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MASTER

POSITRON EMITTING NUCLIDES AND THEIR SYNTHETIC INCORPORATION IN RADIOPHARMACEUTICALS

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The recent progress which has been made in the design of photon imaging instruments using annihilation coincidence counting to detect the radiation produced by the decay of positron emitting nuclides has renewed interest in the use of organic radiopharmaceuticals labeled with these nuclides (1,2,3).

Of the most abundant elements occurring in organic molecules, carbon, nitrogen and oxygen have radioisotopes (^{11}C, ^{13}N, ^{15}O) which decay by the emission of radiation which can be detected outside the body barrier. The incorporation of these isotopes into organic molecules, therefore, offers the potential to trace the distribution of these molecules in humans and animals without significant alteration in biological activity which often occurs on labeling with a foreign radioelement. Therefore the positron emitting nuclides, ^{11}C, ^{13}N and ^{15}O, are unique in their potential applicability to the study of metabolism in humans. These nuclides are usually cyclotron produced and their incorporation into radiopharmaceuticals and use in biological studies encompasses the combined expertise of individuals in many disciplines. It is within this broad context that the synthesis of radiopharmaceuticals tagged with short-lived positron emitting nuclides must be considered.

The topics covered here include a general description of the many unique problems accompanying the synthesis and use of radiopharmaceuticals labeled with short-lived positron emitting nuclides and selected examples of radiopharmaceutical synthesis using the positron-emitting nuclides carbon-11 ($t_{\frac{1}{2}}$: 20.4 min), nitrogen-13 ($t_{\frac{1}{2}}$: 10 min) and fluorine-18 ($t_{\frac{1}{2}}$: 110 min). For a more comprehensive treatment of this and related topics, the reader is refered to several articles which have appeared recently (4,5,6,7,8).

SPECIAL PROBLEMS IN THE SYNTHESIS OF SHORT-LIVED POSITRON EMITTING RADIOPHARMACEUTICALS

Radiopharmaceutical Design. It has become increasingly apparent that the design of new radiopharmaceuticals for imaging or for probing the metabolic function(s) of a particular organ especially as they are effected by disease or drug therapy requires a far greater store of usable information than actually exists. In the absence of this badly needed basic information, radiopharmaceutical design has relied heavily on the laborious empirical approach. Recently positron-emitting radiopharmaceuticals have been used to probe the effect of chemical structure variation on the interactions between chemicals and biological systems, so as to add to the information store which can be tapped when new problems are encountered (9,10,11).

The Development of Rapid Synthetic and Analytic Methods. Both classical chemical synthesis and biosynthesis have been used in the incorporation of positron-emitting nuclides into radiopharmaceuticals. The incorporation of any short-lived nuclide into radiopharmaceuticals requires the adjustment of such reaction conditions as temperature, solvents and pressure so that the

synthesis, purification, and formulation for injection can be carried out within a few half-lives of the nuclide. Enzyme catalyzed reactions are, by their nature, especially attractive in the synthesis of radiopharmaceuticals labeled with ^{11}C and ^{13}N. Advantages include rapid formation of product and in some cases stereospecificity. The disadvantages of difficulty in producing a pyrogen-free product have been overcome, in some cases, by the use of immobilized enzymes (12). The application of positron emitting radiopharmaceuticals to disease diagnosis and to the study of metabolism also requires the development of rapid methods for the extraction, identification and quantification of blood and tissue metabolites.

Specific Activity. Positron emitting tracers have potential value in the study of metabolic reactions in vivo especially in view of the high specific activities available. The nature of diagnostic and metabolic studies with short-lived positron emitting radiopharmaceuticals generally requires that not only the radiation dose from a given study be minimal but also that the physiological reactions or perturbations from a radiopharmaceutical be undetectable. Therefore, an important challenge in the synthesis of radiopharmaceuticals for imaging and metabolic studies is that of devising microscale reactions and purification schemes so that radiopharmaceuticals of exceedingly high specific activity are produced. This is especially important in tracer studies with radiopharmaceuticals which are physiologically active in small quantities (for example, the catecholamines and fluoroacetate). Furthermore, in some cases, the loading dose affects tissue distribution of a radiopharmaceutical (13,14,15).

Quality Control of Radiopharmaceuticals. The determination of chemical and radiochemical purity is mandatory for any application of radiotracers. All too often in radiopharmaceutical research, a "shake and bake" approach to chemical bond formation between a radionuclide and substrate is taken. Since the use of radiotracers often requires the expertise of many individuals of varying backgrounds for a single experiment, the time and effort which is wasted by lack of attention to product identity and purity (both chemical and radiochemical) can become enormous. Furthermore, biological studies on a given radiopharmaceutical have little meaning if the radiopharmaceutical is some form of "mystery mixture", and the benefit-to-risk ratio in doing a diagnostic study in humans is negative if one injects an unknown.

Since ^{11}C, ^{13}N and ^{18}F are all short-lived, the analytical methods used to determine radiochemical purity must be rapid. Thin layer chromatography, paper chromatography, gas-liquid chromatography, ion exchange chromatography high pressure liquid chromatography and electrophoresis are commonly used (16). The correlation of the R_f of radioactivity with the R_f of a chemical structure (detected by standard means on thin layer chromatograms is a simple and rapid technique. Gas chromatographic analysis of the radiopharmaceutical or its derivatives is also an excellent rapid analytical tool.

The production of a radiopharmaceutical labeled with ^{11}C, ^{13}N or ^{18}F for intravenous injection usually requires the establishment of a "protocol" which has been demonstrated to yield a sterile, pyrogen-free product, and then strictly adhering to this protocol in the production of the radiopharmaceutical for human use (17). The protocol should require testing for sterility and apyrogenicity (as well as chemical and radiochemical purity) at some short

time period before the actual run. Since the short half-life usually does not allow time for testing before injection, part of the sample can be reserved for "after the fact" testi .g of the product.

The short half-life of ^{11}C, ^{13}N and ^{18}F as well as the thermal lability of many organic molecules often precludes sterilization by autoclaving. Terminal sterilization using a 0.22 μ millipore filter is the usual and satisfactory alternative.

In-house testing for pyrogens using the in vitro limulus test is a sensitive assay for endotoxin-contaminated radiopharmaceuticals. Studies have shown that the limulus test is far more sensitive to endotoxins than the USP pyrogen test (rabbit pyrogen test) (17). It is not, however, a permissible substitute for the rabbit test under FDA regulations and should only be used for screening and informal checks on processes.

In summary, a systematic approach to all aspects of radiopharmaceutical quality control is necessary in order that (1) the results of a given study have a sound basis for interpretation and (2) that the radiopharmaceutical will not cause injury to the human subject either because of bacterial or chemical contamination or because of a radiochemical impurity which may cause an excessive radiation burden due to its distribution.

Radiation Exposure. The safe handling of high levels of radioactivity by the chemist is certainly a problem which has received increasing recognition and attention as the field has grown. Radiation monitoring equipment, shielding, awareness of the potential dangers and innovation on the part of the researcher are primary considerations.

CARBON-11 LABELED RADIOPHARMACEUTICALS

Carbon-11 was first reported in 1934 (18) and there were a number of important precursors and compounds prepared and used in biomedical studies in the period 1939-1942 (19). Interestingly, there was little or no further medical application of carbon-11 until the late 1960's (20).

The synthesis of carbon-11 labeled radiopharmaceuticals requires the development of synthetic procedures using carbon-11 labeled precursors which are either available directly from the cyclotron or through simple on-line synthesis. Since, at the precursor stage, activity levels may be quite high, the development of presursor syntheses which require a minimum of handling is required. Although this is necessary throughout a synthesis, it is especially important in the initial stages.

Table 1 lists some of the simple precursor molecules which have been prepared and used in radiopharmaceutical synthesis. Of these precursors, ^{11}C-carbon dioxide and ^{11}C-cyanide are particularly useful since they can be synthesized in direct on-line systems with minimal handling.

Carbon-11 labeled precursors have been incorporated into organic molecules via biosynthesis and enzyme-catalyzed synthesis as well as classical organic synthesis. Some examples, serve to illustrate these types of radiopharmaceutical synthesis.

^{11}C-Labeled Carboxylic Acids. The carboxylation of Grignard and other organometallic reagents with $^{11}CO_2$ represents a facile route to ^{11}C-labeled carboxylic acids. This reaction has been used in the synthesis of a series of ^{11}C-carboxylates in order to study their *in vivo* tissue distribution as a function of variations in structure (11).

^{11}C-Labeled acetoacetic acid, a radiopharmaceutical which was of interest in brain metabolism studies, was synthesized via the addition of $^{11}CO_2$ to the enolate anion of acetone (21) as shown in Fig. 1.

Biosynthesis of ^{11}C-Labeled Glucose. The biosynthesis of ^{11}C-glucose described by Lifton and Welch (22) and by Wolf (23) is a modification of a method used for preparing ^{14}C-glucose. This exemplifies the adaptation of a synthetic method to labeling with a very short-lived isotope. The sequence involves the recirculation of $^{11}CO_2$ around fresh (light starved) Swiss chard leaves in the presence of incandescent light. Recently ion exchange separation (24) and liquid chromatography (25) have been used in the synthesis and purification of ^{11}C-glucose.

^{11}C-Labeled Psychotropic Drugs and Proteins via N-Methylation. The preparation of ^{11}C-formaldehyde was first described by Christman and coworkers who used it in the enzyme catalyzed synthesis of ^{11}C-thymidine (26). ^{11}C-Formaldehyde has since been used in reductive methylation reactions to produce ^{11}C-labeled imipramine, chlorpromazine and nicotine (27,28) (Fig. 1) as well as ^{11}C-labeled proteins (29).

^{11}C-Labeled Amines. High yields of essentially carrier-free H^{11}CN can be produced on line using a $N_2 + H_2$ target (30). This is an "on-line" system which requires no handling and therefore makes H^{11}CN one of the most conveniently (and safely) produced ^{11}C-precursors. ^{11}C-cyanide has been used to synthesize a number of ^{11}C-labeled amines (9,13,31,32), aminonitriles (33) and hydantoins (34,35). For example, a relatively complex alkaloid, salsolinol, can be labeled with carbon-11 by first synthesizing ^{11}C-dopamine and then converting this to ^{11}C-salsolinol by the Pictet-Spengler condensation with acetaldehyde (36) (Fig. 1).

NITROGEN-13 LABELED RADIOPHARMACEUTICALS

The chemical forms of ^{13}N which are relatively easily produced are nitrogen gas (37), nitrous acid (38) and ammonia (6). The complexity of ^{13}N-labeled radiopharmaceuticals which can be produced using classical synthetic organic techniques is restricted by this nuclide's 10-minute half-life. Therefore ^{13}N-labeled radiopharmaceuticals are most commonly produced via enzyme-catalyzed syntheses which are not only rapid, but also yield specific products which are often optically pure in the case of compounds which can exist as optical isomers.

^{13}N-Labeled L-Amino Acids. ^{13}N-L-Glutamic acid is produced using immobilized glutamic acid dehydrogenase using α-ketoglutarate and $^{13}NH_3$ as shown in Fig. 2. The ^{13}N-glutamic acid is then used to form ^{13}N-L-alanine

in a reaction catalyzed by glutamic-pyruvic transaminase (also immobilized). The use of immobilized enzymes yields radiopharmaceuticals which are free of macromolecular contamination (12).

Nitroso-^{13}N-Labeled Nitrosoureas. Recently, Pettit and coworkers described the incorporation of ^{13}N into nitrosoureas using organic synthesis (38). Although the synthesis time is long (60-65 min) and the radiochemical yields and specific activity are probably too low to allow for biological studies, this represents the first organic radiopharmaceutical labeled with nitrogen-13 to be synthesized using standard organic synthetic techniques.

FLUORINE-18 LABELED RADIOPHARMACEUTICALS

Fluorine-18 has been used principally as a bone scanning agent in nuclear medicine. Although several groups have developed syntheses leading to ^{18}F-labeled compounds for various applications in nuclear medicine, as yet there is no clinical application of an ^{18}F-labeled radiopharmaceutical. The prospects for the use of ^{18}F-radiopharmaceuticals as analog molecules and in dynamic organ function studies have been discussed by Robinson (5). The introduction of fluorine into a molecule has been used to mimic or enhance the biological reactivity of a natural molecule or to take advantage of any altered metabolism caused by fluorine substitution.

Labeling with ^{18}F magnifies the complexities encountered in organofluorine chemistry. The intriguing radiopharmaceutical applications of fluorine-18 which can be envisioned are too often encumbered by the lack of synthetic methods which can produce these molecules rapidly, in high yield and in high specific activity.

The most common chemical form of fluorine-18 is as fluoride ion. Electrophilic fluorinating agents such as $NO^{18}F$ and $^{18}F\text{-}F_2$ have also been used in radiopharmaceutical synthesis (Table 1). ^{18}F-Labeled aromatic fluorides have been synthesized using the Schiemann reaction with ^{18}F-fluoride. ^{18}F-Fluoride has also been used in the preparation of aliphatic fluorides. Electrophilic fluorination reagents such as $NO^{18}F$ and $^{18}F\text{-}F_2$ have been used in the synthesis of ^{18}F-labeled steroids (39) and 5-fluorouracil (40). The following examples serve to illustrate the synthetic incorporation of ^{18}F into organic molecules.

^{18}F-Fluoroethanol. ^{18}F-Fluoride most commonly is produced by ^{3}He or α irradiation of a H_2O target and thus the reagent is available as ^{18}F-fluoride in water. Robinson (41) has found that a useful agent in nucleophilic substitution reactions is ^{18}F-fluoride on an anion exchange resin. This form of fluoride is conveniently used in substitution reactions to produce fluorocarboxylates. ^{18}F-2-Fluoroethanol is thus synthesized by the displacement reaction of fluoride on ethyl bromoacetate followed by hydrolysis and reduction (Fig. 3). This radiopharmaceutical is of interest because of its apparently irreversible localization in well-perfused brain (5).

^{18}F-Labeled Amino Acids. The Schiemann reaction has been used to synthesize a number of ^{18}F-labeled aromatic amino acids (14,42,43,44,45) and the neuroleptic drug, haloperidol (46). Although the Schiemann reaction leaves a lot to be desired in terms of labeling efficiency, presently there is no other route to ^{18}F-labeled aryl fluorides.

Fluorine-18 labeled DL-aryl amino acids have been prepared as potential pancreas imaging agents (14,42) and may be prepared with relatively high specific activities (0.5-1.0 mCi mg^{-1}) (47). In an attempt to improve the pancreas:liver ratio in the distribution of ^{18}F-p-fluorophenylalanine, Goulding and Gunasekera (15) developed a method for producing ^{18}F-L-p-fluorophenylalanine using the fungal enzyme L-amino acylase (Fig. 3).

^{18}F-Labeled 5-fluorodopa (44,45), a fluorinated analog of the amino acid, 3,4-dihydroxyphenylalanine (DOPA), has been shown to be a substrate for DOPA decarboxylase and is being evaluated as a brain scanning agent. This is an excellent example of work which not only has potential clinical value but also provides basic information which will probably have applications in other problems.

For a number of reasons, among them being the strength of the C-F bond and the steric similarity of hydrogen and fluorine, the development of the synthetic methodology for synthesizing ^{18}F-labeled radiopharmaceuticals is an important and challenging area. Actually, the labeling of organic molecules with ^{18}F is keeping pace with new developments in fluorination of organic molecules in that new fluorination methods are rapidly applied to ^{18}F-labeling. An example is the synthesis of ^{18}F-5-fluorouracil which utilizes $^{18}F\text{-}F_2$ (40) (Fig. 3). Along this line explorations into the feasibility of using F_2 in the fluorination of other saturated and unsaturated organic molecules would be not only a contribution to the field of organic fluorination but also one which has potential applicability to the field of nuclear medicine.

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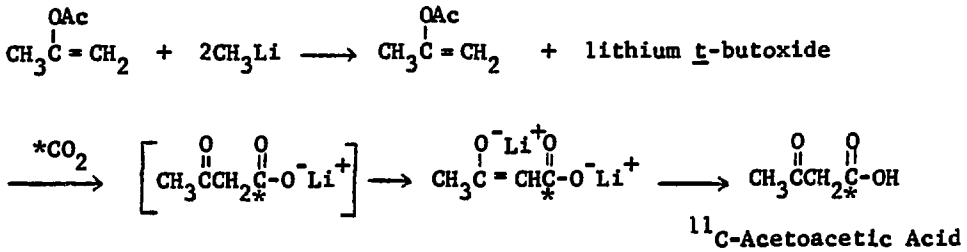
TABLE 1. LABELED PRECURSORS COMMONLY USED FOR ORGANIC SYNTHESIS[a]

Carbon-11		Nitrogen-13		Fluorine-18	
Labeled Molecule	Reference	Labeled Molecule	Reference	Labeled Molecule	Reference
^{11}CO	48,49,30			$^{18}F^-$	51,52,53
$^{11}CO_2$	49,30	$^{13}NH_3$	6	$^{18}F_2$	40,53
$H^{11}CN$	30	$H^{13}NO_2$	38	^{18}NOF	39
$H^{11}CHO$	26,28			$H^{18}F$ (anhydrous)	54
$^{11}CH_3OH$	50				
$^{11}CH_3I$	50				

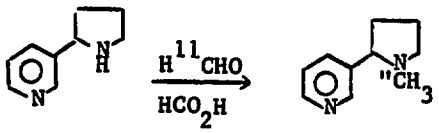
[a]There are many references which describe precursor preparation. These selected references are intended as a guide and further references are cited within these selected references and in a recent bibliography by Christman and Karlstrom (8).

Figure 1. The Synthesis of ^{11}C-Labeled Radiopharmaceuticals

^{11}C-Carboxylation with $^{11}CO_2$ (Straatman, Hortmann and Welch, 1974)

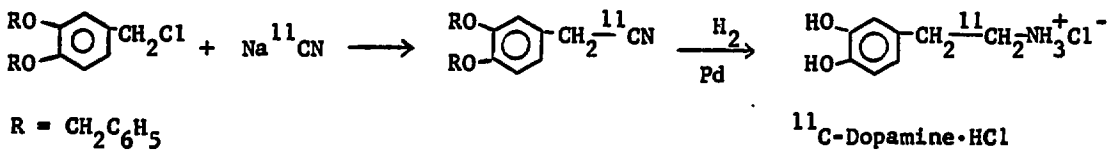


N-Methylation with H^{11}CHO (Maziere, Marazano and Comar, 1974)



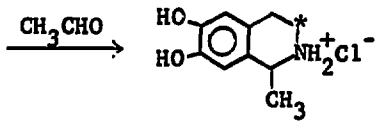
^{11}C-Nicotine

^{11}C-Amines from H^{11}CN (Fowler, Wolf, Christman et al., 1975)



R = $CH_2C_6H_5$

^{11}C-Dopamine·HCl



^{11}C-Salsolinol·HCl

Figure 2. The Synthesis of ^{13}N-Labeled Radiopharmaceuticals

^{13}N-L-Alanine via ^{13}N-L-Glutamate (Cohen, Spolter, Chang et al., 1974)

$$\alpha\text{-ketoglutarate} + \text{NADH} + {}^{13}NH_3 \xrightleftharpoons[\text{(immobilized)}]{\text{glutamic acid dehydrogenase}} {}^{13}\text{N-L-glutamate} + \text{NAD} + H_2O$$

$$^{13}\text{N-L-glutamic acid} + \text{pyruvic acid} \xrightleftharpoons[\text{(immobilized)}]{\text{glutamic-pyruvic transaminase}} {}^{13}\text{N-L-alanine} + \alpha\text{-ketoglutaric acid}$$

Figure 3. The Synthesis of ^{18}F-Labeled Radiopharmaceuticals

^{18}F-2-FLuoroethanol from ^{18}F-Fluoride (Robinson, 1974)

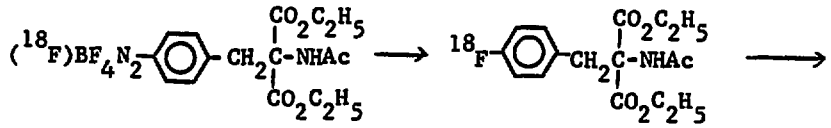
$$BrCH_2CO_2C_2H_5 + {}^{18}F\text{-Reagent}^{*} \xrightarrow{180^{o}} {}^{18}FCH_2CO_2C_2H_5$$

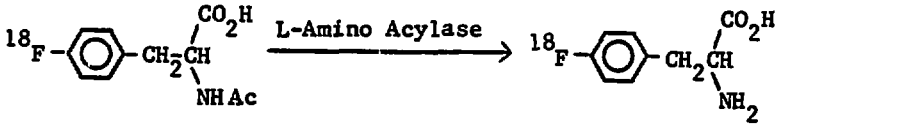
$$\longrightarrow {}^{18}FCH_2CO_2H \longrightarrow {}^{18}FCH_2CH_2OH$$

*Dowex 1X-4($^{18}F^-$)

^{18}F-2-Fluoroethanol

^{18}F-L-p-Fluorophenylalanine (Goulding and Gunasekera, 1975)

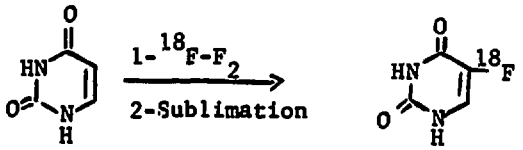




(DL)

^{18}F-L-p-Fluorophenylalanine

^{18}F-5-Fluorouracil from ^{18}F-F_2 (Fowler, Finn, Lambrecht et al., 1973)



^{18}F-5-Fluorouracil