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Radiosynthesis of [^{18}F]PBR111, a selective radioligand for imaging the translocator protein (18 kDa) with PET

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PBR111 (2-(6-chloro-2-(4-(3-fluoropropoxy)phenyl)imidazo[1,2-*a*]pyridin-3-yl)-*N*,*N*-diethylacetamide) is a novel, reported, high-affinity and selective ligand for the translocator protein (18 kDa). PBR111 has been labelled with fluorine-18 (half-life: 109.8 min) using our Zymate-XP robotic system. The process involves (A) a simple one-step tosyloxy-for-fluorine nucleophilic aliphatic substitution (performed at 165°C for 5 min in DMSO using K[^{18}F]F-Kryptofix®222 and 6.8–7.6 µmol of the corresponding tosylate as precursor for labelling) followed by (B) C-18 PrepSep cartridge pre-purification and (C) semi-preparative HPLC purification on a Waters Symmetry® C-18. Up to 4.8 GBq (130 mCi) of [^{18}F]PBR111 could be obtained with specific radioactivities ranging from 74 to 148 GBq/µmol (2–4 Ci/µmol) in 75–80 min (HPLC purification and SepPak®-based formulation included), starting from a 37.0 GBq (1.0 Ci) [^{18}F]fluoride batch. Overall non-decay-corrected isolated yields were 8–13% (13–21% decay-corrected).

Keywords: fluorine-18; PBR111; PBR; TSPO

Introduction

Microglia activation is considered as the predominant cellular response to inflammation within the central nervous system.[1,2] This process is characterized by a drastic change in the morphology of these cells and by the notable overexpression on the outer mitochondrial membranes of the so-called peripheral benzodiazepine binding site, also known as peripheral benzodiazepine receptor[3] (PBR) or as recently proposed, translocator protein (18 kDa) or TSPO.[4] Since over two decades, these binding sites are clearly recognized and proposed as early markers of neuroinflammation, supporting extensive efforts into the design of radiolabelled TSPO-ligands for tomographic imaging. The radiolabelling of PK11195 with the positron-emitter carbon-11 in the mid-eighties paved the way to the current concept of positron emission tomography (PET) imaging of neuroinflammation using TSPO radioligands.[5] Today, [^{11}C]PK11195 is still used, but the short half-life of carbon-11 (20.38 min) is a limit for the dissemination and wide clinical use of this ligand. Moreover, [^{11}C]PK11195 displays a low brain uptake, a high level of non-specific binding (both leading to a poor signal-to-noise ratio) and an extensive binding to plasma proteins, which appears to complicate severely quantitative analysis of the receptor density with this ligand.

Often with the longer half-life positron-emitter fluorine-18 in mind (109.8 min), several compounds have been designed and synthesized in order to circumvent some of the limitations observed with PK11195.[6] They belong to different chemical classes among which two dominant families.[7,8] The first one is that of the *N*-benzyl-*N*-(2-phenoxyaryl)-acetamides (with only the fluorine-18-labelled candidates represented in Figure 1). This series results from the ring-opening of the atypical benzodiazepine 4′-chlorodiazepam (Ro 5-4864), and includes [^{18}F]FE-DAA1106.[9–17] The second one comprises derivatives structurally related to Alpidem, a compound known to recognize both the peripheral and central benzodiazepine binding sites. This class is constituted by a series of imidazo[1,2-*a*]pyridineacetamides (with [^{18}F]PBR102[18] and [^{18}F]PBR111[18]) as well as two bioisoteric series: the pyrazolo[1,5-*a*]pyrimidineacetamides (including [^{18}F]DPA-714[19–22]) and the imidazo[1,2-*b*]pyridazineacetamides ([^{18}F]PBR132[23,24]) (see Figure 1 for again only the fluorine-18-labelled candidates).

In the present work, the Zymate-XP-assisted radiosynthesis of [^{18}F]PBR111 ([^{18}F]-**1**, 2-(6-chloro-2-(4-(3-[^{18}F]fluoropropoxy)phenyl)imidazo[1,2-*a*]pyridin-3-yl)-*N*,*N*-diethylacetamide) from its tosyloxy derivative as precursor for the labelling with fluorine-18 is reported.

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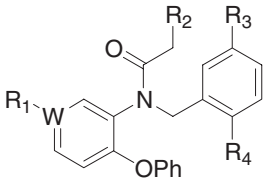
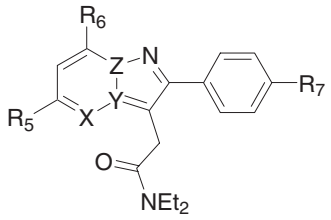
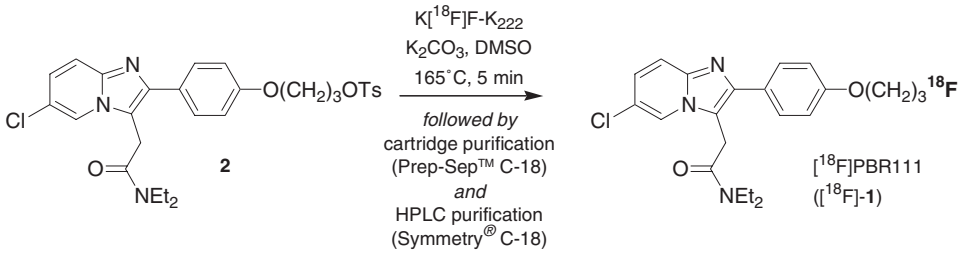


R_1	R_2	R_3	R_4	W	
H	^{18}F	OCH_3	OCH_3	C	[^{18}F]PBR06
^{18}F	H	OCH_3	OCH_3	C	[^{18}F]DAA1106
F	H	OCH_3	$OCH_2{}^{18}F$	C	[^{18}F]FMDAA1106
F	H	OCH_3	$OCD_2{}^{18}F$	C	[^{18}F]d_2FMDAA1106
F	H	OCH_3	$O(CH_2)_2{}^{18}F$	C	[^{18}F]FEDAA1106
-	H	H	$O(CH_2)_2{}^{18}F$	N	[^{18}F]FEPPA



R_5	R_6	R_7	X	Y	Z	
Cl	H	$O(CH_2)_2{}^{18}F$	C	N	C	[^{18}F]PBR102
Cl	H	$O(CH_2)_3{}^{18}F$	C	N	C	[^{18}F]PBR111
CH_3	CH_3	$O(CH_2)_2{}^{18}F$	N	C	N	[^{18}F]DPA-714
CH_3	CH_3	$O(CH_2)_3{}^{18}F$	N	C	N	[^{18}F]PBR146
^{18}F	H	$C(CH_3)_3$	N	N	C	[^{18}F]PBR132

Figure 1. Selected fluorine-18-labelled TSPO PET-radioligands including [^{18}F]PBR111 ([^{18}F]-**1**).



Scheme 1.

Results and discussion

PBR111 (**1**, 2-(6-chloro-2-(4-(3-fluoropropoxy)phenyl)imidazo-[1,2-*a*]pyridin-3-yl)-*N*,*N*-diethylacetamide) and its tosyloxy derivative **2** (2-(6-chloro-2-(4-(3-tosyloxypropoxy)phenyl)imidazo[1,2-*a*]pyridin-3-yl)-*N*,*N*-diethylacetamide) as precursor for labelling with fluorine-18 were both synthesized in nine chemical steps from 2-bromo-4′-methoxyacetophenone and 2-amino-5-chloropyridine by procedures, which have been reported elsewhere,[25] and were obtained in 8.7 and 11.6% overall yield, respectively.

PBR111 (**1**) was labelled with fluorine-18[26–31] at its 3-fluoropropyl moiety from the corresponding tosyloxy analog **2** using a one-step radiochemical process as outlined in Scheme 1.

Optimized fluorination with the cyclotron-produced [^{18}F]fluoride as the, no-carrier-added, activated K[^{18}F]F-Kryptofix®222 complex[32,33] was performed in DMSO using 6.8–7.6 μmol (3.9–4.3 mg) of the tosylate **2** at 165°C for 5 min in an open tube without stirring the contents. After cooling, 97 to over 99% of the initial radioactivity was still present. TLC analyses showed only one radioactive peak (R_f: 0.75, see experimental), co-migrating with PBR111 (**1**), beside a peak at R_f 0, assumedly [^{18}F]fluoride. The radiochemical yields (RCYs) of fluorine-18 incorporation, calculated from the TLC-radiochromatogram and defined as the ratio of radioactivity area of [^{18}F]-**1** over total radioactivity area, were about 30–50%. At this stage [^{18}F]-**1** was rapidly trapped and isolated from the water-diluted reaction mixture on a C-18 PrepSep™ cartridge, which does not retain the unreacted [^{18}F]fluoride. Then, [^{18}F]-**1** was eluted from the cartridge with CH_2Cl_2. It represented 25–45% of the total radioactivity amount engaged in the fluorination process and was more than 95% radiochemically pure according to radio-TLC. These values clearly confirmed the RCYs measured in the crude reaction mixture with radio-TLC. About 1–4% of the cartridge-trapped radioactivity remained on the cartridge after elution and less than 3% of the total starting radioactivity was left behind in the initial fluorination reactor tube. Finally, [^{18}F]-**1** was further purified by HPLC on a semi-preparative Symmetry® C-18 column (HPLC A, see experimental), using an acid buffered mixture of H_2O and CH_3CN as the eluent. Using these conditions, [^{18}F]-**1** (t_R: 13–14 min) could be obtained with a > 95% chemical and radiochemical purity and was completely separated from the remaining tosylate **2** (t_R: > 40 min). Final HPLC purification was also tried with a classical mixture of H_2O, CH_3CN and TFA as the eluent, on this column as well as on semi-preparative X-Terra™ RP18 and SunFire™ C18 columns with however poor results in terms of final chemical purity (<75%).

Formulation of [^{18}F]PBR111 ([^{18}F]-**1**) as an *i.v.* injectable solution was performed using a homemade SepPak® Plus C18 device. The HPLC-collected fraction containing the radiotracer was diluted with water and the resulting solution was passed through a C18 SepPak® cartridge. The cartridge was then washed with water, partially dried with nitrogen and finally eluted with ethanol followed by physiological saline. The solution was then sterile-filtrated and diluted with physiological saline to an ethanol concentration below 10%.

Quality controls of [^{18}F]PBR111 ([^{18}F]-**1**) were performed on an aliquot of the preparation ready for *i.v.* injection. The radiotracer preparation was a clear and colourless solution with a measured pH between 5 and 7. As demonstrated by analytical HPLC analysis (HPLC B, see experimental), the radiotracer preparation was found to be > 95% chemically and radiochemically pure (**1**, t_R: 3.08 min, HPLC B). The preparation was also shown to be free of the non-radioactive precursor, the tosylate **2**

(t_R: 13.55 min, HPLC B; t_R: 2.27 min, HPLC C), and was chemically and radiochemically stable for at least 120 min.

LogP (*n*-octanol/water partition coefficient) and logD (*n*-octanol/buffer pH 7.4 partition coefficient) of [^{18}F]PBR111 ([^{18}F]-**1**) were measured using the shake-flask method and values of 2.14 and 2.07 were found, respectively.

Conclusion

The novel imidazo[1,2-*a*]pyridine PBR111 (**1**) has been labelled with fluorine-18 using our Zymate-XP robotic system by a simple one-step tosyloxy-for-fluorine nucleophilic aliphatic substitution. Typically, 3.0–4.8 GBq (80–130 mCi) of [^{18}F]PBR111 ([^{18}F]-**1**) could be obtained with specific radioactivities ranging from 74 to 148 GBq/μmol (2–4 Ci/μmol) in 75–80 min (HPLC purification and SepPak®-based formulation included), starting from a 37.0 GBq (1.0 Ci) [^{18}F]fluoride batch (overall non-decay-corrected isolated yields were 8–13% (13–21% decay-corrected)). *In vivo* pharmacological and imaging properties of [^{18}F]PBR111 are currently evaluated in a rat-model of neuroinflammation (unilateral intrastriatal injection of AMPA) using a small-animal dedicated PET tomograph (Focus Concorde 220) and data will be compared to that already reported for [^{11}C]PK11195, [^{11}C]DPA-713 and [^{11}C]CLINME.[34,35]

Experimental

General

Chemicals, flash chromatography and TLC analysis: Chemicals were purchased from Aldrich, Fluka or Sigma, France and were used without further purification, unless otherwise stated. Flash chromatographies were conducted on silica gel or alumina gel (0.63–0.200 mm, VWR) columns. TLCs were run on pre-coated plates of silica gel 60F_{254} (VWR). The compounds were localized when possible at 254 nm using a UV-lamp and/or by dipping the TLC-plates in a 1% ethanolic ninhydrin solution or a 1% MeOH/H_2O (1/1, v:v) FeCl3 solution and heating on a hot plate. Radioactive spots were detected using a Berthold TraceMaster 20 automatic TLC linear analyser.

Spectroscopies: NMR spectra were recorded on a Bruker Advance (400 MHz) apparatus using the hydrogenated residue of the deuterated solvent CD_3CN ($\delta = 1.93$ ppm) or TMS ($\delta = 0.0$ ppm) as internal standards for ^{1}H-NMR as well as the deuterated solvents CD_3CN ($\delta = 118.2$ and 1.3 ppm) or DMSO-d_6 ($\delta = 39.5$ ppm) as internal standard for ^{13}C-NMR. The chemical shifts are reported in ppm, downfield from TMS (s, d, t, q, m for singlet, doublet, triplet, quadruplet and multiplet, respectively). The mass spectra were measured on a Micromass ZMD quadrupole mass spectrometer.

HPLC analysis [HPLC A]: Equipment: system equipped with a Waters 600 pump and a Waters 600 Controller, a Shimadzu SPD10-AVP UV-multi-wavelength detector and a miniature ionization chamber probe; column: semi-preparative Symmetry® C-18, Waters (300 × 7.8 mm); porosity: 7 μm; eluent H_2O/CH_3CN: 60/40 (v/v) containing Low-UV PIC® B7 reagent (20 mL for 1000 mL); flow rate: 5 mL/min; temperature: RT; absorbance detection at $\lambda = 254$ nm. [HPLC B]: Equipment: Waters Alliance 2690 (or a Waters binary HPLC pump 1525) equipped with a UV spectrophotometer (Photodiode Array Detector, Waters 996) and a Berthold LB509 radioactivity detector; column: analytical Symmetry-M® C-18, Waters (50 × 4.6 mm); porosity: 5.0 μm; conditions: isocratic elution with solvA/solvB: 50/50 (v/v) [solvent A: H_2O containing Low-UV PIC® B7 reagent (20 mL for 1000 mL); solvent B: H_2O/CH_3CN: 30:70 (v/v) containing Low-UV PIC® B7 reagent (20 mL for 1000 mL)]; flow rate: 2.0 mL/min; temperature: RT; absorbance detection at $\lambda = 254$ nm. [HPLC C]: Equipment: Waters Alliance 2690 (or a Waters binary HPLC pump 1525) equipped with a UV spectrophotometer (Photodiode Array Detector, Waters 996) and a Berthold LB509 radioactivity detector; column: analytical Symmetry-M® C-18, Waters (50 × 4.6 mm); porosity: 5.0 μm; conditions: isocratic elution with solvA/solvB: 30/70 (v/v) [solvent A: H_2O containing Low-UV PIC® B7 reagent (20 mL for 1000 mL); solvent B: H_2O/CH_3CN: 30:70 (v/v) containing Low-UV PIC® B7 reagent (20 mL for 1000 mL)]; flow rate: 2.0 mL/min; temperature: RT; absorbance detection at $\lambda = 254$ nm.

Radioisotope production: No-carrier-added fluorine-18 (half-life: 109.8 min) was produced via the [^{18}O(p,n)^{18}F] nuclear reaction by irradiation of a 2 mL [^{18}O]water target (>97% enriched, Rotem (CortecNet, Paris, France)) on an IBA Cyclone-18/9 (IBA, Louvain-la-Neuve, Belgium) cyclotron (18 MeV proton beam) and the aqueous radioactive solution was then transferred to the appropriate hot cell. *Target hardware*: commercial, 2 mL, two-port, stainless steel target holder equipped with a domed-end niobium cylinder insert. *Target to hot cell liquid-transfer system*: 60 m PTFE line (0.8 mm internal diameter; 1/16 in external diameter), 2.0 bar helium drive pressure, transfer time 3–6 min. Typical production of [^{18}F]fluoride at the end of bombardment for a 20 μA, 30 min (10 μA h) irradiation: 27.7–29.6 GBq (750–800 mCi).

Miscellaneous: Radiosyntheses using fluorine-18, including the HPLC purifications, were performed in a shielded cell (7.5 cm lead) using a computer assisted Zymate-XP robot system (Zymark corporation, USA).

Chemistry

2-(6-chloro-2-(4-(3-fluoropropoxy)phenyl)imidazo[1,2-a]pyridin-3-yl)-N,N-diethylacetamide (*PBR111,* ***1***): Synthesized from 2-bromo-4′-methoxyacetophenone and 2-amino-5-chloropyridine according to reference.[25] R_f: 0.75 (SiO_2-TLC (EtOAc)). t_R: 13–14 min (HPLC A), 3.08 min (HPLC B), 1.03 min (HPLC C). mp 160–162°C. ^{1}H NMR (CD_3CN) δ: 1.13 (t, $J = 7.1$ Hz, 3 H), 1.18 (t, $J = 7.1$ Hz, 3 H), 2.20 (m, 2 H), 3.40 (q, $J = 7.1$ Hz, 2 H), 3.44 (q, $J = 7.1$ Hz, 2 H), 4.11 (s, 2 H), 4.17 (t, $J = 6.2$ Hz, 2 H), 4.67 (dt, $J = 47.3$, 5.9 Hz, 2 H), 7.05 (d, $J = 8.8$ Hz, 2 H), 7.24 (dd, $J = 9.5$, 2.0 Hz, 1 H), 7.54 (dd, $J = 9.5$, 0.8 Hz, 1 H), 7.58 (d, $J = 8.8$ Hz, 2 H), 8.24 (dd, $J = 2.0$, 0.8 Hz, 1 H). ^{13}C NMR (CD_3CN) δ: 13.3, 14.5, 29.9 (d, $J = 19.9$ Hz), 30.2, 41.1, 42.9, 64.7 (d, $J = 5.4$ Hz), 80.9 (d, $J = 161.4$ Hz), 115.6, 117.3, 118.1, 120.1, 123.6, 125.6, 128.0, 130.3, 143.8, 145.1, 159.6, 168.0. MS ES(+) *m/z* 418 (M+1).

2-(6-chloro-2-(4-(3-tosyloxypropoxy)phenyl)imidazo[1,2-a]pyridin-3-yl)-N,N-diethylacetamide (***2***): Synthesized from 2-bromo-4′-methoxyacetophenone and 2-amino-5-chloropyridine according to reference.[25] t_R: 42–45 min (HPLC A), 13.55 min (HPLC B), 2.27 min (HPLC C). mp 150–152°C. ^{1}H NMR (CD_3CN) δ: 1.15 (t, $J = 7.0$ Hz, 3 H), 1.23 (t, $J = 7.0$ Hz, 3 H), 2.08 (m, 2 H), 2.38 (s, 3 H), 3.38 (q, $J = 7.0$ Hz, 2 H), 3.42 (q, $J = 7.0$ Hz, 2 H), 3.96 (t, $J = 5.8$ Hz, 2 H), 4.10 (s, 2 H), 4.22 (t, $J = 5.8$ Hz, 2 H), 6.88 (d, $J = 8.8$ Hz, 2 H), 7.25 (dd, $J = 9.6$, 1.8 Hz, 1 H), 7.33 (d, $J = 8.0$ Hz, 2 H), 7.53 (d, $J = 8.8$ Hz, 2 H), 7.54 (d, $J = 9.6$ Hz, 1 H), 7.75 (d, $J = 8.0$ Hz, 2 H), 8.24 (d, $J = 1.8$ Hz, 1 H). ^{13}C NMR (DMSO-d_6) δ: 13.0, 14.1, 21.0, 28.1, 28.6, 37.8, 41.6, 63.1, 67.5, 114.5, 116.4, 117.0, 118.6, 123.0,

125.4, 126.5, 127.5, 128.9, 130.1, 132.1, 142.3, 143.2, 144.8, 157.8, 167.0. MS ES(+) *m/z* 570 (M+1).

Radiochemistry

Preparation of the K[^{18}F]F-K$_{222}$-complex: No-carrier-added cyclotron-produced fluorine-18 was isolated as [^{18}F]fluoride ion by passing the irradiated [^{18}O]water target, using helium pressure (1.5–2.0 bar), through an anion exchange resin (SepPak® Light Waters Accell™ Plus QMA cartridge, chloride form, beforehand washed with 1 M aq. $NaHCO_3$ (2 mL) and rinsed with water (20 mL) and CH_3CN (10 mL)). Helium was blown through the column to maximally extract [^{18}O]water. The [^{18}F]fluoride ion was then eluted from the resin, using an aq. K_2CO_3 solution (1.0 mL of a 4.5 mg/mL solution), into a Vacutainer® tube containing Kryptofix®222 (K_{222}: 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane, 12.0–15.0 mg). The resulting solution was then gently concentrated to dryness at 145–150°C under a nitrogen stream for 10 min to give no-carrier-added K[^{18}F]F-K$_{222}$ complex as a white semi-solid residue.

Preparation of 2-(6-chloro-2-(4-(3-[^{18}F]fluoropropoxy)phenyl)-imidazo[1,2-a]pyridin-3-yl)-N,N-diethylacetamide ([^{18}F]PBR111, [^{18}F]-**1**): *Fluorine-18 incorporation and HPLC purification*. DMSO (600 μL) containing **2** (3.9–4.3 mg, 6.8–7.6 μmol) was added into the Vacutainer® tube containing the dried K[^{18}F]F-K$_{222}$ complex. The tube (open) was thoroughly vortexed (30 s) and then placed in a heating block (at 165°C, for 5 min) without stirring the contents. The reaction vessel was then cooled using an ice-water bath, the remaining radioactivity was measured and the reaction mixture was analysed by radio-TLC. The reaction yield was calculated from the TLC-radiochromatogram and defined as the ratio of radioactivity area of [^{18}F]PBR111 ([^{18}F]-**1**) over total fluorine-18 radioactivity area (SiO_2-TLC (EtOAc): R_f: [^{18}F]-**1**: 0.75 - R_f: [^{18}F]fluoride ion: 0.0). The reaction mixture was then diluted with water (1 mL) and transferred onto a C18 cartridge (PrepSep™ R-C18 Extraction Column, Fisher Scientific, activated beforehand with EtOH (2 mL) and then rinsed with water (10 mL)), pre-filled with water (2 mL). The tube was rinsed twice with water (1 mL), which was also transferred and added to the diluted reaction mixture on top of the cartridge. An additional portion of water (2 mL) was further added to the diluted reaction mixture on top of the cartridge. The whole was then passed through the cartridge, which was then washed with water (3 mL) and partially dried for 0.5 min by applying a nitrogen stream. [^{18}F]-**1** was eluted from the cartridge with CH_2Cl_2 (3 mL) into an empty 5 mL reaction vial. Elution was repeated twice with 1 mL of CH_2Cl_2 for maximal transfer of [^{18}F]-**1**. The incorporation yield was estimated after the C18 cartridge elution by the CH_2Cl_2 over total eluted radioactivity (DMSO/H_2O+CH_2Cl_2) ratio. The CH_2Cl_2 solution was then concentrated to dryness at 65–75°C under a gentle nitrogen stream for 3–5 min. Finally, the residue was re-dissolved in the HPLC solvent used for purification (1.0 mL) and the solution was injected onto HPLC (HPLC A).

Formulation: Formulation of the labelled product for *i.v.* injection was effected as follows: The HPLC-collected fraction containing the radiotracer was diluted with water (30 mL). The resulting solution was passed through a SepPak® Plus C18 cartridge (Waters, washed with 2 mL of EtOH and then rinsed with 10 mL of water prior to use). The cartridge was washed with water (10 mL) and partially dried by applying a nitrogen stream for 10 s. The radiotracer was eluted with 2 mL of EtOH followed by 8 mL of physiological saline (less than 10% of the total radioactivity was left on the cartridge) and filtered on a 0.22 μm GS-Millipore filter (vented). Finally, physiological saline was added to take the EtOH concentration below 10%. This whole process was performed using a remote-controlled dedicated homemade device based on a literature procedure.[36]

Quality control: The radiotracer preparation was visually inspected for clarity, absence of colour and particulates. An aliquot of the preparation was taken for determination of pH using standard pH-paper. Chemical and radiochemical purities were also assessed on this aliquot by HPLC (HPLC B and C), with a sample of authentic **1**. Particular attention was paid to the absence of non-radioactive precursor **2**. Chemical and radiochemical stability of the entire preparation were tested by HPLC (HPLC B) at regular 15 min intervals during 150 min. Specific radioactivity of the radiotracer was calculated from three consecutive HPLC (HPLC B) analyses (average) and determined as follows: the area of the UV absorbance peak corresponding to the radiolabelled product was measured (integrated) on the HPLC chromatogram and compared to a standard curve relating mass to UV absorbance. The specific radioactivity follows from the found mass and the associated collected radioactivity.

LogP/logD determination: LogP (*n*-octanol/water partition coefficient): [^{18}F]-**1** (1 to 5 kBq in 50 μL of water) was added to a two-layer system of *n*-octanol (500 μL) and water (450 μL) in an Eppendorf cap. The vessel was strongly vortexed for 3 min and then quickly centrifuged at 3000 rpm for 2 min. An aliquot of each layer (100 μL) was assessed for radioactivity in a cross-calibrated Perkin-Elmer Cobra Quantum γ-counter (Les Ulis, France). LogD (*n*-octanol/buffer pH 7.4 partition coefficient): The procedure described above was repeated by replacing water (450 μL) by 0.1 M PBS buffer pH 7.4 (450 μL). The partition coefficients (logP and logD) were calculated as the decimal logarithm of the ratio between the counted radioactivity in the *n*-octanol phase and the counted radioactivity in the aqueous phase.

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