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One-step radiosynthesis of 4-nitrophenyl 2-[^{18}F]fluoropropionate ([^{18}F]NFP); improved preparation of radiolabeled peptides for PET imaging

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The versatile ^{18}F-labeled prosthetic group, 4-nitrophenyl 2-[^{18}F]fluoropropionate ([^{18}F]NFP), was synthesized in a single step in 45 min from 4-nitrophenyl 2-bromopropionate, with a decay corrected radiochemical yield of 26.2% ± 2.2%. Employing this improved synthesis of [^{18}F]NFP, [^{18}F]GalactoRGD — the current 'gold standard' tracer for imaging the expression of $\alpha_V\beta_3$ integrin — was prepared with high specific activity in 90 min and 20% decay corrected radiochemical yield from [^{18}F]fluoride.

Keywords: radiofluorination; PET imaging; fluoropropionate; RGD peptide; [^{18}F]fluoride

Introduction

Positron emission tomography (PET) is a powerful molecular imaging technique, which enables the real-time imaging of *in vivo* biochemistry, provides valuable insight into the staging of disease, and uniquely allows one to observe and monitor the affects of intervention on a timescale not readily available to more conventional structural imaging techniques. The successful application of this technique relies largely upon the development of radiolabeled agents, which probe molecular targets specific to the disease being interrogated.

The use of radiolabeled peptides and proteins in PET has the potential to provide an inexhaustible number of agents with which to probe disease.[1–4] This has in part been borne out in the molecular imaging of cancer with agents such as radiolabeled analogs of the somatostatin receptor-selective agent octreotate[5,6] and radiolabeled 'RGD' peptides that target the $\alpha_v\beta_3$ integrin.[7–11]

The radionuclide ^{18}F is ideally suited to PET imaging due to its optimal half life (110 min), high positron emission efficiency (97%), low positron energy (0.64 MeV), and its amenity to chemical incorporation into molecules of biological interest. Therefore, the development of radiofluorinated peptides remains of important clinical interest. Most commonly, ^{18}F is incorporated into a peptide through the attachment of a radiolabeled prosthetic group. There exists a range of prosthetic groups for this purpose, the most common being 4-fluorobenzoate and 2-fluoropropionate, each imparting its own pharmacokinetic characteristics upon the resultant adduct.[12]

The most versatile of the reagents available for fluorobenzoylation and fluoropropionylation are the corresponding activated esters; *N*-succinimidyl 4-[^{18}F]fluorobenzoate ([^{18}F]SFB) and 4-nitrophenyl 2-[^{18}F]fluoroproprionate ([^{18}F]NFP), respectively. Both of these agents have been used in the radiolabeling of numerous peptides for PET imaging, including the $\alpha_v\beta_3$ integrin-targeting RGD peptides,[13–17] cysteine-knot peptides,[10] bombesin derivatives,[18] and somatostatin analogs.[19,20] 2-[^{18}F]Fluoropropionate[12] offers considerable advantages due to its relatively small size, minimal effect on the hydrophobicity of the peptide, and its metabolic stability.[16]

One of the most widely studied and clinically applied PET tracers targeting $\alpha_v\beta_3$ integrin is [^{18}F]GalactoRGD **1** (Figure 1).[4,12,15] The imaging of integrin expression is an important strategy for monitoring the neovasculature of tumors, as $\alpha_v\beta_3$ integrin plays an important role in tumor angiogenesis[6–11,21–25] and metastasis.[26,27] [^{18}F]GalactoRGD **1** incorporates an aminomethyl galacturonic acid linker between the cyclic peptide and the [^{18}F] fluoropropionyl group to improve biodistribution. Despite the

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Abbreviations: *DMSO, dimethyl sulfoxide; NFP, 4-nitrophenyl 2-fluoropropionate; K_{222}, Kryptofix®222; n.d.c., non decay corrected; TBA, tetrabutylammonium; TLC, thin layer chromatography.*

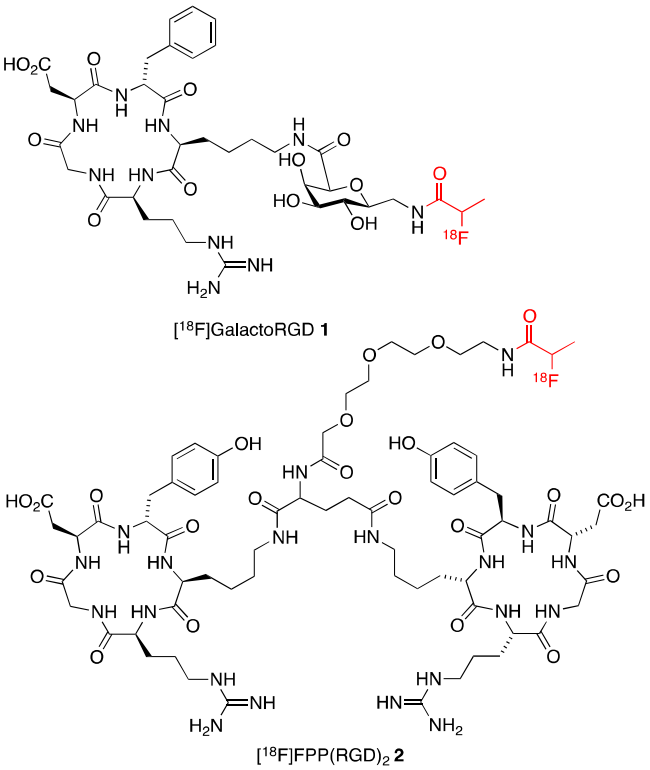


Figure 1. [^{18}F]-Fluoropropionylated peptides for PET imaging of $\alpha_v\beta_3$ integrin expression.

desirable properties of **1** as a PET imaging agent, its lengthy, multistep synthesis presents a considerable limitation, and there remains a need to improve its preparation in order for it to be widely available for clinical use. The syntheses of both the galacturonic acid moiety and the activated ester [^{18}F]NFP **7** are lengthy and complicated. The standard method for the synthesis of [^{18}F]NFP **7** is a multistep, labor intensive and time consuming exercise (Scheme 1).[9,16] Because of the volatile nature of simple fluoropropionate esters, a bulky 9-anthrylmethyl ester is employed for ease of handling during the radiolabeling procedure. Treatment of 2-bromopropionyl bromide **3** with 9-anthrylmethanol generates ester **4**, which is then treated with [^{18}F]KF/K_{222} under typical nucleophilic radiofluorination conditions to incorporate the radionuclide. The fluorinated ester **5** is purified and then hydrolyzed to give [^{18}F]2-fluoropropionate **6a,** and subsequent treatment with *p*-nitrophenyl carbonate generates the active ester [^{18}F]NFP **7**. The overall process incorporates three radiochemical steps and two radio-HPLC purifications, which are both time-consuming and has to date presented considerable challenges to the automation of this process.

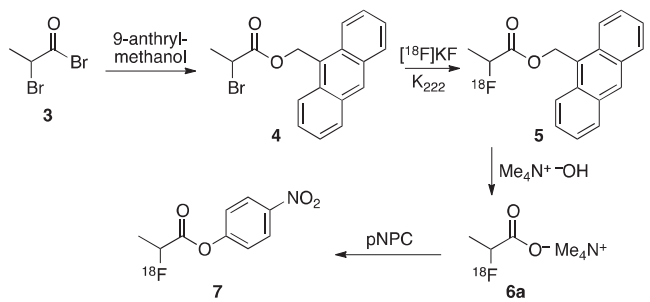
Recently, Chen and co-workers reported the preparation of [^{18}F]FPP(RGD)$_2$ **2** (Figure 1),[13,15,28,29] a promising new tracer currently undergoing clinical trials.[14,30] In their preparation of [^{18}F]NFP **7**, Chen and co-workers adapted Stöcklin's synthesis[31,32] of [^{18}F]2-fluoropropionic acid ([^{18}F]FPA, **6b**) in order to improve the overall synthesis of [^{18}F]NFP **7** (Scheme 2). Although this improved method can be conducted in one pot and therefore a single radiosynthesis module, it still requires multiple radiochemical steps, separated by an azeotropic drying of the 2-[^{18}F] fluoropropionate **6b**.[10,30]

Improvements in the radiochemical synthesis of [^{18}F]NFP **7** would greatly assist the clinical preparation of ^{18}F-labeled peptides, such as **1** and **2**, for PET imaging. Incorporation of the ^{18}F radionuclide in the final step of the synthesis of **7** would clearly be optimal as this would minimize the number of processes and thereby simplify automation and reduce the time from end-of-beam to the final, ready-to-inject tracer.

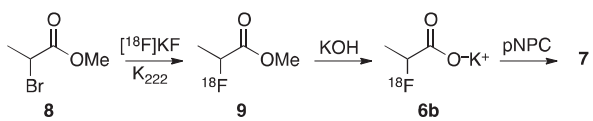
Herein, we report an improved synthesis of [^{18}F]NFP **7** in a single radiochemical step and the use of this process in the preparation of the clinically relevant tracers for PET imaging of $\alpha_v\beta_3$-related tumors, [^{18}F]GalactoRGD **1** and [^{18}F]FPP(RGD)$_2$ **2**.

Materials and methods

All reagents were purchased from commercially available sources and were used as received. No-carrier-added [^{18}F] fluoride ion was obtained from a PETtrace 16.5 MeV cyclotron incorporating a high pressure niobium target (GE Healthcare, USA and Cyclotek, Vic., Australia) via the ^{18}O(p,n)^{18}F nuclear reaction. ^{18}F-Separation cartridges (Waters Accell Plus QMA Sep-Pak Light, MA, USA) were pre-conditioned with the base employed in the radiofluorination step (K_2CO_3, TBA–HCO_3, $K_2C_2O_4$, or $KHCO_3$). Reversed phase SPE cartridges (Phenomenex, Strata X 33 μ polymeric reversed phase (30 mg/mL), CA, USA) were pre-conditioned with ethanol and water before use. Radio-HPLC analyses were performed using a Shimadzu HPLC (SCL-10AVP system controller, SIL-10ADVP auto injector, LC-10ATVP solvent delivery unit, CV-10AL control valve, DGU-14A degasser, and SPD-10AVPV detector, Kyoto, Japan) coupled to a scintillation detector (Ortec 276 Photomultiplier Base with Preamplifier, Ortec 925-SCINT ACE mate Preamplifier, Amplifier, BIAS supply and SCA, and a Bicron 1 M 11/2 Photomultiplier Tube). Manual radio-HPLC purifications were achieved using a similar system fitted with a manual injector. Semi-preparative HPLC purification of non-radioactive materials was performed using an Agilent 1200 series HPLC system. Analytical HPLC was performed on an Agilent 1100 series HPLC system. The following columns, solvents and flow rates were used for the purification of both radioactive and non-radioactive material: NFP and its precursor; Synergi 10 μ Hydro-RP 80 Å, 250 × 15 mm, (0.1% TFA in 20–100% CH_3CN–H_2O over 80 min), 8 mL/min. [^{18}F]NFP **7**; Macherey–Nagel EP250/16 nucleosil 100-7 C18 column, (0.1% TFA in 60:40 CH_3CN–H_2O), 6 mL/min.



Scheme 1. Synthesis of [^{18}F]NFP **7** via anthrylmethyl ester.



Scheme 2. Chen's synthesis of [^{18}F]NFP **7**.

GalactoRGD; Protecol C18 HQ305, 250 × 4.6 mm, 5 μ, 300 Å, (0.1% TFA in 0–80% CH_3CN–H_2O over 40 min), 8 mL/min. [^{18}F]GalactoRGD **1** and [^{18}F]FPP(RGD)$_2$ **2**; Luna 5 μ C18(2) 100 Å, 250 × 10.00 mm, 5 μ, (0.1% TFA in 10–80% CH_3CN–H_2O over 40 min) 4 mL/min. QC and specific activity determination of [^{18}F]NFP **7**; Luna 5 μ C18(2), 150 × 4.60 mm, (0.1% TFA in 60:40 H_2O–CH_3CN), 1 mL/min. QC and specific activity determination of [^{18}F]peptides: Phenomenex Jupiter 5u Proteo 90 Å, 250 × 4.6 mm, (0.1% TFA in 2–80% CH_3CN–H_2O over 40 min), 1 mL/min. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were obtained on a Varian Unity INOVA-500 MHz spectrometer or a Bruker AVANCE III-600 MHz spectrometer. MS data was obtained using Agilent 6510 Q-TOF LC/MS mass spectrometer (CA, USA) equipped with an Agilent 1100 LC system. [^{18}F]NFP **7** was synthesized using a GE TRACERlab FX_{FN} radiosynthesis module.

*4-Nitrophenyl 2-bromopropionate **15***

To a solution of (±)-2-bromopropionylbromide (0.50 g, 2.32 mmol) in CH_2Cl_2 (10 mL), triethylamine (0.32 mL, 2.32 mmol) and *p*-nitrophenol (0.33 g, 2.32 mmol) were added at 0 °C. The mixture was stirred for 1 h, then the precipitate formed was removed by filtration and washed with CH_2Cl_2. The filtrate was evaporated under vacuum, and the residue was purified by crystallization from ethyl acetate to yield the title compound (0.61 g, quant.) as white crystals, m.p. 37–39 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, 2H, ArH), 7.31 (d, 2H, ArH), 4.60 (q, 1H, CH), 1.95 (d, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8 (C=O), 155.0 (Ar–O), 145.6 (Ar–NO_2), 126.3 (Ar–C), 122.0 (Ar–C), 39.0 (C–Br), 21.2 (CH_3).

*4-Nitrophenyl 2-[^{18}F]fluoropropionate ([^{18}F]NFP **7**)*

[^{18}F]Fluoride in [^{18}O]water was transferred to the TRACERlab FX_{FN} radiosynthesis module and passed through a pre-conditioned QMA cartridge. Trapped [^{18}F]fluoride (12.3–29.7 GBq) was eluted to the reactor with a solution containing $KHCO_3$ (3–7 mg, 0.03–0.07 mmol) and Kryptofix 222 (12–14 mg, 0.03–0.04 mmol) in CH_3CN–H_2O (60:40, 1.0 mL). The solution was evaporated at 65 °C under helium flow and vacuum for 13 min, followed by heating at 120 °C under helium then vacuum for a further 7 min. To the anhydrous [^{18}F]KF/K_{222}/$KHCO_3$ residue, 4-nitrophenyl 2-bromopropionate **15** (20 mg, 0.05 mmol) in *t*BuOH–CH_3CN (4:1, 2 mL) was added. After 5 min at 100 °C, the solvent was evaporated to half volume, and the residue was diluted with mobile phase (0.1% TFA in 60:40 CH_3CN–H_2O, 1.5 mL). The mixture was transferred to the loop injection vial. The reaction vial was washed with mobile phase (1.5 mL) and transferred to the loop injection vial. [^{18}F] NFP **7** was then purified by preparative HPLC to afford the title compound (3.2–7.7 GBq, 29% highest decay corrected radiochemical yield), with the highest specific activity achieved being 474 GBq μmol^{-1}. The total reaction time was 45 min.

When [^{18}F]NFP **7** was subsequently used for peptide labeling experiments, the collected HPLC fraction was diluted in water (60 mL) and passed through a Strata X reversed phase SPE cartridge. [^{18}F]NFP **7** was retained on the cartridge. The cartridge was rinsed with water (10 mL) and then removed from the radiosynthesis module to perform further labeling experiments.

[^{18}F]GalactoRGD 1

[^{18}F]NFP **7** (3.7 GBq) isolated on a Strata X cartridge was eluted with DMSO (300 μL) into a vial charged with Galacto-RGD (1.0 mg, 1.2 μmol). DMSO–TEA (20:1, 10 μL) was then added to the same vial. The reaction mixture was left at room temperature for 2 min, and then a portion (620 MBq) of the mixture was diluted with water (1.5 mL) and purified by HPLC. To remove mobile phase and concentrate [^{18}F]GalactoRGD **1**, the HPLC fraction containing **1** was diluted with water (20 mL) and passed through a pre-conditioned reversed phase SPE cartridge. Cartridge retained [^{18}F]GalactoRGD **1** was then washed with phosphate buffered saline (PBS) (5 mL, pH 7.4) and finally eluted using ethanol (0.6 mL). The eluent was diluted with PBS (7 mL, pH 7.4) and filtered to obtain [^{18}F]GalactoRGD **1** (350 MBq, 69% decay corrected radiochemical yield). Specific activity was 122 GBq μmol^{-1}.

*[^{18}F]FPP(RGD)$_2$ **2***

[^{18}F]NFP **7** (5.0 GBq) isolated on a pre-conditioned reversed phase SPE cartridge was eluted with CH_2Cl_2 (2 mL) into a vial, via an anhydrous sodium sulfate drying cartridge. The CH_2Cl_2 was evaporated at room temperature for 3 min and at 70 °C for a further 2 min. MiniPEG-E(RGD)$_2$ (1 mg, 0.6 μmol) and TEA (15 μL, 0.11 μmol) in DMSO (0.35 mL) were added. The reaction was heated at 70 °C for 5 min. Water containing 0.1% TFA (3 mL) was added to the reaction mixture. The reaction was left at 70 °C for 5 min and then diluted with additional water (3 mL) and purified by HPLC. The HPLC fraction containing **2** was diluted with water (40 mL) and isolated on a pre-conditioned reversed phase SPE cartridge. The cartridge was washed with PBS (5 mL, pH 7.4) and eluted with ethanol (0.6 mL). The eluent was diluted with PBS (7 mL, pH 7.4) and filtered to obtain [^{18}F]FPP(RGD)$_2$ **2** (1.1 GBq, 30% decay corrected radiochemical yield). Specific activity was 255 GBq μmol^{-1}.

Results and discussion

A simple, one-step synthesis of a small and versatile radiolabeled prosthetic group has long been considered a valuable addition to a radiochemist's armamentarium. Indeed, [^{18}F]NFP **7** represents such an agent, except for its problematic preparation. Until now, the synthesis of [^{18}F]NFP **7** has necessarily incorporated multiple substitution reactions of the propionate group, including substitution of the 2-bromo substituent with [^{18}F]fluoride and conversion of the acid to the 'activated' ester (Schemes 1 and 2). In order to minimize the number of radiochemical steps, substitution of the bromide with [^{18}F]fluoride should be performed as late as possible. Ideally, the substitution reaction with [^{18}F]fluoride would be performed as the final step, but this would involve selective substitution of a secondary alkyl bromide in the presence of an activated ester, with the obvious potential side reactions of fluoride substitution at the acyl position and hydrolysis of the activated ester. Indeed, Block et al.[31] attempted the aliphatic substitution of activated esters of 2-bromoacetate with [^{18}F]fluoride in acetonitrile, without success. Other substitution reactions in the presence of activated esters have also met with limited success.[33] However, Kim et al.[34] recently reported that the use of the tertiary alcoholic solvents generates a *tert*-alcohol-solvated fluoride ion that reacts as a strong nucleophile yet moderate base, with minimal base-catalyzed side reactions. Olberg et al.[35] employed *t*-butanol solvent mixtures in the radiofluorination of a nicotinic acid tetrafluorophenyl ester. We therefore envisaged that there may be a window of reactivity of an activated 2-bromopropionate ester in which the activated ester was relatively stable to hydrolysis during the radiofluorination stage, yet would still be reactive enough to acylate peptides rapidly and in good yield.

Accordingly, the preparation of a variety of activated esters (see Figure 2) of 2-bromopropionate (**10–15**) was attempted, through treatment of 2-bromopropionylbromide **3** with the respective hydroxy compounds N-hydroxysuccinimide (NHS), N-hydroxybenzotriazole (HOBt), N-hydroxy-7-azabenzotriazole (HOAt), 2,3,5,6-tetrafluorophenol, 2,4-dinitrophenol, and 4-nitrophenol. Most reactions proceeded to generate the corresponding active esters **10–15** in good conversion, according to TLC analysis. However, the NHS, HOBt, and HOAt esters **10–12** were unstable and hydrolyzed to the corresponding acid during chromatography. Reaction of 2,4-dinitrophenol gave a mixture of the desired dinitrophenyl ester **14** together with the hydrolysis product, presumably because of the dinitrophenol containing water as an additive to minimize its explosive nature. This active ester was not pursued further. The tetrafluorophenyl ester **13** was stable but due to its volatility was lost upon removal of the solvent under reduced pressure. Uniquely, the 4-nitrophenyl ester **15** was prepared in excellent yield and afforded a white, non-volatile, crystalline solid that was stable to HPLC, column chromatography, and crystallization conditions. Radiofluorination of **15** was therefore investigated.

Treatment of **15** under typical radiofluorination conditions ([^{18}F]KF/K_{222}/K_2CO_3, CH_3CN, 80–100 °C, see Scheme 3 and Table 1) gave only trace amounts of the desired product **7**, with mainly unreacted starting material **15** returned (Table 1, entry 1). Nevertheless, it was promising that the *p*-nitrophenylester **15** was not hydrolyzed significantly under these conditions.

Use of tertiary alcoholic solvents according to the method of Kim et al.[34] was next investigated. Use of *t*-amyl alcohol resulted in an increase in decay corrected yield to 14%, whereas use of acetonitrile/*t*-butanol (1:4)[35] resulted in a further increase to 29% decay corrected yield (Table 1, entries 2-3). Optimization of temperature, time, base, and concentration of starting material were investigated. A temperature of 100 °C was found to be optimal, with slightly lower yields at 80 °C and 120 °C (Table 1, entries 6-7). Increasing the reaction time resulted in significantly reduced yields, presumably because of partial degradation of the product at 100 °C over time (Table 1, entries 4-5). Potassium hydrogen carbonate was the optimal base, with potassium carbonate, potassium oxalate, and tetrabutylammonium hydrogen carbonate all giving reduced yields (Table 1, entries 8-10). Decreasing the concentration of the bromopropionate starting material **15** resulted in lower yields. The optimum conditions were found to be the use of acetonitrile/*t*-butanol solvent with [^{18}F]KF/K_{222}/$KHCO_3$ at 100 °C for 5 min, which provided [^{18}F]NFP **7** in 26.2% ± 2.2% (maximum 29%) decay corrected radiochemical yield (Table 1, entry 3). The [^{18}F]NFP **7** was prepared in >99% radiochemical purity (Figure 3), with a specific activity of 474 GBq μmol^{-1}.

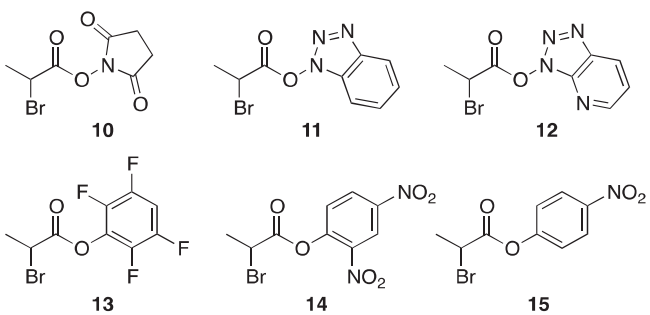
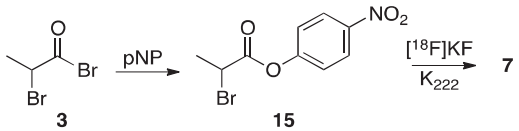


Figure 2. Activated esters of 2-bromopropionate.

This redesigned route to [^{18}F]NFP **7** has enabled the synthesis of this valuable radiolabeled prosthetic group in a single radiochemical step. Furthermore, the synthesis of [^{18}F]NFP **7** was fully automated on a TRACERlab FX_{FN} system, with the overall preparation time reduced to an amenable 45 min.

We sought to exemplify the utility of this improved route to [^{18}F]NFP **7** by incorporating this method into the preparation of both the current gold standard 'RGD' peptide for clinical PET imaging, [^{18}F]GalactoRGD **1**, and the recently reported dimeric 'RGD' peptide tracer, [^{18}F]FPP$(RGD)_2$ **2**.

Treatment of GalactoRGD with [^{18}F]NFP **7** according to the method of Haubner et al.[16] in our laboratory resulted in sluggish reaction and consequently low yields of [^{18}F]GalactoRGD **1**. We



Scheme 3. One-step radiosynthesis of [^{18}F]NFP **7**.

Table 1. Optimisation of [^{18}F]NFP **7** synthesis*

Entry	Solvent	Time (min)	Temp. (°C)	Yield % (d.c.)
1†	CH_3CN	5	100	4
2	*t*-Amyl alcohol	5	100	14
3	**CH_3CN–*t*BuOH**	**5**	**100**	**29¶**
4	CH_3CN–*t*BuOH	10	100	19
5	CH_3CN–*t*BuOH	15	100	11
6	CH_3CN–*t*BuOH	5	80	20
7	CH_3CN–*t*BuOH	5	120	21
8†	CH_3CN–*t*BuOH	5	100	17
9‡	CH_3CN–*t*BuOH	5	100	18
10§	CH_3CN–*t*BuOH	5	100	9

Bold signifies the optimum conditions for the preparation of compound 7.
*Standard reaction conditions; [^{18}F]KF/K_{222}, $KHCO_3$, 100 °C, 5 min, CH_3CN–*t*BuOH (1:4).
†K_2CO_3 used in place of $KHCO_3$.
‡Bu_4NHCO_3 used in place of $KHCO_3$.
§$K_2C_2O_4$ used in place of $KHCO_3$.
¶Over three runs; 26.2% ± 2.2%.

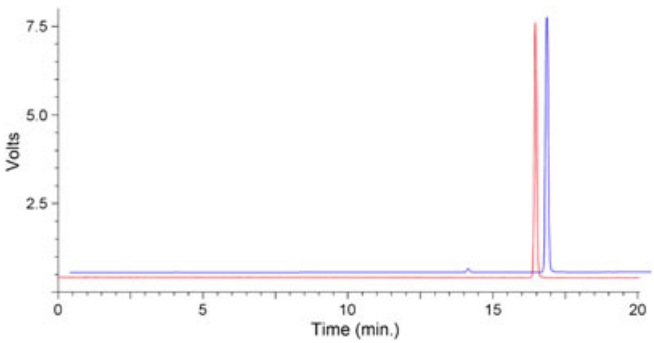


Figure 3. Co-injection of [^{18}F]NFP **7** with cold standard (red, radio-HPLC trace; blue, UV trace (254 nm)).

found that the ligation of [^{18}F]NFP **7** to GalactoRGD was enhanced when triethylamine was added, resulting in quantitative labeling as judged by HPLC analysis of the reaction mixture (see SI). The purified tracer **1** was isolated in 69% decay corrected radiochemical yield from [^{18}F]NFP **7**. Employing our new method for the preparation of [^{18}F]NFP **7** in combination with a modified method for conjugation to GalactoRGD resulted in the production of [^{18}F]GalactoRGD **1** in overall 20% decay corrected yield. The specific activity was 122 GBq μmol^{-1} at end of synthesis, and the total synthesis time was 90 min.

Conjugation of [^{18}F]NFP **7** to miniPEG-E(RGD)$_2$ was performed according to the method of Chin et al,[30] to provide [^{18}F]FPP(RGD)$_2$ **2** in overall 7% decay corrected yield. The specific activity was 255 GBq μmol^{-1} at end of synthesis, and the total reaction time was 100 min.

In summary, a one-step radiochemical synthesis has been developed for the preparation of [^{18}F]NFP **7**. The *p*-nitrophenyl ester moiety appears uniquely stable under nucleophilic radiofluorination conditions, yet is reactive enough to couple with peptides in 5 min. This route to the synthesis of [^{18}F]NFP **7** was automated on a TRACERlab FX$_{FN}$ system and enables the preparation of PET imaging agents, such as [^{18}F]GalactoRGD **1** and [^{18}F]FPP(RGD)$_2$ **2**, with greatly reduced reaction times and potentially higher specific activities.

Supporting Information

Experimental procedures for the preparation of precursors and non-radiolabeled standards; 4-nitrophenyl 2-fluoropropionate, GalactoRGD, FP-GalactoRGD, E(RGD)$_2$, miniPEG-E(RGD)$_2$, FP-P(RGD)$_2$. HPLC traces of crude and purified [^{18}F]GalactoRGD **1** and [^{18}F]FPP(RGD)$_2$ **2**.

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Conflict of Interest

The authors did not report any conflict of interest.

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