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Research Article

Synthesis of 1,1′ [^{11}C]-methylene-di-(2-naphthol) ([^{11}C]ST1859) for PET studies in humans

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Summary

1,1′-Methylene-di-(2-naphthol) (ST1859), a candidate drug for the treatment of Alzheimer's disease, was radiolabelled with carbon-11 with the aim to perform PET microdosing studies in humans. The radiosynthesis was automated in a commercial synthesis module (Nuclear Interface PET tracer synthesizer) and proceeded via reaction of [^{11}C]formaldehyde with 2-naphthol. [^{11}C]formaldehyde was prepared by catalytic dehydrogenation of [^{11}C]methanol (conversion yield: $48 \pm 11\%$ ($n = 19$)) employing a recently developed silver-containing ceramic catalyst. Starting from 69 ± 3 GBq of [^{11}C]carbon dioxide ($n = 19$), 4 ± 1 GBq of [^{11}C]ST1859 (decay-corrected to the end of bombardment), readily formulated for intravenous administration, could be obtained in an average synthesis time of 38 min. The specific radioactivity of [^{11}C]ST1859 at the end of synthesis exceeded 32 GBq/μmol.

Key Words: [^{11}C]formaldehyde; 1,1′-methylene-di-(2-naphthol); PET; microdosing

Introduction

1,1′-Methylene-di-(2-naphthol) (ST1859, Figure 1), which prevents *in vitro* the aggregation and fibril formation of β-amyloid peptides, is currently developed as a potential drug to treat Alzheimer's disease.[1] It has been shown that the carbon-14-labelled compound ([^{14}C]ST1859) rapidly crosses the blood–brain

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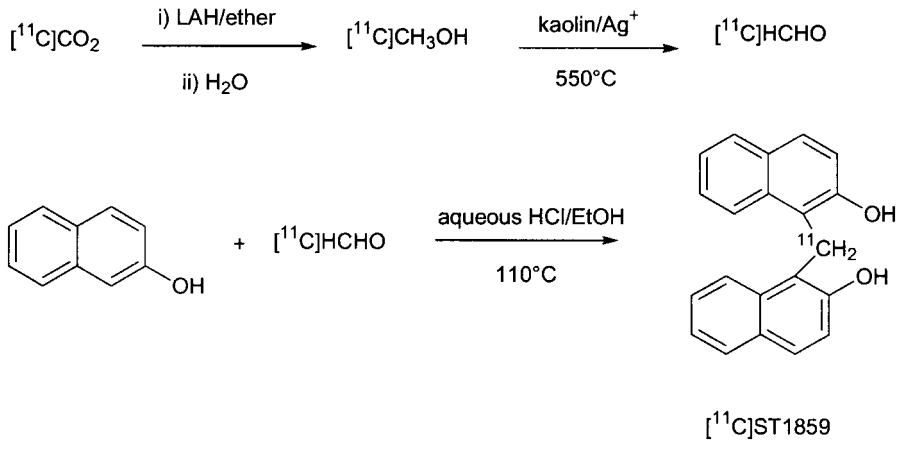

Figure 1. Reaction scheme for the radiosynthesis of [^{11}C]ST1859

barrier of rats, achieving several-fold higher concentrations in brain than in plasma.[1] Positron emission tomography (PET) with carbon-11- or fluorine-18-labelled drugs has proven a useful method to study the tissue distribution of drug candidates in humans (microdosing studies).[2] The aim of the present work was to develop a synthesis of carbon-11-labelled ST1859 (i.e. [^{11}C]ST1859), which is intended to be used for investigating the brain penetration, the pharmacokinetics and the peripheral metabolism of ST1859 in healthy subjects and patients with Alzheimer's disease.

When inspecting the structure of ST1859 (Figure 1), the methylene bridge appears to be the only possible position for radiolabelling with ^{11}C. In analogy to the previously published synthesis of [^{14}C]ST1859,[3,4] we therefore planned to synthesize [^{11}C]ST1859 by reacting 2-naphthol with [^{11}C]formaldehyde (Figure 1). [^{11}C]formaldehyde, which has been used as an intermediate in the synthesis of diverse carbon-11-labelled PET tracers, has previously been prepared using different methods, such as catalytic oxidation[5–7] or enzymatic conversion of [^{11}C]methanol.[8] Roeda and Dollé have recently developed a new method for the synthesis of [^{11}C]formaldehyde,[9] which is based on the dehydrogenation of [^{11}C]methanol using a new silver-containing ceramic catalyst.[10] In the present work, we describe our experience with adapting a commercial synthesis module to the preparation of [^{11}C]formaldehyde, using the method described by Roeda, and the subsequent synthesis and purification of [^{11}C]ST1859. Moreover, an HPLC system suitable for the analysis of radiolabelled metabolites was developed.

Results and discussion

In analogy to the synthesis of the carbon-14-labelled compound, where [^{14}C]formaldehyde was coupled with 2-naphthol,[3,4] [^{11}C]ST1859 was

synthesized by reacting 2-naphthol with [^{11}C]formaldehyde (Figure 1). [^{11}C]formaldehyde, the key intermediate of the radiosynthesis, was produced employing a recently published method that proceeded via catalytic oxidation of [^{11}C]methanol (Figure 1).[9,10] The synthetic procedure was performed in a commercial synthesis module that had been upgraded with a commercial tube furnace. The furnace was integrated into the flow system as shown in Figure 2. [^{11}C]methanol was produced using the classical approach via reduction of cyclotron-produced [^{11}C]carbon dioxide followed by hydrolysis of the [^{11}C]methoxy lithium aluminium hydride (LAH) complex with water (Figure 1).[7,11] However, whereas in most literature examples[7,11] tetrahydrofuran (THF) was used as a solvent for the reduction of [^{11}C]carbon dioxide, diethyl ether was the preferred solvent in the present work. This was because HPLC analysis of final [^{11}C]ST1859 showed that the specific radioactivity of the radiotracer was about 10–50-fold higher for the use of diethyl ether as compared to syntheses with THF. This observation confirms the assumption that traces of THF carried along with the vector gas might serve as a source of unlabelled formaldehyde by decomposition on the silver catalyst.[9] The trapping efficiency of LAH in diethyl ether for [^{11}C]carbon dioxide was lower than that of THF ($\sim$70% for LAH/diethyl ether versus $>$95% for LAH/THF) (Table 1). This was counterbalanced by the fact that owing to the lower boiling point of diethyl ether (36°C) compared to THF (65–67°C) lower temperatures could be used for the removal of solvent, which resulted in

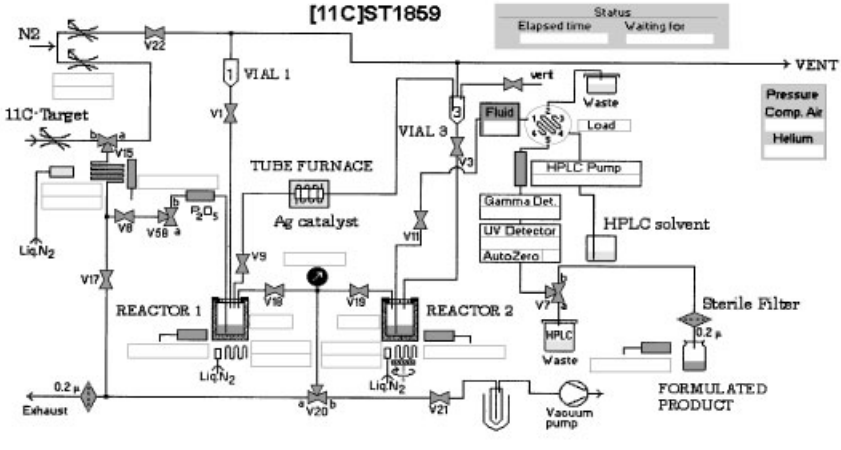

Figure 2. Schematic outline of the flow system for the synthesis of [^{11}C]ST1859. The synthesis was automated in an adapted Nuclear Interface PET tracer synthesizer. The shown scheme is modified from the original furnished with the synthesis module, where those parts that are not used in the radiosynthesis are not shown

Table 1. Radioactivity balance for the synthesis of [^{11}C]ST1859 employing the optimized reaction conditions (see Experimental part)

Step	% Radioactivity	Elapsed time (min)
[^{11}C]carbon dioxide produced in cyclotron	100	0
Trapped in reactor 1	73 ± 9	7
Reactor 1 after evaporation and hydrolysis	71 ± 9	11
Remaining in reactor 1 after distillation	9 ± 4	18
Transferred to reactor 2 after distillation	27 ± 5	18
Reactor 2 after coupling reaction	23 ± 6	28
Formulated product	6 ± 2	38

The percent of radioactivity based on cyclotron-produced [^{11}C]carbon dioxide and the elapsed time after individual steps of the synthesis are stated. All values are decay-corrected to the end of bombardment and represent the mean ± standard deviation of 19 radiosyntheses.

smaller losses of radioactivity during evaporation (< 5% loss for diethyl ether versus ~20% loss for THF) (Table 1). After removal of the solvent, the [^{11}C]methoxy LAH complex was hydrolysed with water. HPLC analysis (system B) showed that [^{11}C]methanol was the only radiolabelled product contained in the reaction mixture. The formed [^{11}C]methanol was then distilled over the heated silver catalyst using the optimized conditions described by Roeda (carrier gas flow rate: 40 ml/min, oven temperature: 550°C, catalyst bed length: 5 mm).[9] About one-half of the radioactivity liberated from reactor 1 was collected in the aqueous trapping solution, whereas the remainder was lost in the tubing (Table 1). A possible explanation for the radioactivity losses was the condensation of water vapour in the tubing, which presumably trapped [^{11}C]methanol and [^{11}C]formaldehyde. Therefore, we tried to keep the tubing going into and coming from the furnace as short as possible. Moreover, the aqueous trapping solution was not directly placed into reactor 2 but rather into vial 3, which represented a shorter path length and avoided the use of an additional valve (Figure 2). As a further measure to reduce heat loss, the tubing and the connecting parts of the glass tube were wrapped with aluminium foil. Two different methods of hydrolysing the [^{11}C]methoxy LAH complex were tested, i.e. the use of water alone and the use of di(ethyleneglycol)butylether containing 1% water.[9] The percentage of radioactivity (based on liberated [^{11}C]methanol) distilled into vial 3 appeared to be higher when di(ethyleneglycol)butylether/water (99/1) was used (60–70% versus 40–60% for water alone). However, HPLC analysis (system B) showed that for hydrolysis with water almost all the trapped radioactivity (> 90%) represented [^{11}C]formaldehyde, whereas for di(ethyleneglycol)butylether/water unreacted [^{11}C]methanol accounted for 50–60% of the trapped radioactivity. Results from the HPLC analysis were in good agreement with the percentage of [^{11}C]formaldehyde determined with the dimedone precipitation method.[9] This observation indicated that the amount of potential radiolabelled

byproducts that co-eluted on HPLC (system B) with [^{11}C]formaldehyde (i.e. [^{11}C]formic acid) was negligible.[9] Using the optimized conditions (i.e. LAH in diethyl ether and water for hydrolysis), 19 ± 4 GBq ($n = 19$) of [^{11}C]formaldehyde (decay-corrected to the end of bombardment, EOB) could be obtained starting from 69 ± 3 GBq of [^{11}C]carbon dioxide in a synthesis time of 17–20 min. The average [^{11}C]formaldehyde conversion yield based on liberated [^{11}C]methanol ($48 \pm 11\%$, $n = 19$) was in the same range as the yield reported by Roeda and Dolle (54%).[9]

The next step of the radiosynthesis was the coupling of [^{11}C]formaldehyde with 2-naphthol using acidic reaction conditions (Figure 1).[4] HPLC analysis (system C) showed that after 8 min of heating at 110°C the desired product [^{11}C]ST1859, whose identity was verified by co-injection of the non-labelled reference compound, represented 30–40% of total radioactivity contained in the crude reaction mixture. The remainder of radioactivity was distributed in about equal parts between unreacted [^{11}C]formaldehyde and an unidentified hydrophilic by-product. This by-product eluted closely after [^{11}C]formaldehyde on HPLC system C and was not identical to 1-hydroxy[^{11}C]methyl-2-naphthol (i.e. the product resulting from a single 2-naphthol addition to [^{11}C]formaldehyde). In an attempt to improve the incorporation yield of [^{11}C]formaldehyde, the reaction temperature was varied between 70 and 150°C. Whereas low temperature caused even lower incorporation yields, higher temperatures resulted in losses of volatile radioactivity in the course of the reaction. Reaction times longer than 8 min were considered unpractical due to the short physical half-life of ^{11}C. We also tried the use of alkaline (i.e. aqueous potassium hydroxide) reaction conditions[3] as an alternative to the acidic conditions, which also failed to give improved yields.

Crude [^{11}C]ST1859 was purified by semipreparative HPLC (system A) using aqueous ethanol as a mobile phase. The collected production fraction could be directly formulated for intravenous administration, thus obviating the need for a time-consuming removal of solvents by rotary evaporation or solid-phase extraction. The employed Chromolith Performance RP-18e HPLC column was well suited for chromatography with highly viscose ethanol/water mixtures, which are often problematic to use with conventional C18 columns due to high back pressure. Starting from 69 ± 3 GBq of [^{11}C]carbon dioxide ($n = 19$), 4 ± 1 GBq of [^{11}C]ST1859 (decay-corrected to EOB), readily formulated for intravenous administration, could be obtained in an average synthesis time of 38 min. The radiochemical purity of the product always exceeded 99%. The content of unlabelled ST1859 in the formulated product solution (total volume: 20–22 ml) was < 0.5 μg/ml, which corresponded to a specific radioactivity > 32 GBq/μmol at the end of synthesis (EOS).

[^{11}C]ST1859 was formulated for intravenous administration in physiological saline/ethanol (85/15). When stored at room temperature and unprotected

from light the radiotracer was found to be stable for at least 4 h after EOS as assessed by HPLC (system D). Angelini *et al.* have reported that carbon-14-labelled ST1859 decomposed in aqueous acetonitrile under light exposure to unlabelled 1,2-diethynylbenzene and 1,3-butadinylbenzene, a process which proceeded via 1-hydroxy[^{14}C]methyl-2-naphthol as an intermediate.[4] In the course of our stability test, 1-hydroxy[^{11}C]methyl-2-naphthol could not be detected, as confirmed by HPLC co-injection of the commercially available, non-labelled reference compound. [^{11}C]ST1859 was also found to be stable when incubated in human plasma for 2 h at 37°C. HPLC system D was developed for the future analysis of radiolabelled metabolites in human plasma samples obtained during PET studies. We used acetonitrile for the precipitation of plasma proteins, which afforded better (>90%) recovery of radioactivity than the use of methanol (50–60% recovery) or 20% aqueous perchloric acid (~10% recovery). The supernatant obtained after protein precipitation was diluted with water and could then be directly injected into the HPLC system, which avoided a time-consuming evaporation of solvent. The whole procedure for work-up and analysis of a plasma sample took about 15 min. This assay was therefore well suited for the rapid processing of plasma samples, which is a prerequisite for metabolite studies with carbon-11-labelled tracers. As a measure of lipophilicity, the log *D* of [^{11}C]ST1859 was determined by a shake-flask method described by Wilson *et al.*[12] We took care to pre-wash the radiotracer solution in 1-octanol several times with phosphate-buffered saline, in order to remove small amounts of hydrophilic impurities that are known to cause considerable errors in log *P* determinations employing radiotracers.[12] The log *D* of [^{11}C]ST1859 at pH 7.4 was 3.12 ± 0.07 ($n = 5$).

Experimental

Reagents

1,1′-Methylene-di-(2-naphthol) (ST1859) and 2-naphthol were obtained from Sigma Tau Industrie Farmaceutiche Riunite (Italy). LAH in tetrahydrofuran (0.1 M, low ^{12}C content) was bought from ABX advanced biochemical compounds (Germany). A solution of 0.1 M LAH in diethyl ether was prepared from LAH in diethyl ether (1.0 M) and dry diethyl ether (both from Sigma-Aldrich) and stored in 1 ml portions under nitrogen in sealed glass vials. 1-Hydroxymethyl-2-naphthol was purchased from ChemPacific Corporation (USA). All other chemicals were obtained from Sigma-Aldrich Chemie GmbH (Germany) or Merck KGaA (Germany) and used without further purification.

Catalyst preparation

Silver-containing ceramic catalyst (silver content: 20%) was prepared as described in the literature.[9,10] The catalyst (85–100 mg) was placed between

wads of glass wool (catalyst bed length: 5 mm) in the middle section of a custom-made quartz tube (total length: 300 mm, diameter: 10 mm; middle section: length: 50 mm, diameter: 5 mm). The glass tube was horizontally placed in a Carbolite MTF 10/15/130 tube furnace (Carbolite GmbH, Germany) which was integrated into the flow system as shown in Figure 2. The connecting parts of the glass tube and the tubing leading into and out of the furnace were wrapped with aluminium foil in order to reduce heat loss and premature condensation of the distilled radioactivity. Immediately before the experiment, the catalyst was conditioned under a dry nitrogen stream (20 ml/min) by heating at 550°C for 2–3 h.

Production of [^{11}C]carbon dioxide

[^{11}C]carbon dioxide was produced in a PETtrace cyclotron (General Electrics, USA) via the $^{14}N(p,\alpha)^{11}C$ nuclear reaction using a nitrogen + 0.5% oxygen gas target. Typically, an irradiation duration of 35–40 min with a beam current of 55 μA yielded 65–70 GBq of [^{11}C]carbon dioxide.

Radiosynthesis of 1,1′ [^{11}C]-methylene-di-(2-naphthol) ([^{11}C]ST1859)

The radiosynthesis was performed in a PET tracer synthesizer for [^{11}C]-methylation (Nuclear Interface GmbH, Münster, Germany; now sold as General Electrics TRACERlab FX_c module), a commercial synthesis unit for the production of ^{11}C-labelled compounds. Pure nitrogen gas (99.9999%) was used as a carrier gas. The synthesis unit was adapted for the synthesis of [^{11}C]ST1859 as shown in Figure 2. Cyclotron-produced [^{11}C]carbon dioxide was frozen out in a stainless-steel loop cooled with liquid nitrogen to −150°C. The loop was then heated to 0°C and the released [^{11}C]carbon dioxide was swept by the carrier gas (flow rate: 4–6 ml/min) through a phosphorus pentoxide (3 g of P_2O_5) trap into reactor 1 (cooled to 0°C) which contained either 0.2 ml of LAH (0.1 M) in diethyl ether or 0.1 ml of LAH (0.1 M) in tetrahydrofuran (THF). When LAH in diethyl ether was used, the mixture was left to react for 30 s at 20°C and then evaporated to dryness by heating to 90°C for 40 s (nitrogen flow rate: 30 ml/min). For LAH in THF, the reaction mixture was directly evaporated to dryness by heating to 170°C for 40 s (nitrogen flow rate: 30 ml/min). After the evaporation of solvent, reactor 1 was cooled to 10°C. Afterwards, either water (0.1 ml) or di(ethyleneglycol)butylether/water (99/1, v/v, 0.3 ml) was added to reactor 1 via vial 1 (prior to use both liquids had been deoxygenated by bubbling nitrogen gas for 10 min). Reactor 1 was then heated to 200°C and the released [^{11}C]methanol was swept by the nitrogen stream (40 ml/min) for 6 min over the heated (550°C) silver catalyst. The radioactivity was trapped in vial 3, which contained a mixture of

2 N aqueous hydrochloric acid and ethanol (0.5 + 0.2 ml). After trapping, the solution was transferred into reactor 2 containing about 5 mg of 2-naphthol (35 μmol) dissolved in 0.2 ml of ethanol. When alkaline reaction conditions were used, the [^{11}C]formaldehyde was trapped in 0.5 ml of water in vial 3 and then transferred to reactor 2 containing 2-naphthol dissolved in 2 M aqueous potassium hydroxide solution (0.2 ml). The reaction mixture was heated for 8 min at 110°C. The crude mixture was then cooled and injected onto a built in semipreparative high-performance liquid chromatography (HPLC) system. A Chromolith Performance RP-18e 100-4.6 mm HPLC column (Merck KGaA, Germany) was eluted isocratically with a 40/60 (v/v) mixture of ethanol and water (both pharmacopoeia-grade) at a flow rate of 5 ml/min (system A). The eluate was monitored in series for UV absorption (wavelength: 254 nm) and for radioactivity. The fraction (6–8 ml) containing pure [^{11}C]ST1859, which eluted with a retention time of 7–8 min (Figure 3), was passed on-line over a vented sterile Millex-GS filter (0.22 μm, Millipore Corporation, Bedford, USA) into a 25 ml sterile vial (TechneVial, Mallinckrodt Medical B.V., Petten, The Netherlands) containing 14 ml of physiological saline solution (0.9%, w/v).

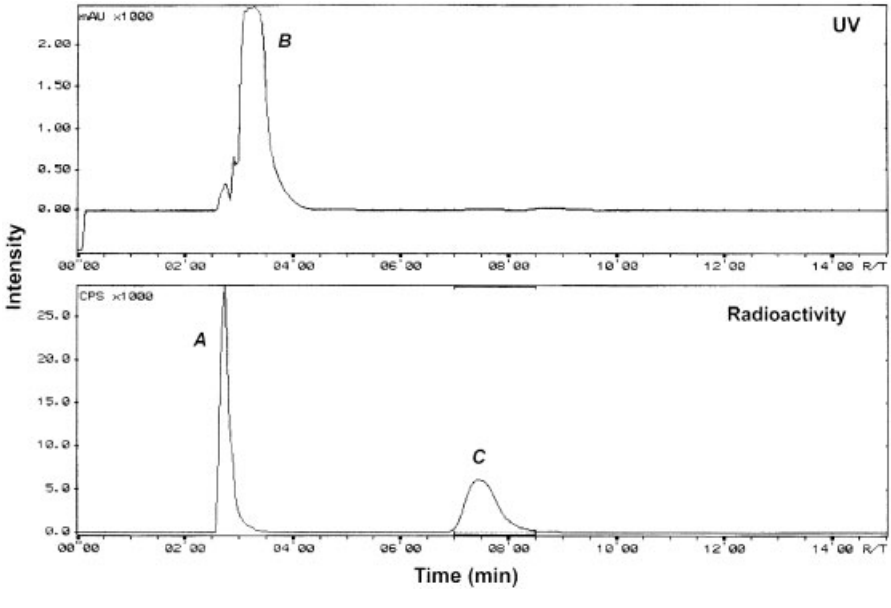

Figure 3. Semipreparative HPLC chromatogram for the purification of crude [^{11}C]ST1859. A Chromolith Performance RP-18e 100-4.6 mm column was eluted with ethanol/water (40/60, v/v) at a flow rate of 5 ml/min (system A). (A) Unreacted [^{11}C]formaldehyde and unidentified hydrophilic by-product, (B) precursor 2-naphthol, (C) [^{11}C]ST1859

Analytical procedures

The radioactivity trapped in vial 3 after passage of [^{11}C]methanol over the silver catalyst was analysed by HPLC using an Aminex HPX-87H (300 mm × 7.8 mm, Bio-Rad Laboratories, USA) column (system B). The column was heated to 44°C and eluted with 1 mM aqueous sulphuric acid (flow rate: 0.6 ml/min) employing a refractive index and a radioactivity detector. The retention times of [^{11}C]formaldehyde and [^{11}C]methanol were 16–17 and 22–23 min, respectively. In some cases, aliquots of the aqueous trapping solution were additionally analysed by a dimedone precipitation method described in the literature.[9] In this assay, the dissolved [^{11}C] formaldehyde was precipitated by reaction with dimedone (i.e. 5,5-dimethyl-1,3-cyclohexanedione). The precipitate was filtered off and counted for radioactivity in order to calculate the percentage of [^{11}C]formaldehyde contained in the solution. For analysis of crude [^{11}C]ST1859, a Waters μBondapak C18 HPLC column (300 mm × 3.9 mm, 10 μm, Waters Corporation, USA) was eluted with a mixture of 10 mM aqueous phosphoric acid and acetonitrile (60/40, v/v) at a flow rate of 2 ml/min (system C). The eluate was monitored for UV absorption (wavelength: 254 nm) and for radioactivity. On this system, the retention times of [^{11}C]formaldehyde, 2-naphthol, l-hydroxymethyl-2-naphthol and [^{11}C]ST1859 were 1–2, 3–4, 5–6 and 9–10 min, respectively. The same HPLC system was used for quality control and determination of specific radioactivity of purified [^{11}C]ST1859. The specific radioactivity of [^{11}C]ST1859 was measured by comparing the UV absorption of unlabelled ST1859 contained in the formulated product solution with that of known amounts of ST1859.

Determination of the stability of [^{11}C]ST1859

The stability of [^{11}C]ST1859 was determined by HPLC using a Chromolith Performance RP-18e 100-4.6 mm column that was eluted with water (solvent A) and acetonitrile (solvent B) at a flow rate of 5 ml/min (HPLC system D). The following gradient time program was used: 0–4 min, (A/B, v/v) 80/20 isocratic; 4–6 min, (A/B) 80/20–40/60; 6–9 min, (A/B) 40/60 isocratic; 9–10 min, (A/B) 40/60–80/20; 10–11 min, (A/B) 80/20 isocratic. UV absorption was detected at a wavelength of 254 nm. A Packard Radiomatic Flo-one Beta Flow scintillation analyzer (Perkin Elmer Life Sciences Inc., Boston, USA) equipped with a Perkin Elmer Radiomatic Flowbeta FSA150 detector cell (volume 500 μl) was employed for radioactivity detection. On this system, the retention times of [^{11}C]ST1859 and 1-hydroxymethyl-2-naphthol were 6.5–7 and 4.5–5 min, respectively. The detection limit of [^{11}C]ST1859 was about 0.1 kBq. For the stability test, [^{11}C]ST1859 formulated in physiological saline/ethanol (85/15, v/v) was kept at room temperature and unprotected from light

in a glass vial. At different time points, aliquots of the radiotracer solution were removed and diluted with water (containing a small amount of unlabelled ST1859) and analysed by HPLC. The stability of [^{11}C]ST1859 was also determined in human plasma. For this test, 1 ml aliquots of heparinized human plasma were mixed with 100 µl diluted radiotracer solution (in physiologic saline) and incubated at 37°C in a gently shaking water bath. At different time points, samples were removed from the water bath and counted for radioactivity in a Packard Cobra II auto-gamma counter (Packard Instrument Company, USA). The plasma samples were then mixed with 1.5 ml of acetonitrile (containing 100 µg/ml of unlabelled ST1859) for precipitation of proteins, and then centrifuged for 2 min at 12 000 g (4°C). The supernatants were counted in the gamma counter to determine the recovery of radioactivity. Subsequently, the supernatants were mixed with 1.5 ml of water and injected (2 ml sample loop) onto the HPLC system.

Determination of the lipophilicity of [^{11}C]ST1859

The log *D* (i.e. the logarithm of the partition coefficient between 1-octanol and phosphate-buffered saline, pH 7.4, PBS) of [^{11}C]ST1859 was determined by a shake-flask method following procedures described in the literature.[12] For removal of ethanol, the radiotracer solution obtained after semipreparative HPLC purification was diluted with 90 ml of water and passed over a C18 Sep-Pak Plus cartridge (Waters Corporation, USA), that had been pre-washed with ethanol (5 ml) and water (10 ml). The cartridge was washed with 6 ml of water and the radiotracer was then eluted with 1-octanol (10 ml). For removal of hydrophilic radiolabelled impurities, the radiotracer solution was washed three times with 10 ml of PBS in a separatory funnel. Aliquots of the washed radiotracer solution (20 µl) were added to tubes containing 2.0 ml of 1-octanol and 2.0 ml of PBS. The tubes were first vortexed for 4 min and then centrifuged for 5 min at 3000 rpm. Aliquots (1 ml) of each phase were then counted for radioactivity in the gamma counter. The partition coefficient (*D*) was defined as the ratio of the decay-corrected radioactivity counts in 1-octanol and PBS, respectively.

Conclusion

A commercially available synthesis module was adapted for the preparation of [^{11}C]ST1859 in sufficiently high radioactivity amounts for PET microdosing studies. The specific radioactivity obtained in the radiolabelling of [^{11}C]ST1859 (> 32 GBq/µmol) is expected to permit a safe use of the radiotracer in humans.

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