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Facile and rapid one-step radiosynthesis of [^{18}F]BAY94-9172 with a new precursor

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Abstract

Introduction: [^{18}F]BAY94-9172 (Florbetaben) (Compound **8**) is a positron emission tomography (PET) tracer that is currently in Phase III study for in vivo mapping of fibrillar amyloid β as a pathological hallmark for Alzheimer's disease. This work reports new methods for the synthesis of [^{19}F]BAY94-9172 and its two different precursors and radiosynthesis of [^{18}F]BAY94-9172 with the two precursors by purification using Sep-Pak cartridge.

Methods: The reference standard [^{19}F]BAY94-9172 and the new precursor (Compound **9**) were obtained from the reactions of (*E*)-4-methylamino-4′-hydroxystilbene (Compound **1**) with methanesulfonic acid 2-[2-(2-fluoro-ethoxy)-ethoxy]-ethyl ester (Compound **11**) and methanesulfonic acid 2-[2-(2-methanesulfonyloxy-ethoxy)-ethoxy]-ethyl ester (Compound **13**), respectively. The reported precursor (Compound **6**) is an *N*-BOC-protected mesylate compound, which was obtained from Compound **9**. The one-step radiosynthesis of [^{18}F]BAY94-9172 was carried out in the modified PET-MF-2V-IT-1 synthesizer by [^{18}F]fluorination of the new precursor (Compound **9**) and purification with plus C18 Sep-Pak cartridges and was compared with two-step one-pot radiosynthesis using the reported precursor (Compound **6**) and Sep-Pak cartridge purification.

Results: For one-step radiosynthesis, the uncorrected radiochemical yield of [^{18}F]BAY94-9172 was 23±3% (n=5, based on [^{18}F]fluoride) within 30 min and the radiochemical purity was greater than 95%. For two-step one-pot radiosynthesis, the uncorrected radiochemical yield of [^{18}F]BAY94-9172 was 17±2% in 45 min (n=4, based on [^{18}F]fluoride) with the radiochemical purity being above 95% after the Sep-Pak cartridge purification.

Conclusion: [^{19}F]BAY94-9172 and the two precursors were synthesized by a short synthetic route. Compared with HPLC purification, the use of Sep-Pak purification of [^{18}F]BAY94-9172 reduced the total radiosynthesis time. The one-step radiosynthesis of [^{18}F]BAY94-9172 is convenient and can easily be applied to the commercial PET tracer synthesizer for automated synthesis.

Keywords: Alzheimer's disease; PET; BAY94-9172; Florbetaben; Radiosynthesis

1. Introduction

Alzheimer's disease (AD) is a progressive and neurodegenerative disorder of the brain with loss of memory and other cognitive functions. Fibrillar amyloid β (Aβ) has been proposed as one of the pathological hallmarks of AD [1]. Radiolabeled imaging agents for direct mapping of Aβ in vivo with noninvasive techniques such as positron emission tomography (PET) and single-photon emission computed tomography would facilitate presymptomatic identification of this disorder and evaluation of therapies [2,3]. Some radiolabeled imaging agents that bind specifically to Aβ

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have been reported [4]. The binding studies of radiolabeled derivatives of Congo red [5], aminonaphthalene [6], thioflavin [7], stilbene [8], curcumin [9] and acridine orange [10] have been studied in postmortem human brain tissue and in transgenic mice. Some radiolabeled imaging agents, such as [^{11}C]PIB [11], [^{11}C]SB-13 [12], [^{18}F]AH110690 [13], [^{18}F]BAY94-9172 [14] and [^{18}F]AV-45 [15], are currently in clinical trials (Fig. 1). Bayer's Florbetaben ([^{18}F]BAY94-9172) is one such promising radiolabeled imaging agent that entered into Phase III clinical trial on November 30, 2009.

[^{18}F]BAY94-9172 is a stilbene derivative with some structural similarities to PIB. It has been shown to bind in a near identical pattern to that of [^{11}C]PIB *in vitro* and to provide a similar effect size and accuracy in discriminating AD from controls and front temporal lobar degeneration [14]. [^{18}F]BAY94-9172 had a lower binding affinity (K_i) of 6.7±0.3 nM for aggregated Aβ fibrils in competition with [^{125}I]IMPY, and the K_i for [^{11}C]PIB was 2.8±0.5 nM in the same experiment [16]. The effective dose (ED) of [^{18}F]BAY94-9172 is almost three times as much as that of [^{11}C]PIB, as the EDs of [^{18}F]BAY94-9172 and [^{11}C]PIB are 14.67±1.39 and 5.29±0.66 mSv/MBq, respectively [17]. Compared with [^{11}C]PIB, the longer physical half-life of [^{18}F]BAY94-9172 is an advantage for multicenter clinical use and studies.

[^{19}F]BAY94-9172 and the previously reported precursor of [^{18}F]BAY94-9172 [methanesulfonic acid 2-{2-[2-(4-{2-[4-(*tert*-butoxycarbonyl-methyl-amino)-phenyl]-vinyl}-phenoxy)-ethoxy]-ethoxy}-ethyl ester (**6**)] were synthesized from multi-step reactions using (*E*)-4-methylamino-4′-hydroxystilbene (**1**) [16]. [^{18}F]BAY94-9172 (**8**) was obtained by a two-step reaction sequence, consisting of [^{18}F]fluorination of the *N*-BOC-protected mesylate (Compound **6**) and subsequent deprotection of the BOC-group by hydrolysis. Automated synthesis of [^{18}F]BAY94-9172 (Compound **8**) has been reported using HPLC purification with a radiochemical yield of 20–30% (corrected) and a synthesis time of approximate 60 min [16]. In this work, [^{19}F]BAY94-9172, a new precursor [methanesulfonic acid 2-[2-(2-{4-[2-(4-methylamino-phenyl)-vinyl]-phenoxy}-ethoxy)-ethoxy]-ethyl ester (**9**)] and the previously reported precursor of [^{18}F]BAY94-9172 (Compound **6**) were synthesized by a short synthetic route. [^{18}F]BAY94-9172 (Compound **8**) with high radiochemical yield was obtained by one-step radiosynthesis using the new precursor (Compound **9**) and Sep-Pak cartridges purification instead of preparative HPLC in a modified PET-MF-2V-IT-1 synthesizer. This one-step radiosynthesis of [^{18}F]BAY94-9172 (Compound **8**) using the new precursor (Compound **9**) and Sep-Pak cartridge purification compares favorably with the previously reported two-step one-pot radiosynthesis.

2. Materials and methods

2.1. General

All reagents used in the synthesis were commercial products and used without further purification unless otherwise indicated. ^{1}H NMR spectra were recorded on a Varian INOVA at 500 MHz. Coupling constants are reported in hertz. Multiplicity is defined by s (singlet), d (doublet), t (triplet), br (broad) and m (multiplet). Flash chromatography was performed on silica gel (300–400 mesh). TLC was run on pre-coated aluminium plates (Kieselgel 60 F254, Merck, Germany) and visualized with UV light or basic aqueous potassium permanganate. For each procedure, "catalytic amount of 18-crown-6" as being 10% molar ratio of potassium carbonate was used in the reaction. Analytical HPLC system (Agilent 1200 Series; Agilent Technologies, USA) equipped with a UV detector (Agilent interface 35900E, Agilent Technologies) and a B-FC-3200 high-energy PMT Detector (Bioscan. Inc, Washington, DC, USA) was used to purify and confirm the radiolabeled compound. The [^{18}F]BAY94-9172 was purified with preparative HPLC (Alltima C18, Alltech, USA) equipped with UV detector (Alltech 201, USA) and radioactivity detector (Beijing PET Co. Ltd., China), and radiochemical purities were checked by analytical HPLC. No-carrier-added [^{18}F]fluoride in [^{18}O]water was produced by irradiation of 10-MeV proton to

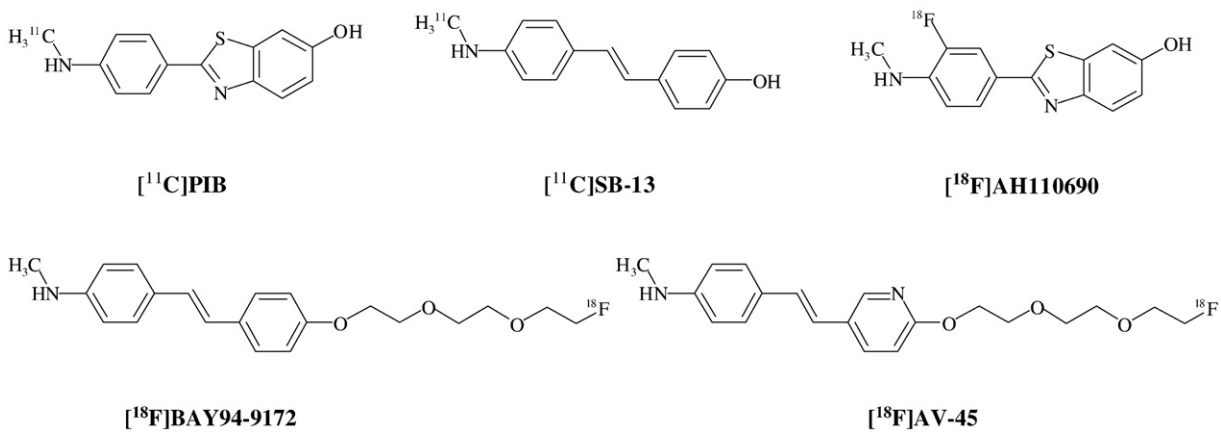


Fig. 1. Structures of reported tracers for Aβ imaging in clinical trials.

[^{18}O]water using Cyclone 10/5 cyclotron (IBA Technologies, Belgium). Kryptofix 222 (K222) was obtained from Sigma-Aldrich. Sep-Pak Light QMA (quaternary methylammonium anion-exchange resin) and Sep-Pak plus C-18 cartridges were obtained from Waters (Milford, MA, USA). Radioactivity was determined using a calibrated ion chamber (Capintec, CRC-15R, USA). The PET-MF-2V-IT-1 synthesis module was purchased from Beijing PET Co. Ltd.

2.2. Synthesis

2.2.1. Synthesis of {4-[2-(4-{2-2[2-(2-fluoro-ethoxy)-ethoxyl]-ethoxy}-phenyl)-vinyl]-phenyl}-methylamine, [^{19}F] BAY94-9172

Under N_2 atmosphere, Compound **1** (0.2 g, 0.89 mmol) and methanesulfonic acid 2-[2-(2-fluoro-ethoxy)-ethoxy]-ethyl ester (**11**) (0.41 g, 1.78 mmol) were dissolved in dry acetone (10 ml) followed by addition of potassium carbonate (0.46 g, 3.3 mmol) and a catalytic amount of 18-crown-6. The mixture was heated to 70°C and stirred. The solvent was removed under reduced pressure, water (10 ml) was added and the mixture was extracted with ethyl acetate (3×30 ml). The combined ethyl acetate extracts were dried with Na_2SO_4 and concentrated. The residue was recrystallized from a mixture of ethyl acetate and petroleum ether to afford the [^{19}F]BAY94-9172 as crystals (0.1 g, 31%). ^{1}H-NMR (500 MHz, $CDCl_3$, δ ppm) 2.87 (s, 3 H), 3.71–3.81 (m, 6 H), 3.86–3.89 (m, 2 H), 4.14–4.17 (m, 2 H), 4.51–4.54 (m, 1 H), 4.61–4.63 (m, 1 H), 6.63 (d, 2 H, *J*=8.5 Hz), 6.83–6.93 (m, 4 H), 7.34–7.41 (m, 4 H).

2.2.2. Synthesis of Compound 9

Compound **9** was prepared from Compound **1** (0.5 g, 2.2 mmol) and methanesulfonic acid 2-[2-(2-methanesulfonyloxy-ethoxy)-ethoxy]-ethyl ester (**13**) (1.02 g, 3.3 mmol) in dry acetone (10 ml) with potassium carbonate (0.92 g, 6.6 mmol) and a catalytic amount of 18-crown-6, using the same procedure as described for [^{19}F]BAY94-9172. Compound **9** (0.70 g, 73%): ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) 2.87 (s, 3 H), 3.06 (s, 3 H), 3.69–3.79 (m, 6 H), 3.84–3.87 (m, 2 H), 4.12–4.15 (m, 2 H), 4.36–4.40 (m, 2 H), 6.62 (d, 2 H, *J*=8.5 Hz), 6.83–6.93 (m, 4 H), 7.34–7.41 (m, 4 H).

2.2.3. Synthesis of Compound 6

Under N_2 atmosphere, Compound **9** (0.7 g, 1.6 mmol) was dissolved in dry THF (20 ml) followed by BOC anhydride (1.27 g, 5.8 mmol). The solution was refluxed overnight. THF was removed under reduced pressure and water (10 ml) was added. The mixture was extracted with ethyl acetate (3×30 ml). The combined ethyl acetate extracts were dried with Na_2SO_4 and concentrated, and the residue was recrystallized with ethyl acetate and petroleum ether to afford Compound **6** as crystals (0.67 g, 75%). ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) 1.46 (s, 9 H), 3.06 (s, 3 H), 3.27 (s, 3 H), 3.69–3.74 (m, 4 H), 3.76–3.79 (m, 2 H), 3.84–3.87 (m, 2 H), 4.09–4.14 (m, 2 H), 4.36–4.39 (m, 2 H), 6.90 (d, 2 H, *J*=8.7 Hz), 6.98 (q, 2 H, *J*=16.3 Hz), 7.21 (d, 2 H, *J*=8.1 Hz), 7.44 (d, 4 H, *J*=8.3 Hz).

2.2.4. Synthesis of Compound 11

Methanesulfonyl chloride (1.55 ml, 15.8 mmol) was added to a stirred solution of 2-[2-(2-fluoro-ethoxy)-ethoxy]-ethanol (**10**) (2.0 g, 13.1 mmol) and Et_3N (3 ml, 21.6 mmol) in CH_2Cl_2 (30 ml) at 0°C. After addition, the mixture was stirred at room temperature for 4 h. Water (20 ml) was added and the mixture was extracted with CH_2Cl_2 (3×30 ml). The combined organic extracts were concentrated and the residue was purified by silica gel column chromatography (EtOAc/Petroleum ether, 4/1 as eluent) to afford Compound **11** as a colorless oil (2.53 g, 84%). ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) 3.08 (s, 3 H), 3.69–3.72 (m, 5 H), 3.75–3.80 (m, 3 H), 4.38–4.41 (m, 2 H), 4.50–4.53 (m, 1 H), 4.60–4.62 (m, 1 H).

2.2.5. Synthesis of Compound 13

Compound **13** was prepared from 2-[2-(2-hydroxy-ethoxy)-ethoxy]-ethanol (**12**) (1.05 g, 7 mmol), Et_3N (5 ml, 36 mmol) and methanesulfonyl chloride (2.5 ml, 25.4 mmol) in dry CH_2Cl_2 (20 ml) using the same procedure as described for Compound **11**. Compound **13** (2 g, 78%): ^{1}H-NMR (500 MHz, $CDCl_3$, δ ppm) 3.08 (s, 6 H), 3.68 (s, 4 H), 3.76–3.78 (m, 4 H), 4.36–4.39 (m, 4 H).

2.3. Radiosynthesis

2.3.1. [^{18}F]Fluorination of Compound 9

[^{18}F]Fluoride, produced by a cyclotron using ^{18}O (p, n) ^{18}F reaction, was passed through a Sep-Pak Light QMA cartridge as an aqueous solution in [^{18}O]-enriched water. The cartridge was dried by air flow, and the ^{18}F activity was eluted with 1.5 ml of K222/K_2CO_3 solution (17.7 mg of K222 and 4.1 mg of K_2CO_3 in CH_3CN/H_2O 10/1). The solvent was removed at 116°C under a nitrogen stream. The residue was azeotropically dried with 2 ml of dry CH_3CN at 116°C with a nitrogen stream. A solution of the precursor (Compound **9**) (5 mg) in DMSO (0.5 ml) was added to the reaction vessel containing the dried ^{18}F activities. The solution was heated at 120°C for 6 min.

2.3.1.1. Purification of [^{18}F]BAY94-9172 with Sep-Pak C18 cartridge. The solution was cooled to 50°C, water (10 ml) was added, and it was passed through a plus Sep-Pak C18 cartridge (Waters Sep-Pak) and collected as waste. Ethanol (1.5 ml) was used to rinse the reaction vessel and elute the product from the C18 cartridge. Radioactivity in the ethanol solution, radioactivity in the waste and residual radioactivity on the C18 cartridge and reaction vessel were measured in a dose calibrator, respectively, for yield calculation. The radiochemical purity and the specific activity were determined by analytical HPLC [Agilent Eclipse XDB-C18 analytical column (4.6×150 mm, 5 μm); CH_3CN/0.1 M ammonium formate (6/4, v/v); flow rate of 1 ml/min and UV wavelength of 254 nm]. Retention time of [^{18}F]BAY94-9172 (Compound **8**) in this system was 6.7 min. Specific activity was estimated by comparing the UV peak intensity of the purified F-18-labeled compound with reference nonradioactive compound of known concentration.

2.3.1.2. Purification of [^{18}F]BAY94-9172 with HPLC. The reaction mixture was dissolved in 1 ml solution (CH_3CN/0.1 M ammonium formate, 6/4) and transferred to a new vial and then injected to HPLC for purification [250×10 mm, 10 μm, CH_3CN/ammonium formate (0.1 M) 6/4; flow rate of 3 ml/min, at 254 nm]. Retention time of [^{18}F]BAY94-9172 (Compound **8**) was 25 min. The [^{18}F]BAY94-9172 (Compound **8**) fraction was collected, diluted with water (20 ml) and passed through a plus C18 cartridge. The purified product was trapped on C18 cartridge and eluted with absolute ethanol (1.5 ml). The chemical and the radiochemical purities were checked by analytical HPLC.

*2.3.2. [^{18}F]Fluorination of Compound **6***

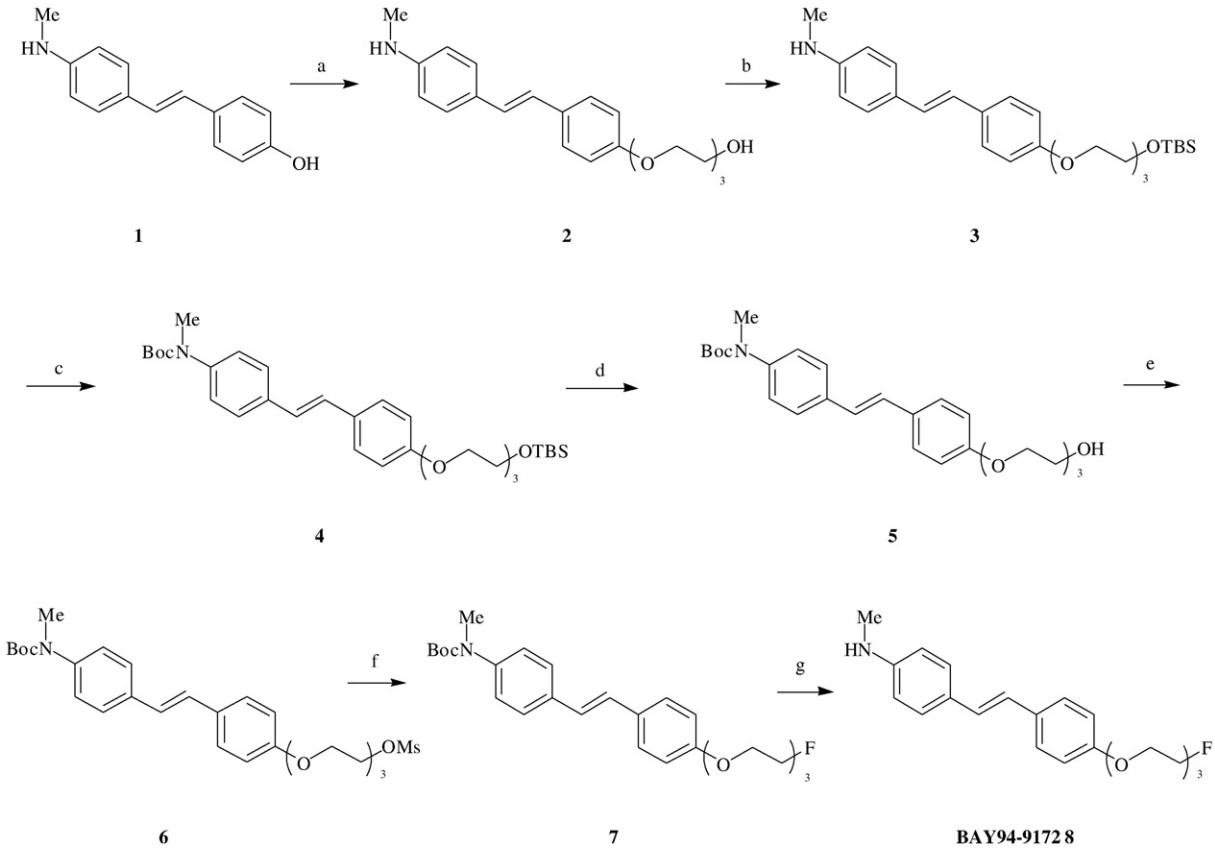
A solution of *N*-BOC-protected mesylate precursor (Compound **6**) (5 mg) in DMSO (0.5 ml) was added to the reaction vessel containing the dried ^{18}F activities and heated at 120°C for 6 min. The solution was cooled down for 1 min, 10% hydrochloric acid (2 ml) was added and the mixture was heated at 120°C again for 5 min. Aqueous NaOH (6 M) was added to adjust the pH to basic (pH 8–9). [^{18}F]BAY94-9172 (Compound **8**) was purified with a plus C18 cartridge using the same procedure as described above.

3. Results and Discussions

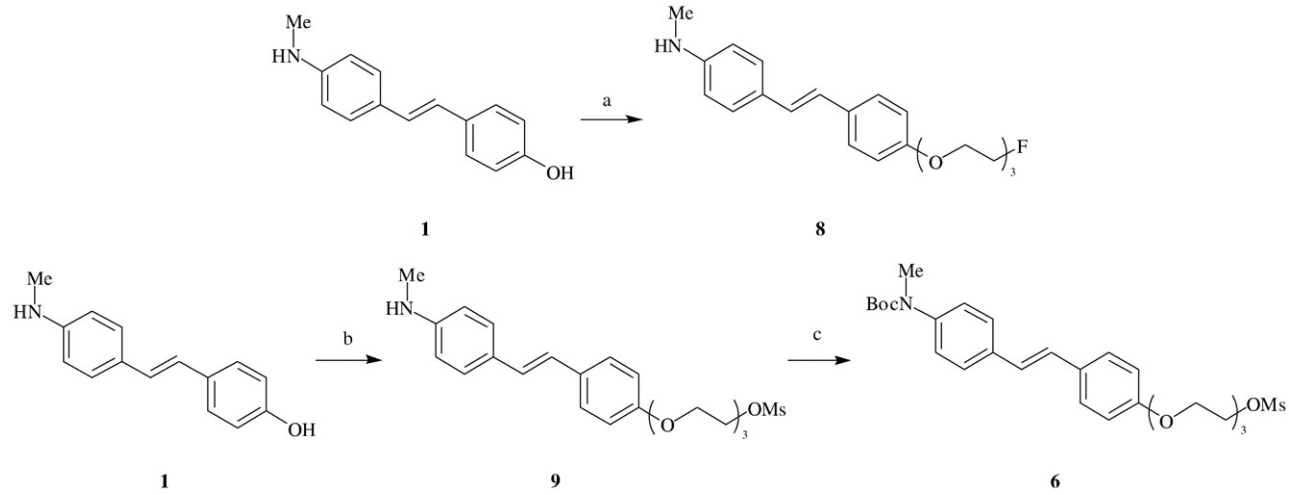
3.1. Chemistry

The reported syntheses of [^{19}F]BAY94-9172 and the precursors for [^{18}F]BAY94-9172 were shown in Scheme 1. The precursor of [^{18}F]BAY94-9172 (Compound **6**) was synthesized from Compound **1** by a sequence of five-step reactions. The "cold" fluorinated BAY94-9172 was obtained by refluxing the precursor (Compound **6**) (*N*-BOC-protected mesylate compound) in anhydrous TBAF/THF, followed by stirring with TFA to remove the BOC protection group [16]. Recently, Huynh et al. reported the synthesis of "cold" fluorinated BAY94-9172 using a Sonogashira coupling reaction combined with a stereoselective diarylalkyne reduction [18].

In this study, the reference [^{19}F]BAY94-9172, the new precursor of [^{18}F]BAY94-9172 (Compound **9**) and the previously reported precursor (Compound **6**) were prepared by a new synthetic route shown in Scheme 2. The "cold" fluorinated BAY94-9172 and the new precursor of [^{18}F]BAY94-9172 (Compound **9**) were obtained by the reactions of 4-methylamino-4′-hydroxystilbene (Compound **1**) [19] with Compound **11** and Compound **13**, respectively. The previously reported precursor (Compound **6**) was synthesized from treatment of Compound **9** with BOC anhydride. For the



Scheme 1. (a) $Cl(CH_2CH_2O)_3H$, K_2CO_3, DMF; (b) TBDMSCI, imidazole, DCM; (c) $(BOC)_2O$, THF; (d) TBAF (1 M), THF; (e) MsCI, Et_3N, DCM; (f) TBAF (anhydrous), THF; (g) TFA, DCM.



Scheme 2. (a) $MsO(CH_2CH_2O)_2CH_2CH_2F$ (Compound **11**), K_2CO_3, acetone, 18-crown-6; (b) $MsO(CH_2CH_2O)_2CH_2CH_2OMs$ (Compound **13**), K_2CO_3, acetone, 18-crown-6; (c) $(BOC)_2O$, THF.

preparation of Compounds **11** and **13**, Compound **10** and commercially available Compound **12** were treated with methanesulfonyl chloride in the presence of triethylamine to convert them into the corresponding mesylates [20]. Compound **10** was prepared from Compound **12** using the literature procedure [21].

We synthesized [^{19}F]BAY94-9172 and the two precursors (Compounds **6** and **9**) using a parallel synthetic strategy. Some protection and deprotection steps were not needed, and the uses of special catalysts such as $PdCl_2$ were avoided in this new route.

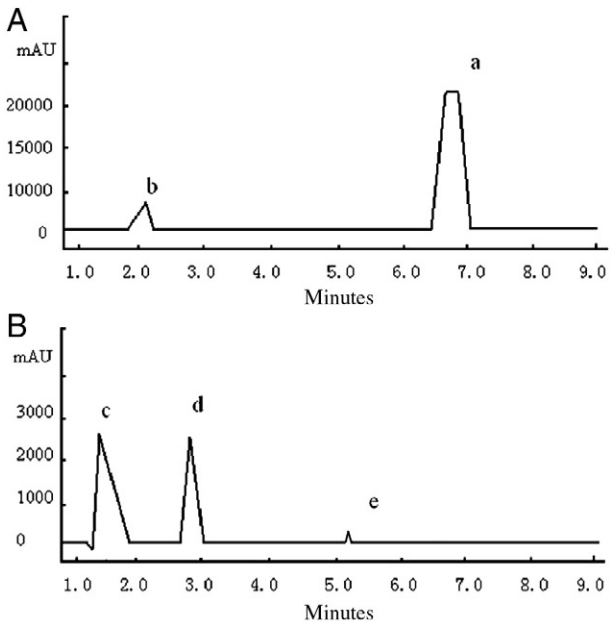


Fig. 2. HPLC chromatogram of [^{18}F]BAY94-9172 after [^{18}F]fluorination of the new precursor (Compound **9**). (A) The radioactive chromatogram for crude [^{18}F]BAY94-9172 reaction mixture, *a*, [^{18}F]BAY94-9172; *b*, unreacted [^{18}F] fluoride. (B) The UV chromatogram for crude [^{18}F]BAY94-9172 reaction mixture at 254 nm, *c*, DMSO; *d*, hydrolysis by-product; *e*, Compound **9**.

3.2. Radiochemistry

To prepare the desired [^{18}F]BAY94-9172 (Compound **8**), Compound **9** was employed as the new precursor. Compound **9** was mixed with [K/K222]$^{+}$^{18}F complex in DMSO and heated at 120°C for 6 min to give [^{18}F]BAY94-9172 (Compound **8**). [^{18}F]BAY94-9172 (Compound **8**) was obtained by one-step [^{18}F]fluorination with a high radiochemical yield from [^{18}F]fluoride (Fig. 2). After [^{18}F]

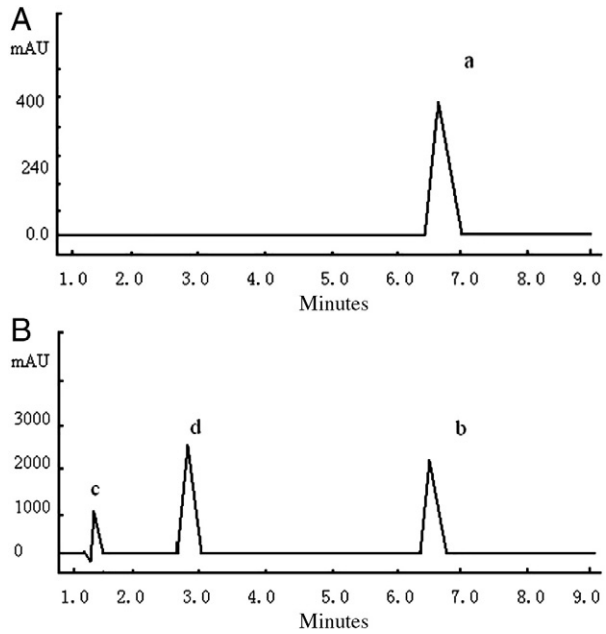


Fig. 3. HPLC chromatogram of [^{18}F]BAY94-9172 (Compound **9** as the precursor) purified with plus C18 Sep-Pak cartridge and coinjected with [^{19}F]BAY94-9172. (A) The radioactive chromatogram for [^{18}F]BAY94-9172 purified with plus C18 Sep-Pak, *a*, [^{18}F]BAY94-9172. (B) The UV chromatogram for [^{18}F]BAY94-9172 purified with plus C18 Sep-Pak mixed with [^{19}F]BAY94-9172 at 254 nm, *b*, [^{19}F]BAY94-9172; *c*, DMSO; *d*, the hydrolysis by-product.

fluorination, the reaction mixture was diluted with water and passed through a plus C18 Sep-Pak cartridge, where [^{18}F]BAY94-9172 (Compound **8**) was retained on the C18 cartridge while the majority of unreacted fluoride was eluted. [^{18}F]BAY94-9172 (Compound **8**) was eluted from C18 cartridge with ethanol. The preparation of [^{18}F]BAY94-9172 (Compound **8**) took about 30 min, the radiochemical yield was 23±3% (n=5, decay uncorrected) and the radiochemical purity was above 95% (Fig. 3). The specific activity of [^{18}F]BAY94-9172 **8** was approximately 720–900Ci/mmol (n=5) after preparation.

In this study, [^{18}F]BAY94-9172 (Compound **8**) was also obtained from [^{18}F]fluorination of the previously reported precursor Compound **6**. Although the precursor (Compound **6**) was labeled with [^{18}F]fluoride with a relatively good yield, the intermediate ^{18}F-labeled Compound **7** was not hydrolyzed completely with 2% hydrochloric acid at 120°C for 10 min as described in the literature [16], and the [^{18}F]**7** and [^{18}F]BAY94-9172 (Compound **8**) coexisted in the final product after the plus C18 Sep-Pak cartridge purification (Fig. 4A). Thus, HPLC purification of [^{18}F]BAY94-9172 (Compound **8**) was needed for obtaining high radiochemical purity. In order to achieve the completed hydrolysis for the deprotection of the BOC-group in [^{18}F]**7**, a higher concentration of hydrochloric acid (10% aqueous solution) was used at 120°C for 5 min. [^{18}F]BAY94-9172 (Compound **8**) was obtained with the uncorrected radiochemical yield of 17±2% (n=4, decay uncorrected) and the radiochemical purity was above 95% after plus C18 Sep-Pak cartridge purification within 45 min (Fig. 4B), and the average specific activity of the final product was found to be 680–810 Ci/mmol (n=4).

With either Compound **9** or Compound **6** as precursor, the radiochemical purity of [^{18}F]BAY94-9172 after plus C18 Sep-Pak cartridge treatment was above 95%. However, the chemical purity of [^{18}F]BAY94-9172 was not satisfactory, as the hydrolysis by-product and traces of DMSO were detected by analytical HPLC, as shown in the UV chromatogram of [^{18}F]BAY94-9172 in Figs. 2B and 4C. In order to obtain [^{18}F]BAY94-9172 with high chemical purity, [^{18}F]BAY94-9172 (using Compound **9**) was purified with preparative HPLC in a decay-uncorrected radiochemical yield of 18±2% (n=5) with radiochemical purity >99% (Fig. 5). The total synthesis time

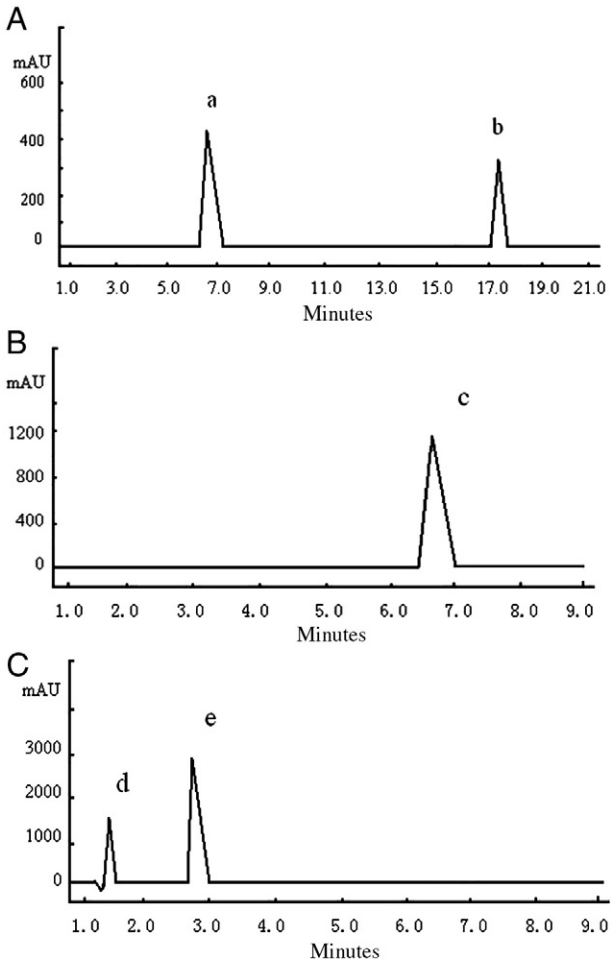


Fig. 4. HPLC chromatogram of [^{18}F]BAY94-9172 (Compound **6** as the precursor) purified with plus C18 Sep-Pak cartridge. (A) The radioactive chromatogram for [^{18}F]BAY94-9172 produced by 2% HCl hydrolysis at 120°C for 10 min, *a*, [^{18}F]BAY94-9172; *b*, [^{18}F]**7**. (B) The radioactive chromatogram for [^{18}F]BAY94-9172 purified with plus C18 Sep-Pak cartridge after completed hydrolysis with 10% HCl, *c*, [^{18}F]BAY94-9172. (C) The UV chromatogram for [^{18}F]BAY94-9172 purified with plus C18 Sep-Pak cartridge after completed hydrolysis with 10% HCl, at 254 nm. *d*, DMSO; *e*, the hydrolysis by-product deprotected with BOC-group.

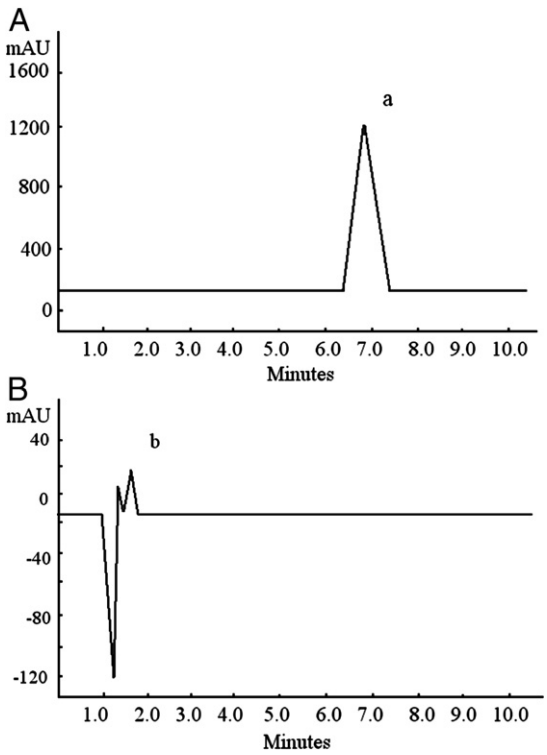


Fig. 5. Analytical HPLC chromatogram of [^{18}F]BAY94-9172 (Compound **9** as the precursor) purified with preparative HPLC. (A) The radioactive chromatogram for [^{18}F]BAY94-9172 injection, *a*, [^{18}F]BAY94-9172. (B) The UV chromatogram for [^{18}F]BAY94-9172 injection.

took about 50 min and the specific activity was estimated to be 1100–1300 Ci/mol (n=5) for the final product. The HPLC purification gave a slightly lower uncorrected radiochemical yield than Sep-Pak cartridge purification. One-step radiosynthesis of [^{18}F]**8** with plus C18 Sep-Pak purification in this study had obvious advantages with short radiosynthesis time and high specific activity.

The chemical purity of [^{18}F]BAY94-9172 (Compound **8**) with C18 Sep-Pak purification was somewhat inferior to that with HPLC purification, as shown in Figs. 2B and 5B. However, preliminary animal experiments showed that there was no significant differences between the uptakes of [^{18}F]BAY94-9172 (Compound **8**) purified with Sep-Pak cartridge and the ones with HPLC in the brains of the AD mice models (details of that study will be reported in due course). Further study is needed to understand the effect of chemical impurities in the final [^{18}F]BAY94-9172 (Compound **8**) on PET imaging and distribution in model mice.

4. Conclusions

In conclusion, a facile synthesis of [^{19}F]BAY94-9172 and two precursors (Compounds **6**and **9**) for [^{18}F]BAY94-9172 is described. This one-step radiosynthesis of [^{18}F]BAY94-9172 (from Compound **9**) has advantages of high uncorrected radiochemical yield (23±3%, n=5) and short radiosynthesis time (30 min) compared with the two-step radiosynthesis (from Compound **6**) (17±2%, n=4 and 45 min). The radiochemical purity of [^{18}F]BAY94-9172 (Compound **8**) with C18 Sep-Pak purification is greater than 95%, which is comparable to that of HPLC purification. C18 Sep-Pak purification greatly reduces the radiosynthesis time, and the one-step radiosynthesis of [^{18}F]BAY94-9172 (Compound **8**) is also suited to automated synthesis for future clinical applications.

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