Supporting Information

Synthesis of [^{18}F]Arenes via the Copper-mediated [^{18}F]Fluorination of Boronic Acids

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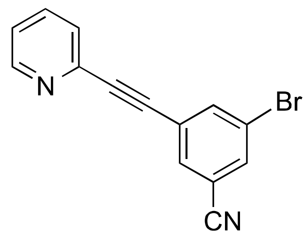
1. General Procedures and Materials and Methods

Instrumental Information: NMR spectra were obtained on a Varian MR400 (400.52 MHz for ^{1}H; 100.71 MHz for ^{13}C; 376.87 MHz for ^{19}F), a Varian VNMRS 500 (500.10 MHz for ^{1}H), or a Varian VNMRS 700 (699.76 MHz for ^{1}H; 175.95 MHz for ^{13}C) spectrometer. ^{1}H and ^{13}C NMR chemical shifts are reported in parts per million (ppm) relative to trimethylsilane (TMS), with the residual solvent peak used as an internal reference. ^{19}F NMR spectra are referenced based on an internal standard, 1,3,5-trifluorobenzene (–110.00 ppm). ^{1}H and ^{19}F multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). High performance liquid chromatography (HPLC) was performed using a Shimadzu LC-2010A HT system equipped with a Bioscan B-FC-1000 radiation detector. Radio-TLC analysis was performed using a Bioscan AR 2000 Radio-TLC scanner with EMD Millipore TLC silica gel 60 plates (3.0 cm wide x 6.5 cm long).

Materials and Methods: Boronic acid precursors were purchased from Frontier Scientific, Oakwood Products and Sigma Aldrich. and used as received, unless otherwise stated in Section 2. Fluorine-19 reference standards were also sourced commercially and used as received, unless otherwise stated in Section 3.

2. Synthesis and Characterization of Boronic Acids



(**S1**)

3-bromo-5-(pyridin-2-ylethynyl)-benzonitrile (Br-PEB, **S1**) was prepared by the following procedure adapted from the literature.[1] In a glovebox, 2-((trimethylsilyl)ethynyl)pyridine (873.7 mg, 5.0 mmol, 1.0 equiv), 3,5-dibromobenzonitrile (1304.4 mg, 5.0 mmol, 1.0 equiv), $Pd(PPh_3)_2Cl_2$ (350.0 mg, 0.50 mmol, 0.1 equiv), CuI (182.6 mg, 1.0 mmol, 0.2 equiv), and Et_3N (1.4 mL, 2.0 mmol, 0.4 equiv) were placed in a 25 mL flask equipped with a stir bar. DMF (8.6 mL, 0.6 M) was added to the mixture and the flask was capped with a septum and taken out of the glovebox. Under N_2, the flask was stirred at 80 °C for 30 minutes. A solution of $(n\text{-}Bu)_4NF$ (1.695 g, 6.1 mmol, 1.2 equiv) in THF (1.0 M, 6.0 mL) was added dropwise. The reaction mixture was stirred at 80 °C until TLC showed no starting material was present (average time 4 hours). The reaction mixture was cooled to room temperature and diluted with methyl *tert*-butyl ether (MTBE, 10 mL) and poured into aqueous NH_4OH (1.0 M, 15 mL). The aqueous layer was washed with MTBE (3 x 10 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (15% EtOAc/hexanes), which afforded Br-PEB **S1** as a yellow powder (687.0 mg, 2.4 mmol, 49 % yield).

The ^{1}H and ^{13}C NMR spectroscopic data for **S1** were identical to that reported.[2]

HRMS (ESI^+) [$M+H^+$] Calculated for $C_{14}H_7BrN_2$: 282.9865; Found 282.9865.

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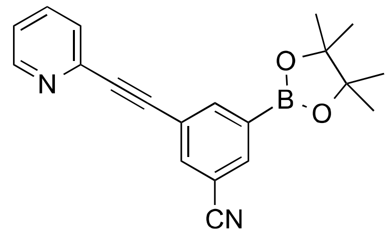
[1] Telu, S. *et al.*, *Org. Biomol. Chem.*, **2011**, *9*, 6629.

[2] Kil, K-E. *et al.*, *ACS Med. Chem. Lett.,* **2014**, *5*, 652.



(**S2**)

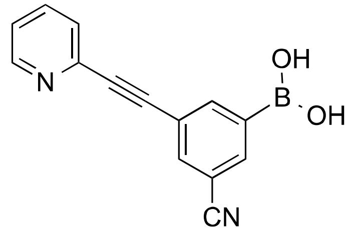
(3-cyano-5-(pyridin-2-ylethynyl)phenyl)boronic acid, pinacol ester (Bpin-PEB, **S2**) was prepared by the following procedure adapted from the literature.[3] In a glovebox, Br-PEB (**S1**) (297.5 mg, 1.1 mmol, 1 equiv), bis(pinacolato)diboron (295.0 mg, 1.2 mmol, 1.1 equiv), potassium acetate (308.1 mg, 3.1 mmol, 3.0 equiv), and Pd(dppf)Cl_2 (116.6 mg, 0.14 mmol, 0.14 equiv) were placed in a 20 mL vial equipped with a stir bar. DMSO (5.8 mL, 0.2 M) was added to the mixture and the vial was sealed with a Teflon cap and taken out of the glovebox. The vial was stirred at 80 °C for 15 hours. The reaction mixture was cooled to room temperature and diluted with diethyl ether (10 mL) and filtered through Celite®. The organic layer was washed with H_2O (3 x 15 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated *in vacuo*. The product was washed with $NaHCO_3$ (2 x 10 mL) to remove excess pinacol, which afforded substrate **S2** as a black oil (200.7 mg, 0.6 mmol, 58% yield).

^{1}H NMR (700 MHz, $CDCl_3$): δ 8.63 (d, *J* = 4.9 Hz, 1H) 8.23 (s, 1H), 8.04 (s, 1H), 7.90 (s, 1H), 7.70 (td, *J* = 7.7, 1.7 Hz, 1H), 7.52 (d, *J* = 7.7 Hz, 1H), 7.28 (dd, *J* = 4.9, 2.1 Hz, 1H), 1.33 (s, 12H).

^{13}C NMR (176 MHz, $CDCl_3$): δ 150.2, 142.7, 142.2, 138.0, 137.0, 136.3, 127.3, 123.3, 123.3 , **117.9**, **112.6**, 90.5, 86.5, 84.7, 25.0, 24.8. C-CN and CN carbons in **bold.**

HRMS (ESI^+) [$M+H^+$] Calculated for $C_{20}H_{19}BN_2O_2$: 331.1612; Found 331.1617.

[3] Perttu, E. K. *et al*., *Tetrahedron Lett.,* **2005**, 46, 8753.



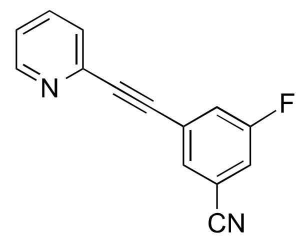
(**19**)

(3-cyano-5-(pyridin-2-ylethynyl)phenyl)boronic acid ($B(OH)_2$-PEB) (**19**) was prepared by the following procedure adapted from the literature.[4] Bpin-PEB (**S2**) (271.9 mg, 0.8 mmol, 1 equiv) and sodium periodate (529.9 mg, 2.5 mmol, 3 equiv) were stirred in 6.7 mL of a 4:1 mixture of THF and water for 30 minutes at room temperature. After that time, aqueous hydrochloric acid (1N, 0.6 mL) was added to the suspension. The solution was stirred at ambient temperature overnight (18 hr). The reaction mixture was diluted with ethyl acetate (10 mL) and washed with water (2 x 20 mL) and brine (20 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was washed with hexanes to give $B(OH)_2$-PEB as a yellow solid (109.2 mg, 54 % yield).

^{1}H NMR (700 MHz, CD_3OD and 1 drop of CD_3COOD): δ 8.63 (d, *J* = 4.9 Hz, 1H) 8.15 (s, 1H), 8.03 (s, 1H), 7.97 (t, J = 1.4 Hz, 1H), 7.91 (td, *J* = 7.7, 2.1 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.47 (ddd, *J = 7.7, 5.3, 1.4, 0.7* Hz, 1H).
^{13}C NMR (176 MHz, $CDCl_3$): δ 150.20, 142.65, 142.20, 138.02, 137.02, 136.27, 127.29, 123.28, **117.93**, **112.57**, 90.55, 86.48, 84.72. C-CN and CN carbons in **bold.**
HRMS (ESI$^+$) [M+H$^+$] Calculated for $C_{14}H_9BN_2O_2$: 248.0830; Found 248.0834.

[4] Tzschucke, C. C. *et al.*, *Org. Lett.*, **2007**, 9, 761.

3. Synthesis and Characterization of Fluorinated Standards

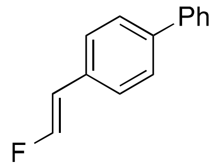


(**S3**)

3-fluoro-5-(pyridin-2-ylethynyl)benzonitrile (F-PEB, **S3)** was prepared by the following procedure adapted from the literature.[1] In a glovebox, 2-((trimethylsilyl)ethynyl)pyridine (177.7 mg, 1.0 mmol, 1.0 equiv), 3,5-dibromobenzonitrile (205.6 mg, 1.0 mmol, 1.0 equiv), $Pd(PPh_3)_2Cl_2$ (74.4 mg, 0.10 mmol, 0.10 equiv), CuI (39.5 mg, 0.2 mmol, 0.20 equiv),and Et_3N (0.3 mL, 2.1 mmol, 2.1 equiv) were placed in a flask with DMF (1.75 mL, 0.6 M). The flask was placed under N_2 flow and stirred at 80 °C for 30 min. A solution of $(n\text{-}Bu)_4NF$ (1.129 g, 4.0 mmol, 4.0 equiv) in THF (1.0 M, 4.0 mL,1.1 equiv) was added dropwise. The reaction mixture was stirred at 80 °C until TLC showed no starting material was present. The reaction mixture was cooled to room temperature and diluted with methyl *tert*-butyl ether (MTBE) (10 mL) and poured into aqueous NH_4OH (1.0 M, 15 mL). The aqueous layer was washed with MTBE (3 x 10 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (15% EtOAc/hexanes), which afforded F-PEB **S3** as a brown solid (142.9 mg, 0.64 mmol, 63 % yield).

The ^{1}H and ^{13}C NMR spectroscopic data for **S3** were identical to that reported.[5]
^{19}F NMR (658 MHz, $CDCl_3$): δ -108.9.
HRMS (ESI^+) [$M+H^+$] Calculated for $C_{14}H_7FN_2$: 223.0666; Found 223.0664.

[5] Alagille, D. *et al*., *Bioorg. Med. Chem. Lett.,* **2011**, *21*, 3243.



(**S4**)

4-(2-fluorovinyl)-1,1'-biphenyl (**S4**) was prepared by the following procedure adapted from literature.[6] 2-([1,1'-biphenyl]-4-yl)vinyl boronic acid (46 mg, 0.21 mmol, 1.0 equiv) was dissolved with a 0.24 M methanolic NaOH solution (1 mL, 0.24 mmol, 2.4 equiv) in a flask. The mixture was capped with a septum and stirred for 15 min at room temperature, then cooled to 0 °C in an ice water bath. Silver trifluoromethanesulfonate (156 mg, 0.61 mmol, 3.0 equiv) was added to the reaction mixture, and the mixture was capped and stirred for an additional 30 min at 0° C. Solvent was then evaporated under reduced pressure using a rotary evaporator at 3 °C**.** Then acetone aliquots (2 x 1mL) were added to the reaction mixture and evaporated to remove any additional volatile components. The dry residue was dissolved in 1 mL of acetone and approx. 300 mg of 4 Å molecular sieves were added to the solution, followed by Selectfluor® (75 mg, 0.21 mmol, 1.0 equiv). The mixture was capped with a septum and stirred at 0 °C for 60 min. The reaction was quenched with 30 mL water and extracted with dichloromethane (3 x 30 mL). The organic layer was washed twice with brine and passed through silica, thereby decolorizing it. The filtrate was loaded onto silica and purified by flash chromatography on silica gel (hexanes). The solvent was removed *in vacuo* to afford the product **S4** as a white powder (12 mg, 0.06 mmol, 29 % yield).

The ^{1}H and ^{13}C NMR spectroscopic data for **S4** were identical to that previously reported.[6]

^{19}F NMR (470 MHz, $CDCl_3$): δ -129.5.

HRMS (ESI^+) [$M+H^+$] Calculated for $C_{14}H_{11}F$: 198.0845; Found 198.08444**.**

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[6] Furuya, T. and Ritter, T. *Org. Lett.* **2009,** *11*, 2860.

4. Radiochemistry

4.1 General Materials and Methods

Materials and Methods. Unless otherwise stated, reagents and solvents were commercially available and used without further purification. HPLC grade acetonitrile, anhydrous *N*,*N*-dimethylformamide, potassium trifluoromethanesulfonate and potassium carbonate were purchased from Fisher Scientific. Pyridinium p-toluenesulfonate was purchased from Sigma-Aldrich. Sterile product vials were purchased from Hollister-Stier. QMA-light Sep-Paks were purchased from Waters Corporation. QMA-light Sep-Paks were flushed with 10 mL of ethanol, followed by 10 mL of 90 mg/mL potassium trifluoromethanesulfonate solution, and finally 10 mL of sterile water prior to use.

Synthesis of $K^{18}F$.

All loading operations were conducted under an ambient atmosphere. Argon was used as a pressurizing gas during automated sample transfers. Potassium [^{18}F]fluoride was prepared using a TRACERLab FX_{FN} automated radiochemistry synthesis module (General Electric, GE). [^{18}F]Fluoride was produced via the $^{18}O(p,n)^{18}F$ nuclear reaction using a GE PETTrace cyclotron (40 µA beam for 2-5 min generated ca. 150-375 mCi of [^{18}F]fluoride). The [^{18}F]fluoride was delivered to the synthesis module in a 1.5 mL bolus of [^{18}O]water and trapped on a QMA-light Sep-Pak to remove [^{18}O]water and other impurities. [^{18}F]Fluoride was eluted into the reaction vessel using 550 µL of aqueous solution containing 5 mg potassium trifluoromethanesulfonate and 50 µg of potassium carbonate. One milliliter of acetonitrile was added to the reaction vessel, and the resulting solution was dried by azeotropic distillation to provide anhydrous $K^{18}F$. Azeotropic drying/evaporation was achieved by heating the reaction vessel to 100 °C and drawing vacuum for 6 min. The reaction vessel was then subjected to an argon stream and simultaneous vacuum draw for an additional 6 min. Overall, 70% of activity remained after azeotropic drying (68 ± 9%, n=12; calculated from TRACERLab FX_{FN} reactor radiation detector by comparing activity before and after azeotropic drying). *N*,*N*-dimethylformamide (6 mL) was added to the dried reagent, and heated at 120 °C with stirring for 5 min. The resulting solution was cooled to 40 °C and was transferred to a sterile vial for subsequent use in reactions (% activity recovery into dose vial: 40 ± 10%, n=7; calculated by comparing activity of recovered solution by Capintec with final reading from TRACERLab FX_{FN} reactor radiation detector. As an example, approx. 80 mCi of prepared $K^{18}F$ in 6 mL DMF is isolated with a 5 min beam. It should be noted that % recovery data is only relevant for manual reactions, not automated one-pot syntheses).

4.2 Synthesis of ^{18}F-Labeled Molecules

Manual Synthesis

Unless otherwise noted, this procedure was used for the synthesis of the [^{18}F] fluorinated substrates described in Figure 1 of the main text. Stock solutions of boronic acid precursor (40 mM), copper (II) trifluoromethanesulfonate (200 mM), and pyridine (1 M) in DMF were prepared immediately prior to the start of the reaction. Aliquots of these solutions were used to carry out subsequent [^{18}F]fluorination reactions. In a typical reaction, a 100 µL (20 µmol, 5 equiv) of copper (II) trifluoromethanesulfonate aliquot was mixed with a 500 µL (500 µmol, 25 equiv) pyridine aliquot in a colorless borosilicate 4 mL scintillation vial. The solution was briefly agitated using a vortex shaker (Barnstead® Thermolyne Type 16700), then a 100 µL (4 µmol, 1 equiv) aliquot of boronic acid precursor was added. The reaction vial was sealed under an atmosphere of ambient air with a PTFE/Silicone septum cap, and a 100-300 µL aliquot of $K^{18}F$ (150-3000 µCi, depending on the time required for HPLC analysis) was added to the reaction vial through the septum via a syringe. Additional anhydrous DMF was also added (as required) to bring the total solution volume to 1000 µL. The vial was then heated in an aluminum block (Chemglass Part# CG-1991-04) without stirring at 110 ºC for 20 min. After 20 min, the reaction was allowed to cool to room temperature. Radio-TLC analysis was conducted to determine radiochemical conversion (RCC %). Crude reaction mixture was spotted onto standard silica coated glass plates and developed with 1:1 hexane/ethyl acetate in a glass TLC chamber. The RCC was determined by dividing the integrated area under the fluorinated product spot by the total integrated area of the TLC plate. To prepare samples for HPLC analysis, 50 μL of the reaction mixture was mixed with 50 μL acetonitrile (labeled “reaction” in graphs found in section S4.6) or spiked with 50 μL of 1 mg/mL fluorinated standard solution in acetonitrile (labeled “coinject” in graphs found in section S4.6). Eluent systems and columns used for HPLC analysis are described below.

$$RCC = Integration\ of\ 18F product\ peak RCC\ = Integration\ of\ product\ peak \div Sum\ of\ integration\ of\ all\ peaks$$

Automated Synthesis

All loading operations were conducted under an ambient atmosphere. Argon was used as a pressurizing gas during automated sample transfers. Potassium [^{18}F]fluoride was prepared using a TRACERLab FX_{FN} automated radiochemistry synthesis module (General Electric, GE). [^{18}F]Fluoride was produced via the $^{18}O(p,n)^{18}F$ nuclear reaction using a GE PETTrace cyclotron. [^{18}F]KF was produced as indicated above. A solution containing copper(II)trifluoromethanesulfonate (20 μmol, 5 equiv, 0.02 M), pyridine (500 μmol, 125 equiv, 0.5 M), and boronic acid (4 μmol, 1 equiv, 0.004 M) precursor in 1 mL anhydrous DMF (prepared from separate stock solutions of the three reagents) was added to the reactor containing dry [^{18}F]KF by applying Argon (Ar) gas through the valve containing the reagent solution. Open valves leading out of the reactor were closed and the mixture was stirred for 20 min at 110 ºC. The mixture was then cooled to 50 ºC with compressed air cooling and 5 mL of DMF was added to the reactor. Mixture was allowed to stir for approximately 1 min and was then transferred to an 8 mL sterile product vial with Ar gas. The dose vial was transferred out of the synthesis module in a lead pig. Total activity, RCC, and identity were then determined by a capintec dose calibrator, Radio-TLC scanner, and HPLC, respectively and as described previously. Activity, RCC and specific activity determination data pertaining to compounds **2** and **20** synthesized in this manner can be found in section 4.4

4.3 HPLC conditions

HPLC Condition A.

Condition: 40 % MeCN in H_2O, 10mM NH_4OAc pH: 5.9

Flow Rate: 1 mL/min

Column: Phenomenex® Luna C-8 Column 150 x 4.6 mm. 3 µm.

HPLC Condition B.

Condition: 50 % MeCN in H_2O, 10mM NH_4OAc pH: 6.4

Flow Rate: 2 mL/min

Column: Waters® Spherisorb C-8 Column 150 x 4.6 mm. 5 µm.

HPLC Condition C.

Condition: 30 % MeCN in H_2O, 10mM NH_4OAc pH: 6.9

Flow Rate: 2 mL/min

Column: Waters® Spherisorb C-8 Column 150 x 4.6 mm. 5 µm.

HPLC Condition D.

Condition: 15 % MeCN in H_2O, 10mM NH_4OAc pH: 5.9

Flow Rate: 1 mL/min

Column: Phenomenex® Luna C-8 Column 150 x 4.6 mm. 3 µm.

4.4 Specific Activity Calculation.

The specific activity of radiofluorinated products was determined by the following method. A sample of known volume of the crude reaction mixture was transferred to a vial, and the activity of the vial was counted using a calibrated CAPINTEC (CRC-15R) detector. The activity in the vial was then multiplied by the RCC (obtained from radio-TLC analysis) to determine the total activity of the product in the vial. A concentration of activity in Ci/mL was thus obtained. An aliquot of the sample was then injected onto the HPLC using one of the four isocratic methods listed above. The UV peak corresponding to the radiofluorinated product was determined by overlaying the UV and RAD traces (with a 0.1 min offset). The UV area was then used to calculate the concentration of the product based on linear regression analysis of appropriate [^{19}F]fluoroarene standard. A standard curve was generated from standard solutions, each run in duplicate (1 mg/mL to 10 µg/mL). This, in turn, was used to determine the concentration of the product in mmol/mL. Dividing the activity concentration (Ci/mL) by the HPLC-derived concentration of product (mmol/mL) provided the specific activity in Ci/mmol (or alternate units if desired). This reflects an end of synthesis (EoS) specific activity. See main text for specific values.

4.4.1 [^{18}F]Fluoroacetophenone 2 calibration curve and specific activity data

4FAP = fluoroacetophenone

	HPLC UV detector response		
4FAP [M]	1	2	Mean
1	27533960	27770686	27652323
0.1	3598805	3621650	3610227.5
0.01	352213	355334	353773.5
0.001	33938	33836	33887
0.0001	3722	3584	3653
0.00005	1977	1944	1960.5
0.00001	585	595	590

y= 36119482.4766x - 2235.7955 y: detector response

x= (y+2235.8)/36120000 x: F-PEB conc (M)

Trial 1

UV detector response	Conc. 4FAP (M)	total vol soln (mL)	4FAP (mg)	4FAP MW (g/mol)
25788	0.000775853	7	0.005430969	137
mols FAP	RCC	Total Activity (mCi)	mCi/mol	**Ci/mmol**
3.96421E-08	0.124	645	2018000000	2018

Trial 2

UV detector response	Conc. 4FAP (M)	total vol soln (mL)	4FAP (mg)	4FAP MW (g/mol)
14828	0.00047242	7	0.003306938	137
mols 4FAP	RCC	Total Activity (mCi)	mCi/mol	**Ci/mmol**
2.41382E-08	0.081	569	1909000000	1909

4.4.2 [^{18}F]F-PEB 20 calibration curve and specific activity data

F-PEB HPLC UV detector response

F-PEB (M)	1	2	Mean
1	33547665	33162506	33355086
0.1	3931326	2966898	3449112
0.01	374113	353732	363922.5
0.001	56066	40038	48052
0.0001	5989	5166	5577.5
0.00005	3049	2649	2849

y=	34413474.4451x - 8891.0631	y: detector response
x=	(y+8891.1)/34413474	x: F-PEB conc (M)

Trial 1

UV detector response	Conc. F-PEB (M)	total vol soln (mL)	mg F-PEB	MW F-PEB (g/mol)
3364	0.000356113	6	0.0021367	222.3

mols F-PEB	RCC	Total Activity (mCi)	mCi/mol	**Ci/mmol**
9.6117E-09	0.042	178	777800000	**777.8**

Trial 2

UV detector response	Conc. F-PEB (M)	total vol soln (mL)	mg F-PEB	MW F-PEB (g/mol)
10294	0.000557488	6	0.0033449	222.3

mols F-PEB	RCC	Total Activity (mCi)	mCi/mol	**Ci/mmol**
1.50469E-08	0.031	355	731400000	**731.4**

4.5 Optimization Screens

Unless otherwise stated, 4-acetylphenylboronic acid was used for all optimization screens. The reaction scheme as well as accompanying tables in each subsection describe the reaction conditions employed, with **bold** typeface in the reaction scheme denoting the variable tested in each case (see S4.2 for additional information). All reactant values are expressed in μmol quantities for brevity and simplicity. Red typeface denotes the ^{18}F source used, typically 100 μL of a 6 mL DMF solution containing [^{18}F]KF, 5 mg KOTf and 50 μg K_2CO_3 (see main text and section S4.1 for additional information regarding ^{18}F production and formulation).

S1: Absence of Reagents

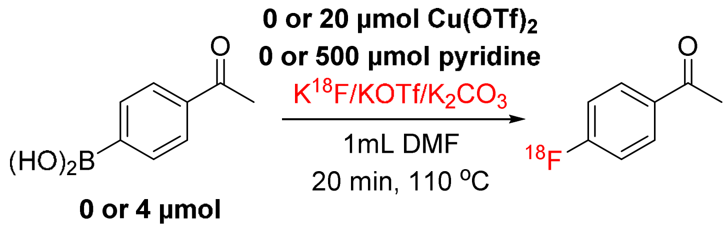


Table S1: Absence of Reagents

substrate µmol	**4**	**4**	**4**	**0**
$CuOTf_2$ µmol	**40**	**0**	**0**	**40**
pyridine µmol	**0**	**500**	**0**	**500**
Expt 1	3.4%	0%	0%	0%
Expt 2	4.1%	0%	0%	0%
Expt 3	1.3%	0%	0%	0%
Mean RCC	**3%**	**nd**	**nd**	**nd**
SD	**2%**			

S2: Alternate Cu salts

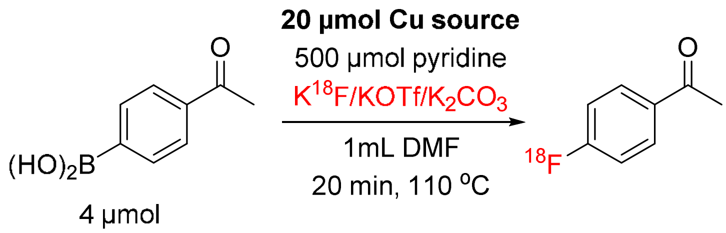
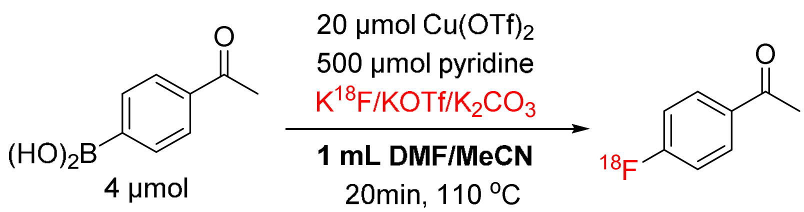


Table S2: Alternate Copper Sources

Copper source	**$CuBr_2$**	**$CuSO_4$**	**$Cu(tBuCN)_2OTf$**
substrate µmol	4	4	4
Cu µmol	20	20	20
pyridine µmol	500	500	500
RCC	**nd**	**nd**	**nd**

S3: Acetonitrile addition screen



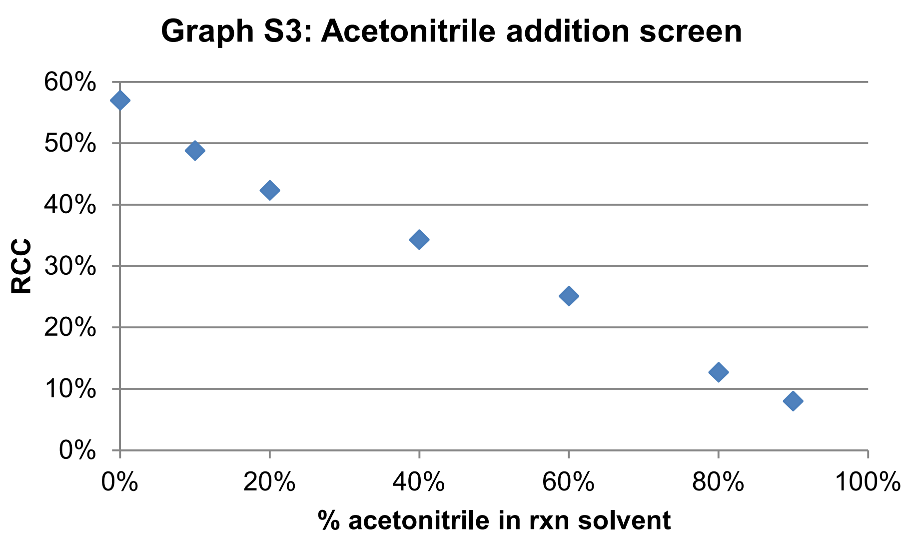
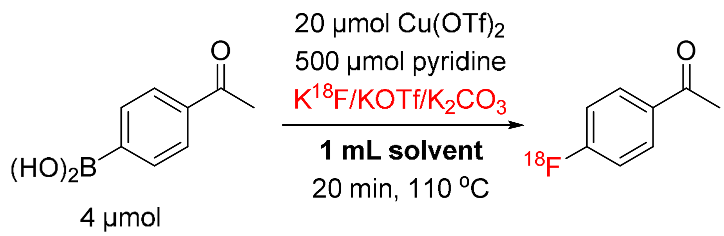


Table S3: Acetonitrile addition screen

Substrate µmol	4	4	4	4	4	4	4
$CuOTf_2$ µmol	20	20	20	20	20	20	20
pyridine µmol	500	500	500	500	500	500	500
%MeCN	**0%**	**10%**	**20%**	**40%**	**60%**	**80%**	**90%**
RCC	**57%**	**49%**	**42%**	**34%**	**25%**	**13%**	**8%**

S4: DMF vs. MeCN screen



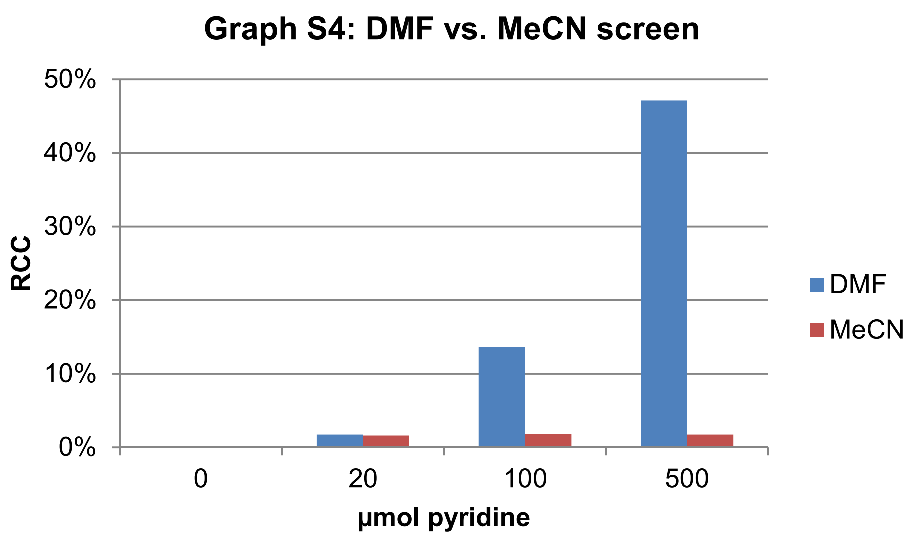
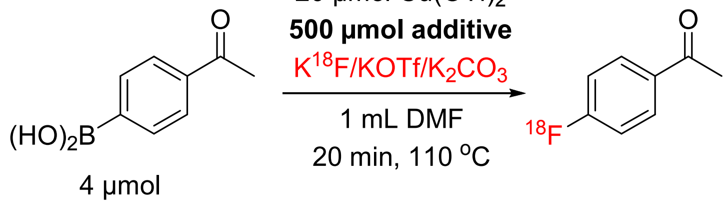


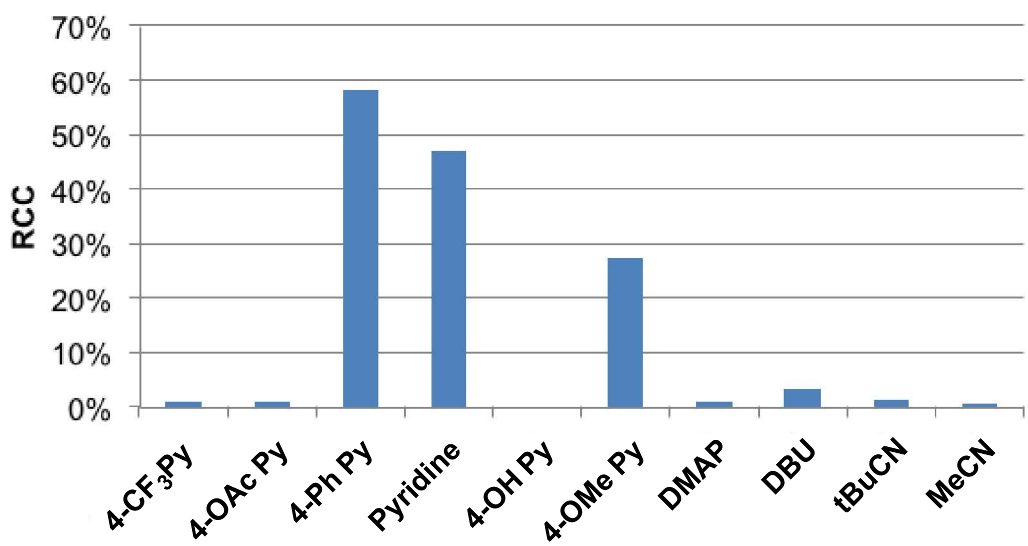
Table S4: DMF vs. MeCN screen

substrate µmol	4	4	4	4
$CuOTf_2$ µmol	20	20	20	20
pyridine µmol	**0**	**20**	**100**	**500**
DMF RCC	**nd**	**2%**	**14%**	**47%**
MeCN RCC	**nd**	**2%**	**2%**	**2%**

S5: Pyridine Additives screen



Graph S5: Alternate Additives Screen



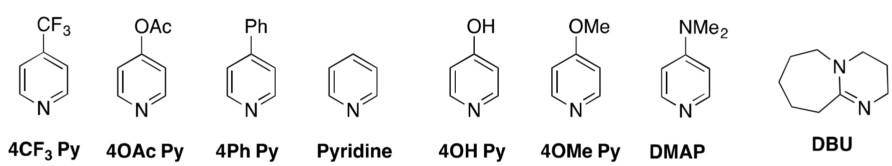
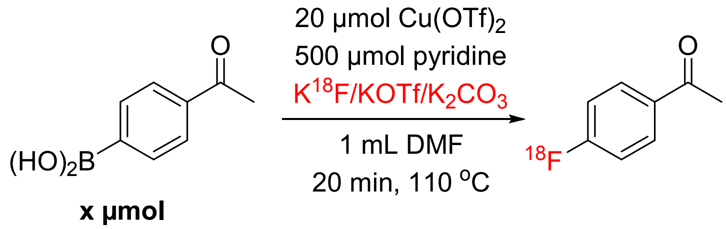


Table S5: Pyridine Additives screen

substrate µmol	4	4	4	4	4	4	4
$CuOTf_2$ µmol	20	20	20	20	20	20	20
additive µmol	500	500	500	500	500	500	500
additive	**4CF_3 Py**	**4OAc Py**	**4Ph Py**	**Pyridine**	**4OH Py**	**4OMe Py**	**DMAP**
RCC	**1%**	**1%**	**58%**	**47%**	**nd**	**27%**	**1%**

substrate µmol	4	4	4
$CuOTf_2$ µmol	20	20	20
additive µmol	500	500	500
additive	**DBU**	**tBuCN**	**MeCN**
RCC	**3%**	**1%**	**1%**

S6: Boronic Acid Concentration Screen



Graph S6: Boronic Acid Concentration Screen

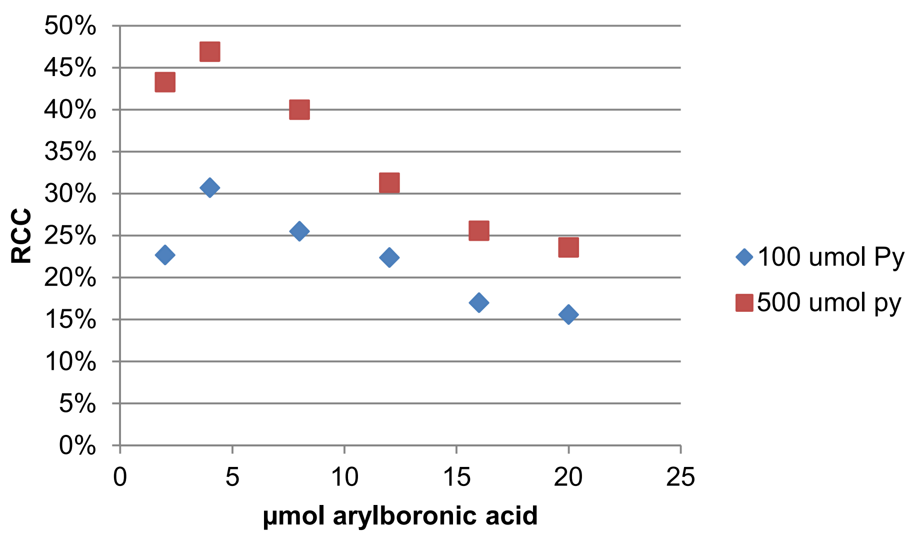
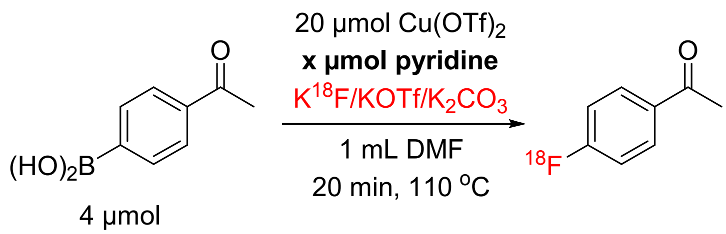


Table S6: Boronic Acid Concentration Screen

substrate μmol	**2**	**4**	**8**	**12**	**16**	**20**
$CuOTf_2$ μmol	20	20	20	20	20	20
500 μmol pyridine RCC	**43%**	**47%**	**40%**	**31%**	**26%**	**24%**
100 μmol pyridine RCC	**23%**	**31%**	**26%**	**22%**	**17%**	**16%**

S7: Pyridine Concentration Screen



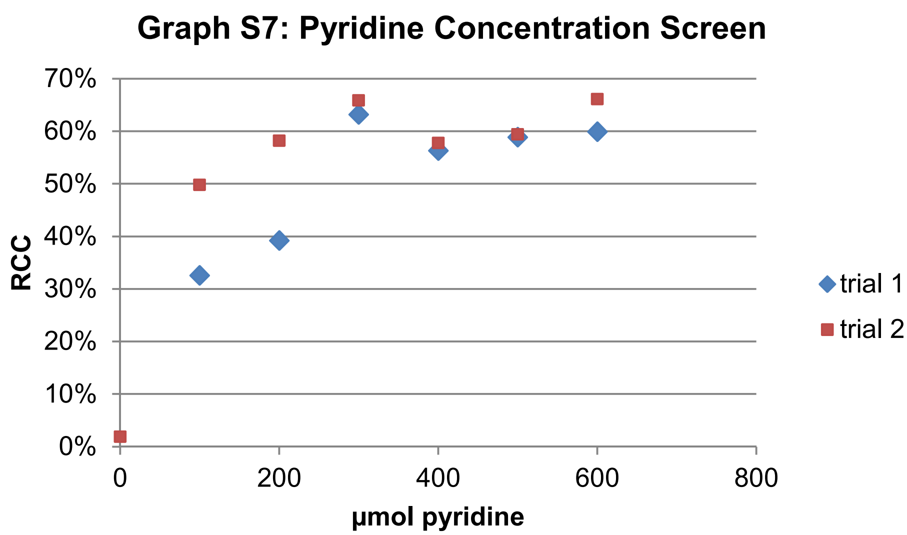


Table S7: Pyridine Concentration Screen

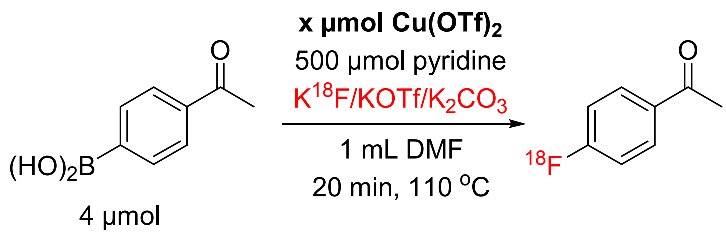
Trial 1

substrate µmol	4	4	4	4	4	4
$CuOTf_2$ µmol	20	20	20	20	20	20
pyridine µmol	**100**	**200**	**300**	**400**	**500**	**600**
RCC	**33%**	**39%**	**63%**	**56%**	**59%**	**60%**

Trial 2

substrate µmol	4	4	4	4	4	4	4
$CuOTf_2$ µmol	20	20	20	20	20	20	20
pyridine µmol	**0**	**100**	**200**	**300**	**400**	**500**	**600**
RCC	**2%**	**50%**	**58%**	**66%**	**58%**	**59%**	**66%**

S8: Copper(II) Triflate Loading Study



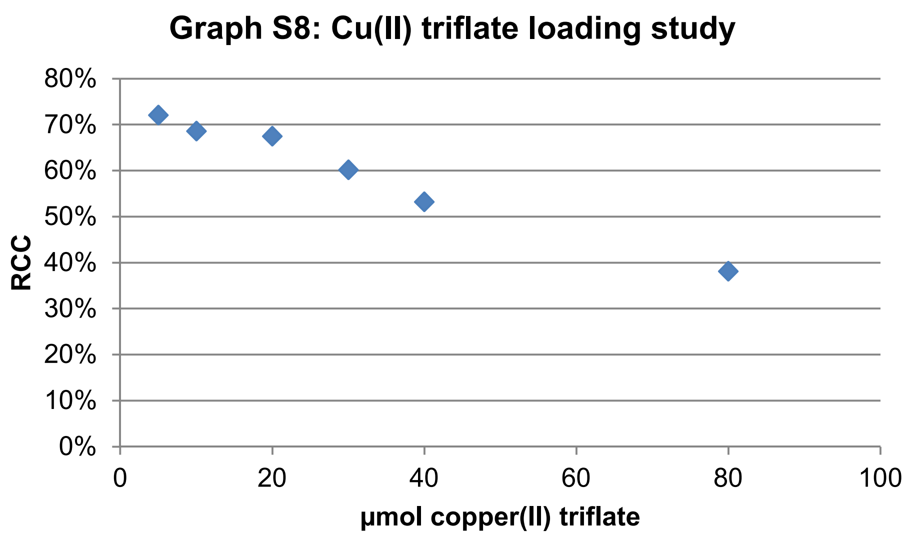
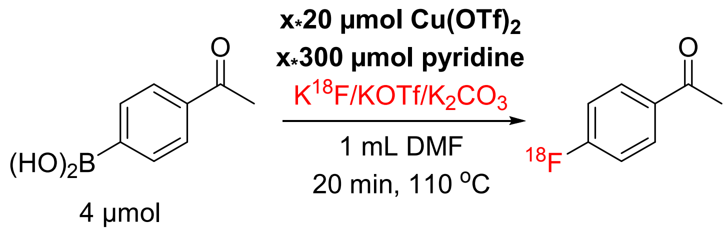


Table S8: Copper(II) triflate loading study

substrate μmol	4	4	4	4	4	4
$CuOTf_2$ μmol	**5**	**10**	**20**	**30**	**40**	**80**
pyridine μmol	500	500	500	500	500	500
RCC	**72%**	**69%**	**68%**	**60%**	**53%**	**38%**

S9: Copper(II) Triflate/Pyridine Loading Study



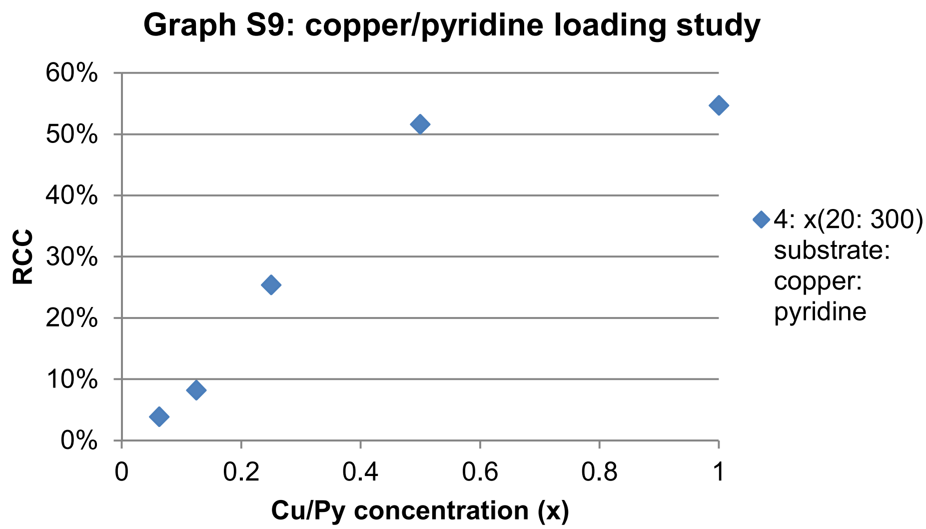
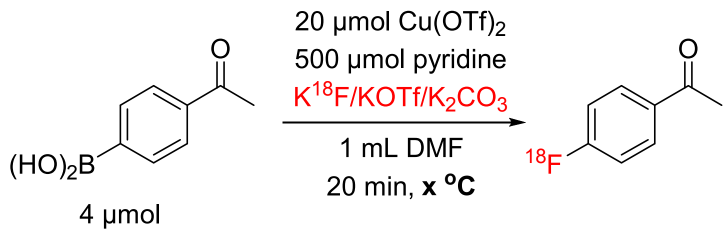


Table S9: Copper/Pyridine loading study

substrate µmol	4	4	4	4	4
X =	**0.0625**	**0.125**	**0.25**	**0.5**	**1**
$CuOTf_2$ µmol	**1.25**	**2.5**	**5**	**10**	**20**
pyridine µmol	**19**	**37.5**	**75**	**150**	**300**
RCC	**4%**	**8%**	**25%**	**52%**	**55%**

S10: Temperature Study



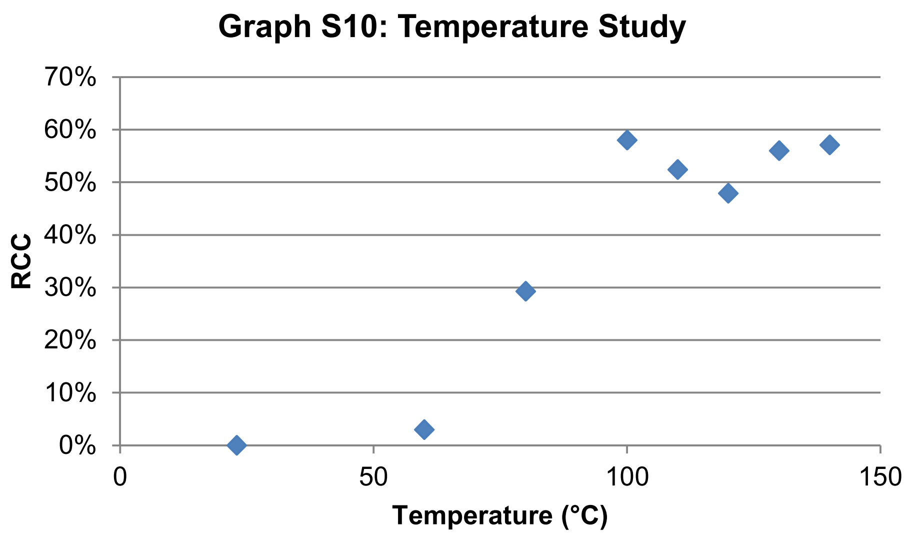
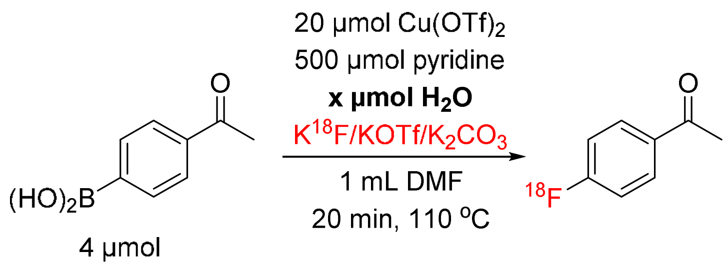


Table S10: Temperature Study

substrate µmol	4	4	4	4	4	4	4	4
$CuOTf_2$ µmol	20	20	20	20	20	20	20	20
pyridine µmol	500	500	500	500	500	500	500	500
temperature °C	**23**	**60**	**80**	**100**	**110**	**120**	**130**	**140**
RCC	**nd**	**3%**	**29%**	**58%**	**52%**	**48%**	**56%**	**57%**

S11: Water Addition Study



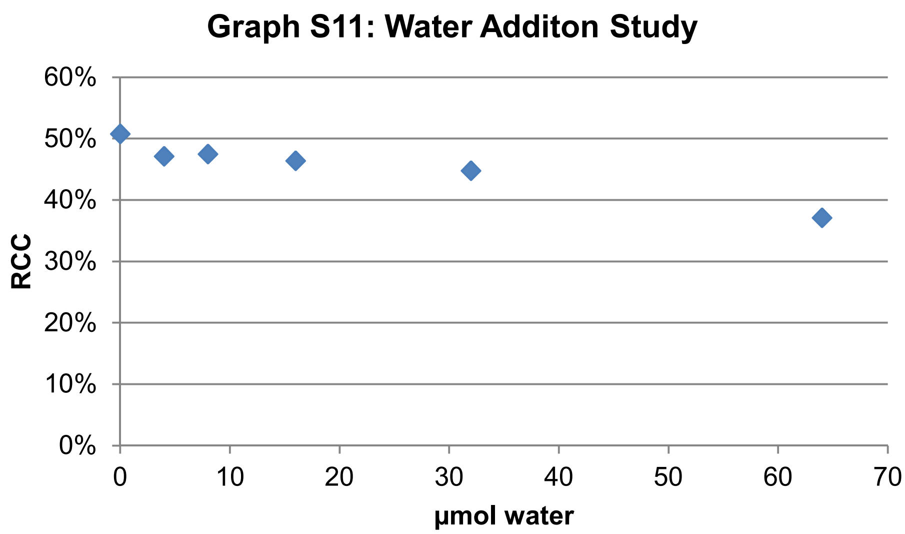
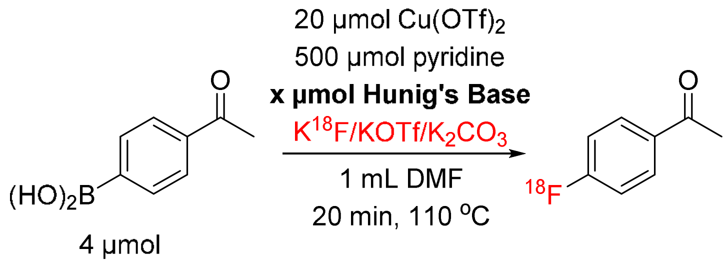


Table S11: Water Addition Study

substrate µmol	4	4	4	4	4	4
$CuOTf_2$ µmol	40	40	40	40	40	40
pyridine µmol	500	500	500	500	500	500
H_2O µmol	**0**	**4**	**8**	**16**	**32**	**64**
RCC	**51%**	**47%**	**48%**	**46%**	**45%**	**37%**

S12: Diisopropylethylamine Addition Study



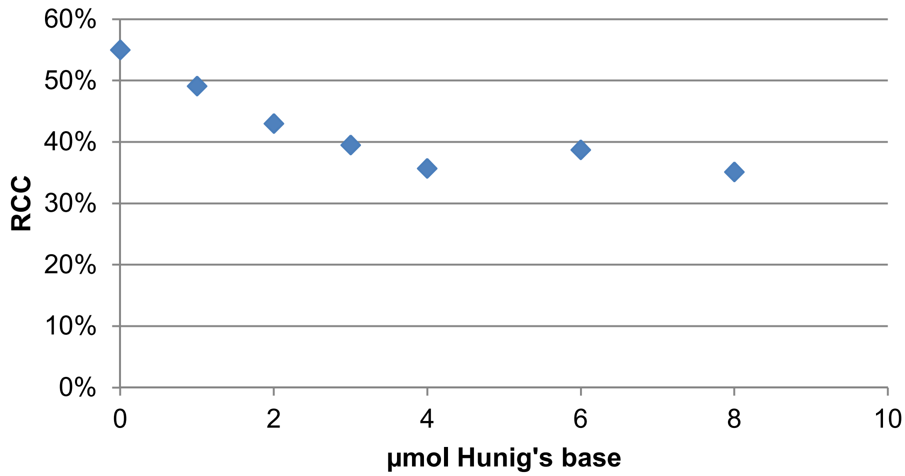
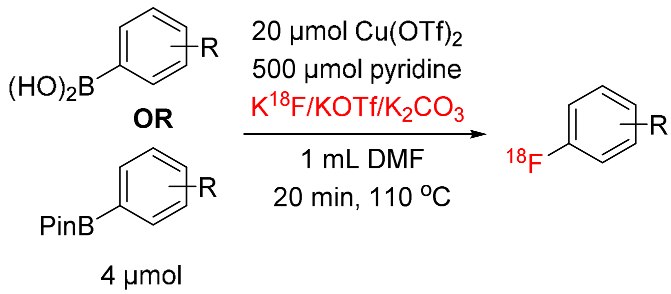


Table S12: Hunig's Base Addition Study

substrate µmol	4	4	4	4	4	4	4
$CuOTf_2$ µmol	40	40	40	40	40	40	40
pyridine µmol	500	500	500	500	500	500	500
Hunig's base µmol	**0**	**1**	**2**	**3**	**4**	**6**	**8**
RCC	**55%**	**49%**	**43%**	**40%**	**36%**	**39%**	**35%**

S13: Bpin vs. $B(OH)_2$ Comparison



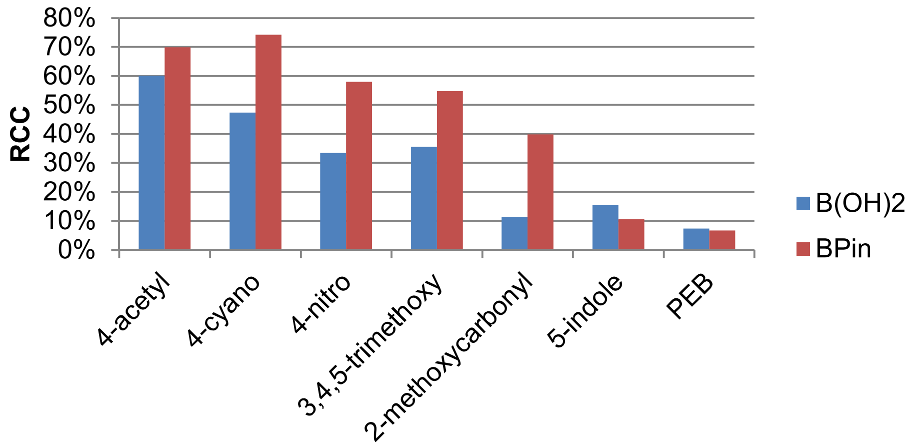


Table S13: Bpin vs. $B(OH)_2$ comparison

Compound #	**2**	**5**	**7**	**8**	**15**	**16**	**19**
substrate µmol	4	4	4	4	4	4	4
$CuOTf_2$ µmol	20	20	20	20	20	20	20
pyridine µmol	500	500	500	500	500	500	500
Phenylboronate Substituent	**4-acetyl**	**2-methoxy carbonyl**	**4-cyano**	**4-nitro**	**3,4,5-trimethoxy**	**5-indole**	**PEB**
RCC $B(OH)_2$	**60%**	**11%**	**47%**	**33%**	**36%**	**15%**	**7%**
RCC Bpin	**70%**	**40%**	**74%**	**58%**	**55%**	**11%**	**7%**

S14: Temperature Screen with Trifluoroborate Salts

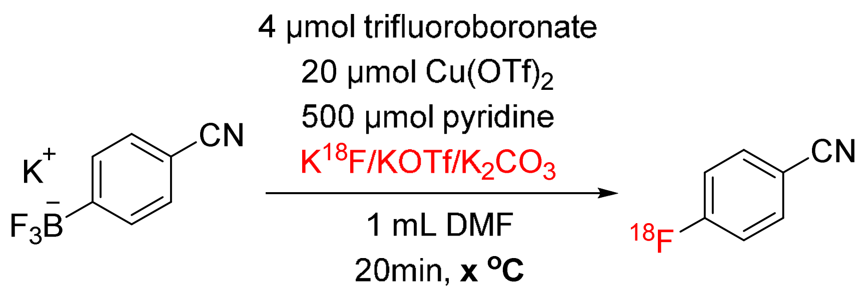
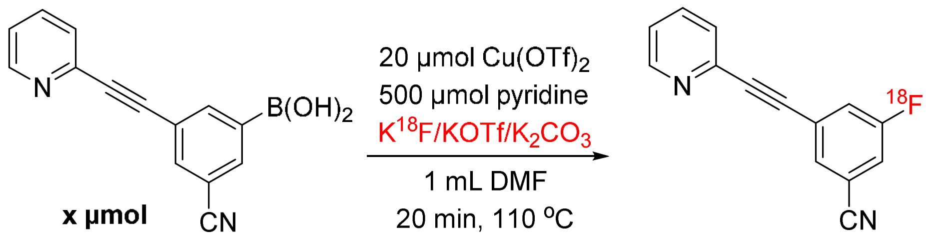


Table S14: Temperature Screen with Trifluoroborate Salts

substrate µmol	4	4	4	4	4
Cu µmol	20	20	20	20	20
Pyridine µmol	500	500	500	500	500
Temperature (°C)	23	70	80	90	100
RCC	**nd**	**nd**	**0.3%**	**1%**	**4%**

substrate µmol	4	4	4	4	4
Cu µmol	20	20	20	20	20
Pyridine µmol	500	500	500	500	500
Temperature (°C)	110	120	130	140	150
RCC	**5%**	**6%**	**6%**	**5%**	**6%**

S15: PEB Substrate Addition Screen



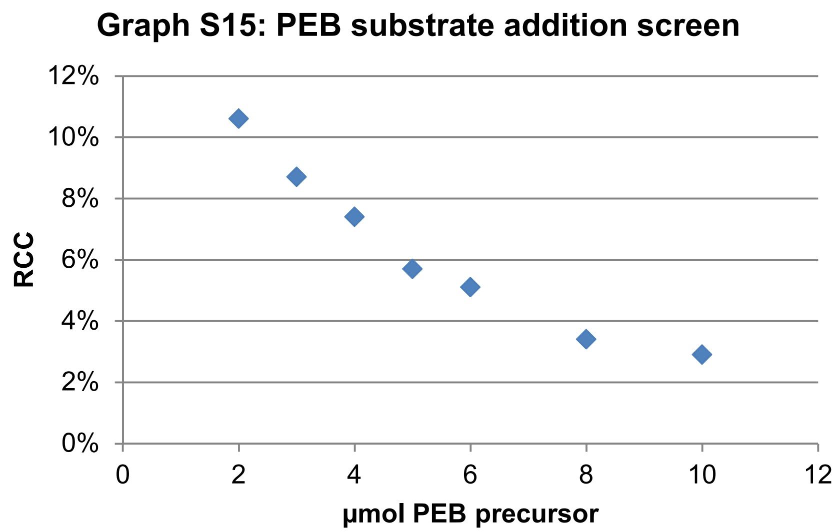
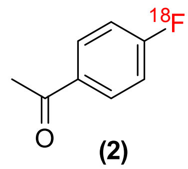


Table S15: PEB substrate addition screen

substrate µmol	**2**	**3**	**4**	**5**	**6**	**8**	**10**
$CuOTf_2$ µmol	20	20	20	20	20	20	20
pyridine µmol	500	500	500	500	500	500	500
RCC	**11%**	**9%**	**7%**	**6%**	**5%**	**3%**	**3%**

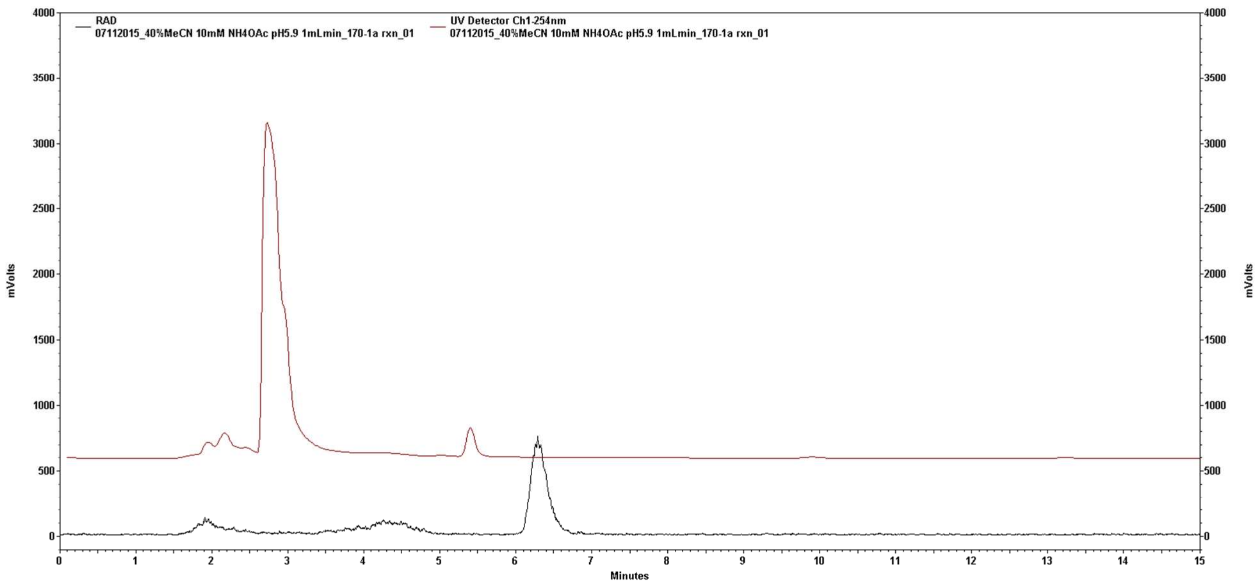
4.6 Radio-HPLC/Radio-TLC Analysis for ^{18}F-Labeled Compounds 2-18 and 20



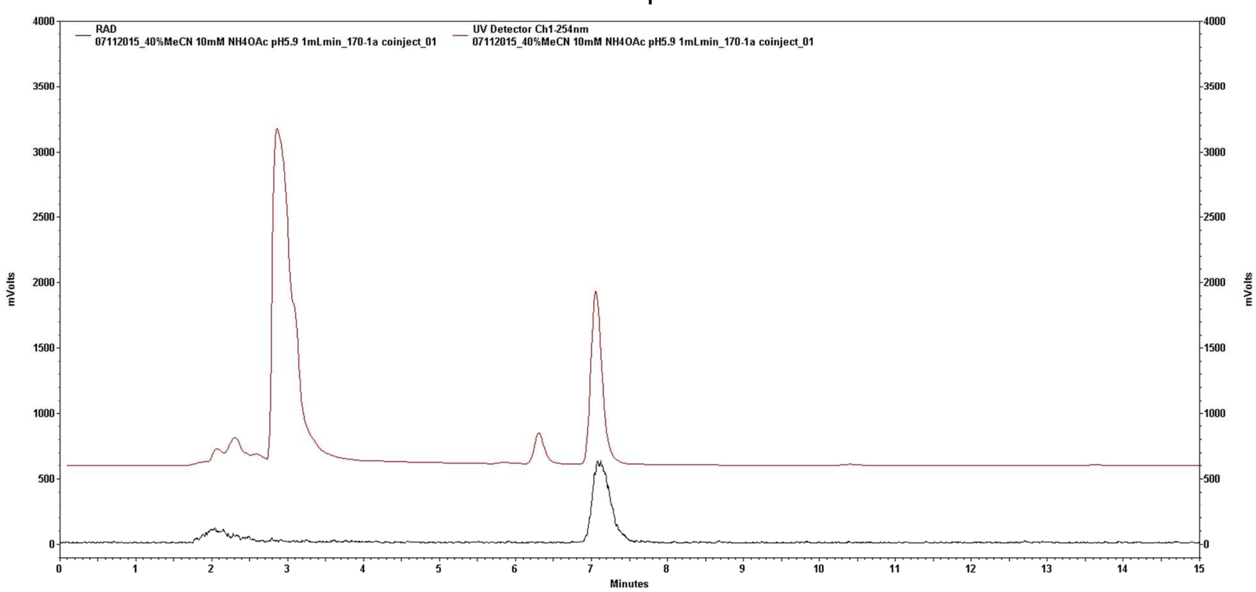
(2)

HPLC Condition: General HPLC Condition A

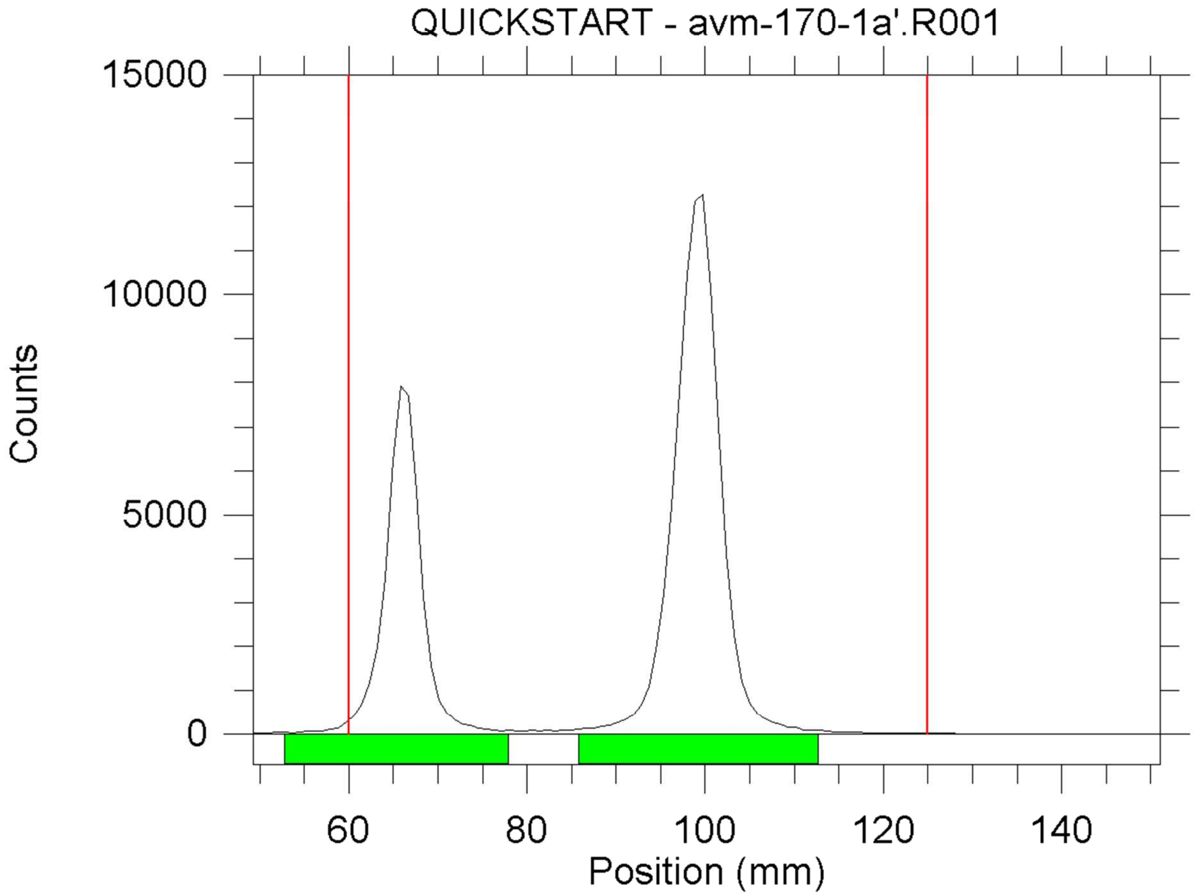
4-[^{18}F]fluoroacetophenone **2** RAD trace overlaid with UV trace (256 nm)



4-[^{18}F]fluoroacetophenone **2** RAD trace overlaid with UV trace (256 nm) spiked with 4-fluoroacetophenone

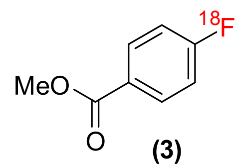


4-[^{18}F]fluoroacetophenone **2** Radio-TLC spectrum



4-[^{18}F]fluoroacetophenone **2** Radio-TLC Yields (RCC):

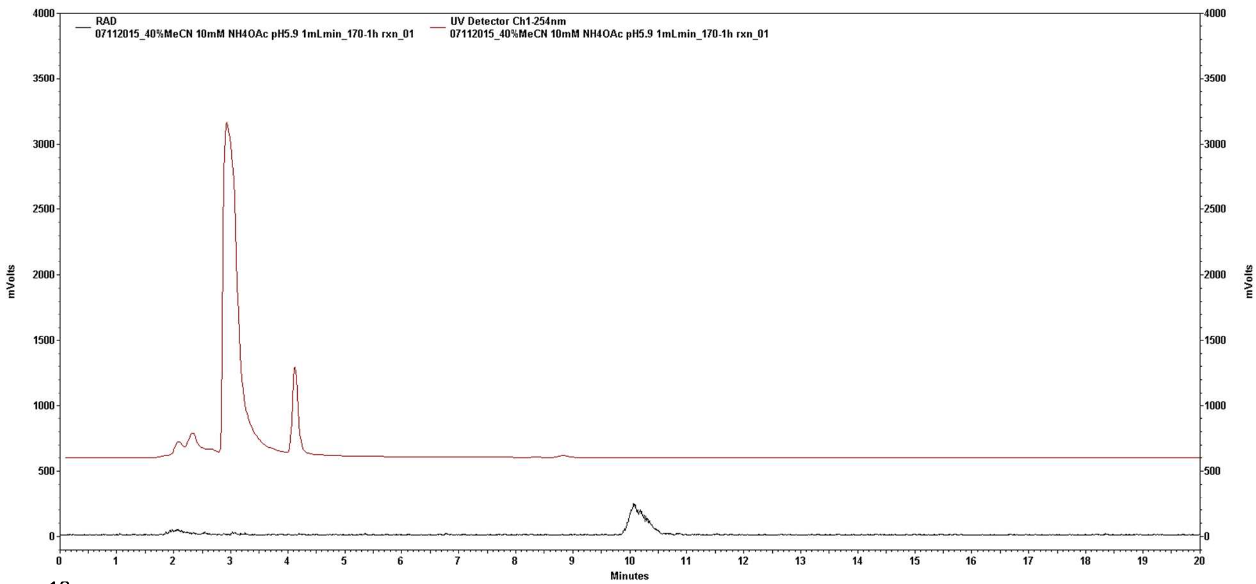
Replicate	TLC Yield
1	**46%**
2	**55%**
3	**66%**
4	**66%**
5	**70%**
6	**66%**
7	**62%**
Mean	**61%**
Standard Deviation	**8%**



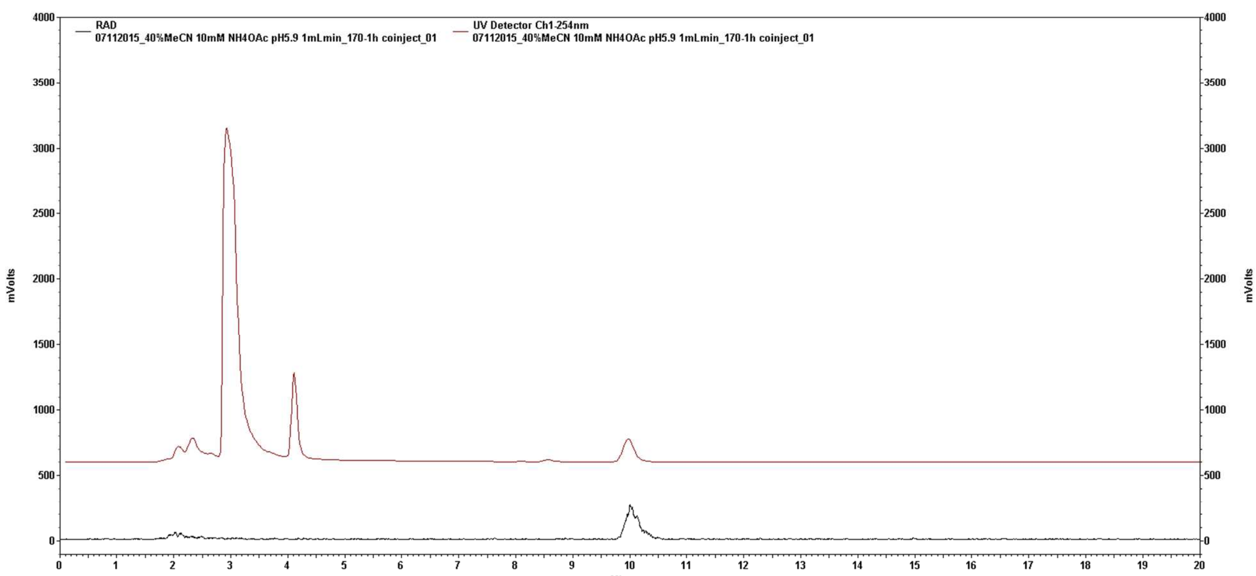
(3)

HPLC Condition: General HPLC Condition A

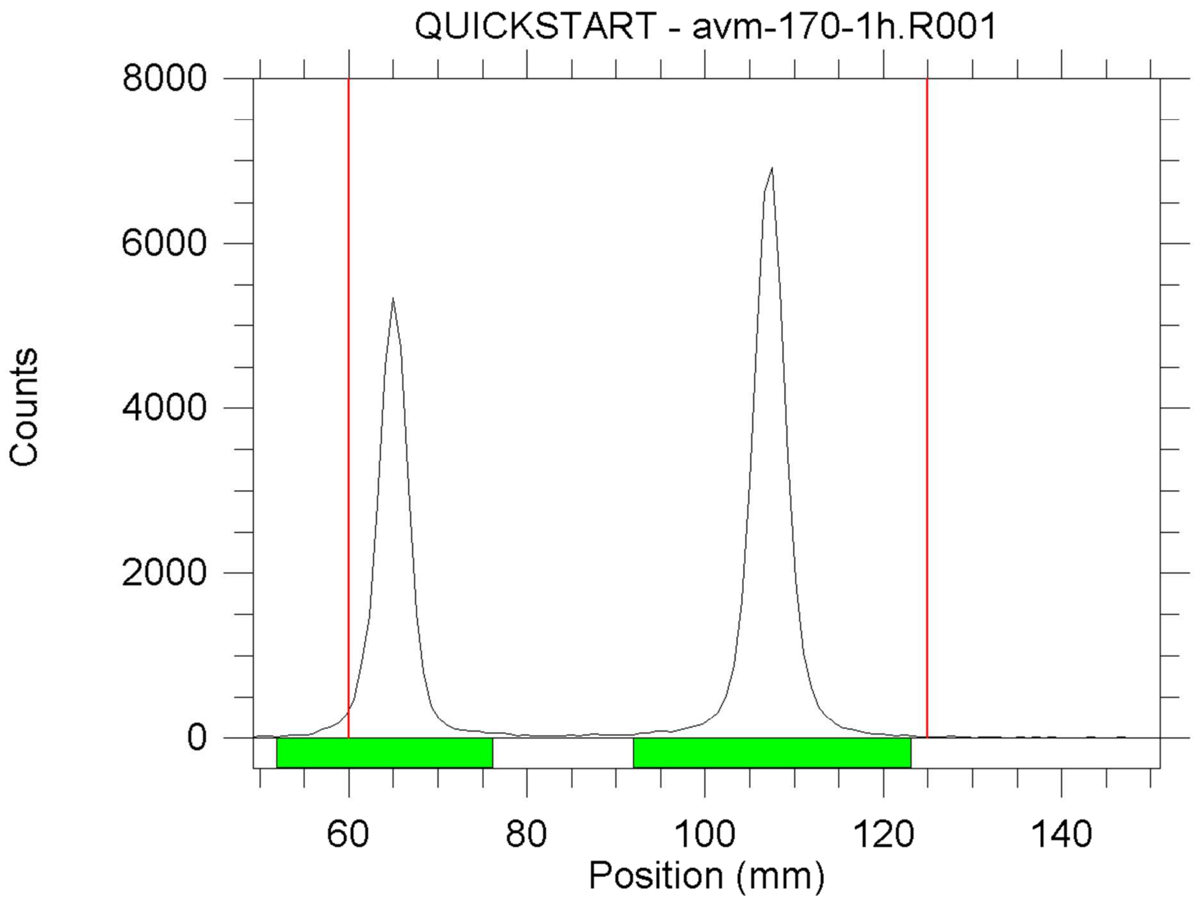
4-[^{18}F]fluoromethylbenzoate **3** RAD trace overlaid with UV trace (256 nm)



4-[^{18}F]fluoromethylbenzoate **3** RAD trace overlaid with UV trace (256 nm) spiked with 4-fluoromethylbenzoate

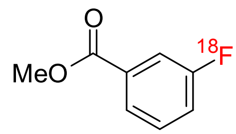


4-[^{18}F]fluoromethylbenzoate **3** Radio-TLC spectrum



4-[^{18}F]fluoromethylbenzoate **3** Radio-TLC Yields (RCC):

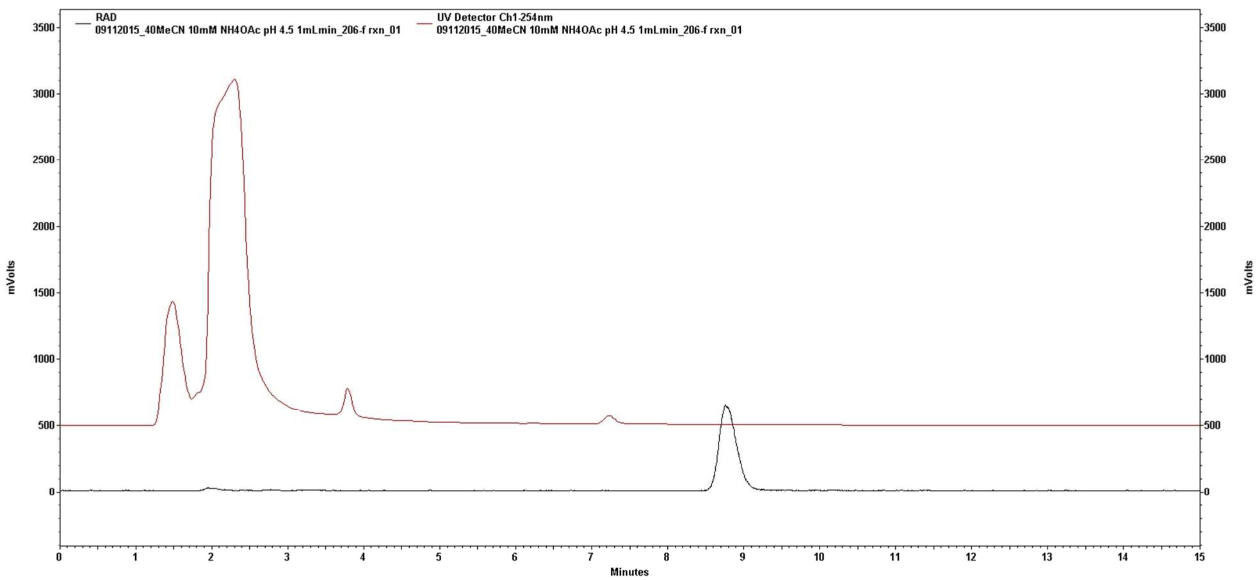
Replicate	TLC Yield
1	**42%**
2	**46%**
3	**59%**
Mean	**49%**
Standard Deviation	**9%**



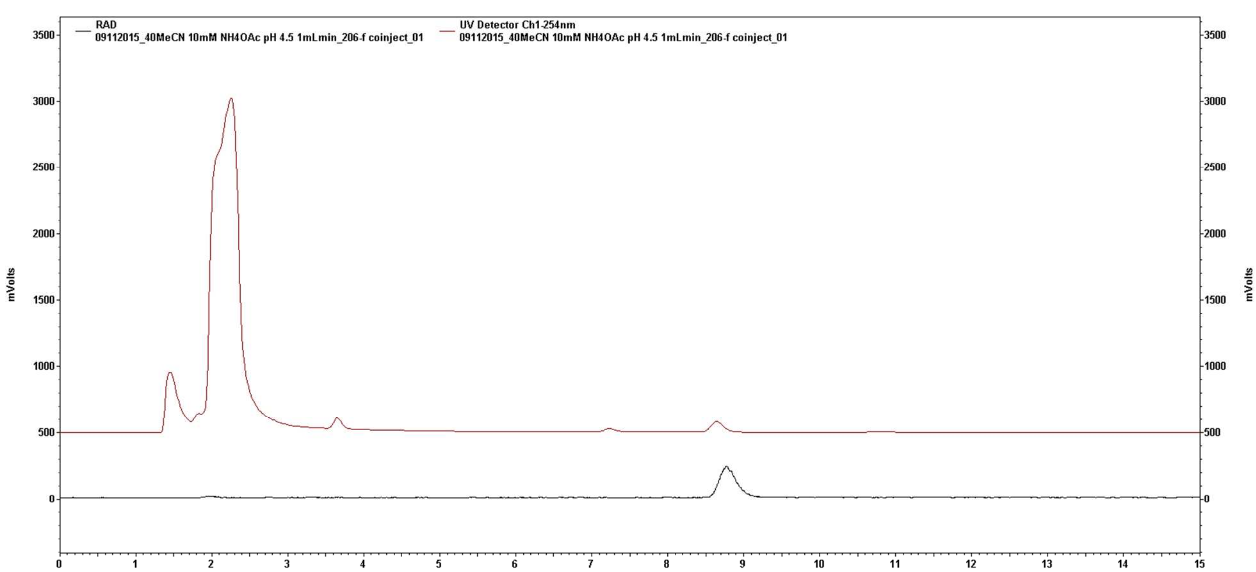
(4)

HPLC Condition: General HPLC Condition A, pH 7.29

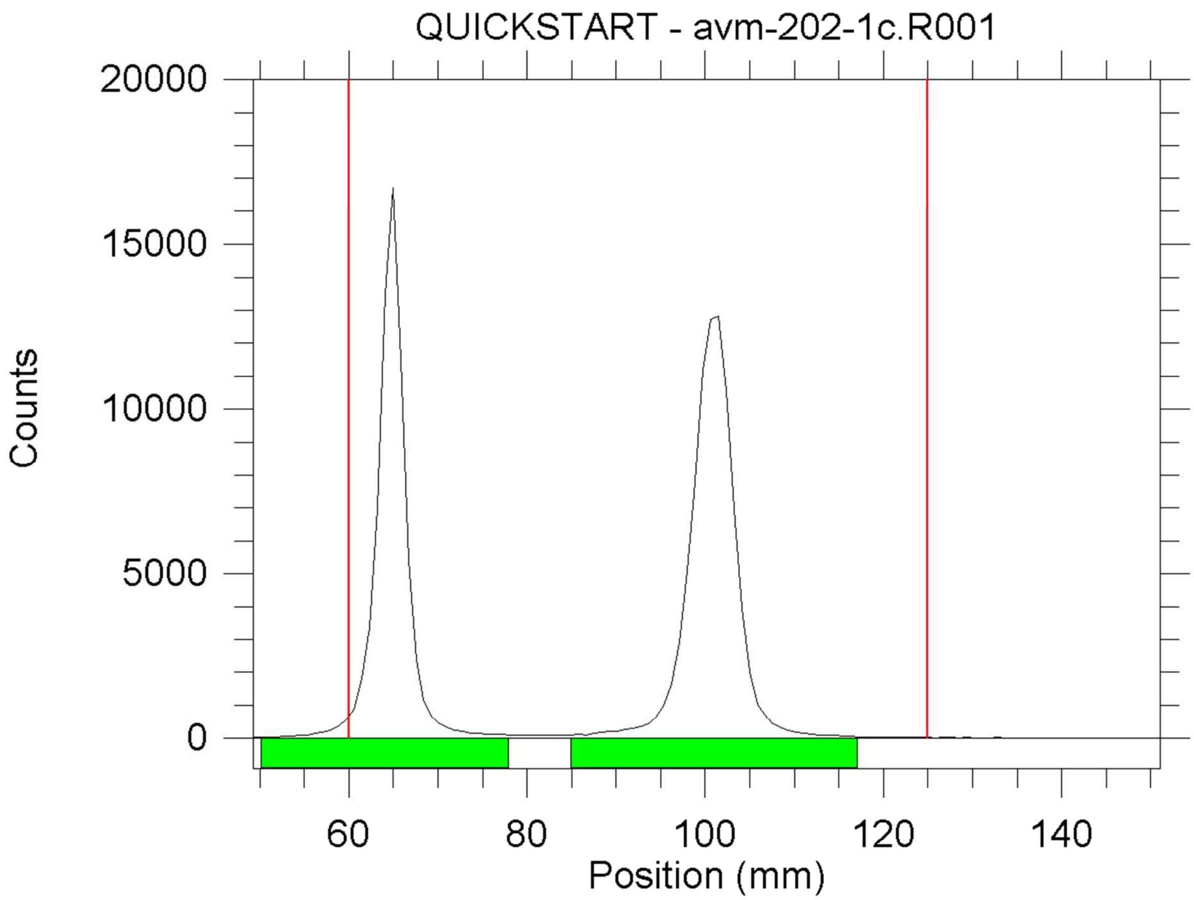
3-[^{18}F]fluoromethylbenzoate **4** RAD trace overlaid with UV trace (256 nm)



3-[^{18}F]fluoromethylbenzoate **4** RAD trace overlaid with UV trace (256 nm) spiked with 3-fluoromethylbenzoate

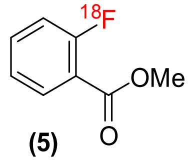


3-[^{18}F]fluoromethylbenzoate **4** Radio-TLC spectrum



3-[^{18}F]fluoromethylbenzoate **4** Radio-TLC Yields (RCC):

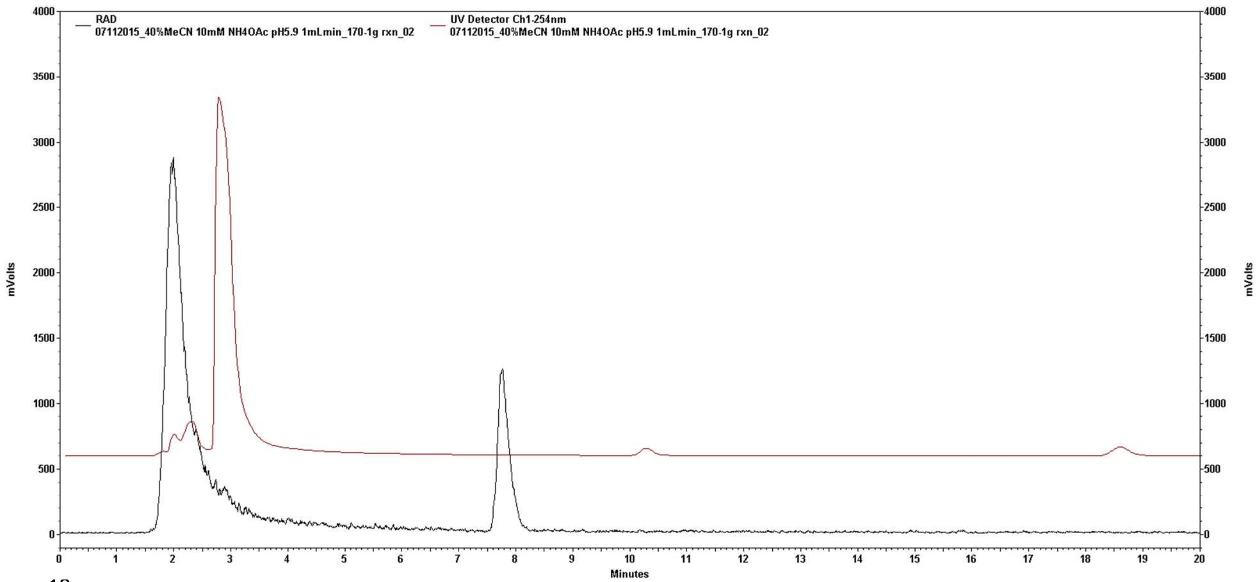
Replicate	TLC Yield
1	**55%**
2	**57%**
3	**55%**
Mean	**56%**
Standard Deviation	**1%**



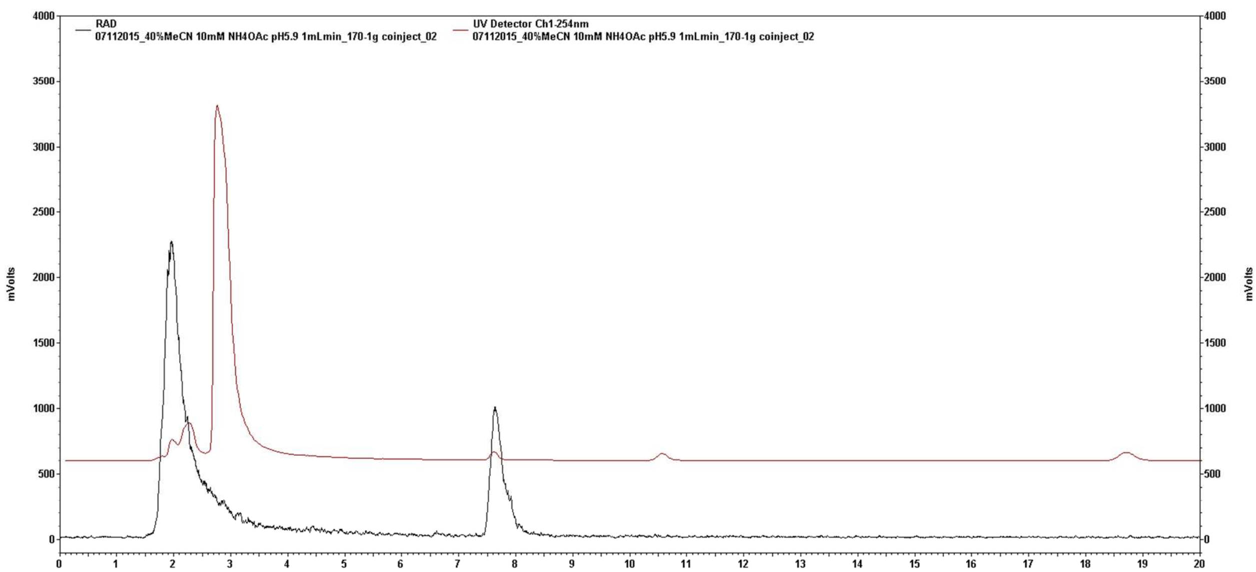
(5)

HPLC Condition: General HPLC Condition A

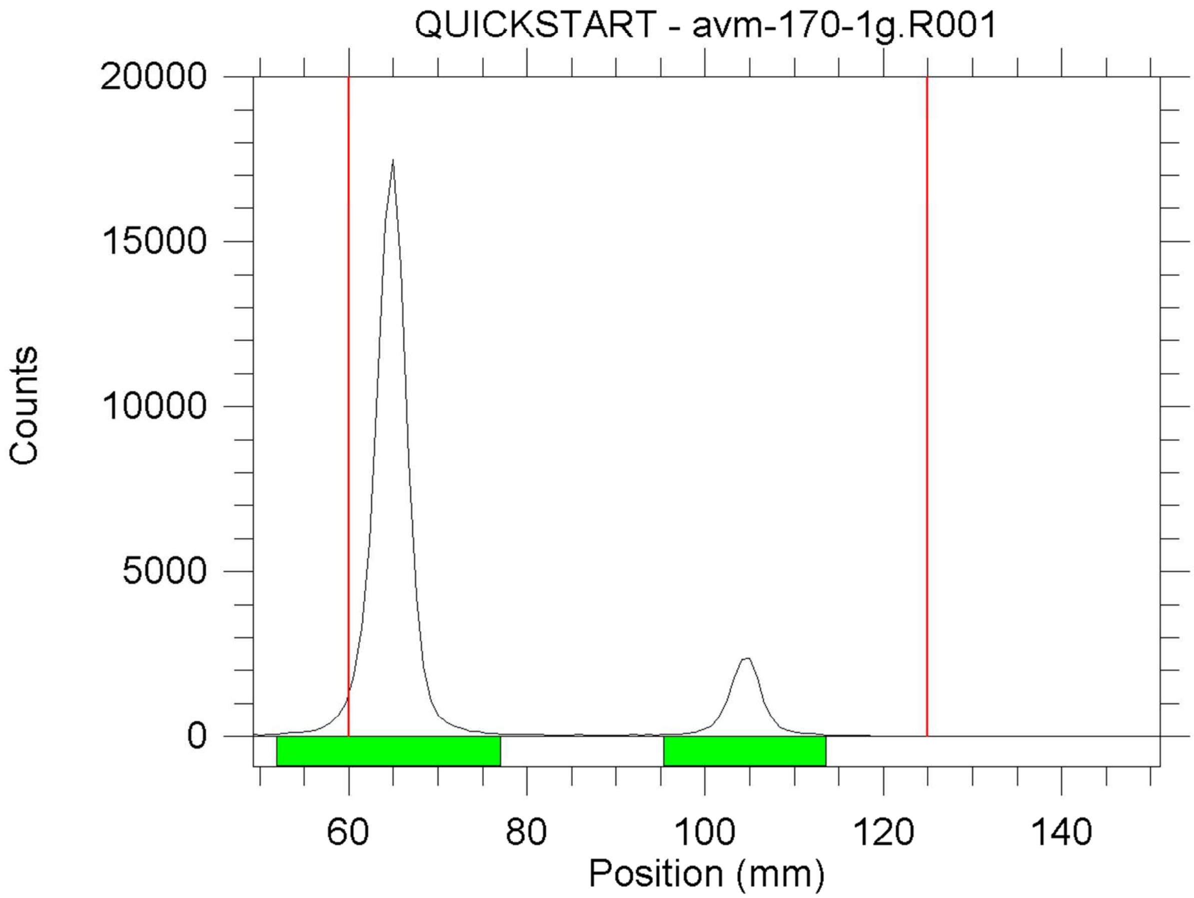
2-[^{18}F]fluoromethylbenzoate **5** RAD trace overlaid with UV trace (256 nm)



2-[^{18}F]fluoromethylbenzoate **5** RAD trace overlaid with UV trace (256 nm) spiked with 2-fluoromethylbenzoate

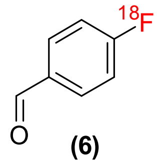


2-[^{18}F]fluoromethylbenzoate **5** Radio-TLC spectrum



2-[^{18}F]fluoromethylbenzoate **5** Radio-TLC Yields (RCC):

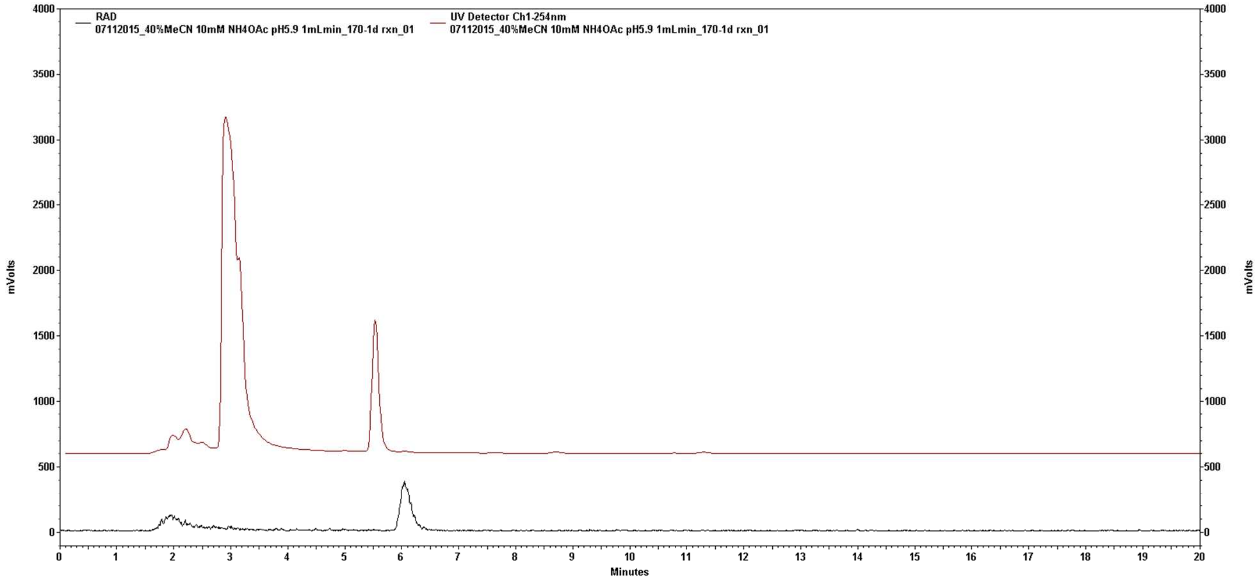
Replicate	TLC Yield
1	**12%**
2	**9%**
3	**13%**
Mean	**11%**
Standard Deviation	**2%**



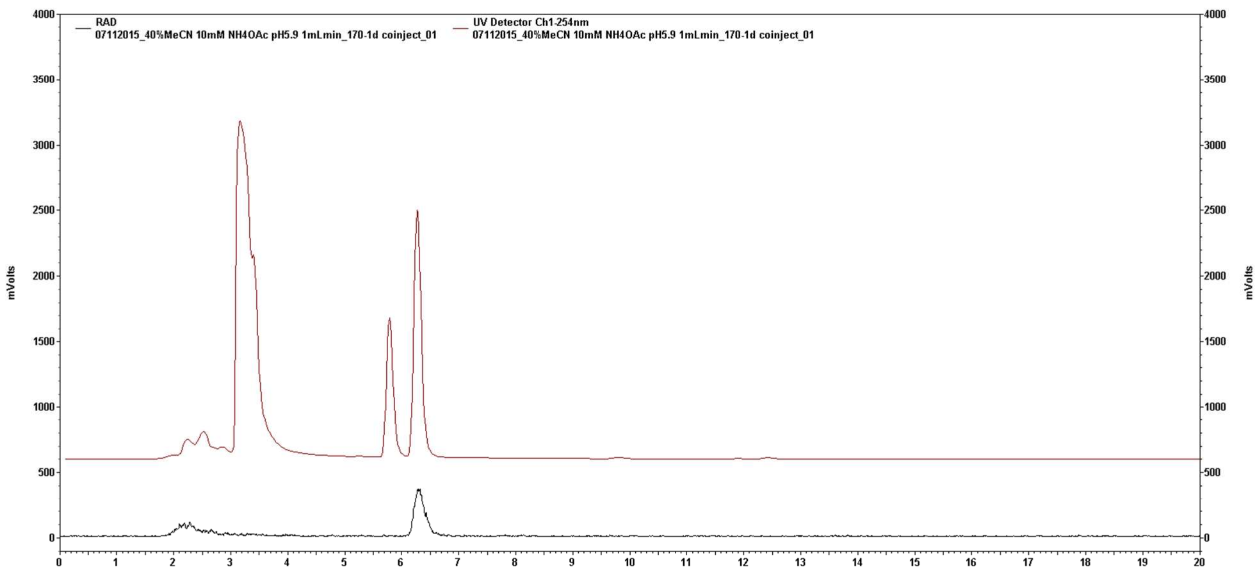
(6)

HPLC Condition: General HPLC Condition A

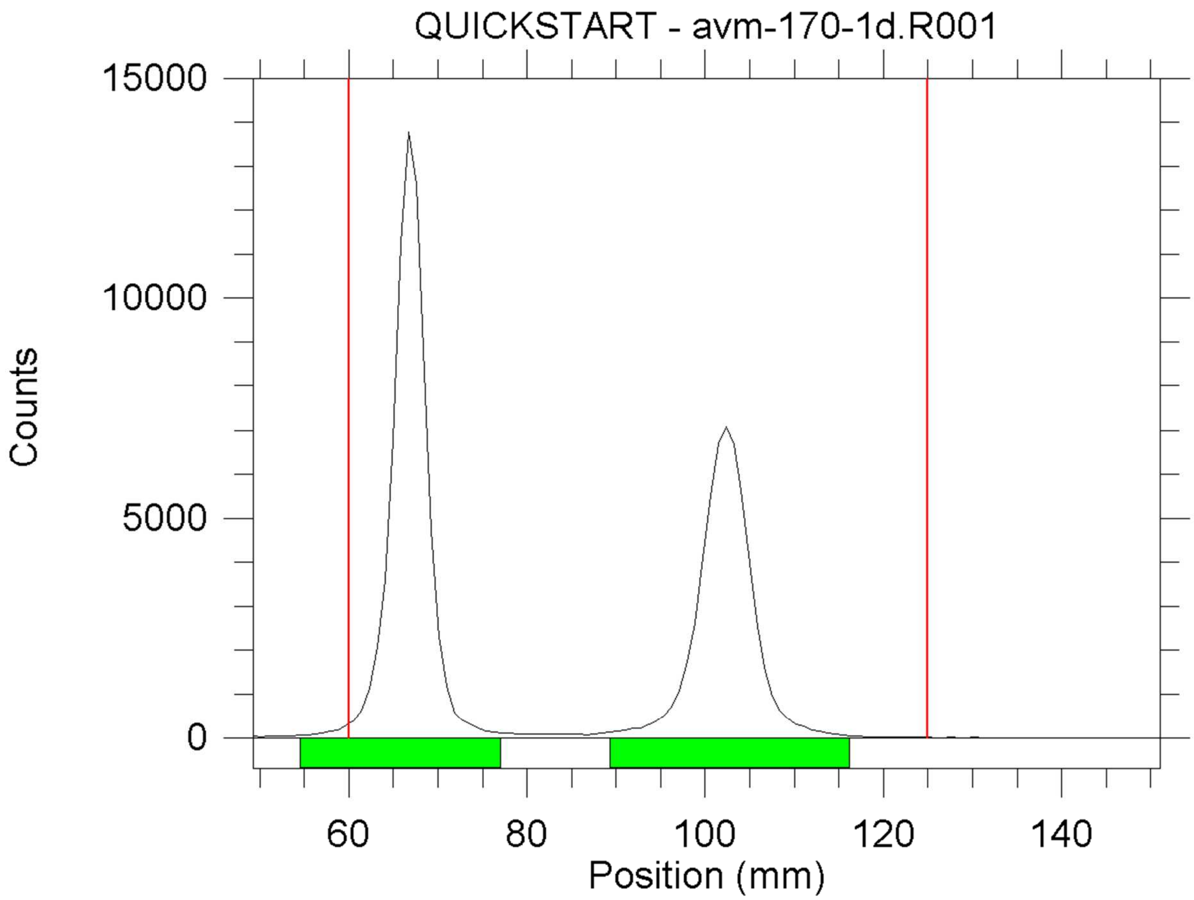
4-[^{18}F]fluoroacetaldehyde **6** RAD trace overlaid with UV trace (256 nm)



4-[^{18}F]fluoroacetaldehyde **6** RAD trace overlaid with UV trace (256 nm) spiked with 4-fluoroacetaldehyde

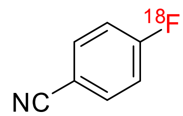


4-[18F]fluoroacetaldehyde **6** Radio-TLC spectrum



4-[18F]fluoroacetaldehyde **6** Radio-TLC Yields (RCC):

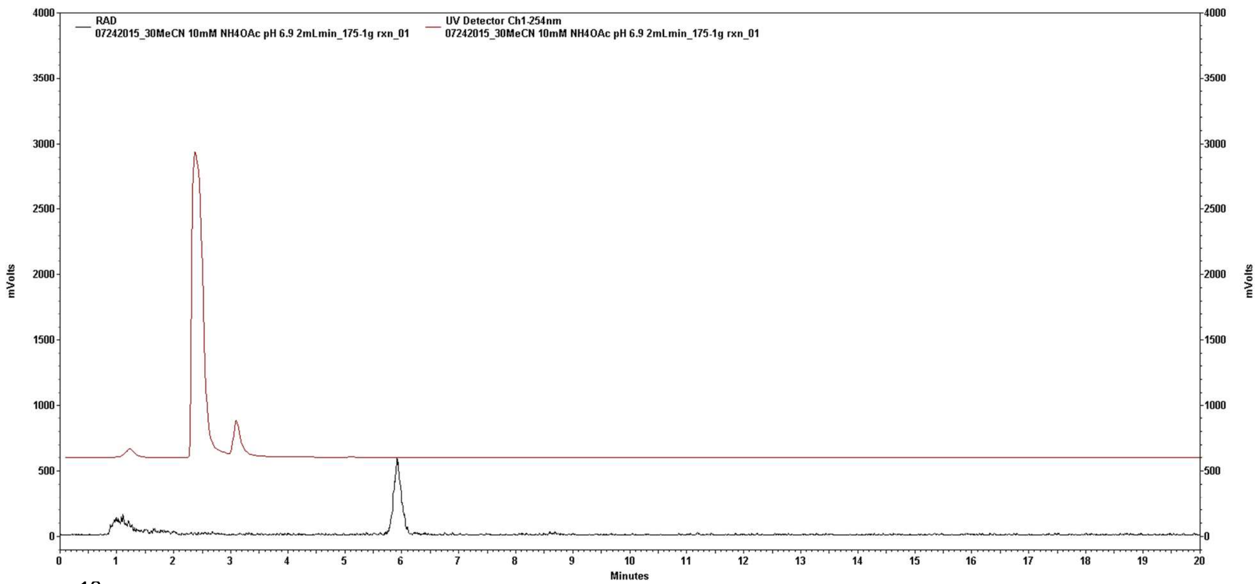
Replicate	TLC Yield
1	**44%**
2	**47%**
3	**43%**
4	**58%**
5	**51%**
Mean	**49%**
Standard Deviation	**6%**



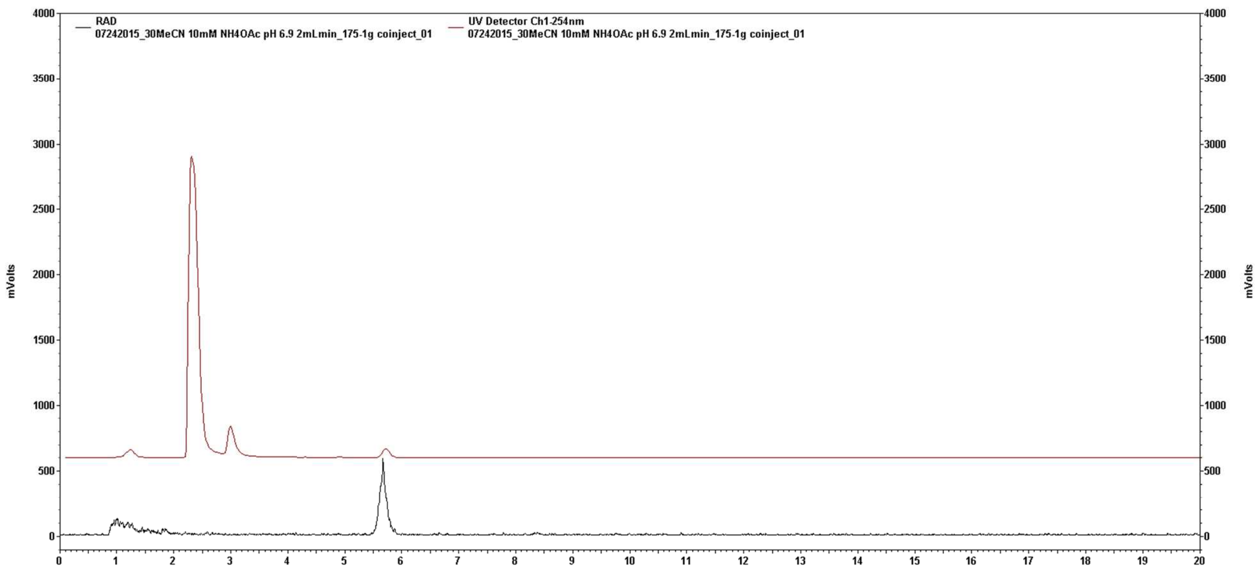
(7)

HPLC Condition: General HPLC Condition C

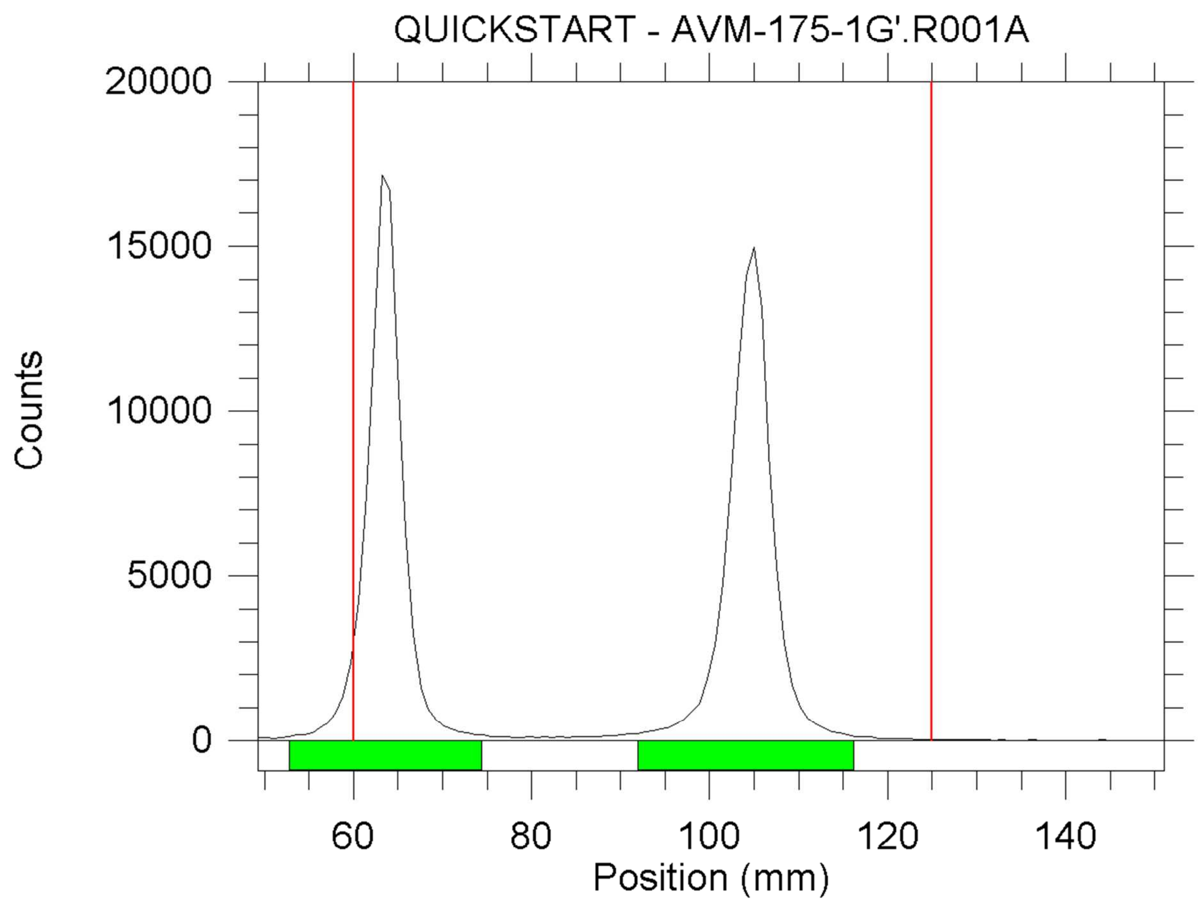
4-[^{18}F]fluorobenzonitrile **7** RAD trace overlaid with UV trace (256 nm)



4-[^{18}F]fluorobenzonitrile **7** RAD trace overlaid with UV trace (256 nm) spiked with 4-fluorobenzonitrile

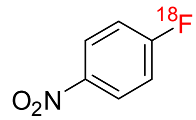


4-[^{18}F]fluorobenzonitrile **7** Radio-TLC spectrum



4-[^{18}F]fluorobenzonitrile **7** Radio-TLC Yields (RCC):

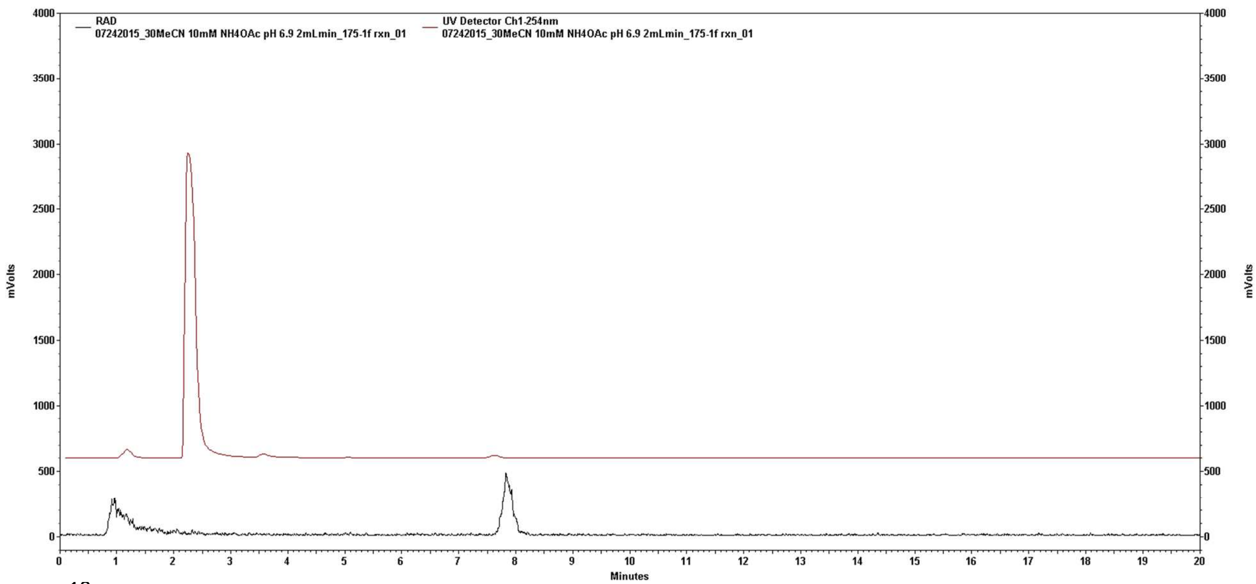
Replicate	TLC Yield
1	**35%**
2	**42%**
3	**60%**
4	**52%**
Mean	**47%**
Standard Deviation	**11%**



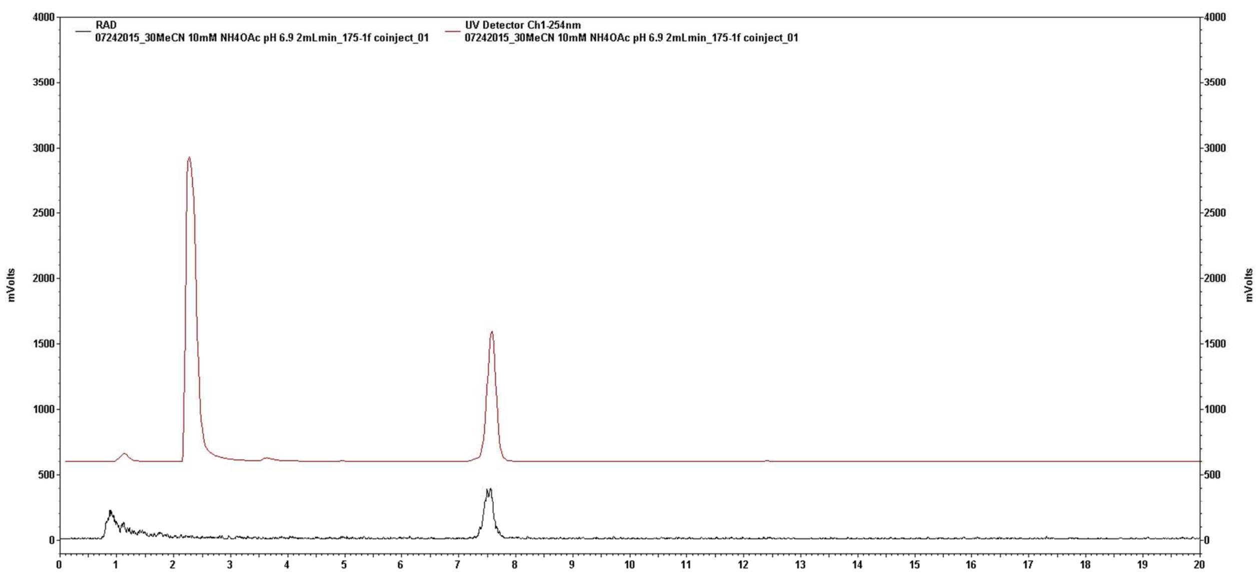
(8)

HPLC Condition: General HPLC Condition C

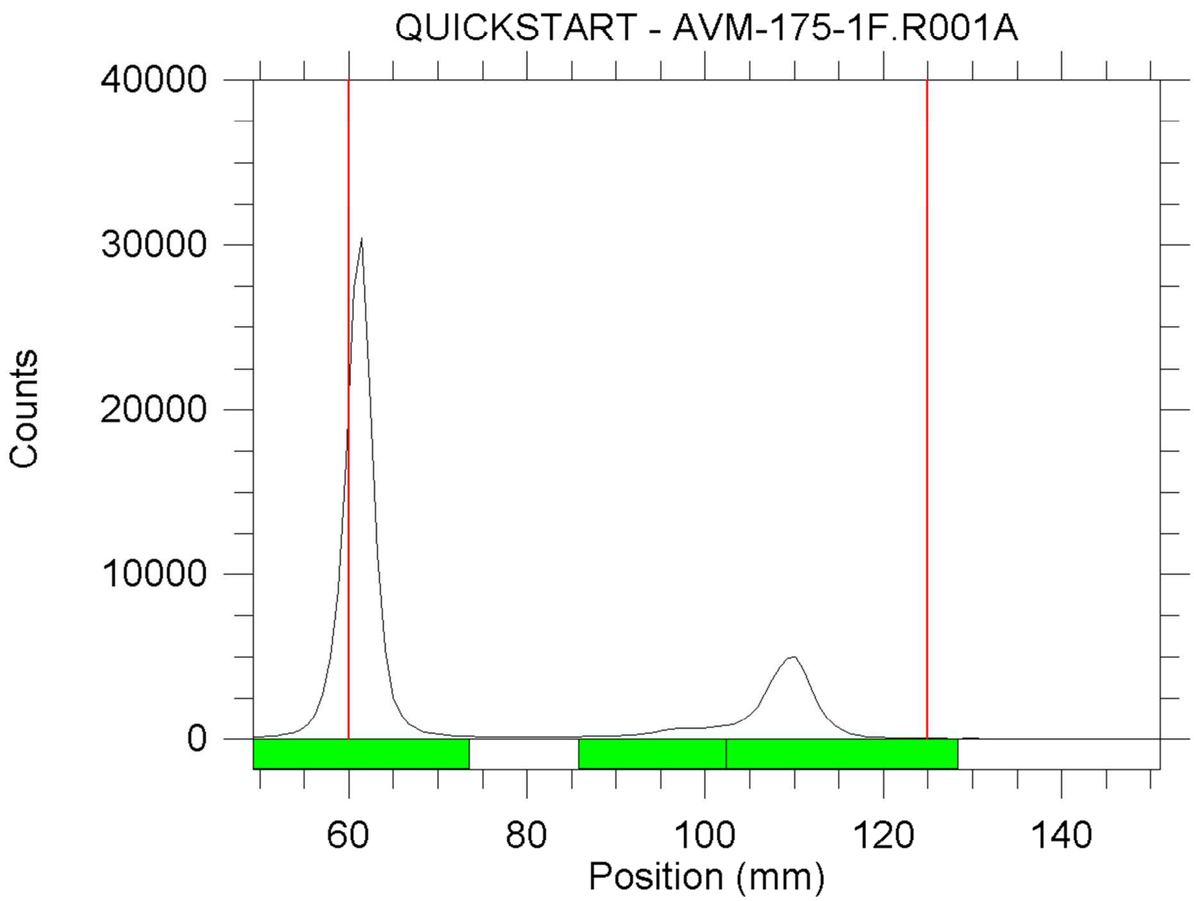
4-[^{18}F]fluoronitrobenzene **8** RAD trace overlaid with UV trace (256 nm)



4-[^{18}F]fluoronitrobenzene **8** RAD trace overlaid with UV trace (256 nm) spiked with 4-fluoronitrobenzene

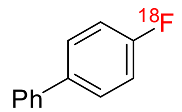


4-[^{18}F]fluoronitrobenzene **8** Radio-TLC spectrum



4-[^{18}F]fluoronitrobenzene **8** Radio-TLC Yields (RCC):

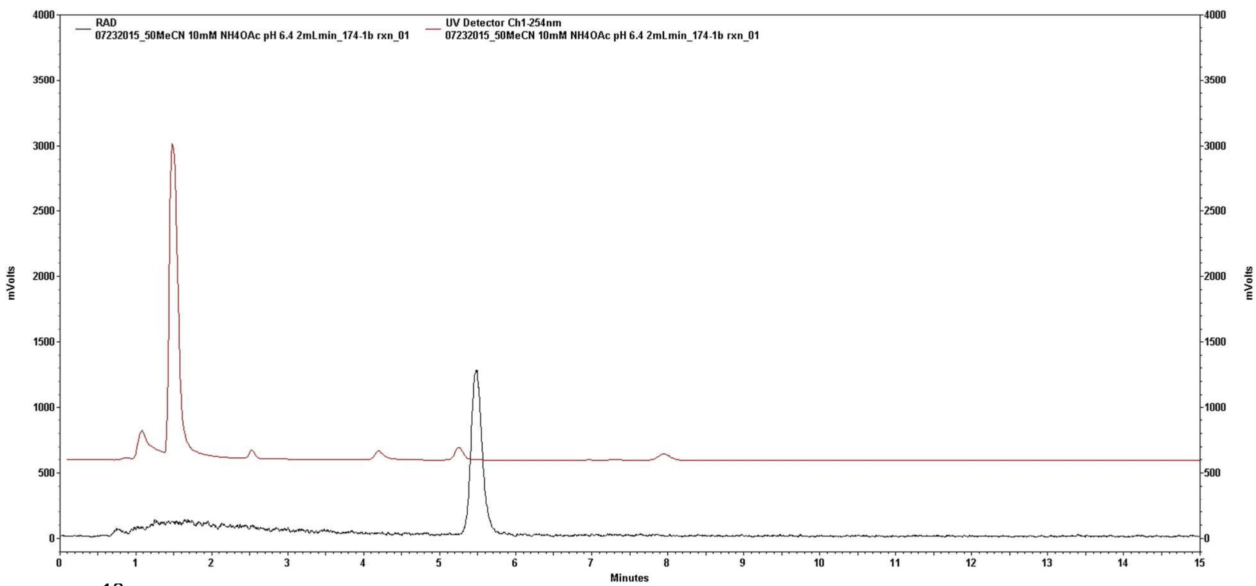
Replicate	TLC Yield
1	**26%**
2	**32%**
3	**38%**
4	**38%**
Mean	**33%**
Standard Deviation	**6%**



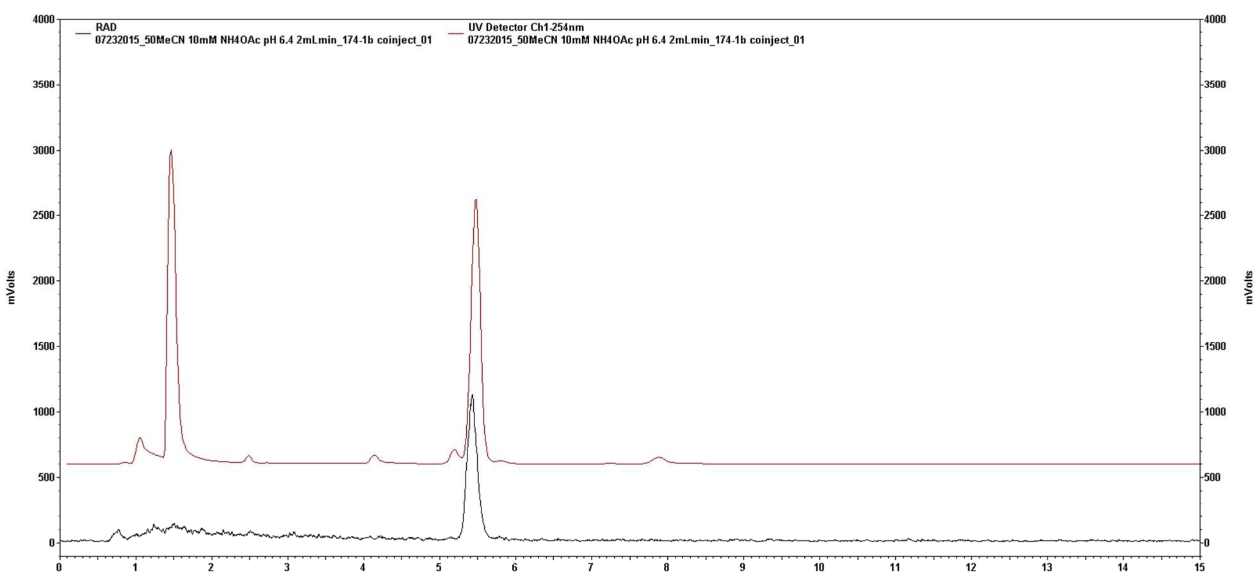
(9)

HPLC Condition: General HPLC Condition B

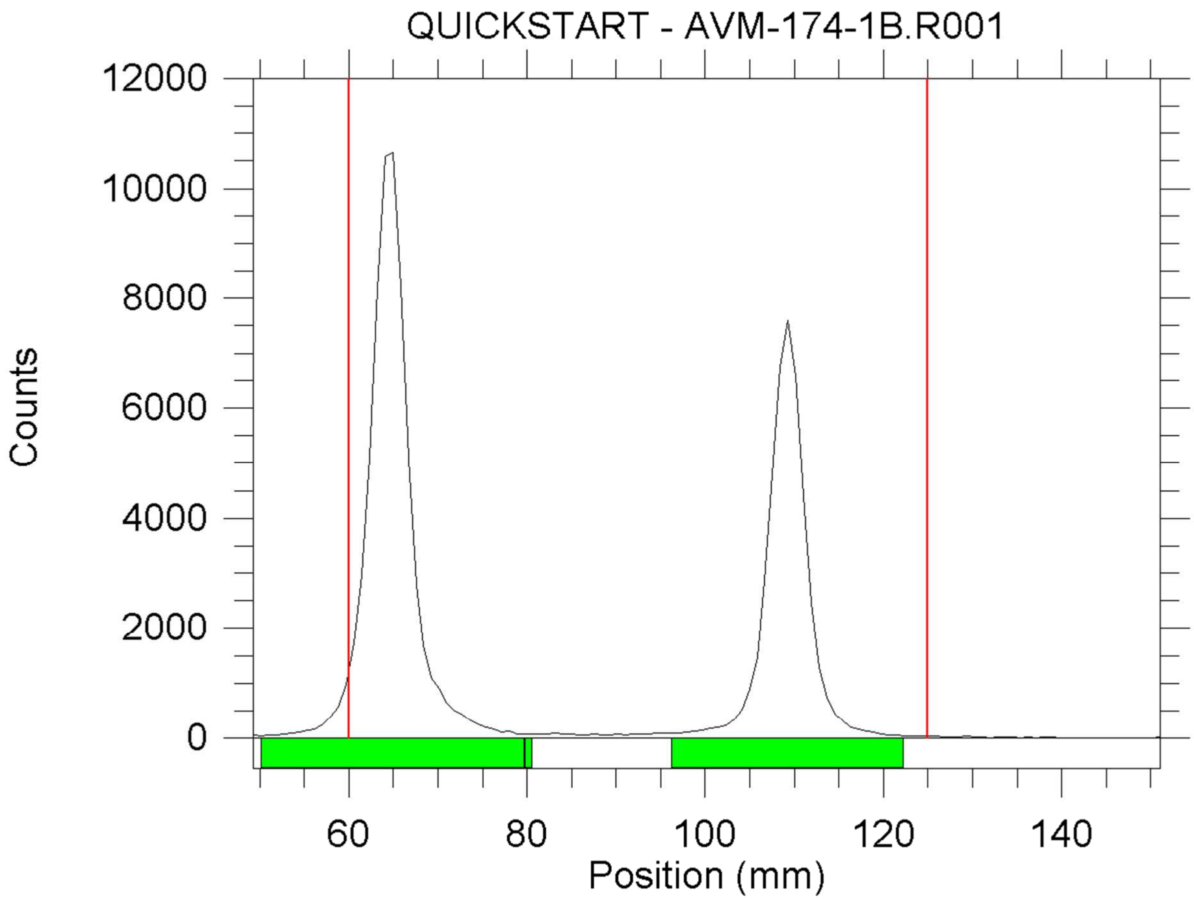
4-[^{18}F]fluorobiphenyl **9** RAD trace overlaid with UV trace (256 nm)



4-[^{18}F]fluorobiphenyl **9** RAD trace overlaid with UV trace (256 nm) spiked with 4-fluorobiphenyl

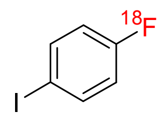


4-[^{18}F]fluorobiphenyl **9** Radio-TLC spectrum



4-[^{18}F]fluorobiphenyl **9** Radio-TLC Yields (RCC):

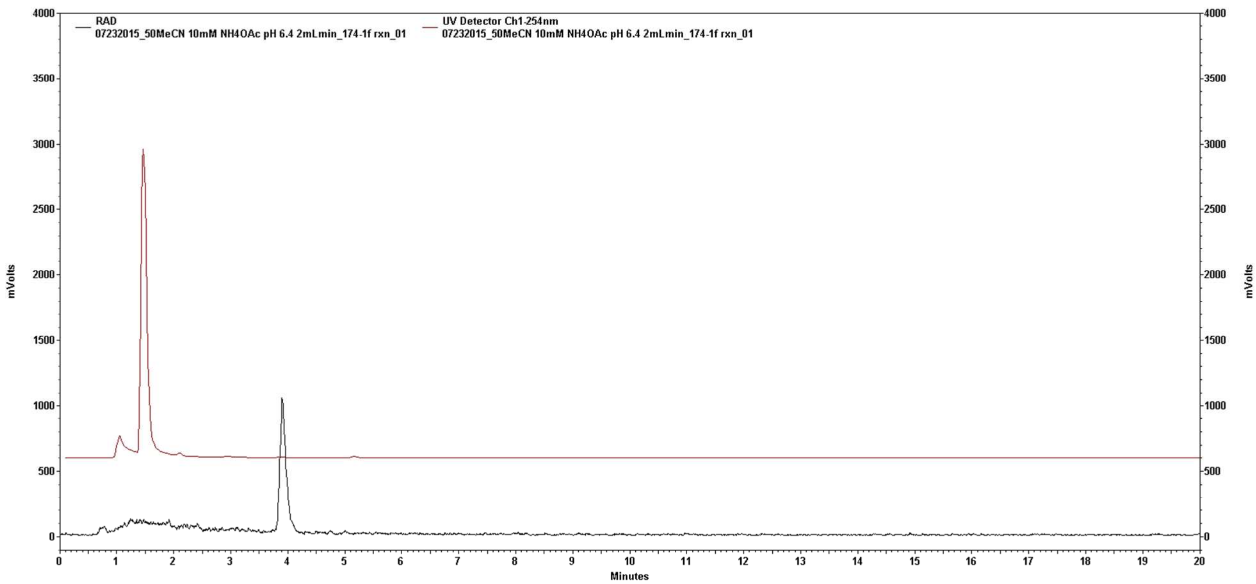
Replicate	TLC Yield
1	**44%**
2	**48%**
3	**44%**
4	**40%**
5	**56%**
Mean	**46%**
Standard Deviation	**6%**



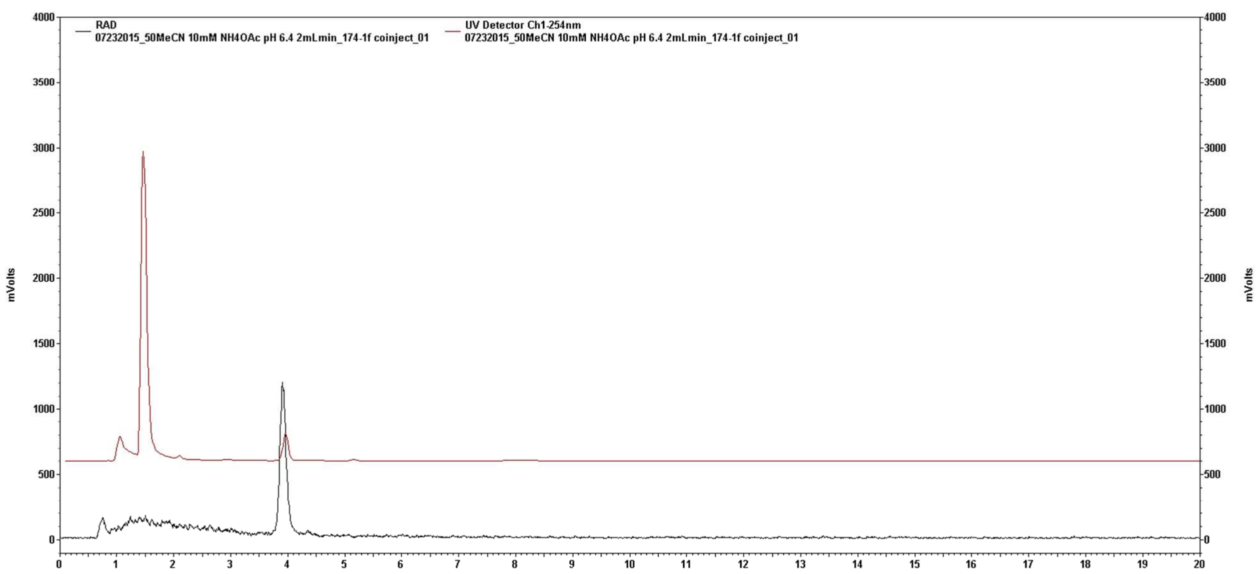
(10)

HPLC Condition: General HPLC Condition B

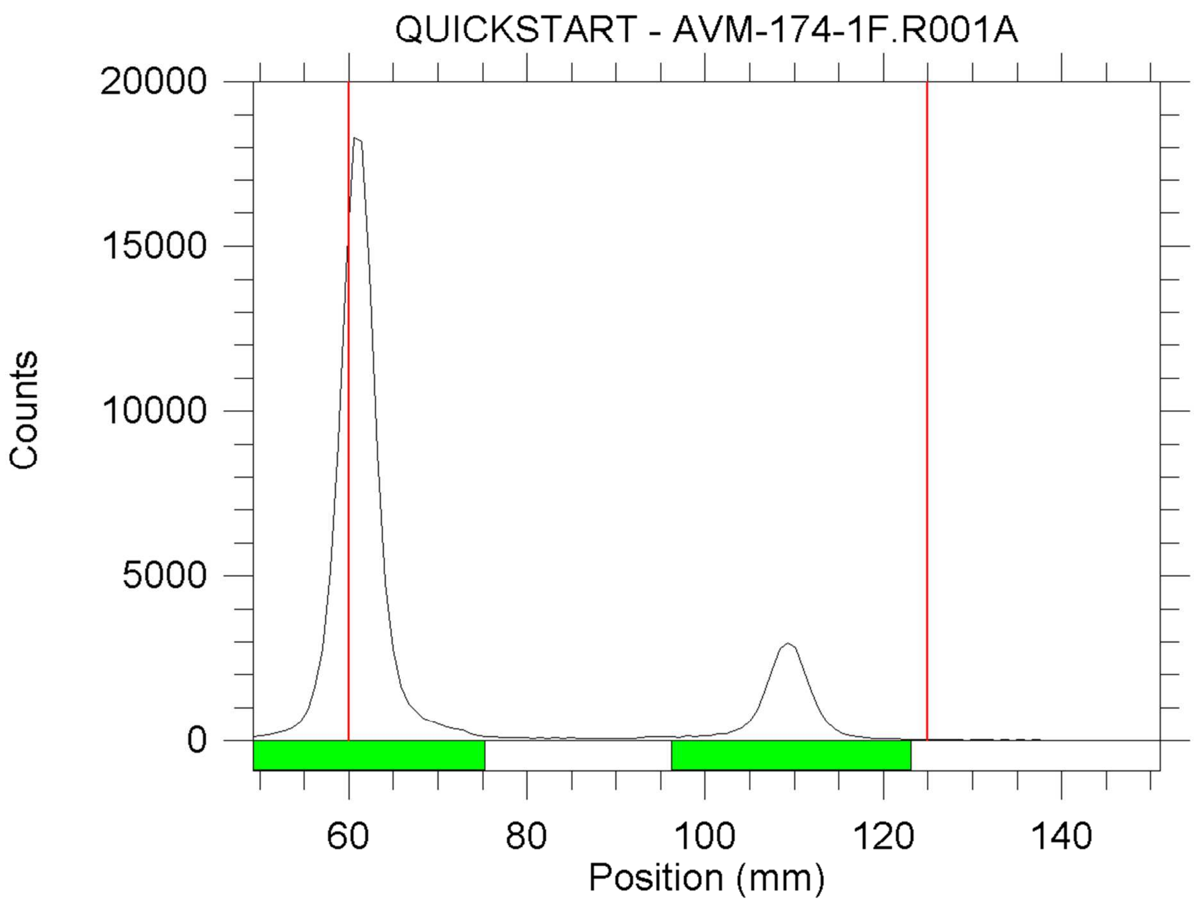
4-[^{18}F]fluoroiodobenzene **10** RAD trace overlaid with UV trace (256 nm)



4-[^{18}F]fluoroiodobenzene **10** RAD trace overlaid with UV trace (256 nm) spiked with 4-fluoroiodobenzene

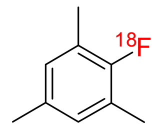


4-[^{18}F]fluoroiodobenzene **10** Radio-TLC spectrum



4-[^{18}F]fluoroiodobenzene **10** Radio-TLC Yield (RCC):

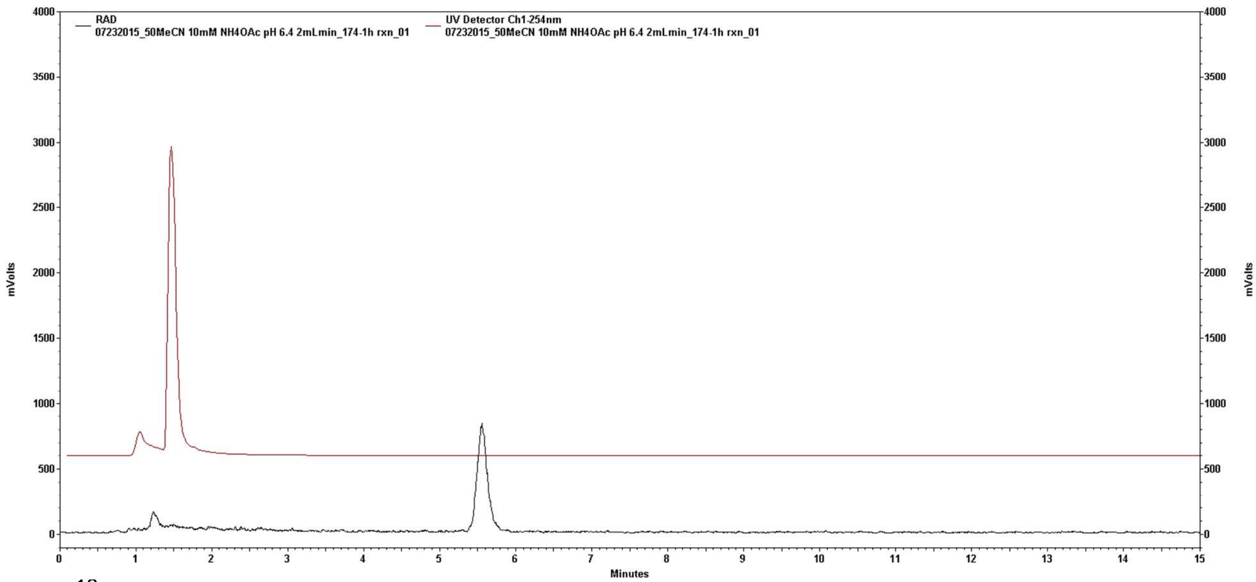
Replicate	TLC Yield
1	**8%**
2	**28%**
3	**17%**
4	**22%**
Mean	**18%**
Standard Deviation	**8%**



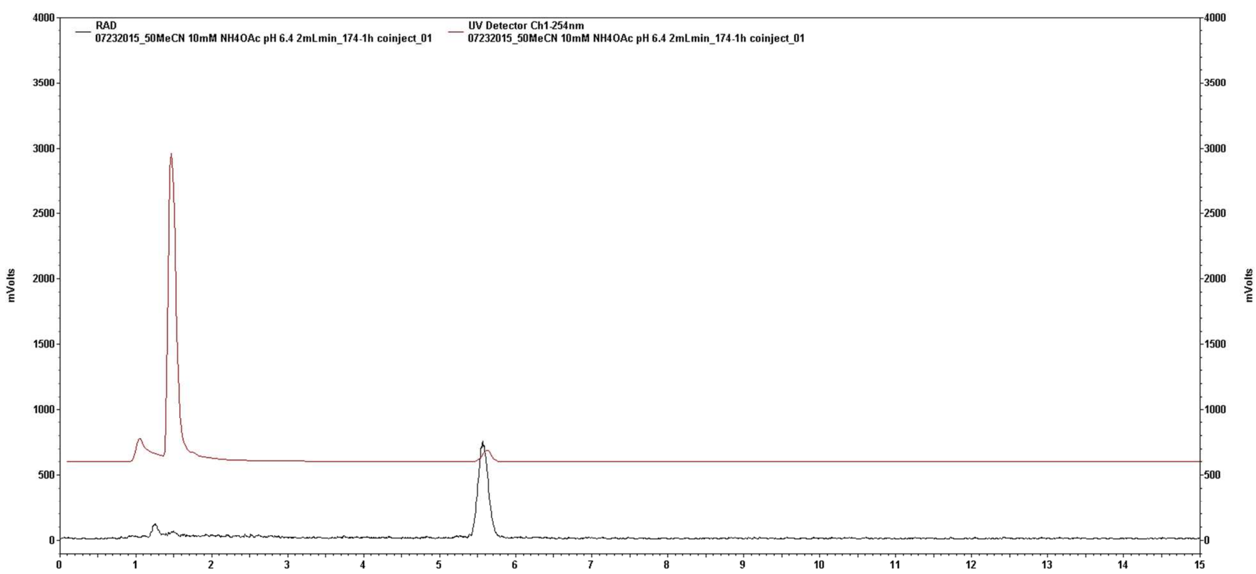
(11)

HPLC Condition: General HPLC Condition B

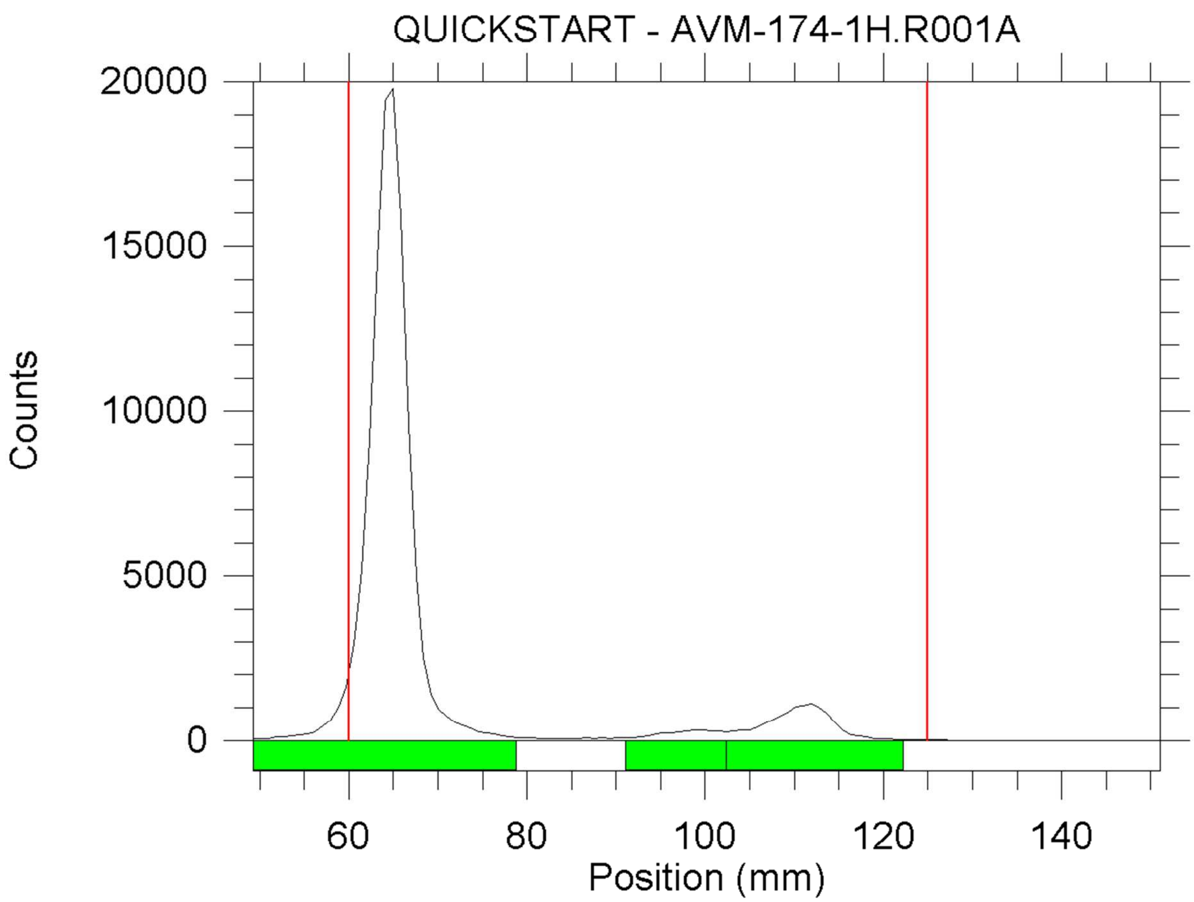
1-[^{18}F]fluoromesitylene **11** RAD trace overlaid with UV trace (256 nm)



1-[^{18}F]fluoromesitylene **11** RAD trace overlaid with UV trace (256 nm) spiked with 4-fluoromesitylene

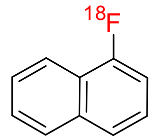


1-[^{18}F]fluoromesitylene **11** Radio-TLC spectrum



1-[^{18}F]fluoromesitylene **11** Radio-TLC Yields (RCC):

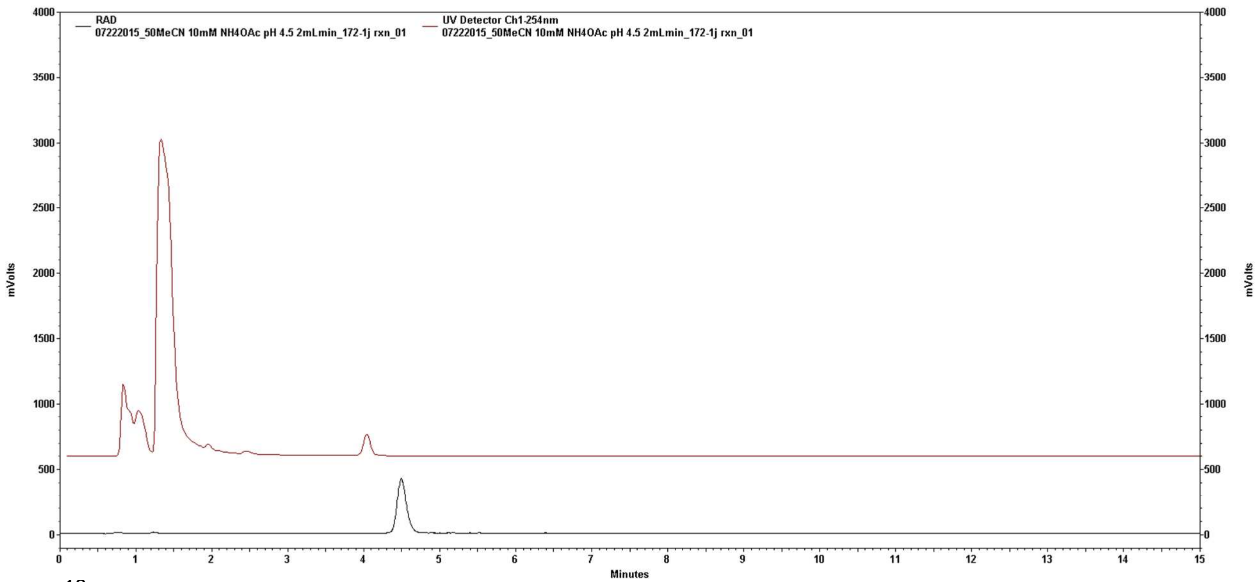
Replicate	TLC Yield
1	**12%**
2	**8%**
3	**8%**
4	**11%**
5	**20%**
Mean	**12%**
Standard Deviation	**5%**



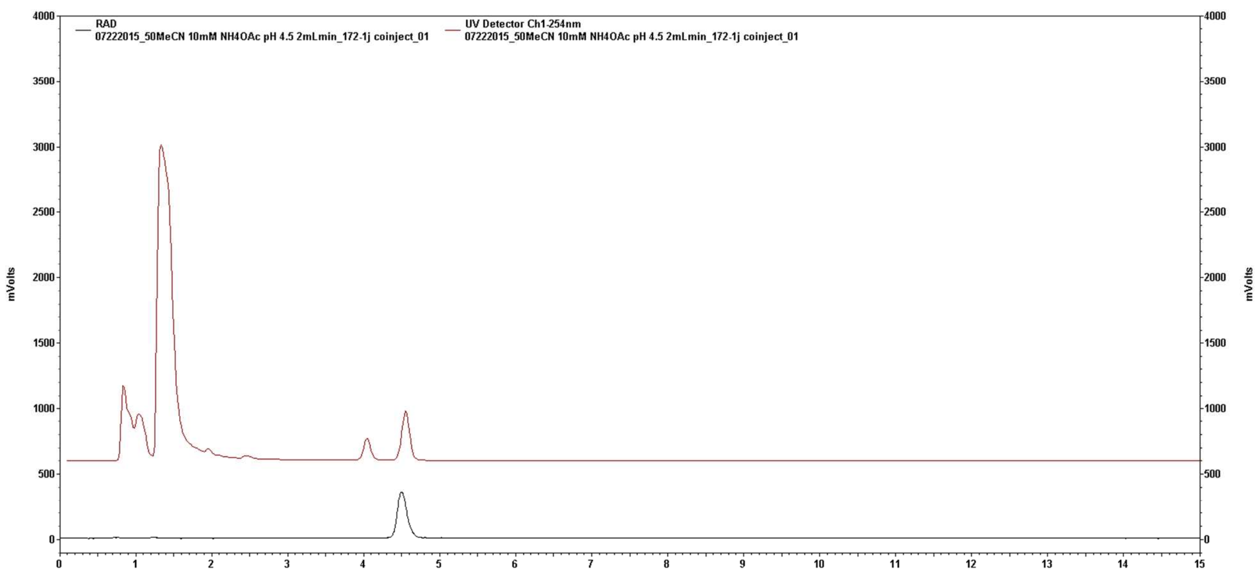
(12)

HPLC Condition: HPLC Condition B, pH 4.5

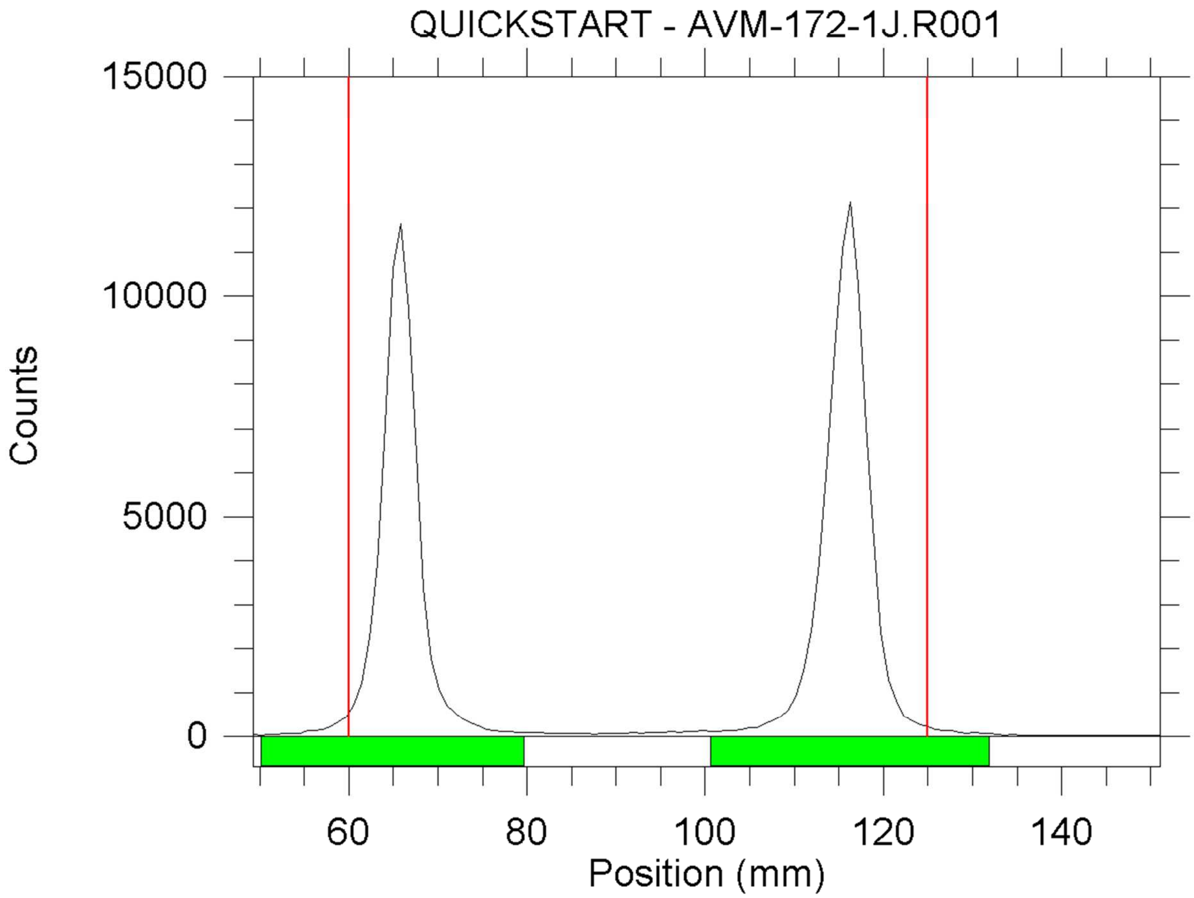
1-[^{18}F]fluoronaphthalene **12** RAD trace overlaid with UV trace (256 nm)



1-[^{18}F]fluoronaphthalene **12** RAD trace overlaid with UV trace (256 nm) spiked with 1-fluoronaphthalene

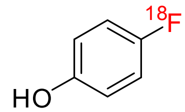


1-[^{18}F]fluoronaphthalene **12** Radio-TLC spectrum



1-[^{18}F]fluoronaphthalene **12** Radio-TLC Yield (RCC):

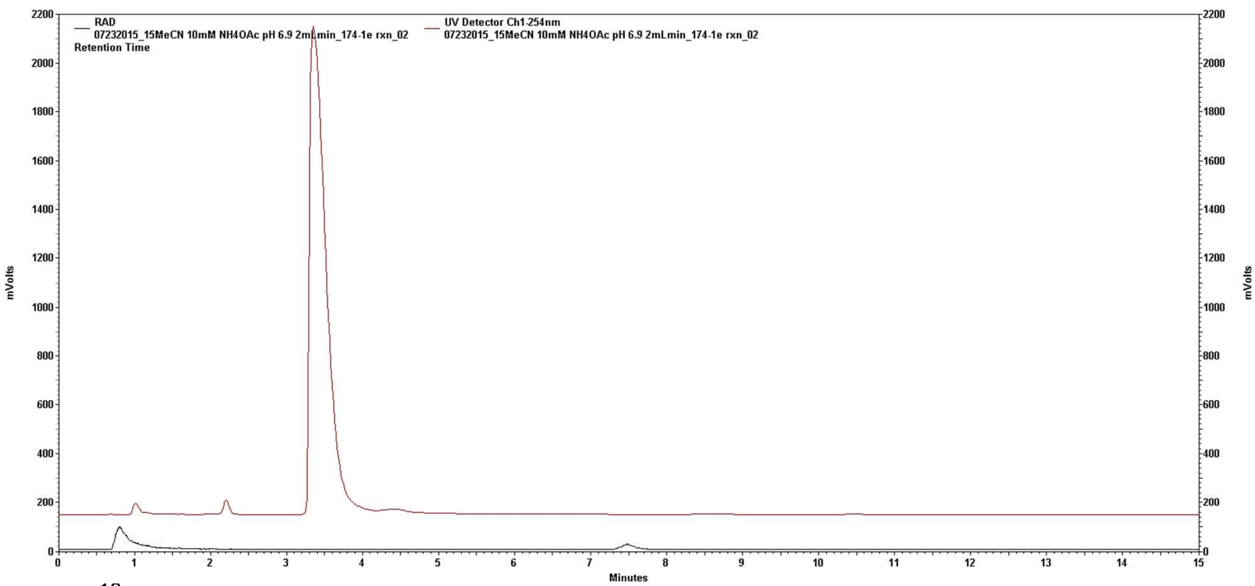
Replicate	TLC Yield
1	**40%**
2	**55%**
3	**66%**
4	**33%**
Mean	**48%**
Standard Deviation	**15%**



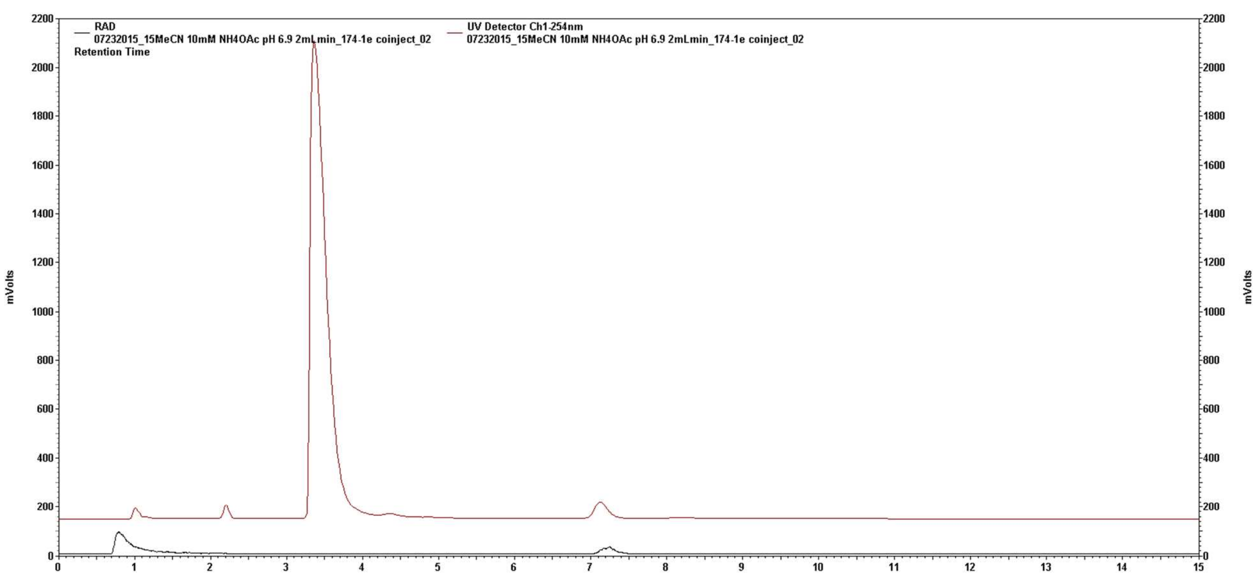
(13)

HPLC Condition: General HPLC Condition D

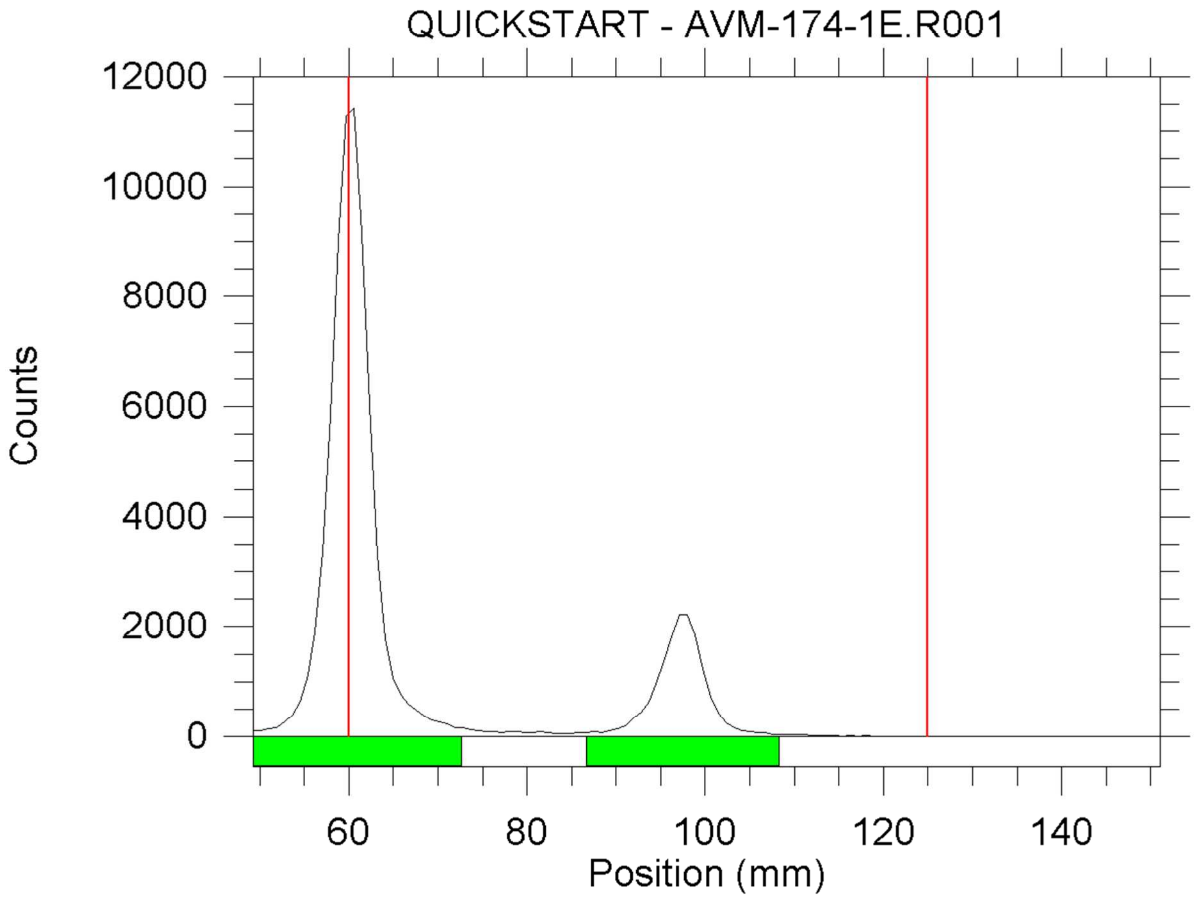
4-[^{18}F]fluorophenol **13** RAD trace overlaid with UV trace (256 nm)



4-[^{18}F]fluorophenol **13** RAD trace overlaid with UV trace (256 nm) spiked with 4-fluorophenol

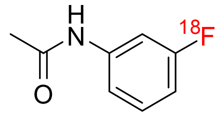


4-[^{18}F]fluorophenol **13** Radio-TLC spectrum



4-[^{18}F]fluorophenol **13** Radio-TLC Yields (RCC):

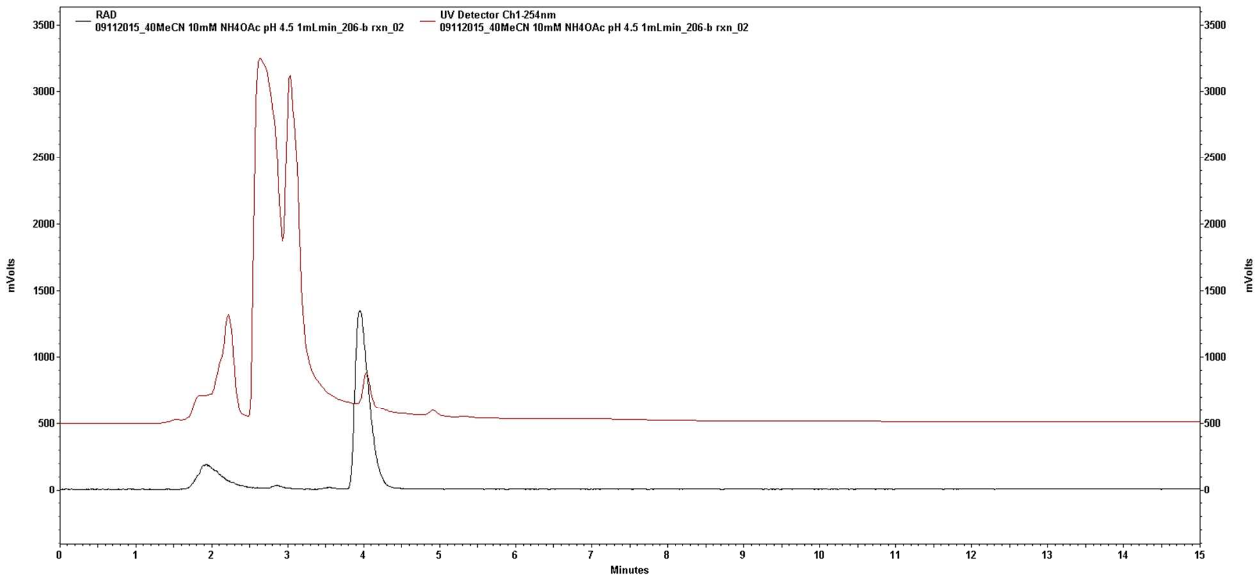
Replicate	TLC Yield
1	**16%**
2	**12%**
3	**18%**
4	**14%**
Mean	**15%**
Standard Deviation	**3%**



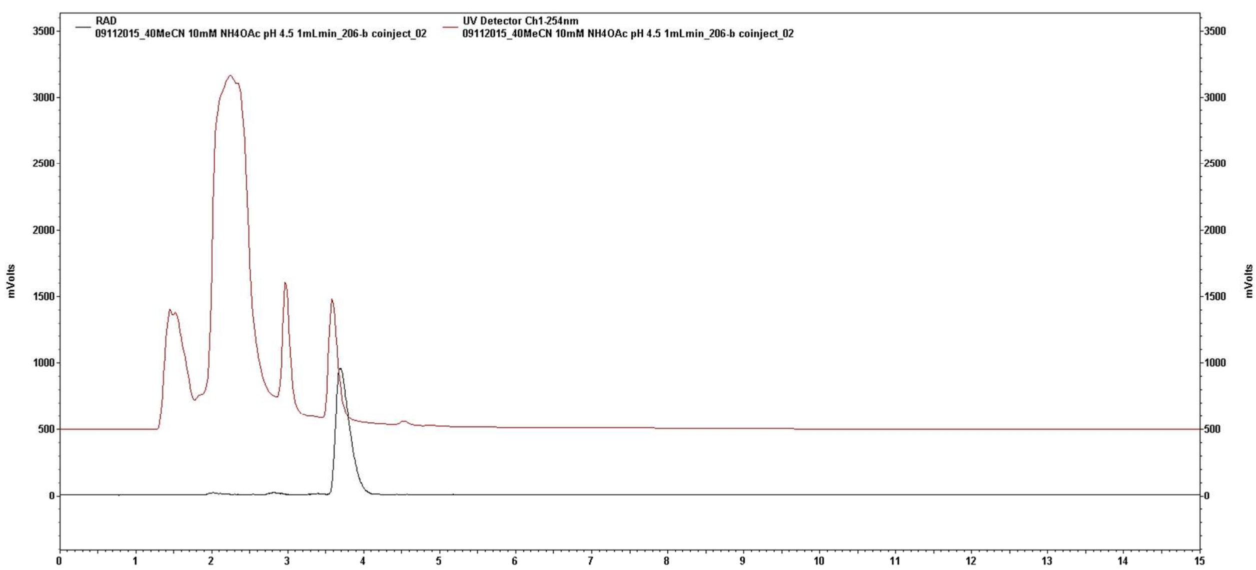
(14)

HPLC Condition: General HPLC Condition A, pH 7.3

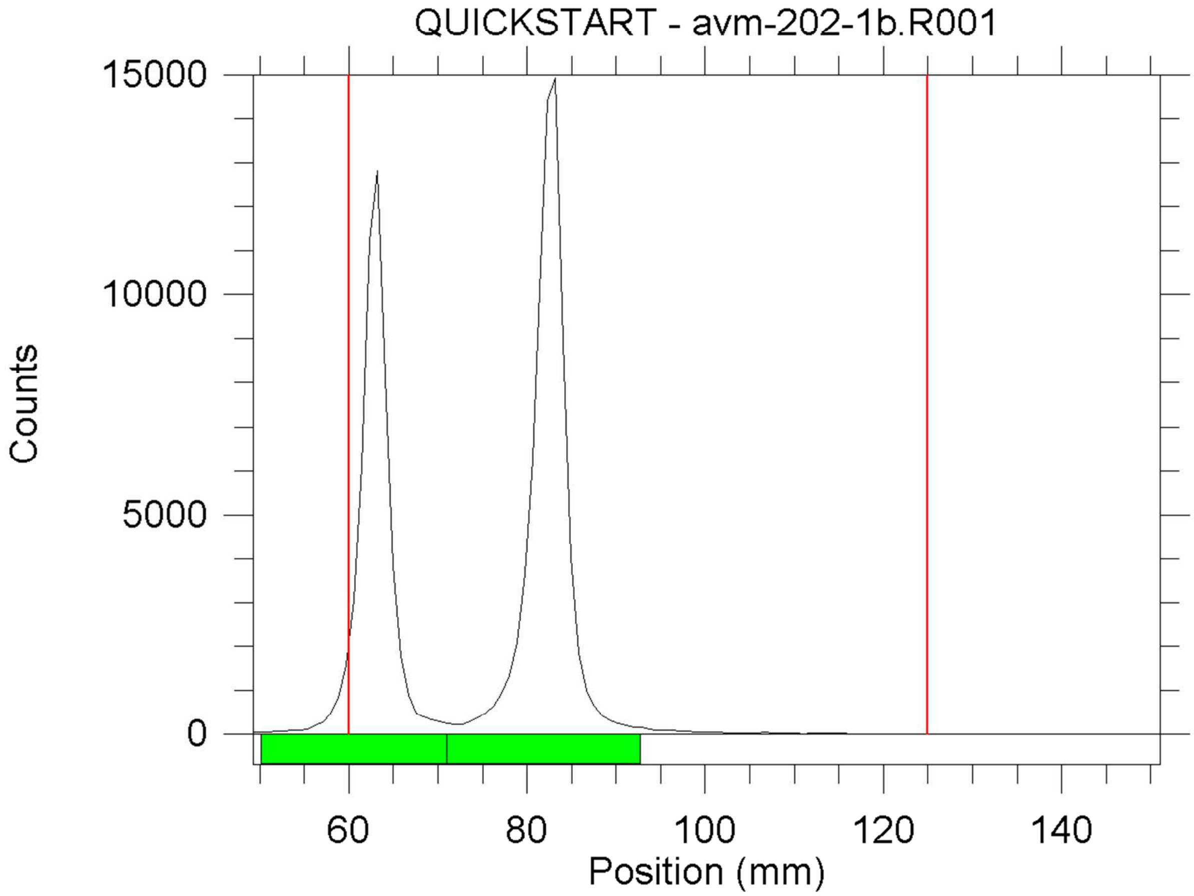
3-[^{18}F]fluoroacetamide **14** RAD trace overlaid with UV trace (256 nm)



3-[^{18}F]fluoroacetamide **14** RAD trace overlaid with UV trace (256 nm) spiked with 3-fluoroacetamide

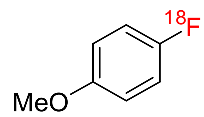


3-[^{18}F]fluoroacetamide **14** Radio-TLC spectrum



3-[^{18}F]fluoroacetamide **14** Radio-TLC Yields (RCC):

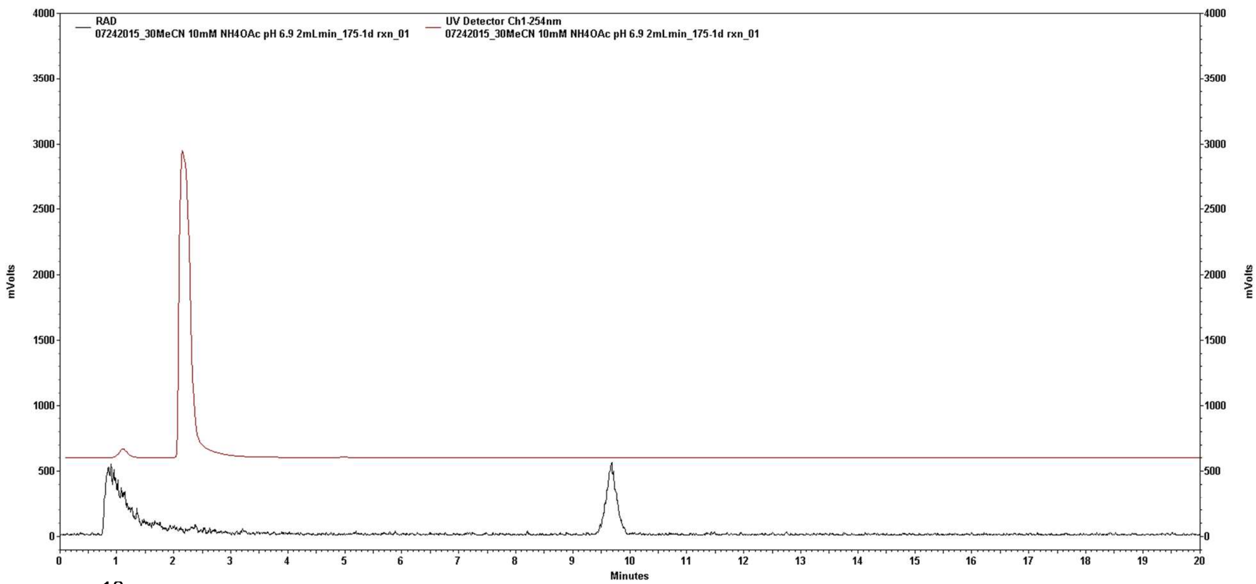
Replicate	TLC Yield
1	**53%**
2	**70%**
3	**58%**
Mean	**60%**
Standard Deviation	**9%**



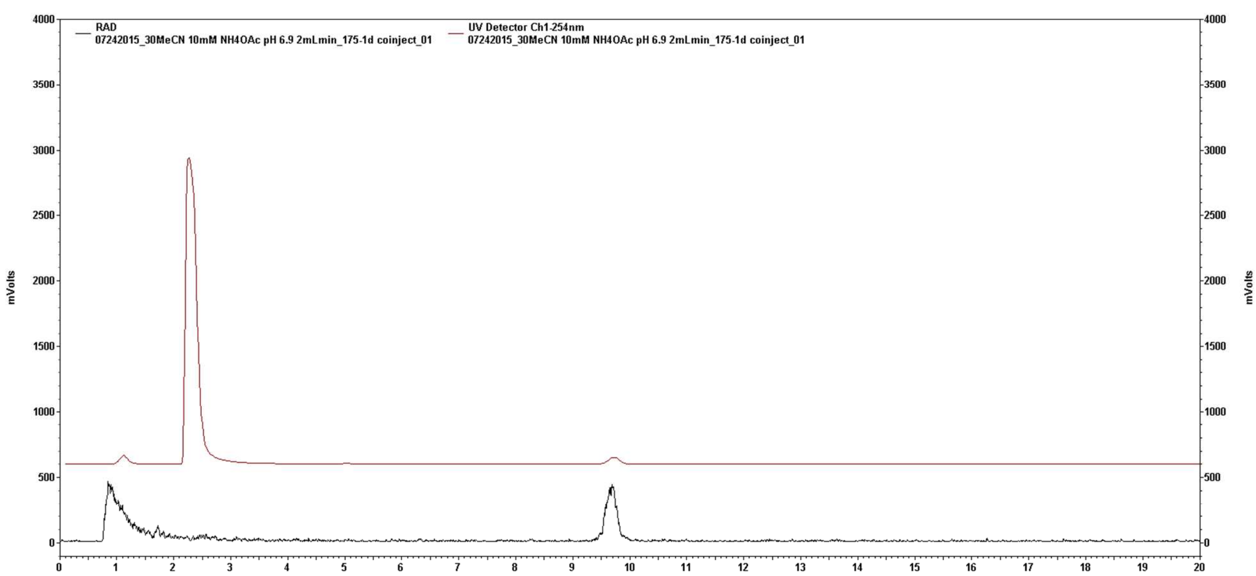
(15)

HPLC Conditions: General HPLC Conditions C

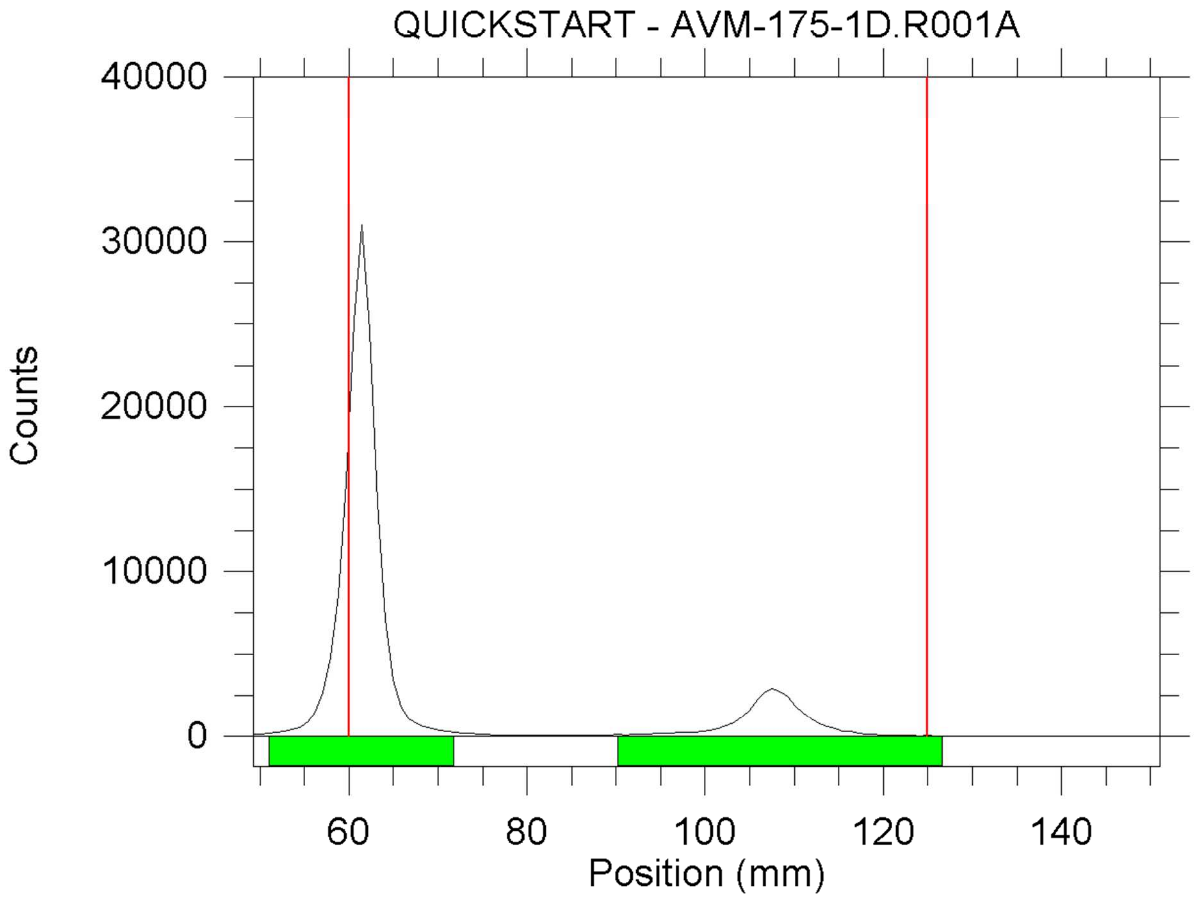
4-[^{18}F]fluoroanisole **15** RAD trace overlaid with UV trace (256 nm)



4-[^{18}F]fluoroanisole **15** RAD trace overlaid with UV trace (256 nm) spiked with 4-fluoroanisole

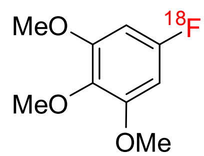


4-[^{18}F]fluoroanisole **15** Radio-TLC spectrum



4-[^{18}F]fluoroanisole **15** Radio-TLC Yields (RCC):

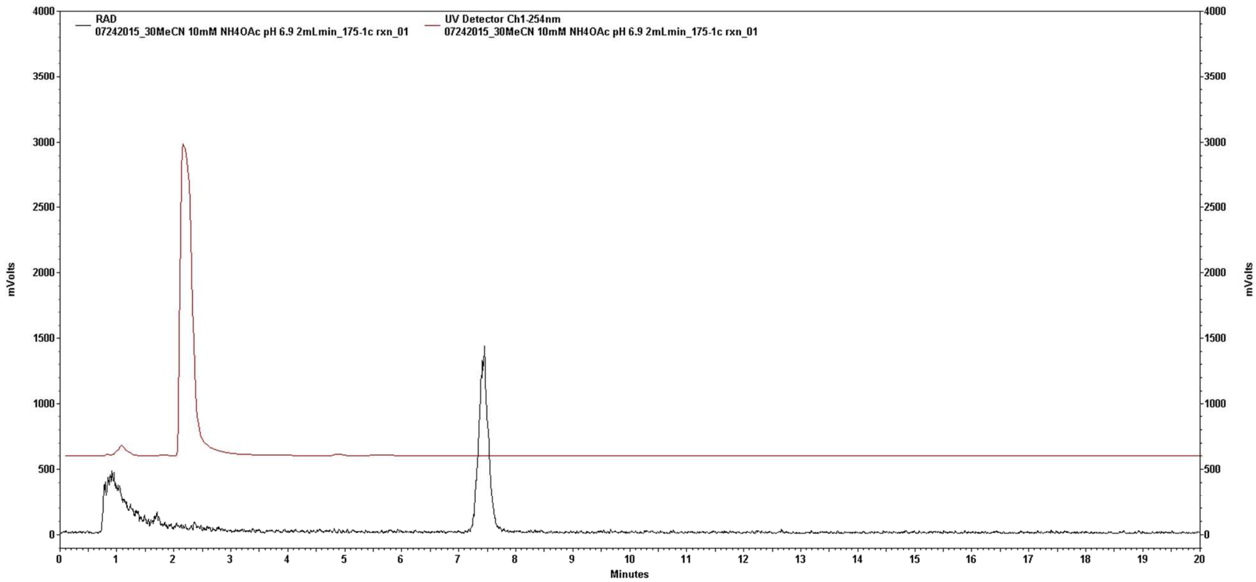
Replicate	TLC Yield
1	**19%**
2	**21%**
3	**16%**
Mean	**19%**
Standard Deviation	**3%**



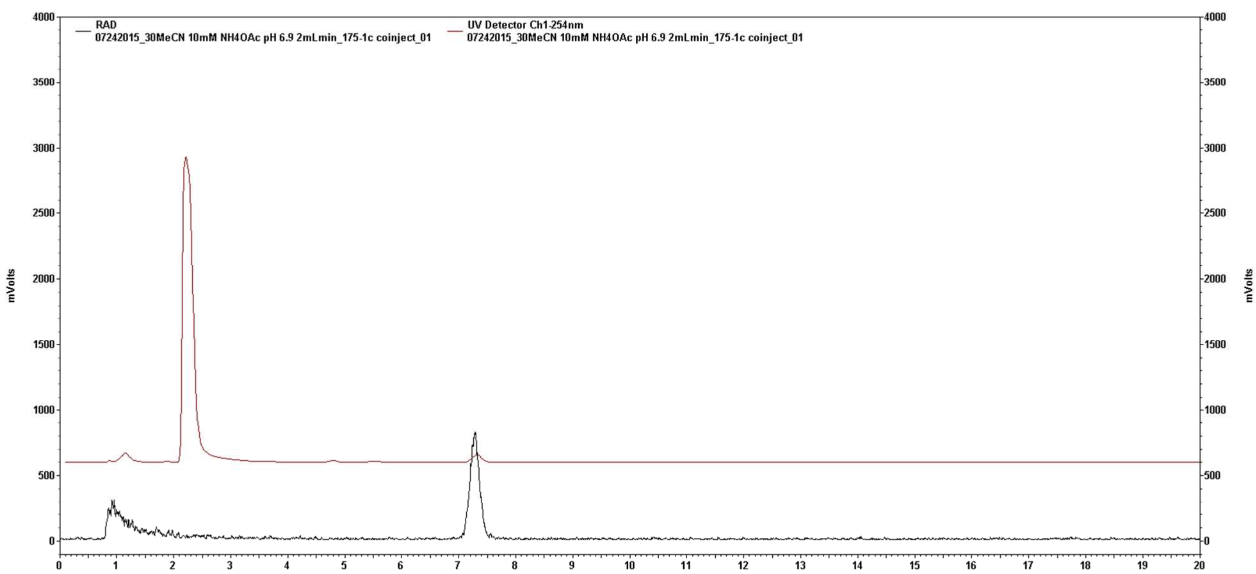
(16)

HPLC Condition: General HPLC Condition C

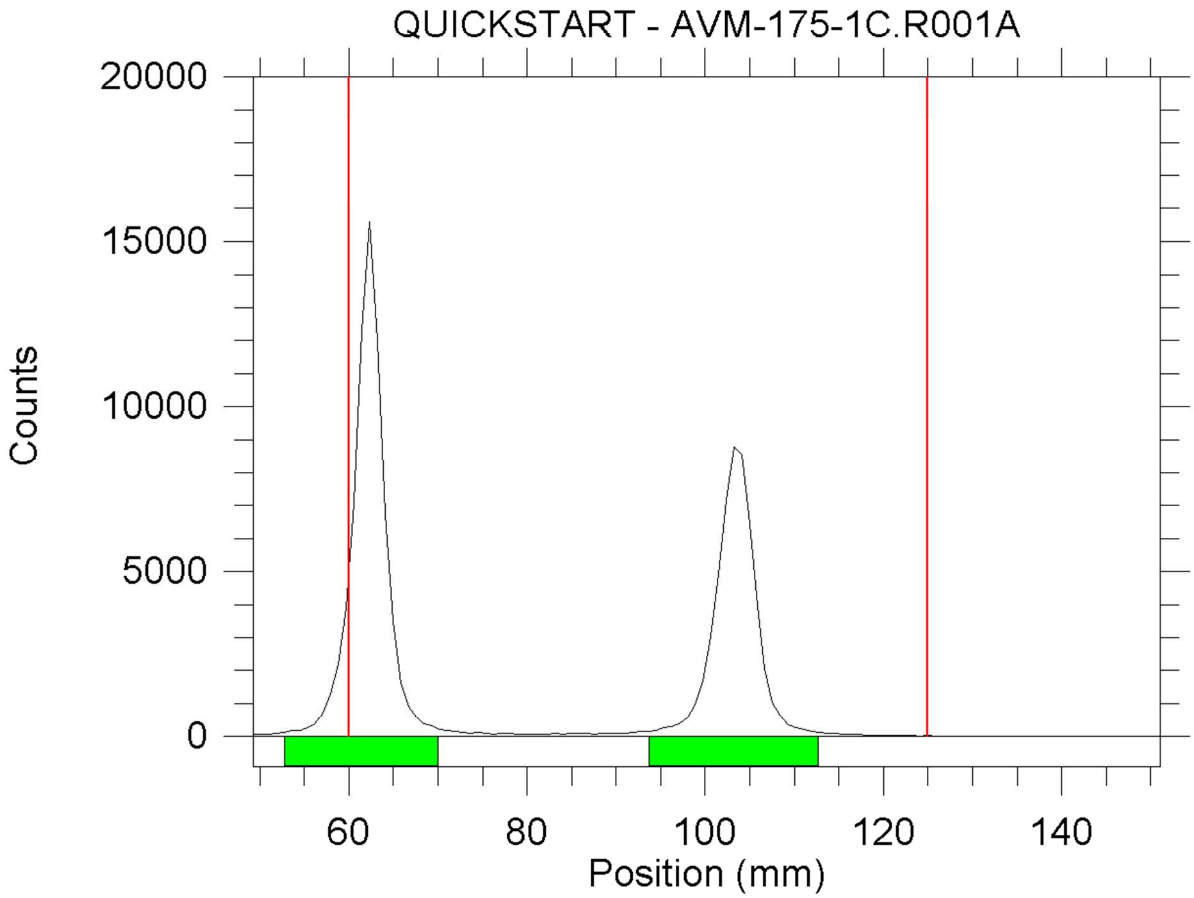
1-[^{18}F]fluoro-3,4,5-trimethoxybenzene **16** RAD trace overlaid with UV trace (256 nm)



1-[^{18}F]fluoro-3,4,5-trimethoxybenzene **16** RAD trace overlaid with UV trace (256 nm) spiked with 1-fluoro-3,4,5-trimethoxybenzene

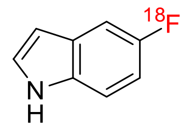


1-[^{18}F]fluoro-3,4,5-trimethoxybenzene **16** Radio-TLC spectrum



1-[^{18}F]fluoro-3,4,5-trimethoxybenzene **16** Radio-TLC Yields (RCC):

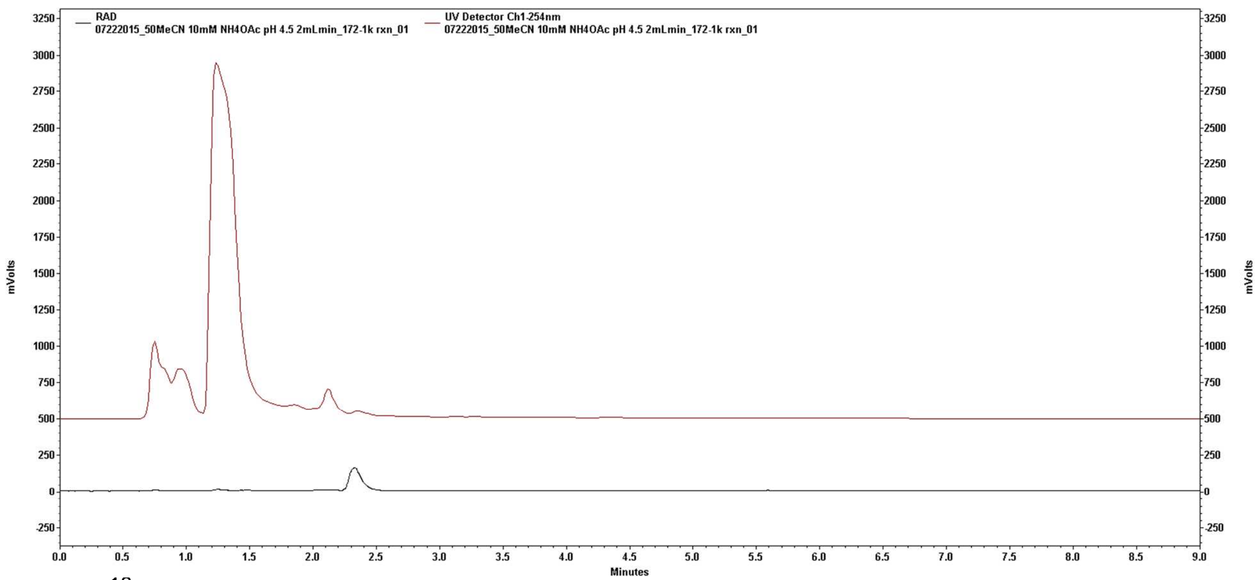
Replicate	TLC Yield
1	**16%**
2	**37%**
3	**45%**
4	**31%**
5	**41%**
6	**43%**
Mean	**36%**
Standard Deviation	**11%**



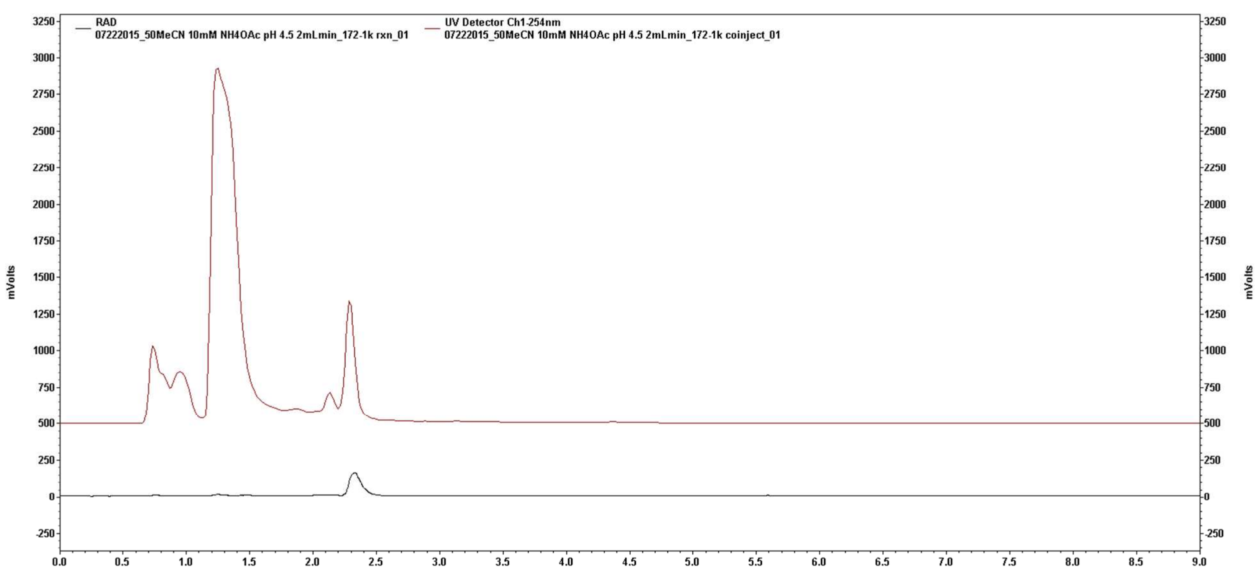
(17)

HPLC Conditions: HPLC Conditions B, pH 4.5

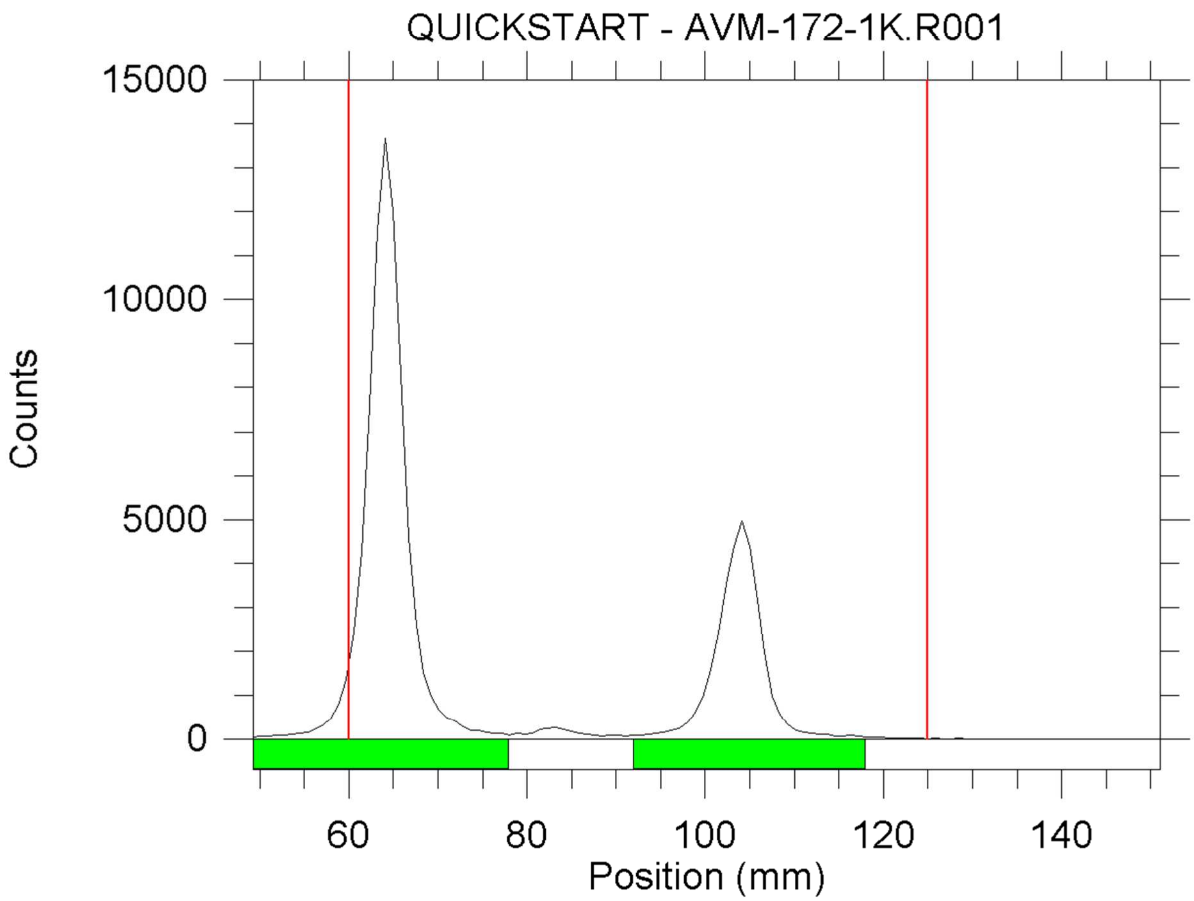
5-[^{18}F]fluoroindole **17** RAD trace overlaid with UV trace (256 nm)



5-[^{18}F]fluoroindole **17** RAD trace overlaid with UV trace (256 nm) spiked with 5-fluoroindole

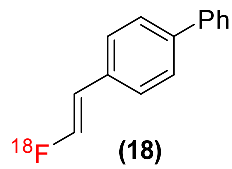


5-[^{18}F]fluoroindole **17** Radio-TLC spectrum



5-[^{18}F]fluoroindole **17** Radio-TLC Yields (RCC):

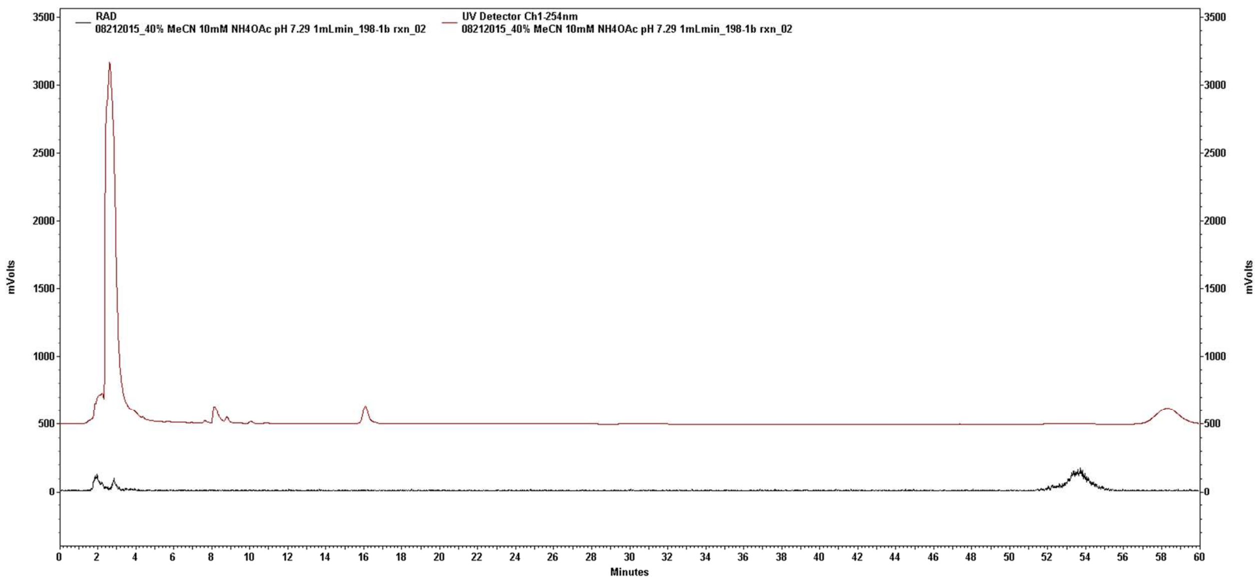
Replicate	TLC Yield
1	**6%**
2	**29%**
3	**30%**
4	**14%**
5	**9 %**
Mean	**18%**
Standard Deviation	**11%**



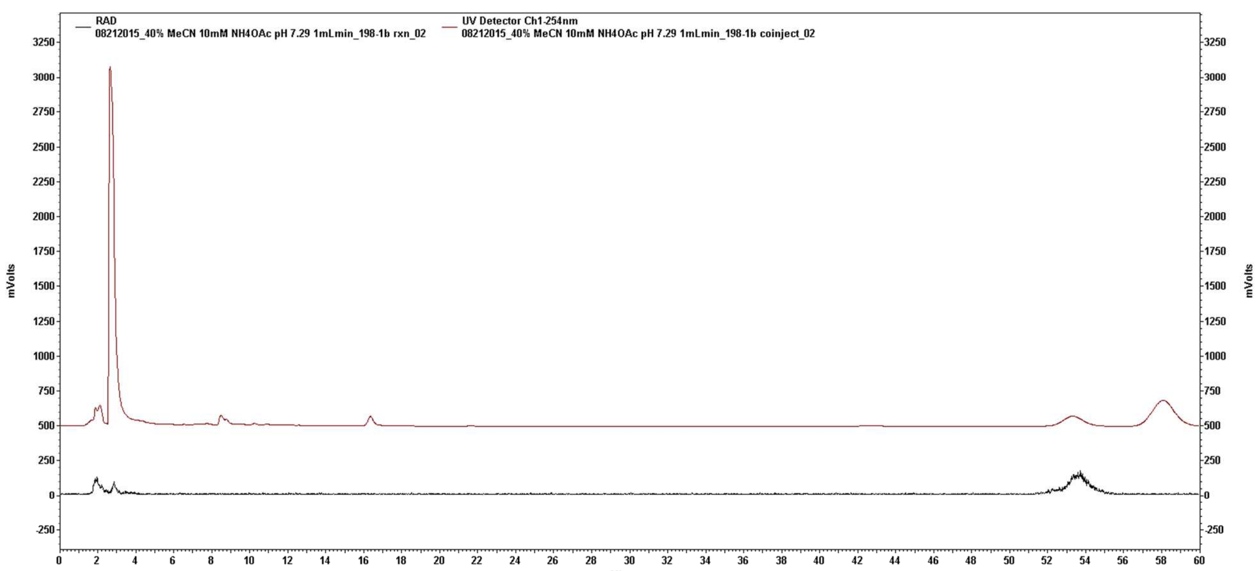
(18)

HPLC Condition: HPLC Condition A, pH 7.3

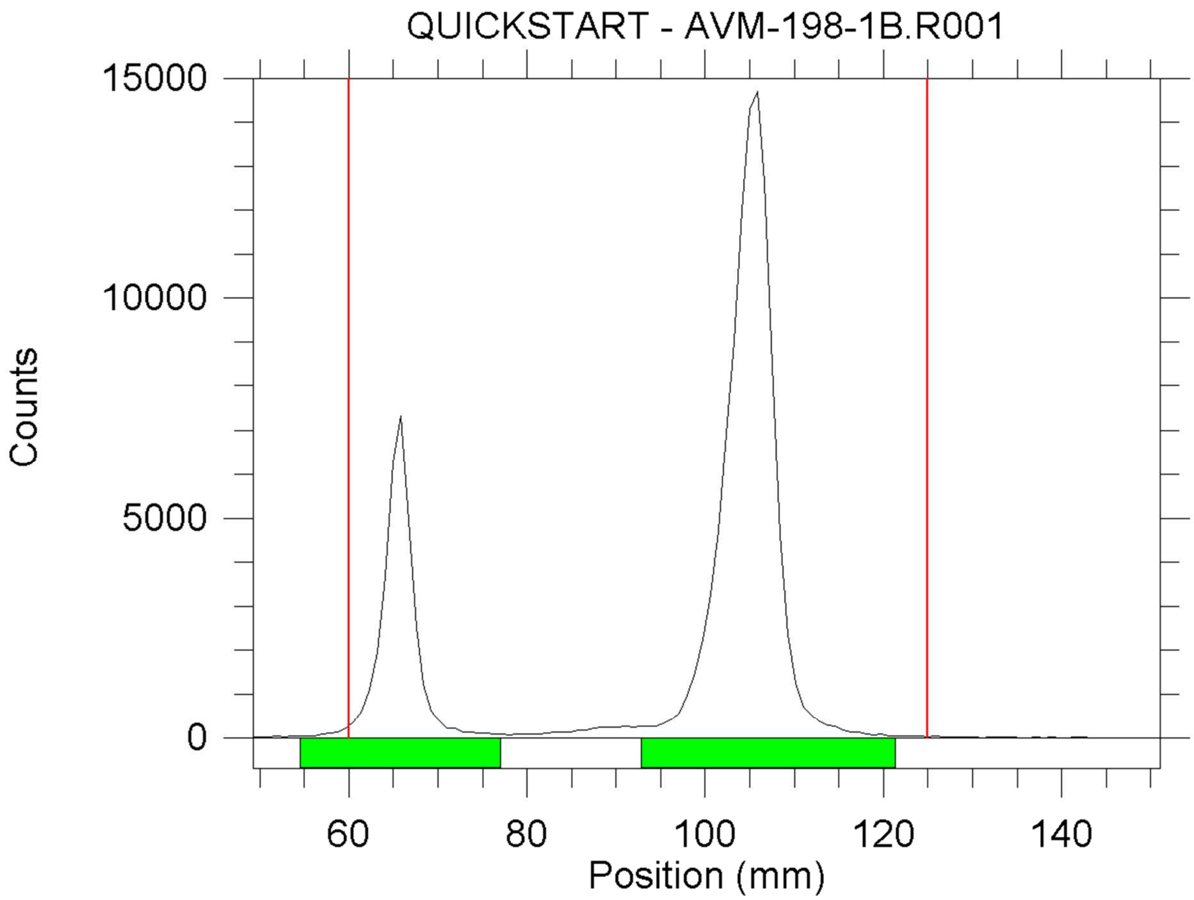
4-(2-[^{18}F]fluorovinyl)-1,1'-biphenyl **18** RAD trace overlaid with UV trace (256 nm)



4-(2-[^{18}F]fluorovinyl)-1,1'-biphenyl **18** RAD trace overlaid with UV trace (256 nm) spiked with 4-(2-fluorovinyl)-1,1'-biphenyl

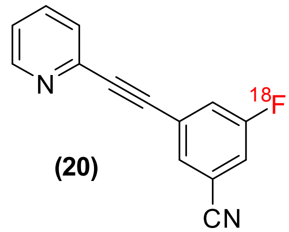


4-(2-[^{18}F]fluorovinyl)-1,1'-biphenyl **18** Radio-TLC spectrum



4-(2-[^{18}F]fluorovinyl)-1,1'-biphenyl **18** Radio-TLC Yields (RCC):

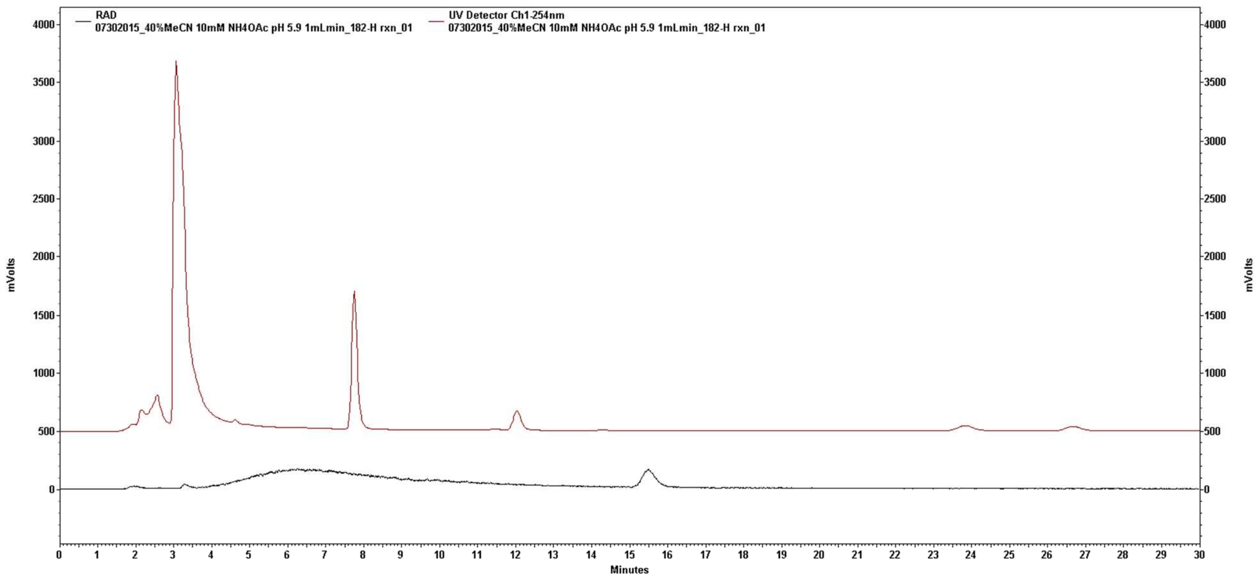
Replicate	TLC Yield
1	**61%**
2	**82 %**
3	**77%**
4	**73%**
Mean	**73%**
Standard Deviation	**9%**



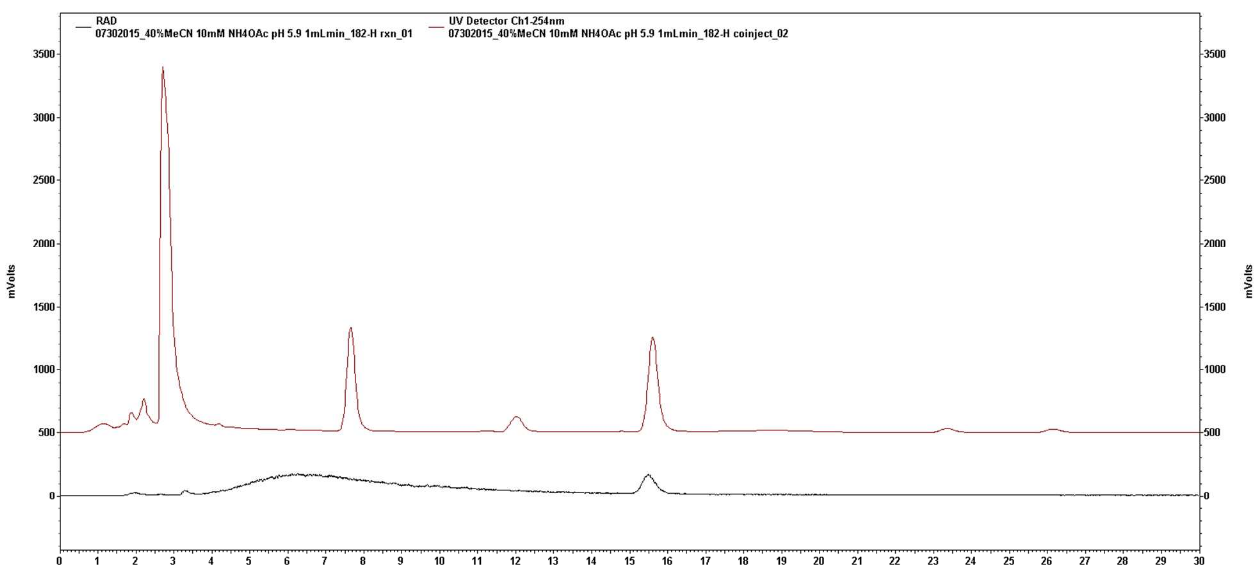
(20)

HPLC Condition: HPLC Condition A

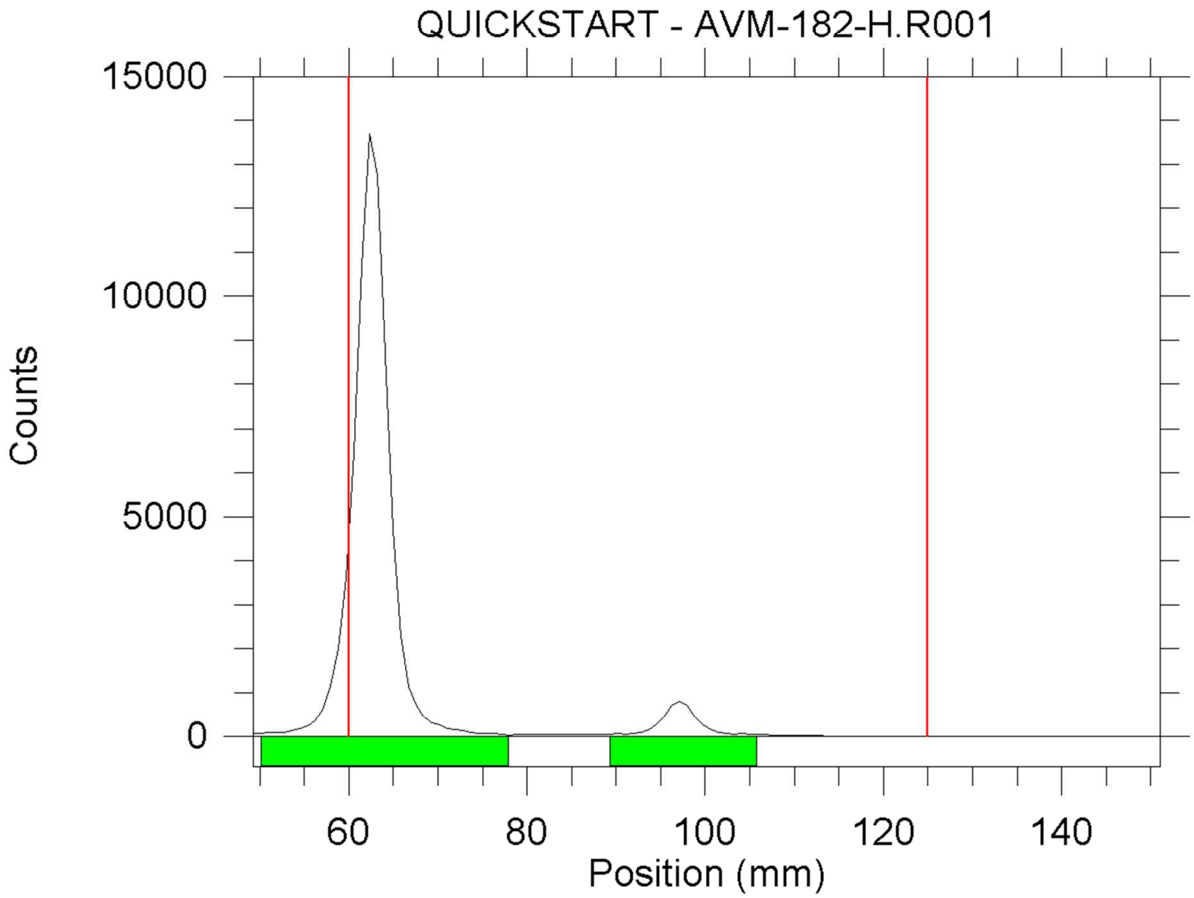
[^{18}F]F-PEB **20** RAD trace overlaid with UV trace (256 nm)



[^{18}F]F-PEB **20** RAD trace overlaid with UV trace (256 nm) spiked with F-PEB



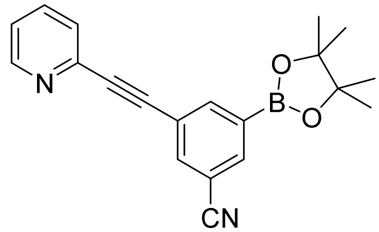
[^{18}F]F-PEB **20** Radio-TLC spectrum

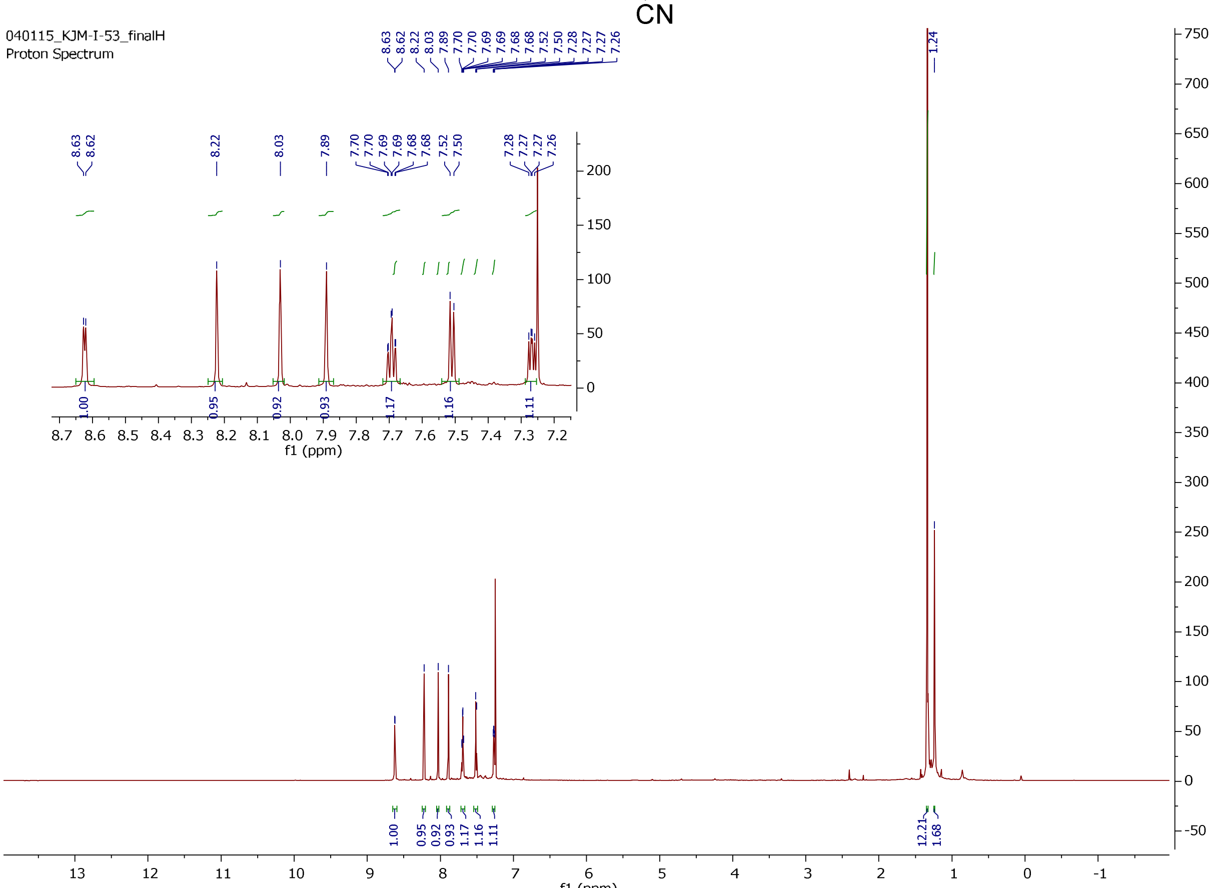


[^{18}F]F-PEB **20** Radio-TLC Yields (RCC):

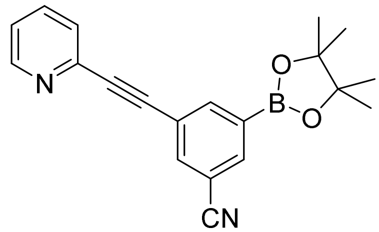
Replicate	TLC Yield
1	**6%**
2	**9%**
3	**8%**
4	**11%**
Mean	**8%**
Standard Deviation	**2%**

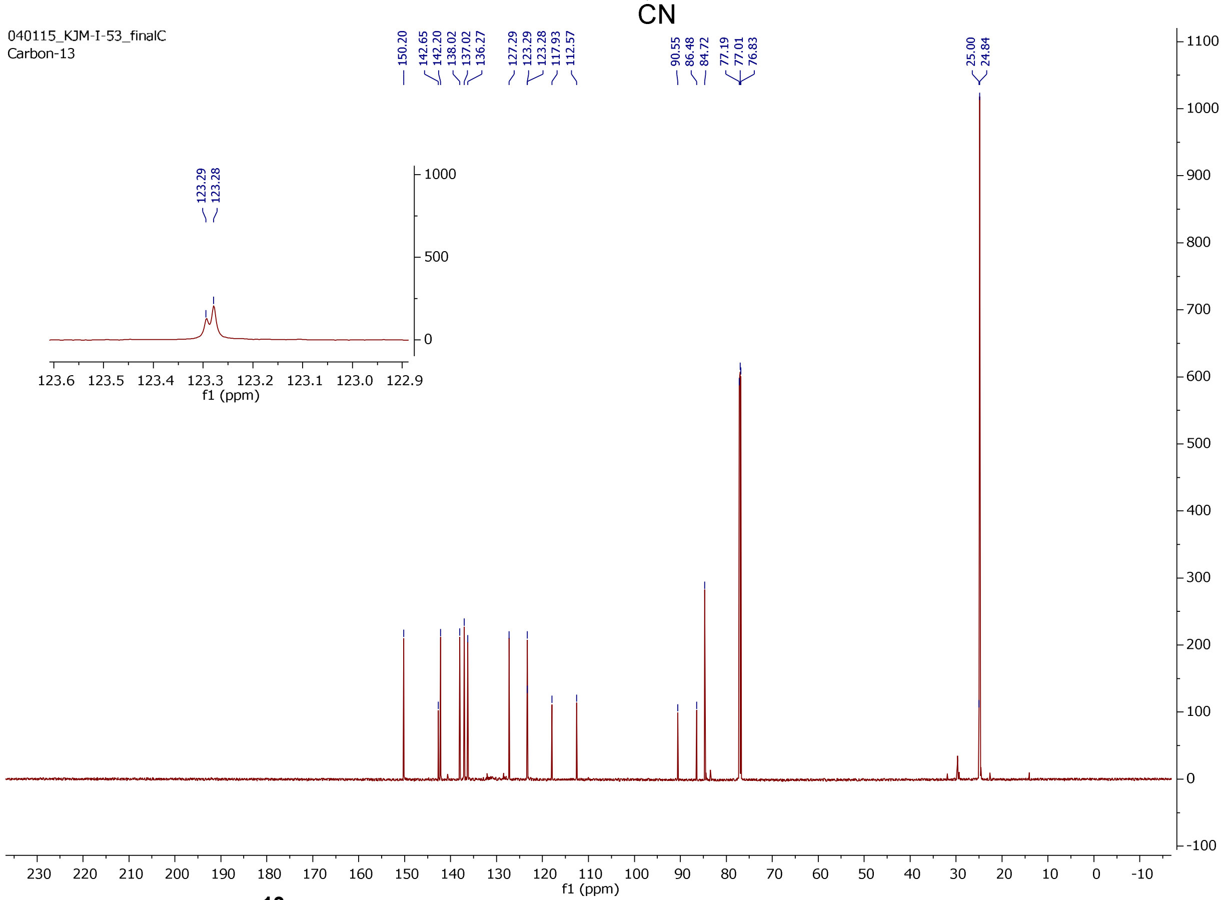
5. ^{1}H, ^{13}C and ^{19}F NMR Spectra



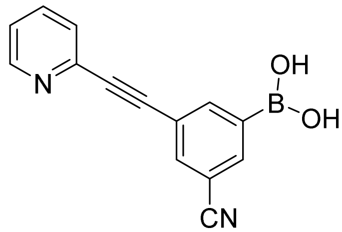


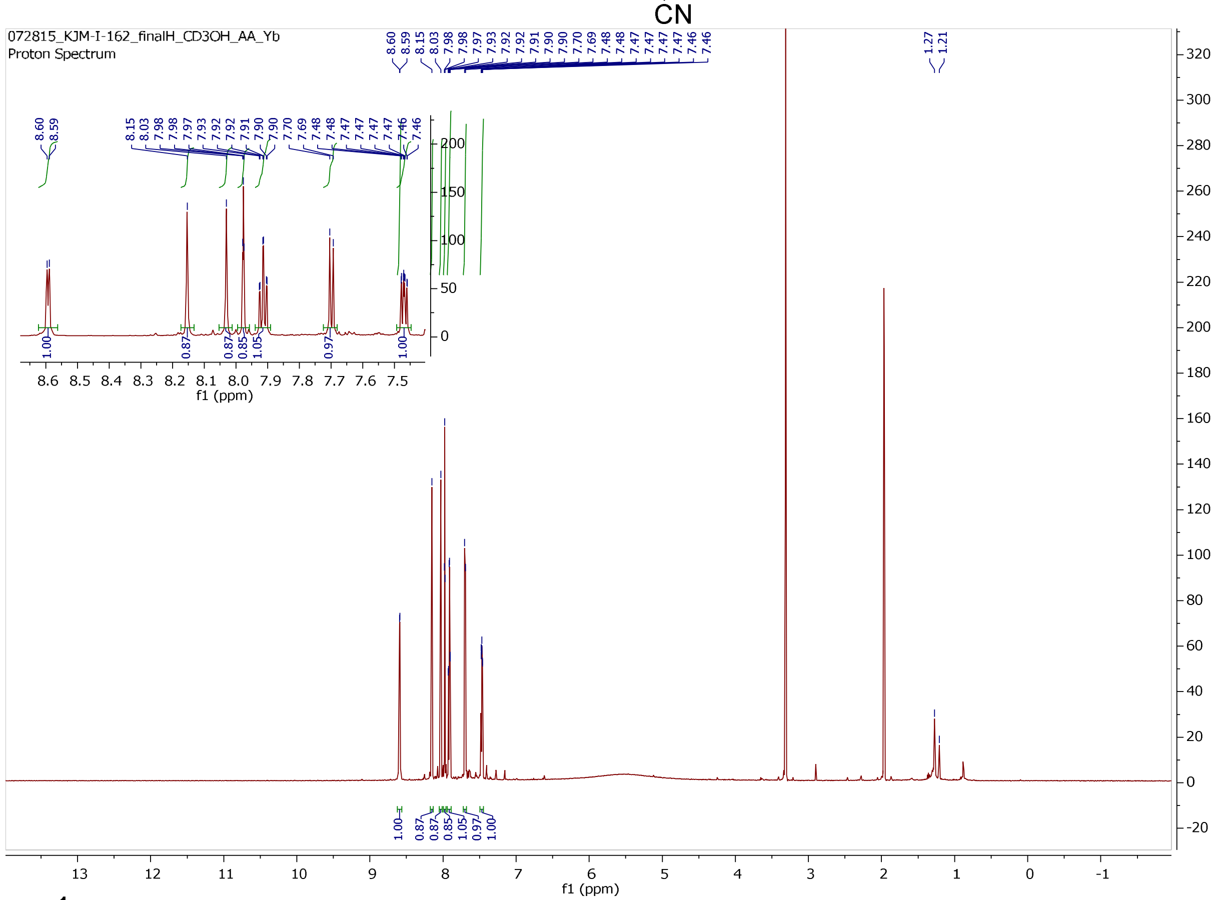
^{1}H Spectrum of S2 (Bpin-PEB) [700 MHz; $CDCl_3$]





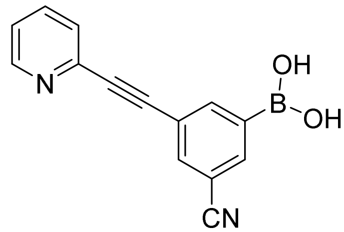
^{13}C Spectrum of S2 (Bpin-PEB) [176 MHz; $CDCl_3$]

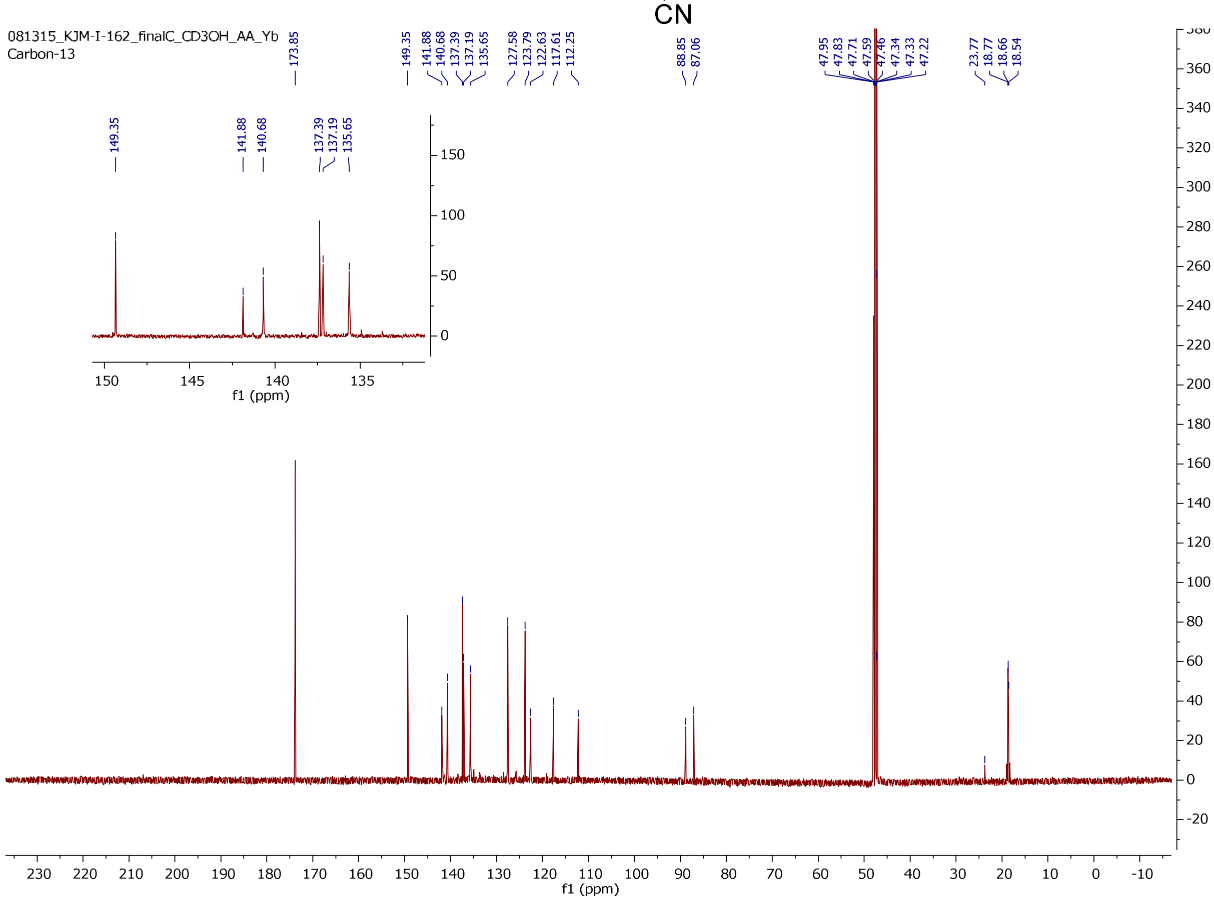




^{1}H Spectrum of 19 (B(OH)$_2$-PEB) [700 MHz; CD_3OD and 1 drop of CD_3COOD]

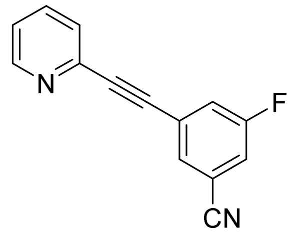
Note: Small degree of starting material contamination (2), as evidenced by pinacolyl methyl peaks at c.a 1.25ppm

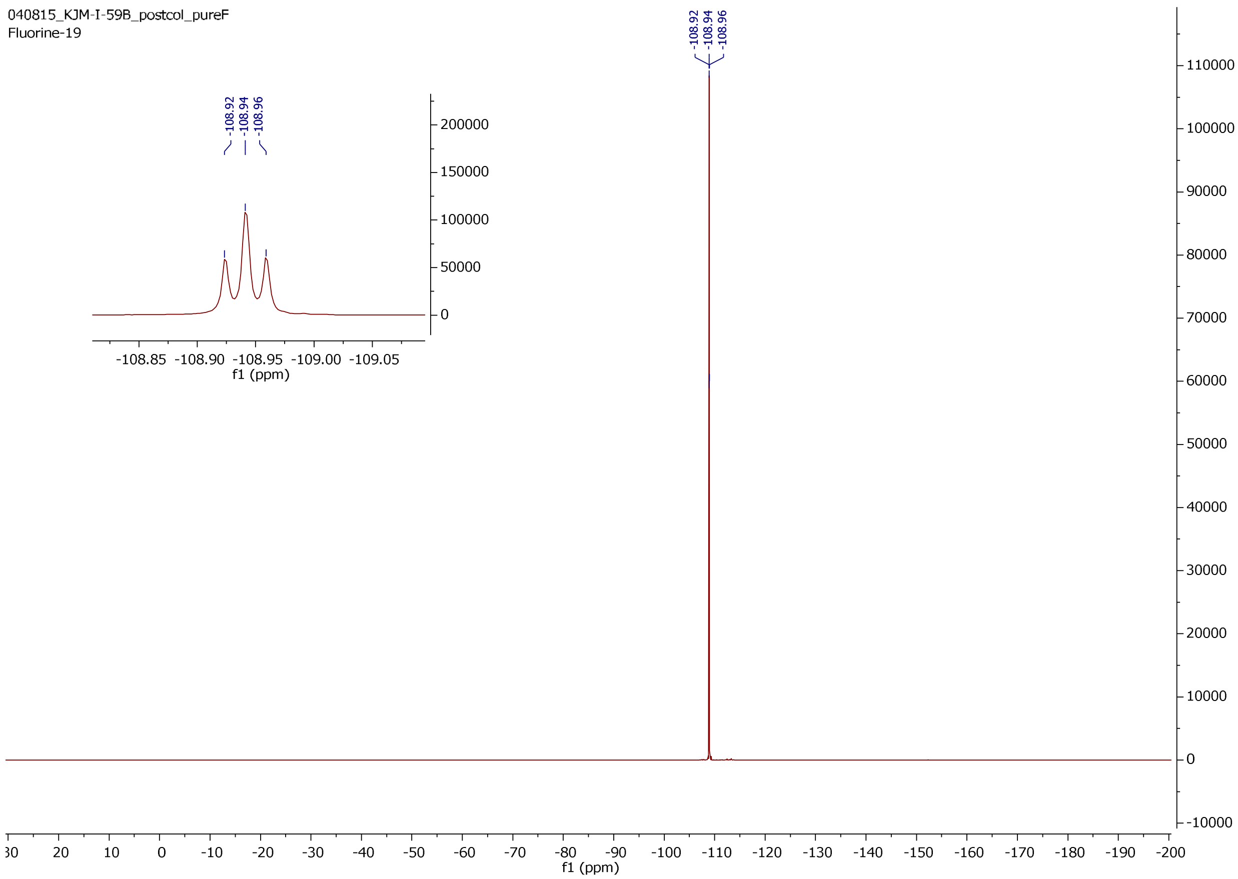




^{13}C Spectrum of 19 (B(OH)$_2$-PEB) [176 MHz; CD_3OD and 1 drop of CD_3COOD]

Note: Small degree of starting material contamination (cmpd 2), as evidenced by pinacolyl methyl peaks at c.a 24ppm





^{19}F Spectrum of S3 (F-PEB) [658 MHz; $CDCl_3$]