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Development of ^{18}F- and 11C-Labeled Radiopharmaceuticals

Continuing Education for Nuclear Pharmacists
and
Nuclear Medicine Professionals

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Development of ^{18}F- and 11C-Labeled Radiopharmaceuticals

By
Robert H. Mach, Ph.D.

DEVELOPMENT OF ^{18}F- AND 11C-LABELED RADIOPHARMACEUTICALS

STATEMENT OF LEARNING OBJECTIVES:

Upon completion of this course, participants will be able to:

1. To understand the basic principles of carbon-11 radiochemistry;

2. To understand the basic principles of fluorine-18 radiochemistry;

3. To recognize the limitations and advantages of ^{11}C-labeled radiotracers in clinical research studies using PET;

4. To understand the basic principles of the design of radiotracers that can be labeled with fluorine-18.

COURSE OUTLINE

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Presented at 2008 Annual APhA Meeting

DEVELOPMENT OF ^{18}F- AND 11C-LABELED RADIOPHARMACEUTICALS

By

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Positron Emission Tomography (PET) has evolved over the past 40 years from a powerful tool in the field of biomedical research to a bona fide clinical imaging procedure. The key step in this evolutionary process was the clear demonstration that PET imaging studies using [^{18}F]Fluorodeoxyglucose ([^{18}F]FDG), a radiolabeled analog of glucose, provided a sensitive imaging procedure for diagnosing certain types of tumors, and added important functional information to anatomical imaging procedures such as CT and MRI. In order for PET to remain at the forefront of molecular imaging in clinical Nuclear Medicine, newer radiotracers that provide more detailed biochemical information than differences in glucose utilization between normal and diseased tissue are clearly needed.

The main limitations on the development of new radiotracers for use with PET are the time constraints created by working with radionuclides having the short half-lives inherent to carbon-11 and fluorine-18, the main radionuclides use in PET radiotracer development. Over the past decade there have been a number of developments in the radiosynthetic methods used in PET chemistry, advances that are expected to lead to an increase in the number of radiotracers making the transition from clinical research studies to clinical PET studies. The following is a concise review of the developments in PET radiochemistry that will facilitate this process, and a review of the rationale radiopharmaceutical chemists use in the design of new PET radiotracers.

INTRODUCTION

Radionuclides used in PET Tracer Development

There are four positron-emitting radionuclides that make up the majority of PET radiotracer development: oxygen-15 (O-15); nitrogen-13 (N-13), carbon-11 (C-11), and fluorine-18 (F-18). There are a number of reasons why these radionuclides are used in the majority of PET imaging applications. The first is that most of these radionuclides can be substituted into biologically-active molecules with a "hot-for-cold" substitution. That is, C-11 can be substituted for nonradioactive, C-12 in a biologically-active molecule without altering the biological properties of the molecule. In this example, C-11 is a true radiotracer since the structure of the biologically-active molecule has not been altered in order to introduce the PET radiolabel. A similar situation holds for both O-15 and N-13; however, the short half lives of O-15 and N-13 have limited their use in PET radiotracer development, and these radionuclides are largely used as perfusion tracers, [^{15}O]water for brain perfusion studies and [^{13}N]ammonia for heart perfusion studies.

An exception to the above principle is F-18; unlike the carbon, oxygen, and nitrogen, the natural abundance of fluorine in endogenous biomolecules is very limited. However, fluorine is a commonly-used substituent in the field of drug development, and there are a number of fluorine-containing drugs that are capable of serving a lead compounds for PET radiotracer development, particularly in the field of PET radiotracers for studying neurotransmitter receptors in the central nervous system (CNS).

Table 1. Radionuclides commonly used in PET.[1]

Radionuclide	Half-Life (min)	Nuclear Reaction	Average B + Energy (keV)	B+ range mm (H_2O)	Maximum Specific Activity (Ci/μmol)
O-15	2	N-15(p,n)O-15	735	8.2	91,730
N-13	10	C-13(p,n)N-13	491	5.39	18,900
C-11	20	N-14(p,α)C-11	385	4.1	9,220
F-18	110	O-18(p,n)F-18	242	2.39	1,710

A second reason for the prominent use of these radionuclides in PET imaging studies is that each can be produced in high yield and high specific activity with a low energy (i.e., 11 – 17 MeV), medical cyclotron using either the p,n (O-15, N-13, F-18) or p,α (C-11) nuclear reaction (Table I).[1] Since the target material is either a gas (O-15, C-11) or liquid (N-13, F-18), the radionuclides can be conveniently transferred from the cyclotron target to a hot cell in the radiochemistry lab where the radionuclide can be incorporated into a biologically-active molecule. There are also a number of commercially-available automated chemistry systems which are capable of converting the cyclotron-produced radionuclides, obtained as low molecular weight species from the cyclotron target, into either a chemically-reactive species or a radiolabeled prosthetic group. Automated chemistry systems are also designed to conduct 2-3 organic reactions, followed by either a resin-based or HPLC purification step, leading to the synthesis of a PET radiotracer that is designed to image a well-defined protein or biosynthetic pathway. Although simplistic in theory, the adaptation of a commercially-available automated PET chemistry system to enable the synthesis of structurally-diverse PET radiotracers requires considerable expertise in the field of organic chemistry and chemical engineering.

Carbon-11 Radiochemistry

C-11 is produced in the cyclotron target using the $^{14}N(p,\alpha)^{11}C$ nuclear reaction. The target material is nitrogen (N_2) containing trace quantities of oxygen (0.5% O_2) to convert the C-11 into $[^{11}C]CO_2$.[1,2] The $[^{11}C]CO_2$ is then transferred from the target to a chemistry module that converts it into a reactive chemical species that facilitates incorporation into biologically active molecules. The exception to this is the synthesis of the metabolic tracers [^{11}C]acetate and [^{11}C]palmitate (Figure 1). The synthesis of these radiotracers involves the direct venting of the $[^{11}C]CO_2$ into a solution of either methylmagnesium bromide or 1-pentadecylmagnesium bromide.

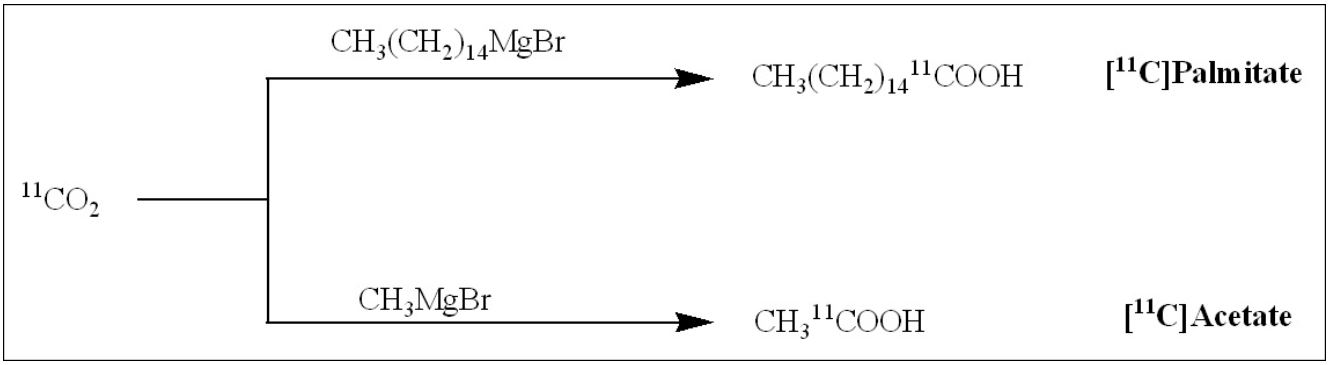

Figure 1. Synthesis of $[^{11}C]$palmitate and $[^{11}C]$acetate using $[^{11}C]CO_2$.

The most common transformation of $[^{11}C]CO_2$ is into the chemically-reactive species, $[^{11}C]$methyliodide ($[^{11}C]CH_3I$). $[^{11}C]CH_3I$ is a highly reactive species that can be used to introduce C-11 into biologically-active molecules via alkylation of N-, O-, or S-nucleophiles (Figure 2). The initial method for preparing $[^{11}C]CH_3I$ involved bubbling $[^{11}C]CO_2$ through a solution of lithium aluminum hydride ($LiAlH_4$) and tetrahydrofuran (Figure 3), followed by quenching with hydrioidic acid (HI). The more common way of synthesizing $[^{11}C]$methyl iodide today is to initially catalytically reduce $[^{11}C]CO_2$ to $[^{11}C]$methane ($[^{11}C]CH_4$), followed by iodination with molecular iodine (I_2) to produce $[^{11}C]CH_3I$. Another method for preparing $[^{11}C]CH_3I$ involves the direct production of $[^{11}C]CH_4$ by using a target gas composition of 10% H_2/N_2 in the target, followed by iodination with molecular I_2. Because of the lower levels of methane in the atmosphere (~1.6 ppm) versus CO_2 (~300 ppm), the specific activity of ^{11}C-labeled compounds is generally much higher than that using $[^{11}C]CO_2$ from the target.[1,2] Specific activities using the direct $[^{11}C]CH_4$ to $[^{11}C]CH_3I$ route have been reported in the range of 10 Ci/μmol (370 GBq/μmol). However, it should be noted that this specific activity is considerable lower that the maximum theoretical specific activity of C-11 (Table 1). Therefore, with a ^{11}C-labeled radiotracer having a specific activity of 10 Ci/mmol, only 1 in 10,000 tracer molecules contain C-11, with the remaining containing C-12.

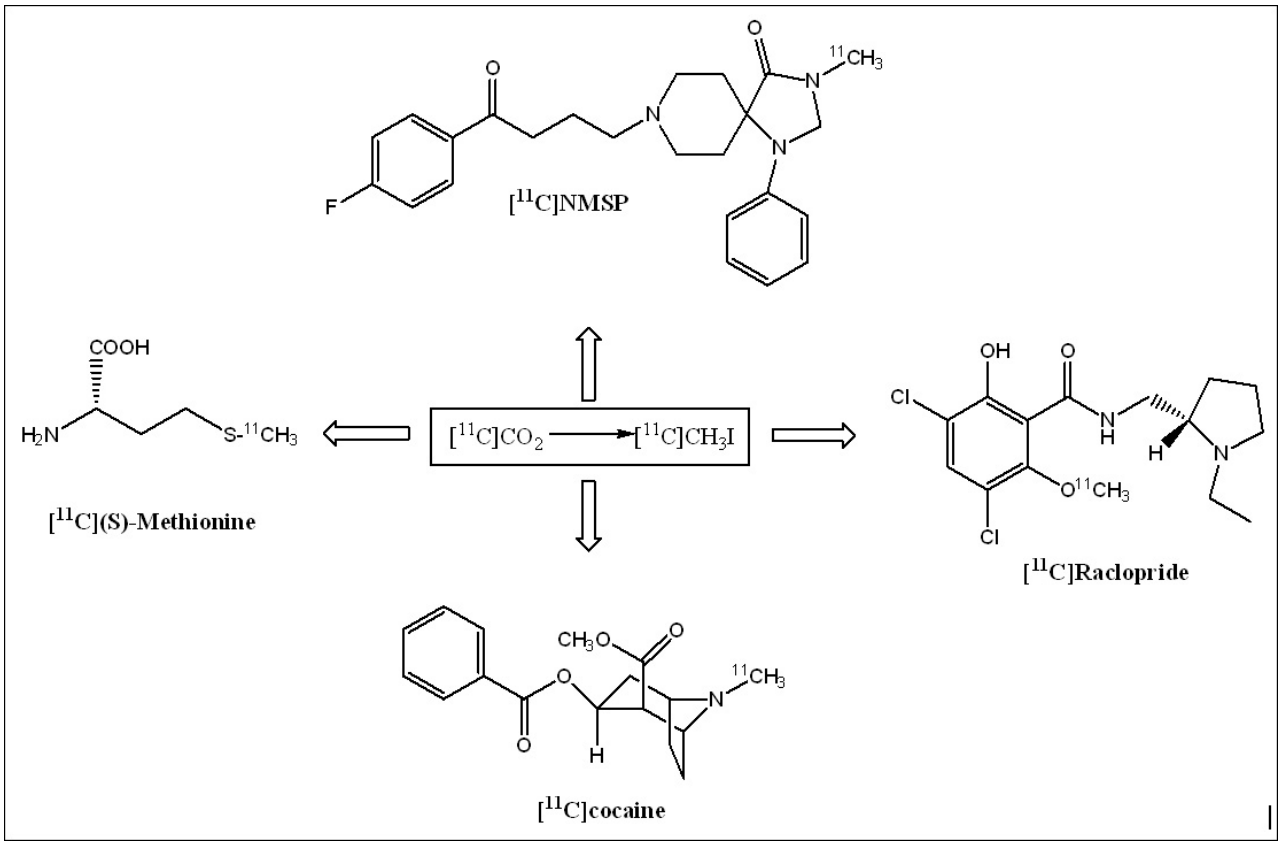

Figure 2. Examples of ^{11}C-labeled radiotracers synthesized using $[^{11}C]CH_3I$.

Another highly reactive form of C-11 is [^{11}C]methyltriflate ([^{11}C]CH_3OTf). [^{11}C]CH_3OTf is formed by passing gaseous [^{11}C]CH_3I over a column containing silver triflate (AgOTf) at 200°C.[2] The advantage of [^{11}C]CH_3OTf is that this method generally requires lower reaction temperatures, shorter reaction times, and lower amounts of the *des*-methyl precursor for labeling than what is usually required to label a compound using [^{11}C]CH_3I. Examples comparing radiolabeling with [^{11}C]CH_3I and [^{11}C]CH_3OTf are shown in Figure 4.[3,4]

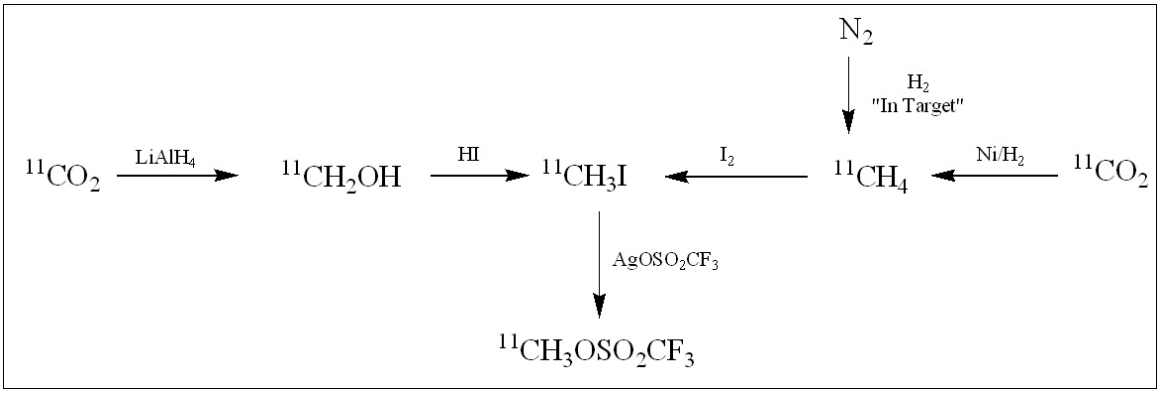

Figure 3. Synthesis of [^{11}C]methyl triflate.

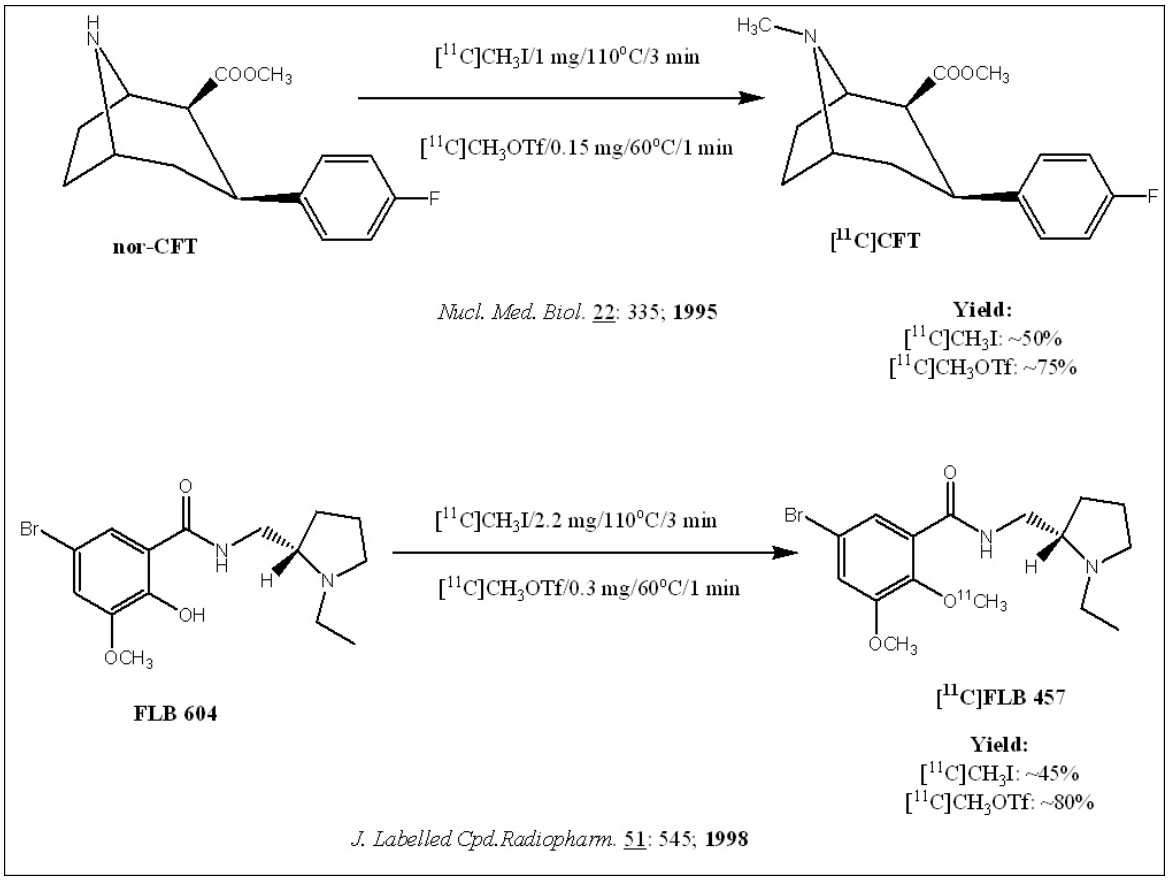

Figure 4. Comparison of ^{11}C-radiolabeling using [^{11}C]CH_3I and [^{11}C]CH_3OTf.

Fluorine-18 Radiochemistry

There are two forms of Fluorine18 that are used in the synthesis of PET radiotracers, nucleophilic and electrophilic. Nucleophilic fluoride is produced in the target via the $^{18}O(p,n)^{18}F$ nuclear reaction using [^{18}O]water as the target material. This results in the formation of [^{18}F]HF, which is transferred from the target to either a reaction vessel containing a base such as potassium carbonate (to make [^{18}F]KF) or tetrabutylammonium hydroxide (to give [^{18}F]TBAF). Alternatively, the radioactivity can be passed through an anion exchange resin which traps the activity as [^{18}F]fluoride. The activity is then removed the anion exchange resin by elution with a base solution to give [^{18}F]fluoride as a salt (i.e., [^{18}F]KF or [^{18}F]TBAF). An advantage of [^{18}F]TBAF is that it can be directly solubilized into organic solvents such as acetonitrile and DMSO, whereas [^{18}F]KF requires the crown ether [2.2.2]kryptofix to solubilize the reactivity.

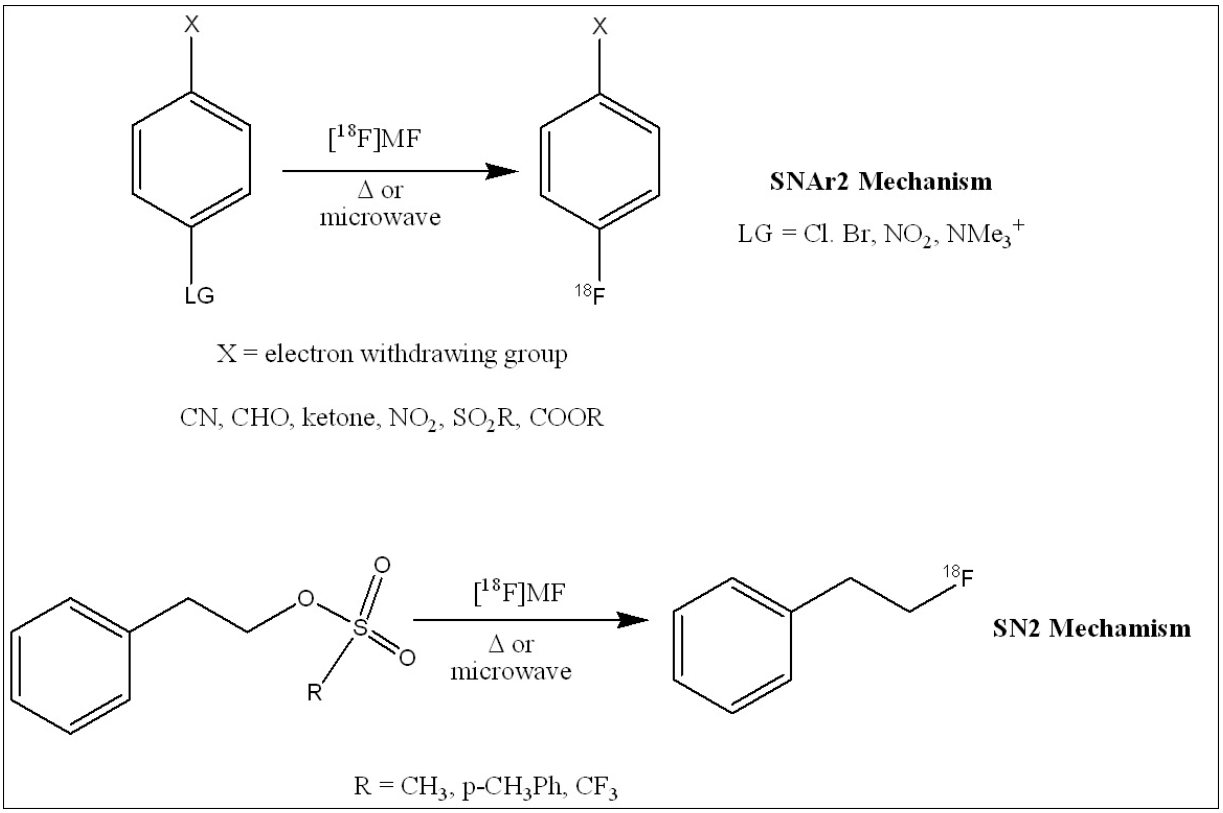

Figure 5. Reaction mechanism for introducing F-18 into organic molecules. M refers to a positive action such as K^+. Cs^+. or $(Bu)_4N^+$.

There are two types of reaction mechanism in which [^{18}F]fluoride is incorporated into biologically active molecules, the SN2 and SNAr2. The SN2 mechanism occurs when an appropriate leaving group is displaced from an aliphatic (i.e., sp3) carbon atom. An example of the SN2 mechanism is shown in Figure 5. The SNAr2 mechanism occurs when the leaving group is displaced from an

aromatic (i.e., sp2) carbon atom such as a benzene ring. Fluoride is a relatively unreactive nucleophile; however, high yields are usually obtained in the SN2 mechanism if the precursor contains a strong leaving group such as a triflate or mesylate. In the case of the SNAr2 mechanism, the para position must be activated by an electron-withdrawing group in order to increase the rate of reaction so that an acceptable yield of the labeled compound is obtained. Examples of activating groups are the cyano (CN), nitro (NO_2), keto (RC=O) and aldehyde (HC=O) groups. The trimethylammonium group has replaced the nitro group as the most commonly used leaving group in SNAr2 displacements because of its rapid rate of reaction. The two methods used for increasing the rate of reactivity of [^{18}F]fluoride are heating the reaction mixture (from 90 – 160^{o}C) and microwave-assisted fluoride incorporation. The microwave-assisted route is rapidly becoming the preferred method of nucleophilic fluoride incorporation since the reaction time needed to achieve a high radiochemical yield of the product is typically much faster than the thermal method of incorporation.

Although activation of the para-position with one of these groups facilitates the incorporation of [^{18}F]fluoride, it does not necessarily guarantee a high radiochemical yield. An example of this is shown in Figure 6.[5] Whereas [^{18}F]fluoride is readily incorporated into the nitro-precursor, resulting in

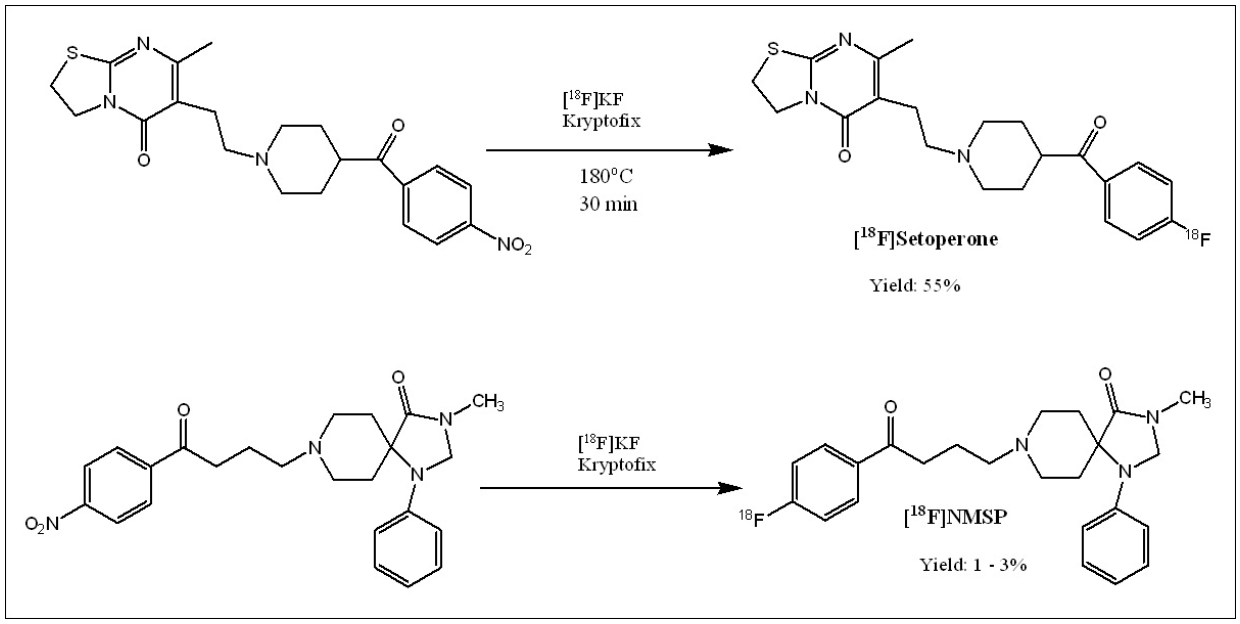

Figure 6. Examples of nucleophilic incorporation of [^{18}F]fluoride. Note the difference in radiochemical yield even though both substrates are activated by a ketone group in the para position.

a high radiochemical yield of [^{18}F]setoperone, similar reaction conditions result in only a low yield of [^{18}F]N-methylspiperone even though both substrates have a ketone as the activating group in the para position. Because of the relatively long half-life of F-18 (110 min), a multistep synthesis of [^{18}F]NMSP was developed by the PET group at Brookhaven National Lab (Figure 7).[6]

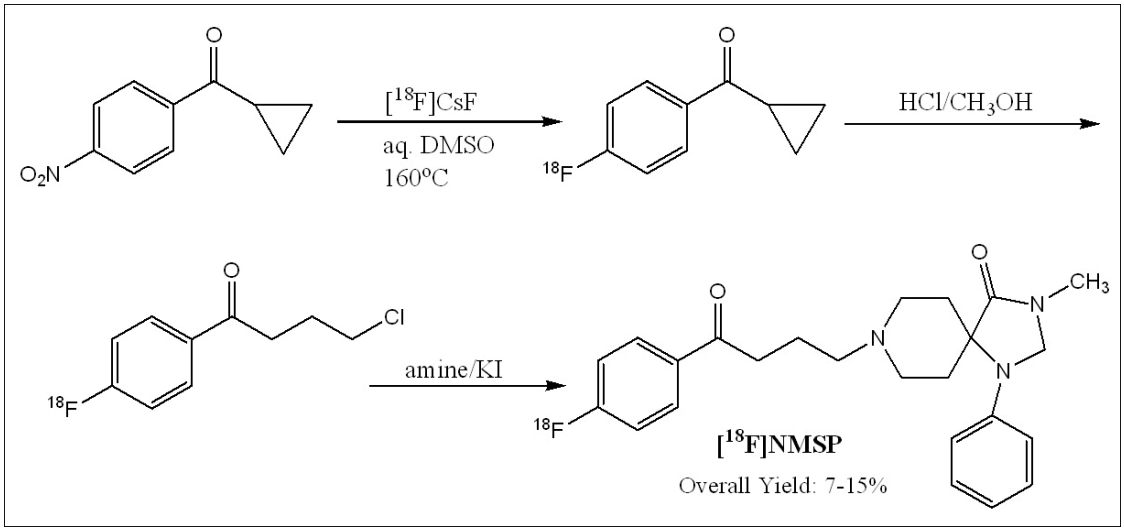

Figure 7. Synthesis of [^{18}F]NMSP by the PET group at Brookhaven National Laboratory.

A second example of the SNAr2 reaction mechanism for incorporating F-18 into biologically-active molecules involves the displacement of a leaving group in either the 2- or 6-position of a pyridine ring. Since pyridine is a p-deficient heteroaromatic ring system, it is prone to nucleophilic attack at the 2-, 4-, and 6-positions. Therefore, a pyridine ring does not require the presence of an electron-withdrawing group to activate the ring system to nucleophilic attack by [^{18}F]fluoride. This strategy has been used extensively in the synthesis of ligands for imaging nicotinic α4β2 receptors (Figure 8).[7,8,9]

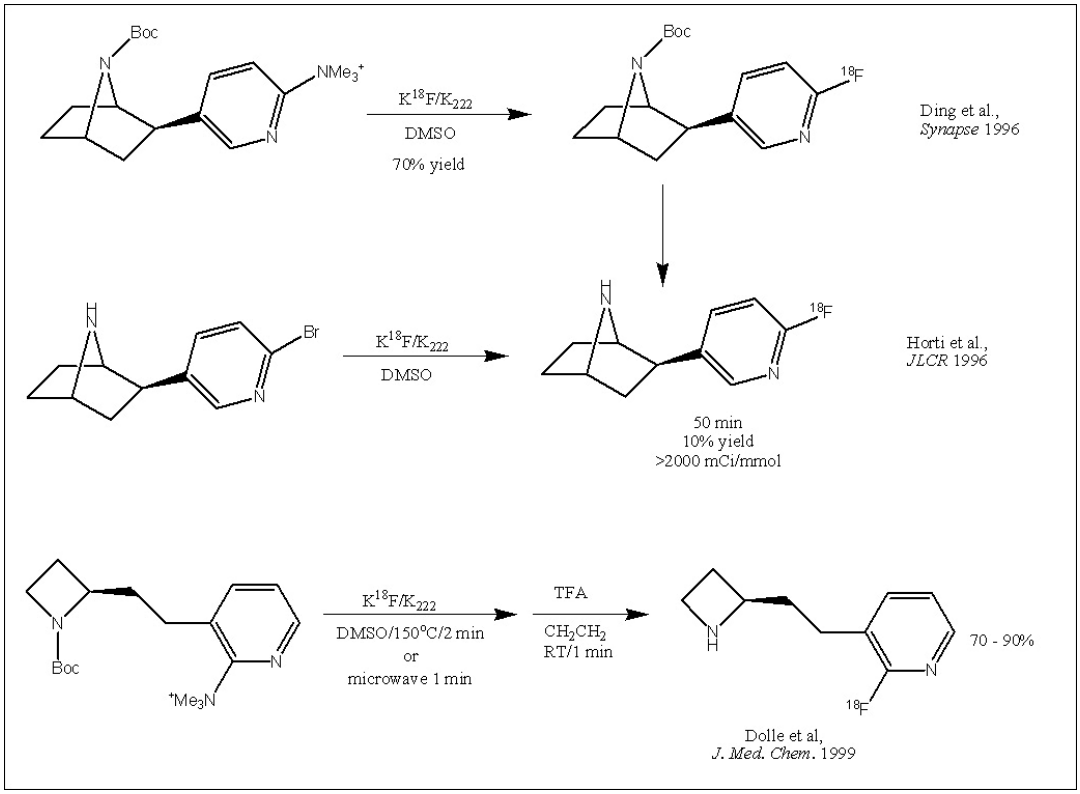

Figure 8. Synthesis of ^{18}F-labeled radiotracers involving the direct introduction of F-18 into the 2-position of a pyridine ring.

An alternative strategy for introducing high specific activity, nucleophilic [^{18}F]fluoride into ligands is to use an ^{18}F-labeled prosthetic group. This method uses essentially the same principles as labeling a molecue with [^{11}C]CH_3I, which is, essentially a ^{11}C-labeled prosthetic group. In this case, F-18 is incorporated into a small organic molecule, which is then used to alkylate a precursor leading to an ^{18}F-labeled radiotracer. As with [^{11}C]CH_3I, the most common reaction is the alkylation of a nitrogen atom. Two different ^{18}F-labeled prosthetic groups have been used to date: 1) [^{18}F]2-fluoroethoxytriflate and, 2) [^{18}F]4-fluorobenzyl iodide (or bromide). Examples of the use of these prosthetic groups are shown in Figure 9.[5]

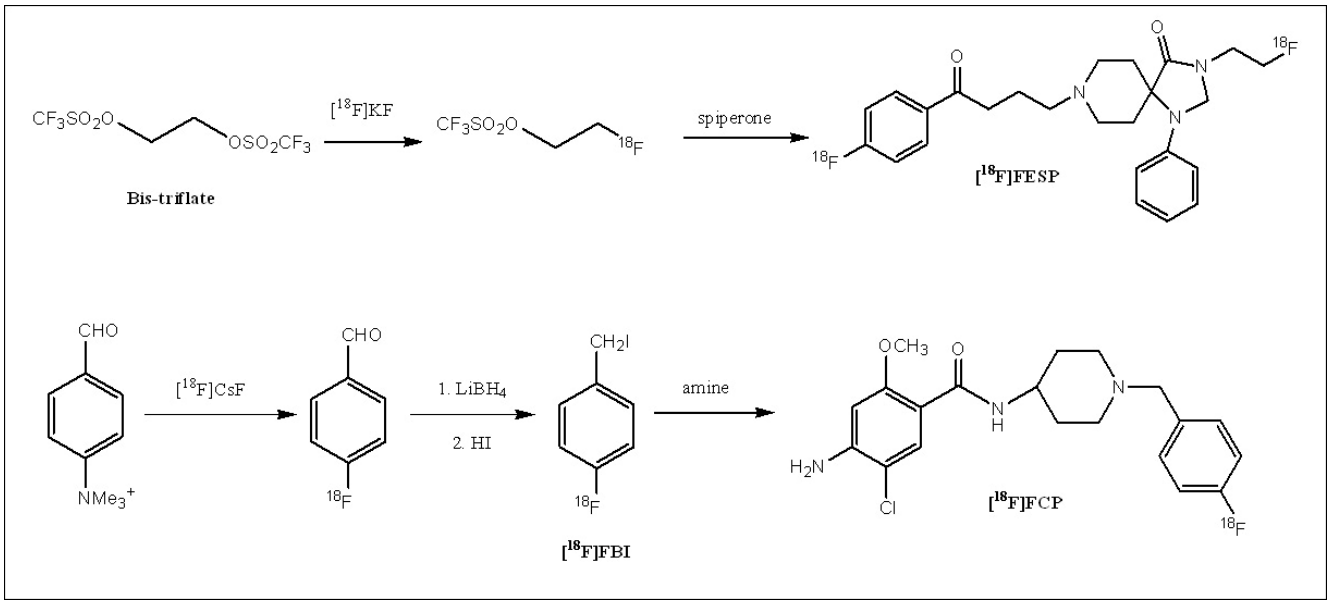

Figure 9. Examples of F-18 radiolabeling using the prosthetic groups, [^{18}F]2-fluoroethoxytriflate (top) and [^{18}F]4-fluorobenzyl iodide (bottom).

Some methods for labeling peptides are shown in Figure 10. These methods involve tagging either the N-terminus or amine group of a lysine in the peptide (i.e., amine reactive prosthetic group), or sulfur atom of a cysteine residue (i.e., sulfur reactive prosthetic group) with a reactive group such as an activated ester, benzimidate, or maleimide ring.[10]

A recent development in the field of PET radiochemistry is the use of copper-assisted 1,3-dipolar cycloaddition reactions to prepare ^{18}F-labeled compounds. The method, referred to as "click chemistry", uses [^{18}F]2-fluoroethylazide as the prosthetic group (Figure 11).[11] Reported radiochemical yield using this strategy have been very high, often in excess of 80%. This labeling strategy is expected to be useful in the radiolabeling labeled peptides since it avoids the need to protect the

multiple functional groups in a polypeptide that can react with the prosthetic groups currently used in producing ^{18}F-labeled peptides.

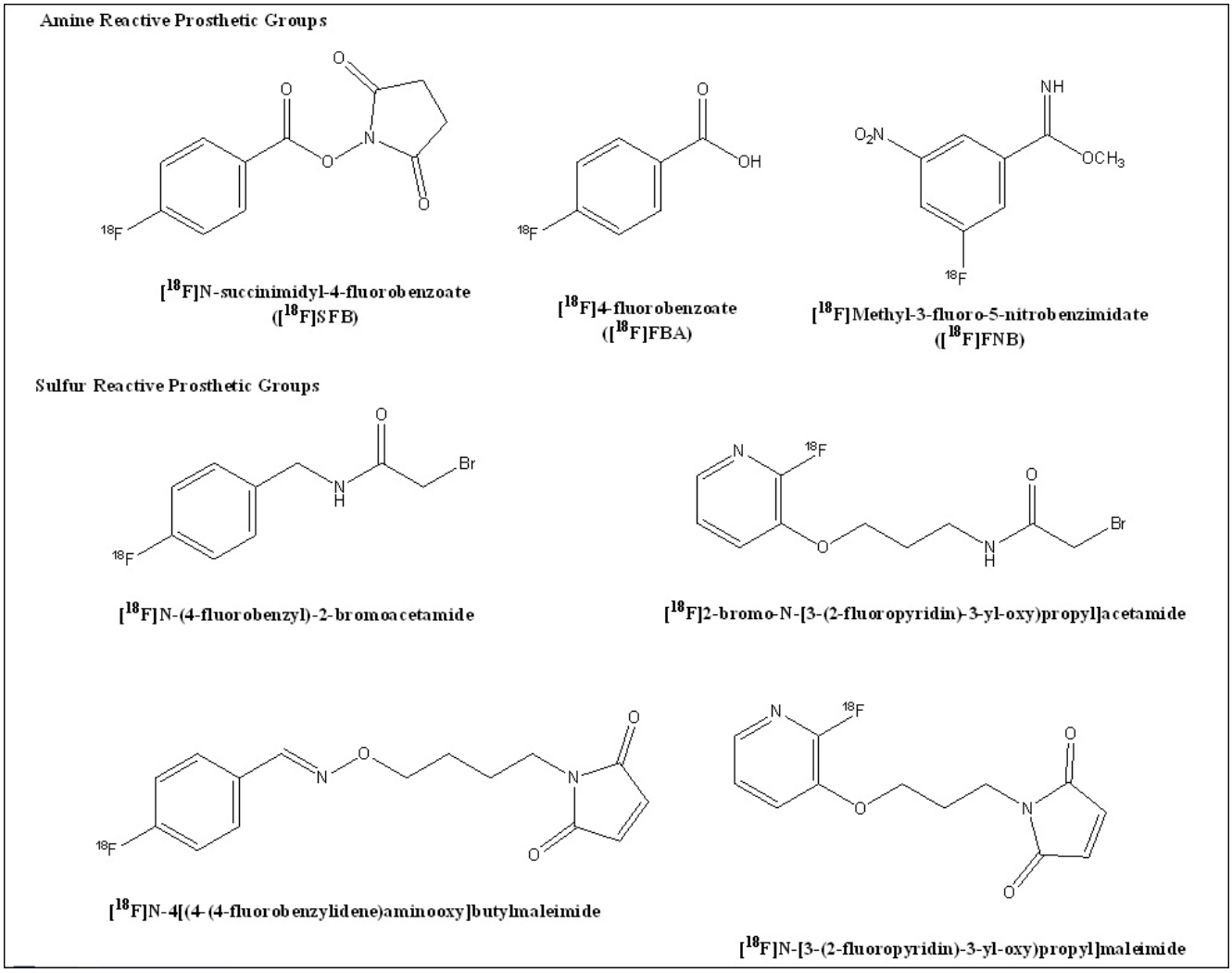

Figure 10. Prosthetic groups used in the labeling of peptide with F-18.

F-18 can also be introduced into biologically-active molecules using an electrophilic fluorination reaction with $[^{18}F]F_2$. There are two different way to produce electrophilic $[^{18}F]F_2$. The first method, which requires a cyclotron designed to accelerate deuterons, is the $^{20}Ne(d,\alpha)^{18}F$ nuclear reaction (Figure 11). The neon target gas contains ~2% F_2 in order to complete the in target production of $[^{18}F]F_2$. The second method for producing $[^{18}F]F_2$ involves the $^{18}O(p,n)^{18}F$ nuclear reaction. This method, which is generally used on proton-only cyclotrons, requires a multistep process is required to produce $[^{18}F]F_2$. The first step involves irradiation of 2% F_2/Ar mixture to "passivate" the target. The target is then filled with $[^{18}O]O_2$, and a second irradiation is conducted to produce ^{18}F-labeled species that are deposited onto the interior surface of the target. This deposition of the F-18 onto the target

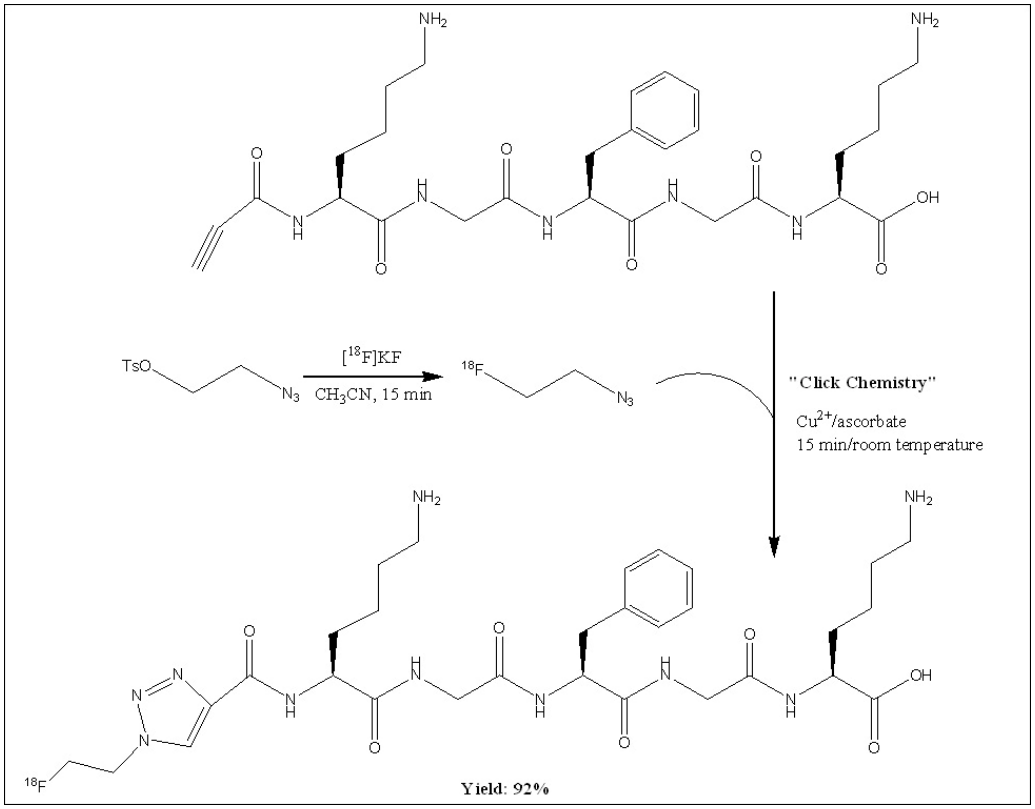

Figure 11. Click chemistry and an example of its use in the field of ^{18}F-labeled peptide chemistry.[12]

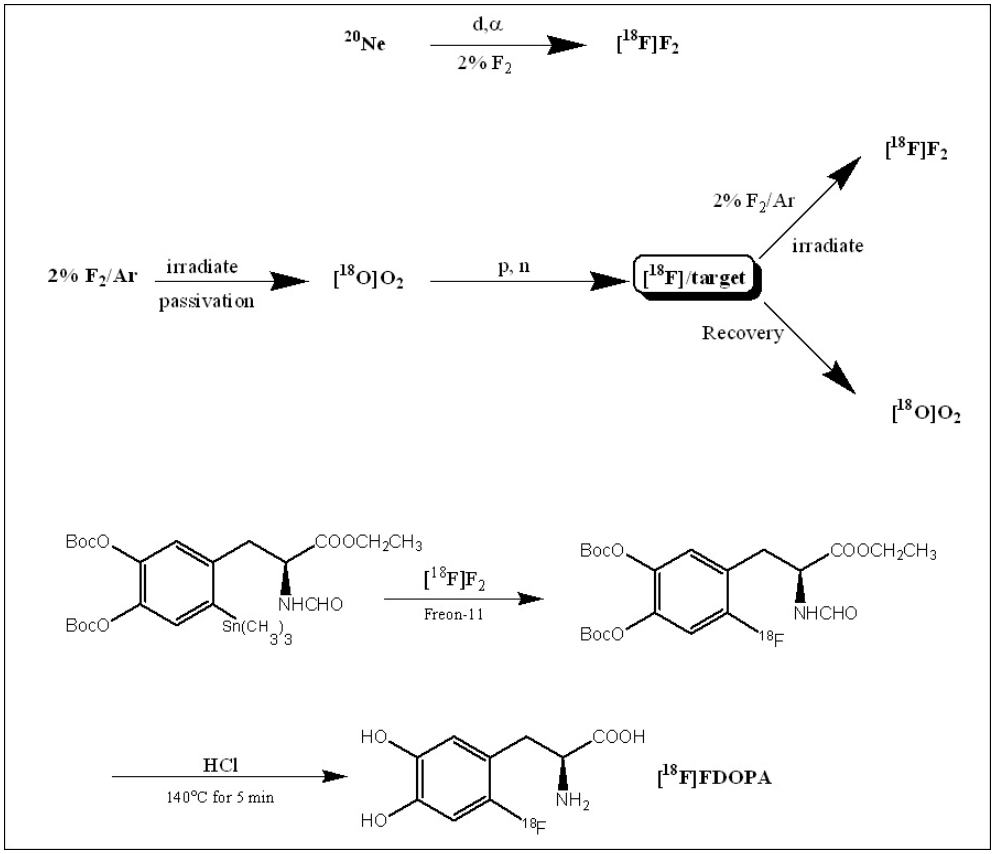

Figure 12. Production of $[^{18}F]F_2$ for electrophilic fluorinations reactions. The synthesis of [^{18}F]FDOPA is also shown. The specific activity of [^{18}F]FDOPA prepared using electrophilic $[^{18}F]F_2$ is ~1,700 mCi/mmol (USP 100 mCi/mmol), which is much lower that what is routinely obtained with radiotracers synthesized using nucleophilic [^{18}F]fluoride.

surface enables the recovery of the [^{18}F]O_2 target gas. Once the [^{18}O]O_2 has been recovered, the target is filled with 2%F_2/Ar and a third irradiation is conducted to recover the [^{18}F]F_2. Electrophilic fluorination with [^{18}F]F_2 is the preferred method for making [^{18}F]FDOPA, a radiotracer that measures presynaptic dopaminergic terminal density (Figure 12). The main drawback to using electrophilic fluorination for introducing F-18 is low specific activity that is achieved using [^{18}F]F_2. This is caused by the requirement of adding unlabeled F_2 to recover the radioactivity from the target.

Factors Used in the Design of PET Radiotracers

One of the advantages of [^{11}C]CH_3I and [^{11}C]CH_3OTf in the development of PET radiotracers is that there are many "lead compounds" in the literature which have an N-methyl group in the parent structure that simplifies the development of a ^{11}C-labeled radiotracer. In this case, a ^{11}C-labeled radiotracer can be prepared by reacting the corresponding des-methyl precursor with [^{11}C]CH_3I/[^{11}C]CH_3OTf. Consequently, the ^{11}C-labeled analog is a true radiotracer since the ^{11}C is incorporated in the parent compound. This is occasionally true with ^{18}F-labeled radiotracers, and [^{18}F]setoperone and [^{18}F]NMSP are examples where an ^{18}F for ^{19}F substitution lead to a relatively straightforward preparation of an ^{18}F-labed radiotracer. However, in many cases this is not an option, and a ^{11}C- or ^{18}F-labeled radiotracer must be designed using a lead compound in which there is no obvious way to incorporate the C-11 or F-18 radiolabel. In this case, the radiolabel must be introduced into the lead compound in a manner that does not reduce the affinity of the ligand for the target macromolecule. The discussion below highlights some of the logic used by radiochemists in the design of PET radiotracers using a lead compound in which there is no simple method (i.e., "hot" for "cold" atom substitution) for accomplishing this goal.

Table 2. Substituent Constants for Radionuclides and Labeling Strategies Used in PET.

Substituent	π	σ_p	MR
H	0.00	0.00	0.1
OH	-0.67	-0.37	2.85
CH_3	0.56	-0.17	0.57
F	0.14	0.06	0.1
I	1.12	0.18	1.39
Br	0.86	0.23	0.89
CH_2CH_2F	0.85	-0.15	0.93
$CH_2CH_2CH_2F$	1.59	-	1.48

The left hand column of Table 2 shows the primary radionuclides and labeling strategies for incorporating C-11 or F-18 into a lead compound. The second column shows the Hansch lipophilicity constant (p) value for each substituent; the π value is a measure of the relative lipophilicity of the substituent. The third column lists the Hammet substituent constant (σ_p), which is a measure of the electron withdrawing or electron donating properties of the substituent. A negative σ_p value indicates the substituent donates electron to an aromatic ring system, whereas a positive σ_p constant indicates that this is an electron-withdrawing substituent. MR is the molar refractivity of the substituent, which is a measure of the steric bulk of each functional group.

Substitution of an H atom of a primary or secondary amine with an [^{11}C]methyl group is a useful strategy provided that there is enough steric bulk in the region of the nitrogen atom (MR for a CH_3 group = 0.57 vs. 0.1 for an H atom). Substitution of a CH_3 for an H atom also increases the lipophilicity of the PET radiotracer by 0.56 π units, which results in a higher degree of nonspecific binding relative to the parent compound.

The synthesis of ^{18}F-labeled compounds often involves the substitution of an F for H substitution. This rarely alters the affinity and physicochemico properties of the parent compound since the substituent constants of an F atom are very similar to that of an H atom. However, F is also capable of serving as a hydrogen bond acceptor; therefore, a second case that has been used in the design of ^{18}F-labeled radiotracers is a substitution of an F atom for an OH group.

The use of a 2-fluoroethyl or 3-fluoropropyl group for introducing F-18 into a lead compound is increasing in popularity since the radiochemical yields of an SN2 reaction are generally very high. However, the substituent constants in terms of lipophilicity (π) and steric bulk (MR) limits the options where these groups can be substituted into a lead compound. For example, the substitution of a 2-fluoroethyl or 3-fluoropropyl group for a H atom is not expected to work since it would result is a large increase in the lipophilicity (i.e., log P) of the compound, and also introduces a large amount of steric bulk into the region of the molecule where the substitution occurs. A 2-fluoroethyl or 3-fluoropropyl for methyl substitution will work provided that; 1) the increase in lipophilicity does not increase the nonspecific binding to the point where the tracer does not have a suitable signal:noise ratio for imaging purposes, and 2) the increase steric bulk does not reduce the affinity of the ligand for the target protein. A more appropriate substitution is a 2-fluoroethyl group for Br atom, and a 3-fluoropropyl group for I

atom. Note the similarity in the substituent constants for the 2-fluoroethyl group and a Br atom, and the 3-fluoropropyl group for an I atom. In addition, since many lead compounds contain either a Br or I atom in the parent structure, this strategy often leads to the development of a successful PET radiotracer without the need of conducting a rigorous structure-activity relationship study. Examples of the different strategies for PET radiotracer design described above are shown in Figure 13.

SUMMARY

The development of ^{11}C- and ^{18}F-labeled probes for use with PET continues to be an active area of research. C-11 will continue to be a useful radiotracer in clinical research studies since the short half-life of this radionuclide (20.4 min) permits imaging sessions in which multiple traces can be administered (after a short delay to allow for radioactive decay). Therefore, two or more proteins comprising a biochemical pathway or neurotransmitter system can be studies in the same imaging session when using ^{11}C-labeled radiotracers. F-18 will continue to be the radionuclide of choice for imaging studies using a single radiotracer. Advances in ^{18}F-labeling strategies such as the development of click chemistry will likely have a large impact on the future development of ^{18}F-labeled radiotracers.

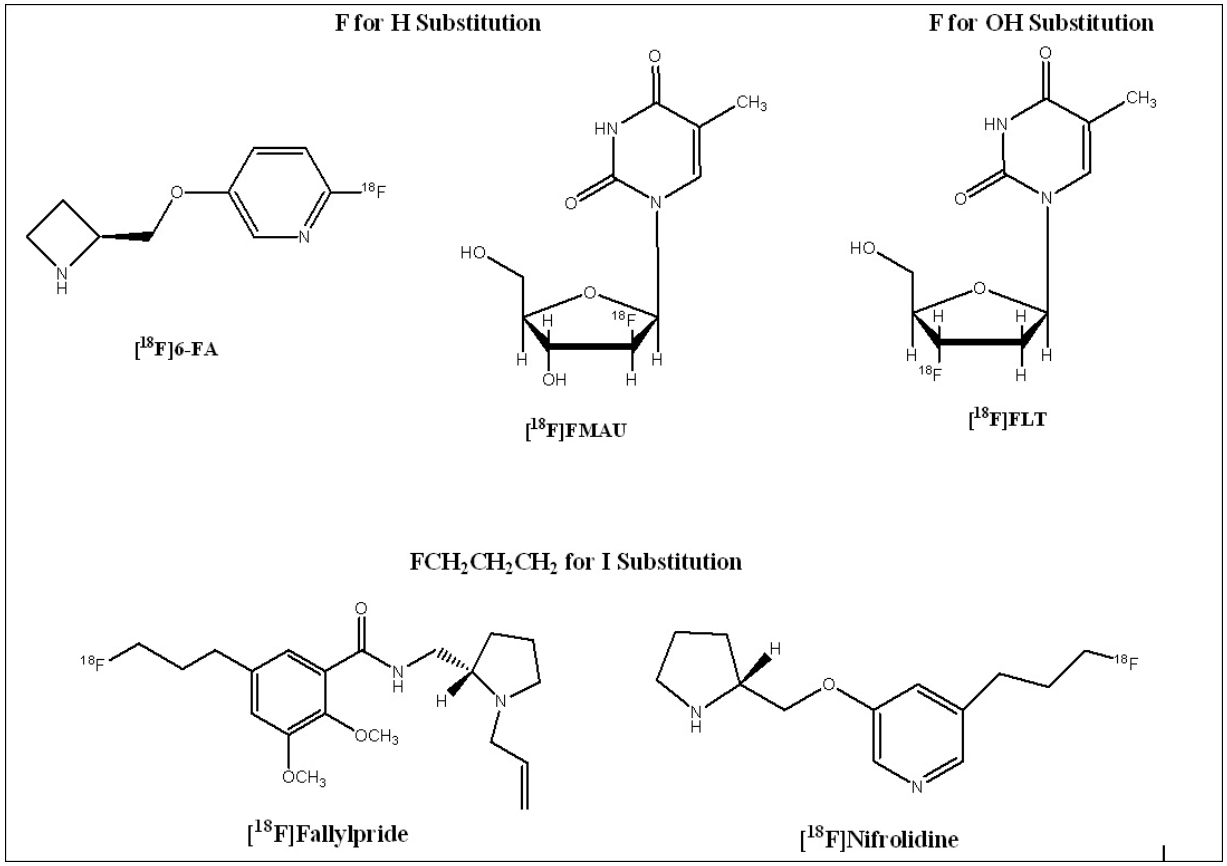

Figure 13. Examples of F-18 radiotracer development.

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ASSESSMENT QUESTIONS

1. Which of the following is a true statement:
    a. The maximum specific activity of a PET radionuclide is directly proportional to its half-life
    b. The maximum theoretical specific activity of F-18 is greater than that of carbon-11
    c. The specific activity of carbon-11 obtained in the hot lab is about 1000-fold lower than the maximum obtained specific activity
    d. Because of the low natural abundance of fluorine, the specific activity of F-18 is near the maximum theoretical specific activity

2. Which of the following statements is false:
    a. [^{11}C]MeOTf is more reactive than [^{11}C]MeI
    b. Methylations with [^{11}C]MeOTf require either a higher temperature or a longer reaction time versus that of [^{11}C]MeI
    c. [^{11}C]MeOTf typically give high yields with a lower amount of substrate than that of [^{11}C]MeI
    d. [^{11}C]MeI is a precursor to the preparation of [^{11}C]MeOTf

3. The synthesis of [^{18}F]FDOPA:
    a. uses electrophilic fluorination with [^{18}F]F_2
    b. uses a tin precursor to direct the position where the F-18 is attached
    c. requires a base deprotection step following incorporation of F-18

4. True or False: The nitro group is a better leaving group that the trimethylammonium group in nucleophilic aromatic fluorination reactions with [^{18}F]fluoride.
    a. True
    b. False

5. Which of the following is a good substitution in the design of an F-18 labeled radiotracer in which the lead compound does not contain a Fluorine atom:
    a. F for a methyl group
    b. 2-fluoroethyl for a H atom
    c. 2-fluoroethyl for a Br atom
    d. 3-Fluoropropyl for a hydroxyl (OH) group