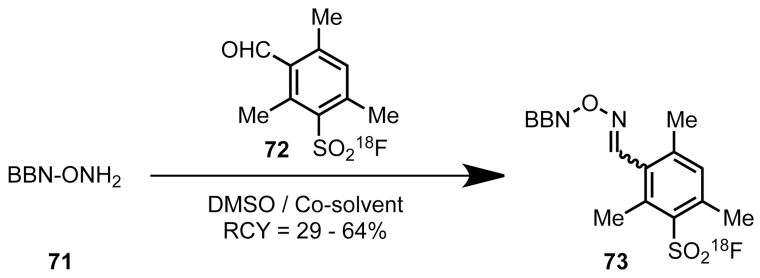
Scheme 29. Multicomponent Reactions with Fluorine-18



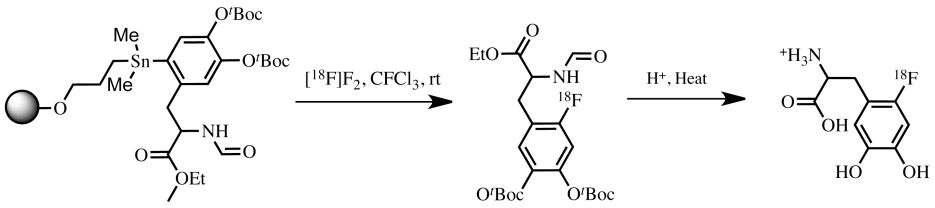
Scheme 30. Enzymatic Radiochemical Reactions Mediated by Fluorinase



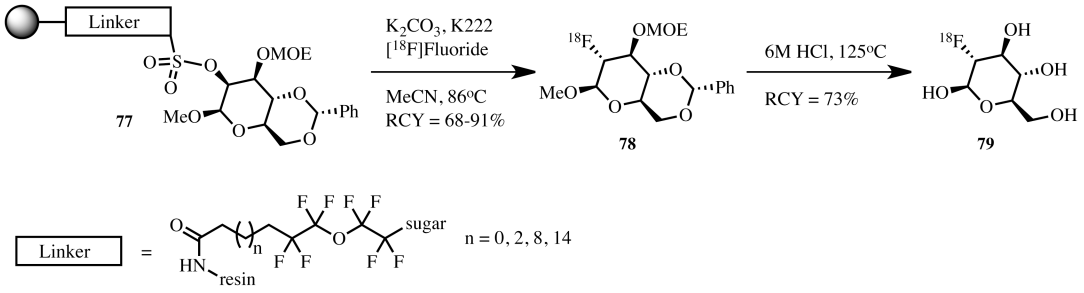
Scheme 31. Fluorine-18 Acceptor Chemistry



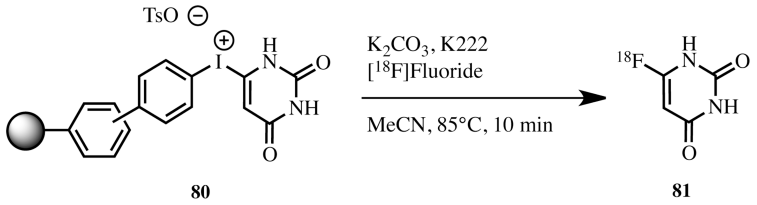
Scheme 32. [^{18}F]Sulfonyl Fluoride-based Prosthetic Groups



Scheme 33. Solid-phase synthesis of [^{18}F]FluoroDOPA

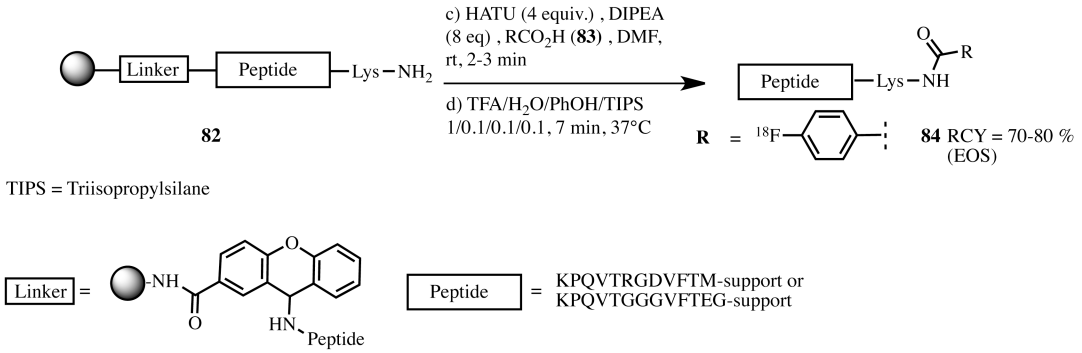


Scheme 34. Solid-phase Synthesis of [^{18}F]FDG



80 **81**

Scheme 35. Solid-phase Synthesis of [^{18}F]Fluorouracil



Scheme 36. Solid-phase Synthesis of Fluorine-18 Labeled Prosthetic Groups

Table 1

Physical Properties of Fluorine-18 and Other Commonly Used PET Radioisotopes

Nuclide	$T_{1/2}$	Decay	Maximum Energy (MeV)	Theoretical Specific Activity (GBq/μmol)	Decay Product
^{18}F	109.77 min	β+ (97%), EC (3%)	0.64	6.3×10^4	^{18}O
^{11}C	20.38 min	β+ (99%)	0.97	3.4×10^5	^{11}B
^{13}N	9.96 min	β+ (100%)	1.20	7.0×10^5	^{13}C
^{15}O	2.03 min	β+ (100%)	1.74	3.4×10^6	^{15}N

EC: electron capture

Table 2
Nuclear Reactions Used to Produce Fluorine-18[20]

$^{18}O(p,n)^{18}F$	$^{20}Ne(d,\alpha)^{18}F$	$^{6}Li(n,\alpha)3H$, $^{16}O(^{3}H,n)^{18}F$
$^{16}O(^{3}He,p)^{18}F$	$^{20}Ne(p,2n)^{18}F$	
$^{16}O(\alpha,pn)^{18}F$	$^{20}Ne(^{3}He,n)^{18}Ne$, ^{18}Ne-^{18}F	