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(54) Title: IODO PRECURSOR FOR A PET IMAGING AGENT OF AMYLOID PLAQUES

(57) Abstract: The invention relates to a precursor for a [%F]-labeled PET tracer for imaging of Alzheimer's Disease, its synthesis and the process for preparing the respective [%F]-labeled PET tracer.
Iodo precursor for a PET imaging agent of amyloid plaques

The present invention is directed to a novel precursor of a Positron Emitting Tomography (PET) imaging agent for binding and imaging amyloid deposits and the process for producing said imaging agent.

Background of the Invention

Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by loss of memory, cognition, and behavioral stability. AD is defined pathologically by extracellular senile plaques comprised of fibrillar deposits of the beta-amyloid peptide (Aβ) and neurofibrillary tangles comprised of paired helical filaments of hyperphosphorylated tau. The 39 to 43 amino acids comprising Aβ peptides are derived from the larger amyloid precursor protein (APP). In the amyloidogenic pathway, Aβ peptides are cleaved from APP by the sequential proteolysis of β- and γ-secretases. Aβ peptides are released as soluble proteins and can be detected at low levels in the cerebrospinal fluid (CSF) in normal aging brains. During the progress of AD the Aβ peptides aggregate and form amyloid deposits in the parenchyma and vasculature of the brain, which can be detected post mortem as diffuse and senile plaques and vascular amyloid during histological examination (for a recent review see: Blennow et al. Lancet. 2006 Jul 29;368(9533):387-403).

Alzheimer's disease is becoming a great health and social economical problem all over the world. There are great efforts being made to develop techniques and methods for the early detection and effective treatment of the disease. Currently, diagnosis of AD in an academic setting of memory-disorder clinics is approximately 85-90% accurate (Petrella JR et al. Radiology. 2003 226:315-36). It is based on the exclusion of a variety of diseases causing similar symptoms and the careful neurological and psychiatric examination, as well as neuropsychological testing. However, post mortem histological examination of the brain is still the only definite diagnosis of this disease. Thus the in vivo detection of one pathological feature of the disease – the deposition of amyloid aggregates in the brain – is thought to have a big impact on the early detection of AD and differentiation from other dementias. Additionally, most disease modifying therapies that are under development are aiming at lowering the amyloid load in the brain. Thus imaging the amyloid load in the brain may provide an essential tool for patient stratification and treatment monitoring.

In addition, amyloid deposits are also known to play a role in amyloidoses, in which amyloid proteins are abnormally deposited in different organs and/or tissues, causing disease. For a recent review see Chiti et al. Annu Rev Biochem. 2006;75:333-66.

Besides their specific binding to amyloid deposits in the brain, the currently most promising PET tracers show a disadvantageous non-specific accumulation, especially in white matter brain regions in AD patients as well as in healthy controls. Generally, non-specific background binding interferes with the image quality and could e.g. impair the quantification of amyloid and the diagnosis of very early stages of the disease.

Recently, the compound of formula

![Chemical structure](image)

has been found to be a suitable PET tracer for the detection of amyloid deposits in patients with amyloid-related diseases with high specificity at an early stage of the disease (PCT/EP2009/006406). Hence, there is a need for a commercially useful process for producing the tracer with high yield and for a precursor useful in such method. This problem has been solved by the provision of a precursor using Iodine as a leaving group.

**Description of the invention**

F-18 labeled pyridine analogues are generally synthesized by heteroaromatic nucleophilic substitution reactions. Described leaving groups are: Chloro, Bromo, Iodo, Nitro, and Trimethyl ammonium groups. Wherein this pool Nitro and Trimethyl ammonium are widely considered to be the most reactive in regard to be substituted by F-18 followed by Bromo and Chloro. The Iodo leaving group is considered to be the less reactive one. [1]
Only in one example Zhang and Horti describe the iodo as beneficial over the Bromo leaving group. [2] They describe poor yields (2-7%) for their Bromopyridine precursor if one uses [18F]Fluoride/Kryptofix 222/Potassium carbonate (K₂CO₃) in Dimethyl sulfoxide (DMSO). When they used the respective iodo precursor the radiochemical yield was 6 to 8 % higher and reached an absolute level of 8-15% yield.

We surprisingly found the iodo Precursor 1d to be more reactive than the Bromo precursor 2a and therefore more applicable for said radiofluorination, i.e. the synthesis of the [18F] Tracer 3. In contrast to Zhang, who uses [18F]Fluoride/Kryptofix 222/K₂CO₃ in DMSO, we used a different fluorination protocol and we found a much higher fluorination yield than one would expect from the current state of the art.

![Precursor 1d](image1)

![Precursor 2a](image2)

![[18F] Tracer 3](image3)

Using [18F]fluoride/Tetrabutylammonium hydroxide (TBAOH) in DMSO for Bromo precursor 2a we achieved a radiochemical yield of ~15 % corrected for decay. When we switched to the iodo precursor 1d the radiochemical yield was 40% higher and reached an absolute value of 56% radiochemical yield corrected for decay.

Thus, one embodiment of the invention is the compound of the formula
or a suitable salt thereof, preferably a pharmaceutically acceptable salt thereof.

In the context of the present invention, preferred suitable salts are pharmaceutically acceptable salts of the compounds according to the invention. The invention also comprises salts which for their part are not suitable for pharmaceutical applications, but which can be used, for example, for isolating or purifying the compounds according to the invention. Pharmaceutically acceptable salts of the compounds according to the invention include acid addition salts of mineral acids, carboxylic acids and sulphonic acids, for example salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonfonic acid, ethanesulphonfonic acid, toluenesulphonfonic acid, benzenesulphonfonic acid, naphthalene disulphonfonic acid, acetic acid, trifluoroacetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid and benzoic acid.

Furthermore, another embodiment of the invention is a method for the preparation of a compound of the formula

![Chemical structure](image)

wherein the compound of formula

![Chemical structure](image)

is reacted with a radiofluorination agent.

An even more preferred embodiment of the invention is a method for the preparation of a compound according to formula
wherein the compound of formula

is reacted with a radiofluorination agent at elevated temperatures in organic solvents or mixtures thereof.

Temperature ranges can be 140 – 220 °C, preferably 160 – 200 °C, and even more preferably 170 – 190 °C, even more preferably 175 – 185 °C.

Optionally, a microwave reactor may be used. In that case the reaction may be performed at the same or even more elevated temperatures in shorter reaction times.

In a preferred embodiment [\textsuperscript{18}F]fluoride/TBAOH and a solvent is used as a fluorination agent.

In a preferred embodiment, the fluorination agent is 4,7,13,16,21,24-Hexaoxa-1,10 diazabicyclo[8.8.8]-hexacosane K\textsuperscript{18}F (crownether salt Kryptofix K\textsuperscript{18}F), K\textsuperscript{18}F, H\textsuperscript{18}F, KH\textsuperscript{18}F\textsubscript{2} or tetraalkylammonium salt of \textsuperscript{18}F. More preferably, the fluorination agent is K\textsuperscript{18}F, H\textsuperscript{18}F, or KH\textsuperscript{18}F\textsubscript{2}.

The solvents used can be N,N-Dimethylformamide (DMF), Dimethylsulfoxide (DMSO), Acetonitrile (MeCN), N,N-Dimethylacetamide (DMA) etc., preferably DMSO, MeCN or DMF. The solvents can also be a mixture of solvents as indicated above.

One further aspect of the invention is a method for the preparation of the compound of the formula

wherein the compound of formula
is reacted with 2-iodopyridine-4-carboxylic acid.

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One preferred aspect of the invention is a method for the preparation of the compound of the formula

wherein a salt of the compound of formula

is reacted with 2-iodopyridine-4-carboxylic acid.

Preferably the salt is the hydrochloride.

One further aspect of the invention is a method for the preparation of the compound of the formula

wherein the compound of formula
is deprotected and then reacted with 2-iodopyridine-4-carboxylic acid.

F-18 radiolabeling procedures

[F-18] radiolabeling procedures are well known to the person skilled in the art. For example, radiolabeling can be performed as described in the following.

[F-18] Fluoride can be produced by proton bombardment in a cyclotron using a silver target (1 mL) filled with [O-18] water for the ^18O (p,n) ^18F reaction. The aqueous [F-18] fluoride can be passed through a cartridge (e.g. QMA-resin cartridge Waters, Sep Pak Light QMA Part.No.: WAT023525 ). The trapped [F-18] fluoride can then be eluted from the cartridge by adding e.g. a Kryptofix K2.2.2/ K2CO3 solution (Kryptofix is 4,7,13,16,21,24-Hexaoxa-1,10-diazabicyclo[8.8.8]-hexacosane). The nucleophilic substitution of the precursor works preferably in the presence of a base such as Tetrabutylammonium hydroxide (NBu₄OH), Tetrabutylammonium carbonate ((NBu₄)₂CO₃), Tetrabutylammonium hydrogen carbonate (NBu₄HCO₃), K₂CO₃ etc. and at elevated temperatures. The addition of crown ethers such as Kryptofix (K2.2.2) can influence the reaction positively, especially in the presence of K₂CO₃ as the base.

The potassium fluoride Kryptofix complex is preferably dried by repeated azeotropic distillation with sequential addition of acetonitrile. Solvents such as acetonitrile, DMF, DMSO etc. can be used as a reaction solvent. The labeling product can be purified by solid phase extraction using cartridges. Preferred cartridges are Sep-Pak Plus C18 cartridge (Waters, WAT020515). The cartridge can be rinsed with water and the compound can be eluted with acetonitrile. The eluted compound can be diluted with water and can then be subjected to preparative HPLC purification. Preferred HPLC columns are reversed phase columns such as Gemini 5 µC 18 110 Å, 250 * 10 mm (Phenomenex, 00G-4435-N0). Mixtures of buffer solution, acids, water etc. with organic solvents such as acetonitrile, methanol, ethanol etc. can be used as mobile.

The solution can then be diluted with e.g. water to be passed through a cartridge for concentration and solvent change.


**Brief description of the figures**

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**Figure 1:** Preparative HPLC chromatogram for purification of 3 starting from precursor 1d.

**Figure 2:** Analytical HPLC chromatogram of 3 starting from precursor 1d (Gamma detection).

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**Figure 3:** Analytical HPLC chromatogram of 2b (UV detection) corresponding to Fig. 2.

**Figure 4:** Preparative HPLC chromatogram for purification of 3 starting from precursor 2a.

**Figure 5:** Analytical HPLC chromatogram of 3 starting from precursor 2a (Gamma detection).

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**Figure 6:** Analytical HPLC chromatogram of 2b (UV detection) corresponding to Fig. 5.
Examples

A method for synthesizing and labeling is exemplified in the following Examples. These examples illustrate certain aspects of the above-described method and advantageous results and are shown by way of illustration and not by way of limitation.

Example 1

N-(2-[4-[(benzyloxy)pyridin-2-yl]piperazin-1-yl]-2-oxoethyl)-2-iodopyridine-4-carboxamide

a) 5-Benzylxoy-2-bromo-pyridine

To a solution of 10.0 g (57.47 mmol) of 2-bromo-5-hydroxypyridine in 400 mL N,N-dimethylformamide (DMF) was added 14.75 g (86.21 mmol) of benzyl bromide and 23.82 g (172.4 mmol) of potassium carbonate. The mixture was stirred for 6 h at 60°C and overnight at room temperature. The suspension was filtered off and after evaporation of the solvent the residue was chromatographed on silica gel using a dichloromethane/methanol gradient. Yield: 14.82 g (96.7 %).

MS (ESIpos): m/z = 264, 266 [M+H]+

1H-NMR (300MHz, CHLOROFORM-d): δ [ppm]= 5.10 (s, 2H), 7.16 (dd, 1H), 7.32 - 7.47 (m, 6H), 8.14 (d, 1H).

b) 1-(5-Benzylxoy-pyridin-2-yl)-piperazine

All glassware was dried at 100°C. To a solution of 5.27 g (61.22 mmol) of piperazine in 180 mL toluene was added 561 mg (0.61 mmol) of tris(dibenzylidene acetone) dipalladium(0) and 520 mg (0.83 mmol) of BINAP (2,2′-bis(diphenyl phosphino)-1,1′-binaphthyl). Then, a solution of 14.7 g (55.66 mmol) of 5-benzylxoy-2-bromo-pyridine (example 1a) in tetrahydrofuran
(THF) was added followed by a suspension of 8.02 g (83.48 mmol) of sodium t-butylate in THF.
The reaction mixture was refluxed for 6 h and stirred at room temperature overnight. After evaporation of the solvents the residue was chromatographed on silica gel using a dichloromethane/methanol gradient.
Yield: 7.12 g (47.0 %).

MS (ESIpos): m/z = 270 [M+H]^+

^1^H-NMR (300MHz, CHLOROFORM-d): δ [ppm]= 2.97 - 3.07 (m, 4H), 3.36 - 3.46 (m, 4H), 5.04 (s, 2H), 6.63 (d, 1H), 7.21 (dd, 1H), 7.29 - 7.48 (m, 5H), 8.00 (d, 1H).

c) tert-butyl (2-{4-[5-(benzyl oxy)pyridin-2-yl]piperazin-1-yl}-2-oxoethyl)carbamate

To a solution of 4.63 g (26.43 mmol) t-Butoxycarbonyl-glycine (Aldrich) in 500 mL THF and 5 mL triethyl amine (35.87 mmol) at –15°C, 3.43 mL (26.43 mmol) isobutyl chloroformate were added dropwise and the solution was maintained at this temperature for another 15 min. Then, 7.12 g of 1-{5-Benzyl oxy-pyridin-2-yl}-piperazine (1b) and 18 mL triethyl amine (129 mmol) in 200 mL THF/dichloromethane (1:1) were added slowly to this cold solution, the temperature was kept below -10°C for another 15 min and was then allowed to reach room temperature. After stirring overnight the solvent was evaporated and the residue was taken up in ethyl acetate. This solution was washed successively with aqueous sodium carbonate, water, 1 M aqueous hydrochloric acid (HCl) solution, saturated aqueous sodium chloride solution, finally dried over magnesium sulfate and then evaporated. This residue was chromatographed on silica gel using a hexane/ethyl acetate gradient.
Yield: 8.04 g (70.6 %).

MS (ESIpos): m/z = 427 [M+H]^+

^1^H-NMR (300MHz, CHLOROFORM-d): δ [ppm]= 1.46 (s, 9H), 3.36 - 3.45 (m, 2H), 3.51 (br. s., 4H), 3.70 - 3.81 (m, 2H), 4.02 (d, 2H), 5.05 (s, 2H), 5.53 (br. s., 1H), 6.65 (d, 1H), 7.23 (dd, 1H), 7.30 - 7.48 (m, 5H), 8.00 (d, 1H).

d) N-(2-{4-[5-(benzyl oxy)pyridin-2-yl]piperazin-1-yl}-2-oxoethyl)-2-iodopyridine-4-carboxamide
8.0 g (18.76 mmol) of tert-butyl (2-[4-[5-(benzyloxy)pyridin-2-yl]piperazin-1-yl]-2-oxoethyl) carbamate (1c) were suspended in 160 mL 2N HCl in diethyl ether and stirred overnight at room temperature. The precipitate was filtered off and washed with ether and dried at 40°C in vacuo.

Yield: 7.4 g (quantitative). The product was used in the next step without further purification.

MS (ESIpos): m/z = 327 [M+H]⁺

To a solution of 274 mg (1.10 mmol) of 2-iodopyridine-4-carboxylic acid (Alfa Aesar) and 363 mg (1.0 mmol) of hydrochloride prepared above in 15 mL DMF were added 624 mg (1.2 mmol) Benzotriazol-1-yl)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) and 0.70 mL (4 mmol) N-ethyl-N,N-diisopropylamine and the reaction mixture was stirred overnight at room temperature. After evaporation of the solvent the residue was taken up in ethyl acetate. This solution was washed with water and saturated aqueous sodium chloride solution, dried over sodium sulfate and then evaporated. This residue was chromatographed on silica gel using an dichloromethane/methanol gradient and the appropriate fractions were combined and concentrated.

Yield: 320 mg (53.8 %).

MS (ESIpos): m/z = 558 [M+H]⁺

¹H-NMR (600MHz, DMSO-d₆): δ [ppm]= 2.52 (m, 2H), 2.60 (m, 2H), 2.74-2.76 (m, 4H), 3.36-3.37 (m, 2H), 4.24 (s, 2H), 6.02 (d, 1H), 6.46-6.62 (m, 6H), 6.96 (d, 1H), 7.12 (d, 1H), 7.38 (d, 1H), 7.69 (d, 1H), 8.17-8.22 (m, 1H).

Example 2

a) N-(2-[4-[5-(benzyloxy)pyridin-2-yl]piperazin-1-yl]-2-oxoethyl)-2-bromopyridine-4-carboxamide
8.0 g (18.76 mmol) of tert-butyl (2-{4-[5-(benzyl oxy)pyridin-2-yl]piperazin-1-yl}-2-oxoethyl) carbamate (1c) were suspended in 160 mL 2N HCl in diethyl ether and stirred overnight at room temperature. The precipitate was filtered off and washed with ether and dried at 40°C in vacuo.

Yield: 7.4 g (quantitative). The product was used in the next step without further purification.

MS (ESIpos): m/z = 327 [M+H]+

To a solution of 1.01 g (5.01 mmol) of 2-bromopyridine-4-carboxylic acid (Aldrich) and 2.0 g (5.51 mmol) of hydrochloride prepared above in 160 mL DMF were added 3.13 g (6.0 mmol) PyBOP and 2.75 mL N-ethyl-N,N-diisopropylamine and the reaction mixture was stirred overnight at room temperature. After evaporation of the solvent the residue was chromatographed on silica gel using an ethyl acetate/ethanol gradient and the appropriate fractions were combined and concentrated.

Yield: 739 mg (27.7%).

MS (ESIpos): m/z = 510, 512 [M+H]+

1H-NMR (400MHz, DMSO-d6): δ [ppm]= 2.72 (s, 1H), 2.88 (s, 1H), 3.40 - 3.48 (m, 2H), 3.51 - 3.64 (m, 4H), 4.21 (d, 2H), 5.07 (s, 2H), 6.86 (d, 1H), 7.25 - 7.48 (m, 6H), 7.81 (dd, 1H), 7.95 (d, 1H), 8.02 (s, 1H), 8.56 (d, 1H), 9.06 (s, 1H).

b) N-(2-{4-[5-(benzyl oxy)pyridin-2-yl]piperazin-1-yl}-2-oxoethyl)-2-fluoropyridine-4-carboxamide (cold standard)

8.0 g (18.76 mmol) of tert-butyl (2-{4-[5-(benzyl oxy)pyridin-2-yl]piperazin-1-yl}-2-oxoethyl) carbamate (1c) were suspended in 160 mL 2N HCl in diethyl ether and stirred overnight at room temperature. The precipitate was filtered off and washed with ether and dried at 40°C in vacuo.

Yield: 7.4 g (quantitative). The product was used in the next step without further purification.

MS (ESIpos): m/z = 327 [M+H]+

To a solution of 177 mg (1.25 mmol) of 2-fluoropyridine-4-carboxylic acid (Aldrich) and 501 mg (1.38 mmol) of hydrochloride prepared above in 40 mL DMF were added 784 mg (1.5 mmol) PyBOP and 0.80 mL N-ethyl-N,N-diisopropylamine and the reaction mixture was
stirred overnight at room temperature. After evaporation of the solvent the residue was chromatographed on silica gel using an ethyl acetate/ethanol gradient.
Yield: 315 mg (50.2 %).

MS (ESIpos): m/z = 449 [M+H]⁺

1H-NMR (400MHz, DMSO-d₆): δ [ppm]= 3.37 (br. s., 2H), 3.44 (br. s., 2H), 3.52 - 3.66 (m, 4H), 4.22 (d, 2H), 5.07 (s, 2H), 6.83 (d, 1H), 7.27 - 7.47 (m, 6H), 7.53 (s, 1H), 7.70 - 7.81 (m, 1H), 7.95 (d, 1H), 8.39 (d, 1H), 9.01 (t, 1H).

Example 3

- $[^{18}F]$-N-(2-{4-[5-(benzlyoxy)pyridin-2-yl]piperazin-1-yl}-2-oxoethyl)-2-fluoropyridine-4-carboxamide by labeling of N-(2-{4-[5-(benzlyoxy)pyridin-2-yl]piperazin-1-yl}-2-oxoethyl)-2-bromopyridine-4-carboxamide (Example 2a)

Aqueous $[^{18}F]$Fluoride (38.7 GBq) was trapped on a QMA cartridge (Waters) (activated with 5 mL 0.5M K₂CO₃ solution, 10 mL water and 10mL air) and eluted with 2 mL of a TBAOH solution (1.5 mL MeCN, 0.5 mL H₂O + 8 µL TBAOH sol. (40%)) into the reactor. The solvent was removed by heating at 80°C for 3 min (N₂ stream and vacuum) and at 120 °C for additional 3 min (vacuum). Anhydrous MeCN (1 mL) was added and evaporated as before. A solution of precursor 2a (5 mg) in 500 µl anhydrous dimethyl sulfoxide (DMSO) was added. After heating at 180 °C for 20 min the crude reaction mixture was diluted with 4 mL water/MeCN (50:50) and purified by preparative HPLC: ACE 5-C18-HL 250mmx10mm; isocratic, 25 % acetonitrile in water with 0.1 % trifluoroacetic acid, flow: 4 mL/min; tᵣ~22 min. The collected HPLC fraction was diluted with 40 mL water and immobilized on a Sep-Pak plus short tC18 cartridge (Waters), which was washed with 5 mL water and eluted with 1 mL ethanol to deliver the 3.5 GBq of the F-18 labeled product (15.5 % rc. yield, corrected for decay; >96% HPLC) in 1000 µl ethanol in a overall synthesis time of ~80 min. The desired F-18 labeled product 3 (tᵣ=3.2 min) was analyzed using analytical HPLC: ACE3-C18 50 mm x 4.6 mm; solvent gradient: start 5 % acetonitrile – 95 % acetonitrile in 0.1% trifluoroacetic acid in 7 min., flow: 2 mL/min and confirmed by co-injection with the corresponding non-radioactive F-19 fluoro-standard 2b on the analytical HPLC (tᵣ=3.1 min).
Alternatively to the method described above the QMA cartridge (Waters) can also be eluted with 2 mL of a tetrabutylammonium hydroxide (TBAOH) solution (1.5 mL acetonitrile
(MeCN), 0.3 mL H₂O + 8 μL TBAOH sol. (40 %)) into the reactor. The solvent was then removed by heating the open vial at 120 °C for 10 min in an aluminium heating block under a stream of nitrogen. Anhydrous MeCN (1 mL) was added and evaporated as before.

- [¹⁸F]-N-(2-[4-[5-(benzyloxy)pyridin-2-yl]piperazin-1-yl]-2-oxoethyl)-2-fluoropyridine-4-carboxamide by labeling of N-(2-[4-[5-(benzyloxy)pyridin-2-yl]piperazin-1-yl]-2-oxoethyl)-2-iodopyridine-4-carboxamide (Example 1d)

Aqueous [¹⁸F]Fluoride (11 GBq) was trapped on a QMA cartridge (Waters) (activated with 5 mL 0.5M K₂CO₃ solution, 10 mL water and 10mL air) and eluted with 2 mL of a TBAOH solution (1.5 mL MeCN, 0.5 mL H₂O + 8 μL TBAOH sol. (40%)) into the reactor. The solvent was removed by heating at 80°C for 3 min (N₂ stream and vacuum) and at 120 °C for additional 3 min (vacuum). Anhydrous MeCN (1 mL) was added and evaporated as before. A solution of precursor 1d (5 mg) in 500 μl anhydrous DMSO was added. After heating at 180 °C for 20 min the crude reaction mixture was diluted with 4 mL water/MeCN (50:50) and purified by preparative HPLC: ACE 5-C18-HL 250mmx10mm; isocratic, 23% acetonitrile in water with 0.1% trifluoroacetic acid, flow: 4 mL/min; tₑ=33 min.

The collected HPLC fraction was diluted with 40mL water and immobilized on a Sep-Pak plus short tC18 cartridge (Waters), which was washed with 10 mL water and eluted with 1 mL ethanol into the product vial to deliver the F-18 labeled product 3 (3.4 GBq) in an overall synthesis time of ~95 min and in a radiochemical yield of 56% corrected for decay (radiochemical purity >99% (HPLC).

The desired F-18 labeled product 3 (tₑ=3.2 min) was analyzed using analytical HPLC: ACE3-C18 50 mm x 4.6 mm; solvent gradient: start 5 % acetonitrile – 95 % acetonitrile in 0.1% trifluoroacetic acid in 7 min., flow: 2mL/min and confirmed by co-injection with the corresponding non-radioactive F-19 fluoro-standard 2b on the analytical HPLC (tₑ=3.0 min).

Alternatively to the method described above the QMA cartridge (Waters) can also be eluted with 2 mL of a tetrabutylammonium hydroxide (TBAOH) solution (1.5 mL acetonitrile (MeCN), 0.3 mL H₂O + 8 μL TBAOH sol. (40 %)) into the reactor. The solvent was then removed by heating the open vial at 120 °C for 10 min in an aluminium heating block under a stream of nitrogen. Anhydrous MeCN (1 mL) was added and evaporated as before.
Claims

1. A compound of the formula

![Chemical structure 1]

or a suitable salt thereof.

2. A method for the preparation of a compound of the formula

![Chemical structure 2]

wherein the compound of formula

![Chemical structure 3]

is reacted with a radiofluorination agent.

3. A method for the preparation of a compound of the formula

![Chemical structure 4]

wherein the compound of formula

![Chemical structure 5]
is reacted with a radiofluorination agent at elevated temperatures in organic solvents or mixtures thereof.

4. A method according to claim 2 or 3, wherein $[^{18}\text{F}]$fluoride/TBAOH is used as a fluorination agent.

5. A method for the preparation of a compound of the formula

![Chemical Structure 1]

6. A method for the preparation of a compound of the formula

![Chemical Structure 2]

wherein the compound of formula

![Chemical Structure 3]

is reacted with 2-iodopyridine-4-carboxylic acid.

7. A method for the preparation of a compound of the formula

![Chemical Structure 4]

wherein a salt of the compound of formula
is reacted with 2-iodopyridine-4-carboxylic acid.

8. A method according to claim 7, wherein the salt is the hydrochloride.

9. A method for the preparation of a compound of the formula

wherein the compound of formula

is deprotected and then reacted with 2-iodopyridine-4-carboxylic acid.
INTERNATIONAL SEARCH REPORT

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

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P 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, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tbody>
<tr>
<td>A</td>
<td>WO 02/36581 A1 (SCHERING AG [DE]) 10 May 2002 (2002-05-10) the whole document in particular abstract, pages 20-21 example 3 and claims 1, 13 and 14</td>
<td>1-9</td>
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Data of the actual completion of the international search

11 March 2011

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