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Synthesis and stability of *S*-(2-[^{18}F]fluoroethyl)-L-homocysteine for potential tumour imaging

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The F-18 labelled methionine derivative *S*-(2-[^{18}F]fluoroethyl)-L-homocysteine ([^{18}F]FEHCys) was prepared by a one-pot two-step synthesis via the protected *S*-(2-bromoethyl)-L-homocysteine 1 and *S*-(2-chloroethyl)-L-homocysteine 2 precursors. The bromoethyl derivative 1 gave higher radiochemical yields (40% at 5 min) at 100°C compared with the chloro-analogue (22% at 100°C in 30 min). However, [^{18}F]FEHCys was found to be unstable in aqueous systems being transformed to the corresponding hydroxyl derivative within 20 min.

Keywords: *S*-(2-[^{18}F]fluoroethyl)-L-homocysteine; FEHCys; amino acids; nucleophilic [^{18}F]-fluorination

Introduction

[^{18}F]fluoro-2-deoxy-D-glucose (FDG) is the most widely used radiotracer in tumour diagnosis using positron emission tomography (PET). However, clinical studies have demonstrated that in some instances, it is difficult to differentiate neoplasms from inflammatory tissues.[1] Radiolabelled amino acids, particularly those incorporating the PET radionuclides carbon-11 and fluorine-18, have been used to overcome some of the disadvantages of FDG.

For this purpose, radiolabelled amino acids and in particular *S*-(2-[^{11}C]methyl)-L-methionine ([^{11}C]MET) have been extensively used in PET tumour imaging in both animals and man; however, the short half-life of carbon-11 ($t_{1/2}$ = 20 min) limits the widespread application of these tracers.[2] This has prompted the development of ^{18}F-labelled amino acids ($t_{1/2}$ = 110 min) such as 4-[^{18}F]fluoro-L-phenylalanine[3] and 2-[^{18}F]fluoro-L-tyrosine.[4,5] These amino acids demonstrated suitable imaging characteristics, but the radiosynthesis of these compounds is difficult, long and the radiochemical yield is low.

Currently, *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine ([^{18}F]FET),[6,7] which shows good imaging properties in differentiating neoplasms and inflammatory tissues, is a lead candidate in the development of ^{18}F-labelled amino acids. More recently, a new amino acid analogue of MET, *S*-(2-[^{18}F]fluoroethyl)-l-homocysteine ([^{18}F]FEHCys), was synthesized in 10% yield by a two-step process using 2-[^{18}F]fluoroethyl tosylate as an intermediate.[8] [^{18}F]FEHCys was reported to exhibit similar characteristics to [^{18}F]FET in potential tumour imaging.[9,10]

In this study, we have developed new precursors and a one-pot two-step radiolabelling method for the synthesis of [^{18}F]FEHCys. In addition, we have evaluated the stability of this tracer for potential biological and clinical applications. For this purpose, suitably protected *S*-(2-bromoethyl)-L-homocysteine **1** and *S*-(2-chloroethyl)-L-homocysteine **2** were synthesized as precursors and labelled by classical fluorine-18 nucleophilic substitution.

Results and discussion

Chemistry

Our aim was to establish an efficient one-pot synthesis of [^{18}F]FEHCys. Synthesis of the required precursors, protected *S*-(2-bromoethyl)-l-homocysteine **1** and *S*-(2-chloroethyl)-L-homocysteine **2**, was achieved in four steps (Scheme 1). Protection of L-homocysteine with di-*tert*-butyl dicarbonate[11,12] followed by reaction of compound **3** with *tert*-butyl-2,2,2-trichloroacetimidate[13,14] in dichloromethane at room temperature afforded quantitatively compound **4**. Cleavage of the disulphide bond to form protected L-homocysteine **5** was achieved in 90% yield, using tributylphosphine in DMF.[12,15,16] Precursors **1** and **2** and compounds **6** and **7** were prepared in 38–93% yields by coupling 1-bromo-2-haloethane or 2-bromoethanol with thiol **5** in the presence of potassium carbonate in DMF at room temperature.[15,16] The overall yields of the brominated and chlorinated precursors **1** and **2** for the four steps were 34 and 74%, respectively. The moderate yield obtained for precursor **1** was due to extensive decomposition during purification and its instability in the presence of water. The presence of a sulphur mustard structure[17] in these compounds accelerates halide hydrolysis, particularly with the better leaving group (bromide) present in **1** (Scheme 2). For this reason, attempts to prepare the corresponding *S*-(2-tosyloxyethyl)-L-homocysteine **8**, by reaction of alcohol **7** with *p*-(toluenesulphonyl) chloride, were unsuccessful, due to the high instability of **8**. Although conversion of **7** into **8** was

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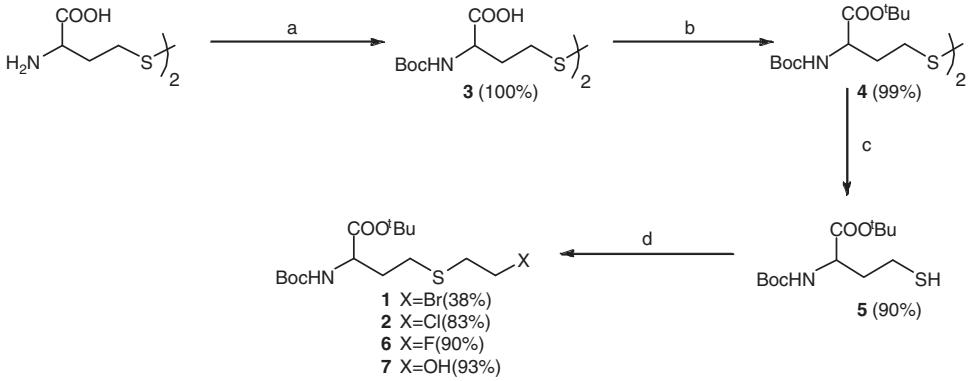
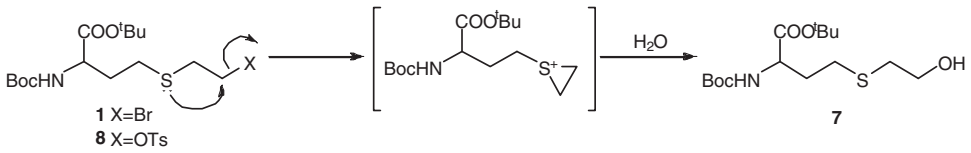
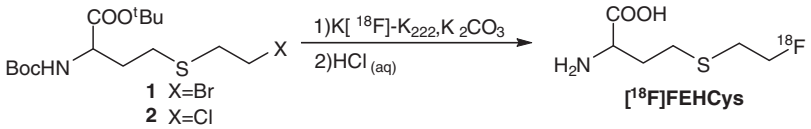


Scheme 1. Synthesis of precursors 1-2. Reagents and conditions: (a) Boc_2O, dioxane, $Na_2CO_{3(aq)}$, RT; (b) *tert*-butyl-2,2,2-trichloroacetimidate, CH_2Cl_2, RT; tributylphosphine, DMF, RT; and (d) 1-bromo-2-haloethane or 2-bromoethanol, K_2CO_3, DMF, RT.2



Scheme 2. Proposed mechanism of the hydrolysis of the sulfur mustards.



Scheme 3. Radiosynthesis of [^{18}F]FEHCys.

observed by TLC analysis of the reaction mixture, all attempts to isolate the tosylate resulted in its hydrolysis to alcohol **7**.

Radiochemistry

The radiosynthesis of [^{18}F]FEHCys from **1** and **2** was accomplished in two steps,[13,14,18] by classical fluorine-18 nucleophilic substitution, followed by acid hydrolysis of the protecting groups (Scheme 3). Optimization of the reaction conditions involved the reaction of [^{18}F]fluoride at different temperatures (50–100°C) with 5 mg quantities of precursors **1** and **2** in acetonitrile containing 10 mg K_{222} and 2 mg potassium carbonate (Figure 1). At 50°C the brominated precursor **1** showed higher reactivity (30% yield at 30 min) than the chlorinated analogue **2** (3%). However, the radiochemical yield of both precursors was significantly increased at 100°C. At this temperature, the chlorinated precursor **2** delivered a continuously increasing yield over the 30-min reaction until a maximum of 22% radiochemical yield was reached. Unlike the chlorinated precursor **2**, which is stable up to 100°C at high temperature, the brominated precursor **1** showed significant decomposition at 80°C after 15 min of reaction, while this decomposition was apparent at 100°C after only 5 min. The highest labelling efficiency (40%) was obtained using 5 mg of precursor **1** at 100°C for 5 min.

The radiosynthesis of [^{18}F]FEHCys was then completed by acid hydrolysis to remove both protecting groups. Hydrolysis of protected [^{18}F]FEHCys (generated from **1** at 100°C) was performed with 6 N HCl at 100°C for 5 min. This reaction was then quenched with 6 N NaOH and diluted in water. The resulting solution was analysed by HPLC, which confirmed complete hydrolysis and formation of [^{18}F]FEHCys. However, during HPLC analysis, instability of [^{18}F]FEHCys was observed. Indeed, 20 min after quenching this reaction, [^{18}F]FEHCys was totally transformed to the corresponding alcohol (*S*-(2-hydroxyethyl)-l-homocysteine (HOEHCys)).

Stability of [^{18}F]FEHCys

To investigate the observed instability of [^{18}F]FEHCys, a comparative study on non-radioactive FEHCys was carried out. Non-radioactive FEHCys was prepared by acid hydrolysis of **6** at room temperature, which also yielded about 5% of the corresponding alcohol as by-product (Scheme 4). The stability of FEHCys in water at room temperature was studied by HPLC in H_2O and NMR in D_2O using this 95:5 mixture of FEHCys and HOEHCys. Hydrolysis of FEHCys, in H_2O, was observed by HPLC after 20 min giving the corresponding alcohol (HOEHCys), with total transformation after 80 min (Figure 2). The same hydrolysis reaction was observed by NMR in D_2O; however, this hydrolysis was much slower, which even after 7 days was not totally transformed (Figure 3). This is expected from the mechanism shown in Scheme 2, because the strong hydrogen bonding between H_2O and fluoride, which assists the formation of the intermediate thiirane salt from FEHCys, is known to be much weaker in D_2O.[19] This comparative study on non-radioactive

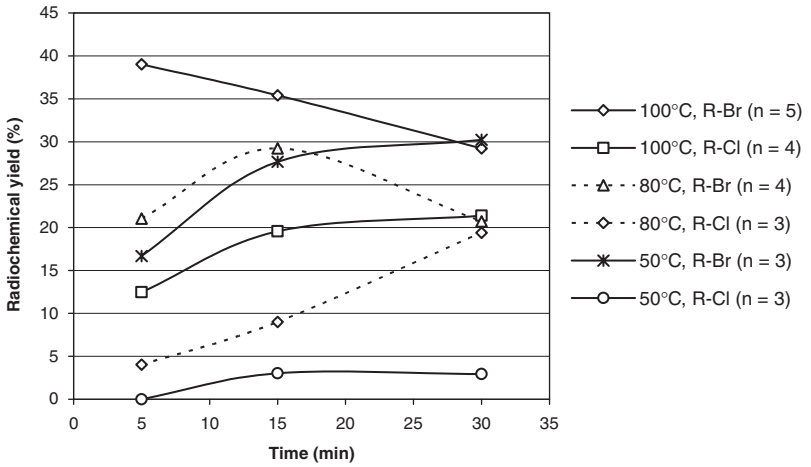
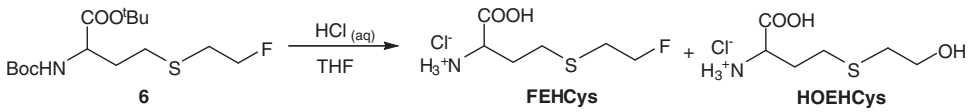


Figure 1. Radiolabelling of bromo- and chloro-precursors **1** and **2** (5 mg) in acetonitrile (1 mL) with K_{222} (10 mg) and K_2CO_3 (2 mg) as a function of temperature and time.



Scheme 4. Hydrolysis of compound **6**.

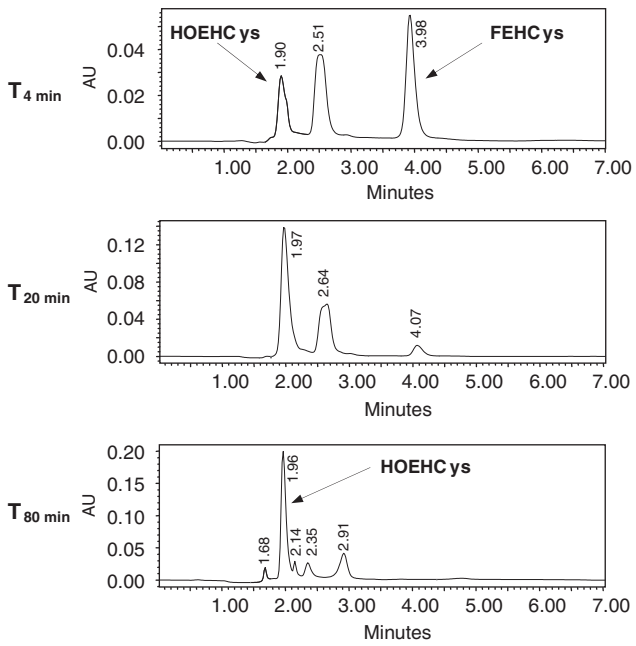


Figure 2. Investigation of the stability of FEHCys by HPLC (sample: 1 mg of a 95:05 mixture of FEHCys and HOEHCys in 500 µL of water; HPLC conditions: Grace AlltimaC18 column (150 × 4.6 mm, 5 µm); mobile phase CH_3CN/H_2O 10/90, v/v; flow rate 1 mL/min; λ = 210 nm).

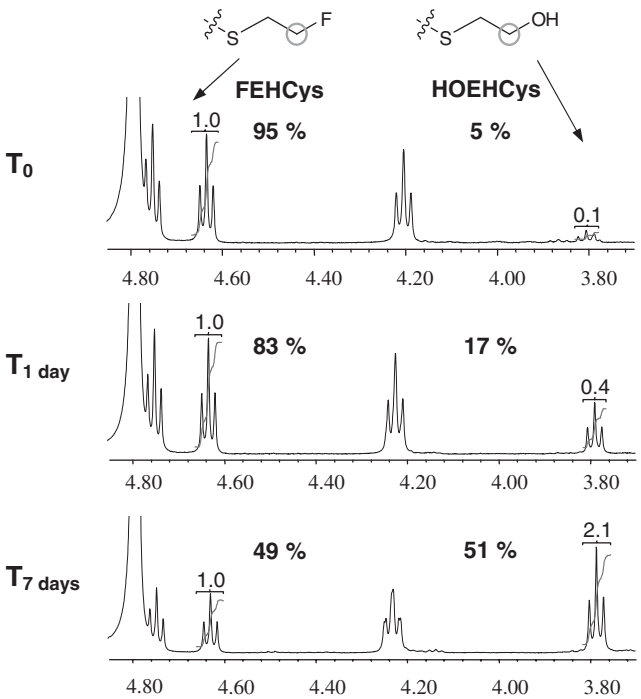


Figure 3. Investigation of the stability of FEHCys by NMR (sample: 3 mg of a 95:5 mixture of FEHCys and HOEHCys in 600 µL of D_2O).

FEHCys demonstrated that the fluorine is easily displaced to give the corresponding alcohol and confirmed that FEHCys is unstable in aqueous systems.

The radiosynthesis[8] and preliminary biological evaluation[9,10] of [^{18}F]FEHCys were described by Tang *et al* with no information on the stability of the product. In order to verify the stability/instability of FEHCys, we repeated the two-step procedure, using 2-[^{18}F]fluoroethyl tosylate, as described in the literature. However, the same transformation of the resulting [^{18}F]FEHCys was observed by HPLC, confirming the instability of FEHCys in aqueous systems.

Experimental

General

All reagents and solvents were purchased from Lancaster, Fluka or Sigma-Aldrich. All chemicals and solvents were used without further purification.

All melting points were determined in open capillary tubes using an SRS Optimet automated melting point system, MPA 100, and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured on a Brucker DPX 400 at 400 MHz (^{1}H) and 100 MHz (^{13}C) in an appropriate deuterated solvent ($CDCl_3$, CD_3OD, D_2O). Chemical shifts are reported as parts per million (δ) relative to tetramethylsilane (0.00 ppm), which was used as an internal standard. Coupling constants are given in Hz and coupling patterns are abbreviated as: s (singlet), d (doublet), t (triplet), m (mutiplet) and dt (doublet of triplet). Low-resolution mass spectrometry (LRMS) was performed on a Waters Micromass ZQ Quadrupole Mass Spectrometer, whereas high-resolution mass spectrometry (HRMS) was performed using a Micromass Qtof Ultima or AutoSpec TOF. TLCs were run on pre-coated aluminium plates of silica gel $60F_{254}$ (Merck) and R_f was established using an UV lamp at 254 nm. Column chromatography was undertaken on Merck 60 silica gel (40–63 μm) columns.

[^{18}F]HF was produced on a GE PET trace cyclotron via the $^{18}O(p, n)^{18}F$ nuclear reaction (Cyclotek, Australia). The intermediate product labelled with fluorine-18 was analysed by HPLC, consisting of a Waters 510 pump, a linear UVIS detector ($\lambda = 210$ nm) in series with a Berthhold β^+-flow detector, on a Phenomenex Bondclone C18 column (300 × 7.8 mm, 10 μm) at 2 mL/min with CH_3CN/H_2O (70:30, v/v) as the mobile phase. Quality control analysis of the hydrolysed radioligand was performed on a Waters 600 W pump, a Waters 2996 photodiode array detector ($\lambda = 210$ nm) in series with an Ortec ACE Mate β^+-flow detector on a Phenomenex Synergi Hydro RP column (250 × 10 mm, 5 μm) at 2 mL/min with CH_3CN/H_2O (10:90, v/v) as the mobile phase. The identity of the labelled compound was confirmed by co-injection with the authentic compound on HPLC. Radioactivity was measured with a Capintec R15C dose calibrator.

Chemistry and radiochemistry

*N,N′-di(tert-butoxycarbonyl)-L-homocystine (**3**)*

Prepared by the published procedure.[12] The following additional analytical data were obtained: m.p. 158–159°C; ^{13}C NMR (CD_3OD) δ 175.68, 158.16, 80.69, 53.72, 35.80, 32.54, 28.82; LRMS: ES (+ve) *m/z* 469 (M+1); HRMS: ES (+ve) calcd. for $C_{18}H_{32}N_2O_8S_2$ (M+1) 469.1703, found 469.1678.

*Di(tert-butyl) N,N′-bis(tert-butoxycarbonyl)-L-homocystinate (**4**)*

Tert-butyl-2,2,2-trichloroacetimidate (11.0 g, 47.77 mmol) was added to a solution of **3** (4.47 g, 9.55 mmol) in dichloromethane (39 mL) under nitrogen. After overnight stirring at room temperature, the solvent was removed under reduced pressure and the crude residue purified by chromatography on silica gel (heptanes/ethyl acetate 80:20) to give **4** (5.50 g, 99%) as a white solid: m.p. 66–68°C; ^{1}H NMR and ^{13}C NMR identical to published data[12]; LRMS: ES (+ve) *m/z* 581 (M+1); HRMS: ES (+ve) calcd. for $C_{26}H_{48}N_2O_8S_2$ (M+1) 581.2938, found 581.2930.

*Tert-butyl N-(tert-butoxycarbonyl)-L-homocysteinate (**5**)*

To a solution of **4** (3.20 g, 5.51 mmol) in DMF (45 mL) was added water (4 mL) and tributylphosphine (1.26 g, 6.06 mmol) and the mixture stirred under nitrogen at room temperature overnight. The reaction mixture was quenched with water (500 mL) and the aqueous phase thoroughly extracted with ethyl acetate (3 × 240 mL). The combined organic layers were washed with brine (2 × 150 mL), dried ($MgSO_4$) and the solvents evaporated. The crude residue was purified by chromatography on silica gel (heptanes/ethyl acetate 90:10) to give **5** (2.90 g, 90%) as a colourless oil. ^{1}H NMR and ^{13}C NMR identical to published data[12]; LRMS: ES (+ve) *m/z* 292 (M+1); HRMS: ES (+ve) calcd. for $C_{13}H_{25}NO_4S$ (M+1) 292.1579, found 292.1583.

*Tert-butyl N-(tert-butoxycarbonyl)-S-(2-fluoroethyl)-L-homocysteinate (**6**)*

To a solution of **5** (200 mg, 0.68 mmol) in DMF (3 mL) was added 1-bromo-2-fluoroethane (133 mg, 1.03 mmol) followed by potassium carbonate (190 mg, 1.37 mmol) and the resultant white solution stirred for 24 h at room temperature under nitrogen. The reaction mixture was diluted with water (40 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water (40 mL), dried ($MgSO_4$) and the solvents evaporated. The crude residue was purified by chromatography on silica gel (heptanes/ethyl acetate 90:10) to give **6** (207 mg, 90%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 5.15–5.05 (m, 1H), 4.54 (dt, $J = 47.1$, 6.4 Hz, 2H), 4.35–4.20 (m, 1H), 2.80 (dt, $J = 19.9$, 6.4 Hz, 2H), 2.65–2.55 (m, 2H), 2.15–2.05 (m, 1H), 1.95–1.80 (m, 1H), 1.46 (s, 9H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.35, 155.47, 83.17 ($J = 171.0$ Hz), 82.40, 79.97, 53.44, 33.40, 31.87 ($J = 21.5$ Hz), 28.49, 28.45, 28.13; LRMS: ES (+ve) *m/z* 338 (M+1); HRMS: ES (+ve) calcd. for $C_{15}H_{28}NO_4SF$ (M+1) 338.1805, found 338.1801.

*Tert-butyl N-(tert-butoxycarbonyl)-S-(2-hydroxyethyl)-L-homocysteinate (**7**)*

This compound was synthesized as described for **6** from **5** (791 mg, 2.71 mmol) and 2-bromoethanol (535 mg, 4.07 mmol). The crude residue was purified by chromatography on silica gel (heptanes/ethyl acetate 70:30) to give **7** (849 mg, 93%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 5.12 (d, $J = 6.7$ Hz, 1H), 4.35–4.25 (m, 1H), 3.71 (dt, $J = 5.8$, 5.8 Hz, 2H), 2.71 (t, $J = 5.8$ Hz, 2H), 2.65–2.50 (m, 2H), 2.39 (s, br, 1H), 2.15–2.05 (m, 1H), 1.95–1.80 (m, 1H), 1.46 (s, 9H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.46, 155.59, 82.43, 80.06, 60.44, 53.33, 35.53, 33.44, 28.45, 28.14, 27.65; LRMS: ES (+ve) *m/z* 336 (M+1); HRMS: ES (+ve) calcd. for $C_{15}H_{29}NO_5S$ (M+1) 336.1846, found 336.1845.

*Tert-butyl S-(2-bromoethyl)-N-(tert-butoxycarbonyl)-L-homocysteinate (**1**)*

This compound was synthesized as described for **6** from **5** (200 mg, 0.68 mmol) and 1,2-dibromoethane (390 mg, 2.06 mmol). The crude residue was purified by chromatography

on silica gel (heptanes/ethyl acetate 90:10) to give **1** (104 mg, 38%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 5.15–5.05 (m, 1H), 4.35–4.20 (m, 1H), 3.46 (t, J = 8.3 Hz, 2H), 2.93 (t, J = 8.2 Hz, 2H), 2.65–2.50 (m, 2H), 2.15–2.05 (m, 1H), 1.95–1.80 (m, 1H), 1.47 (s, 9H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.29, 155.48, 82.50, 80.05, 53.36, 34.36, 33.47, 30.42, 28.46, 28.27, 28.16; LRMS: ES (+ve) *m/z* 398 (M[Br^{79}]+1), 400 (M[Br^{81}]+1); HRMS: ES (+ve) calcd. for $C_{15}H_{28}NO_4SBr$ (M[Br^{79}]) 397.0932, found 397.0922.

*Tert-butyl N-(tert-butoxycarbonyl)-S-(2-chloroethyl)-L-homocysteinate (**2**)*

This compound was synthesized as described for **6** from **5** (200 mg, 0.68 mmol) and 1-bromo-2-chloroethane (301 mg, 2.06 mmol). The crude residue was purified by chromatography on silica gel (heptanes/ethyl acetate 90:10) to give **2** (199 mg, 83%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 5.15–5.05 (m, 1H), 4.35–4.20 (m, 1H), 3.62 (t, J = 7.8 Hz, 2H), 2.86 (t, J = 7.8 Hz, 2H), 2.65–2.50 (m, 2H), 2.15–2.05 (m, 1H), 1.95–1.80 (m, 1H), 1.47 (s, 9H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.29, 155.46, 82.46, 80.02, 53.37, 43.09, 34.40, 33.44, 28.44, 28.34, 28.13; LRMS: ES (+ve) *m/z* 376 (M[Cl^{35}]+Na), 378 (M[Cl^{37}]+Na); HRMS: ES (+ve) calcd. for $C_{15}H_{28}NO_4SCl$ (M[Cl^{35}]+Na) 376.1335, found 376.1325.

S-(2-fluoroethyl)-L-homocysteine hydrochloride (FEHCys)

To a solution of the protected amino acid **6** (50 mg) in THF (445 μL) was added 6 N hydrochloric acid (890 μL) and the reaction mixture stirred at room temperature for 90 min. The solvent was removed under reduced pressure, and the resulting solid washed with ethyl acetate (3 × 6 mL), dried under vacuum to give FEHCys (21 mg, 58%) as a white solid. Analysis of this solid by NMR in D_2O indicated a 95:05 mixture of FEHCys and of the corresponding alcohol (HOEHCys). For FEHCys: ^{1}H NMR (D_2O) δ 4.69 (dt, J = 47.0, 5.8 Hz, 2H), 4.24 (t, J = 6.1 Hz, 1H), 2.95 (dt, J = 24.8, 5.8 Hz, 2H), 2.90–2.75 (m, 2H), 2.40–2.15 (m, 2H); ^{13}C NMR (D_2O)δ 173.13, 84.69 (d, J = 164.1 Hz), 53.15, 32.21 (d, J = 19.9 Hz), 30.89, 28.05. For HOEHCys: ^{1}H NMR (D_2O) δ 4.24 (t, J = 6.1 Hz, 1H), 3.79 (t, J = 6.1 Hz, 2H), 2.90–2.75 (m, 4H), 2.40–2.15 (m, 2H); ^{13}C NMR (D_2O) δ 172.94, 61.37, 52.99, 34.34, 30.81, 27.71.

Radiosynthesis of S-(2-[^{18}F]fluoroethyl)-L-homocysteine ([^{18}F]FEHCys)

An aqueous [^{18}F]fluoride solution (6–7 GBq) was added to a 10 mL vial containing a solution of K_2CO_3 (2 mg, 20 μL in H_2O) and K_{222} (10 mg, 100 μL in CH_3CN). The solvent was evaporated under a stream of nitrogen at 100°C under vacuum and the residue azeotropically dried twice more by further addition of anhydrous acetonitrile (2 × 1 mL). To the activated K_{222}/potassium [^{18}F]fluoride was added the precursor **1** (5 mg, 13 μmol) in acetonitrile (1 mL) and the mixture heated at 100°C for 5 min before the addition of 6 N HCl (500 μL). After 5 min at 100°C, 6 N NaOH (500 μL) and water (1 mL) were added and the resulting solution was directly analysed on a semi-preparative HPLC column (Phenomenex Synergi Hydro RP column (250 × 10 mm, 5 μm); mobile phase CH_3CN/H_2O 10/90, v/v; flow rate 2 mL/min; λ = 210 nm) and [^{18}F]FEHCys was observed at 15.2 min. However, 20 min after quenching the reaction mixture, [^{18}F]FEHCys had almost completely transformed to the corresponding alcohol.

Conclusion

We have developed a one-pot two-step synthesis of [^{18}F]FEHCys via the protected *S*-(2-bromoethyl)-L-homocysteine **1** and *S*-(2-chloroethyl)-L-homocysteine **2** precursors. The bromoethyl derivative **1** gave higher radiochemical yields (40% at 5 min) at 100°C. However, [^{18}F]FEHCys was found to be unstable in aqueous systems, which was confirmed by determining the stability of unlabelled FEHCys in H_2O by HPLC and in D_2O by NMR. Attempts to prepare [^{18}F]FEHCys by the method described in the literature[8] gave the same result, confirming the instability of [^{18}F]FEHCys prepared by both methods.

Acknowledgement

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