Chemistry of Organic Radionuclides (C, N, and O)

11

Science is built up of facts, as a house is built of stones; but an accumulation of facts is no more a science than a heap of stones is a house.

Henri Poincaré

11.1 Advantages of Organic Radionuclides

All natural organic molecules or biochemicals in the human body and many drug molecules are made up of carbon, hydrogen, nitrogen and oxygen. The organic radionuclides useful for developing radiotracers for PET are ^{11}C, ^{13}N, and ^{15}O (Table 11.1). These three elements, however, do not have any radionuclides suitable for developing radiotracers for SPECT.

Among the three organic radionuclides, ^{11}C offers the greatest potential to develop radiotracers for routine clinical applications because ^{11}C, as a label, can be easily substituted for a stable carbon in an organic compound without changing the biochemical and pharmacological properties of the molecule. Furthermore, the short half-life of ^{11}C provides favorable radiation dosimetry to perform multiple studies in the same subject under different conditions. The short half-life of ^{11}C may be disadvantageous for commercial production of radiotracers, but has significant potential for developing

- Radiotracers with high SA to study drug interactions associated with very small concentrations of neuroreceptors and
- Radiolabeled drugs for monitoring the response to treatment

In addition, the relatively short physical half-life of ^{11}C (20 min) allows for multiple imaging studies to be obtained in the same subject within a short period of time (3–4 h) with the same tracer (at base line followed by experimental intervention) or with multiple tracers to assess the specificity of the receptor interaction.

Compared to ^{11}C, the potential clinical utility of ^{13}N and ^{15}O radiotracers is very limited. In the last three decades, [^{13}N]ammonia and [^{15}O]water are the only tracers that have shown clinical utility in the assessment of regional blood flow and perfusion. The radiochemistry of ^{13}N and ^{15}O is described briefly at the end of this chapter.

11.2 ^{11}C Labeled Radiopharmaceuticals

^{11}C was first produced in 1934 (Crane and Lauritsen 1934) and the first biological application was based on the use of [^{11}C]CO_2 to investigate the photosynthesis in plants (Ruben et al. 1939). [^{11}C]CO was the first radiotracer used in human subjects to investigate the fixation of CO by red blood cells (Tobias et al. 1945). Several reviews have extensively discussed the chemistry and potential application of ^{11}C labeled radiotracers (Långström et al. 1999; Fowler and Ding 2002; Antoni et al. 2003). In the last three decades, a number of ^{11}C labeled radiotracers have been developed for clinical studies (Table 11.2).

11.2.1 Production of ^{11}C

The most commonly used method of ^{11}C production is based on the nuclear reaction, ^{14}N(p,α)^{11}C, in which the natural nitrogen gas is used as the target.

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Table 11.1 Organic elements: stable and radioactive isotopes

Element	Radionuclide	Decay mode	Half-life	β^+ Energy (MeV)
Carbon	^{10}C	β^+ and γ	19.3 s	3.65
	^{11}C	β^+ and EC	20.3 m	1.982
	^{12}C	Stable (98.9%)		
	^{13}C	Stable (1.1%)		
	^{14}C	β^-	5715 y	0.156 (β^-)
Nitrogen	^{13}N	β^+ decay	9.97 m	2.2205
	^{14}N	Stable (99.634%)		
	^{15}N	Stable (0.366%)		
Oxygen	^{14}O	β^+ and γ	70.6 s	5.143
	^{15}O	β^+ decay	122.2 s	2.754
	^{16}O	Stable (99.762%)		
	^{17}O	Stable (0.038%)		
	^{18}O	Stable (0.20%)		

One of the competing nuclear reactions is $^{14}N(p,pn)^{13}N$, but the relative amount of ^{13}N activity produced is dose-dependent, and short irradiation times may lead to relatively large amounts of ^{13}N (Qaim et al. 1993). With trace amounts of oxygen in the target (<1%), [^{11}C]CO_2 and [^{11}C]CO are formed (Bida et al. 1978). With relatively higher proton energies (>13 MeV), longer irradiation times (>30 min), and higher beam currents (>30 μA), the most predominant ^{11}C precursor generated is [^{11}C]CO_2 gas. In the presence of hydrogen (5%) in the target, [^{11}C]methane (CH_4) and [^{11}C]hydrogen cyanide (HCN) can be produced by a recoil synthesis, however, due to radiolysis, [^{11}C]CH_4 is the main precursor available for processing (Lamb et al. 1971; Christman et al. 1975).

^{11}C radioactivity from the cyclotron target can be recovered in the form of two major precursors;

Table 11.2 PET radiotracers for neurotransmitter systems

Biological process/neurotransmitter	Radiotracer	Mechanism of uptake and localization
Membrane synthesis	[^{11}C]Choline	Substrates for *choline kinase* in choline mtabolism
DNA synthesis	[^{11}C]Thymidine	Substrates for *thymidine kinase (TK)* in DNA synthesis
Amino acid (AA) transport	[^{11}C]L-methionine	Transport into the cells involves AA carrier protein
	[^{11}C]5-Hydroxy-tryptophan (5HTP)	Precursor for the synthesis of serotonin
Oxygen metabolism	[^{11}C]Acetate	Substrate for oxidative phosphorylation
β-Amyloid plaques	[^{11}C]PIB	Binding to β-Amyloid plaques
Dopamine	[^{11}C]-L-DOPA	Analog of L-DOPA, substrate for AAAD
	[^{11}C]Cocaine	Bind selectively to dopamine transporters
	[^{11}C]WIN35,428	
	α-(+)-[^{11}C]dihydro-tetrabenazine	Binds to vesicular amine transporters (VMAT) in presynaptic terminals
	[^{11}C]NMSP	High affinity D_2 receptor binding
	[^{11}C]Raclopride	Moderate affinity D_2 receptor binding
	[^{11}C]Chlorgyline	Suicide inactivators of *MAO*
	[^{11}C]-L-Deprenyl	
	[^{11}C]SCH23390	D_1 receptor antagonist
	(+)-[^{11}C]NNC-112	High affinity D_1 receptor antagonist
Serotonin	[^{11}C]5-HTP	Precursor for serotonin synthesis
	[^{11}C]WAY 100635	$5HT_{1A}$ receptor antagonist
	[^{11}C]MDL-100907	$5HT_{2A}$ receptor antagonist
	(+)-[^{11}C]McN-5652	Binds to serotonin transporter
	[^{11}C]DSAB	
	[^{11}C]Citalopram	
Opiate system	[^{11}C]Carfentanil	High affinity μ opiate receptor agonist
	[^{11}C]Diprenorphine	Nonsubtype (mixed) opiate receptor agonist
Benzodiazepine	[^{11}C]Flumazenil	Central BDZ receptor ($GABA_A$) antagonist
(BDZ) system	[^{11}C]Iomezanil	
	[^{11}C]PK11195	Peripheral BDZ receptor antagonist. Binds to activated microglia and macrophages
Cholinergic system	[^{11}C]Dexetimide	Muscarinic cholinergic receptor antagonist
Adrenergic system	[^{11}C]Hydroxyephedrine	Transported into sympathetic presynaptic terminals in myocardium

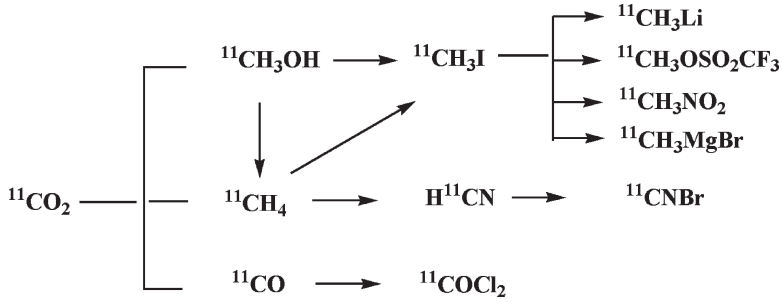

Fig. 11.1 ^{11}C labeled precursors prepared from [^{11}C]carbon dioxide and [^{11}C] methane

Table 11.3 Specific activity (SA) of ^{11}C and ^{18}F

Radio-nuclide	Half-life	Theoretical SA		Practical SA	
	min	Ci nmol^{-1}	nmol Ci^{-1}	Ci nmol^{-1}	nmol Ci^{-1}
^{11}C	20.4	9.22	0.108	0.01–0.1	10–100
^{18}F	110	1.71	0.585	0.001–0.02	50–1000

[^{11}C]carbon dioxide or [^{11}C]methane. Subsequently, these gases can be converted into several secondary precursors (Fig. 11.1), such as methyl iodide, methyl triflate, HCN, nitromethane, and phosgene.

11.2.1.1 Specific Activity (SA) of ^{11}C

The theoretical SA of ^{11}C is 9,220 Ci µmol^{-1} or 9.22 Ci nmol^{-1} (Table 11.3). Since the contamination of the target and the gas lines with stable ^{12}C is unavoidable, ^{11}C is always contaminated with ^{12}C atoms. Also, both CO_2 and CH_4 gases are present in the atmosphere and provide a ubiquitous source of carrier as a contaminant that decreases the SA. As a consequence, the practical SA of ^{11}C precursors achieved from the typical production in a cyclotron target varies from 0.01 to 0.1 Ci nmol^{-1} depending on a number of factors. In other words, every ^{11}C atom is contaminated with 100 or 1,000 atoms of stable carbon atoms, which implies that the majority of the mass is mostly due to stable ^{12}C and very little of the carbon is from the ^{11}C activity. There is a significant potential and also a need to improve the SA of ^{11}C production with the current cyclotron targets and generate ^{11}C precursors with ultrahigh SA.

11.2.2 ^{11}C Precursors

[^{11}C]Methyl iodide is the precursor of choice for introducing ^{11}C into organic molecules. However, a number of other precursors (Fig. 11.1) have been developed in the last few decades in order to meet the demands of synthetic strategies used for the development of ^{11}C labeled radiotracers. [^{11}C]Methyl iodide can also be used to prepare a number of secondary ^{11}C precursors, such as methyl triflate ($CH_3OSO_2CF_3$), methyl lithium, nitromethane, and methyl magnesium iodide or bromide. Starting with [^{11}C]methane, precursors, such as hydrogen cyanide, cupric cyanide, carbon tetrachloride, and phosgene can be prepared (Ferrieri 2003; Antoni and Långström 2005). Synthesis of several ^{11}C precursors is shown in Fig. 11.2.

Methyl triflate, introduced in 1991 as an alkylating agent, is more advantageous than methyl iodide for alkylation reactions under mild conditions (Jewett 1991). More specifically, it can be easily prepared by passing [^{11}C]methyl iodide through a small soda-glass column containing sliver triflate-impregnated graphitized carbon and the conversion to [^{11}C]methyl triflate is very efficient, and fast. The other precursor for methylations under mild conditions is methyl lithium [^{11}C]CH_3Li, which can be prepared by an equilibrium reaction between *n*-butyl lithium (*n*-BuLi) and [^{11}C] methyl iodide (Reiffers et al. 1980).

The Grignard reagent, methyl magnesium iodide, [^{11}C]CH_3MgI, is useful to add a methyl group to a carbonyl (CO) group in a molecule. This precursor can be prepared by the interaction of [^{11}C]methyl iodide with magnesium turnings mixed with iodobenzene in ether (Elsinga et al. 1995).

Nitroalkanes, such as nitromethane [^{11}C]CH_3NO_2 can easily be converted into carbon nucleophile in the presence of a base. Also, an aldehyde group in a molecule can easily be substituted with a nitromethane. Subsequently, the nitrogroup can be reduced to an amine (Schoeps et al. 1993). [^{11}C]CH_3NO_2 can also be easily prepared by the reaction of methyl iodide with silver nitrate at 80°C (Schoeps et al. 1989). Other nitroalkanes such as nitroethane and nitropropane can also be prepared similarly.

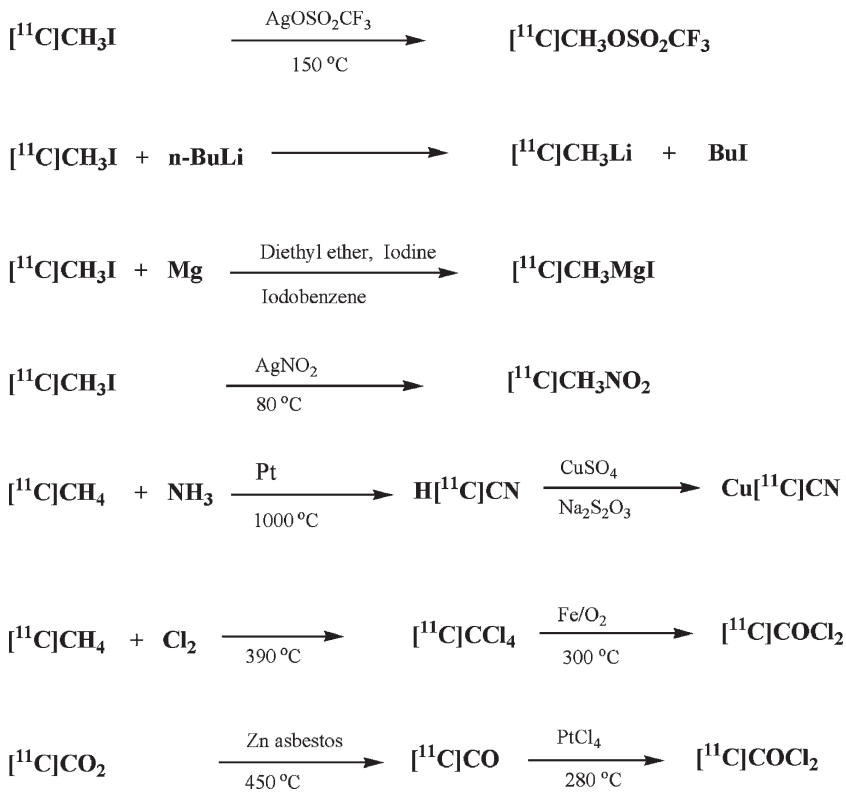

Fig. 11.2 Methods for the synthesis of ^{11}C labeled precursors

Cyanide (HCN) can be an extremely useful precursor for replacing halogen atoms, through nucleophilic substitution, with the cyano group. [^{11}C]HCN can be used to label amines, amino acids, aldehydes and acids, and can be easily prepared by the reaction of [^{11}C]methane with ammonia over a platinum catalyst, at a very high temperature (Christman et al. 1975). Since copper salts mediate certain aromatic nucleophilic substitutions, [^{11}C]HCN can easily be converted to Cu[^{11}C]CN (Ponchant et al. 1997).

Phosgene, [^{11}C]$COCl_2$) is a useful precursor that can be prepared easily by the catalytic chlorination of [^{11}C]CO, which typically is produced through the reduction of [^{11}C]CO_2 over hot zinc (Roeda et al. 1978). Phosgene can also be prepared by converting [^{11}C]methane to carbon tetrachloride, [^{11}C]CCl_4 through reaction with hot Cl_2 gas. Carbon tetrachloride is then mixed in a stream of oxygen gas and passed through a second furnace at 300°C containing iron granules (Steel et al. 1999). [^{11}C]Phosgene has been used to prepare [^{11}C]urea, a precursor for the synthesis of 2-[^{11}C]thymidine.

11.2.2.1 [^{11}C]Methyl Iodide

[^{11}C]CH_3I is the most common precursor used to make ^{11}C radiotracers. It was first prepared in 1976 to synthesize [^{11}C]methionine (Långström and Lundqvist 1976). Two methods are used for the synthesis of [^{11}C]CH_3I (Fig. 11.3). In a "liquid-phase" synthesis, [^{11}C]CO_2 is first reduced to methanol [^{11}C]CH_3OH, using lithium aluminum hydroxide ($LiAlH_4$) which then reacts with hydroiodic acid (HI) to generate methyliodide. In a "gas-phase" synthesis, [$^{11}CH_4$] gas (either from the target directly or produced from [$^{11}CO_2$]) reacts with iodine vapors generating methyl iodide (Larsen et al. 1997; Link et al. 1997). Commercial automated synthesis modules (Fig. 11.4) are available to synthesize [^{11}C]methyl iodide.

The *GE MicroLab* and *GE TracerLab FXc Pro* modules were designed to generate methyl iodide based on the gas phase method, while *Bioscan MeI-Plus* was designed based on the liquid phase method.

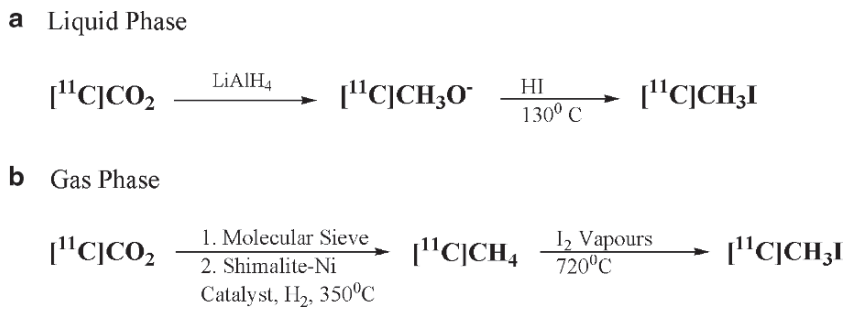

Fig. 11.3 Synthesis of [^{11}C]methyl iodide: Liquid phase method (**a**) and gas phase method (**b**)

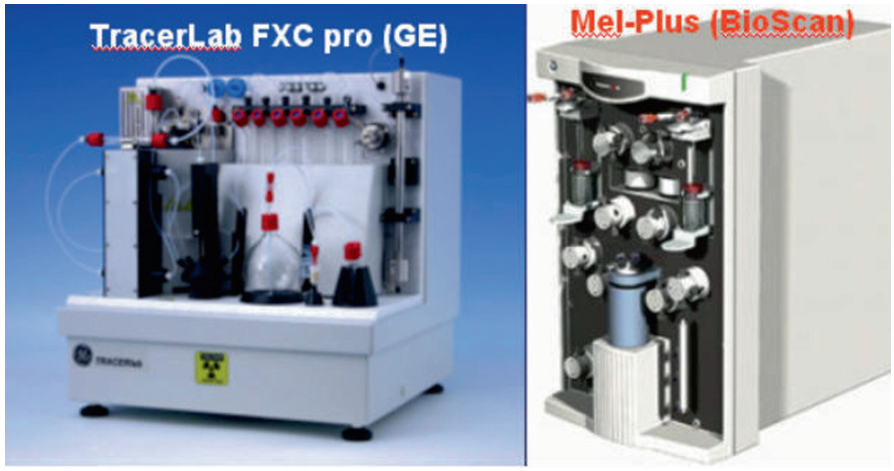

Fig. 11.4 Commercial automated synthesis modules for the production of [^{11}C] Methyl iodide: TracerLab$_{FXC}$ pro based on gas phase method and MeI-plus based on liquid phase method

Tracerlab FXc Pro consists of the following major components:

- Molecular sieve and Ni catalyst column to trap [^{11}C] CO_2 from the cyclotron and convert it to $^{11}CH_4$
- [^{11}C]CH_4 trap (CO_2 passes through it)
- I_2 oven to generate I_2 vapor
- MeI oven, where [^{11}C]CH_4 is converted to [^{11}C] CH_3I
- MeI trap, to trap [^{11}C]CH_3I; 5) glass reaction vessel where [^{11}C]CH_3I is collected in a solvent (DMF)
- [^{11}C]CH_3I is finally delivered into the reaction vessel approximately 15 min after EOB

MeI-Plus consists of the following major components:

- Molecular sieve column to trap [^{11}C]CO_2
- LAH dispenser (10 mL vial)
- HI dispenser (10 mL vial)
- One mL conical glass vial, where [^{11}C]CO_2 is reduced with LAH and converted to [^{11}C]CH_3I
- One mL glass vial containing 0.2 mL solvent (DMF) to trap [^{11}C]CH_3I
- [^{11}C]CH_3I is delivered into the reaction vial in <10 min after EOB. After each run, the system cleans itself with ethanol, acetone, and ether

Generally, the radiochemical purity, and SA of [^{11}C] CH_3I depend on the synthesis procedure and the automated module employed (Makiko et al. 2005; Kothari et al. 2005). The specific activity of [^{11}C]CH_3I (collected in DMF or acetone) can be determined by analytical HPLC using a Novapak C_{18} column (Waters, 4.6 × 150 mm) and a mobile phase, consisting of acetonitrile/water (40/60) containing 0.1 M ammonium formate at a flow rate of 2 mL min^{-1}. The retention time of [^{11}C]CH_3I is 2.7 min (Fig. 11.5). The gas-phase method generates higher SA of [^{11}C]CH_3I and may be appropriate for receptor binding radiotracers.

11.2.3 Synthesis of ^{11}C Labeled MIPs

A number of ^{11}C labeled molecular imaging probes of significant clinical interest have been developed, in

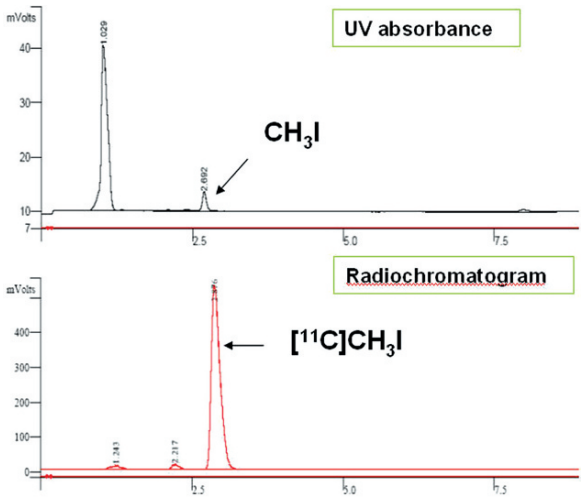

Fig. 11.5 Radiochemical purity of [^{11}C]methyl iodide (produced based on gas phase method) based on analytical HPLC

the last few decades (Table 11.2). Historically, several different approaches have been used for the production of ^{11}C labeled radiotracers, but the most practical approaches have been based on either (a) organic synthetic methods, or (b) enzyme catalysis (Antoni et al. 2003; Antoni and Långström 2005).

The methods based on organic synthesis typically involve alkylations of C, N, O, and S nucleophiles with [^{11}C]methyl iodide or methyl triflate. The alkylation reactions require an organic precursor, also known as *nor* compound (a molecule of interest without a methyl group on a specific C, N, O, or S atom). If a molecule of interest has several reactive groups, the organic precursors must have protective groups that can be easily deprotected by hydrolysis following methylation to generate the final drug product. This is the most common synthetic approach used in the routine production of ^{11}C labeled radiopharmaceuticals. Several examples are discussed below.

11.2.3.1 L-[S-methyl-^{11}C]Methionine

The amino acid L-Methionine, labeled with ^{11}C in the methyl position, has been used for brain imaging of brain tumors. The routine production involves an alkylation on a sulfur nucleophile by the reaction of [^{11}C] methyl iodide with *S*-benzyl-L-homocysteine in the presence of liquid ammonia and sodium, as shown in Fig. 11.6 (Långström and Lundqvist 1976; Schmitz et al. 1995). Following reverse phase HPLC of the reaction mixture, the final drug product, L-[S-methyl-^{11}C]methionine, is eluted using a phosphate buffer.

11.2.3.2 Synthesis of [O-methyl-^{11}C]Raclopride

Raclopride is a dopamine D_2 receptor antagonist and is one of the most extensively used neuroreceptor imaging probes. Raclopride is labeled with ^{11}C by *O*-methylation using [^{11}C]methyl iodide, as shown in Fig. 11.7. The enantiomerically pure *S*-precursor (*O*-desmthylraclopride) in DMSO is reacted with [^{11}C] CH_3I in the presence of sodium hydroxide. The purified drug product, [^{11}C]raclopride, is obtained following reverse phase HPLC of the reaction mixture using a C-18 column, a 10 mM phosphoric acid, and acetonitrile (70:30 v/v) as an eluent. The fraction containing [^{11}C]raclopride is subsequently evaporated to remove acetonitrile, reformulated in physiological saline, and sterilized by membrane filtration.

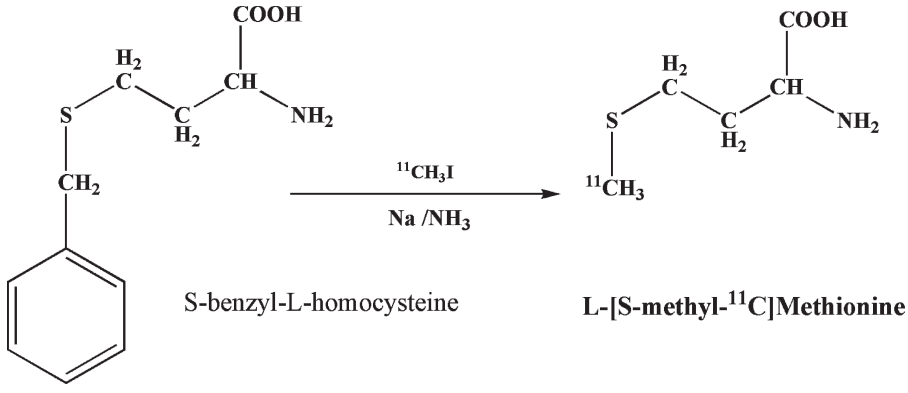

Fig. 11.6 Synthesis of L-[S-methyl-^{11}C]methionine

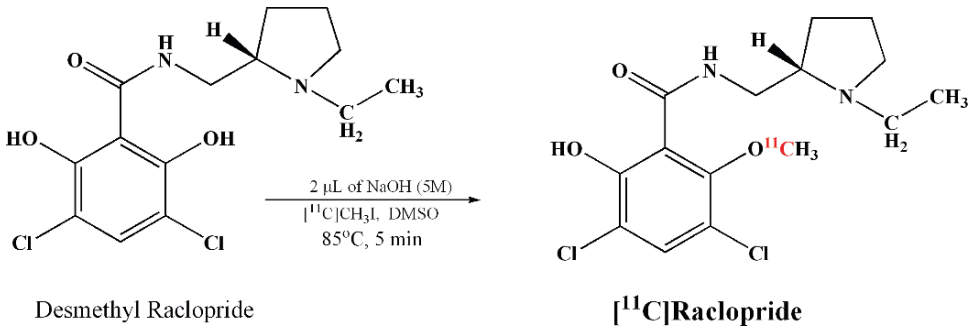

Fig. 11.7 Synthesis of [^{11}C]Raclopride

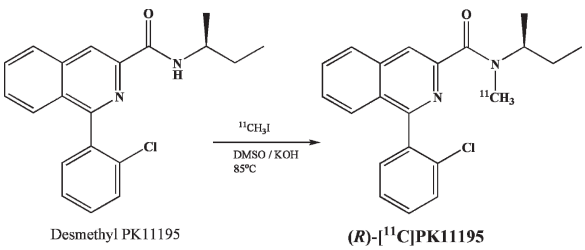

Fig. 11.8 Synthesis of [^{11}C]PK11195

11.2.3.3 Synthesis of R-[N-methyl-^{11}C]PK11195

PK11195, a peripheral benzodiazepine receptor ligand, labeled with ^{11}C, was originally developed as a tracer to image activated microglia in the brain (Banati et al. 1999; Hashimoto et al. 1989). PK11195 can be labeled with ^{11}C by *N*-methylation using [^{11}C]methyl iodide, as shown in Fig. 11.8. The precursor, *R*-desmethyl PK11195 (1.0 mg), is mixed with KOH (20 mg) in DMSO (0.4 mL) for 5 min. Subsequently, the mixture is reacted with [^{11}C]CH_3I for 3 min at 80°C. The mixture is diluted with 2–3 mL of mobile phase (70% methanol and 30% water) and purified using reverse phase HPLC column. The eluent fraction containing the drug product is passed through a C18 sep-pack cartridge to remove methanol. The final drug product is reformulated in 10% ethanol and physiological saline, and sterilized by membrane filtration.

11.2.3.4 [^{11}C]PIB

Based on an amyloid dye thioflavin-T, a ^{11}C tracer, *N*-Methyl-^{11}C-2-(4′-methylaminophenyl)-6-hydroxybenzothiazole (^{11}C-6-OH-BTA-1, also known as

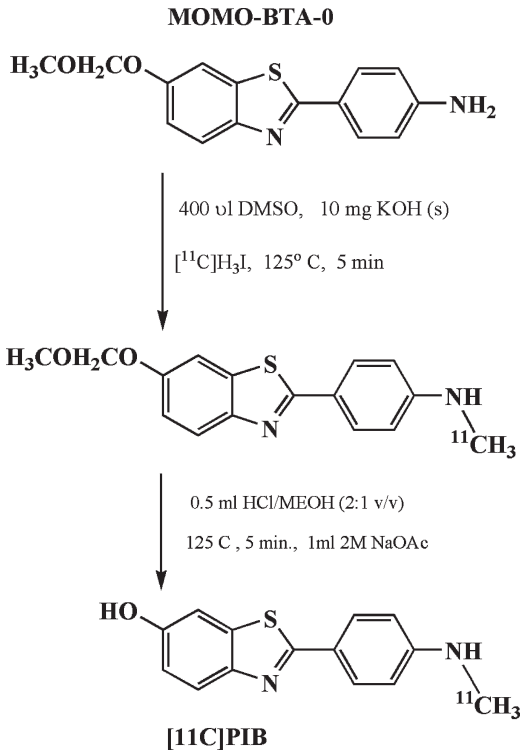

Fig. 11.9 Synthesis of [^{11}C]PIB

"Pittsburgh Compound-B" or [^{11}C]-PIB), was developed to image brain amyloid plaques in patients with Alzheimer's disease (Mathis et al. 2002, 2003). PIB can be labeled with ^{11}C by *N*-methylation using [^{11}C] methyl iodide as shown in Fig. 11.9. The precursor, desmethyl PIB with a protective group known as MOMO-BTA-0 (1.5 mg) is mixed with KOH (10 mg) in DMSO (0.4 mL) for 5 min. Subsequently, the mixture is reacted with [^{11}C]CH_3I for 5 min at 125°C. At the end, the protective group is removed by hydrolysis

at 80°C for 5 min using 0.5 mL of methanolic HCl (2:1). The mixture is diluted with mobile phase (35%) acetonitrile and 65% triethyl ammonium phosphate, pH 7.2) and purified using reverse phase HPLC. The eluent fraction containing [^{11}C]PIB is passed through the C18 sep-pak cartridge to remove the organic solvent. The final drug product can be reformulated in physiological saline with 10% ethanol and sterilized by membrane filtration.

11.2.3.5 Synthesis of [^{11}C]5-Hydroxy-L-tryptophan (HTP)

Preparation of certain ^{11}C radiopharmaceuticals can be very complicated and may involve many steps in the synthesis followed by purification procedures. ^{11}C labeled amino acids can be prepared using enzyme catalyzed reactions (especially to prepare the desired enantiomer with biological activity rather than a racemic mixture). For example, in the synthesis of [^{11}C]5-HTP (Bjurling et al. 1989), [^{11}C]-L-alanine is synthesized first, by reacting [^{11}C]CH_3I with *N*-(Diphenyl methylene)glycine tertiary butyl ester. Subsequently, [^{11}C]-L-alanine is converted to pyruvic acid using enzymes GPT, DAO and GPT. The interaction of labeled alanine with 5-hydroxyindole, in the presence of *tryptophanase*, will finally produce [^{11}C]5-HTP (Fig. 11.10). The final drug product is purified by HPLC and sterilized by membrane filtration.

11.3 ^{13}N Labeled Radiopharmaceuticals

^{13}N was first produced by the bombardment of boron with α particles using the ^{10}B(α,*n*)^{13}N reaction (Joliot and Curie 1934). The first ^{13}N radiotracer of biological interest was [^{13}N]ammonia (NH_3) and, based on cyclotrons, a number of nuclear reactions were used over the years to produce ^{13}N (Schlyer 2003). However, the most popular method of producing ^{13}N is based on the proton (8–15 MeV) bombardment of natural oxygen gas, using the ^{16}O(*p*,α)^{13}N reaction (Tibury et al. 1977). ^{13}N can also be produced by the proton (4–9 MeV) bombardment of isotopically enriched ^{13}C using the ^{13}C(*p*,*n*)^{13}N reaction (Ferrieri et al. 1983).

11.3.1 [^{13}N]Ammonia (NH_3)

The most predominant chemical species of ^{13}N produced in the water target is [^{13}N]nitrate (NO_3^-), while the other two species, [^{13}N]nitrite (NO_2) and [^{13}N] ammonia may represent only a small fraction of the total ^{13}N radioactivity (Table 11.4). [^{13}N]ammonia is formed as the primary product by the abstraction of hydrogen atoms from the water, as shown in the Fig. 11.11. As the irradiation dose to target is increased, radiolytic oxidation occurs producing oxoanions of nitrogen, consisting of mainly nitrates and nitrites (Clark and Aigbirhio 2003). The most common method

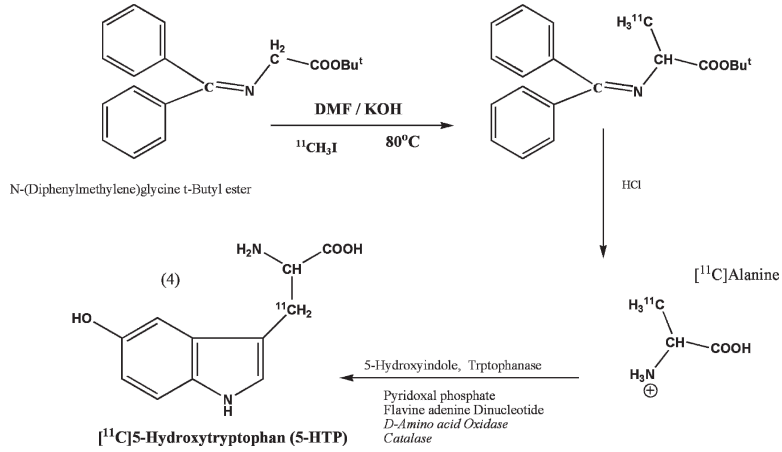

Fig. 11.10 Synthesis of [^{11}C]5-Hydroxytryptophan (5HTP)

Table 11.4 Methods for the production of ^{13}N and ^{15}O radiotracers

Target material	Nuclear reaction	In-target product(s)	Post irradiation treatment	Final product
H_2O	$^{16}O(p,\alpha)^{13}N$	NO_3^-,BO_2^-,NH_2^+	Reduction of anions using DeVarda's alloy and NaOH	$[^{13}N]NH_3$
H_2O/Ethanol (1 mM)	$^{16}O(p,\alpha)^{13}N$	NH_4^+	Radiochemical purification using cation exchange cartridge	$[^{13}N]NH_3$
N_2/O_2 (0.1–4.0%)	$^{14}N(d,n)^{15}O$ $^{15}N(d,n)^{15}O$	$[^{15}O]O_2$	Remove traces of NO_2 and O_3	$[^{15}O]O_2$
N_2/CO_2 (0.1–2.0%)	$^{14}N(d,n)^{15}O$	$[^{15}O]CO_2$	Remove traces of $[^{15}O]O_2$	$[^{15}O]CO_2$ with trace ^{13}N levels
N_2/H_2 (5.0%)	$^{14}N(d,n)^{15}O$	$[^{15}O]CO_2$	Remove traces of $[^{15}O]O_2$	$[^{15}O]CO_2$ with trace ^{13}N levels

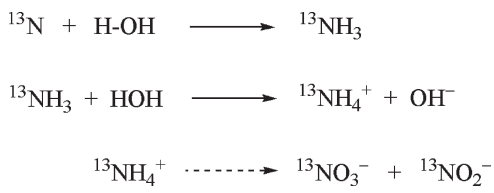

Fig. 11.11 Reactions of ^{13}N with water in the cyclotron target

of increasing the radiochemical yield of [^{13}N]ammonia is by the addition of free radical scavengers, such as ethanol and acetic acid to the target water (Weiland et al. 1991). Subsequently, the $[^{13}N]NH_4^+$ ion can be trapped on a small cation exchange cartridge, from which it can be eluted using physiological saline.

[^{13}N]Ammonia can be used to prepare a number of ^{13}N labeled amino acids for the determination of protein synthesis rates in tumors. [^{13}N]Ammonia has also been used to prepare ^{13}N labeled anticancer drugs, such as CCNU, BCNU, and cisplatin (Clark and Aigbirhio 2003).

11.3.2 Synthesis of [^{13}N]Gemcitabine

Gemcitabine (Gemzar®, Eli Lilly) is a chemotherapy drug most commonly used to treat nonsmall cell lung, pancreatic, bladder, and breast cancer. [^{13}N]Gemcitabine (GT) can be prepared using [^{13}N]ammonia, as shown in Fig. 11.12. Following production of [^{13}N]ammonia based on $^{16}O(p,\alpha)^{13}N$ reaction, the target water is passed through an ion exchange CM cartridge to trap [^{13}N] ammonia. Subsequently, it is eluted into a vial containing a DeTet, (a gemcitabine precursor containing a tetrazol group) using 0.6 mL of sodium acetate buffer (1 M, pH 8.5). The mixture is then heated at 150–160°C for 5 min. Finally, at the end of the reaction, the mixture is filtered and the filtrate is purified by HPLC to isolate the pure [^{13}N]GT, which is then sterilized using membrane filtration (Vallabhajosula et al. 2008).

11.4 ^{15}O labeled Radiotracers

The potential utility of [^{15}O]oxygen to study regional tracer biology was first demonstrated in murine experimental neoplasms at the Washington University in St Louis (Ter-Pogossian and Powers 1958). Since that time, different chemical forms of ^{15}O, such as carbon dioxide (CO_2), carbon monoxide (CO), water (H_2O), and *n*-butanol ($CH_3(CH_2)_3OH$) have been used to study oxygen metabolism, blood volume, and blood flow in humans with PET.

^{15}O can be produced in a cyclotron using a variety of nuclear reactions (Clark and Aigbirhio 2003), but the most commonly used reactions are $^{14}N(d,i)^{15}O$ and $^{15}N(p,n)^{15}O$. The chemical forms of ^{15}O generated in the target vessel, depend on the nuclear reaction, energy of the bombarding particle, and the mixture of target gases (such as N_2/O_2, N_2/CO_2, and N_2/H_2) (Table 11.4).

11.4.1 ^{15}O Labeled Gases

When N_2 gas is bombarded with deuterons, the presence of oxygen (0.1–4.0%) leads to the generation of $[^{15}O]O_2$ with higher radiochemical purity. Subsequently, $[^{15}]O_2$ can be used to synthesize labeled CO and CO_2 gases.

$[^{15}O]CO$ can be synthesized, when $[^{15}]O_2$ is reacted with carbon (activated charcoal) at 900–950°C. However, when $[^{15}]O_2$ reacts with carbon at 400–450°C, the predominant species formed is $[^{15}O]CO_2$.

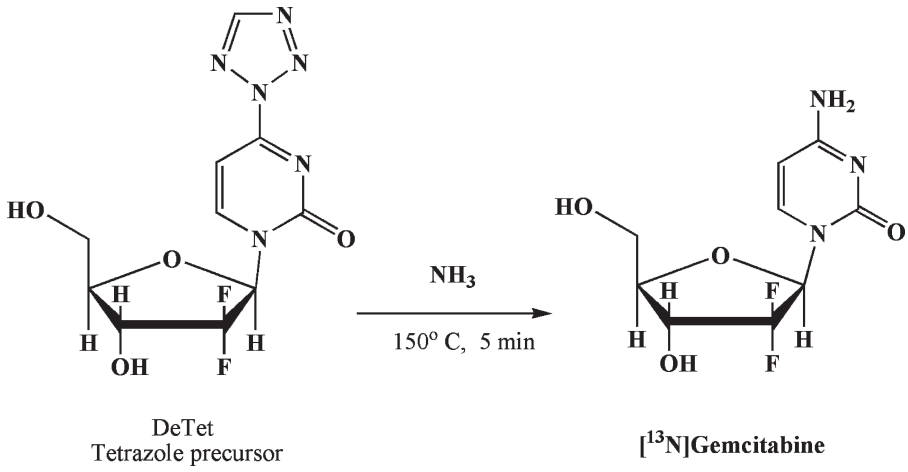

Fig. 11.12 Synthesis of [^{13}N]Gemcitabine

Methods for the in-target production of ^{15}O labeled CO and CO_2 gases have also been developed. When the target N_2 gas is mixed with minimal O_2 levels (0.25%), [^{15}O]CO is produced. Also, the presence of a source of hot carbon within the target volume has been shown to be optimal for the in-target production of [^{15}O]CO (Votaw et al. 1986; Berridge et al. 1990). When N_2/CO_2 gas mixture is used as the target gas, the product $^{15}O_2$ is converted to [^{15}O]CO_2 in the target. Due to secondary nuclear reaction, $^{12}C(d,n)^{13}N$, the major radionuclidic impurity in [^{15}O]CO_2 preparations is [^{13}N]N_2 gas.

11.4.2 Synthesis of [^{15}O]Water

When a N_2/H_2 mixture is bombarded with deuterons, the predominant ^{15}O labeled product in the target vessel is [^{15}O]H_2O (Vera Ruiz and Wolf 1978). Also, [^{15}O]H_2O is readily synthesized outside the target by the palladium-catalyzed reaction of [^{15}O]O_2 with H_2 gas (Clark et al. 1987). A flow of purified [^{15}O]O_2 in nitrogen is mixed with hydrogen and passed over a few pellets of palladium–alumina catalyst, and the resulting [^{15}O]H_2O vapor is trapped by bubbling the nitrogen carrier through sterile saline solution. Based on this principle, an advanced automated system for the administration of [^{15}O]water at the bedside was developed by the investigators at the Hammersmith Hospital in London.

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