SYNTHESIS OF THE RADIOPHARMACEUTICALS FOR POSITRON EMISSION TOMOGRAPHY

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Abstract

In this paper is shown a short overview of the biogenic positron radiopharmaceuticals production and a brief summary of some PET preparation synthesis. At the end the overview of some forward-looking positron radionuclides, which can be used for a preparation of the PET radiopharmaceuticals is said. A short review of diagnostic use of PET radiopharmaceuticals is presented.

Descriptors: Positron computed tomography; radioactive scanning; beta-plus decay; carbon 11; nitrogen 13; oxygen 15; fluoride 18; radiopharmaceuticals; chemical preparation; nuclear chemistry; nuclear reactions; nuclear medicine; bibliographies

INTRODUCTION

Protection of the health and human life belongs to the basic human rights. At the present time when those attributes are often endangered by the conveniences of a modern technical society is required to integrate the science with a prevention process and a prompt muckrake of the most important civilization diseases. Nuclear chemistry has become a one of the scientific disciplines efficient to give a hand to the doctors by solving the global health problems. In this paper we are presenting some methods of the radiopharmaceutical synthesis used in nuclear medicine during a diagnostic method - the positron emission tomography (PET).

In this overview we are showing the synthesis of the radiopharmaceuticals labelled with the short life radionuclides such a carbon-11, nitrogen-13, oxygen-15 and fluor-18. Use of these biogenic elements in positron emission tomography cause much lower radiological strain on the patient organism during the medical examination or therapy then the medical treatment methods traditionally used in oncology, cardiography and neurology, or for the other diagnostic or research purpose.

In termination we are presenting a short description of some other radionuclides – positron emitters efficient for the PET radiopharmaceuticals synthesis and their use in the positron emission tomography.

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1 PET radiopharmaceuticals and their use in nuclear medicine

1.1 A characterization of the PET radiopharmaceuticals

PET radiopharmaceuticals are formed by reactions of the organic compounds with radionuclides or positron emission isotopes. They are also called the labelled compounds. So-called „tracers", required for the production of the radiopharmaceuticals, are usually produced by an accelerator of the elements, a cyclotron, possibly by a nuclear reactor. ^{11}C, ^{13}N, ^{15}O and ^{18}F are the most used in positron emission tomography (next only PET) – scanning technology based on a detection of the gamma radiation, appeared because of the annihilation of the positrons emitted by the radioisotopes, made by PET scanners [1, 31].

An advantage of the positron emission radionuclides is their short half-life time. For that reason, a patient gets much smaller radiation dose then during the other similar medical examinations.

In the Table 1 biogenic radionuclides mostly used for a synthesis of the PET radiopharmaceuticals and their characteristics are presented.

Table. 1. Biogenic radionuclides mostly used for a synthesis of the PET radiopharmaceuticals.

Nuclide	Decay Mode (%)	Half-Life $t_{1/2}$	Max. energy, MeV	Nuclear reaction	Extent of energy, MeV	Max. specific activity, Ci·mmol^{-1}	Refs.
^{11}C	β^+ (99.8), E.C. (0.2)	20.3 min	0.96	$^{14}N(p,\alpha)^{11}C$ $^{11}B(p,n)^{11}C^*$ $^{10}B(d,n)^{11}C^*$	5,0 ÷ 22,0 6,48 ÷ 20,5 0.479 ÷ 5.02	$9.22\cdot10^9$	[49] [50] [51]
^{13}N	β^+ (100)	9.97 min	1.19	$^{12}C(d,n)^{13}N$ $^{16}O(p,\alpha)^{13}N$	0.523 ÷ 5.6 15.6 ÷ 27.8	$1.89\cdot10^9$	[51] [52]
^{15}O	β^+ (99.9), E.C. (0.1)	122 s		$^{14}N(d,n)^{15}O$ $^{15}N(p,n)^{15}O$ $^{16}O(p,d)^{15}O$	0.893 ÷ 5.27 15.9 ÷ 28.1 18.5 ÷ 18.5		[53] [54] [55]
^{18}F	β^+ (97), E.C. (3)	109.8 min	0.635	$^{20}Ne(d,\alpha)^{18}F$ $^{18}O(p,n)^{18}F$ $^{16}O(^3He,p)^{18}F$	24.7 ÷ 76.0 2.52 ÷3.87 2.40 ÷ 9.70	$1.7\cdot10^9$	[56] [57] [58]

1.1 Positron decay of the radionuclides

Positron (β^+) decay occurs in the radionuclides with the lack of the neutrons. By the radioactive decay the positron (β^+) is emitted simultaneously with electron neutrino ν_e. The basis of the β^+ decay is a conversion of a proton on a neutron.

$$p \rightarrow n + \beta^+ + \upsilon\,. \tag{1}$$

Positron decays these radionuclides can be described by equations:

$$^{11}_{6}C_5 \rightarrow ^{11}_{5}B_6 + \beta^+ + \upsilon \tag{2}$$

$$^{13}_{7}N_6 \rightarrow ^{13}_{6}C_7 + \beta^+ + \upsilon \tag{3}$$

$$^{15}_{8}O_7 \rightarrow ^{15}_{7}N_8 + \beta^+ + \upsilon \tag{4}$$

$$^{18}_{9}F_9 \rightarrow ^{18}_{8}O_{10} + \beta^+ + \upsilon \tag{5}$$

1.2 A preparation of the radionuclides

The experiments showed that the appropriate amounts of the four positron emitters frequently used in PET can be obtained by flow of the protons with energy 10 MeV and deuterons with energy % MeV [3].

The targets for the preparation of the radiopharmaceuticals can be gases, liquids and solid materials. The preparation of needed radionuclides precedes the radiopharmaceuticals synthesis. For the preparation of the artificial radionuclides in required amount for a study of chemical and biological processes is necessary to have a high intensity of the bombarding particles flow with the adequate energy.

The cyclotron produce from 10^{14} to 10^{15} accelerated particles per second. It can be protons, deuterons, hellions and heavy nucleuses. The targets mentioned previously are irradiating with a bunch of the accelerated particles.

These reactions are employed for it:

$$^{14}_{7}\mathrm{N} + ^{1}_{1}\mathrm{H} \rightarrow ^{11}_{6}\mathrm{C} + ^{4}_{2}\mathrm{He} \tag{7}$$

$$^{16}_{8}\mathrm{O} + ^{1}_{1}\mathrm{H} \rightarrow ^{13}_{7}\mathrm{N} + ^{4}_{2}\mathrm{He} \tag{8}$$

$$^{14}_{7}\mathrm{N} + ^{2}_{1}\mathrm{H} \rightarrow ^{15}_{8}\mathrm{O} + ^{1}_{0}\mathrm{n} \tag{9}$$

$$^{18}_{8}\mathrm{O} + ^{1}_{1}\mathrm{H} \rightarrow ^{18}_{9}\mathrm{F} + ^{1}_{0}\mathrm{n} \tag{10}$$

$$^{20}_{10}\mathrm{Ne} + ^{2}_{1}\mathrm{H} \rightarrow ^{18}_{9}\mathrm{F} + ^{4}_{2}\mathrm{He} \tag{11}$$

Results of the nuclear reaction are the radionuclides with oversupply of protons, which are spontaneously stabilized by emitting of positron, positron decay.

Carbon-11 is produced by bombarding the natural nitrogen with protons via nuclear reaction $^{14}N(p,\alpha)^{11}C$. Radioactive carbon dioxide ($^{11}CO_2$) and methane ($^{11}CH_4$) will be produced from a gas target made by mixing 2% of oxygen in nitrogen and 5% of hydrogen in nitrogen. Carbon oxide (^{11}CO) is made by reduction of $^{11}CO_2$ with coal at 900°C.

A possibility of the low-energy deuterons accelerating offers an advantage of the **oxygen-15** production by bombarding the natural gaseous nitrogen by nuclear reaction $^{14}N(d,n)^{15}O$. The ^{15}O can be produced as molecular oxygen ($^{15}O_2$) or straight as carbon dioxide ($C^{15}O_2$) by mixing a gaseous target with 5% of natural CO_2 such a carrier. Carbon oxide ($C^{15}O$) is also easily made by reduction of $C^{15}O_2$ with coal at 900°C.
Gaseous oxygen labelled with ^{15}O is used for a study of the oxygen metabolism, carbon oxide for a study of a blood volume and water ($H_2{}^{15}O$) for a study of a blood circulation in a brain.
Nitrogen-13 is made by bombarding of distillated water with protons via nuclear reaction $^{16}O(p,\alpha)^{13}N$. With relatively low-energy bunch of protons in cyclotron (10 MeV) can be efficient production yield 3.7 GBq (100 mCi) achieved by irradiating for 20 minutes. Using a mixture of water and ethanol is obtained more useful chemical form ammonia ($^{13}NH_3$). Another form also used is nitrate anion ($^{13}NO_3^-$).

Fluoride-18 is prepared by bombarding oxygen-18 enriched water with protons via nuclear reaction $^{18}O(p,n)^{18}F$. Fluorine-18 is back obtained as an aqueous solution of ions $^{18}F^-$ and can be easily separated by ion exchange chromatography. Ionizated ^{18}F can be transferred into the organic solvent and used for the stereospecific nucleofil substitutions. ^{18}F with specific activity 8000 GBq.μmol^{-1} can be produced after one hour of the irradiation. Fluor-18 can be also make as a radioactive gas via reaction $^{20}Ne(d,\alpha)^{18}F$. This method is useful for the electrofil substitutions and requires an addition of the gas fluorine-19 to a target as a carrier. Specific activity of a product is lower then 1 GBq·μmol^{-1} [10].

Gaseous oxygen, radioactive water, carbon dioxide, carbon oxide, labelled ^{15}O are used for a study of the oxygen metabolism, the blood volume, and ammonia for an examination of the blood flow in a brain [3].

These four radionuclides may be also produced by radiation of the stabile isotopes with an isotope of helium-3 with energy 9 MeV by following reactions:

A preparation of ^{11}C:

$$^{12}C(^3He,^4He)^{11}C \quad (12)$$

A preparation of ^{13}N:

$$^{12}C(^3He,pn)^{13}N \quad (13)$$

$$^{14}N(^3He,^4He)^{13}N \quad (14)$$

A preparation of ^{15}O:

$$^{16}O(^3He,\alpha)^{15}O \quad (15)$$

$$^{14}N(^3He,pn \text{ or } d)^{15}O \quad (16)$$

A preparation of ^{18}F:

$$^{16}O(^{3}He,p)^{18}F \quad (17)$$

$$^{16}O(^{3}He,n)^{18}Ne \xrightarrow{\beta^+} {}^{18}F \quad (18)$$

$t_{1/2}(^{18}Ne) = 1.67$ s

Nuclear reactions with ^{3}He for production of the beneficial amounts of PET radiopharmaceuticals are not often used, because the sufficient flow of the ^{3}He elements is not accessible [5, 16]. Fluorine-18 decays by emitting positron having maximum energy of 635 keV and mean range of 2.39 mm in water.

2 Synthesis of the radiopharmaceuticals

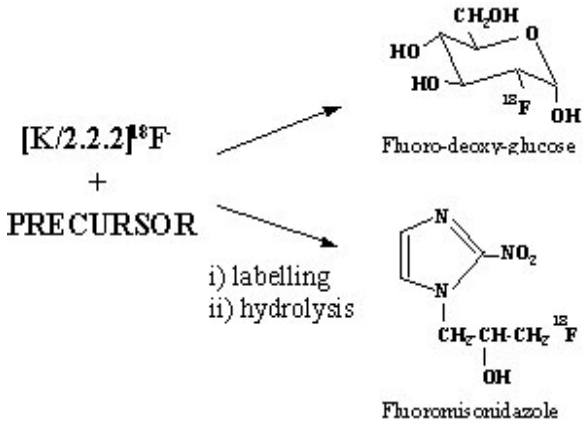
Radionuclides produced in the cyclotrons are not usually in an appropriate chemical and pharmaceutical form for the use as the biological isotope indicators, therefore, the synthesis of the suitable compounds are realized in radiopharmacological laboratories [2].

In the synthesis of the labelled compounds is one of the most critical periods of PET, important factor is time. The qualities of the radionuclide, which can be produced in a specific period of time, determine the energy of an element and a density of the bunch crossing the target.

2.1 Radiopharmaceuticals labelled with fluorine-18

The most used radiopharmaceutical in PET is 2-[^{18}F] fluoro-2-deoxy-D-glucose ([^{18}F]FDG). [^{18}F]FDG is aptly named as the “Molecule of the Millennium” due to its versatility and enormous importance application in oncology, neurology and cardiology. It is the first PET radiopharmaceutical to be included in United States Pharmacopoeia USP 1989 [59]. Its structure is similar to glucose. [^{18}F]FDG is prepared from radioactive isotope ^{18}F. It allows a study of a cellular metabolism of glucose. Representation of the glucose consumption by the cells is a basis of the clinical indications of PET diagnostics with FDG. It gives an advantage for a detection of the change of a cellular function before the structural changes appear [2].

Preparation of the [^{18}F]FDG and the [^{18}F]MISO



Scheme 1

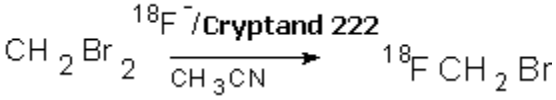
Irradiated water [^{18}O]H_2O is evaporated in presence of a cryptand (aminopolyether potassium carbonate complex - Kryptofix 222), which affect as a catalyst of stereospecific S_{N2} substitution reaction. Dry evaporated mixture with developed $^{18}F^-$ is dissolved in waterless acetonitrile and leave at 90°C to react with prepared precursor, an analog of the mannose-1,3,4,6-tetra-O-acetyl-2-triflate-β-D-mannopyranose, so called the triflate of mannose. Formed 1,3,4,6-tetra-O-acetyl-2-[^{18}F]fluoro-D-glucopyranose hydrolyzes at 110°C with dilute hydrochloric acid (14 minutes) and a product [^{18}F]FDG is clarified with ion exchange chromatography. The synthesis lasts for 30 minutes and radiochemical yield is 65%. The product has got the molar activity higher then 400 GBq·μmol^{-1} [4].
By the same procedure is realized the preparation of the **fluoromisonidazole** ([^{18}F]MISO)**,** however as a precursor is used an analog of misonidazole. Radiochemical yeald is 20% and it's lower then in [^{18}F]FDG preparation. The activity of a product [^{18}F]MISO is 3.7 GBq (100 mCi).

Transformation of fluoride $^{18}F^-$ on the [^{18}F]CH_3F

Into a dry radioactive fluoride $^{18}F^-$ made by bombarding water enriched with ^{18}O is inserted CH_3I. Concentrated $CH_3{}^{18}F$ is purified by gas chromatography and the other reactions with it are analogous of alkylations with $^{11}CH_3I$. Specific activity of a product is 55 GBq·μmol^{-1}. An advantage is a longer half-life time of ^{18}F then ^{11}C.

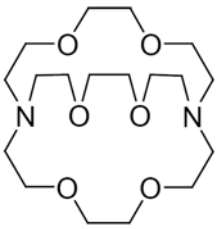
Preparation of the fluorobromomethane

The [^{18}F]fluorobromomethane is prepared [10] from dibromomethane with cryptand 222 and fluorine-18 anion in acetonitrile:



Scheme 2

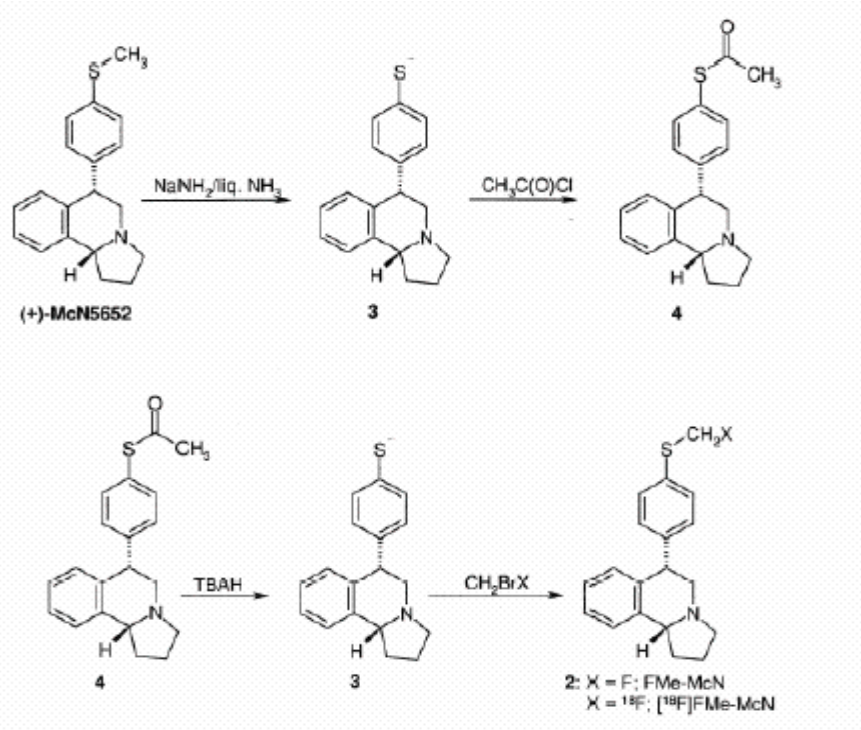
where cryptand 222 is 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane:



Into a pure $^{18}F^-$ is inserted CH_2Br and a prepared product $^{18}FBrCH_2$ is purified on gas chromatographic column. Its specific activity is 1000 GBq·μmol^{-1}. It is applied in a reaction with [^{18}F]fluoromethyl-McN5652 and for the preparation of [^{18}F]fluorocholine according to the named reactions [10].

$$CH_2{}^{18}FBr + HO(CH_2)_2N(CH_3)_2$$
$$\downarrow$$
$$[HO(CH_2)_2N + (CH_3)_2CH_2{}^{18}F]Br^-$$

Scheme 3



Scheme 4

Preparation of [^{18}F]fluoroiodomethane

[^{18}F]Fluorine is dried with acetonitrile and cryptand 222. Then it reacts with diiodomethane and a product is separated by distillation [10]. The yield is 40%. A process of the preparation shows the following scheme:

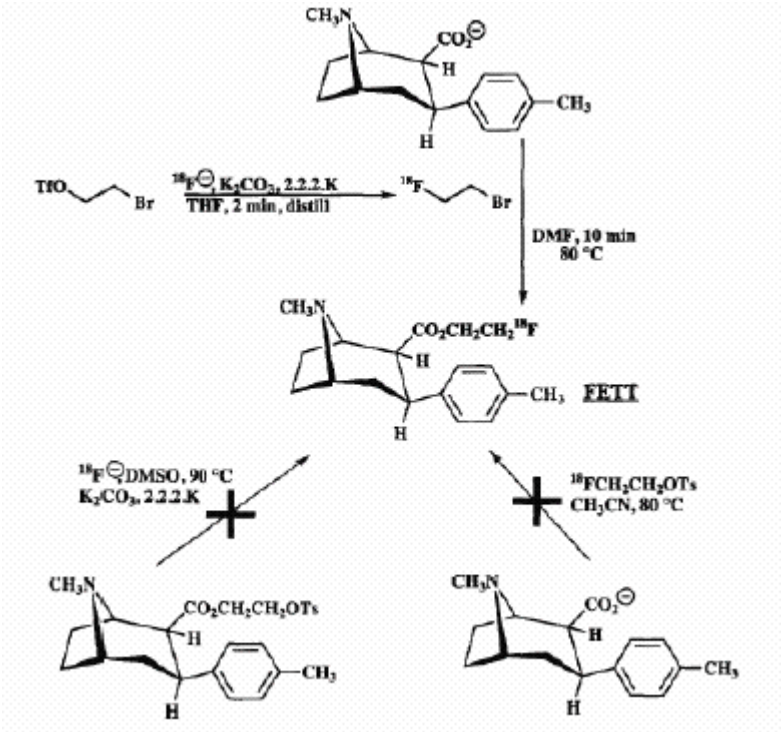
$$CH_2I_2 \xrightarrow[CH_3CN]{^{18}F^- / \text{Cryptand 222}} CH_2{}^{18}FI$$

Scheme 5

Using [^{18}F]FCH_2I the yields of the fluoromethylations are nearly three times higher then in preparation using fluoride [^{18}F]F^- (See Appendix 2,Table 2).

Preparation of [^{18}F]fluorobromoethane

[^{18}F]Fluoromethane dried with acetonitrile and cryptand 222 (2.2.2.K) reacts with 2-brom methyltriflate in THF or dibrommethane in acetonitrile. A product of the first preparation is separated by distillation. A yield of a product made second way is 60-70%. The result product is used in synthesis of the [2'-^{18}F]fluoroethyl(1R-2-exo-3-exo)-8-methyl-3-(4-methylphenyl)-8-azabicyclo[3.2.1]octane-2-carboxylate ([^{18}F]FETT) [32].

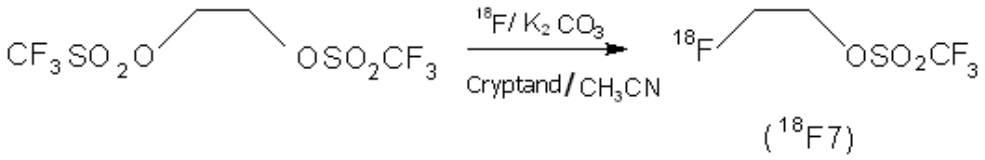


Scheme 6

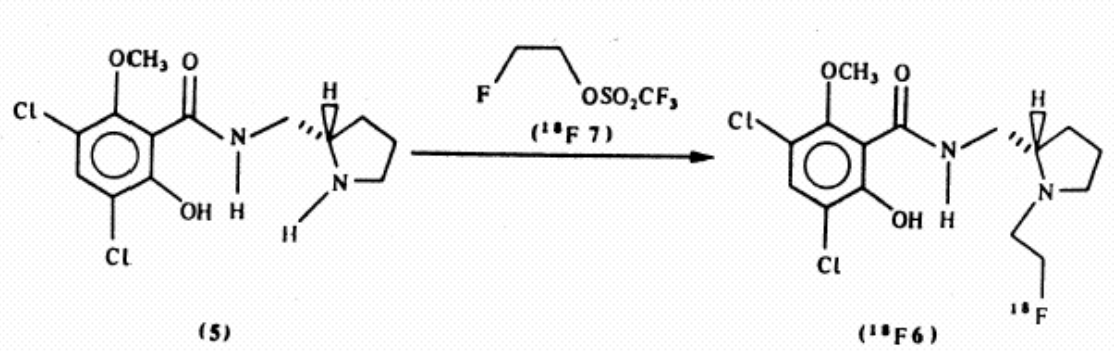
Successful and unsuccessful synthesis of [^{18}F]FETT.

Synthesis of [F-18]fluororaclopride

[^{18}F]Fluoroethyltriflate (^{18}F7) is applied in synthesis of [^{18}F]fluororaclopride (^{18}F6). [^{18}F]Fluoroethyltriflate is prepared [60] by [^{18}F]fluoride displacement on the bistriflate of ethylene glycol:



Scheme 7

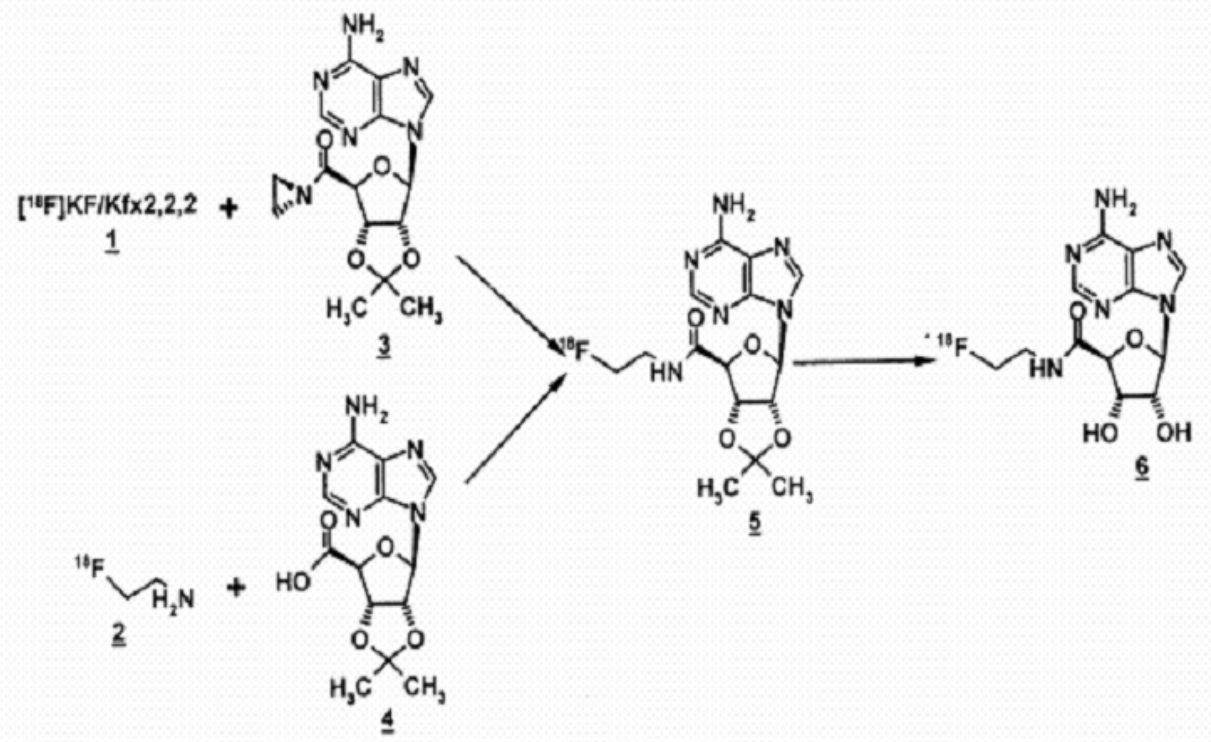


Scheme 8

Synthesis of S-3,5-dichloro-6-methoxy-N-(1-(2-[^{18}F]fluoroethyl)-2-pyrrolidinylmethyl)salicylamide ([^{18}F]fluororaclopride)

Preparation of the [F-18]fluoroethylamine

[^{18}F]Fluoromethane dried with acetonitrile and cryptand 222 reacts with N-[2-(p-toluene sulfonyl-oxy)ethyl]-phtalene. A product hydrolyses with hydrazine and it's separated by distillation. A yield of the reaction is (27 ± 11)%.



Scheme 9

Synthesis of [^{18}F]FNECA: In a preparation is used the [^{18}F]fluoroethylamine [10].

Preparation of the [^{18}F]fluoroethyl tosylate

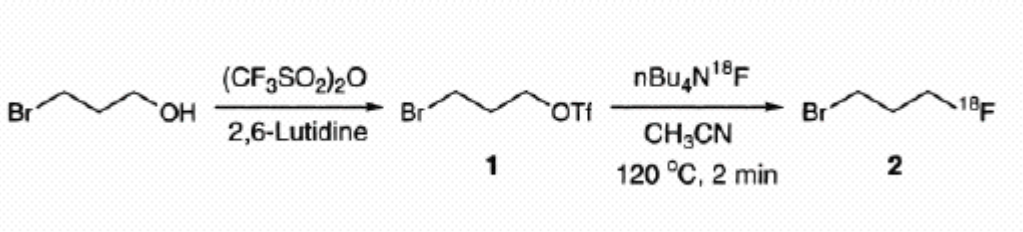
[^{18}F]Fluoromethane dried with acetonitrile and cryptand reacts with ethyleneglycol-1,2-ditosylate in acetonitrile. A product is purified on HPLC and a yield of the reaction is 50% [10].

Preparation of the [^{18}F]fluoroacetone

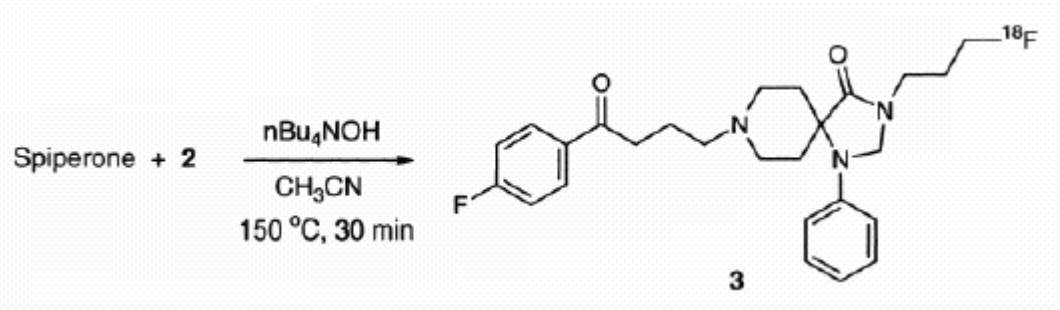
[^{18}F]Fluoromethane dried with acetonitrile and cryptand reacts with acetonetosylate in acetonitrile. A product is separated by distillation and a yield of the reaction is 60-95% [10].

Preparation of the [^{18}F]fluoroprophylbromide

[^{18}F]Fluoromethane dried with acetonitrile/n-Bu_4NOH reacts with 3-bromopropyltriphtalate in acetonitrile. A yield of the reaction is more then 90%. (Scheme 10) Obtained [^{18}F]fluoroprophylbromide might use in another synthesis, such an example on Scheme 11 [10].



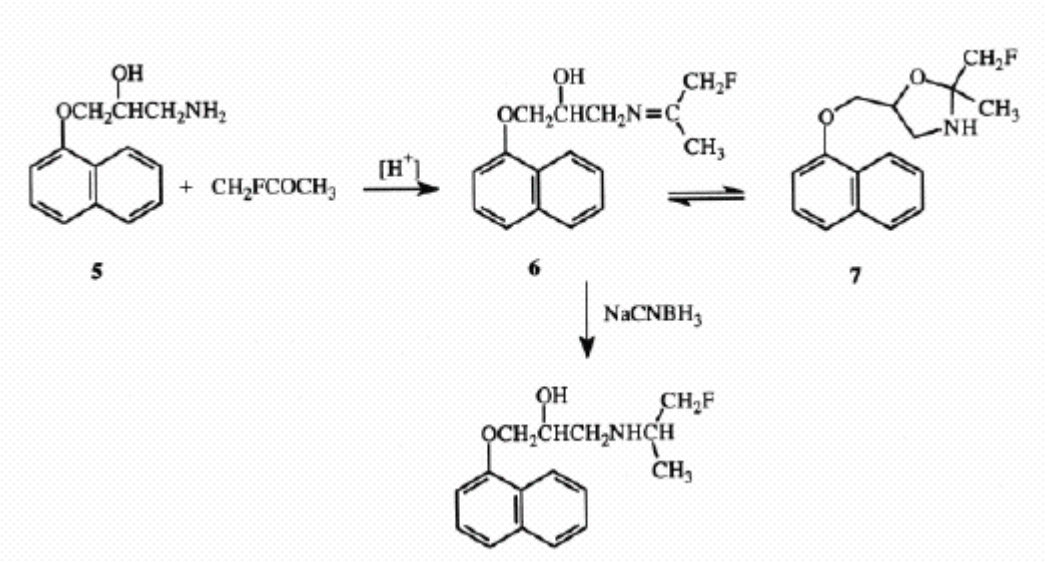
Scheme 10



Scheme 11

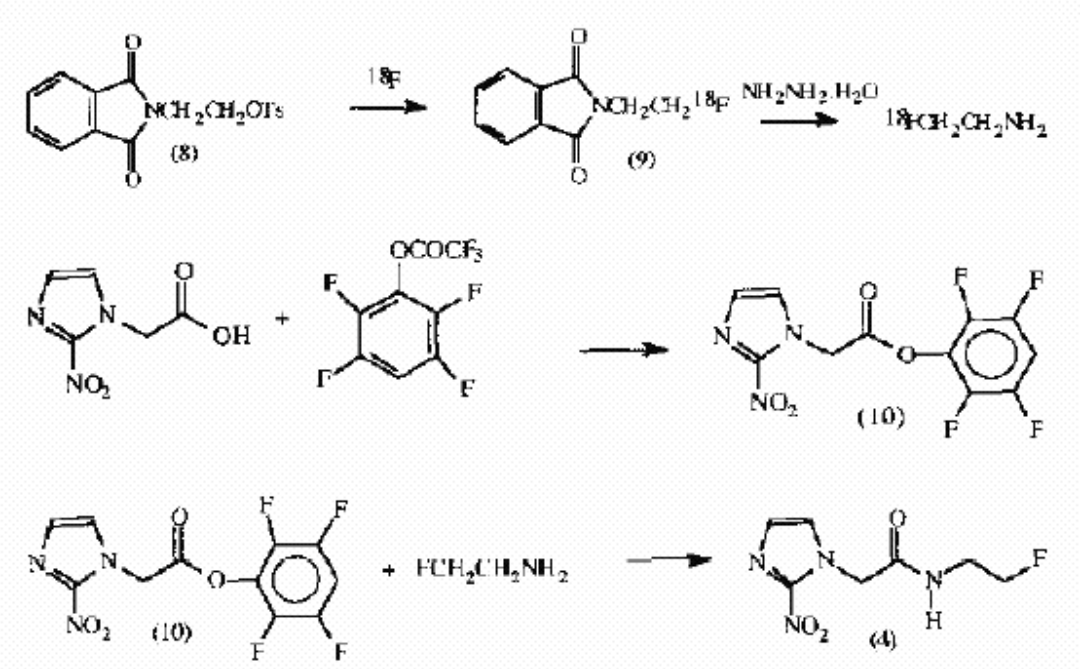
Synhesis of neuroleptic agent spiperone (8-[3-[^{18}F]fluoro{*p*-fluorobenzoyl}propyl]-l-phenyl-l,3,8-triazaspiro-[4.5]decan-4-one). [10]

Preparation of the [^{18}F]fluoropropranolol [10]



Scheme 12

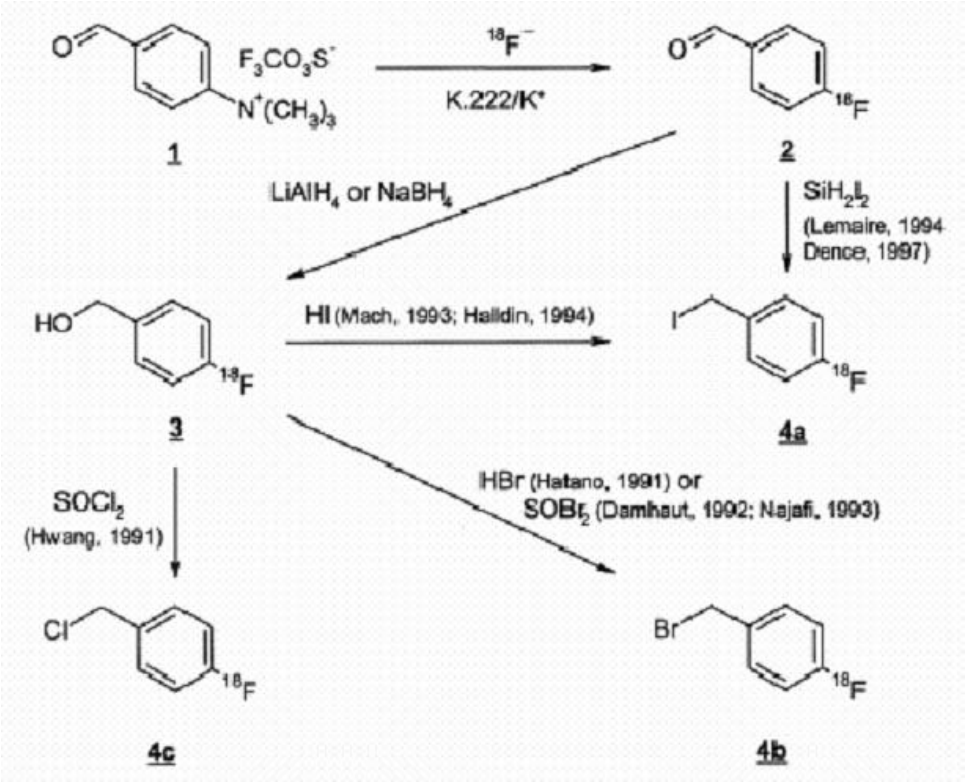
Synthesis using [2-^{18}F]ethylamine ($^{18}FCH_2CH_2NH_2$) [10]



Scheme 13

Synthesis of the [4-^{18}F]fluorobenzylhalogenid

[4-^{18}F]fluorobenzaldehyd is synthesized from [^{18}F]F$^-$ by aromatic nucleofil substitution on 4-trimethylamidebenzaldehydtriflate and effectively reduced on [4-^{18}F]fluorobenzylalcohol with $NaBH_4$. Transformation of the 4-[^{18}F]fluorobenzylalcohol on the [4-^{18}F]fluorobenzyl-halogenid is done with using HI, $SOCl_2$, HBr, $SOBr_2$, PBr3, PI_3, P_2I_4, Ph_3PBr_2 a Ph_3PI_2 in dichloroethane. [10, 12] A procedure of the synthesis shows Scheme 14.

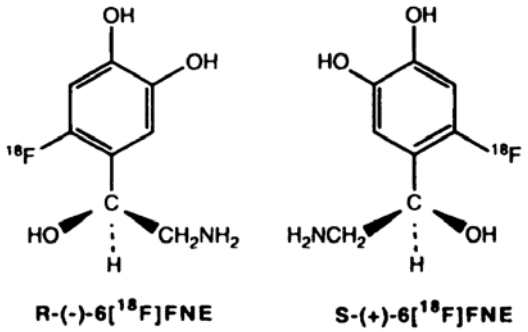


Scheme 14

Synthesis of the [^{18}F]FNE

[6-^{18}F]fluoronorepinephrine (next only [6-^{18}F]FNE), cetacholamine labelled with fluorine-18, is synthesized via nucleofil aromatic substitution. The pure samples of the (-)-[6-^{18}F]FNE and the (+)-[6-^{18}F]FNE are obtained by purifying the racemic mixture on HPLC column. A radiochemical yield at the end of bombarding is 20% with a specific activity 72÷185 GBq·mol^{-1} (2÷5 Ci·mol^{-1}). [11]

PET studies with [6-^{18}F]FNE show the high absorption in a baboon heart. A useful precursor for the radiosynthesis of the other complexes is dihydroxynitrobenzaldehyd. [11]



Scheme 15
Structure of R-(-)- and S-(+)- [6-^{18}F]fluoronorepinephrine

Synthesis of the 2′-deoxy-[2′-^{18}F]fluoro-5-methyl-1-alfa-D-arabinofuranosyluracil (next only [^{18}F]FMAU)

2-deoxy- [2-^{18}F]fluoro-1,3-5-tri-O-benzyol-alpha-D-arabinofuranose is made by a reaction of the applicable triflate with tetrabutylammonium[^{18}F]fluoride. The fluorosaccharide is transformed on 1-bromo-derivate and reacts with thymine. The production mixture is hydrolyzed at basic conditions and purified by HPLC for obtaining the radiolabelled FMAU. A radiochemical yield is 20-30% with a purity higher then 99% and specific activity 85.1 GBq·mol^{-1} (2300 mCi·mol^{-1}). The synthesis period is 3.5÷4 hours [13].

Synthesis of the 9-([3-^{18}F]fluoro-1-hydroxy-2-propoxy)menthylguanine (next only [^{18}F]FHPG)

9-[1,3-dihydroxy-2-propoxy(methyl)]guanine is prepared by tosylation with methoxytrityl-chloride. Tosylate reacts with [^{18}F]KF in a presence of kryptand on 3-fluoro-N-2-O-bis(methoxytrityl)acrivate. Remotion of the saved tosyl-trityl groups is done by hydrolysis. Obtained product [^{18}F]FHPG is purified via HPLC and its specific activity is 19.46 GBq·mol^{-1} (526 mCi·mol^{-1}) [14].

Synthesis of the 9-[4-^{18}F]-fluoro-3-hydroxymethylbuty)guanine (next only [^{18}F]FHBG)

9-(4-hydroxy-3-hydroxymethylbutyl) guanine is changed by tosylation on the 9-[N-2,0-bis(methoxy-trityl)-3-(tosylmethylbutyl)]guanine using methoxytritylchloride. The tosylate reacts with tetrabutylammoniumfluoride or KF in a presence of a cryptand on 4-fluoro-N-2-O-bis-(methoxytrityl) derivate. Remotion of the methoxytrityl groups by hydrolysis is obtained the product FHBG. Radiolabelled product [^{18}F]FHBG is prepared by fluoridation of the tosylate with [^{18}F]cryptand. The product is purified using HPLC [15].

Synthesis of the [16-α-^{18}F]fluoroestradiol-3,17-β-disulphamate (next only [^{18}F]FESDS)

[16-α-^{18}F]fluorestradiol ([^{18}F]FES) is converted on a product [^{18}F]FESDS, with specific activity (150÷200 GBq·mol^{-1}), using the abundance of the suphamoylchloride in acetonitrile in a presence of the cryptand [17].

Synthesis of the [2-^{18}F]fluoroestradiol

[2-^{18}F]fluoroestradiol has got a high affinity for an estrogen receptor and it also binds with sex hormone which binds the globuline. [^{18}F]F^{-} is used as a precursor in a synthesis. Trimethylammonia group in a C-2 position of estrogen is exchanged for the [^{18}F]F^{-}. A yield of the reaction is 20÷50% [19].

Synthesis of the O-[2-^{18}F]fluoroethyl)-L-tyrozine (next only [^{18}F]FET)

[2-^{18}F]fluoroethylbromide (next only [^{18}F]F-EtBr) is prepared by nucleofil substitution of the [^{18}F]F^{-} with 2-bromethyltriflate in acetonitrile at 95°C. [^{18}F]FEtBr is distillated at 85°C in gaseous nitrogen and it is caught in DMSO or DMF, and so added to a suspension of a disodium salt of the L-Tyrosine in DMSO. The radiochemical purity of a product is controlled by HPLC, a synthesis lasts for 80 minutes and its yield is 14÷26% [20].

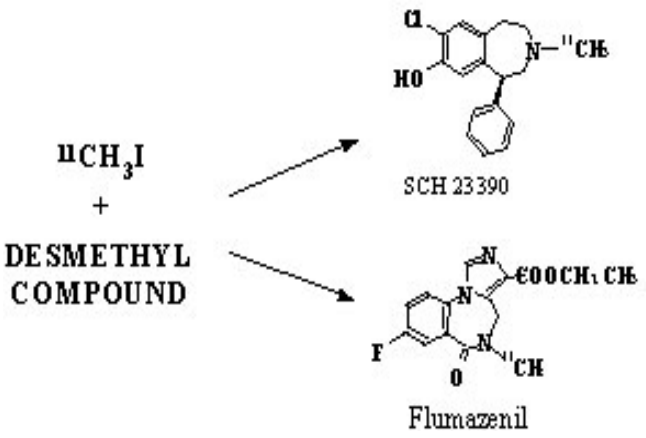
Synthesis of the [^{18}F]fluorocholine

Choline analog of (beta-hydroxyethyl)dimethyl[^{18}F]fluoromethyl-ammonium ([^{18}F]fluorocholine) labelled with fluorine-18 is prepared by [^{18}F]fluoromethylation of the N,N-dimethylaminoethanol. For the mentioned reaction the [^{18}F]fluoromethyltriflate ([^{18}F]CH_2FOTf) and the [^{18}F]fluoromethylbromide ([^{18}F]CH_2BrF) are needed. The [^{18}F]CH_2FOTf is prepared from the [^{18}F]CH_2BrF, synthesized by nucleofil substitution of the CH_2Br_2 with [^{18}F]F^-. [^{18}F]CH_2BrF is quantitatively transformed on the [^{18}F]CH_2FOTf passing through a warmed column with AgOTf. A yield of the reaction is 47%. Final [^{18}F]fluorocholine forms in 30 minutes synthesis with a yield 40% [30].

2.2 Radiopharmaceuticals labelled with carbon-11

Theoretically taken whatever organic compound could be labelled with carbon-11 via isotopic substitution. A method ordinarily used for the ^{11}C radiolabeling of the PET radiopharmaceuticals is a methylation using [^{11}C]methyliodide ($^{11}CH_3I$).

The preparation of the compounds of a benzodiazepine receptor **[^{11}C]SCH23390** and **[^{11}C]flumanezil,** are realized by the methylation with suitable precursor using $^{11}CH_3I$ [3]. This process shows the following reaction scheme:



Scheme 16

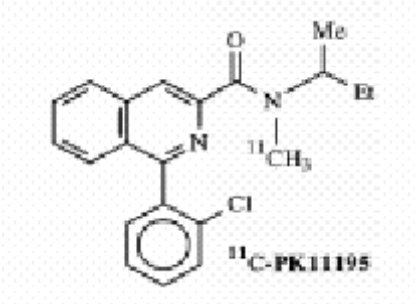
Another radiopharmaceuticals used in the clinical PET procedures are [^{11}C]methyl-derivates and [^{11}C]acetyl-derivates. In their synthesis are used methyliodine, Grignard reagents or acetone as the labeling synthetic precursors [6].

[^{11}C]aldose such the D-**[^{11}C]galactose** and the **D-[^{11}C]glucose** with activity 47 MBq can be produced by Kiliani-Fischer method [8].

[^{11}C]methylation reactions on the functional groups such the phenols and amids require a use of the bases when the [^{11}C]CH_3I is used in a preparation. It is possible to use tetrabuthylammoniumfluoride (next only TBAF) as a base for the preparation of the [^{11}C] radiopharmaceuticals with the high yields.

Preparation of the [^{11}C]PK11195

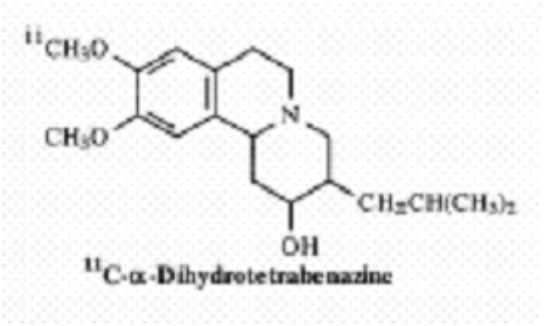
Desmethyl PK11195 (1.5 mg) is dissolved in DMSO (350 µl). The mixture is stirred in an ampule (volume - 5 cm^3) and TBAF itself (3 mg) is added or as a mixture with KOH (0.5 mg) (150 µl, 22 $mg \cdot cm^{-3}$ TBAF, 4 $mg \cdot cm^{-3}$ KOH v DMSO). Then Al/KF in acetonitrile is added 2 minutes before the alkylation. The solution is percolated with [^{11}C]CH_3I at the room temperature and consecutively it has to be warming for 5 minutes [9, 61]. Reaction mixture is purified using HPLC with column Waters Prep Nova Pak C-18 (7,8 cm x 30 cm) and elution reagent is a mixture of ethanol/water (60:40). Radiochemical yields are presented in Appendix 1, Table 1.



Scheme 17

Preparation of the [^{11}C]dihydrotetrabenazine

α-9-O-desmethyldihydrotetrabenazine (200 µg) is dissolved in acetonitrile (350 µl). A mixture in an ampule (volume -5 cm^3) is stirred and TBAF (0.4 mg) is added 3 minutes before the alkylation. Al/KF is used for the reaction. For the reaction with NaOH is DMSO added as a solution with NaOH (8 µl) 3 minutes before the alkylation. The mixture is percolated with [^{11}C]CH_3I and has to be warming for 5 minutes [9, 63]. A product is purified on HPLC using Waters Prep Nova Pak column C-18 (7,8 cm x 30 cm) with an elution reagent CH_3CN/0,1 M and 0,1% acetic acid (17:83). Radiochemical yields are in Appendix 1, Table 1.

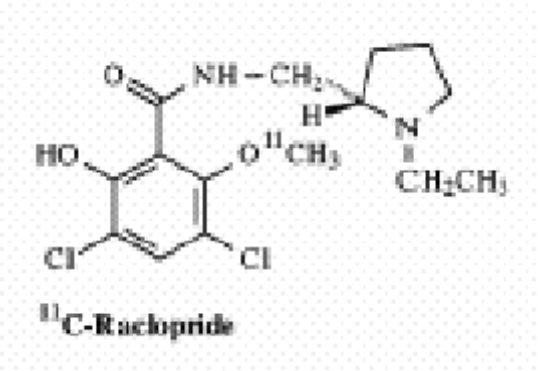


Scheme 18

Preparation of the [^{11}C]raclopride

Desmethyl raclopride (1.7 mg) is dissolved in DMSO. TBAF (2 mg) (250 µl, 14 mg in 1.5 cm^3 DMSO) is added to a solution 20 minutes before alkylation. 3 minutes before alkylation 8 µl KOH is added. A green color will appear only if KOH is used. A solution is percolated with [^{11}C]CH_3I and the mixture has to be warming for 5 minutes [9, 63]. A product is purified on HPLC using Water Prep Nova Pak C-18 column with an elution reagent CH_3CN/0,1 M,

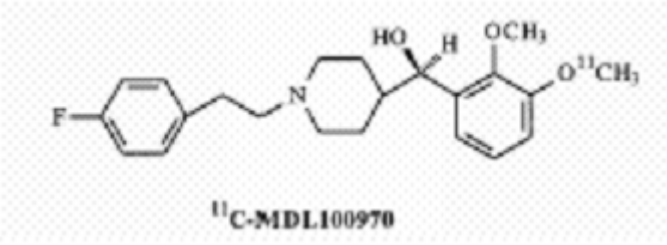
0.5% acetic acid (32:68). NaOH (5 µl), TBAF (3 mg) a KF/Al (10 mg) is used. Radiochemical yields for the other combinations of the solutions and bases are presented in Appendix 1, Table 1.



Scheme 19

Preparation of the [^{11}C]MDL100907

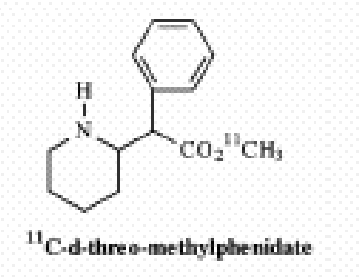
(R)-(+)-α-(3-hydroxy-2-methoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidine-methanol (200 µg) is dissolved in acetone (400 µl) and stirred in an ampule (volume - 5 cm^3). TBAF (0.4 mg) in THF (150 µl, 2,7 mg·cm^{-3}) is added 20 minutes before alkylation. The solution is percolated with [^{11}C]CH_3I and a mixture has to be warming for 5 minutes [9]. Then it is purified with HPLC using Water Prep Nova Pak C-18 column with an elution reagent CH_3CN/0,1 M, 0.5% acetic acid (32:68). 5 µl 5 M NaOH is used. The yields are presented in Appendix 1, Table 1.



Scheme 20

Preparation of the [^{11}C]methylphenidate

N-(protected)-d-*threo*-ritalinicacid (200 µg) is dissolved in acetonitrile (350 µl) and stirred in an ampule (volume 5 cm^3). TBAF (0,4 mg) in acetonitrile is added in the solution 20 minutes before alkylation. In a case of use Al/KF (10 mg) is that added 20 minutes before alkylation, in a case of use NaOH is DMSO in NaOH (0.5 M 8 µl) added. The solution is percolated with [^{11}C]CH_3I and has to be warming for 5 minutes [9, 64]. A mixture is purified with HPLC using Whatman Partisil 10 ODS 3.250 mm x 9.4 mm column with an elution reagent CH_3CN/0.17 M. Radiochemical yields are in Appendix 1, Table 1.



^{11}C-d-threo-methylphenidate

Scheme 21

Tetrabuthylammomiumfluoride is an ideal base for the ^{11}C-metylation reactions of five mentioned compounds, except raclopride, which gives appropriate yields of the radiopharmaceuticals [9].

Synthesis of the [^{11}C]methanol required for a production of the [^{11}C]methyliodide

[^{11}C]CH_3OH is prepared on the Al_2O_3 column impregnated with $LiAlH_4$ caught by [^{11}C]CO_2 from the irradiated target gas. A product [^{11}C]CH_3I is made by hydrolysis and transformation of the LiAl[^{11}C]methylate complex with a 95% yield [18].

Synthesis of the [^{11}C]edrophonium

[^{11}C]edrophonium and its analogs are used in scanning of the heart acetylcholine. Its made by N-[^{11}C]methylation with precursor using [^{11}C]methyltriflate and isolated by extraction with radiochemical yield 50÷65% [21].

Synthesis of the (3-N-[^{11}C]methyl)temozolomide and the [4-^{11}C]carbonyl)temozolomide

8-carbomoyl-[3-^{11}C]methylimidazo[5,1-*d*]-1,2,3,5-tetrazin-4(3H)-(temozolomide) is a radiopharmaceutical used in PET studies. Reaction of the 5-diazoimidazole-4-carboxamide with labelled ([^{11}C]methyl)methylisocynate gives [3-N-(^{11}C)-methyl]temozolomide in 14÷20% yield. Similarly [4-(^{11}C)-carbonyl]temozolomide is made by reaction of the 5-diazomidazole-4-carboxamide with ([^{11}C]carbonyl)methylisocyanate with 10÷15% yield [22].

Synthesis of the [^{11}C]befloxatone

Befloxatone(1-(5R)-5-(methoxymethyl)-3-[4-[(3R)-4,4,4-3-hydroxybutoxy]phenyl]-2-oxazolidinone), oxazolodine derivate, is labelled with carbon-11 using [^{11}C]phosgene. A product with specific activity 18.5÷74.0 GBq·μmol^{-1} (500÷2000 mCi·μmol^{-1}), purified with HPLC is made up by a synthesis lasting for 20 minutes, with a purity and yield 99% [23].

Synthesis of the [^{11}C]methyl-D-glucose

[^{11}C]methyl-D-glucose is produced by methylation of the glucose using [^{11}C]methyltriflate and its obtained as a mixture of the anomers, which are separated by liquid chromatography [24].

Synthesis of the [^{11}C]([R]-3-N,N-dicyklobutylamonio-8-fluoro-3,4-dihydro-2H-1-benzopyran-5-carboxamide) (next only [^{11}C]NAD-299)

[^{11}C]NAD-299 is a radiopharmaceutical used for a visualization of 5-HT_{1A} receptor in a human brain using PET method. It is synthesized from NAD-195 ([R]-3-N,N-dicyclo-butylamino-8-fluoro-5-trifluoromethylsulfonyloxy-3,4-dihydro-2H-1-benzopyrane) with [^{11}C]cyamide by reaction catalyzed with palladium. A labelled nitride, a semifinished product in hydrogen peroxide, is consecutively hydrolyzed with carbon-11. Radiochemical field of the reaction is 20÷40%, specific radioactivity of the product is 24 GBq.mol^{-1} and purity is 99%. The time needed for a synthesis is 40-45 minutes [28].

Synthesis of the [C-11] methyltriflate

[^{11}C]methyltriflate ([C-11]methyltrifluoromethanesulfonate) is made in the high yields from the [^{11}C]metyliodide in supporting nitrogen, which passes through graphite column impregnated with silver triflate at 200°C [29].

2.3 Radiopharmaceuticals labelled with oxygen-15

Synthesis of the buthanol labelled with oxygen-15

1-buthanol and 2-buthanol labelled with oxygen-15 are used for the examination of a blood flow by PET method. They are prepared by reaction of [^{15}O]O_2 with tri-*n*-buthylborane and tri-*sec*-buthylborane in tetrahydrofurane. The reaction products are isolated chromatographically. The yields of the reactions are 50% [25].

Synthesis [^{15}O]N_2O

Nitrous oxide labelled with oxygen-15 is produced by the oxidation of a waterless ammonia in a gaseous mixture of a oxygen labelled with oxygen-15. Labelled gas is purified in a column with H_3PO_4 and KOH. Specific activity of the chromatographically purified [^{15}O]N_2O is 1.85 GBq·mmol^{-1} (50 mCi·mmol^{-1}) and a purity is 98%. It is used for an examination of a blood flow by PET method [27].

Synthesis of the [^{15}O]H_2O_2

[^{15}O]H_2O_2 is thought to be a candidate of attractive injectable tracers for the study of oxygen metabolism with PET. A simple synthetic method yielding [^{15}O]H_2O_2 in saline solution by the autoxidation of 2-ethylanthrahydroquinol with gaseous [^{15}O]O_2 produced by cyclotron target system is described [33].

2.4 Radiopharmaceuticals labelled with nitrogen-13

Synthesis of the [^{13}N]N_2O

^{13}N-labelled nitrous oxide has been prepared in view to study its behaviour into the brain using a technique suggested by Nickles et al. Nitrogen-13 was prepared via the $^{16}O(p,\alpha)^{13}N$ reaction by irradiation of water. Using the medical cyclotron of Liege, with a focused beam of 21 MeV protons at 25 μA current, a 24 minutes irradiation produces 14.8 GBq (400 mCi) of $^{13}NO_3^-$ at the end of bombardment (E.O.B.). The irradiated water (12 cm^3) was concentrated

to 1 cm^3 by rotary evaporation. The pyrolysis of $NH_4{}^{13}NO_3$ was done in the presence of NH_4NO_3 and $(NH_4)_2SO_4$ in sulfuric acid. The $^{13}N_2O$ was evolved at 220°C. Ozone and other oxides of nitrogen were produced in the system. Therefore, great care must be taken to remove them. The purification was done in one-line process requiring no handling other than the manipulation of cold traps at appropriate time. This purification leads to safety $^{13}N_2O$ ready for medical experiments showing less than 0.3 ppm of NO_2, 1.7 ppm of NO and 0.05 ppm of O_3. 20 minutes after E.O.B., 1.85 GBq (50 mCi) of $^{13}N_2O$ are available. It has been used, as such, in 10 normal volunteers and detected by positron emission tomography [34].

Preparation of the $^{13}NH_3$

Nitrogen-13 is prepared in cyclotron via nuclear reaction $^{12}C(d,n)^{13}N$, in which the target is a gaseous methane [35]. The $^{13}NH_3$ formed was collected with a gas-circulating system and trapped in an acidic water solution. After this solution was made basic, the $^{13}NH_3$ was distilled into a slightly acidic saline solution which was then passed through a Millipore filter. The $^{13}NH_3$ preparation was carried out under sterile pyrogen free conditions. The radiochemical purity, as determined by gas-liquid chromatography, was typically 97% $^{13}NH_3$, 0.3% $CHPNH_2$, and 2% unknown [36].

^{13}N-SD-62

In order to study opioid receptor function by PET, it has been desired to develop the radioligand with high specific activity, high receptor affinity and metabolic stability. [^{13}N]ammonia is easily produced and the introducing of ammonia into glycine residue at C-terminal avoid any racemization, ^{13}N-labelled enkephalin-like peptide, H-Tyr-(D)-Met(O)-Phe-Gly-NH_2 (SD-62), was considered as a plausible canditate. ^{13}N-SD-62 was easily synthesized by the use of nitrophenol ester as a precursor. The synthetic time was 3-5 min and yield was about 50%. In the mice distribution studies, the radioactivity in the brain increased along with the time within 30 min after injection. This brain accumulation of ^{13}N-SD-62 showed 10-15 times higher than that of ^{131}I-RISA, a good indication of the permiability through the blood-brain barrier. The gathered data demonstrate that ^{13}N-SD-62 hold great potentiality as a radiopharmaceutical for opioid receptor studies by PET [37].

2.5 Progresses in the synthesis of the PET radiopharmaceuticals

One of the first overview about the synthesis of the PET radiopharmaceuticals was a work of Kabalk, G.W. [38]. Great progress in synthetic methodologies of short half-life radiopharmaceuticals for PET has been made. This article aims to summarize the synthetic methodologies and progress of fluorine-18, carbon-11, oxygen-15 and nitrogen-13 labelled radiopharmaceuticals, with special emphasis on the radiochemistry of those labelled with carbon-11 and fluorine-18 [39].

Step by step, the automatic systems for a production of the radiopharmaceuticals have been developed, which allows obtaining cost-effective source of the positron emitter-labelled radiotracers labelled with carbon-11, nitrogen-13, oxygen-15, and fluorine-18 [65]. The Siemens Radioisotope Delivery System (RDS 112) is a fully automated system dedicated to the production and delivery of positron-emitter labelled precursors and radiochemicals required to support a clinical PET imaging program. Thus, the entire RDS can be thought of as an automated radiochemical processing apparatus [40].

The list of some diagnostic radiopharmaceuticals is in the Table 2.

Table. 2. Review of use of some PET radiopharmaceuticals for diagnostics [66].

Radiopharmaceutical preparation	Use	Recommendation for diagnostics
Ionic radiopharmaceutical preparation		
^{123}I, [^{123}I]KI, (I^-)	Function of thyroid gland	Scintigraphy and radiotherapy of thyroid gland
^{82}RbCl, (Rb^+)	Flow rate of blow in myocardium	Perfusion of myocardium, myocardial infarction
Radiopharmaceutical preparations for binding with receptors		
^{123}I-VIP	Vasoactive intestinal peptide (VIP) receptor	Stomach and intestine adenomas; colorectal cancer; pancreatic adenocarcinomas; neuroendocrine tumours
^{123}I-MIBG	Presynaptic adrenergic receptors	Myocardium scintigraphy, tumors visualization (feochromocytomas, neuroendocrine tumors, neuroblastomas)
[^{11}C]methylspiperone	Dopamine D2 receptors	Visualization of dopamine D2 receptors distribution in brain (Schizophrenia)
[^{11}C]Raclopride	Dopamine D2 receptors	Visualization of dopamine D2 receptors distribution in brain
^{123}I-IBZM	Dopamine D2 receptors	Visualization of dopamine D2 receptors distribution in brain, tumors scintigraphy, malignant melanomas
[^{18}F]fluoroestradiol (FES)	Estrogens receptors	Breast tumors
Labelled substrates of metabolism		
[^{18}F]Fluorodeoxyglucose, ([^{18}F]FDG)	Viability and metabolism of tumors, metabolism of glucose	Visualization of tumors, scintigraphy of brain and myocardium
[^{11}C] or [^{123}I]metyltyrosine	Synthesis and regulation of protein metabolism	Brain tumors
[^{11}C]metionine	Transport of amino acids	Brain and myocardium tumors
[^{11}C]tymidine	Synthesis of DNA, cells proliferation	Brain tumors
[^{18}F] and ^{123}I-fatty acids	Myocardium metabolism	Scintigraphy of myocardium
[^{18}F]Fluoromisonidazol	Hypoxia and metabolism of oxidation	Tumors, remove at radiotherapy

2.6 The other forward-looking positron emitters suitable for a synthesis of the PET radiopharmaceuticals

Apart from the most using positron emitters ^{11}C, ^{13}N, ^{15}O a ^{19}F, a lot of publications are dedicated to the use of ^{68}Ga and ^{82}Rb, obtained from the generators. Respectable number of the works, from a whole number of works about a synthesis of the PET radiopharmaceuticals (according to database INIS - 957 works), is dedicated to a use of the other positron radionuclides in a form of PET radiopharmaceuticals. In a forthcoming time their wider participation as the radiopharmaceuticals using in PET diagnostics is expectable. [41]

In a Table 3 are said the forward-looking positron radionuclides and their half-life times.

Table 3. Positron radionuclides exploitable for PET [42].

Radionuclide	Half-Life $t_{1/2}$	Radionuclide	Half-Life $t_{1/2}$	Radionuclide	Half-Life $t_{1/2}$
^{19}Ne	17,22 s	^{55}Co	17,5 h *	^{77}Kr	1,24 h *
^{22}Na	2,605 r	^{56}Co	77,7 d	^{82}Rb	1,273 min
^{30}P	2,5 min	^{57}Ni	36,1 h *	^{80}Sr	106 min
^{34m}Cl	32,0 min	^{60}Cu	23,2 min *	^{85}Y	2,6 h *
^{38}K	7,63 min	^{61}Cu	3,41 h	^{87}Zr	1,73 h *
^{43}Sc	3,89 h *	^{62}Cu	9,74 min	^{89}Zr	78,43 h *
^{44}Sc	3,93 h *	^{64}Cu	12,701 h **	^{92}Tc	4,44 min *
^{45}Ti	3,078 h	^{63}Zn	38,1 min *	^{93}Tc	2,88 h *
^{49}Cr	42,1 min *	^{68}Ga	68,1 min	^{94m}Tc	52 min
^{47}V	31,3 min *	^{73}Se	7,1 h *	^{110}In	69 min *
^{48}V	15,98 d	^{75}Br	98 min *	^{117}Te	62 min *
^{51}Mn	46,2 min *	^{76}Br	16,1 h *	^{129}Ba	2,5 h *
^{52m}Mn	21,1 min	^{78}Br	6,46 min	^{120}I	81 min
^{52}Mn	5,59 d *	^{74}Kr	11,5 min *	^{122}I	3,6 min
^{52}Fe	8,28 h *	^{75}Kr	4,5 min *	^{123}I	13.27 h
				^{124}I	4.15 d

* Decay modes: β^+ and E.C.; ** β^+, β^-, and E.C.

Besides the other positron emitters, potentially exploitable for a preparation of the PET radiopharmaceuticals are known.

SUMMARY

It has passed 26 years since the first publication about the PET radiopharmaceutical was published. [43, 45] The PET method, using the positron radionuclides, has obtained a stabile position among the diagnostic methods of nuclear medicine during a passed quatre of the century. [44, 45] We can suppose, that in a forthcoming time its use will be even more assert in nuclear medicine, while not the only positron radionuclides ^{11}C, ^{13}N, ^{15}O a ^{19}F used the most until present time, but the other showed in Table 2 will be often used as well.

It's nice, that Slovak republic has also joined the states, which do not only use the PET radiopharmaceuticals for the diagnostic purpose, but can also produce them in an own equipment. In a presence their production is realized in Biont, a.s. (Bratislava) [48, 67].

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Appendix 1

Table 1 Radiochemical yields of the methylations

Compound	Amount of precursor	Solvent	Base	Reaction tempera-ture, °C	Yield, %	Specific activity (Ci/mmol)
Dihydro-tetrabenazine	200 μg	CH_3CN	KF/Al	85	30-40	
	200 μg	CH_3CN	TDAF	85	45	3000-5000
	200 μg	DMSO	NaOH	50	10	
	1,0 mg	DMSO	NaOH	50	30	
Methyl-phenidate	200 μg	CH_3CN	KF/Al	85	27-31	
	200 μg	CH_3CN	TBAF	85	33-40	1500-2500
	200 μg	DMSO	NaOH	85	No	
	1,5 mg	DMF	NaOH	80	30	
PK11195	1 mg	DMSO	KF/Al	100	No	
	1,5 mg	DMSO	TBAF	100	27	2000
	2 mg	DMSO	NaOH	80	2	
	1,5 mg	DMSO	TBAF/ KOH	100	40-50	
	400 μg	DMSO	TBAF/ KOH	100	4	
Raclopride	200 μg	CH_3CN	KF/Al	85	No	
	200 μg	DMF	KF/Al	85	No	
	200 μg	Acetone	KF/Al	85	No	
	200 μg	CH_3CN	TBAF	85	No	
	1,7 mg	DMSO	KF/Al	80	no	
	1,7 mg	DMSO	TBAF	80	No	
	1,7 mg	DMSO	TBAF/ NaOH	80	28-41	7000-10000
	1,7 mg	DMSO	NaOH	80	17-35	
MDL100907	200 mg	Acetone	TBAF	80	30-50	3000-5000
	200 mg	DMSO	TBAF/ NaOH	80	9	

Appendix 2

Table 2. Results of the fluoromethylations using fluoromethyliodide

RX	SOLVENT	Yield in % using	
		$^{18}FCH_2I$	$^{18}F^-$
Diethylamine	Acetonitrile	95	33
Diphenylamine	Acetonitrile	60	22
Phenylcarboxyl acid	Acetonitrile	57	20
Phenylmethantiol	Acetonitrile	12	5
Phenyl-Ona	Methanol	67	25