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Preparation of the novel fluorine-18-labeled VIP analog for PET imaging studies using two different synthesis methods

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Abstract

Vasoactive intestinal peptide (VIP) receptors are expressed on various tumor cells in much higher density than somatostatin receptors, which provides the basis for radiolabeling VIP as tumor diagnostic agent. However, fast proteolytic degradation of VIP in vivo limits its clinical application. With the aim to develop and evaluate new ligands for depicting the VIP receptors with positron emission tomography (PET), the structure modified [$R^{8,15,21}$, L^{17}]-VIP analog was radiolabeled with ^{18}F using two different methods. With the first method, *N*-4-[^{18}F]fluorobenzoyl-[$R^{8,15,21}$, L^{17}]-VIP ([^{18}F]FB-[$R^{8,15,21}$, L^{17}]-VIP **7**) was produced in a decay-corrected radiochemical yield (RCY) of 33.6 ± 3%, a specific radioactivity of 255 GBq/μmol ($n = 5$) within 100 min in four steps. Similarly, *N*-4-[^{18}F](fluoromethyl)-benzoyl-[$R^{8,15,21}$, L^{17}]-VIP ([^{18}F]FMB-[$R^{8,15,21}$, L^{17}]-VIP **8**) was synthesized in a RCY of 34.85 ± 5%, a specific radioactivity of 180 GBq/μmol ($n = 5$) within 60 min in only one step. The two products **7** and **8** were both shown good stability in HSA. Moreover, the low bone uptakes of **7** and **8** in vivo of mice showed good defluorination stability.

Keywords: Fluorine-18; [$R^{8,15,21}$; L^{17}]-VIP; [^{18}F]SFB; [^{18}F]SFMB; PET

1. Introduction

Radiolabeled peptides have drawn enormous attention as tumors diagnosing imaging agents in nuclear medicine due to their rapid blood clearance and specific uptakes in their receptors expressing area. Furthermore, it is well known that positron emission tomography (PET) was superior to single photon emission computed tomography (SPECT) in sensitivity, resolution, and quantification [1]. Among a number of positron-emitting nuclides, ^{18}F, with lower β^+-energy (0.635 MeV), smaller size (van der Waals radii: 1.35 Å) and suitable half-life ($t_{1/2}$: 109.8 min), appeared to be a popular choice for labeling peptides [2]. Based on these characteristics, ^{18}F-labeled bioactive peptides hold great potential for imaging applications when using PET.

Vasoactive intestinal peptide (VIP, H-His-Ser-Asp-Ala-Val-Phe-Thr-Asp-Asn-Tyr-Thr-Arg-Leu-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-Asn-Ser-Ile-Leu-Asn-NH_2) is a 28 amino acids peptide belongs to the glucagons secretin family [3]. Large numbers of VIP receptors are expressed on various tumor cells including brain tumors, neuroendocrine tumors, adenocarcinomas of colon, breast, prostate, pancreatic, stomach and liver, which enables in vivo localization of the primary tumor and its metastases by scintigraphy with radiolabeled VIP analogs [4]. Over the past years, ^{123}I-VIP, ^{99m}Tc-TP3654 (VIP-Aba-Gly-Gly-(D)-Ala-Gly), ^{99m}Tc-P1666 ([des-Met^{17}, S-(CH_2CO-Gly-Gly-Cys-Lys-amide) Hcy^{17}]-VIP) and ^{18}F-(Arg^{15}, Arg^{21})-VIP have shown their potential for diagnosing tumors expressing VIP receptors [5–12]. However, fast proteolytic degradation of VIP analogs in vivo resulted in the lower uptakes of radioactivity in tumors, which hindered their clinical applications. Hence, we have synthesized a novel VIP analog named [$R^{8,15,21}$, L^{17}]-VIP (H-His-Ser-Asp-Ala-Val-Phe-Thr-Arg-Asn-Tyr-Thr-Arg-Leu-Arg-Arg-Gln-Leu-Ala-Val-Lys-Arg-Tyr-Leu-Asn-Ser-Ile-Leu-Asn-NH_2), which was designed with the replacement of Asp^8, Lys^{15}, Lys^{21} by Arg and Met^{17} by Leu in amino acids sequence of VIP peptide. In our previous study, this VIP analog has been proved higher receptor binding activity and better proteolytic stability than native VIP [13].

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All of above have shown that it is worth while to evaluate ^{18}F-labeled [R^{8,15,21}, L^{17}]-VIP as a PET imaging agent. In the past, different ^{18}F-labeling methods for peptides have been used, including acylation, amidation, imidation, alkylation and chemoselective oxime formation [14,15]. Among them, *N*-succinimidyl-4-[^{18}F] fluorobenzoate **4** ([^{18}F]SFB) as an acylation agent has drawn more attention due to its higher radiochemical yields, stability and conjugation yields with various peptides. However, synthesis of [^{18}F]SFB **4** has to be performed three steps reaction, which is time-consuming and tedious [16–19], while *N*-succinimidyl-4-[^{18}F](fluoromethyl)-benzoate **6** ([^{18}F]SFMB) and 4-[^{18}F]Fluoro-benzaldehyde ([^{18}F]FB-CHO) could be achieved with only one step reaction, which have been all used for labeling peptides. However, [^{18}F]SFMB **6** was obtained with low radiochemical yields of 18–25% and need HPLC purification in previous study, such drawbacks have limited its popular use [16]. Additionally, [^{18}F]FB-CHO was only suitable for labeling peptide with modified structure, such as aminooxy-functionalized peptides [15]. In this study, since a free ε-NH$_2$ group of Lys^{21} was existed in the structure of [R^{8,15,21}, L^{17}]-VIP, ^{18}F-labeling peptide through acylation method would be a suited choice. In order to label [R^{8,15,21}, L^{17}]-VIP with ^{18}F in a more convenient way, conjugation of [R^{8,15,21}, L^{17}]-VIP with [^{18}F]SFB **4** and [^{18}F]SFMB **6** were evaluated in detail. Furthermore, as ^{18}F-fluoroacylation agents, defluorination in vivo should be considered, so bone uptakes of radioactivity were also evaluated in mice.

2. Results and discussion

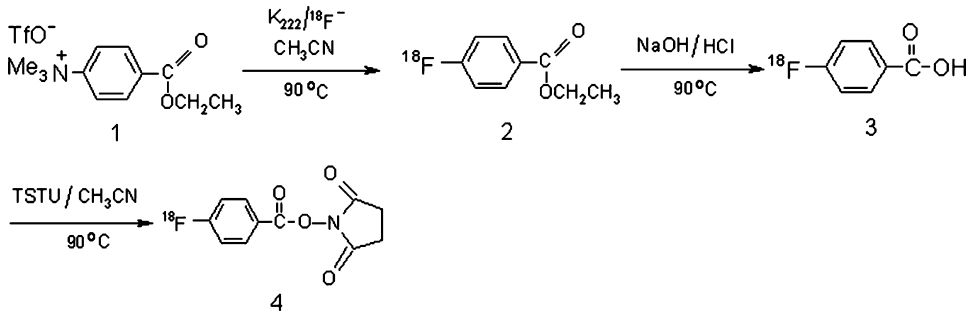
2.1. Preparations, quality control of [^{18}F]SFB 4 and [^{18}F]SFMB 6

[^{18}F]SFB **4** was synthesized in three steps from ethyl 4-(trimethylammonium)benzoate trifluormethane-sulfonate **1** by slight modifications of literature procedures (Scheme 1) [17]. During the first radiochemical step, CH_3CN was chosen as reaction solvent instead of DMSO used in previous papers and reacted at 90 °C for 10 min, giving the desired ethyl 4-[^{18}F]fluorobenzoate **2** with over 93% of labeling yield. The high yield of compound **2** was shown to be more critical for the high yield of [^{18}F]SFB, which was coincidence with the results found by Zijlstra et al. [18]. Additionally, in purification procedure, a $MgSO_4$ cartridge (2 cm length, designed by ourselves) was added at the end of Sep-Pak cartridge. Using this method, removal of water through azeotropic evaporation should be dispensable. The other experimental procedures were referred to the literatures [17]. Based on these modifications, [^{18}F]SFB **4** was obtained in greater than 99% radiochemical purity within 40 min in higher decay-corrected radiochemical yield of 70% at the end of synthesis (EOS) [17–20].

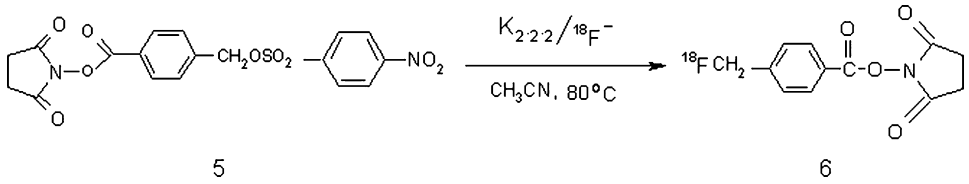
As the product of single-step reaction (Scheme 2), [^{18}F]SFMB **6** possesses huge potential for labeling peptides and proteins conveniently. [^{18}F]SFMB **6** has the similar structure with [^{18}F]SFB **4**, however, low radiochemical yields (18–25%) and requirement of HPLC purification have limited its broad use [16,21,22]. In order to improve its radiosynthesis, we have investigated the reaction parameters and purification methods. Reaction solvents and reaction temperature were found to be more important factors affecting the labeling efficiency. The highest labeling efficiency of 77% was obtained when reacting at 80 °C in CH_3CN for 10 min. In the purification procedure, a Sep-Pak silica cartridge was used instead of HPLC separation. After being eluted from Sep-Pak silica cartridge with 2 mL CH_2Cl_2, purified [^{18}F]SFMB **6** was obtained in greater than 99% of radiochemical purity within 20 min in decay-corrected radiochemical yield of 61.6% (EOS).

2.2. Conjugation of [^{18}F]SFB 4, [^{18}F]SFMB 6 with [R^{8,15,21}, L^{17}]-VIP and quality control

To evaluate and optimize the reaction conditions on ^{18}F-labeling peptide, concentration of peptide, reaction time, solvent and pH were investigated. The pH of the buffered peptide solution was found to be a more important parameter for successful conjugation of prosthetic group to peptide, because competing reactions were existed during the reaction course (Scheme 3). In basic condition, [^{18}F]SFB **4** and [^{18}F]SFMB **6** are susceptible to hydrolyze yielding 4-[^{18}F]fluorobenzoic acid **3** and 4-[^{18}F]fluoromethyl-benzoic acid, respectively, so the suitable pH value was needed for successful conjugation. The affections of pH on the reaction are depicted in Figs. 1 and 2. When [^{18}F]SFB **4** was used, the highest conjugation yield of 43.27% was obtained at pH 8.0. However, the highest conjugation yield of 56.58% was obtained

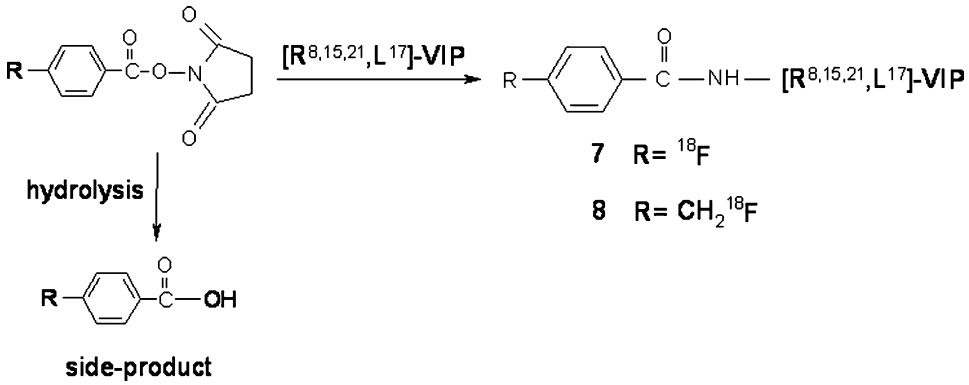


Scheme 1. Synthesis scheme of *N*-succinimidyl-4-[^{18}F] fluorobenzoate **4** via ethyl 4-(trimethyl ammonium)benzoate trifluormethane-sulfonate **1**.



5 6

Scheme 2. Synthesis scheme of *N*-succinimidyl 4-[^{18}F] (fluoromethyl)-benzoate **6** via *N*-succinimidyl-4-[(nitrobenzenslfonyl) oxymethyl]benzoate **5**.



Scheme 3. Synthesis scheme of ^{18}F-labeled [$R^{8,15,21}$, L^{17}]-VIP (**7** and **8**).

at pH 8.7 if [^{18}F]SFMB **6** was used. Other parameters just affected the process of reaction in less manner.

Since [^{18}F]FB-[$R^{8,15,21}$, L^{17}]-VIP (t_R = 11.43 min) and [^{18}F]FMB-[$R^{8,15,21}$, L^{17}]-VIP (t_R = 12.23 min) could be separated from other labeling products and unlabeled peptide (t_R = 7.1 min) using the HPLC system described in this paper (Fig. 3), the specific radioactivity of the products could be determined by labeling agents. The specific radioactivity of [^{18}F]SFB **4** and [^{18}F]SFMB **6** were estimated by radio-HPLC to be 264 GBq/μmol and 186 GBq/μmol at the end of synthesis, respectively. Accordingly, the specific radioactivity of [^{18}F]FB-[$R^{8,15,21}$, L^{17}]-VIP **7** and [^{18}F]FMB-[$R^{8,15,21}$, L^{17}]-VIP **8** were calculated to be 255 GBq/μmol (EOS) and 180 GBq/μmol (EOS). Characterization of compounds 7 and 8 are summarized in Table 1.

2.3. In vitro stability and in vivo defluorination study

According to radio-HPLC analysis, we found that the two compounds were stable up to 4 h in HSA. Additionally, defluorination stability in vivo is a more important effect should be considered on ^{18}F-labeled radiopharmaceuticals [23]. Bone uptakes of radioactivity could monitor the defluorination reaction in vivo, because $^{18}F^-$ in blood could accumulate in bone quickly. In order to evaluate the defluorination stability of two compounds, we calculated percent injected dose per gram

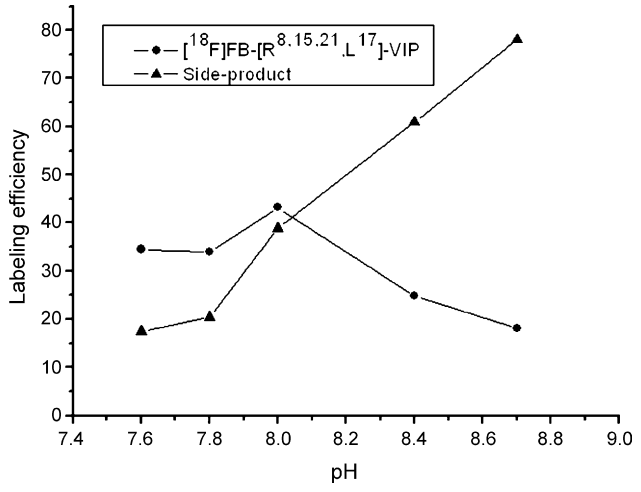


Fig. 1. pH dependence on the radiochemical yield of labeling [$R^{8,15,21}$, L^{17}]-VIP with [^{18}F]SFB **4** and competed hydrolysis yield of [^{18}F]SFB **4** at room temperature.

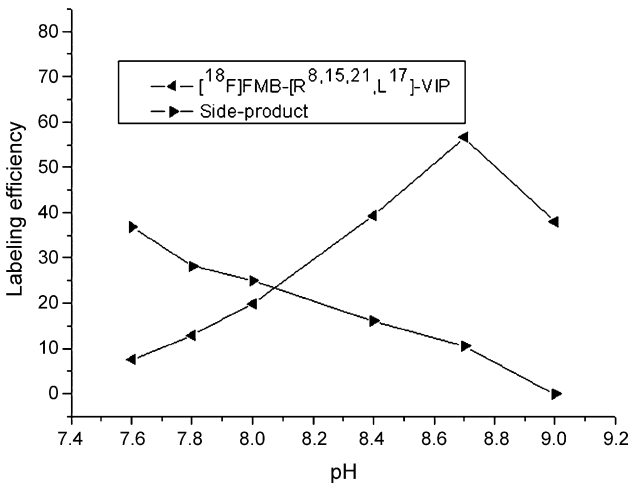


Fig. 2. pH dependence on the radiochemical yield of labeling [$R^{8,15,21}$, L^{17}]-VIP with [^{18}F]SFMB **6** and competed hydrolysis yield of [^{18}F]SFMB **6** at room temperature.

Table 1
Characterization of radiosynthesis of [^{18}F]FB-[R^{8,15,21}, L^{17}]-VIP **7** and [^{18}F]FMB-[R^{8,15,21}, L^{17}]-VIP **8**

Products	[^{18}F]FB-[R^{8,15,21}, L^{17}]-VIP	[^{18}F]FMB-[R^{8,15,21}, L^{17}]-VIP
Reaction steps	4	2
Reaction time	<100 min	<60 min
Radiochemical yield	33.6 ± 3% (EOS)	34.85 ± 5% (EOS)
Radiochemical purity	>99%	>99%
Specific radioactivity	255 GBq/μmol (EOS)	180 GBq/μmol (EOS)
Separation methods	Sep-Pak C18 cartridge and RP-HPLC	Sep-Pak silica cartridge and RP-HPLC

tissue (% ID/g) in vivo of BALB/c mice (Fig. 4). Bone uptake of [^{18}F]FMB-[R^{8,15,21}, L^{17}]-VIP **8** (0.74 ± 0.02% ID/g) is a little higher than that of [^{18}F]FB-[R^{8,15,21}, L^{17}]-VIP **7** (0.46 ± 0.20% ID/g), which may be caused by less tighter bond of C–F existed in [^{18}F]FMB-[R^{8,15,21}, L^{17}]-VIP **7**. Anyway, bone uptakes of [^{18}F]FB-[R^{8,15,21}, L^{17}]-VIP **7** and [^{18}F]FMB-[R^{8,15,21}, L^{17}]-VIP **8** were both as low as other promising ^{18}F-peptide imaging agents [15,24]. In vitro and in vivo stability of two compounds show their potential for further evaluation in mice with induced tumors.

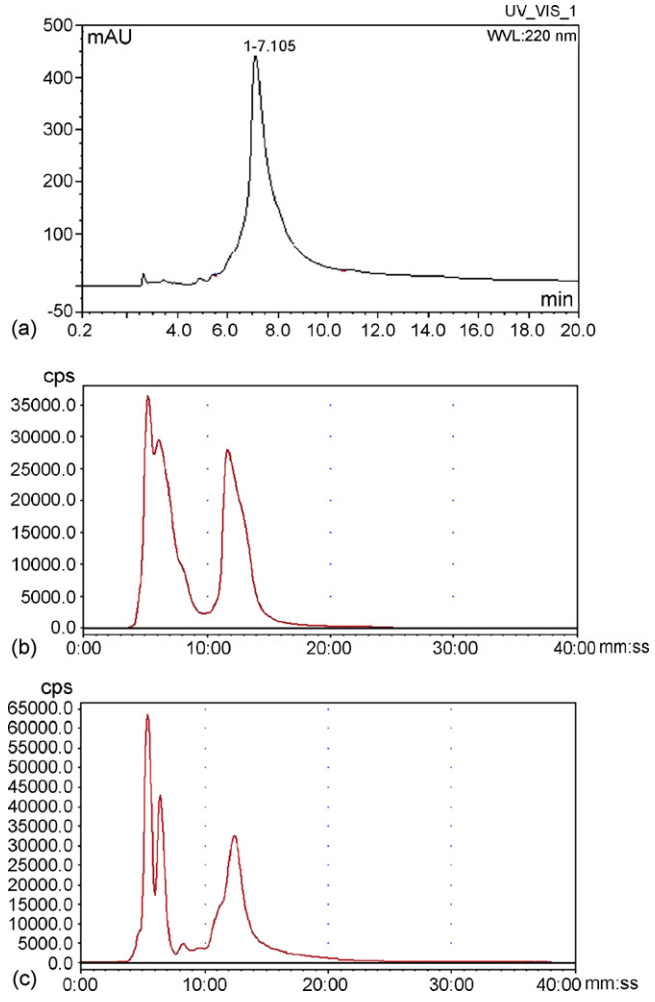


Fig. 3. HPLC trace of the reaction mixture after the conjugation of [R^{8,15,21}, L^{17}]-VIP to [^{18}F]SFB and [^{18}F]SFMB: (a) [R^{8,15,21}, L^{17}]-VIP, UV, λ = 220 nm, t_R = 7.1 min, (b) [^{18}F]FB-[R^{8,15,21}, L^{17}]-VIP, t_R = 11.43 min and (c) [^{18}F]FMB-[R^{8,15,21}, L^{17}]-VIP, t_R = 12.23 min.

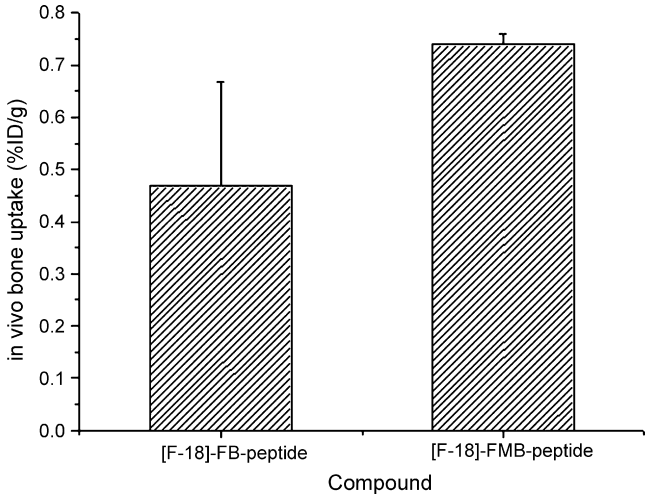


Fig. 4. In vivo bone uptake of radioactivity after injection of compounds 7 and 8, each value presents mean ± S.D. for five mice.

3. Conclusion

Two kinds of ^{18}F-labeling methods for [R^{8,15,21}, L^{17}]-VIP have been evaluated. Using the improved synthesis methods, in decay-corrected radiochemical yields of 33.6 ± 3% (EOS) within 100 min for [^{18}F]FB-[R^{8,15,21}, L^{17}]-VIP **7** and 34.85 ± 5% (EOS) within 60 min for [^{18}F]FMB-[R^{8,15,21}, L^{17}]-VIP **8** are obtained. The specific radioactivity of compounds 7 and 8 are approximately 255 GBq/μmol and 180 GBq/μmol (EOS), respectively. Moreover, the procedure for synthesizing [^{18}F]FMB-[R^{8,15,21}, L^{17}]-VIP **8** is simpler than [^{18}F]FB-[R^{8,15,21}, L^{17}]-VIP **7**, which exhibits advantages for automatization preparation and this work is underway in our laboratory. To sum up, two ^{18}F-peptide analogs are both obtained with sufficient amounts and good stability in vitro and in vivo.

4. Experimental

4.1. General

[R^{8,15,21}, L^{17}]-VIP (in purities of greater than 91%) was supplied by GL Biochemical Corp. (Shanghai, China). No-carrier-added [^{18}F]F$^-$ was supplied by Amersham-Kexing Pharmaceuticals Co., Ltd (Shanghai, China), and was produced via ^{18}O (p, n) ^{18}F reaction using enriched [^{18}O]H_2O on a cyclotron-30 (IBA, Belgium). The other solvents and reagents were commercially available and used without further

purification unless stated. Ethyl 4-(trimethylammonium)benzoate trifluormethane-sulfonate **1** and *N*-succinimidyl-4-[(4-nitrobenzensulfonyl)oxymethyl]benzoate **5** were synthesized according to literatures [20,25], and confirmed by ^{1}H NMR spectral data (300 MHz, D_2O) (compound **1**): δ 1.18–1.23 (3H, t), 3.51 (9H, s), 4.20–4.27 (2H, q), 7.77–7.80 (2H, m), 8.04–8.07 (2H, m); ^{1}H NMR spectral data (300 MHz, $CDCl_3$) (compound **5**): δ = 2.92 (4H, s), 5.26 (2H, s), 7.45 (2H, d, J = 1.33 Hz), 8.11 (4H, d, J = 2.59 Hz), 8.41 (2H, d, J = 1.31 Hz). *N*-succinimidyl-4-fluorobenzoate (SFB) and *N*-succinimidyl-4-(fluoromethyl) benzoate (SFMB) were synthesized as the standard of [^{18}F]SFB **4** and [^{18}F]SFMB **6** referred to literatures. ^{1}H NMR ($CDCl_3$) (SFB): δ 2.89 (4H, s), 7.16–7.26 (2H, m), 8.13–8.18 (2H, m); ^{1}H NMR (DMSO-d_6) (SFMB): δ 2.69 (4H, s), 5.17 (1H, s), 5.43 (1H, s), 7.52–7.61 (2H, m), 8.08–8.13 (2H, m) [26,27].

High-performance liquid chromatography (HPLC) was carried out on a system consisting of a P680pump, a PDA-100 photodiode Array Detector and a NaI (Tl) scintillation detector with the column being LiChrosorb C18 (10 μm, 300 mm × 3.9 mm). Radio-TLC analyses were performed using silica gel 60 GF-254 plates (Merck), a Bioscan system AR-2000 and Winscan software, version 3.09. ^{1}H spectra were obtained using a Bruker AM-300 spectrometer (300 MHz).

4.2. Production of [^{18}F]fluoride

The anhydrous [^{18}F]fluoride was obtained from the mixture of Kryptofix®2.2.2 (1–2 mg) and K_2CO_3 (10–12 mg) solution azeotropically removing water with 0.5 mL acetonitrile for 3 times in a stream of N_2.

4.3. Synthesis of [^{18}F]SFB **4**

Ethyl 4-(trimethylammonium)benzoate trifluormethane-sulfonate **1** (10 mg in 200 μL anhydrous CH_3CN) was added to the vial containing the dried Kryptofix®2.2.2/K^+ complex of [^{18}F]F^- and reacted at 90 °C for 5 min.

Then the ethyl ester **2** was hydrolyzed using 0.5 mL 1 mol/L NaOH at 90 °C for 5 min, and acidified with 0.8 mL 1 mol/L HCl. The solution was diluted with 2 mL H_2O and loaded onto an activated C18 Sep-Pak® cartridge (Waters, Sep-Pak® Plus). The Sep-Pak® cartridge was washed with 2 mL 0.1 mol/L HCl, then a $MgSO_4$ column was connected at the end of the cartridge and the 4-[^{18}F]fluorobenzoic acid **3** ([^{18}F]FBA) was eluted with 2 mL CH_3CN. Radio-TLC revealed radiochemical purity of over 98% (eluent: CH_2Cl_2/EtOAc = 4:1, v/v, R_f = 0.2). Afterwards, tetrapropylammonium hydroxide (15 μL, 1 M in H_2O), O-(*N*-succinimidyl) *N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (10 mg) were added to the vial containing [^{18}F]FBA **3** (CH_3CN solution) and reacted at 90 °C for 5 min. Instantaneous acidification was performed with 3 mL of 5% HOAc and diluted with 6 mL H_2O. The mixture was loaded onto an activated C18 Sep-Pak® cartridge. The cartridge was washed with 10 mL CH_3CN/H_2O (1:7, v/v) and purified [^{18}F]SFB **4** was eluted with 2 mL CH_2Cl_2. The product was analyzed by Radio-HPLC using reverse phase column and identified with reference compound SFB, elution was performed at 1 mL/min with CH_3CN/H_2O (1:1, v/v), t_R = 4.25 min. Radio-TLC: CH_2Cl_2/EtOAc = 4:1, R_f = 0.8.

4.4. Synthesis of [^{18}F]SFMB **6**

N-succinimidyl 4-[(nitrobenzenslfonyl)oxymethyl]benzoate **5** (2 mg in 200 μL anhydrous CH_3CN) was added to the vial containing the dried Kryptofix®2.2.2/K^+ complex of [^{18}F]F^- and reacted at 80 °C for 10 min. After cooling for 2 min, the solution was diluted with 2 mL CH_2Cl_2/Hexane (1:1, v/v) and loaded onto an activated Sep-Pak silica cartridge (Waters, Sep-Pak Plus). Then *N*-succinimidyl-4-[^{18}F] (fluoromethyl)-benzoate **6** ([^{18}F]SFMB) was eluted with 2 mL CH_2Cl_2. The compound **6** was analyzed by radio-HPLC using reverse phase column and identified with reference compound SFMB, elution was performed at 1 mL/min with CH_3CN/H_2O (1:1, v/v), t_R = 4.28 min. Radio-TLC: CH_2Cl_2/EtOAc = 4:1, R_f = 0.9.

4.5. Conjugation of [$R^{8,15,21}$, L^{17}]-VIP with [^{18}F]SFB **4** and [^{18}F]SFMB **6**

In a v-vial containing the 100 μg [$R^{8,15,21}$, L^{17}]-VIP peptide in borate buffer (200 μL, 0.1 mol/L, pH 8.0), [^{18}F]SFB **4** in 50 μL CH_3CN was added. The reaction mixture was kept at room temperature for 20 min. The labeling efficiency was determined by radio-TLC (eluent: CH_3OH/H_2O = 8:3, v/v, R_f = 0.1). The product was purified by radio-HPLC, which was performed at 1 mL/min with a gradient of 0.1% TFA in CH_3CN (solvent A) and 0.1% TFA in water (solvent B) as the following: 0–12 min, 75% B; 12–32 min, 75–30% B. Fraction 1 (t_R = 11.43 min) was collected as [^{18}F]FB-[$R^{8,15,21}$, L^{17}]-VIP **7**. Synthesis of [^{18}F]FMB-[$R^{8,15,21}$, L^{17}]-VIP **8** was operated in a similar procedure as above, only pH was changed to 8.7, and fraction 2 of the product (t_R = 12.23 min) was collected. [^{18}F]FB-[$R^{8,15,21}$, L^{17}]-VIP **7** and [^{18}F]FMB-[$R^{8,15,21}$, L^{17}]-VIP **8** were analyzed by radio-HPLC with over 99% of the radiochemical purity.

4.6. Stability test

To measure the in vitro stability, [^{18}F]FB-[$R^{8,15,21}$, L^{17}]-VIP **7** and [^{18}F]FMB-[$R^{8,15,21}$, L^{17}]-VIP **8** were incubated at 37 °C in HSA, respectively. At the end of incubation, samples were analyzed by radio-HPLC and the same operation was carried out at different time points till 4 h.

In order to evaluate defluorination stability of the products in vivo, 20 μCi of [^{18}F]FB-[$R^{8,15,21}$, L^{17}]-VIP **7** in 200 μL phosphate-buffered saline was injected to BALB/c mice intravenously. One hour post injection mice (n = 5) were sacrificed and bones were isolated for weighing and counting. The bones radioactivity were determined as percent injected dose per gram tissue (% ID/g). The same operations were carried out with [^{18}F]FMB-[$R^{8,15,21}$, L^{17}]-VIP **8**.

Acknowledgements

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