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Semi-Automated Synthesis of [F-18]FBAM, a Thiol Reactive Prosthetic Group, Using Continuous Flow Chemistry

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Abstract

[F-18]FBAM, a thiol reactive bifunctional agent, was successfully synthesized using continuous flow chemistry in a micro reactor that is part of Advion NanoTek Microfluidic Synthesizer. As the radiofluorination was carried out microfluidically, a very small amount of precursor was used and over all radiochemical yield was 38% ± 4% (n = 8, decay corrected) and the radiochemical purity was ≥98% with specific activity of 430 mC/μmol. The total reaction time including HPLC purification was 55 min that is 14 min more than manual synthesis and 6 min less than fully automated synthesis.

Keywords

Bifunctional Agent, Micro-Reactor, 6-Bromohexnol, Radiofluorination, Appel Reaction

1. Introduction

Bioactive peptides and proteins are important key regulators in cell growth and cellular functions in living organisms [1]-[3]. Various peptides, proteins, antibodies, antibody fragments and nucleotides have been radiolabeled and used to image tumors and inflammatory processes [4]. Among these tracers, [F-18] labeled molecular probes are increasingly popular because of the ease of production of ^{18}F and its favorable properties. However, harsh reaction conditions required to directly radiofluorinate these sensitive biomolecules hampered the preparation of the requisite tracers in good yields and high specific activity. To address these problems, radiochemists have taken advantage of bifunctional agents, also known as prosthetic groups. These prosthetic groups are catego-

rized into three classes amine, thiol and carboxylic reactive. Notable thiol reactive bifunctional agents include [^{18}F] FBAM [5] [6], [^{18}F]FBOM [7], [^{18}F]FBABM [8], [^{18}F]FPyAM [9] and [^{18}F]FPyMe [10] (Figure 1).

Microfluidics represents a useful approach to conduct the reactions with minimal quantities of expensive precursors; other advantages include reduced reaction times and increased radiolabeling yields. These effects are realized due to the high surface to volume ratio encountered while the reagents are flowing through the microchannel which is accompanied by rapid mixing of the reagents leading to increased heat transfer between the reactants. One of the commercially available microfluidic devices with micro-channel system (MCS) is the Advion NanoTek Microfluidic Synthesizer. This unit consists of three modules called the reagent, reactor and concentrator modules. The isotope is dried and dissolved in the concentrator module and transferred to a loop attached to the reactor module while the precursor is stored in a second loop attached to reagent module. The reagents are then meter delivered and passed through the microreactor consisting of a 100 μm channel made of quartz. We wish to report an improved synthesis of [^{18}F] FBAM utilizing this microfluidic system involving continuous flow.

2. Results and Discussion

2.1. Chemistry

The reported procedure for preparing requisite precursor **16** required synthesizing [^{18}F] FBAM via the Mitsunobu reaction of *tert*-butyl *N*-[(6-hydroxyhexyl)oxy] carbamate, **6** with maleimide, **8**, in the presence of Ph_3P, diisopropyl acetylene dicaboxylate, and DMF at −78˚C to obtain **7** (Scheme 1).

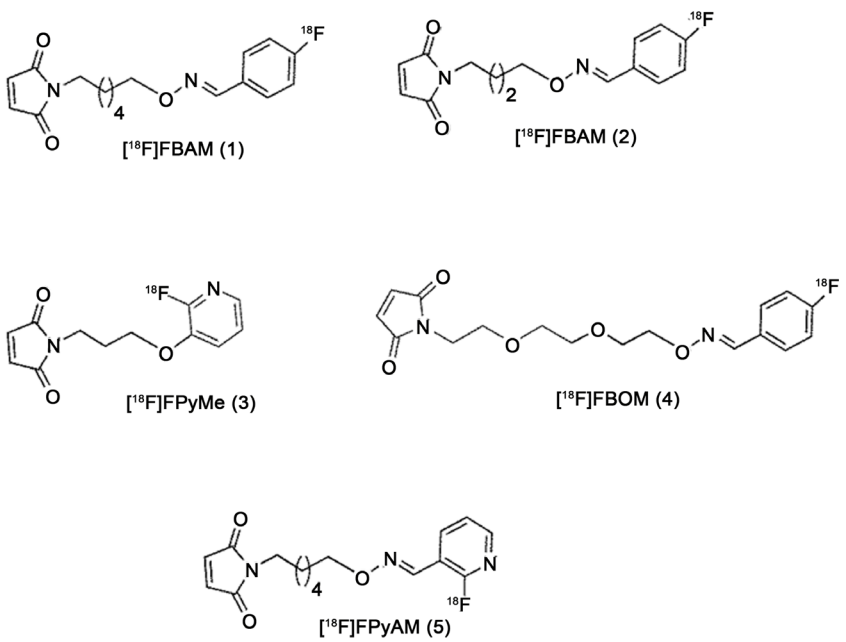
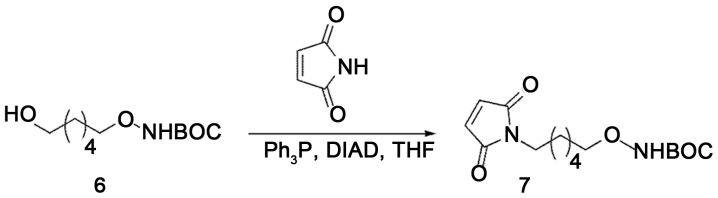


Figure 1. Notable thiol reactive bifunctional agents.

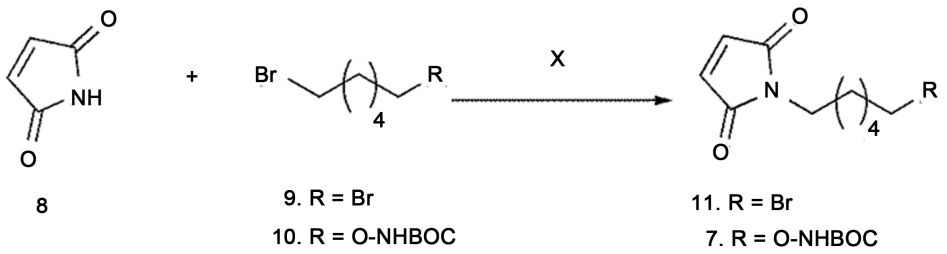


Scheme 1. Mitsunobu reaction.

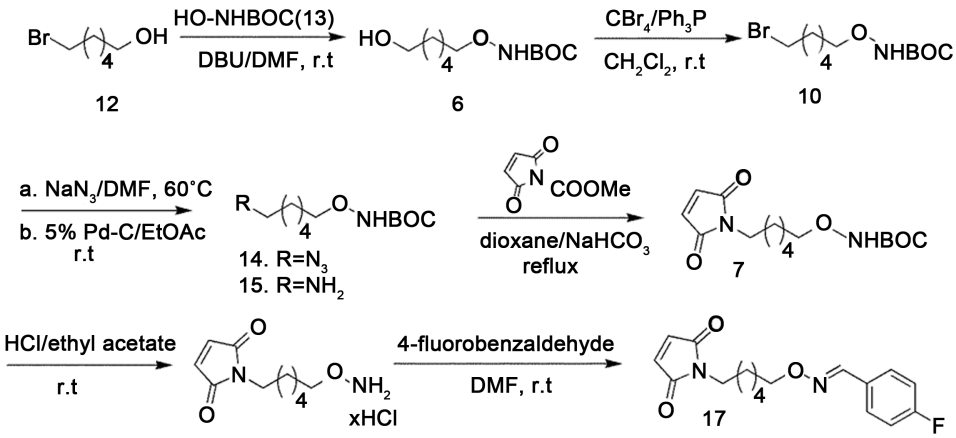
Attempts to directly *N*-akylate maleimide **8** with various alkyl bromides failed or produced very poor yields (Scheme 2). We then treated maleimide **8** with either NaH or K_2CO_3 in THF or DMF at room temperature followed by the addition of 1,6-dibromohexane, **9**; after, stirring the reaction mixture at reflux only trace amounts of the desired product **11** were produced. Adding sodium iodide to catalyze the reaction did not improve the yield. Further experiments using the bromide **10** as an alkylating agent also did not result in the desired product **7**. It is possible that the *N*-Alkylation of maleimide does not proceed as expected because the maleimide anion underwent a 1,4-addition to another molecule of maleimide instead of reacting with alkyl bromide.

Precursor **16** was successfully prepared from 6-bromohexanol, **12,** in six steps in an overall yield of 24.6% (Scheme 3). *tert*-Butyl-*N*-hydroxycarbamate, **13**, was then *O*-alkylated with 6-bromohexanol, **12**, to obtain alcohol **6**, using 1,8-diazabicyclo[5.4.0] undecene (DBU) as the base in DMF at room temperature. Appel reaction [11] of alcohol **6** to bromide **10** was achieved with carbon tetrabromide and triphenylphosphine in CH_2Cl_2 by stirring the reaction mixture at room temperature. Bromide **10** was allowed to react with sodium azide in DMF at 80˚C to obtain azide **14** in nearly quantitative yield. The crude azide **14** was then hydrogenated with 5% Pd-C in EtOAc to obtain amine **15** [12]. Reaction of amine **15** with *N*-methoxycarbonyl-maleimide in thepresence of $NaHCO_3$ bin refluxing in dioxane afforded **7**. The Boc-protecting group was readily removed with HCl/EtOAC at room temperature to obtain 1**6** as the HCl salt. The condensation of **16** with 4-fluorobenzaldehyde in DMF at room temperature gave the **17** as a white solid.

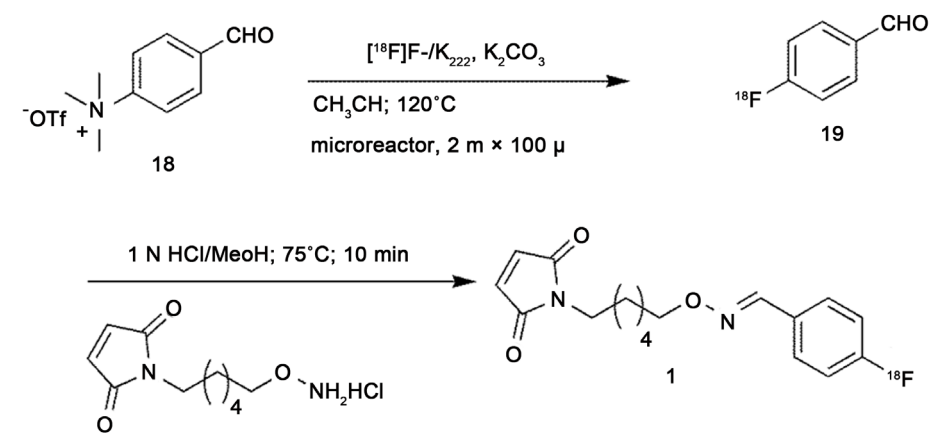
The two step radiosynthesis of [^{18}F]FBAM, **1**, was performed in the Advion NanoTek Microfludic Synthesizer (Scheme 4). Using the drying macros of NanoTek LF 1.4 software, a complex of Kryptofix 222/K_2CO_3/[^{18}F]fluoride was thoroughly dried and allowed to react with 4-*N,N,N*-trimethylamino-benzaldehyde triflate, **18**, in a microreactor (2 m × 100 μ) at 120˚C to obtain 4-[^{18}F]fluorobenz-aldehyde, **19**. The labeling efficiency under microfluidic conditions was compared with the previously reported procedures (Table 1). The outlet tube from the reactor was immersed in a reaction vial containing precursor **16** (8 mg) dissolved in a 1:1 mixture of 1 *N*HCl:MeOH which was then heated at 75˚C for 10 min to obtain [^{18}F]FBAM, **1**, in higher overall radiochemical yield (38% ± 4%) when compared to the earlier reports (29% ± 4%). The crude product **1** was subjected to C_{18} Sep-Pak solid phase extraction before purifying on semi preparative HPLC. [^{18}F]FBAM (29 mCi) was obtained from 100 mCi of [^{18}F] fluoride in 55 min, including HPLC purification, in a radiochemical purity of ≥98%. The identity of the product was confirmed using analytical HPLC by co-elution with **17**.



Scheme 2. N-alkylation of maleimde.



Scheme 3. Synthesis of precursor 16 and the standard 17.



Scheme 4. Synthesis of [^{18}F]FBAM (1).

Table 1. Comparison of amount of precursor 18 used to obtain compound 1.

Method	Precursor 18	Solvent (1 mL)	Yield
[5]	16.2 mg	DMSO	29%
[8]	12.0 mg	DMF	28%
[6]	10.0 mg	CH_3CN	29%
Current	5.0 mg	CH_3CN	38%

2.2. Materials and Methods

All reagents and solvents were purchased from Acros or Aldrich and were used as received. Flash column chromatography was performed using silica gel (60 Å, 230 - 400 mesh, Sorbent Technologies, USA) [13]. Analytical thin-layer chromatography (TLC) was performed using 250 μm silica plates (Analtech, Inc., Newark, DE) with a visualization by UV (254 nm) or phosphomolebdic acid spray. ^{1}H and ^{13}C-nuclear magnetic resonance spectra (NMR) were recorded at 300 or 125 MHz, respectively. Chemical shifts for ^{1}H-NMR and ^{13}C-NMR spectra were referenced to the residual protons of the deuterated solvents or to TMS. High resolution mass spectrometry was performed using a JEOL AccuTOF™ DART Mass Spectrometer. *tert*. Butyl *N*-[(6-hydroxyhexyl)oxy] carbamate was prepared following the literature procedure [14]. No-carrier-added $[^{18}F]F^{-}$, produced from recycled $[^{18}O]$ water, was obtained from PetNet (Knoxville, TN). Thin-layer chromatography visualization was performed with radiation detectors using a BioScan AR-2500 radio-TLC reader and Win Scan 1.3 software. Radio-TLC plates were developed using EtOAc/hexane (50/50). Analytical radio-HPLC analyses were performed on an Agilent 1200 series instrument employing a 254 nm UV detector and a Phenomenex Luna C_{18} column, 5 μ, 4.6 × 250 mm, using 80% acetonitrile/20% 0.1 *N* ammonium formate at a flow rate of 1mL/min. F-18 labelling was performed in 100 μm × 2 m reactor using Advion NanoTek Microfluidic Synthesis System controlled by NanoTek LF 1.4 Software.

tert-Butyl *N*-[(6-Hydroxyhexyloxy]carbamate (**6**)

To a magnetically stirred solution of *N*-(*tert*-butyloxycabonyl)hydroxylamine, **13**, (5.00 g, 37.6 mmol) and 6-bromohexane-1-ol, **12**, (2.71 g, 1.50 mnol) was added DBU (11.4 g, 7.50 mmol) over a period of 5 min. The mixture was allowed to stir for 24 h and then dissolved in CH_2Cl_2 (200 mL), and the resulting solution was washed sequentially with 1 *N* HCl (4 × 25 mL) and brine (25 mL). The aqueous portion was discorded and the CH_2Cl_2 was dried ($MgSO_4$), filtered, and concentrated. The resulting yellow oil was purified by silica gel flash chromatography (3:7, EtOAc:hexane) to provide *tert*-butyl *N*-[(6-hydroxyhexyloxy]-carbamate, **6**, (8.48 g, 75%). ^{1}H NMR $CDCl_3$ (δ) 1.39 (m, 4H), 1.47 (s, 9H), 1.57 - 1.66 (bm, 4H), 3.62 (t, 2H) and 3.84 (t, 2H); ^{13}C NMR $CDCl_3$ (δ) 25.4, 25.6, 27.9, 28.4, 32.5, 62.7, 76.7, 81.5, 157.2; HRMS (ES) calculated for (M+Na) $C_{11}H_{23}NaNO_4$: 256.1525. Found: 256.1530.

tert-Butyl *N*-[(6-Bromohexyloxy]carbamate (**10**)

Triphenylphosphine (9.00 g, 34.0 mmol) and *tert*-butyl *N*-[(6-hydroxyhexyloxy] carbamate, **6,** (4.40 g, 17.2 mmol) were dissolved in anhydrous dichloromethane (30 mL) under an argon atmosphere. Pyridine (2.8 mL, 34.0 mmol) and carbon tetrabromide (1.90 mL, 17.0 mmol) were added, and the reaction mixture stirred at room temperature for 24 h. The mixture was poured into water, extracted with ether (2 × 50 mL) and the combined organic extracts were dried (anhydrous $MgSO_4$), filtered, and concentrated. The product was purified by silica gel flash chromatography (EtOAc/hexane, 2:7) to provide *tert*-butyl *N*-[(6-bromohexyloxy]carbamate, **10**, as a colorless oil (4.13 g, 82%). ^{1}H NMR $CDCl_3$ (δ) 1.39 (m, 4H, CH_2), 1.47 (s, 9H, CH_3), 1.57 - 1.66 (bm, 4H,

CH_2), 3.26 (t, 2H, CH_2Br) and 3.84 (t, 2H, OCH_2); ^{13}C NMR $CDCl_3$ (δ) 25.7, 25.9, 28.2, 28.4, 32.5, 32.9, 76.7, 81.5, 157.2; HRMS (ES) calculated for (M + Na) $C_{11}H_{22}NaNO_3Br$: 318.0681. Found: 318.0685.

tert-Butyl *N*-[(6-Aminohexyloxy]carbamate (**15**)

A mixture of *tert*-butyl *N*-[(6-bromohexyloxy]carbamate, **15** (1.27 g, 4.30 mmol), sodium azide (0.52 g, 8.0 mmol) and 18-crown-6 (0.53 g, 0.10 mmol) in anhydrous benzene (10 mL) was stirred overnight at 60˚C. Insoluble materials were filtered off and benzene was removed under *vacuo* to obtain the crude azide **14** (0.98 g) which was subjected to hydrogenation without purification. Azide **14** (0.98 g) was dissolved in dry EtOAc (20 mL) and hydrogenated at atmospheric pressure with 5%-Pd/C using a hydrogen balloon. The catalyst was removed by filtration, the solvent evaporated and the product purified using silica gel flash chromatography (EtOAc/hexane, 2:7) to give *tert*-butyl *N*-[(6-aminohexyloxy-carbamate)], **15** (0.53 g; 54%). ^1H NMR $CDCl_3$ (δ) 1.40-1.78 (m, 8H, CH_2), 1.46 (s, 9H, CH_3), 2.62 (t, J = 7.3 Hz, 2H, CH_2NH2) and 3.78 (t, J = 7.3 Hz, 2H, CH_2O); ^{13}C NMR $CDCl_3$ (δ) 25.3, 25.8, 27.9, 28.4, 32.5, 41.9, 76.7, 81.5, 157.2; HRMS (ES) calculated for (M + Na) $C_{11}H_{24}NaN_2O_3$: 255.1735. Found: 255.1738.

tert-Butyl *N*-{[6-(1-Maleimidyl)hexyl]oxy}carbamate (**7**).

To a solution of *tert*-butyl *N*-[(6-aminohexyloxy]carbamate, **15**, (1.1 g, 5.0 mmol) in THF (100 mL) was added *N*-methoxycarbonylmaleimide (2.43 g, 25.0 mmol). The mixture was stirred overnight at reflux. A precipitate was formed. After filtration, the filtrate was concentrated to dryness, and the residue purified by flash column chromatography using silica gel and EtOAc/hexane (2:7) to give pure *tert*-butyl *N*-{[6-(1-maleimidyl)hexyl]oxy}carbamate, 7, (1.21 g, 78%). ^1H NMR $CDCl_3$(δ) 1.47 (s, 9H, CH_3), 1.21 - 1.61 (bm, 8H, CH_2), 3.49 (t, J = 7.4 Hz, 2H, NCH_2,), 3.84 (t, J = 6.9 Hz, 2H, OCH_2), 6.64 (s, 2H, maleimide) and 7.10 (br s, 1H, NH). ^{13}C NMR $CDCl_3$ (δ) 25.4, 25.6, 27.9, 28.4, 32.5, 62.7, 76.7, 81.5, 157.2; HRMS (ES) calculated for (M+Na) $C_{15}H_{24}NaN_2O_5$: 335.3513. Found: 335.3518

N-(6-Aminoxyhexyl)maleimide·HCl (**16**).

A solution of *tert*-butyl *N*-{[6-(1-maleimidyl)hexyl]oxy}carbamate, **7**, (1.20 g, 3.84 mmol) in 3 *N* HCl/EtOAc (1:1, 40 mL) was stirred for 30 min at room temperature. The solvent was removed under reduced pressure, and the residue dissolved in methanol (10 mL). Diethyl ether (100 mL) was added and the white suspension was filtered to obtain N-(6-aminoxyhexyl)maleimide HCl, **16**, (0.90 g, 95%), mp =132˚C - 133˚C (lit. 135˚C - 137˚C). ^1H NMR DMSO (δ) 1.21 - 1.52 (bm, 4H, CH_2), 1.61 - 1.74 (bm, 4H, CH_2), 3.48 (t, J = 7.4 Hz, 2H, NCH_2), 3.88 (t, J = 6.9 Hz, 2H, OCH_2), 6.84 (s, 2H, maleimide) and 7.10 (br s, 1H, NH). ^{13}C NMR $CDCl_3$(δ), 24.34, 26.78, 27.59, 30.72, 48.60, 49.58, 134.30 and 170.8

N-[6-(4-Fluorobenzylidine)aminooxyhexyl]maleimide (**17**)

A mixture of 4-fluorobenzaldehyde (0.037 g, 0.40 mmol) and *N*-(6-aminoxyhexyl) maleimide·HCl, **8**, (0.05 g, 0.20 mmol) in dimethyl formamide (5 mL) was stirred for 30 min at room temperature. The reaction mixture was diluted with water (30 mL) and

extracted with diethyl ether (2 × 25 mL). The ether extracts were washed with brine (10 mL) and dried (anhydrous $MgSO_4$). The solvent was evaporated under reduced pressure and the crude product was purified using silica gel flash chromatography (EtAcO/hexanes, 7:3) to give *N*-[6-(4-fluorobenzylidine)aminooxyhexyl]maleimide, **17**, (0.06 g, 94%) as a white solid. ^{1}H NMR $CDCl_3$ (δ) 1.21 - 1.70 (bm, 8H, CH_2), 3.48 (t, J = 7.4 Hz, 2H, NCH_2,), 4.10 (t, J = 6.9 Hz, 2H, OCH_2), 6.68 (s, 2H, maleimide), 7.01 (m, 2H, Ar), 7.51 (dd, J = 5.4, 8.2, 2H, Ar) and 8.06 (s, 1H, CHN). ^{13}C NMR $CDCl_3$ (δ) 26.41, 27.05, 30.72, 49.56, 59.38, 115.73, 130.06, 134.31, 134.75, 163.35 and 170.82; HRMS (ES) calculated for (M + Na) $C_{15}H_{24}NaN_2O_3$: 322.7864. Found: 322.7868

N-{6-(4-[^{18}F]Fluorobenzylidine)aminooxyhexyl}maleimide (**1**)

The details of operation of the NanoTek Microfluidic System have been described previously (Pike 2009, 2010). Cyclotron-produced, no-carrier-added [^{18}F]fluoride ion (100 mCi) in [^{18}O]water (225 - 350 μL) was first adsorbed onto an anion exchange resin ORTG cartridge within the concentrator module of a NanoTek apparatus (Advion Biosciences), and then released with a solution of K_2CO_3 (1.8 mg) plus $K_{2.2.2}$ (12.0 mg) in MeCN/H_2O (9.5:0.5 v/v; 400 μL) into a 5 mL V-vial. The solution was dried by three cycles of azeotropic evaporation with MeCN (0.45 mL) at 100˚C. The dry $^{18}F^-$-$K_{2.2.2}$-K^+ complex (70 mCi) was dissolved in MeCN (0.5 mL). The isotope solution was then loaded into the loop of the reactor module (431 μL), and 4-*N, N, N*-trimethyammoniumbenzaldehyde, **18,** (2.5 mg in 0.5 mL) solution was loaded into the other loop on the reagent module (431 μL). These solutions were concurrently infused into a 2 m long micro reactor coil (100 μm) at a combined flow rate of 200 μL/min. The radiofluorinated product exiting the micro reactor was collected in a vial, in the concentrator module, containing maleimide precursor **16** (8 mg) dissolved in a mixture of methanol and 1.0 *N* HCl (1 mL, 50/50) and the resulting mixture was heated at 75˚C for 10 min. After cooling, the mixture was diluted with water (15 mL) and passed through C_{18} Sep-Pak cartridge to eliminate water soluble precursor and any unreacted isotope. The product was eluted with acetonitrile (3 mL). The pure product was isolated by semi-preparative HPLC column (Phenomenex Luna reverse phase column, 250 × 10 mm, 10 μ), using gradient elution (A: CH_3CN, B: 0.1 *M* ammonium formate, 0.5 min 40% A and 60% B; 5 - 15 min 40%A - 70% A and 15 - 30 min 70%A, flow rate 4 mL/ min). A fraction (16 - 18 min) was collected, diluted with water (10 mL), and passed through a C_{18} Sep-Pak cartridge to trap the desired product. The cartridge was then washed with diethyl ether (2 mL) and the solvent evaporated under a stream of dry N_2 to afford 29 mCi (38% decay corrected) of [^{18}F]FBAM. The identity of the product was confirmed using analytical HPLC by co-injection with a reference standard, **17**, R_t = 6.4 min.

3. Conclusion

[^{18}F]FBAM was successfully synthesized by continuous flow chemistry using an Advion NanoTek Microfludic Synthesis System in high radiochemical yield (38% ± 4%, n = 4; previously reported 29% ± 4%) and radiochemcial purity of ≥98%. The requisite key precursor *N*-(6-amino-oxyhexyl)maleimide·HCl, **16**, was prepared by a different method

then that previously reported. Smaller quantities of expensive precursors were used for the synthesis under microfluidic conditions. The overall time for the synthesis was 55 min and the specific activity was determined to be 430 mCi/μmol.

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