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(71) Applicants *(for all designated States except US)*: **ADVANCED ACCELERATOR APPLICATIONS** [FR/FR]; 20 rue Diesel, F-01630 Saint Genis Pouilly (FR). **ABX GMBH** [DE/DE]; Heinrich-Glaeser-Strasse 10-14, 01454 Radeberg (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **TADINO, Vincent** [BE/FR]; 120 rue des Fontanettes, F-01630 Challex (FR). **MÜLLER, Marco** [DE/DE]; Meyerdamm 8, 28876 Oyten (DE).

(74) Agents: **CABINET PLASSERAUD** et al.; 52, rue de la Victoire, F-75440 Paris Cedex 09 (FR).

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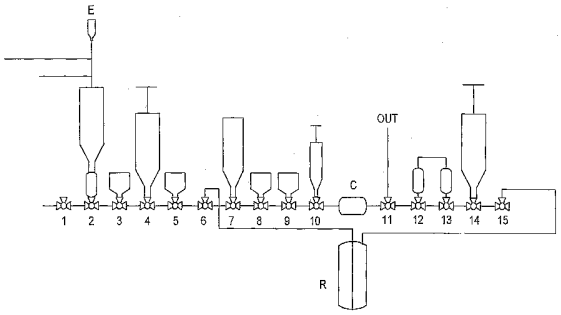
(54) **Title:** PROCESS FOR SYNTHESIZING LABELLED COMPOUNDS



(57) **Abstract:** The main objectives of the invention are notably: the shrinkage of the process time because of the low half-life of [^{18}F]FLT, as well as the increase of the yield, especially without HPLC purification which is a complex and a time consuming step. Other intended improvements are the reduction of the duration and the complexity of the synthesis and of the device. The purpose is to facilitate the methods of synthesis used by the Positron Emission Tomography (TEP) laboratories. The invention concerns a process for synthesizing labelled compounds with an isotopic element, comprising the steps of: a. preparing at least one labelling agent; b. labelling at least one precursor with the labelling agent, wherein the precursor is a protected substrate; c. possibly pre-purifying the labelled precursor; d. retaining the labelled precursor on at least one solid support; e. deprotecting the labelled precursor by hydrolysis so as to obtain the labelled compound, directly on at least one solid support which is contained in at least one column or cartridge; f. recovering the labelled compound by elution g. and purifying the eluate, wherein the labelled compound is 3'-deoxy-3'-[^{18}F]fluorothymidine ([^{18}F]FLT) wherein the deprotectionhydrolysis is carried out by means of at least one deprotectionhydrolysis is carried out by means of at least one deprotecting/hydrolyzing agent selected in the organic acids groups comprising e.g.: trifluoroacetic acid (TFA) and/or the purifying step (g) comprises transferring the eluate containing the labelled compound on at least one hydrophilic-lipophilic water-wettable reversed-phase sorbent for solid-phase extraction.

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PROCESS FOR SYNTHESIZING LABELLED COMPOUNDS

FIELD OF THE INVENTION

The present invention a new fully automated method for the synthesis of labelled compounds such as 3'-deoxy-3'-[^{18}F]fluorothymidine ([^{18}F]FLT), by modifying a commercial FDG synthesizer (for instance the "TRACERlab MX_{FDG} ®, marketed by the GE Medical Systems company) and its disposable fluid pathway.
Other synonyms of [^{18}F]FLT are : (1-(3'-Deoxy-3'-fluoro-β-D-pentofuranosyl)thymine, 3'-Deoxy-3'-fluorothymidine, 3'-Fluorodeoxythymidine, 3'-Fluorothymidine, Alovudine, CL 184824.

The invention also relates to a device for synthesizing said labelled compounds which relies on this method, making an automatic processing possible, including possibly a single use kit of materials.

The process according to the invention relates to synthesis methods for labelled compounds with any isotopic element and used particularly in the medical field (NMR, therapy, medical imaging), based upon the labelling of an organic substrate the functional groups of which are protected beforehand by protecting groups which, after the labelling step, can be easily removed by hydrolysis.
The term "functional groups" means functions such as alcohol, thiol, phenol, thiophenol, amines, ketones, aldehydes, carboxylic acids, etc. The term "protecting groups" means groups (according to the function to be protected) such as acetyl, ethers, esters, thioesters, thioethers, imines, enamines, amides, carbamates, N-alkyles, N-aryles, N-hetero derivates, cetals, acetals, etc.

BACKGROUND OF THE INVENTION

[^{18}F]FLT is a tracer increasingly used in nuclear medical imaging. This molecule labelled with the radionucleide ^{18}F, appears to be the one of the most promising radiopharmaceuticals because of the lack of in vivo degradation, metabolic trapping in proliferating cells, and the favorable half life for Positron Emission Tomography (PET) imaging. This molecule, labelled with the radionucleide ^{18}F, allows the mapping and the quantification of this fundamental mechanism. Recent clinical studies have also

demonstrated that it would be a promising tumor therapy response marker for lung and other kinds of cancer.

Several methods have been developed and are presently used in various (TEP) laboratories to produce [^{18}F]FLT for immediate use closely from the place of synthesis.

Before mentioning the closest prior art relating to [^{18}F]FLT, it is referred hereinafter to a technological background regarding 2-[^{18}F]fluoro-2-deoxy-D-glucose, more commonly called fluoro-deoxy glucose or FDG.

FDG is also a tracer used in nuclear medical imaging. This molecule labelled with the radionucleide ^{18}F, behaves in a way similar to glucose in the first step of its metabolization in the human body and allows to map and quantify this fundamental mechanism. It is indicated for diagnosis of numerous diseases. The most widely spread FDG synthesis method is the so-called Hamacher method, described by Hamacher K., Coenen H. and Stocklin G. in "*Efficient Stereospecific Synthesis of No-carrier-added-2-[^{18}F]fluoro-2-deoxy-D-glucoso Using Aminopolyether Supported Nucleo-philic Substitution*", Journal of Nuclear Medicine 27, 235 (1986).

US-B-6,172,207 discloses a method for synthesizing [^{18}F]fluoro-2-deoxy-D-glucose using multiple stopcock manifolds and disposible sterile syringes. This corresponds to the commercial "TRACERlab MX_{FDG} ®", marketed by the GE Medical Systems company

The synthesis reaction according to US-B-6,172,207 occurs as follows:

1. recovery of the [^{18}O] enriched water using an anionic resin namely the 4, 7, 13, 16, 21, 24-hexaoxo-1,10-diazabicyclo-[8.8.8]-hexacosane [KRYPTOFIX®. (also called K2.2.2)] which is a ^{18}F "activating" agent;
2. recovery, by elution of the anionic resin, of the activity in the form of $[K/222]^{18+}$, F^- in a solution in a mixture CH_3CN/H_2O,
3. evaporation of the solvent by IR heating (105.°C.) under nitrogen flow (2 min. 30 sec.),
4. addition of 1 ml CH_3CN, evaporation (2 min. 30 sec.),
5. addition of 1 ml CH_3CN, evaporation to siccity (determination of the evaporation end through a temperature probe),
6. cooling of the reactor to 70.°C.,
7. addition of a solution of a labelling precursor (15 mg) in CH_3CN (1.7 ml),
8. heating at 95.degree. C. during 3 min. (labelling step),
9. dilution of the resulting solution in 25 ml water,
10. transfer of the diluted solution through a C18 cartridge (conditioned beforehand with 5 ml ethanol followed with 10 ml water) to the waste,
11. rinsing of the cartridge with 10 ml 0.1 N HCl and 10 ml water which are sent to the waste,

12. drying of the cartridge under nitrogen flow,
13. addition of 0.7 ml 1.5M NaOH on the C18 cartridge,
14. deprotection (hydrolysis) 1.5 min. at room temperature,
15. elution of the FDG with 5 ml water into a syringe containing 0.8 ml 1.5M HCl and 5 ml of citrate buffer, and
16. transfer of the resulting solution through a C18 cartridge, a neutral alumina cartridge and a 0.22 μm filter; the solution is collected in a sterile vial.

[^{18}F]FLT is a labelled compound different from FDG and constitutes an interesting alternative to FDG. [^{18}F]FLT offers a better precision than FDG in PET imaging for cancer diagnosis.
Furthermore, to use [^{18}F]FLT in clinical studies, automation is necessary to reduce unnecessary radiation exposure for the operators and to obtain high radiochemical yield with reproducibility.
In this context, there is an obvious interest to improve and to simplify the [^{18}F]FLT synthesis. In particular, the search of higher yield of synthesis is an important issue.

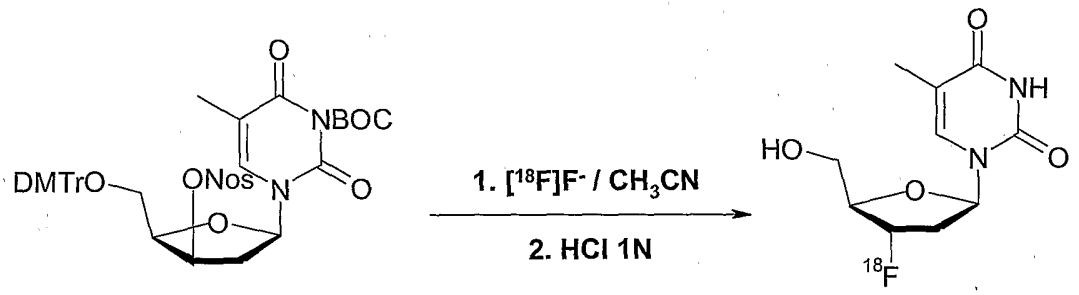
These were the aims of the authors of the following publication: "*Fully automated synthesis system of 3'-deoxy-3'-^{18}F fluorothymidine : Oh, S. J.; Mosdzianowski, C.; Chi, D. Y.; Kim, J. Y.; Kang, S. H.; Ryu, J. S.; Yeo, J. S.; Moon, D. H., Nucl Med Biol, VOLUME 31, N° 6, 2004 Aug, PP 803-9*".
Said publication described a [^{18}F]FLT synthesis with an automated production system based on the commercial [^{18}F]FDG synthesis module, namely the "TRACERlab MX_{FDG} ®, marketed by the GE Medical Systems company" as described in the US-B-6,172,207.
This synthesis is substantially based upon the following operating steps:
Preparation of the fluorinating agent
In a first step, the ^{18}F is activated through "activating" agents such as an anionic resin namely the 4, 7, 13, 16, 21, 24-hexaoxo-1,10-diazabicyclo-[8.8.8]-hexacosane [KRYPTOFIX®. (also called K2.2.2)], so as to make it more reactive. In some publications, they are called "phase transfer agents". The radionucleide is produced beforehand, generally by irradiation of ^{18}O enriched water with a proton beam originating from a particle accelerator, as F^- (for instance H^{18}F, in an aqueous solution).
The labelling of the precursor
The fluorinating agent, made totally anhydrous by additions of acetonitrile (CH_3CN) and dry cvaporations, is put in presence of a labelling substrate (precursor), generally the precursor 1-(2'-Deoxy-3'-O-(4-nitrobenzenesulfonyl)-5'-O-(4,4'-dimethoxytrityl)-beta-D-threo-pentafuranosyl)-3-(*tert*-butyloxycarbonyl)thymine also called 3-*N*-Boc-1-[5-*O*-(4,4'-dimethoxytrityl)-3-*O*-nitrophenylsulfonyl-2-deoxy-β-D-lyxofuranosyl]thymidine (5'-O-

DMTrdimethoxytrityl-2'-deoxy-3'-O-nosyl-β-D-threo-pentofuranosyl)-3-N-BOC-thymine, solubilized in acetonitrile. A substitution reaction then occurs, where the nosyl group of the substrate is replaced by the ^{18}F atom, resulting in the formation of BOC- DMTr-undeprotected product.

Hydrolysis

The fluorination solvent is partially evaporated and the hydrochloric acid is added in the reactor, after heating the solution, hydrolysis is completed, to give a bulk solution of. [^{18}F]FLT

The global chemical mechanism is the following:



Purification

The solution is then neutralized and injected in HPLC for purification.

The final product is collected after HPLC purification and is formulated in a directly injectable solution of water and ethylic alcohol.

The obtained radiochemical yield is 42±5.4% after HPLC.

This known procedure has, however, a number of drawbacks, the main ones of which are: The duration of such a procedure is about fifty minutes, particularly because of the important number of the successive heating and evaporating steps as well as liquid transfers, resulting in a loss of activity just because of the 110 minute half-life of ^{18}F. Moreover, the purification with HPLC is inevitable and the automation of said HPLC purification is almost impossible, and requests addition of hardware.

AIMS OF THE INVENTION

Faced to this prior art, the inventors aimed to improve the method for the synthesis of 3'-deoxy-3'-[18F]fluorothymidine ([18F]FLT), as disclosed in *Oh, S. J.*et al. *Nucl Med Biol, VOLUME 31, N° 6, 2004 Aug.*

So, some of the main objectives of the present invention are notably: the shrinkage of the process time because of the low half-life of [^{18}F]FLT, as well as the increase of the yield using a new hydrolysis method, and, preferably to simplify the process, the possibility to remove (if need and/or wish be) the final HPLC purification which is a complex and a time consuming step.

Other intended improvements are the reduction of the duration and the complexity of the synthesis and of the device.

The purpose is to facilitate the methods of synthesis used by the Positron Emission Tomography (TEP) laboratories.

BRIEF DESCRIPTION OF THE INVENTION

These objectives, among others, have been reached by the present invention, which relates to a process for synthesizing labelled compounds with an isotopic element, comprising the steps of:

a. preparing at least one labelling agent;

b. labelling at least one precursor with the labelling agent, wherein the precursor is a protected substrate;

c. possibly pre-purifying the labelled precursor;

e. deprotecting the labelled precursor by hydrolysis so as to obtain the labelled compound;

f. recovering the labelled compound;

g. and purifying the recovered labelled compound,

wherein the deprotectionhydrolysis is carried out by means of at least one deprotecting/hydrolyzing agent consisting in at least one acid and/or at least one base, with the exception of HCl and NaOH, preferably in at least one organic acid, said organic acid(s) being more preferably selected in the group comprising the acetic acid and its derivates, notably the halogenated acetic acid, and even more preferably in the sub-group comprising: trifluoroacetic acid (TFA), acetic acid, formic acid, the analogs thereof and mixtures thereof.

Preferably, the labelled compound is 3'-deoxy-3'-[^{18}F]fluorothymidine ([^{18}F]FLT).

The process according to the invention makes it possible to raise significantly the [^{18}F]FLT yield, even without HPLC. The hydrolysis allows to increase the yield, that is why purification without HPLC is possible. In summary, better yield are got for the synthesis, which enables to carry out a purification different from HPLC purification (namely, for

example Solid Phase Extraction (SPE) purification), in order to enhance easily the final purity of the labelled compound. In such case priority is given to the purity. So, the overall yield could be a little bit lower, but it's to the credit of the invention to offer this possibilty to give priority to the purity (possibly without HPLC) or to the yield.

The deprotection/hydrolysis step (e) of the process of the invention can occurs in a reactor which is a container (vial, vat, etc.) and/or on and/or into a solid support capable to adsorb/trap the precursor (cartridges, columns, wells, plates and so on...).

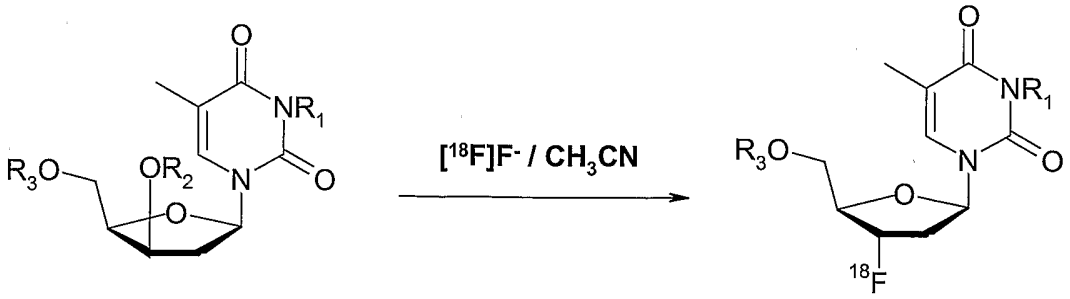
This latter type of reactor is in the core of a preferred way of implementation for the process according to the invention. Said preferred way comprises the steps of:

a. preparing at least one labelling agent;
b. labelling at least one precursor with the labelling agent, wherein the precursor is a protected substrate;
c. possibly pre-purifying the labelled precursor;
d. retaining the labelled precursor on at least one solid support;
e. deprotecting the labelled precursor by hydrolysis so as to obtain the labelled compound, directly on at least one solid support which is contained in at least one column or cartridge;
f. recovering the labelled compound by elution
g. and purifying the eluate.

This embodiment correspond to an automated synthesis which is easy, rapid, reliable and reproductible. Thus, it can be carried out where the injection of [^{18}F]FLT to the patients are done, given the limited half-life of 110 min of this radiolabelling compound.
So, the users of this labelled compound who are not equipped to make chemical synthesis, could implement this process according to the invention, which facilitates the marketing of this promising labelling compound.

One of the keys of the invention consists in the selection of a specific group of acidic hydrolysis agent, which acts, possibly in conjunction with the solid support on which the undeprotected labelled precursor is fixed (preferred embodiment), as a deprotective agent enabling in the case of [^{18}F]FLT, the lysis of the bonds between BOC- & DMTr- groups and FLT molecule.

For the [^{18}F]FLT, the undeprotected labelled precursor is, for example, selected in the group of precursors including those corresponding to the formula in the right of the following reaction schema:



deprotection/hydrolysis agent

with :

R1 = H, BOC, tBOC, C_2 to C_{10} alkyloxy carbonyl

R2 = Nos (*O*-nitrophenylsulfonyl), R-SO_2 (with R= C_1 to C_5 alkyl or unsubstitued phenyl group)

R3=, triphenylmethyl, substituted on the phenyl group, trialkylmetyl, triphenylsilyl substituted on the phenyl group, trialkylsilyl,Trityl, DMTrityl, ,....

In practice, the undeprotected labelled precursor can be 1-(2'-Deoxy-3'-O-(4-nitrobenzenesulfonyl)-5'-O-(4,4'-dimethoxytrityl)-beta-D-threo-pentafuranosyl)-3-(*tert*-butyloxycarbonyl)thymine, or
(5′-O-DMTr-2′-deoxy-3′-O-nosyl-β-D-threo-pentofuranosyl)-3-N-BOC-thymine

The worthwhile amount of precursor used in the process can be comprised –for example- between 1 mg and 100 mg of a solid support. The preferred quantities are from 5 to 50 mg. More preferably, it can be for example 25 mg.

All the numerical values given in the present exposure are given with a tolerance of +/- 10% for example, with or without the adverb "about".

Advantageously, the deprotecting/hydrolyzing agent includes an acid aqueous solution, preferably of TFA.

Practically, the deprotecting/hydrolyzing agent includes, for example, an acid aqueous solution of TFA, which [TFA] concentration is greater or equal to 40% by weight, preferably greater or equal to 50% by weight, and more preferably comprised between 55 and 65% by weight.

According to an interestering feature of the invention, the step (e) of deprotecting/hydrolyzing lasts between 0.1s to 500s (s = seconds), preferably, between 1s and 120s.

The elimination of said protecting groups in the deprotection step (e) is obtained directly on a solid support comprised in a column, a cartridge, in plates or in wells, exhibiting a high affinity to the protected molecule and a low affinity to the deprotected molecule. The term "column" "cartridge" "plates" or "wells" means equally any kind of stationary phase conditioning which may be used in chromatography, possibly including plastic or glass containers, columns, etc. These products are commercially available and are in particular used in SPE (Solid Phase Extraction) applications and in solid phase chromatography.
The column or cartridge containing the solid support which adsorbs the labelled precursor (step -d-) and where the deprotection (e) is directly performed, can be also used for the previous step (d) of pre-purification of the labelled precursor (elimination of the residual reagents and elimination of the used organic solvent(s) e.g. acetonitrile).
The possible cartridge used may be for example of the types C18, C8, tC18, NH2, diol, polystyrene divinylbenzene (SDB) or other polymeric phases, as for example available under the following trademarks: Maxi-clean®. cartridges from Alltech®: C18, 300 mg cartridge (Alltech®No. 20922) C8, 300 mg cartridge (Alltech®No. 20946) NH2, 300 mg cartridge (Alltech®No. 210040) These cartridges also exist in 600 and 900 mg versions. Waters® cartridges, from 50 mg to 10 g, in particular: C18 cartridges of Sep-Pak short body type (Waters®No. WAT 020 515) tC18 cartridges (trifunctional) of Sep-Pak® short body type 400 mg (Waters®No. WAT 036 810) Waters® OASIS® HLB extraction cartridge. Varian® cartridges: Microbond Elut ® C18 (re No. 1214-4002) Microbond Elut® C8 (re No. 1214-4405) Microbond Elut ® PS-SDB (re No. 1214-4011) Macherey-Nagel ® cartridges: Chromabond ® C18 500 mg (re No. 730 003) Chromabond ® Phenyl 500 mg (re No. 730 084).
The cartridges and columns that are used, contain –for example- between 50 mg and 10 g of a solid support. The preferred quantities are from 200 to 800 mg. Other quantities are also possible.

According to an interesting feature of the invention, the solid-support of step (e) is selected in the group comprising: normal phase, reverse phase, intermediate polarity phase, low polarity phase, ion exchange phase and mixtures thereof.

The more preferred supports are, for instance: low polarity phase, ion exchange phase mixtures of one or several ion exchange phase(s) with one or several normal or reverse phases.

Practically, it is suitable that the deprotection step (e) be performed on a column or cartridge selected from the group including the SEP PAK® cartridges marketed by the WATERS® company under the names C18, C8, tC18, NH2, diol, and polystyrene divinylbenzene (SDB).

According to a preferred embodiment of the invention, the purifying step (g) comprises tranferring the eluate containing the labelled compound on one or several –preferably at least two- hydrophilic-lipophilic water-wettable reversed-phase sorbents for solid-phase extraction (SPE).

Advantageously, these sorbents are assimilable to solid supports as described above for the trapping step (d) and the deprotection step (e).
These two or more sorbents are advantageously in serial. That means that the eluate containing the labelled compound is flushed through to a first sorbent and then through a second sorbent (or more) successively.

Actually, the number of sorbents (columns or cartridges) is not the only parameter to take into consideration. Indeed, the mass of the material constituting the sorbent(s). Regarding the the flow and the volume of liquid involved in the process, the man skilled in the art could easily determine this mass. For instance, said mass could be comprised between 900 and 1100 mg.

It is beneficial that the purifying step (g) be carried out at the ambient temperature.

Advantageously, the flow of the eluate through the sorbent(s) is chosen between about 2 to about 5 mL per minute.

Profitably, the hydrophilic-lipophilic water-wettable reversed-phase sorbents can be any of those hereabove described. In particular, the hydrophilic-lipophilic water-wettable reversed-phase sorbent for solid-phase extraction of step (g), can belong to the group of those which contain at least one copolymer comprising at least one hydrophilic comonomer (e.g. N-vinylpyrrolidone) and one lipophilic comonomer (e.g. divinylbenzene). More particularly, the hydrophilic-lipophilic water-wettable reversed-phase sorbents can be selected in the sub-group of the WATERS® OASIS® HLB family of sample extraction products, e.g. cartridges, columns, wells, or plates, the OASIS® HLB cartridges being especially preferred (e.g. OASIS® HLB plus cartridges, 225mg of sorbent, 60µm particle size).

The hydrophilic-lipophilic water-wettable reversed-phase sorbent for solid-phase extraction of step (g) and/or the solid-support of step (e) is (are) contained in a cartridge or column in a amount between 50 mg and 10 g of a solid support/sorbent.

In an remarkable variant, the step (g) is followed by a step (g1) comprising at least one rinsing of the solid sorbent(s) with a liquid selected in the group comprising aqueous solutions, physiological solutions, water, alcohols (preferably ethanol), and mixtures water/alcohol(s).

The step (g1) includes a rinsing (g11) of the solid sorbent(s) with water and a rinsing (g12) of the solid sorbent(s) with a mixture water/alcohol(s), preferably a mixture water/alcohol(s) 99/1 – more than 70/less than 30 by volume, for example about 9/1 by volume. The rinsing step (g12) can be assimilated to an elution of impureties, which affinity for the sorbent(s) is less than the affinity of the labelled compound for said sorbent(s).

The purifying step (g) comprises at least one elution (g2) of the solid sorbent(s) with an eluent selected in the group comprising alcohols (preferably ethanol) and mixtures water/alcohol(s), preferably a mixture water/alcohol(s) 70/30 –0/100 by volume, for example about 70/30 by volume.

According to a worthwhile way of implementation, at least the elution (g2) is e.g. a countercurrent elution of the labelled compound(s)

The hydrophilic-lipophilic water-wettable reversed-phase sorbent for solid-phase extraction of step (g) and/or the solid-support of step (e) is (are) in the form of grains, membranes, sheets or capillaries.

The conditions of injection through the solid support/sorbent, of rinsing and/or of elution (e.g. flow, volume of injection rinsing liquid/eluent, temperature....) are for example those given by the manufacturer and providers of SPE solid support or sorbent, notably of hydrophilic-lipophilic water-wettable reversed-phase sorbents for solid-phase extraction.
For example, these conditions can be as follows:
The uses of syringe drivers and vacuum allows to control exactly the flow through the cartridges.

- To load the solid support of step(s) (d/e), e.g.C-18 cartridge, before the hydrolysis:
  about 7mL/min

- To rinse the solid support of step(s) (d/e), e.g.C-18 cartridge, before hydrolysis: about 7mL/min
- To elute the bulk solution out of the solid support of step(s) (d/e), e.g.C-18 cartridge: about 5mL/min
- To load the bulk on the hydrophilic-lipophilic water-wettable reversed-phase sorbent for solid-phase extraction (SPE), e.g.OASIS® HLB -step (g)-: about 7mL/min
- To rinse the SPE, e.g. OASIS ® HLB –step (g)-: about 7mL/min
- To elute the impurities e.g. with the 9-1 water-ethanol mixture –step (g)-: about 3-5mL/min
- To elute the final product e.g with the 7-3 water-ethanol mixture –step (g)-: about 5mL/min

The process temperature is e.g. the room temperature

Advantageously, the eluate recovered at step (f) comprises organic solvent and, if need be, is diluted in water so as to insure an organic solvent concentration lower or equal to 10% by volume, in order to insure the best trapping efficiency.

According to a possible way of implementation, the purification g) of the eluate containing the labelled compound(s) comprises a HPLC purification, instead of or in addition to a purification on SPE.

DETAILED DESCRIPTION OF THE INVENTION

The steps (a) to (g) are detailed hereinafter:

The preparation (a) of the labelling agent is well known in the art.
The radionucleide is produced beforehand, generally by irradiation of ^{18}O enriched water with a proton beam originating from a particle accelerator, as F^- (for instance $H^{18}F$, in an aqueous solution).
Then, the ^{18}F is recovered under an activated form through "activating" agents such as KRYPTOFIX® (also called K2.2.2), a trademark used in connection with the compound 4, 7, 13, 16, 21, 24-hexaoxo-1, 10-diazabicyclo-[8.8.8]-hexacosane, so as to make it more reactive. In some publications, they are called "phase transfer agents".

Practically, the [^{18}O] enriched water containing [$^{18}F^-$] is passed through an anionic resin that can be contained in a Strong Anionic Exchange cartridge such as the one marketed under the trademark QMA SepPak® Light Waters®.

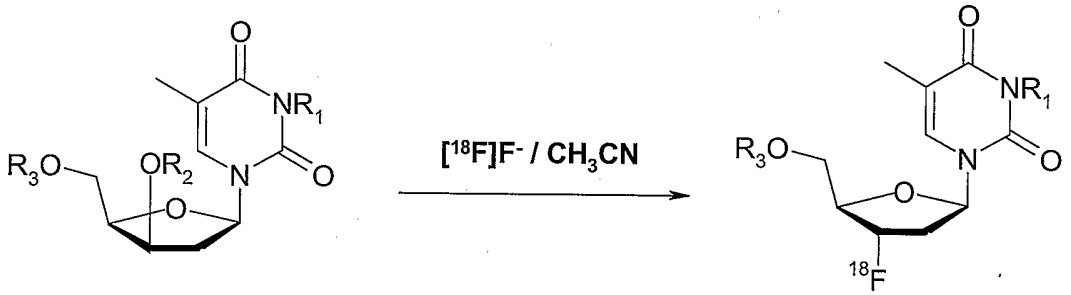
Advantageously, the [^{18}O] enriched water is removed to the ^{18}O water collection vial in the module.

Collected and activated radioactivity is recovered by washing with $K222/K_2CO_3$ CH_3CN/H_2O mixture solution

After this activation, the fluorinating agent, is made totally anhydrous by additions of at least one organic solvent, and by dry evaporations.

Preferably, the organic solvent is selected in the group comprising: acetonitrile (CH_3CN), dimethylsulfoxyde, dimethylformamide, acetone, and mixtures thereof. For example, acetonitrile (CH_3CN) is particularly suitable.

In the labelling step (b), the dried fluorinating agent is put in presence of a labelling substrate (precursor), generally the precursor Nosyl-Boc-DMTr-FLT for the [^{18}F]FLT synthesis said precursor being solubilized in at least one organic solvent, for example: acetonitrile (CH_3CN). A substitution reaction then occurs at 160°C. In the [^{18}F]FLT synthesis, the Nosyl-Boc- groups of the substrate are replaced by the ^{18}F atom and H, resulting in the formation of the undeprotected labelled precursor DMTr-FLT.



With :

R1 = H, BOC, tBOC, C_2 to C_{10} alkyloxy carbonyl

R2 = Nos (O-nitrophenylsulfonyl), R-SO_2 (with R= C_1 to C_5 alkyl or unsubstitued phenyl group)

R3=, triphenylmethyl, substituted on the phenyl group, trialkylmetyl, triphenylsilyl substituted on the phenyl group, trialkylsilyl,Trityl, DMTrityl, ,....

The possible step (c) of prepurification can be carried out as follows

The reaction mixture recovered at step (b) comprising a solution of the undeprotected labelled precursor in the organic solvent(s) can be diluted in water so as to insure an organic solvent (for example: acetonitrile (CH_3CN)), concentration lower or equal to 10% by volume.

Advantageously, once the dilution is completed the diluted reaction mixture recovered at step (b), the prepurification (c) can consists in flushing said diluted reaction mixture through a SPE solid support, preferably the SPE solid support used in the steps (d) and (e), for example those hereinabove described such as a WATERS® C-18 SepPak® cartridge.

The prepurification (c) makes it possible to remove the reagent residues, particularly the Kryptofix® K2.2.2. and the unreacted ^{18}F fluorides.

In the preferred way of implementation consisting in using the same solid support for the prepurification (c), for the selective adsorption (d) and for the deprotection (e), the adsorption or the trapping on the solid support (e.g. C18 SepPak®) of the undeprotected labelled precursor (step (d)), occurs during the migration of the diluted reaction mixture through the solid support (e.g. C18 SepPak®) for the purpose of prepurification (c).

Then, it is preferable that the solid support (e.g. C18 Sep-Pak®) be then rinsed e.g. with water.

The following step is the deprotection step (e), a mixture of water/TFA -e.g.40/60- (deprotecting/hydrolyzing agent) is pushed on the solid support (e.g. C18 Sep-Pak® cartridge), and kept in contact with the solid support for a time of 1s to 120s.

The recovery of [^{18}F]FLT (step (f)) essentially consists in rinsing e.g. with water to elute the bulk solution including the [^{18}F]FLT.

The purifying step (g) which follows, comprises, for instance, tranferring the eluate containing the labelled compound on two hydrophilic-lipophilic water-wettable reversed-phase sorbents for solid-phase extraction. Practically, the aqueous solution is flushed through two OASIS® HLB cartridges, the [^{18}F]FLT and impurities is so trapped on the OASIS® HLB cartridges.

The preferred purification (g) advantageously comprises a a rinsing step (g11) with water and a rinsing step (g12), in which a first mixture of water and at least one rinsing liquid selected from aqueous solutions, physiological solutions, water, alcohols (preferably ethanol) and mixtures water/alcohol(s).organic solvent (e.g. ethylic alcohol), is pushed through the OASIS® HLB cartridges to elute all the impurities and by products. Preferably the first mixture is water/alcohol(s) 9/1 by volume.

After that, the purifying step (g) comprises at least one elution (g2) with a second mixture of water and at least one rinsing liquid selected from aqueous solutions, physiological solutions, water, alcohols (preferably ethanol) and mixtures water/alcohol(s).organic solvent (e.g. ethylic alcohol), is pushed through the OASIS® HLB cartridges to elute all

the pure final product [^{18}F]FLT or [^{18}F]FDG of the solid sorbent(s). Preferably the second mixture is water/alcohol(s) 7/3 by volume.

Advantageously, the elution (g2) is a countercurrent elution of the labelled compound(s).

Possibly, but not necessarily, the purification (g) of the eluate containing the labelled compound(s) comprises a HPLC purification using, for example a Breeze HPLC pump, a UV 2457 (Waters, Milford, USA) and a NaI pin detector system (Bioscan, Washington DC, USA). The UV and NaI detector were installed in the hot-cell but HPLC pump and control PC were installed outside of hot-cells. For sample injection, we used a 10 mL HPLC loop and an automatic injector (Rheodyne, Rohnert Park, USA). To collect purified [^{18}F]FLT, we used one three-way valve between detector outlet point, a waste bottle and a [^{18}F]FLT collection vial, which was operated by a compressed air supply. The reaction mixture was injected to HPLC loop by syringe pressure of the module. Air in the tubing and impurities in reaction mixture were removed by 0.22 μm vented filter before injection. Purification conditions were ethanol:water (10:90), 5 mL/min, and 267 nm (UV detector). A Econosil C18 (Alltech, 10 μm, 10×250 mm) HPLC column is used. Purified [^{18}F]FLT was collected on a 20 mL vial and passed via a sterile 0.22 μm filter.

A last aspect of the present invention concerns the device for the synthesis of 3'-deoxy-3'-[^{18}F]fluorothymidine ([^{18}F]FLT) through the process of the invention, in which a solid support is used in the deprotection step, preferably included in a single use kit of materials. Said device is advantageously automated.

DESCRIPTION OF A PREFERRED EMBODIMENT OF THE INVENTION

The invention will be described more in details, in reference to an example of a specific embodiment which is illustrated schematically in the enclosed of the single figure which is a schematic drawing illustrating the synthesis of 3'-deoxy-3'-[^{18}F]fluorothymidine ([^{18}F]FLT).

EXAMPLES

Materials:

The method to prepare the ^{18}F-FLT according to the examples, consists in using an adapted form of a commercial single use kit which trademark is "TRACERlab MX_{FDG} ®", and which is marketed by the GE Medical Systems company.

The module (kit) includes multiple stopcock manifolds and disposable sterile syringes. This adapted material is described in the single enclosed schematic figure comprising the following single use components mentioned in Table 1:

TABLE 1

Component	Trademark or supplier	Reference	Qty
5-Stopcock-manifold (1)	PVB	888-105	3
Syringe Plastipak 3mL	Becton- Dickinson	300134	1
Syringe Plastipak 30mL	Becton- Dickinson		-
Reactor vint (6)	Alltech	66124	1
Reagent vial (7)	Alltech	6655	4
Tear-off seal	Alltech	66440	1
Septum	Alltech	95305	1
Oasis HLB Plus cartridge	Waters	36810	-
C18 cartridge	Waters	WAT020515	1
QMA	Waters	WAT023525	1
Filter 0.22 um	Millipore	SVGS0250S	7
Female luer plug	Value plastic	FTLLP-6	2

And to insure the connexions, different caps, lueur and needles

Description of the single figure:

TABLE 2

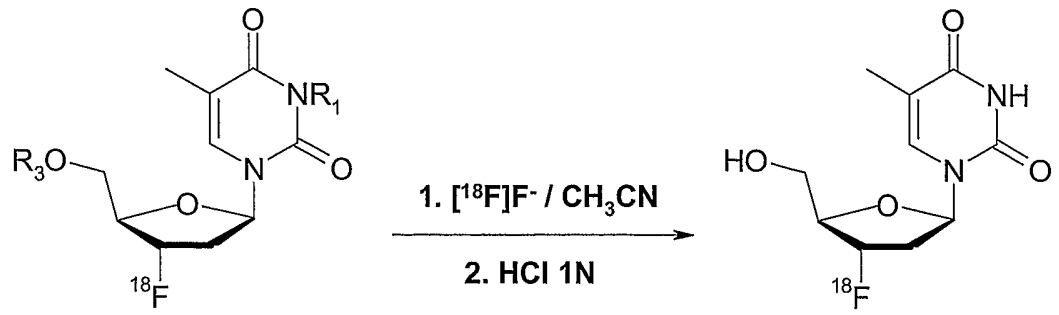
Position	Use
1	Connected to ^{18}O water recovery
2	QMA cartridge and 18F recovery connected to vial of eluant
3	Acetonitrile vial
4	30mL syringe
5	Precursor dissolved in acetonitrile
6	Reactor in
7	Water bag 250mL
8	Vial 1 for purification (EtOH / Water 9/1)
9	Vial 2 for purification (EtOH / Water 7/3)

10	Syringe for hydrolysis (water / trifluoroacetic acid)
11	Outlet for final product
12	Connection for Oasis 1 OASIS® HLB plus cartridge 225mg 60µm WATERS
13	Connection for Oasis 2 OASIS® HLB plus cartridge 225mg 60µm WATERS
14	30mL syringe
15	Reactor out
C Between 10 & 11	One classic C18 cartridge of Sep-Pak® short body type (Waters®No. WAT 020 515)
R Connected to stopcock 6 & 15	Reactor
E	Eluent admission

Chemicals

1-(2'-Deoxy-3'-O-(4-nitrobenzenesulfonyl)-5'-O-(4,4'-dimethoxytrityl)-beta-D-threo-pentafuranosyl)-3-(*tert*-butyloxycarbonyl)thymine (5'-O-DMTr-2'-deoxy-3'-O-nosyl-β-D-threo-pentofuranosyl)-3-N-BOC-thymine was used as a precursor, which was prepared according to the previous methods Solvents and reagents were purchased from Sigma-Aldrich and used as supplied.

COMPARATIVE EXAMPLE 1 (according to the synthesis disclosed in the hereinabove cited prior reference Oh et al)



Preparation of the kit:

Valve 2: QMA + reservoir
Valve 3: 7mL of acetonitrile
Valve 4: disposable 30mL syringe
Valve 5: 40mg of precursor in 3mL of acetonitrile
Valve 6: connexion to reactor in
Valve 7: 250mL of Water For Injection (WFI)
Valve 8: NaOH 2M
Valve 9: HCl 1M
Valve 10: nothing
Valve 11: nothing
Valve 12: HPLC out
Valve 13: Nothing
Valve 14: disposable 30mL syringe
Valve 15: reactor out

In that system, there is no pre-purification cartridge between valve 10 and 11.

Step (a)

a1. recovery of the [^{18}O] enriched water using an anionic resin [KRYPTOFIX®. (also called K2.2.2)] which is a ^{18}F "activating" agent.

a2. recovery, by elution of the anionic resin, of the activity in the form of [K/222].$^{18+}$, F^- in a solution in a mixture CH_3CN/H_2O.

a3. evaporation of the solvent by IR heating (95.°C.) under nitrogen flow (2 min. 30 sec.).

a4. addition of 0.4 ml CH_3CN, evaporation (2 min. 30 sec.).

a5. addition of 0.4 ml CH_3CN, evaporation to siccity.

Step (b)

Labelling of the precursor.

b1. addition of a solution of a labelling precursor (1-50 mg) in CH_3CN (3 ml).

b2. heating at 160.degree. C. during 6 min.

Step (c):

Partial evaporation of the fluorination solvent.

Step (d):
Deprotection (hydrolysis).
d1 addition of 3mL HCl into the reactor.
d2.heating for 300sec at 105 degrees Celcius.

Step (e):
Neutralization of the hydrolysis mixture.
e. addition of NaOH 2M into the reactor.

Step (g):
HPLC injection.

Results :
Yield: average is 50% corrected.
Total synthesis time: 60 minutes including HPLC purification.
In this example, it is emphasized that there is no pre-purification cartridge and that all the process happen in the reactor.

EXAMPLE 2 : Process according to the invention with a HPLC purification

Preparation of the kit:

Valve 2: QMA + reservoir
Valve 3: 7mL of acetonitrile
Valve 4: disposable 30mL syringe
Valve 5: 1 to 50mg of precursor in 3mL of acetonitrile
Valve 6: connexion to reactor in
Valve 7: 250mL of Water For Injection (WFI)
Valve 8: 7mL of ethanol
Valve 9: NaOH ethanolic solution
Valve 10 TFA 60% (v/v) in water 1mL
Valve 11: outlet to HPLC
Valve 12: Nothing
Valve 13: Nothing
Valve 14: disposable 30mL syringe
Valve 15: reactor out

Step (a)

a1. recovery of the [^{18}O] enriched water using an anionic resin [KRYPTOFIX®. (also called K2.2.2)] which is a ^{18}F "activating" agent.

a2. recovery, by elution of the anionic resin, of the activity in the form of [K/222].$^{18+}$, F^- in a solution in a mixture CH_3CN/H_2O.

a3. evaporation of the solvent by IR heating (95.°C.) under nitrogen flow (2 min. 30 sec.).

a4. addition of 0.4 ml CH_3CN, evaporation (2 min. 30 sec.).

a5. addition of 0.4 ml CH_3CN, evaporation to siccity.

Step (b)

Labelling of the precursor.

b1. addition of a solution of a labelling precursor (1-50 mg) in CH_3CN (3 ml).

b2. heating at 160.degree. C. during 6 min.

Step (c) & (d):

Pre-purification with adsorption of the labelled compound on the solid support. between stopcocks 10 & 11.

c1. dilution of the resulting solution in 25 ml water.

c2d1. transfer of the diluted solution through a C18 cartridge (conditioned beforehand with 5 ml ethanol followed with 10 ml water) to the waste.

d2. rinsing of the cartridge with 3 times 10 ml of water which are sent to the waste.

d3. drying of the cartridge under nitrogen flow.

Step (e):

Deprotection (hydrolysis) on solid support in acidic media.

e1 addition of 0.7 ml a 60% (v/v) aqueous solution of trifluoroacetic acid on the C18 cartridge.

e2. deprotection (hydrolysis) 2 min. at room temperature.

Step (f):

Recovery of the labelled compound.

f. elution of the bulk solution with 3 ml of an aqueous solution of NaOH into a syringe.

f1. rinse of the C-18 cartridge with 3mL of water which are sent also to the syringe containing the bulk.

Step (g):

HPLC injection.

Results :

Yield: average is 50% uncorrected 63% corrected to be compared to the 42 % of Oh publication.

Total synthesis time: 38 minutes including HPLC purification.

EXAMPLE 3 : Process according to the invention without a HPLC purification

Preparation of the kit:

Method with cartridges:

Valve 2: QMA + reservoir

Valve 3: 7mL of acetonitrile

Valve 4: disposable 30mL syringe

Valve 5: 5-50mg of precursor in 3mL of acetonitrile

Valve 6: connexion to reactor in

Valve 7: 250mL of WFI

Valve 8: Solution1

Valve 9: Solution 2

Valve 10 TFA water 1mL

Valve 11: To HPLC outlet

Valve 12: Purification cartridge

Valve 13: Purification cartridge

Valve 14: disposable 30mL syringe

Valve 15: reactor out

Step (a)

a1. recovery of the [^{18}O] enriched water using an anionic resin [KRYPTOFIX®. (also called K2.2.2)] which is a ^{18}F "activating".

a2. recovery, by elution of the anionic resin, of the activity in the form of [K/222].$^{18+}$, F^- in a solution in a mixture CH_3CN/H_2O.

a3 evaporation of the solvent by IR heating (95.°C.) under nitrogen flow (2 min. 30 sec.).

a4. addition of 0.4 ml CH_3CN, evaporation (2 min. 30 sec.).

a5. addition of 0.4 ml CH_3CN, evaporation to siccity.

Step (b)

Labelling of the precursor.

b1. addition of a solution of a labelling precursor (25 mg) in CH_3CN (3 ml).

b2. heating at 160.degree. C. during 6 min. (labelling step).

Step (c) & (d):

Pre-purification with adsorption of the labelled compound on the solid support between stopcocks 10 & 11.

c1dilution of the resulting solution in 25 ml water.

c2d1 transfer of the diluted solution through a C18 cartridge to the waste.

d2 rinsing of the cartridge with 3 times 10 ml of water which are sent to the waste.

d3 drying of the cartridge under nitrogen flow.

Step (e):

Deprotection (hydrolysis) on solid support in acidic media.

e1 addition of 0.7 ml a 60% (v/v) aqueous solution of trifluoroacetic acid on the C18 cartridge.

e2. deprotection (hydrolysis) 2 min. at room temperature.

Step (f):

Recovery of the labelled compound.

elution of the bulk solution with 10 ml of an water into a syringe containing 15mL of water.

Step (g):

Final purification on solid support.

g. loading the purification cartridges_12;13, the product remains on the cartridge and the liquid go to waste.

g11. rinse of the purification cartridge with 3mL of water which are sent also to the syringe containing the bulk.

Results :

Yield: 18%

Total synthesis time: 42 minutes

The non use of HPLC makes it possible to gain significant time preparation, e.g. at least 2h with regard to the comparative example 1.

Therefore, it induces economy for the process, and that even more HPLC is expensive.

CLAIMS

1) A process for synthesizing labelled compounds with an isotopic element, comprising the steps of:

a. preparing at least one labelling agent;
b. labelling at least one precursor with the labelling agent, wherein the precursor is a protected substrate;
c. possibly pre-purifying the labelled precursor;
e. deprotecting the labelled precursor by hydrolysis so as to obtain the labelled compound;
f. recovering the labelled compound;
g. and purifying the recovered labelled compound,

wherein the deprotection/hydrolysis is carried out by means of at least one deprotecting/hydrolyzing agent consisting in at least one acid and/or at least one base, with the exception of HCl and NaOH, preferably in at least one organic acid, said organic acid(s) being more preferably selected in the group comprising the acetic acid and its derivates, notably the halogenated acetic acid, and even more preferably in the sub-group comprising: trifluoroacetic acid (TFA), acetic acid, formic acid, the analogs thereof and mixtures thereof.

2) A process according to claim 1, comprising the steps of:

a. preparing at least one labelling agent;
b. labelling at least one precursor with the labelling agent, wherein the precursor is a protected substrate;
c. possibly pre-purifying the labelled precursor;
d. retaining the labelled precursor on at least one solid support;
e. deprotecting the labelled precursor by hydrolysis so as to obtain the labelled compound, directly on at least one solid support which is contained in at least one column or cartridge;
f. recovering the labelled compound by elution
g. and purifying the eluate.

3) A process according to claim 1 or 2 wherein the labelled compound is 3'-deoxy-3'-[^{18}F]fluorothymidine ([^{18}F]FLT).

4) A process according to claim 1 or 2 wherein the deprotecting/hydrolyzing agent includes an acid aqueous solution.

5) A process according to claim 3 wherein the deprotecting/hydrolyzing agent includes an acid aqueous solution, which [acid] concentration is greater or equal to 40% by weight, preferably 50% by weight, and more preferably comprised between 55 an 65% by weight.

6) A process according to any of the preceding claims wherein the step (e) of deprotecting/hydrolyzing lasts between 0.1s to 500s, preferably, between 1s and 120s.

7) A process according to any of the preceding claims wherein the purifying step (g) comprises tranferring the labelled compound on at least one hydrophilic-lipophilic water-wettable reversed-phase sorbent for solid-phase extraction (SPE).

8) A process according to claim 3 wherein the solid-support of step (e) the solid-support of step (e) is selected in the group comprising: normal phase, reverse phase, intermediate polarity phase, low polarity phase, ion exchange phase and mixtures thereof.

9) A process according to claim 3 wherein the deprotection step (e) is performed on a column or cartridge selected from the group including those marketed by the WATERS® company under the names C18, C8, tC18, NH2, diol, and polystyrene divinylbenzene (SDB).

10) A process according to claim 3 wherein the purifying step (g) comprises tranferring the eluate containing the labelled compound on one or several –preferably at least two- hydrophilic-lipophilic water-wettable reversed-phase sorbents for solid-phase extraction (SPE).

11) A process according to claim 7 wherein the step (g) is followed by a step (g1) comprising at least one rinsing of the solid sorbent(s) with a liquid selected in the group comprising aqueous solutions, physiological solutions, water, alcohols (preferably ethanol) and mixtures water/alcohol(s).

12) A process according to claim 11 wherein the step (g1) includes a rinsing (g11) of the solid sorbent(s) with water and a rinsing (g12) of the solid sorbent(s) with a mixture water/alcohol(s), preferably a mixture water/alcohol(s) 99/1 – more than 70/less than 30 by volume, for example about 9/1 by volume.

13) A process according to claim 7 wherein the purifying step (g) comprises at least one elution (g2) of the solid sorbent(s) with an eluent selected in the group comprising alcohols (preferably ethanol) and mixtures water/alcohol(s), preferably a mixture water/alcohol(s) 70/30 –0/100 by volume, for example about 70/30 by volume.

14) A process according to claim 13 wherein at least the elution (g2) is a countercurrent elution of the labelled compound(s).

15) A process according to claim 7 wherein the hydrophilic-lipophilic water-wettable reversed-phase sorbent for solid-phase extraction of step (g), belong to the group of those which contain at least one copolymer comprising at least one hydrophilic comonomer and one lipophilic comonomer, the preferred hydrophilic-lipophilic water-wettable reversed-phase sorbents being selected in the sub-group of the WATERS® OASIS® HLB family of sample extraction products, the OASIS® HLB cartridges being especially preferred.

16) A process according any of the preceding claims, wherein the hydrophilic-lipophilic water-wettable reversed-phase sorbent for solid-phase extraction of step (g) and/or the solid-support of step (e) is (are) contained in a cartridge or column in a amount between 50 mg and 10 g of a solid support/sorbent.

17) The process according any of the preceding claims, wherein the hydrophilic-lipophilic water-wettable reversed-phase sorbent for solid-phase extraction of step (g) and/or the solid-support of step (e) is (are) in the form of grains, membranes, sheets or capillaries.

18) The process according any of the preceding claims, wherein the eluate recovered at step (b) comprises organic solvent and, if need be, is diluted in water so as to insure an organic solvent concentration lower or equal to 10% by volume.

19) The process according to claim 18, wherein the organic solvent is selected in the group comprising: acetonitrile (CH_3CN),, dimethylsulfoxyde, dimethylformamide, acetone, and mixtures thereof.

20) The process according any of the preceding claims, wherein the purification of the eluate containing the labelled compound(s) comprises a HPLC purification.

21) The device for implementing the process according to any of the claims 1 to 20.

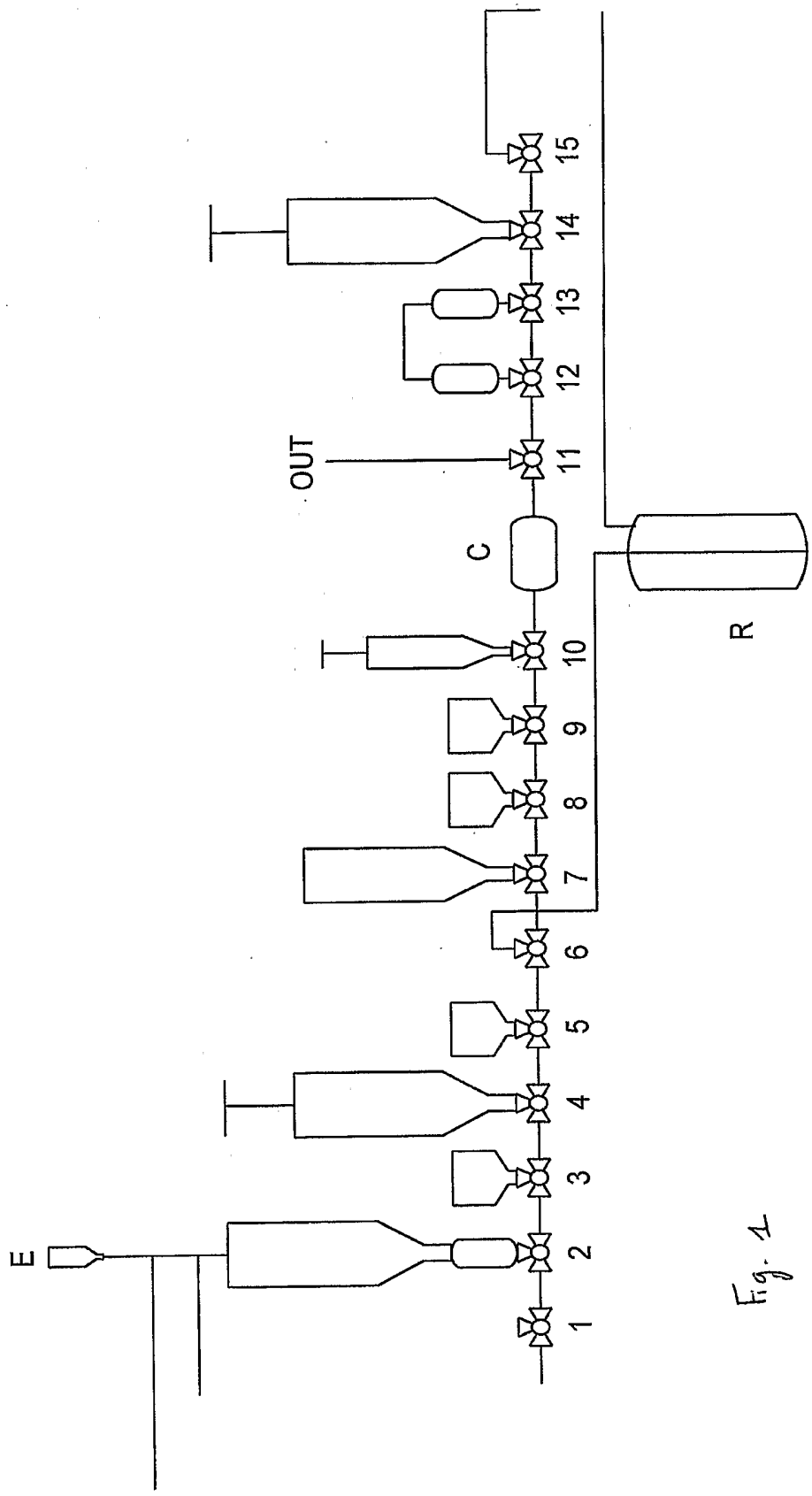


Fig. 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/010051

A. CLASSIFICATION OF SUBJECT MATTER
C07B59/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. R. GRIERSON AND A. F. SHIELDS: "Radiosynthesis of 3'-deoxy-3'-'18F!fluorothymidine: '18F!FLT for imaging of cellular proliferation in vivo" NUCLEAR MEDICINE & BIOLOGY, vol. 27, 2000, pages 143-156, XP002357535 Figures 2-3. page 146, right-hand column, paragraph 3 - page 147, left-hand column, paragraph 2	1,3,6,7, 10-17, 20,21
Y		8,9,18, 19

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 December 2005	06/02/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Menchaca, R

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/010051

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	G. K. MULHOLLAND: "Simple rapid hydrolisis of acetyl protecting groups in the FDG synthesis using cation exchange resins" NUCL. MED. BIOL., vol. 22, no. 1, 1995, pages 19-23, XP002357536 page 19, left-hand column, last paragraph - page 20, right-hand column, paragraph 1	1,2,6,7, 11, 15-17,20
X	M. YUN, S. H. OH, H. HA, J. S. RYU AND D. H. MOON: "High radiochemical synthesis of 3'-deoxy-3'-'18F!fluorothyimidine using (5'-O-dimethoxytrityl-2'-deoxy-3'-O-nosyl-beta-D-threo-pentofuranosyl)thymine and its 3-N-BOC-protected analogue as a labeling precursor" NUCLEAR MEDICINE & BIOLOGY, vol. 30, 2003, pages 151-157, XP002357537 Paragraph 4.1.7 (Experimental section on pages 156-157) page 154, left-hand column, paragraph 2; figure 1	1,3,6,20
X	US 2005/131224 A1 (WALSH JOSEPH C ET AL) 16 June 2005 (2005-06-16) Paragraphs '0045!-'0047! on page 4, claims 33,34	1,3-5
Y	US 6 172 207 B1 (DAMHAUT PHILIPPE E ET AL) 9 January 2001 (2001-01-09) cited in the application column 3, line 25 - column 4, line 55; claims 1-23	8,9,18, 19
A	WO 2005/025519 A (MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH; TRUMP, DAVID, P) 24 March 2005 (2005-03-24) Paragraphs '0009!-'0014! on pages 2-4. Claims 1-28	1,21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2005/010051

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2005131224 A1	16-06-2005	WO 2005058246 A2	30-06-2005
US 6172207 B1	09-01-2001	BE 1010280 A3	05-05-1998
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		EP 0836609 A1	22-04-1998
		JP 11508923 T	03-08-1999
WO 2005025519 A	24-03-2005	NONE	