Electronic Supplementary Material (ESI) for Chemical Communications.

Copper(I)-free Syntheses of [^{11}C/^{18}F]Trifluoromethyl Ketones from Alkyl or Aryl Esters and [^{11}C/^{18}F]Fluoroform

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Supporting Information

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General Information

Septum-sealed glass vials were used for all reactions. Reagents and solvents were measured for reaction within a glove-box. All the reagents, precursors to be labeled, and reference standards were obtained from commercial sources and were used without further purification. Solvents were purchased in an anhydrous state and the DMF used for radiochemistry was obtained as anhydrous DMF stored on molecular sieves. Retention times (t_R) of all standard compounds were determined by reverse-phase HPLC on a UFLC instrument (Shimadzu) using reverse phase analytical HPLC column with an UV absorbance (254 or 295 nm) detector. The column was eluted at 1.5–2.0 mL/min with a gradient elution of acetonitrile (B) and water (A). All the radiochemistry was performed within a lead-shielded hot-cell with remote control to protect personnel from radiation. The apparatus was not fully automated. The HPLC chromatograms were processed using GraphPad Prism 8.

General Procedure for Carbon-11 Labeling

NCA [^{11}C]fluoroform (**~** 200−500 MBq) was prepared and collected in DMF (**~** 200–300 μL) according to the reported method.[1] This was then added to a septum-sealed vial containing *t*-BuOK (15–125 μmol) or KHMDS (15–75 μmol) in DMF (100 μL) at room temperature. The aryl or alkyl esters (from **1a**–**1o**, **1p**; 50 μmol) in DMF (100 μL) was then added, mixed vigorously, kept at room temperature for 10 min and shaken frequently. The reaction mixture was then quenched with 4M HCl (100 μL), placed on a pre-heated heating block at 60 °C for 5 min and then diluted with H_2O–MeCN (1:1 v/v; 300 μL). An aliquot was then analyzed with reversed phase HPLC as described below. The formation of the radiolabeled compounds ([^{11}C]**2a**–**2o** and [^{11}C]**3i**) were confirmed by comparing the retention time of the reference standard compounds (**2a**–**2o** and **3i**) in analytical HPLC.

General Procedure for Fluorine-18 Labeling

NCA [^{18}F]fluoroform (**~** 100−150 MBq) in DMF (~ 200 µL) was prepared according to the reported method.[2] This was then added to a septum-sealed vial containing *t*-BuOK (45 μmol) in DMF (100 μL) at room temperature. The aryl esters (**1a**, **1d** or **1j**; 50 μmol) in DMF (100 μL) was then added, mixed vigorously, kept at room temperature for 10 min and shaken frequently. The reaction mixture was then quenched with 4M HCl (100 μL), placed on a pre-heated heating block at 60 °C for 5 min and then diluted with H_2O–MeCN (1:1 v/v; 300 μL). An aliquot was then analyzed with reversed phase HPLC as described below. The formation of the radiolabeled compounds ([^{18}F]**2a**, [^{18}F]**2d** and [^{18}F]**2j**) were confirmed by comparing the retention time of the reference standard compounds (**2a**, **2d** and **2j**) in analytical HPLC.

Radio-HPLC Analysis

HPLC was performed on a system comprising a Gold 126 solvent module (Beckman Coulter; Fullerton, CA) and a 166 or 168 UV absorbance detector (operating at 254 or 295 nm) plus a photomultiplier tube radioactivity detector (Flow-count; Bioscan, Washington, DC). For ^{11}C/^{18}F-labeled compounds, an aliquot of the quenched reaction mixture was injected onto a reversed phase column to separate the product radioactive peak from its starting material using the HPLC conditions A**–**G as described below. Eluate was monitored for radioactivity and for absorbance at

254 nm. Radiochemical product identities were confirmed by comparison of HPLC retention times with the reference compounds. In some cases, appreciable tailing of product peaks was observed, likely as a result of the equilibrium between the ketone and ketal.

Condition A:

Column: Luna C18(2), 10 μm, 4.6 × 250 mm, i.d.; Phenomenex

Mobile phase: 10–80% MeCN (B)–H_2O (A) for 15 min, then 80% B for 5 min; 2.0 mL/min flow rate.

Condition B:

Column: Luna C18(2), 10 μm, 4.6 × 250 mm, i.d.; Phenomenex

Mobile phase: 30–80% MeCN (B)–H_2O (A) for 15 min, then 80% B for 5 min; 2.0 mL/min flow rate.

Condition C:

Column: XTerra RP_{18}, 5 μm, 4.6 × 250 mm, i.d.; Waters Corp.

Mobile phase: 30–85% MeCN (B)–H_2O (A) for 15 min, then 85% B for 5 min; 1.5 mL/min flow rate.

Condition D:

Column: Luna Phenyl-Hexyl, 5 μm, 4.6 × 250 mm, i.d.; Phenomenex

Mobile phase: 10–80% MeCN (B)–H_2O (A) for 15 min, then 80% B for 5 min; 2.0 mL/min flow rate.

Condition E:

Column: Luna Phenyl-Hexyl, 5 μm, 4.6 × 250 mm, i.d.; Phenomenex

Mobile phase: 10–50% MeCN (B)–H_2O (A) for 10 min, followed by 50–80% for 5 min and then 80% B for 10 min; 2.0 mL/min flow rate.

Condition F:

Column: Luna C18(2), 10 μm, 4.6 × 250 mm, i.d.; Phenomenex

Mobile phase: 10–60% MeCN (B)–H_2O (A) for 10 min, followed by 60–80% for 5 min and then 80% B for 10 min; 2.0 mL/min flow rate.

Condition G:

Column: Luna C18(2), 10 μm, 4.6 × 250 mm, i.d.; Phenomenex

Mobile phase: 10–80% MeCN (B)–0.5% TEA in H_2O (A) for 15 min, then 80% B for 5 min; 2.0 mL/min flow rate.

Experimental Procedure for the Determination of Molar Activity (A_m) of [^{11}C]2e

NCA [^{11}C]fluoroform (~ 2.75 GBq) was prepared from a 15 x 15 μA x min of $^{11}CH_4$ (~ 14 GBq) and collected in DMF (~ 300 μL) according to the reported method.[1] [^{11}C]Fluoroform (~ 2.10 GBq, 250 μL) was then added to a septum-sealed vial containing *t*-BuOK (45 μmol) in DMF (100 μL) at room temperature. The methyl 3-bromobenzoate (**1e**, 50 μmol) in DMF (100 μL) was added, mixed vigorously, kept at room temperature for 10 min, and shaken frequently. The reaction mixture was then quenched with 4M HCl (100 μL), placed on a pre-heated

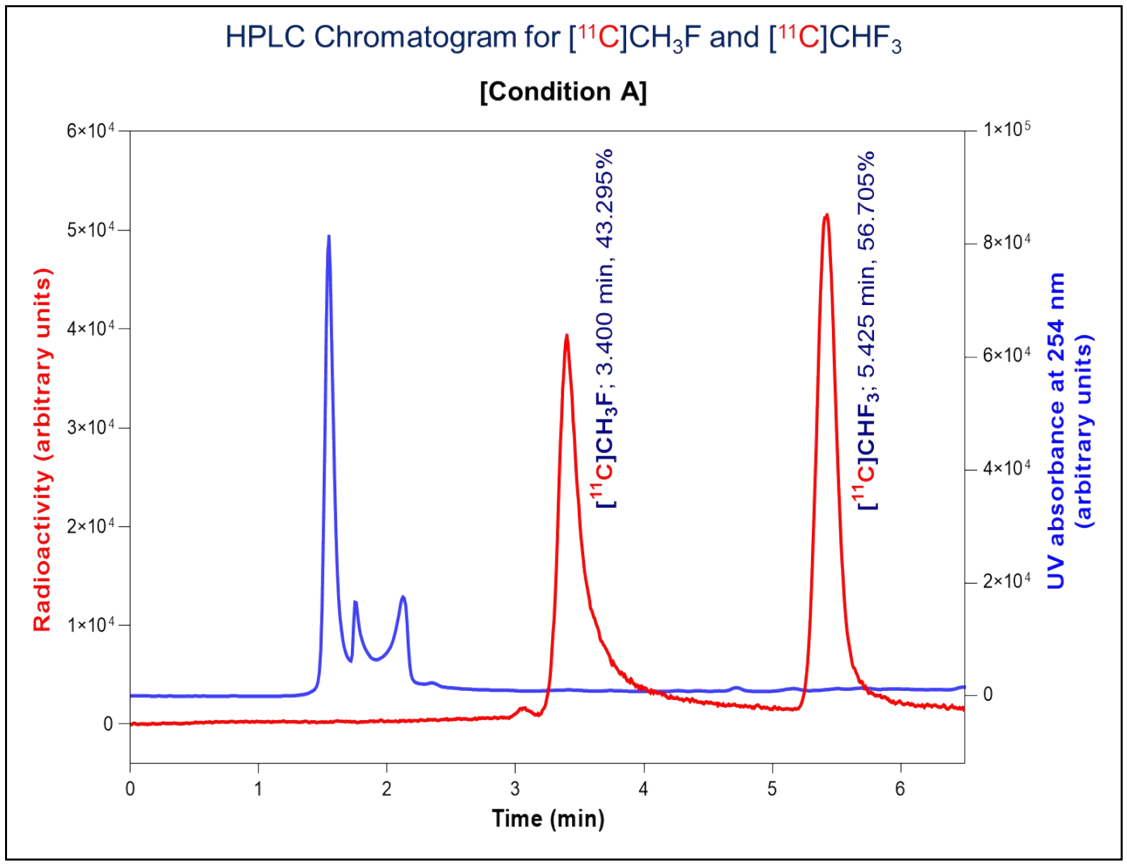
heating block at 60 °C for 5 min, diluted with H_2O–MeCN (1:1 v/v; 3.4 mL, total volume 4 mL), and injected onto a reversed phase semi-preparative HPLC (XTerra RP_{18}, 10 μm, 7.8 × 300 mm, i.d.; Waters Corp.) with isocratic elution of 35% MeCN (B)–65% H_2O (A) at 6.0 mL/min flow rate. Eluate was monitored for radioactivity and for absorbance at 254 nm. The desired product ([^{11}C]**2e**) was collected between 9–12 min in an isolated yield of 83% (decay-corrected to the time of [^{11}C]fluoroform addition into reaction vial; ~ 35 min; [^{11}C]fluoromethane was excluded from calculation). The total synthesis time was 60 min.

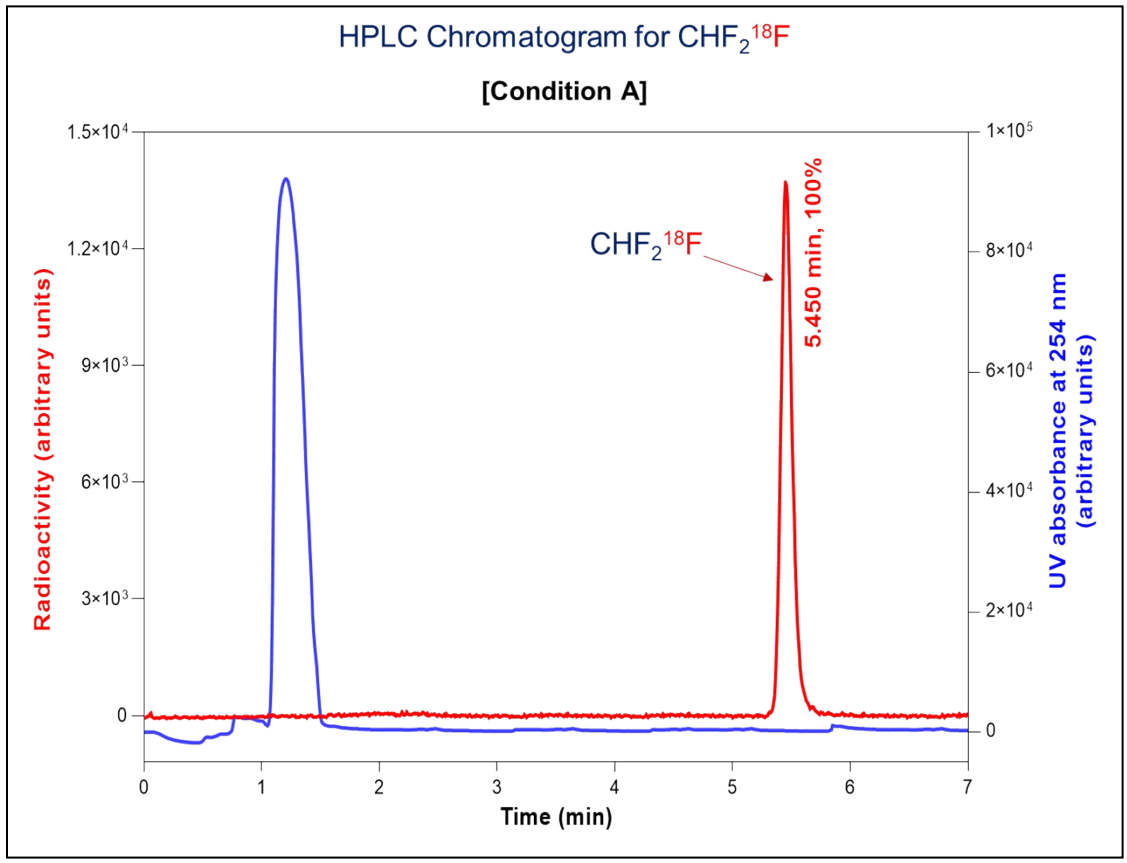
An aliquot of the collected product was then analyzed with reversed phase analytical HPLC (XTerra RP_{18}, 5 μm, 4.6 × 250 mm, i.d.; Waters Corp.) with isocratic elution of 35% MeCN (B)–65% H_2O (A) at 1.5 mL/min flow rate. Eluate was monitored for radioactivity and for absorbance at 200 nm. The radio-HPLC system for analysis of [^{11}C]**2e** was calibrated for UV absorption response versus mass of reference compound in the analyte (Page S32). The radiolabeled product ([^{11}C]**2e**) was obtained with a radiochemical purity of 97.5% and a molar activity (A_m) of 56 ± 6 GBq/μmol (n = 2) at the end of synthesis (EOS) (see A_m calculation in Page S32). The formation of the radiolabeled compounds ([^{11}C]**2e**) was confirmed by co-injection with the reference **2e** in analytical HPLC using the conditions described above.

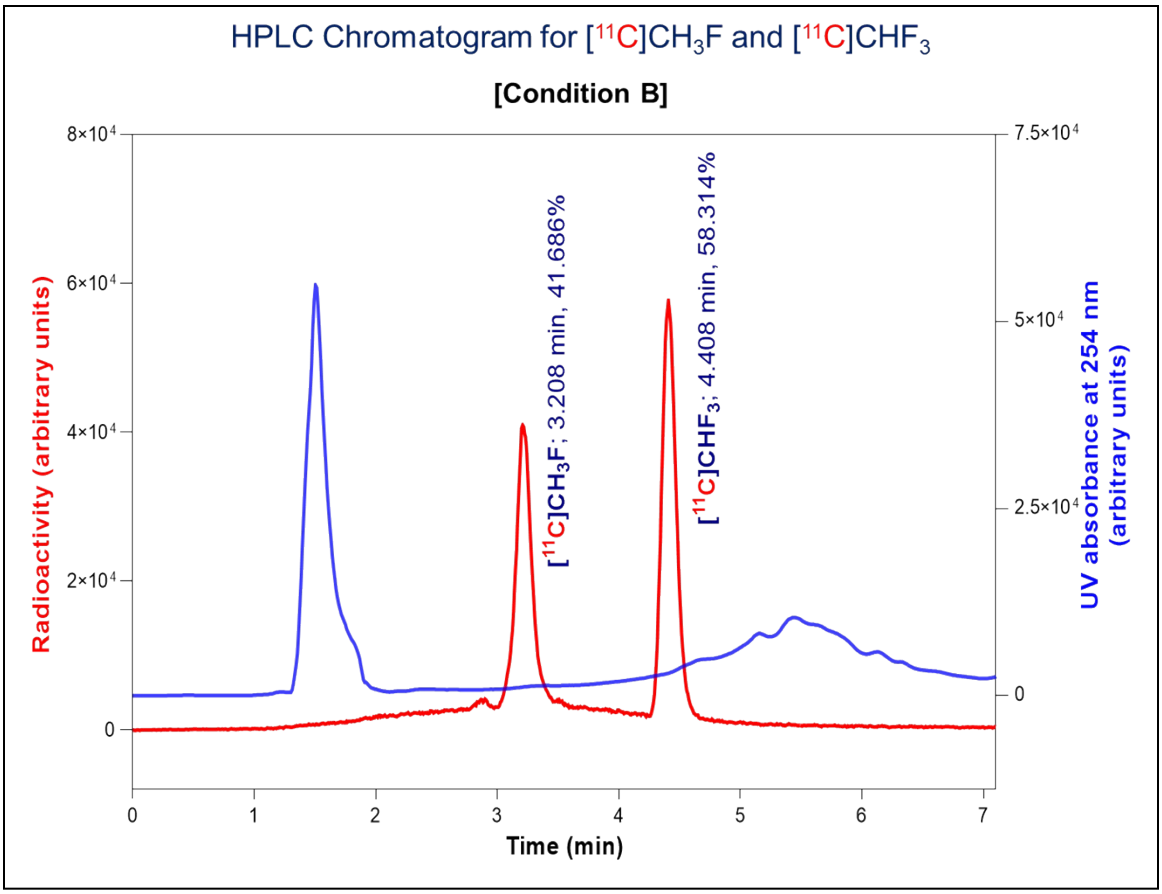
References

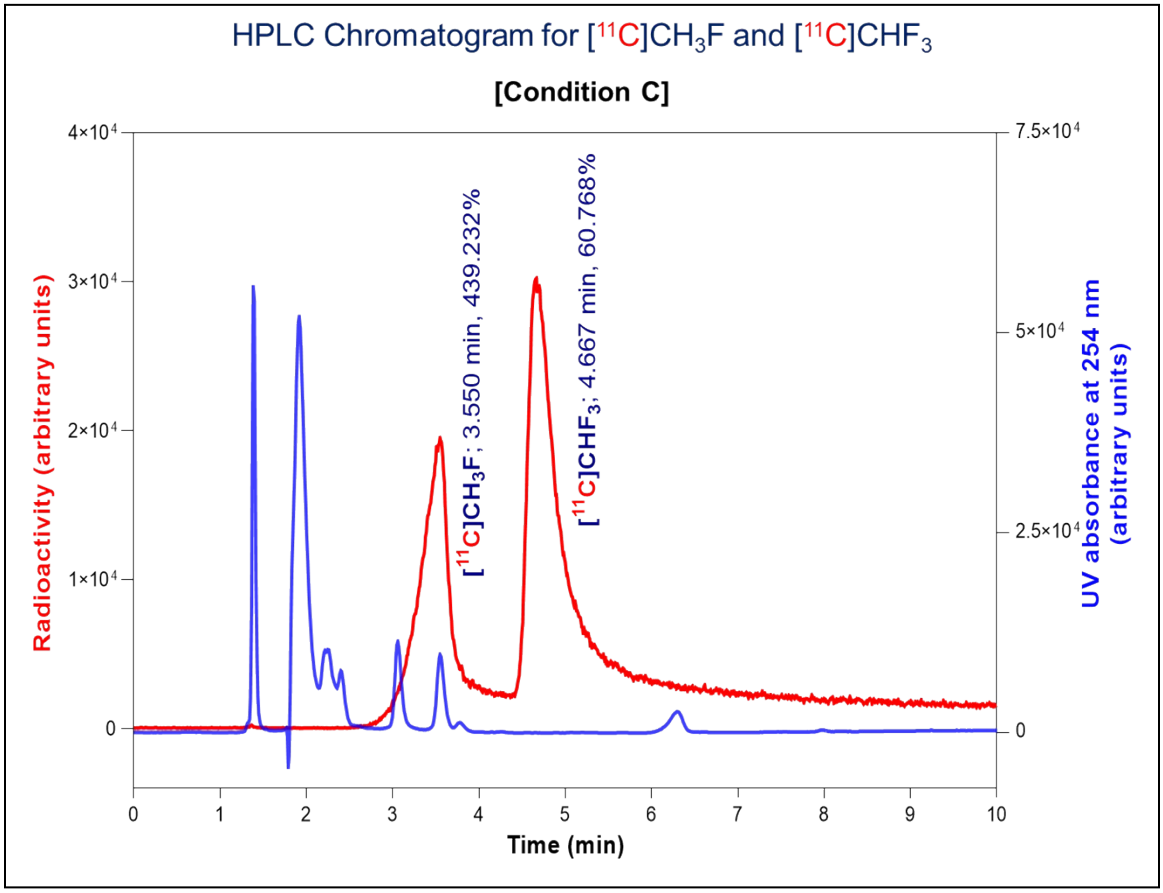
1. Haskali, M. B.; Pike, V. W. *Chem. Eur. J*. **2017**, *23*, 8156.
2. Yang, B. Y.; Telu, S.; Haskali, M. B.; Morse, C. L.; Pike, V. W. *Sci. Rep*. **2019**, *9*, 14835.

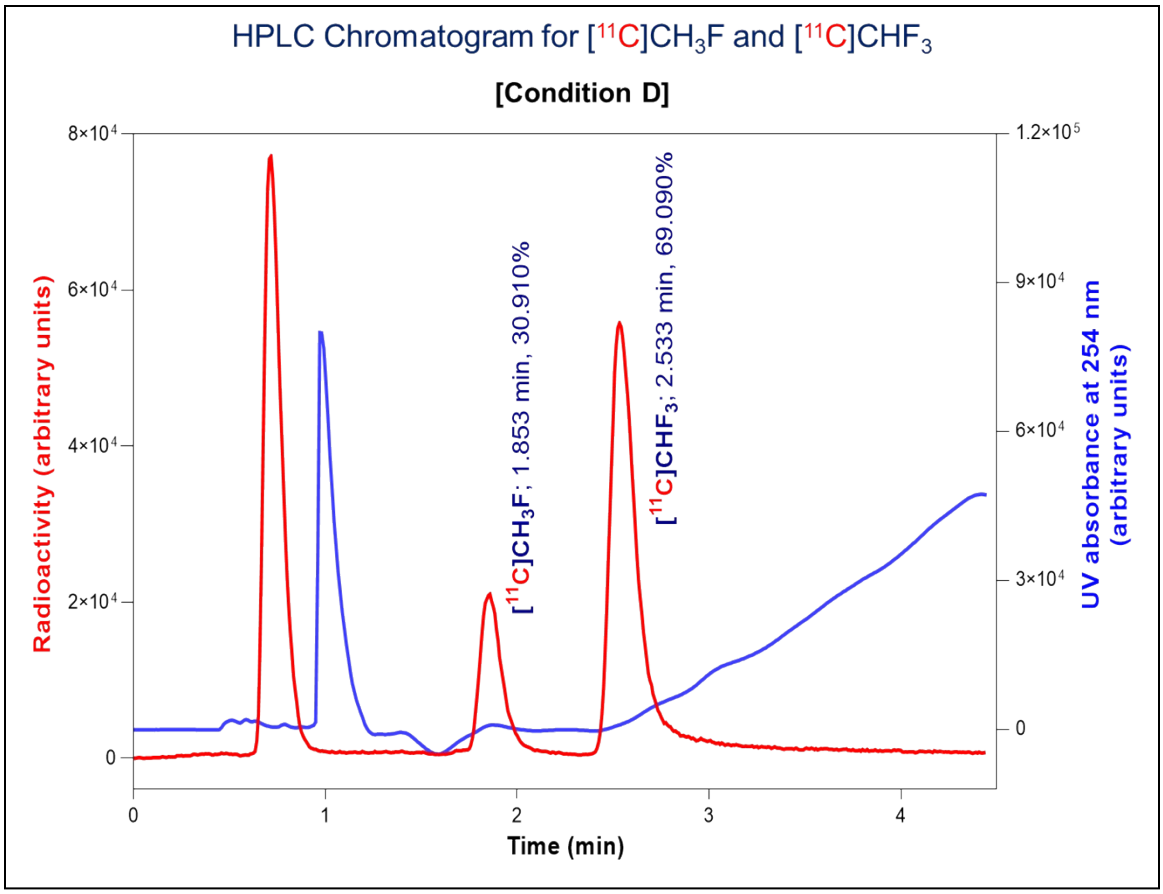
HPLC Chromatograms for $^{11}CHF_3$ and $CHF_2{}^{18}F$

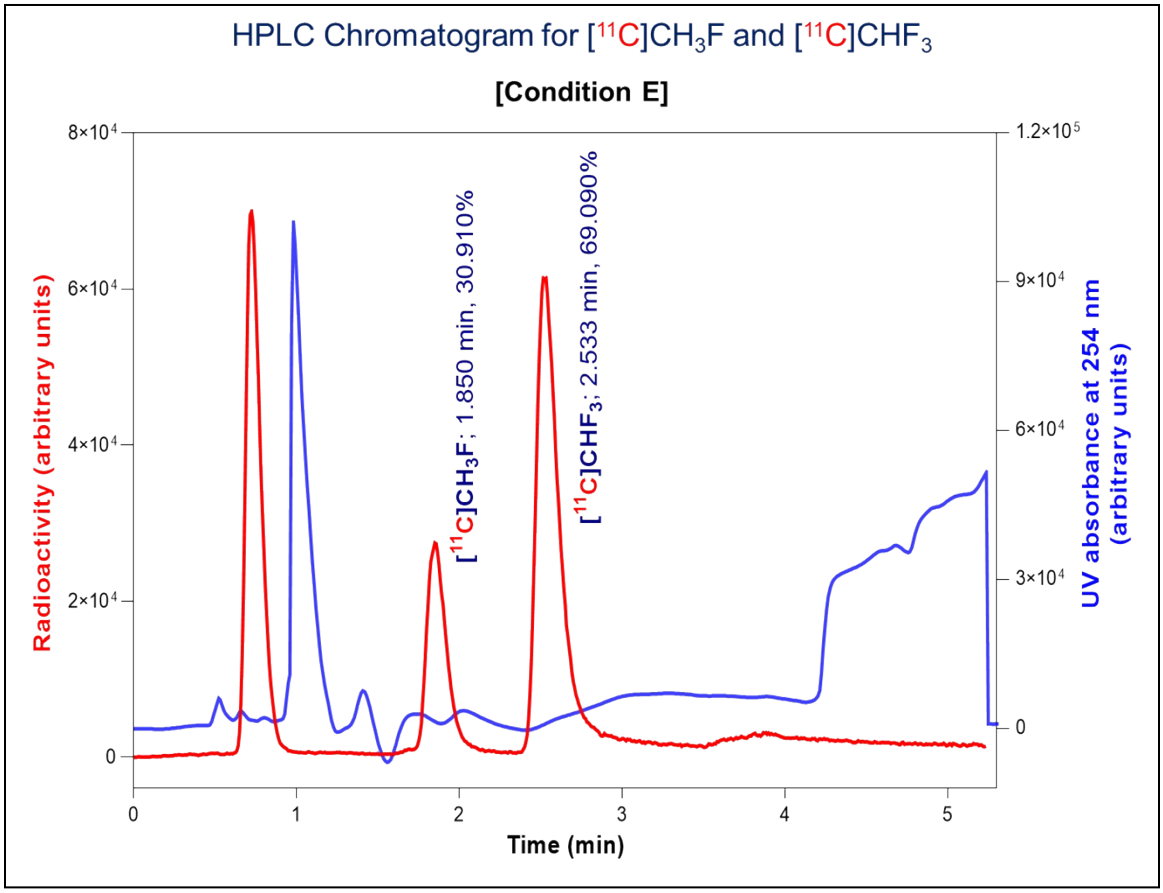


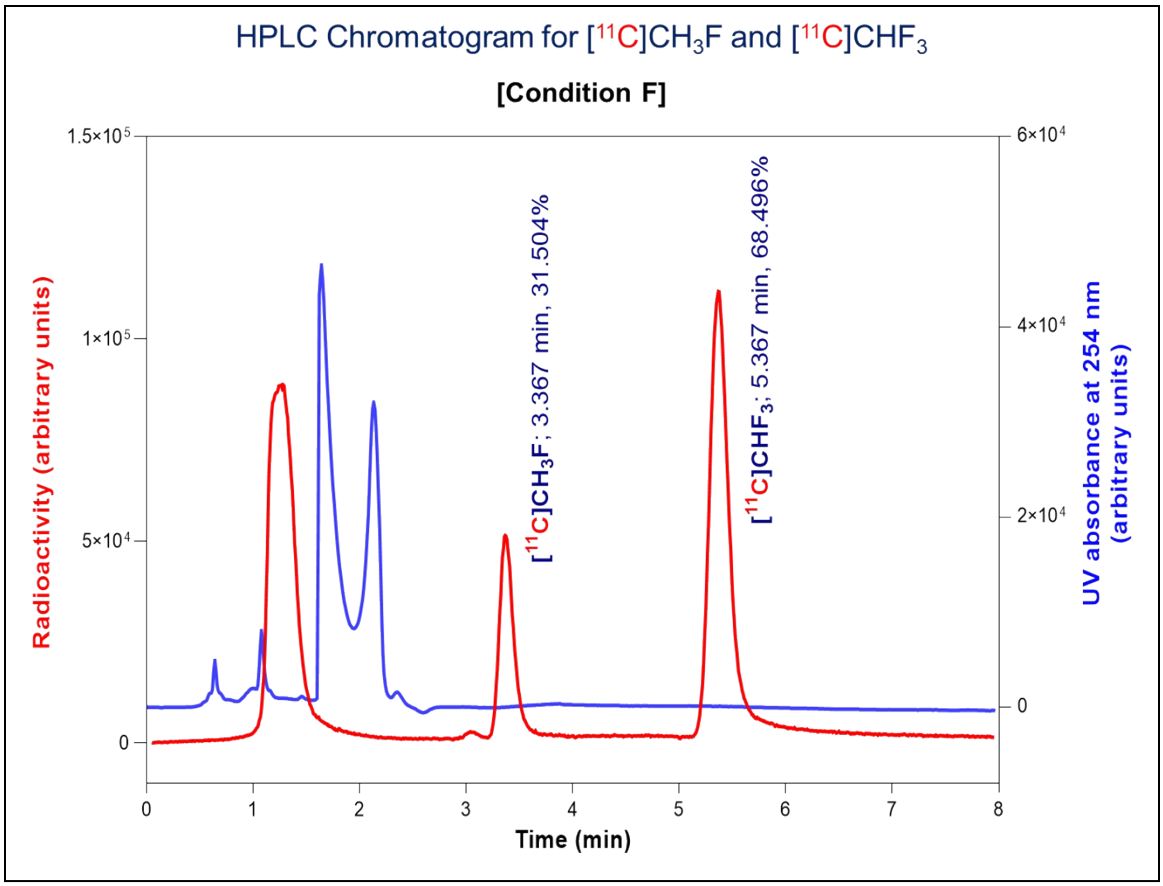


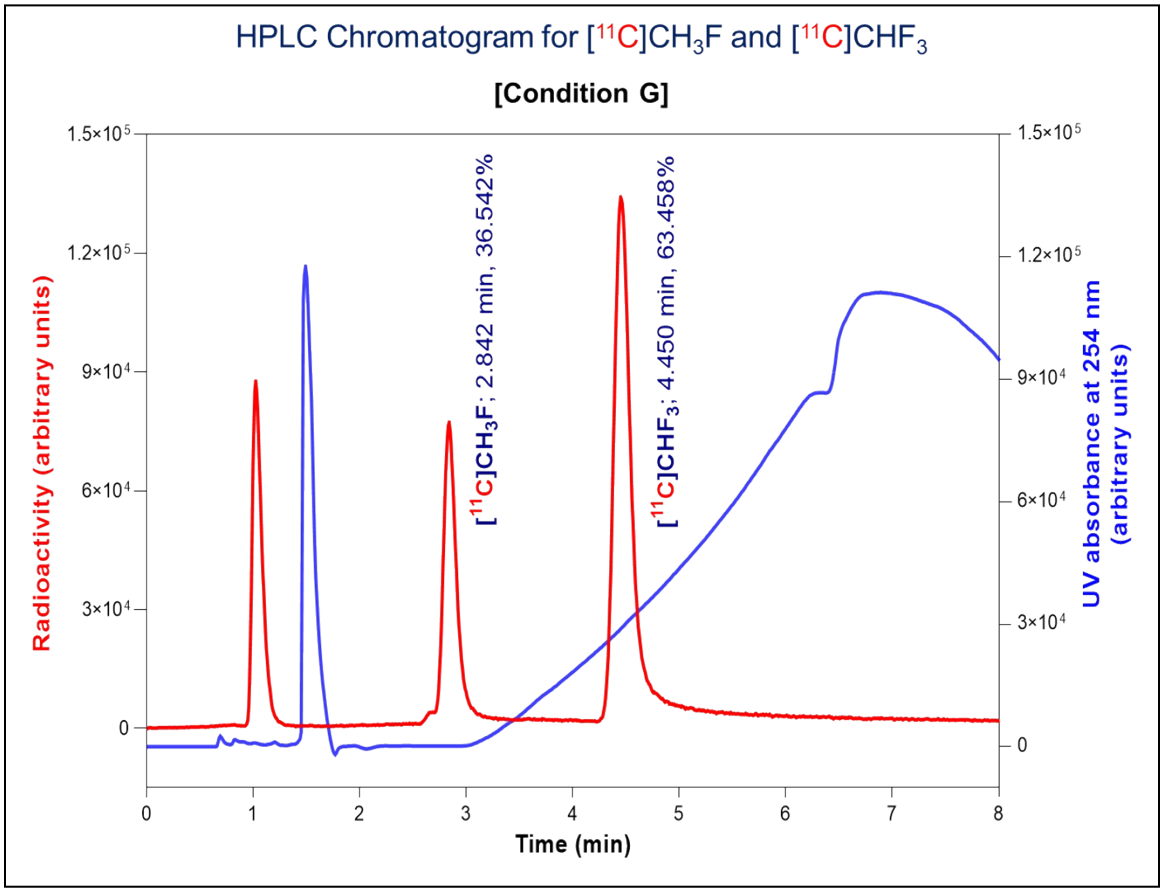

HPLC Chromatogram for [11C]CH3F and [11C]CHF3
[Condition B]
Radioactivity (arbitrary units)
UV absorbance at 254 nm (arbitrary units)
Time (min)
[11C]CH3F; 3.208 min, 41.686%
[11C]CHF3; 4.408 min, 58.314%


HPLC Chromatogram for [11C]CH3F and [11C]CHF3
[Condition C]
Radioactivity (arbitrary units)
UV absorbance at 254 nm (arbitrary units)
Time (min)
[11C]CH3F; 3.550 min, 439.232%
[11C]CHF3; 4.667 min, 60.768%

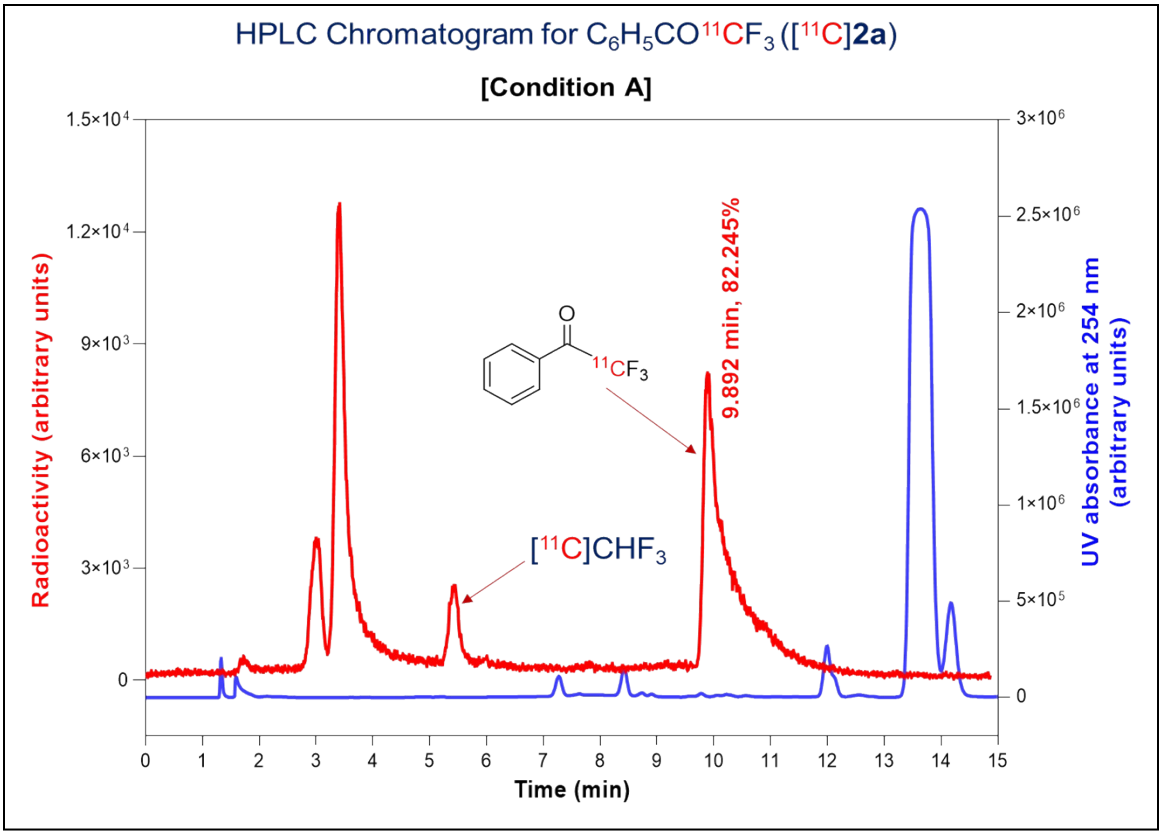

HPLC Chromatogram for [11C]CH3F and [11C]CHF3
[Condition D]
Radioactivity (arbitrary units)
UV absorbance at 254 nm (arbitrary units)
Time (min)
[11C]CH3F; 1.853 min, 30.910%
[11C]CHF3; 2.533 min, 69.090%
8×10^4
6×10^4
4×10^4
2×10^4
0
1.2×10^5
9×10^4
6×10^4
3×10^4
0
0
1
2
3
4

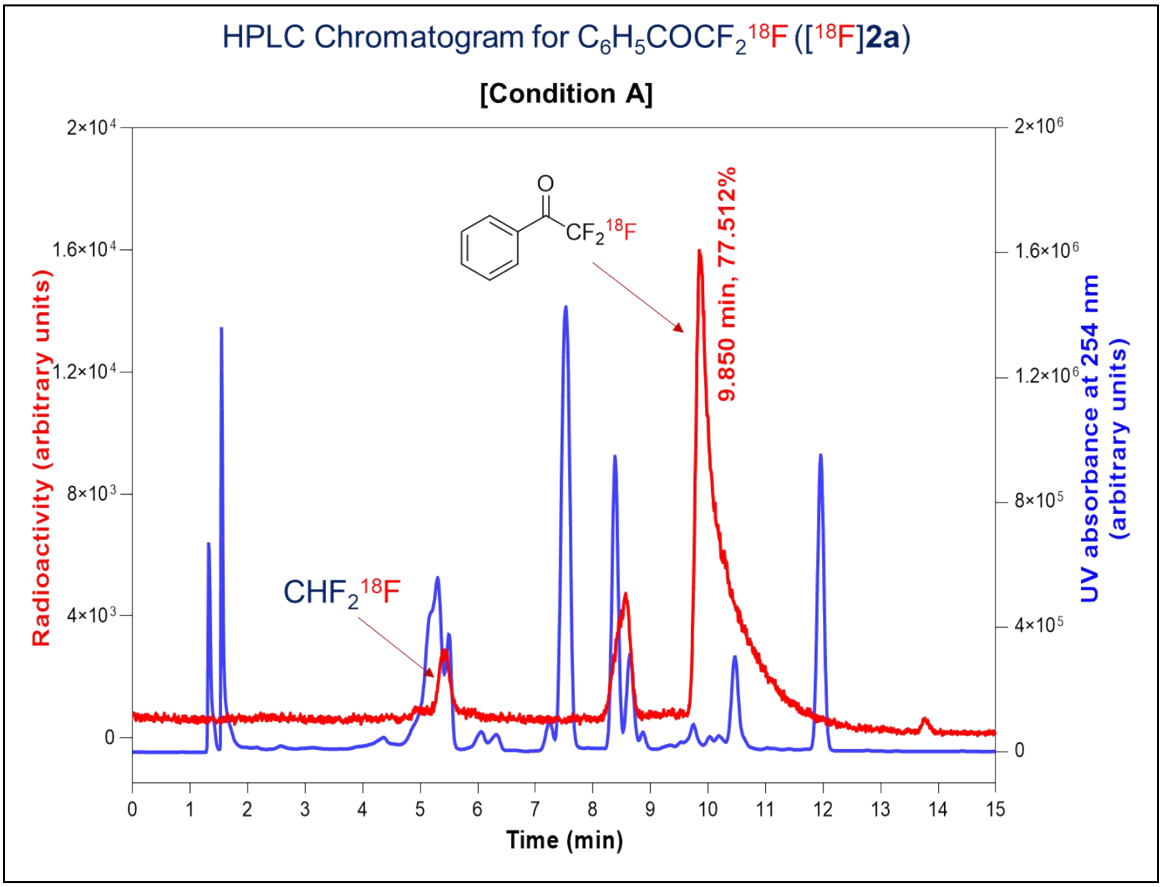

HPLC Chromatogram for [11C]CH3F and [11C]CHF3
[Condition E]
Radioactivity (arbitrary units)
UV absorbance at 254 nm (arbitrary units)
Time (min)
[11C]CH3F; 1.850 min, 30.910%
[11C]CHF3; 2.533 min, 69.090%
8×10^4
6×10^4
4×10^4
2×10^4
0
1.2×10^5
9×10^4
6×10^4
3×10^4
0
0
1
2
3
4
5

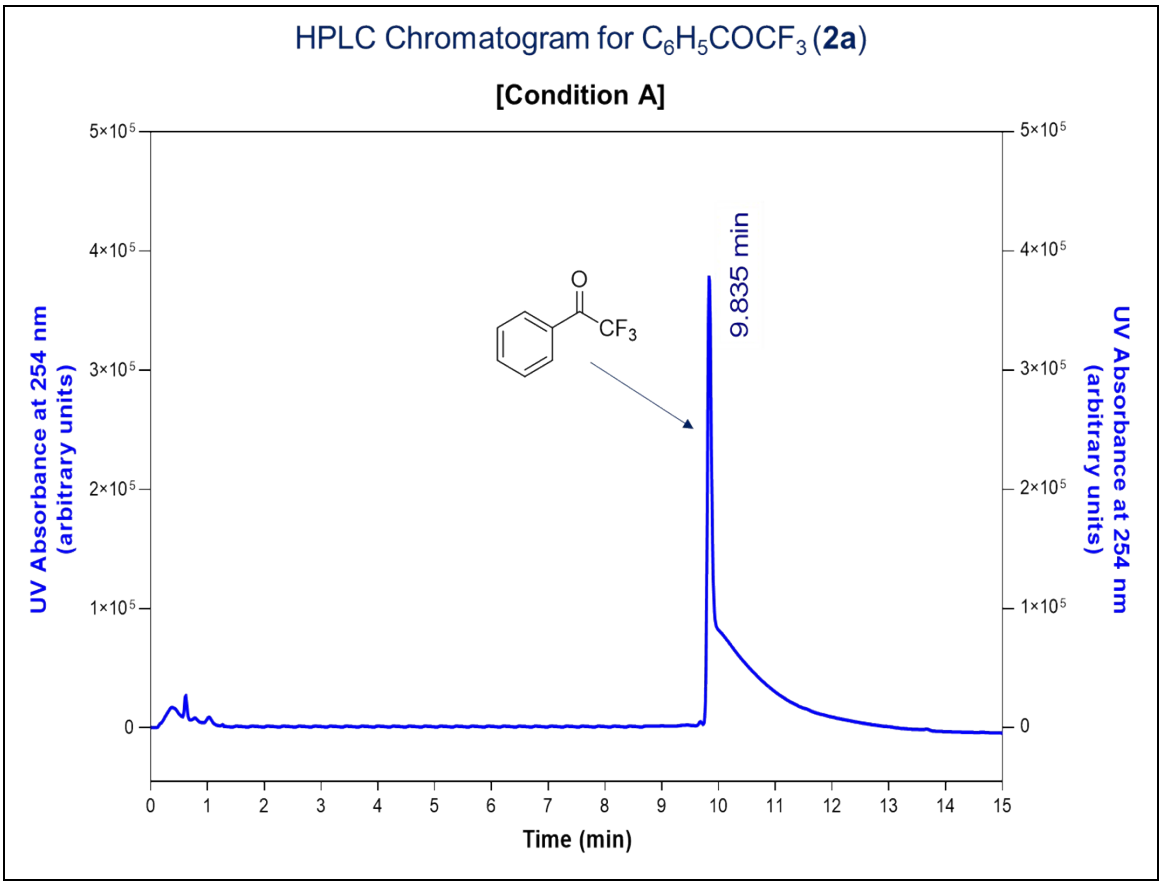

HPLC Chromatogram for [11C]CH3F and [11C]CHF3
[Condition F]
Radioactivity (arbitrary units)
UV absorbance at 254 nm (arbitrary units)
[11C]CH3F; 3.367 min, 31.504%
[11C]CHF3; 5.367 min, 68.496%
Time (min)

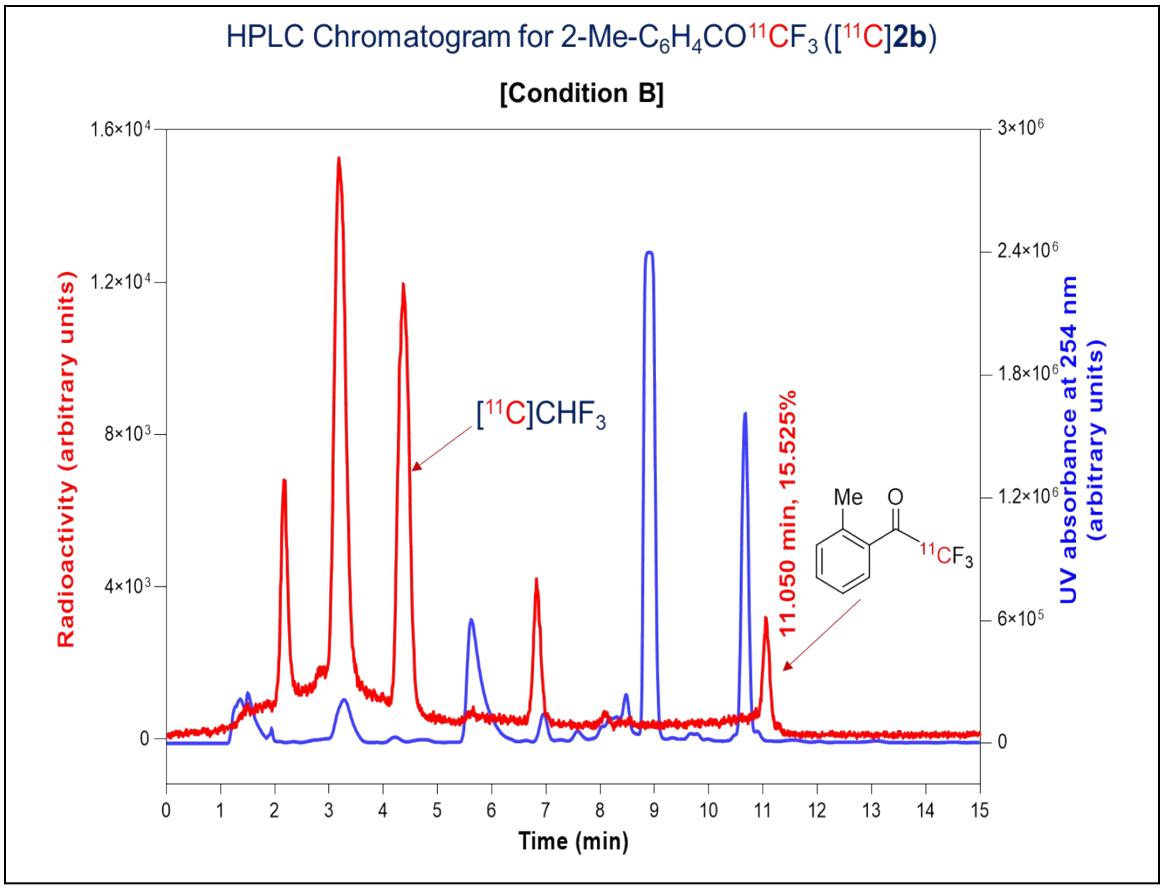

HPLC Chromatogram for [11C]CH3F and [11C]CHF3
[Condition G]
Radioactivity (arbitrary units)
UV absorbance at 254 nm (arbitrary units)
[11C]CH3F; 2.842 min, 36.542%
[11C]CHF3; 4.450 min, 63.458%
Time (min)

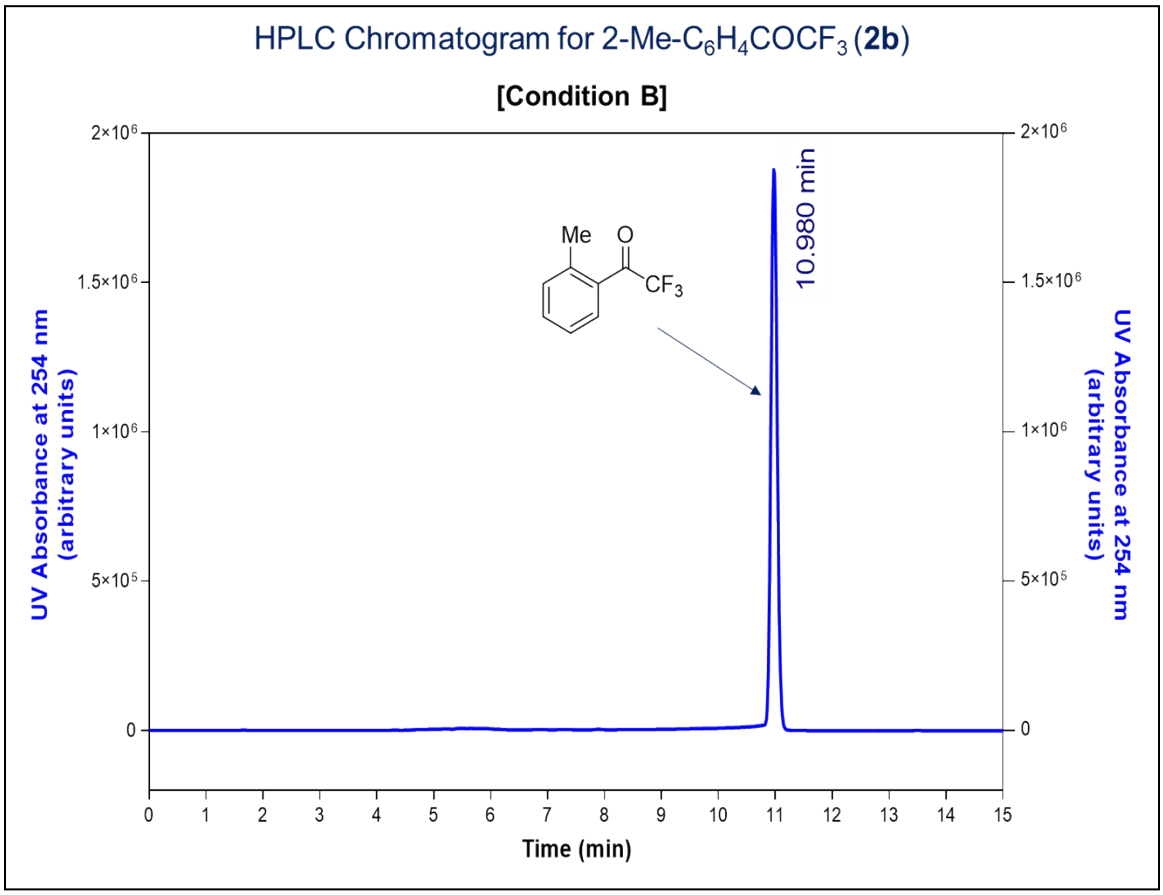
HPLC Chromatograms for [^{11}C]2a–2o and 2a–2o

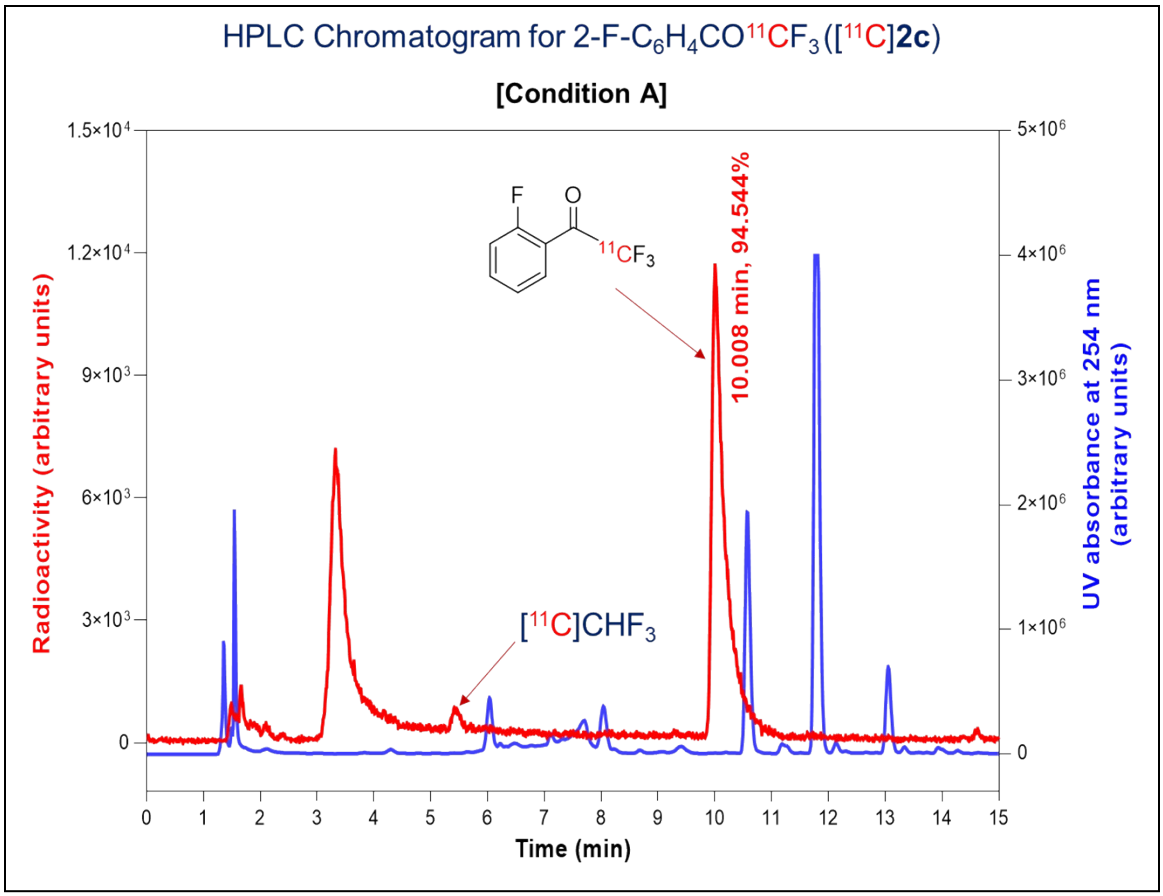


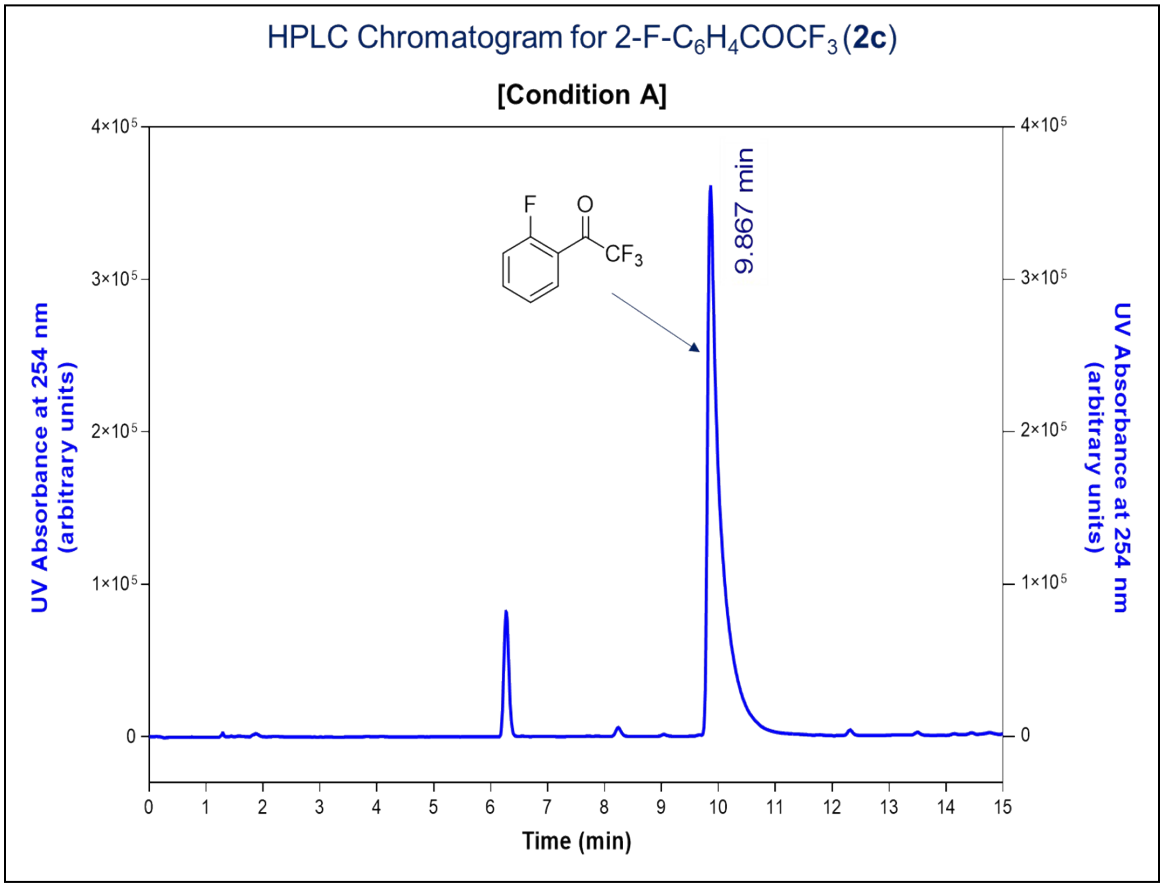


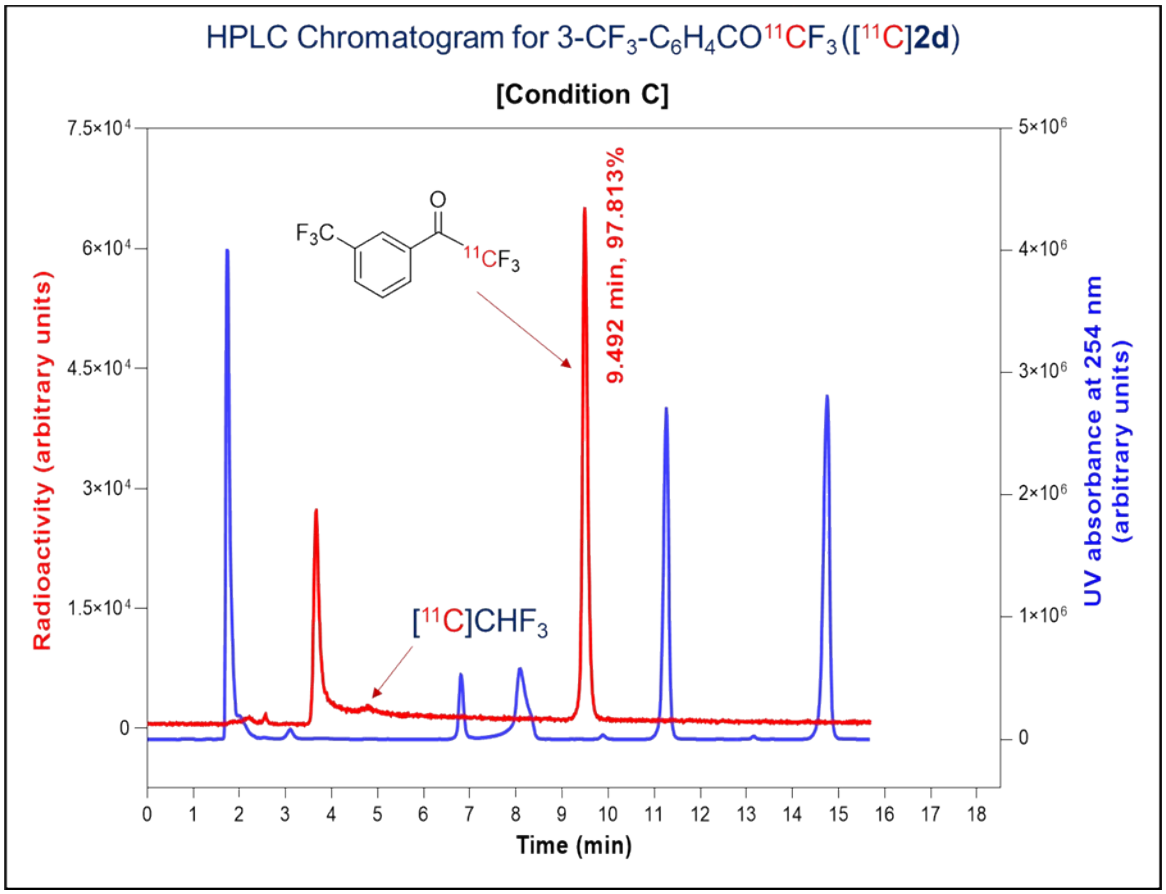

HPLC Chromatogram for $C_6H_5COCF_3$ (**2a**)
[Condition A]
UV Absorbance at 254 nm (arbitrary units)
5×10^5
4×10^5
3×10^5
2×10^5
1×10^5
0
9.835 min
O
CF3
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Time (min)

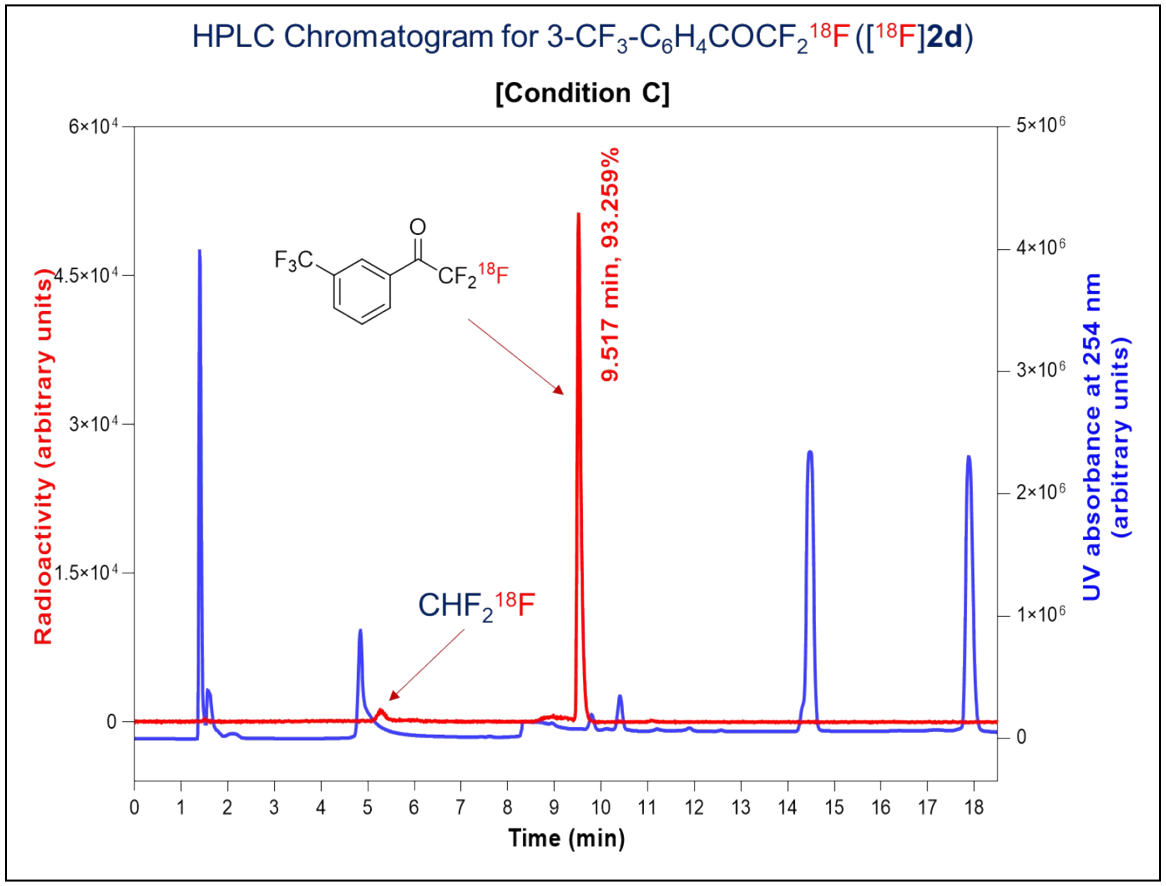

HPLC Chromatogram for 2-Me-C6H4CO11CF3 ([11C]2b)
[Condition B]
Radioactivity (arbitrary units)
UV absorbance at 254 nm (arbitrary units)
[11C]CHF3
11.050 min, 15.525%
Me
O
11CF3
Time (min)

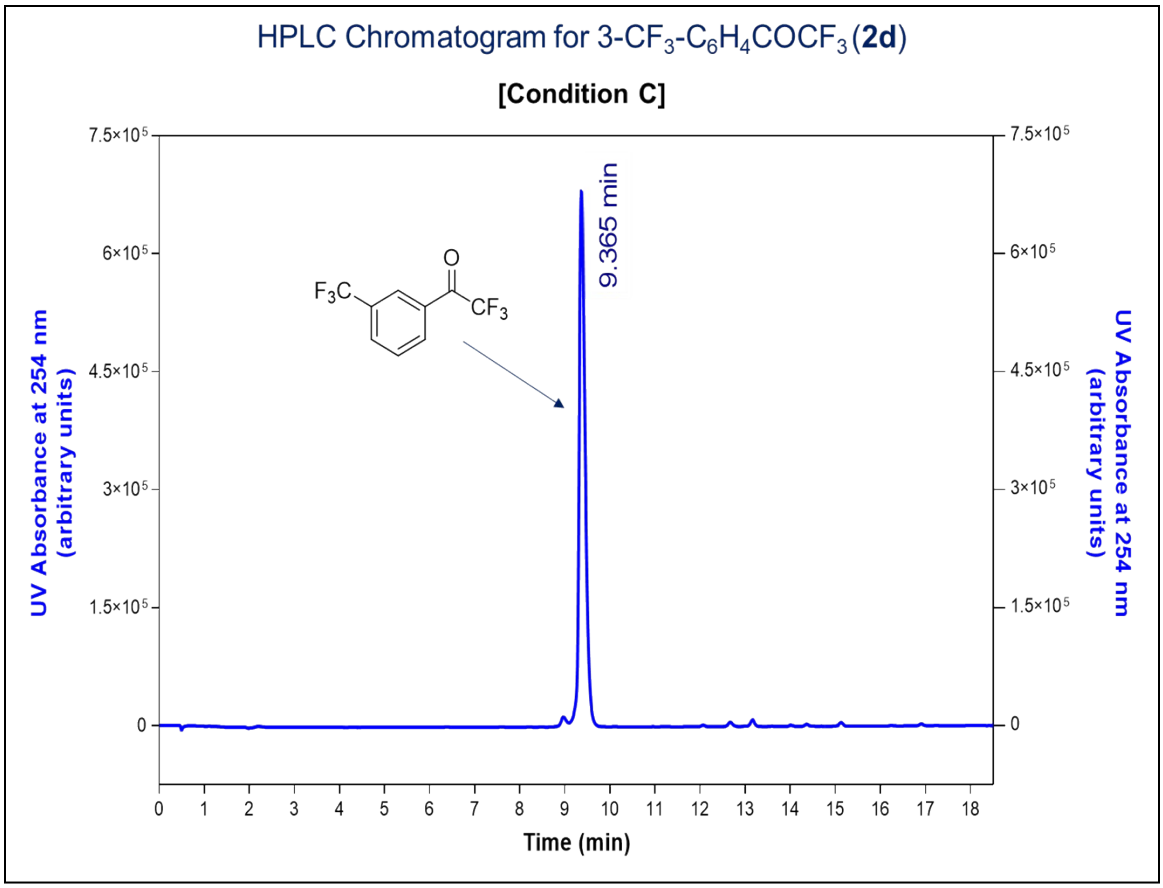

HPLC Chromatogram for 2-Me-C6H4COCF3 (2b)
[Condition B]
UV Absorbance at 254 nm (arbitrary units)
10.980 min
Me
O
CF3
Time (min)

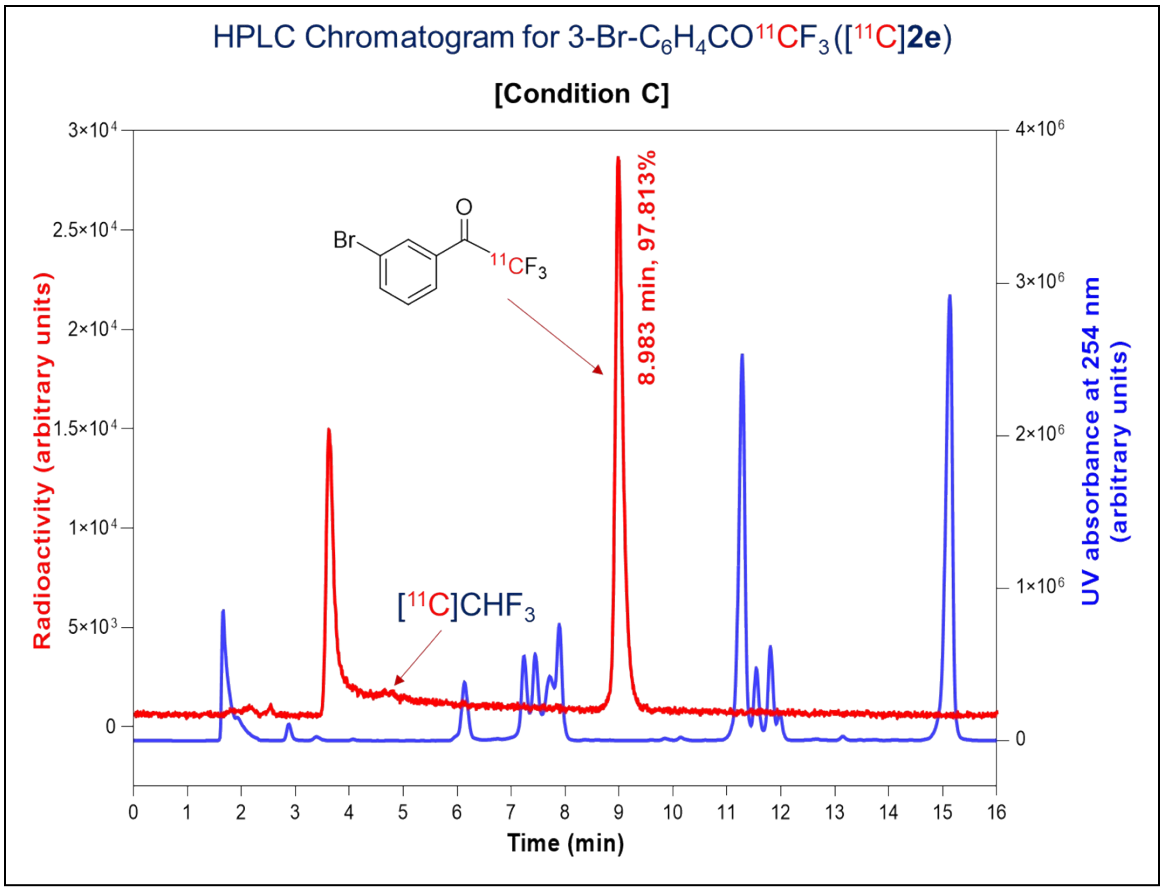

HPLC Chromatogram for 2-F-C6H4CO11CF3([11C]2c)
[Condition A]
Radioactivity (arbitrary units)
UV absorbance at 254 nm (arbitrary units)
Time (min)
10.008 min, 94.544%
[11C]CHF3
F
O
11CF3

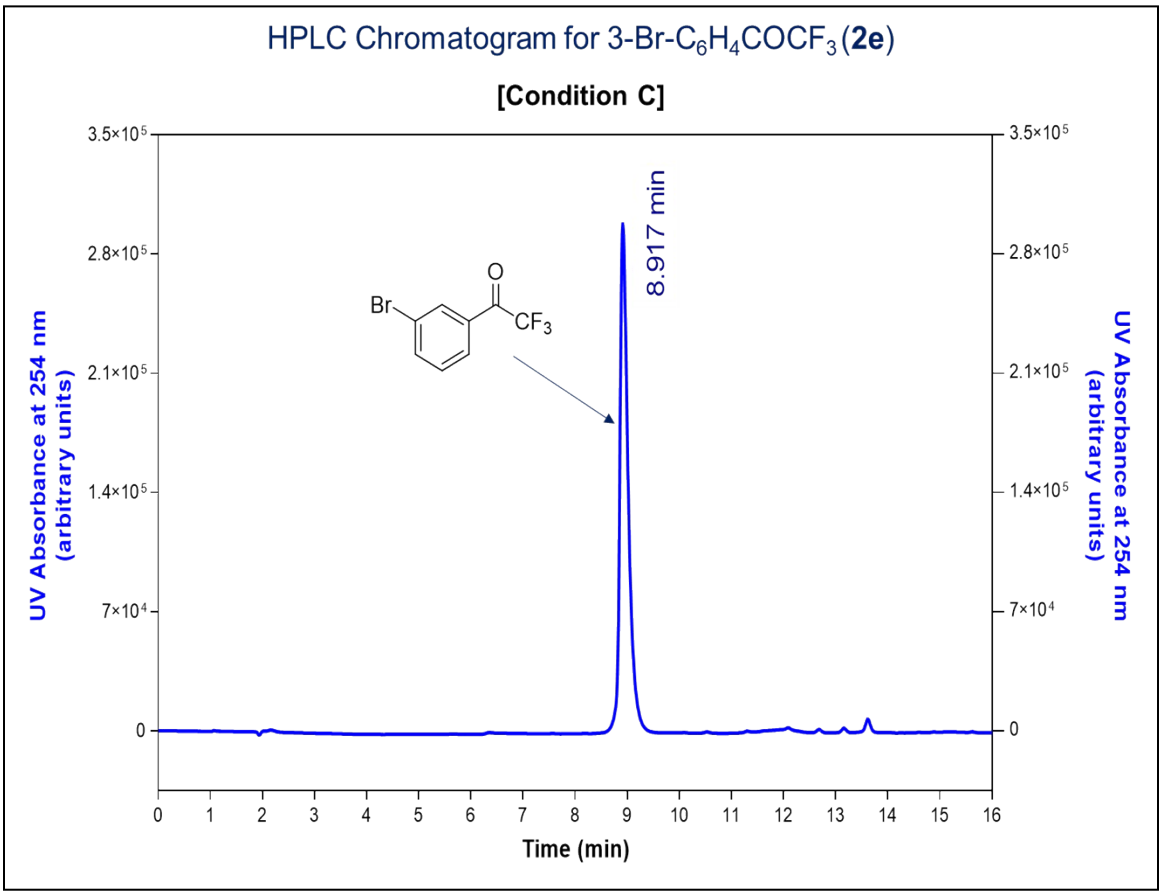

HPLC Chromatogram for 2-F-C6H4COCF3 (2c)
[Condition A]
UV Absorbance at 254 nm (arbitrary units)
UV Absorbance at 254 nm (arbitrary units)
Time (min)
9.867 min
F
O
CF3

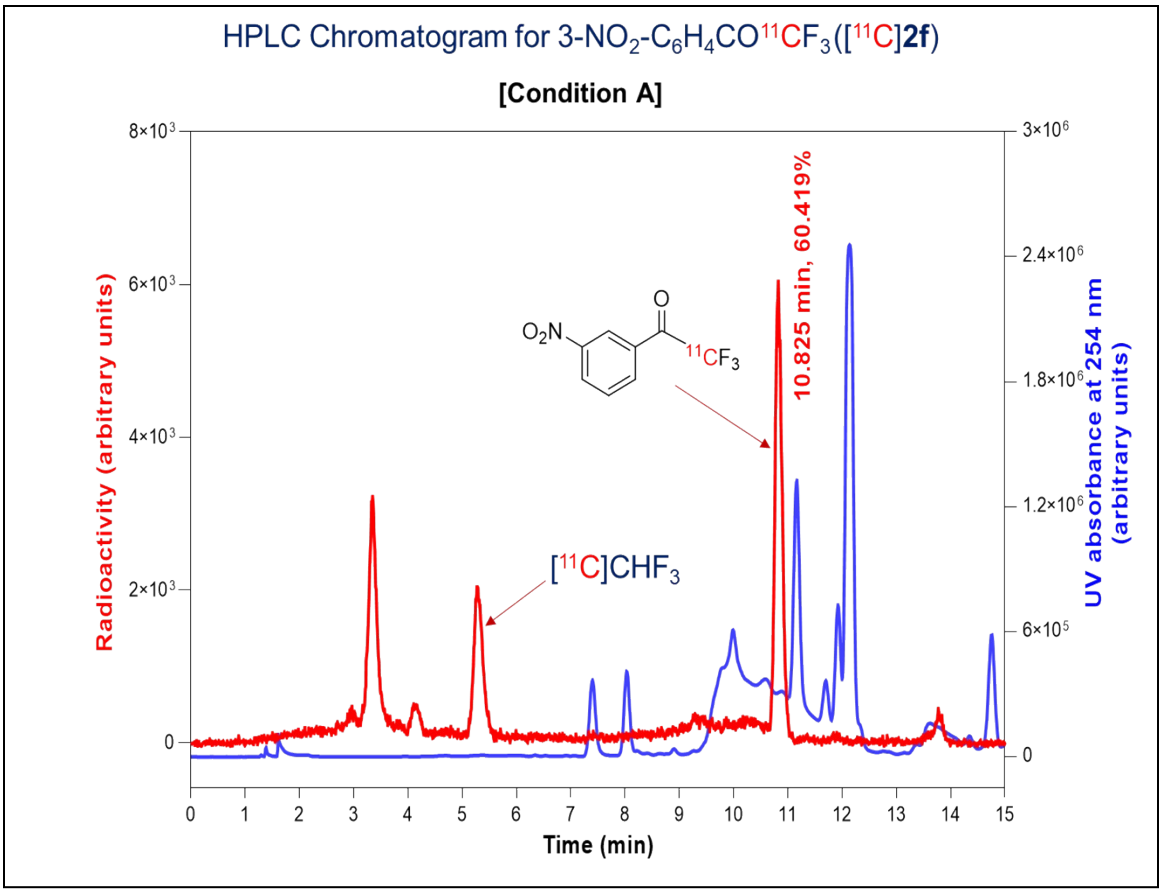

HPLC Chromatogram for 3-CF3-C6H4CO11CF3 ([11C]2d)
[Condition C]
Radioactivity (arbitrary units)
UV absorbance at 254 nm (arbitrary units)
Time (min)
9.492 min, 97.813%
[11C]CHF3
F3C
O
11CF3

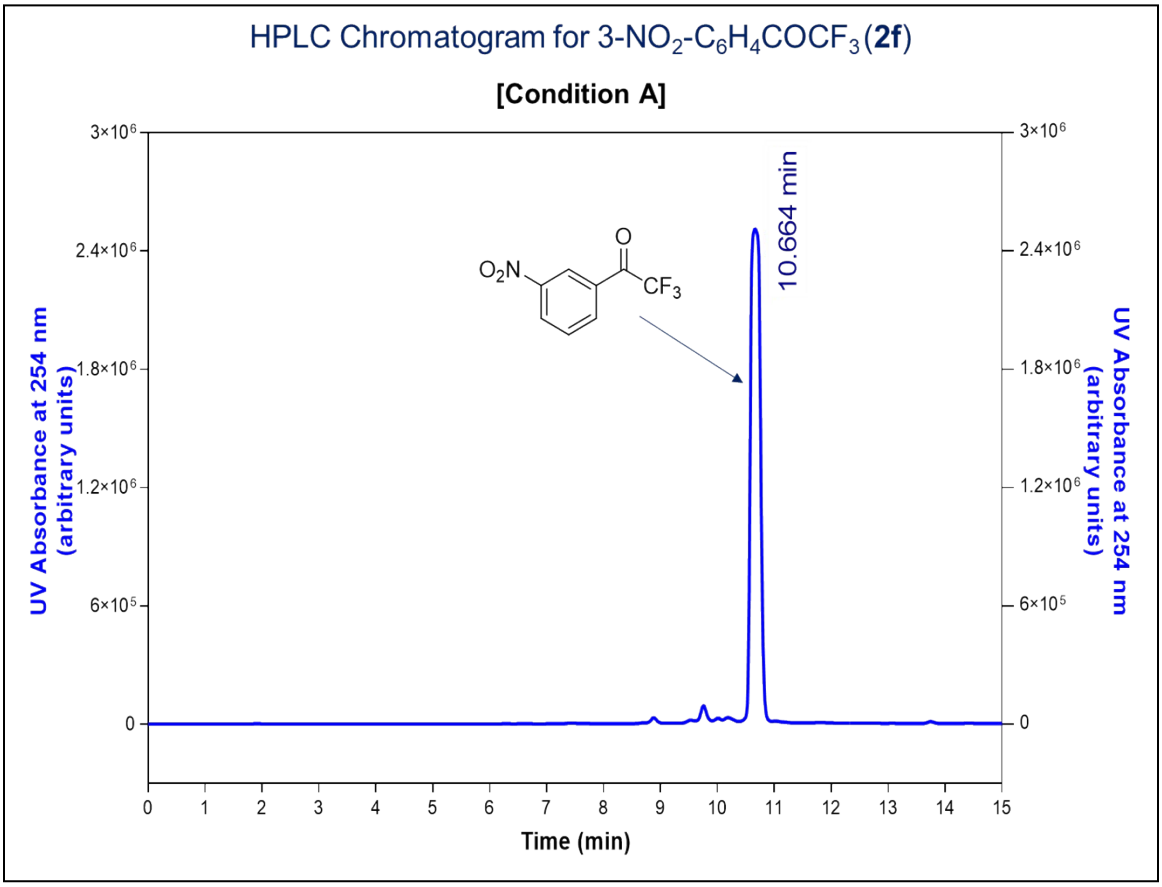

HPLC Chromatogram for 3-CF3-C6H4COCF218F ([18F]2d)
[Condition C]
Radioactivity (arbitrary units)
UV absorbance at 254 nm (arbitrary units)
Time (min)
9.517 min, 93.259%
CHF218F
F3C
O
CF218F

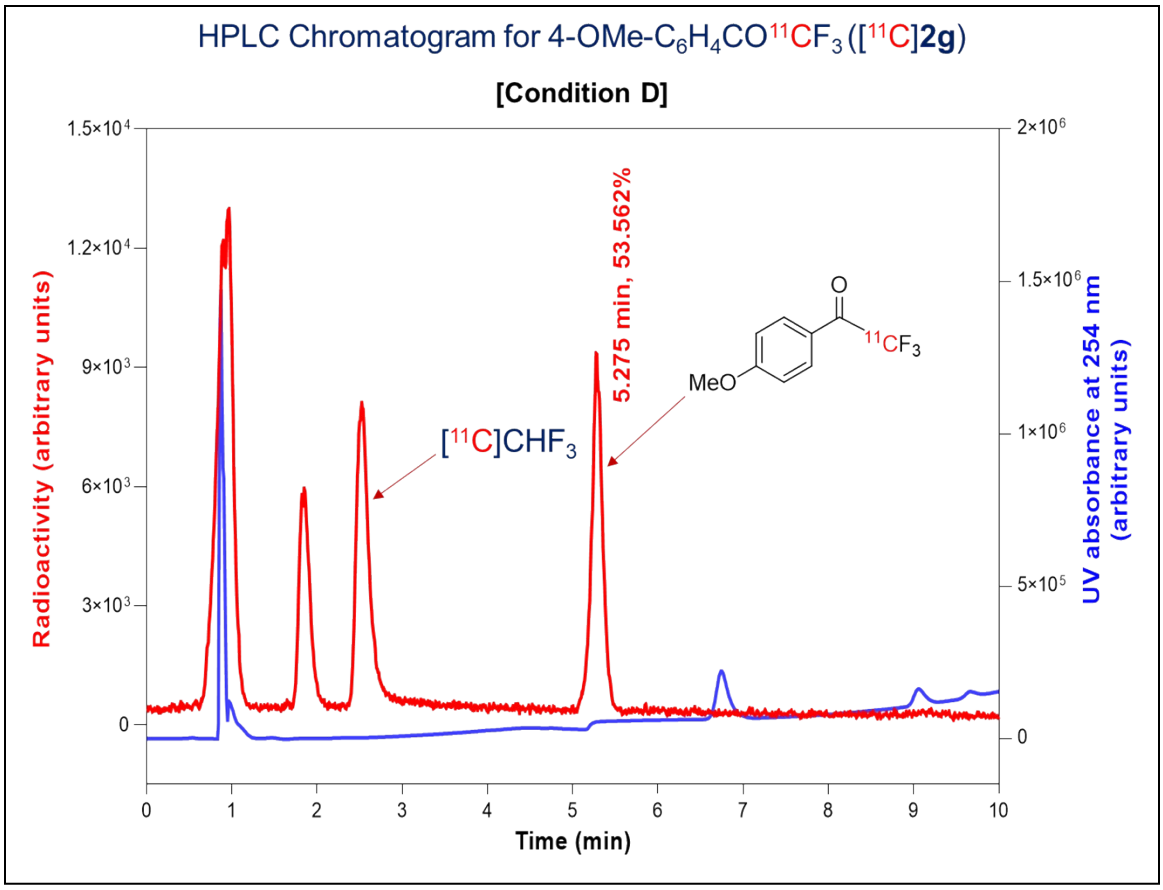

HPLC Chromatogram for 3-CF3-C6H4COCF3 (2d)
[Condition C]
9.365 min
F3C
O
CF3
UV Absorbance at 254 nm (arbitrary units)
Time (min)
7.5×10^5
6×10^5
4.5×10^5
3×10^5
1.5×10^5
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

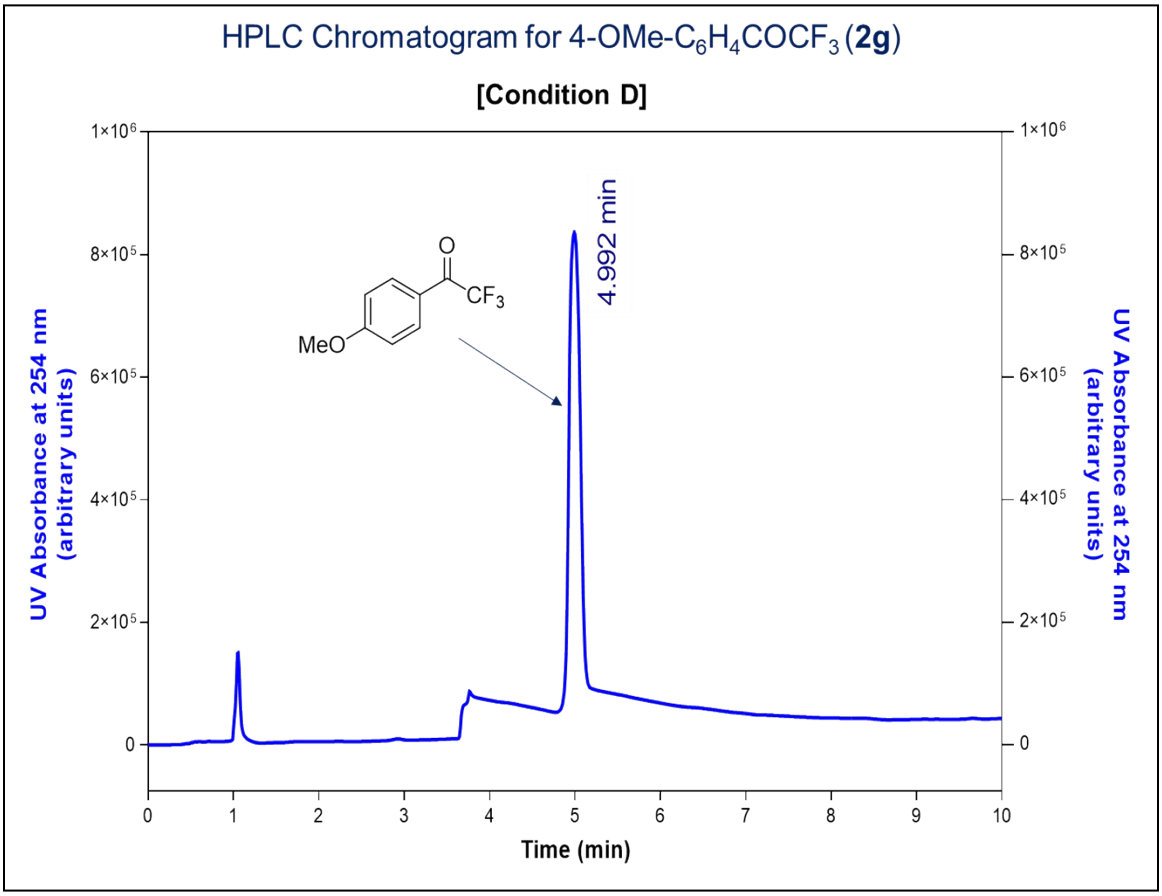

HPLC Chromatogram for 3-Br-C6H4CO11CF3([11C]2e)
[Condition C]
Radioactivity (arbitrary units)
UV absorbance at 254 nm (arbitrary units)
8.983 min, 97.813%
[11C]CHF3
Br
O
11CF3
Time (min)

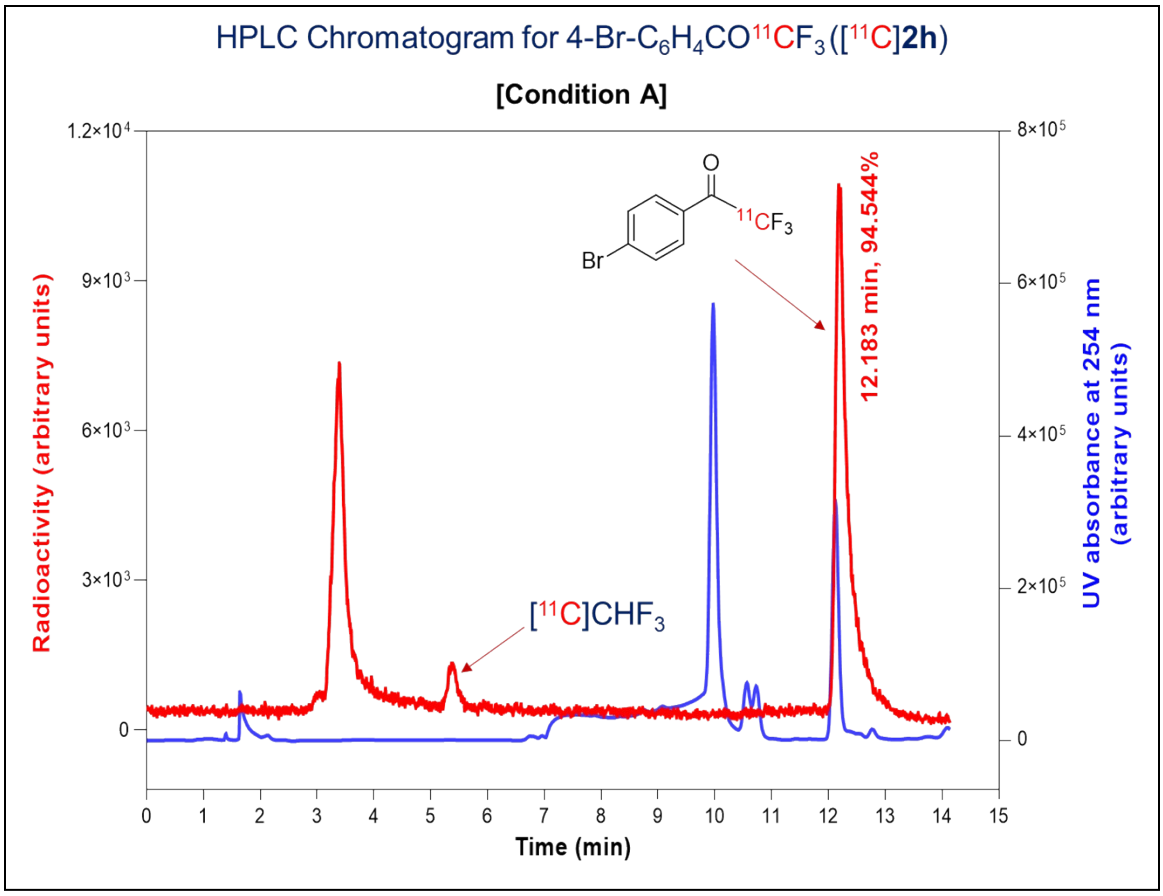

HPLC Chromatogram for 3-Br-C6H4COCF3(2e)
[Condition C]
UV Absorbance at 254 nm (arbitrary units)
8.917 min
Br
O
CF3
Time (min)

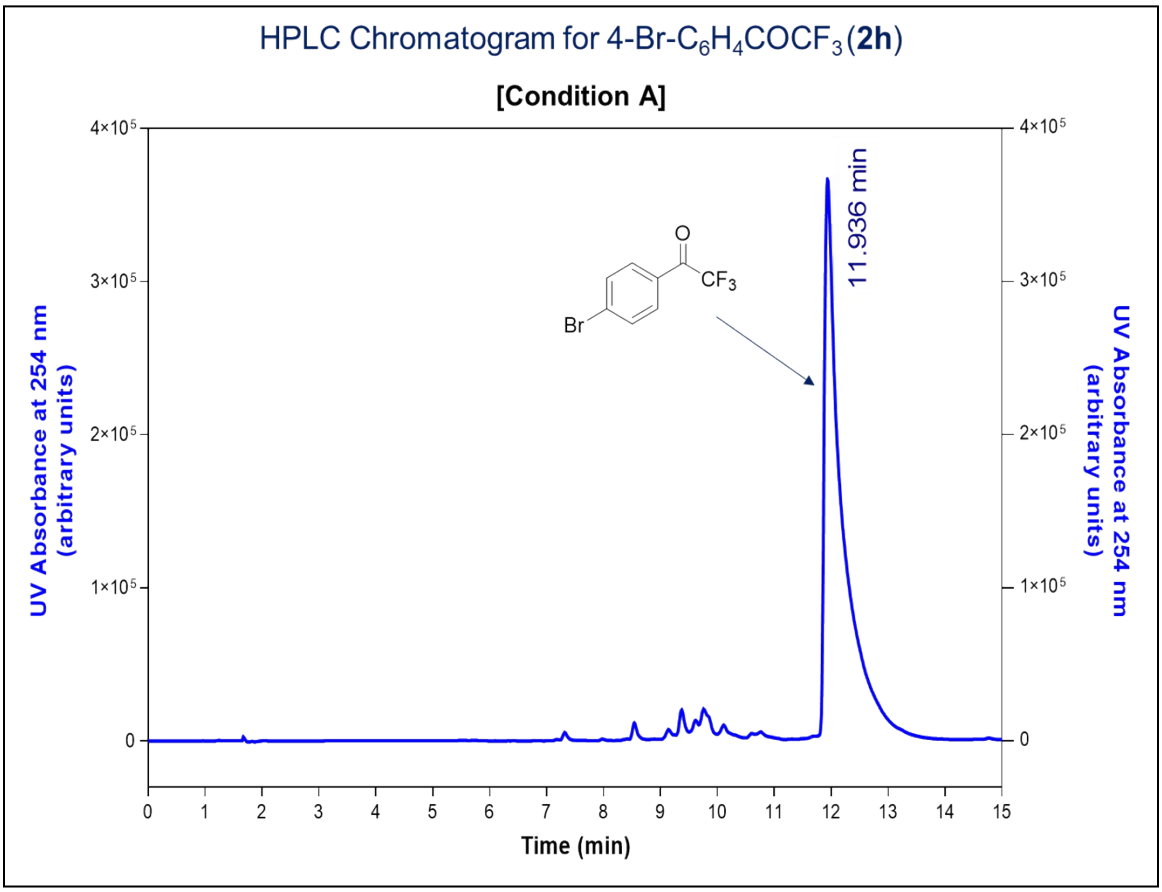

HPLC Chromatogram for 3-NO2-C6H4CO11CF3([11C]2f)
[Condition A]
Radioactivity (arbitrary units)
UV absorbance at 254 nm (arbitrary units)
Time (min)
10.825 min, 60.419%
[11C]CHF3
O2N
O
11CF3

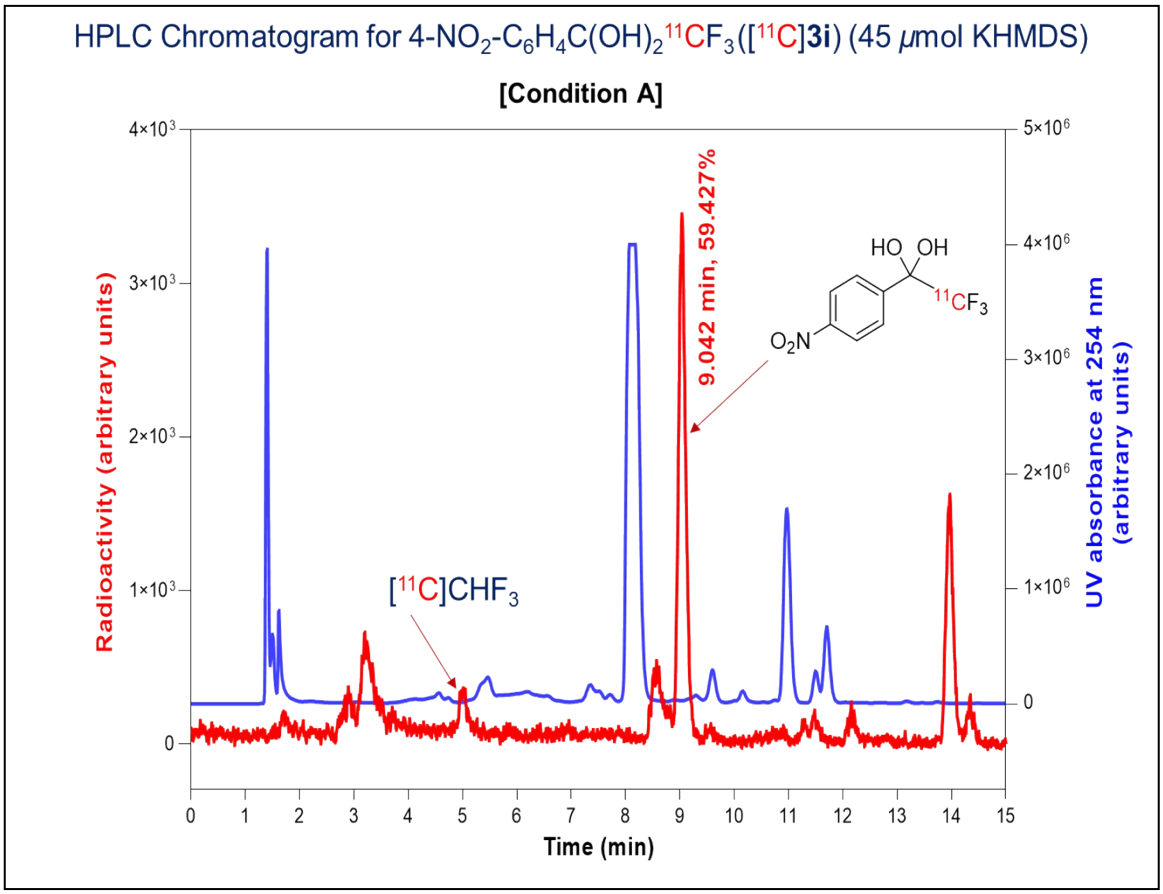

HPLC Chromatogram for 3-NO2-C6H4COCF3(2f)
[Condition A]
UV Absorbance at 254 nm (arbitrary units)
UV Absorbance at 254 nm (arbitrary units)
Time (min)
10.664 min
O2N
O
CF3

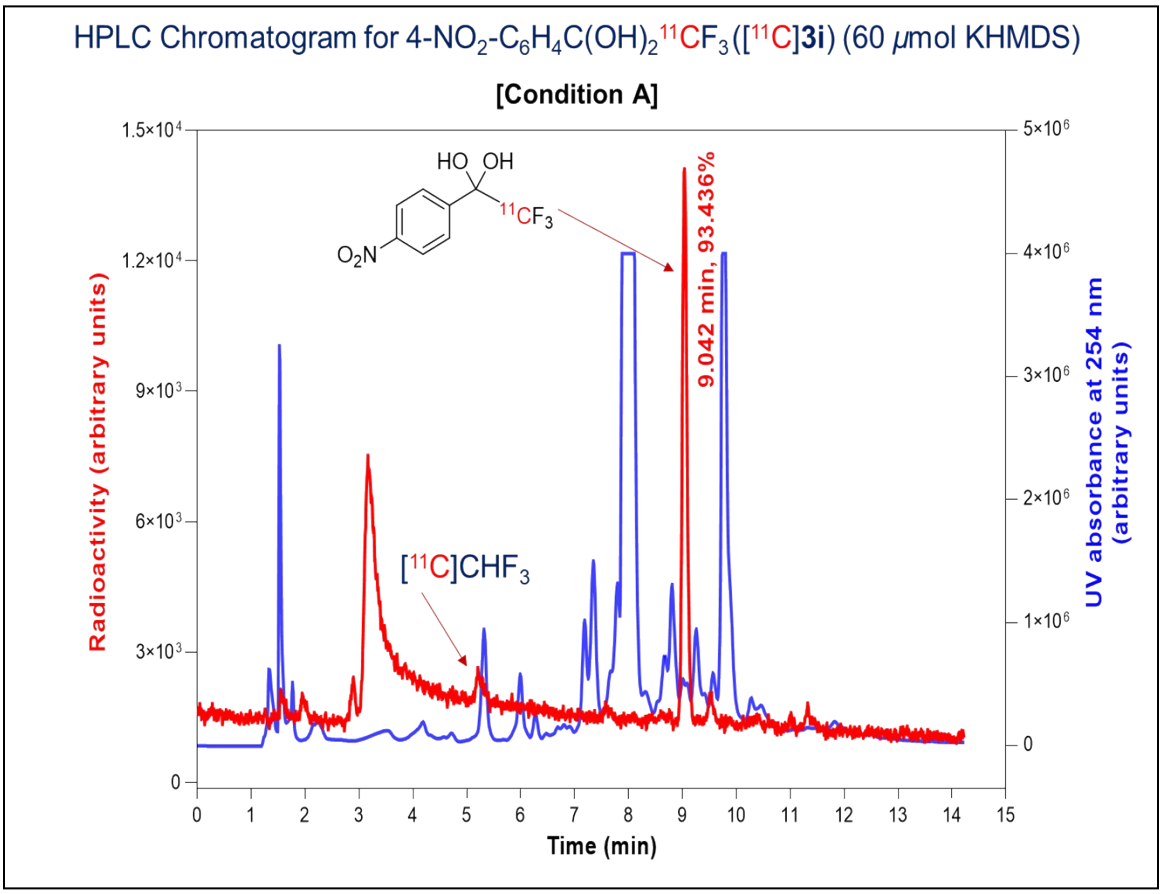

HPLC Chromatogram for 4-OMe-C6H4CO11CF3 ([11C]2g)
[Condition D]
Radioactivity (arbitrary units)
UV absorbance at 254 nm (arbitrary units)
Time (min)
5.275 min, 53.562%
[11C]CHF3
MeO
11CF3
O

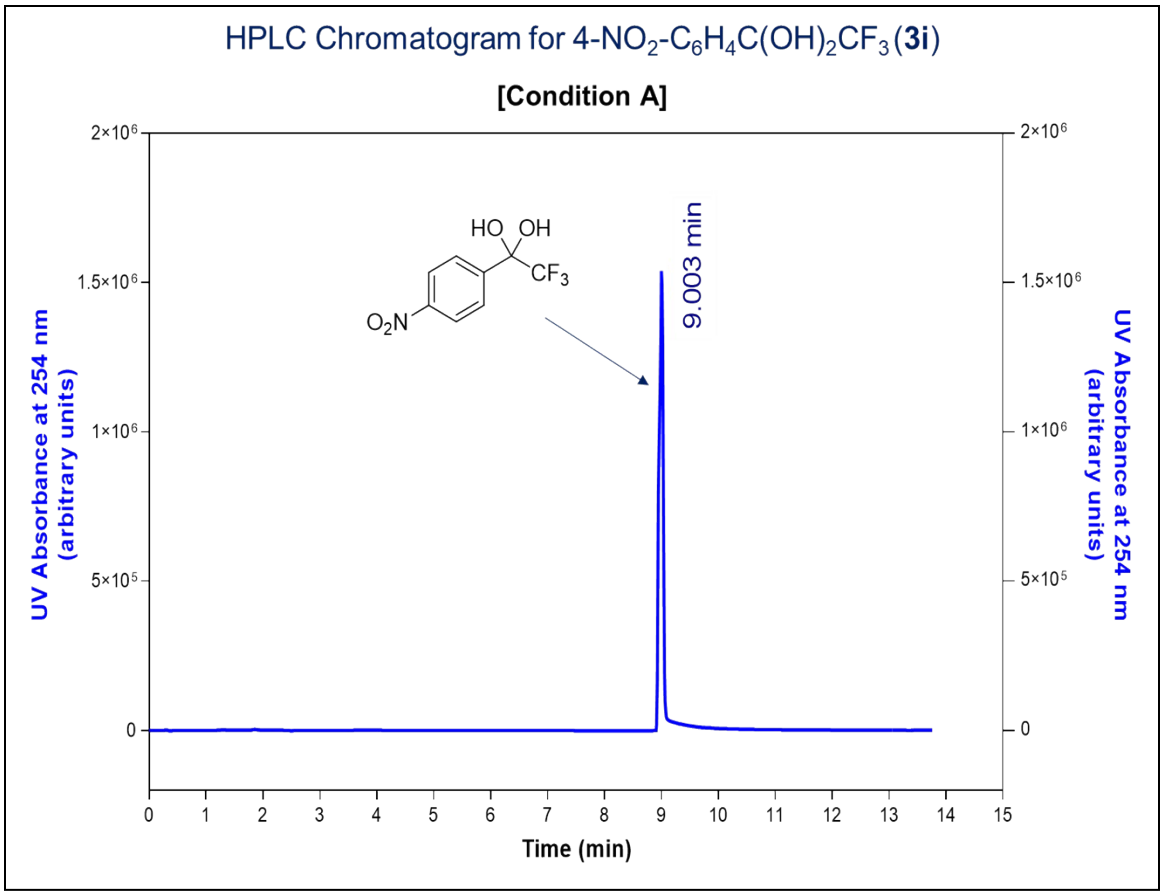

HPLC Chromatogram for 4-OMe-C6H4COCF3 (2g)
[Condition D]
UV Absorbance at 254 nm (arbitrary units)
UV Absorbance at 254 nm (arbitrary units)
Time (min)
4.992 min
MeO
CF3
O

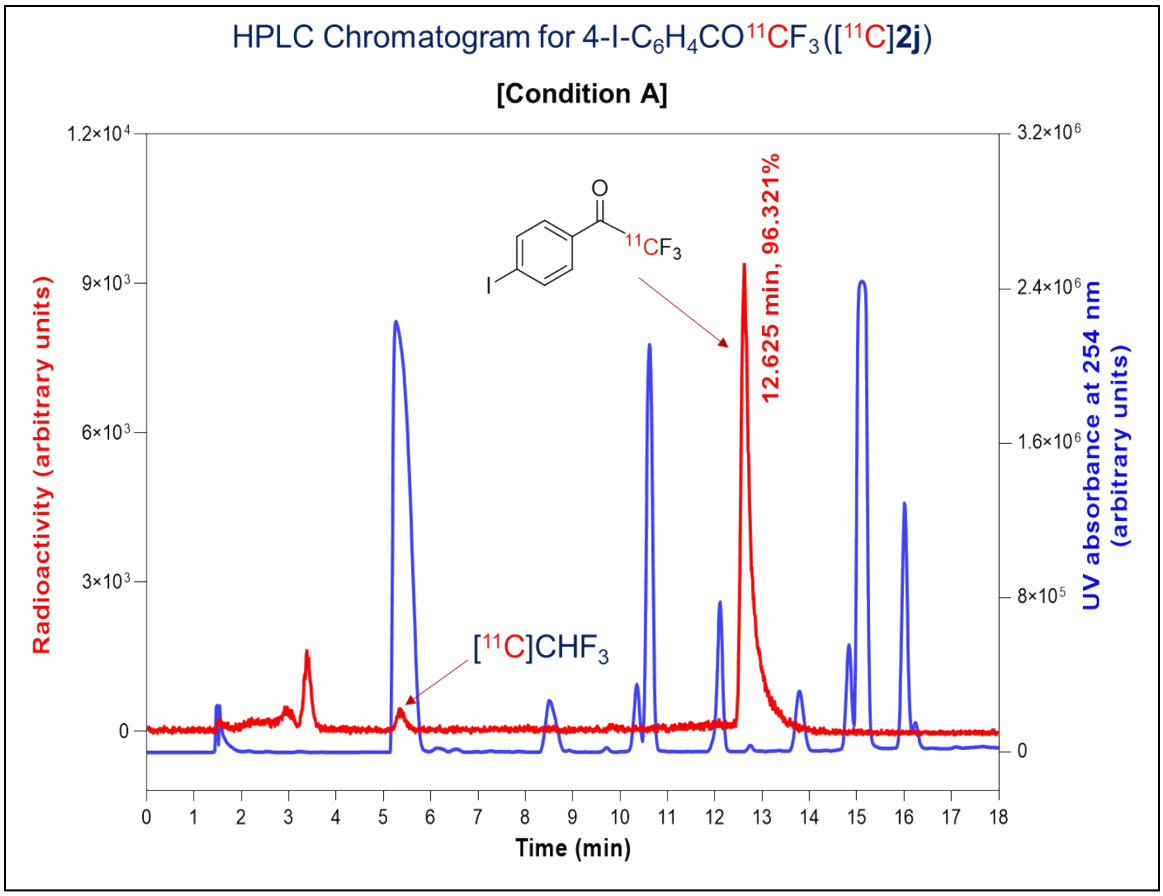

HPLC Chromatogram for 4-Br-C6H4CO11CF3([11C]2h)
[Condition A]
Radioactivity (arbitrary units)
UV absorbance at 254 nm (arbitrary units)
Time (min)
12.183 min, 94.544%
[11C]CHF3
Br
11CF3

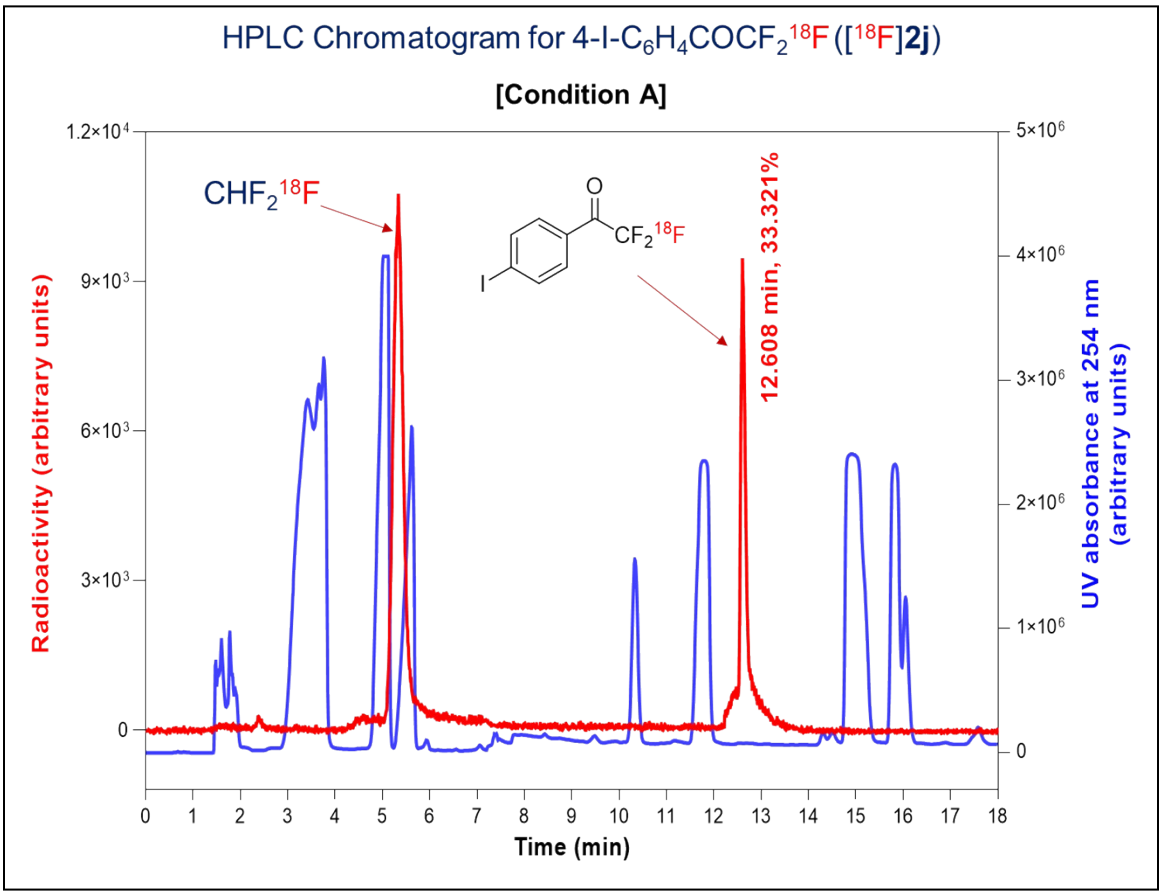

HPLC Chromatogram for 4-Br-C6H4COCF3(2h)
[Condition A]
UV Absorbance at 254 nm (arbitrary units)
UV Absorbance at 254 nm (arbitrary units)
Time (min)
11.936 min
Br
CF3

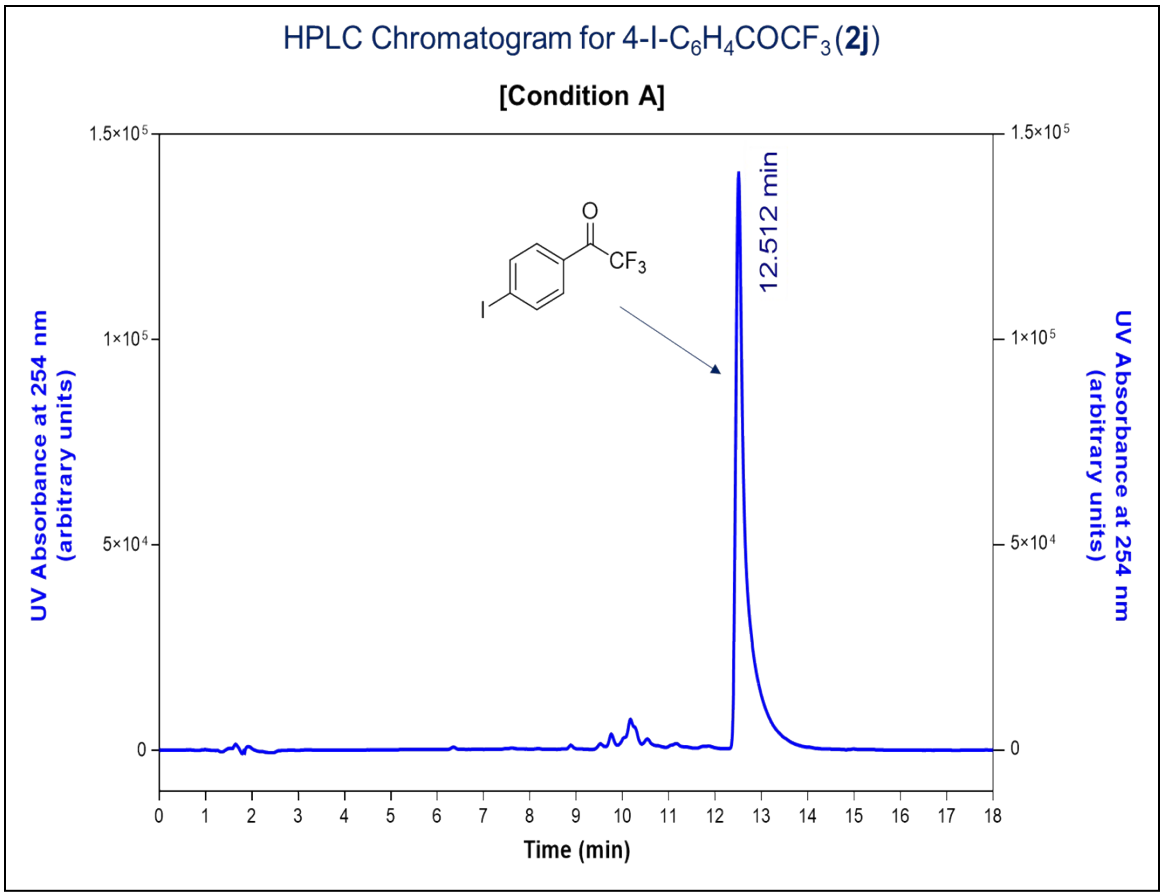

HPLC Chromatogram for 4-NO2-C6H4C(OH)2 11CF3 ([11C]3i) (45 μmol KHMDS)
[Condition A]
Radioactivity (arbitrary units)
UV absorbance at 254 nm (arbitrary units)
Time (min)
9.042 min, 59.427%
[11C]CHF3
HO OH
11CF3
O2N

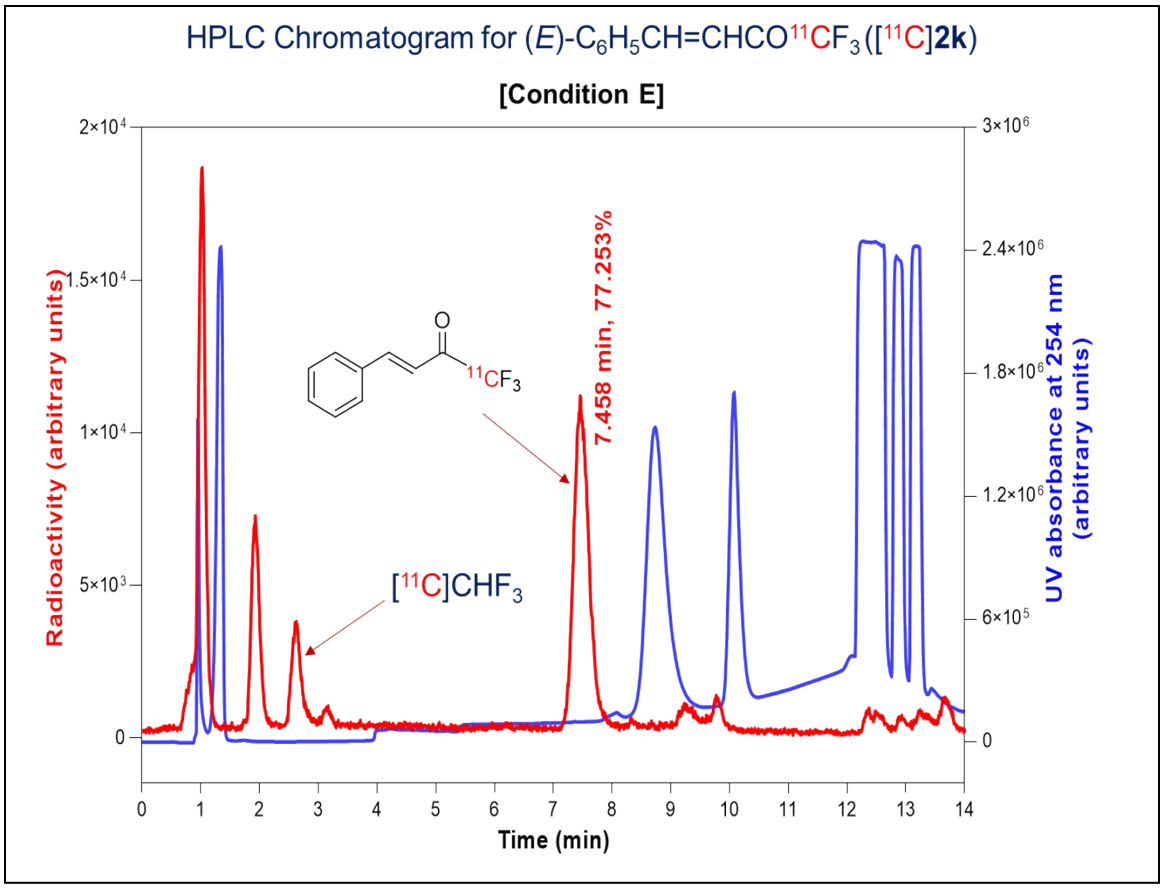

HPLC Chromatogram for 4-NO2-C6H4C(OH)2 11CF3 ([11C]3i) (60 μmol KHMDS)
[Condition A]
Radioactivity (arbitrary units)
UV absorbance at 254 nm (arbitrary units)
Time (min)
9.042 min, 93.436%
[11C]CHF3
HO OH
11CF3
O2N

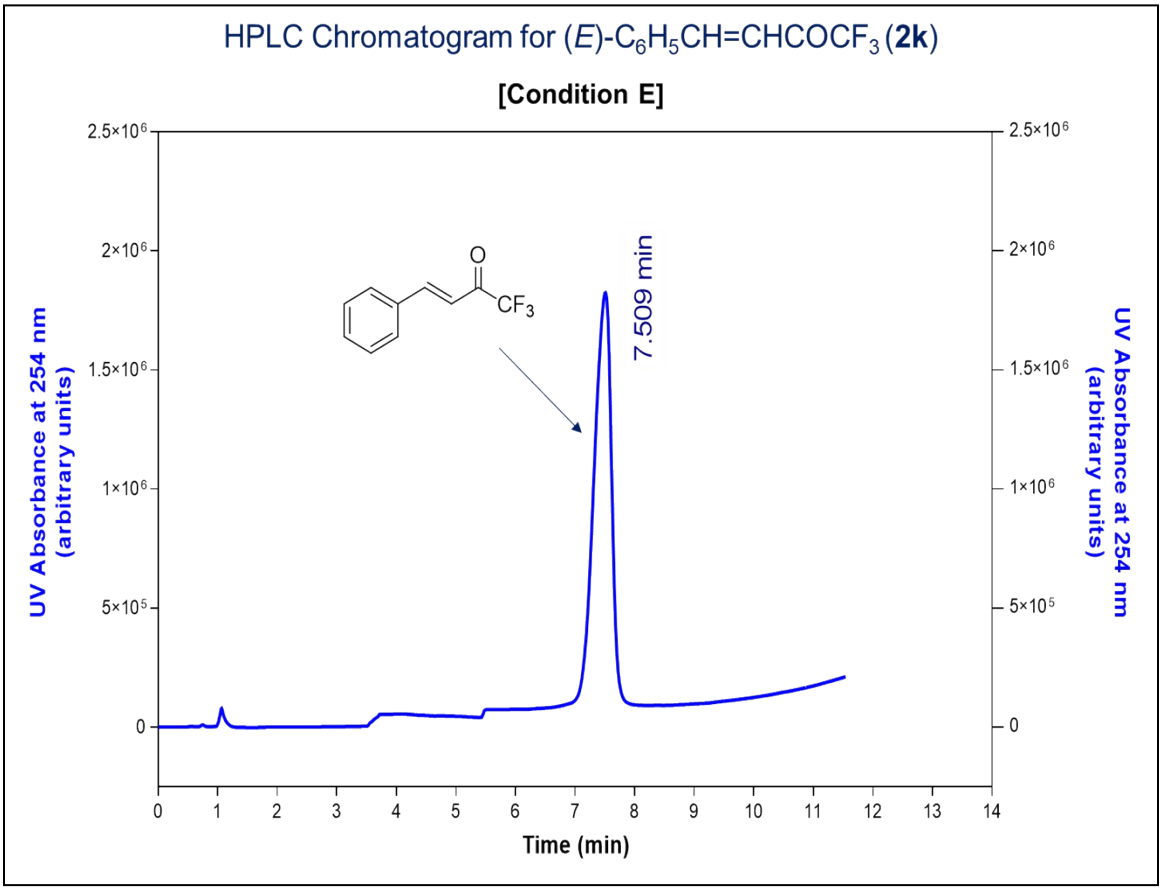

HPLC Chromatogram for 4-NO2-C6H4C(OH)2CF3 (3i)
[Condition A]
UV Absorbance at 254 nm (arbitrary units)
2×10^6
1.5×10^6
1×10^6
5×10^5
0
9.003 min
HO OH
CF3
O2N
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Time (min)

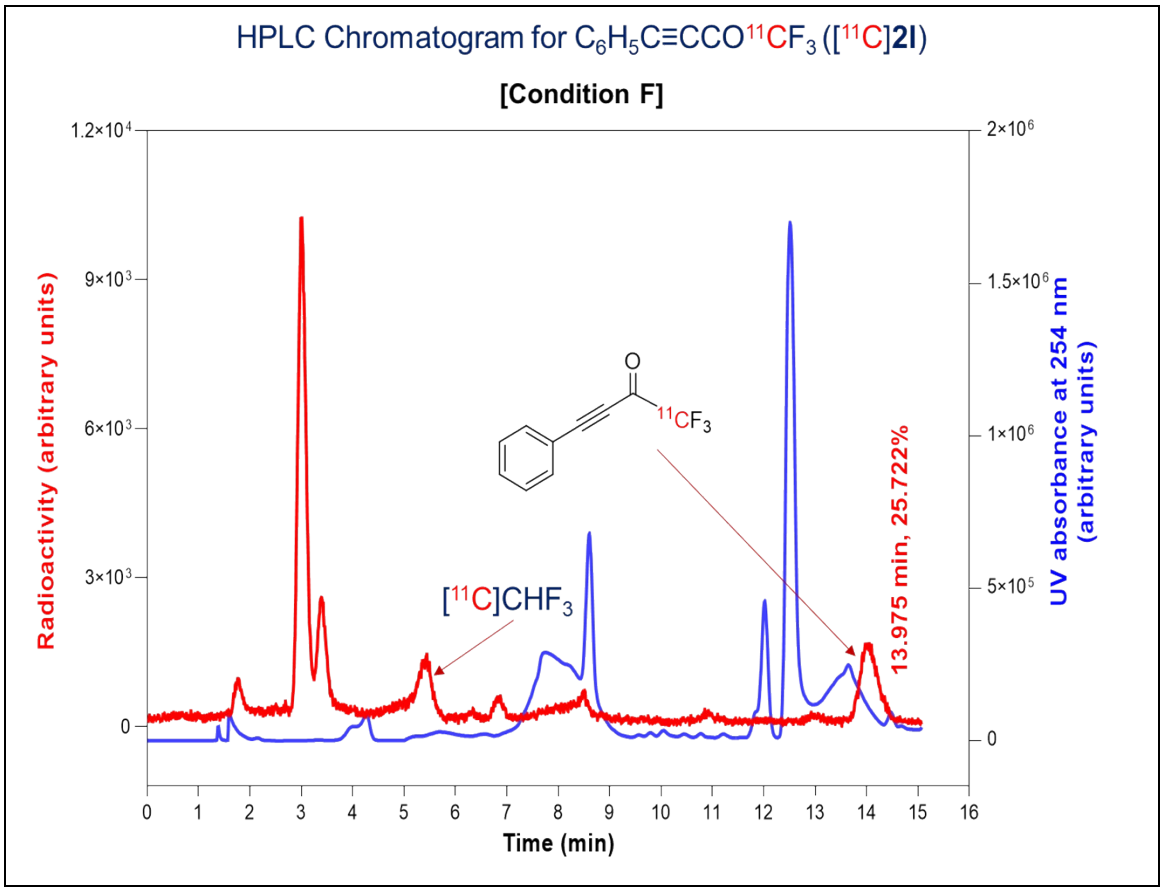

HPLC Chromatogram for 4-I-C6H4CO11CF3 ([11C]2j)
[Condition A]
Radioactivity (arbitrary units)
UV absorbance at 254 nm (arbitrary units)
Time (min)
12.625 min, 96.321%
[11C]CHF3
11CF3

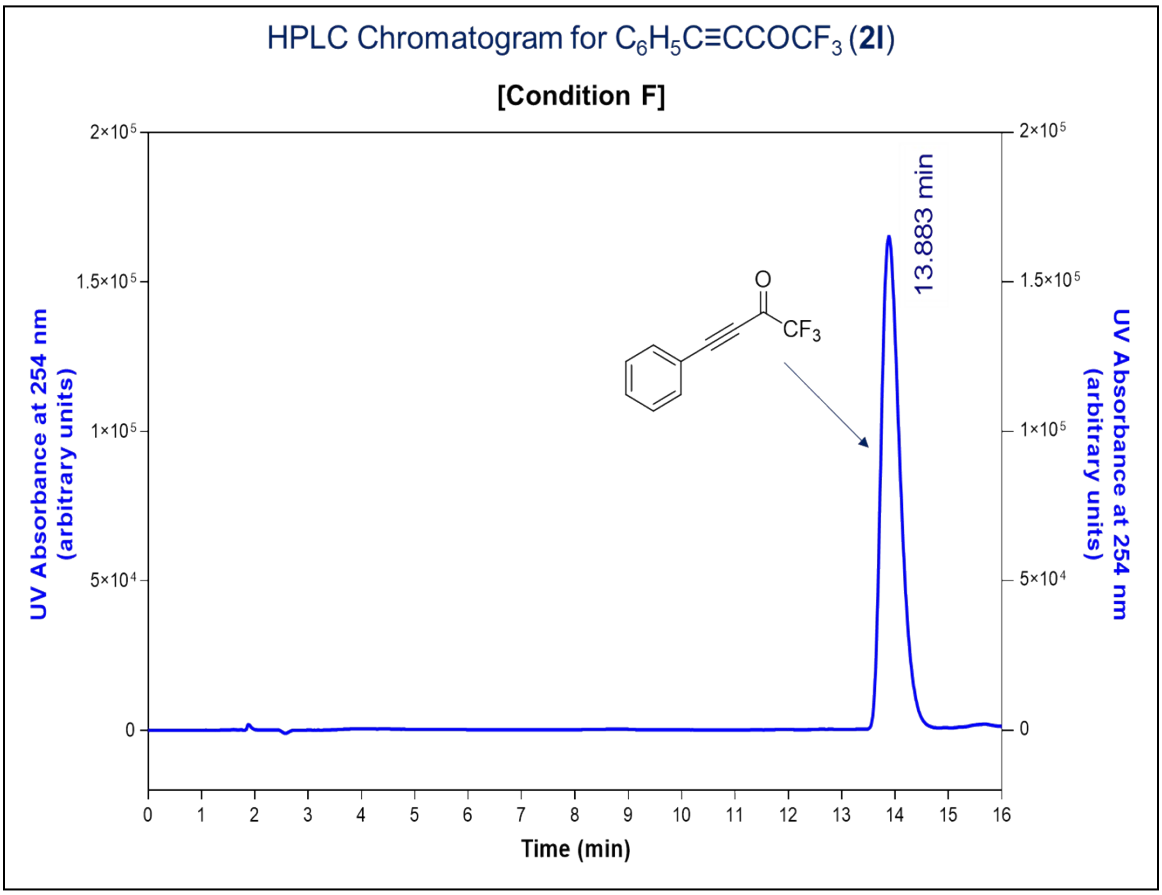

HPLC Chromatogram for 4-I-C6H4COCF218F ([18F]2j)
[Condition A]
Radioactivity (arbitrary units)
UV absorbance at 254 nm (arbitrary units)
Time (min)
12.608 min, 33.321%
CHF218F
CF218F

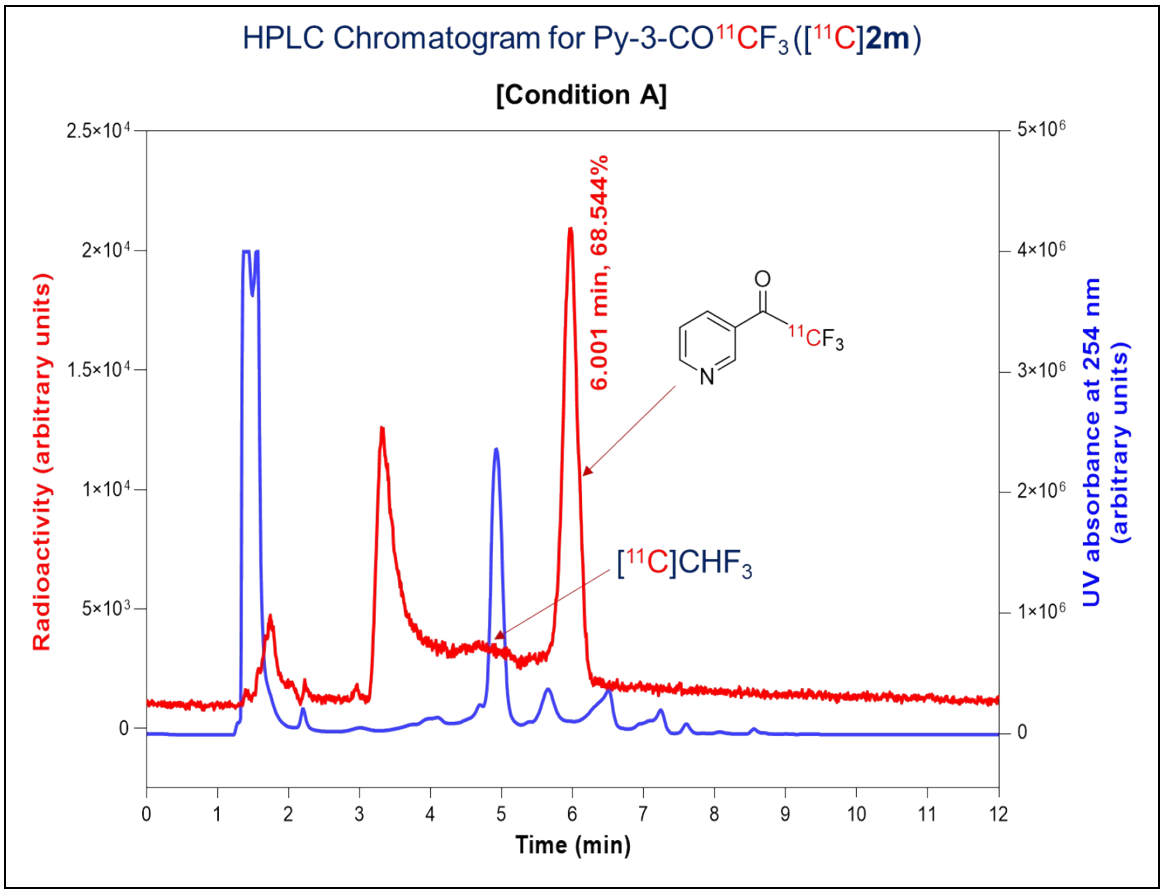

HPLC Chromatogram for 4-I-C6H4COCF3 (2j)
[Condition A]
12.512 min
UV Absorbance at 254 nm (arbitrary units)
Time (min)

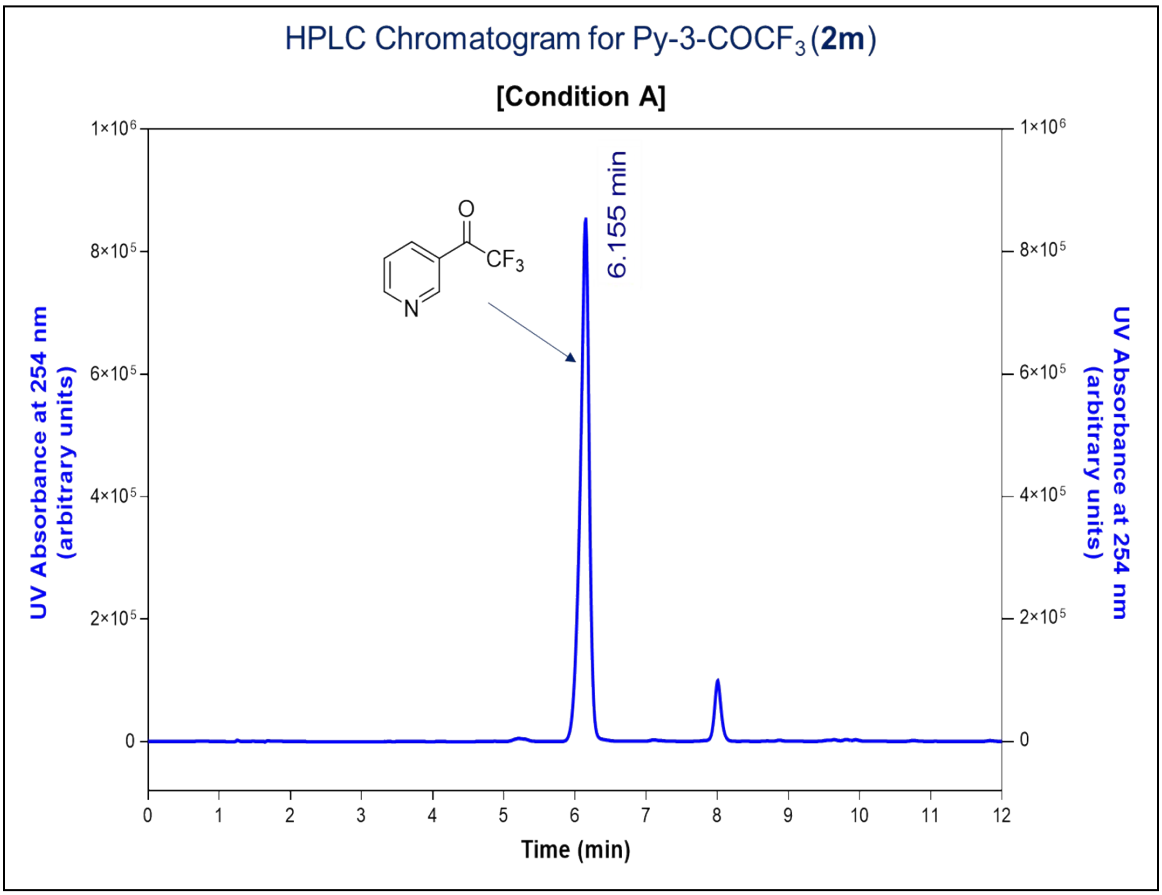

HPLC Chromatogram for (E)-C6H5CH=CHCO11CF3 ([11C]2k)
[Condition E]
Radioactivity (arbitrary units)
UV absorbance at 254 nm (arbitrary units)
7.458 min, 77.253%
[11C]CHF3
Time (min)

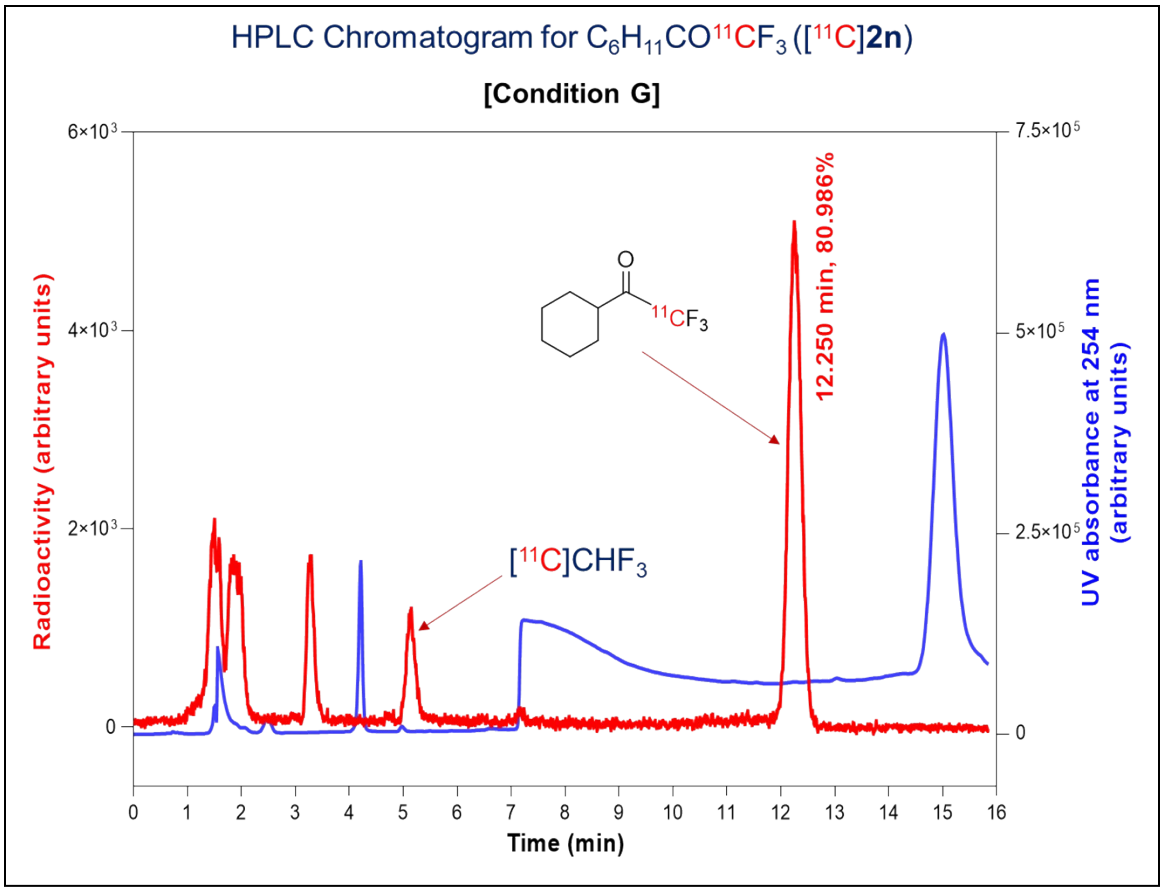

HPLC Chromatogram for (E)-C6H5CH=CHCOCF3 (2k)
[Condition E]
UV Absorbance at 254 nm (arbitrary units)
7.509 min
Time (min)

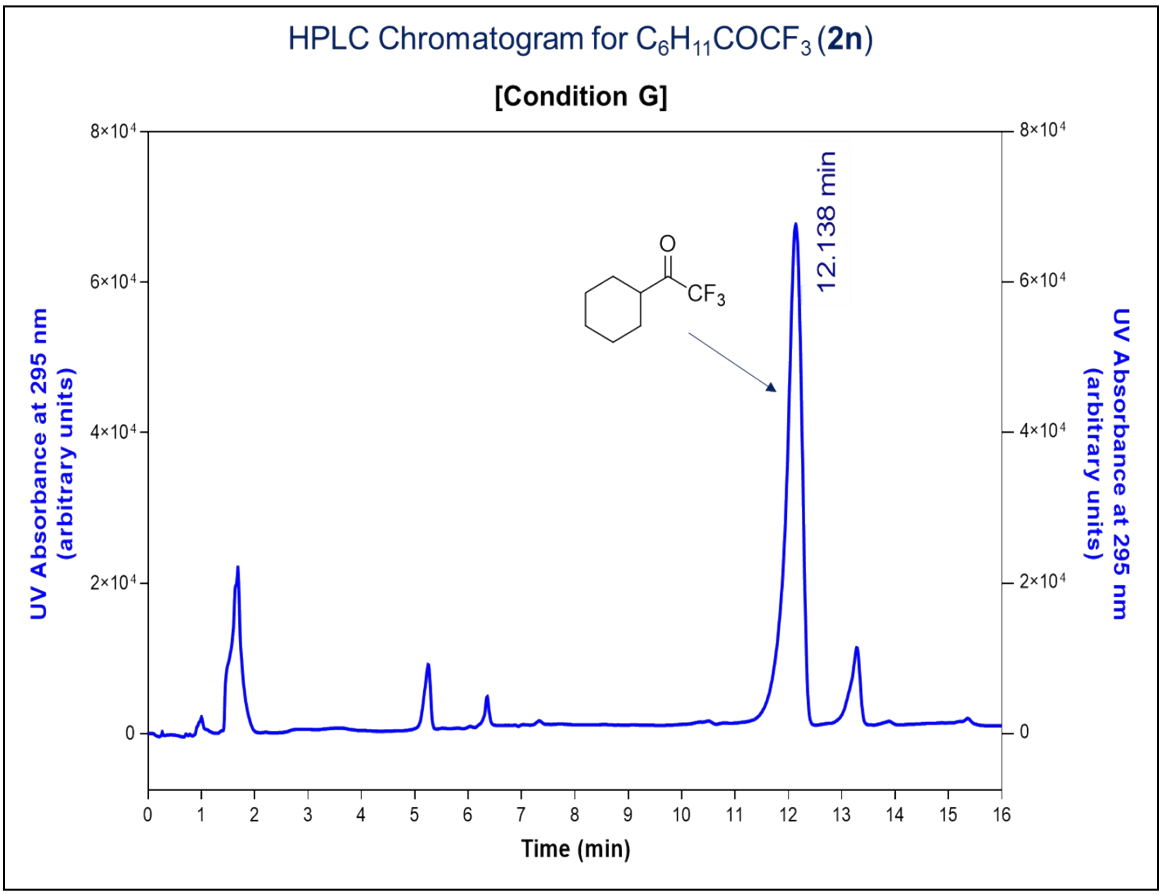

HPLC Chromatogram for $C_6H_5C{\equiv}CCO^{11}CF_3$ ([^{11}C]**2l**)
[Condition F]
Radioactivity (arbitrary units)
UV absorbance at 254 nm (arbitrary units)
[^{11}C]CHF_3
13.975 min, 25.722%
Time (min)

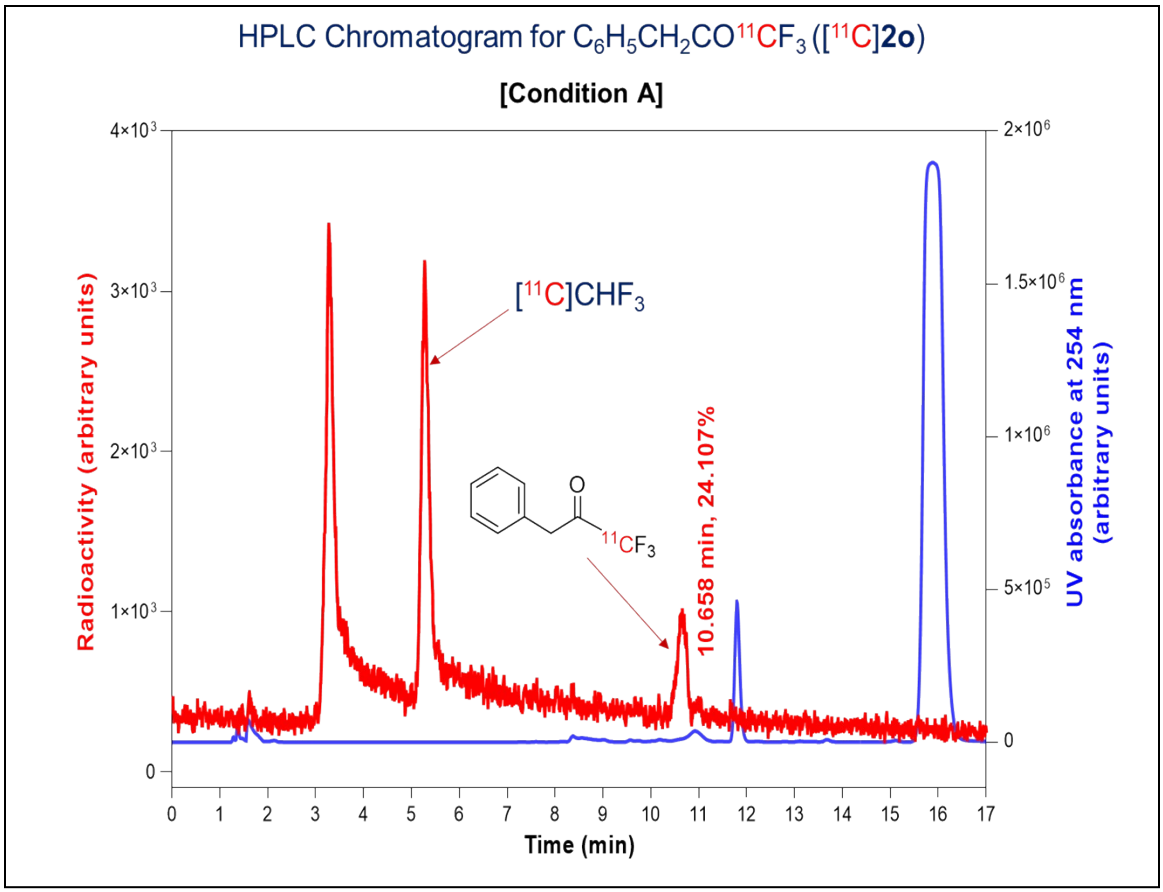

HPLC Chromatogram for $C_6H_5C{\equiv}CCOCF_3$ (**2l**)
[Condition F]
UV Absorbance at 254 nm (arbitrary units)
13.883 min
Time (min)

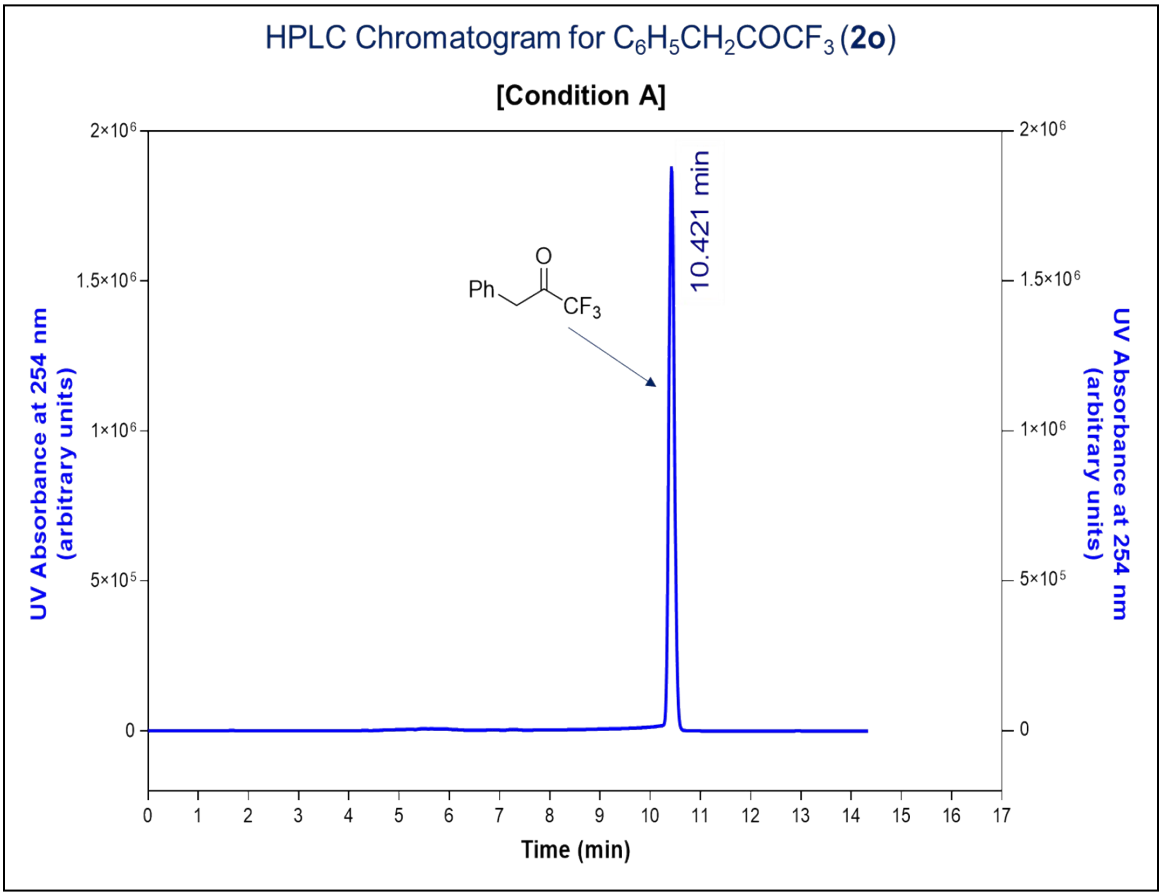

HPLC Chromatogram for Py-3-CO11CF3([11C]2m)
[Condition A]
Radioactivity (arbitrary units)
UV absorbance at 254 nm (arbitrary units)
6.001 min, 68.544%
[11C]CHF3
Time (min)


HPLC Chromatogram for Py-3-COCF3(2m)
[Condition A]
UV Absorbance at 254 nm (arbitrary units)
6.155 min
Time (min)


HPLC Chromatogram for $C_6H_{11}CO^{11}CF_3$ ([^{11}C]**2n**)
[Condition G]
Radioactivity (arbitrary units)
UV absorbance at 254 nm (arbitrary units)
12.250 min, 80.986%
[^{11}C]CHF$_3$
Time (min)


HPLC Chromatogram for $C_6H_{11}COCF_3$ (**2n**)
[Condition G]
UV Absorbance at 295 nm (arbitrary units)
12.138 min
Time (min)


HPLC Chromatogram for $C_6H_5CH_2CO^{11}CF_3$ ([^{11}C]**2o**)
[Condition A]
Radioactivity (arbitrary units)
UV absorbance at 254 nm (arbitrary units)
[^{11}C]CHF_3
10.658 min, 24.107%
$^{11}CF_3$
Time (min)


HPLC Chromatogram for $C_6H_5CH_2COCF_3$ (**2o**)
[Condition A]
UV Absorbance at 254 nm (arbitrary units)
10.421 min
Ph
CF_3
Time (min)

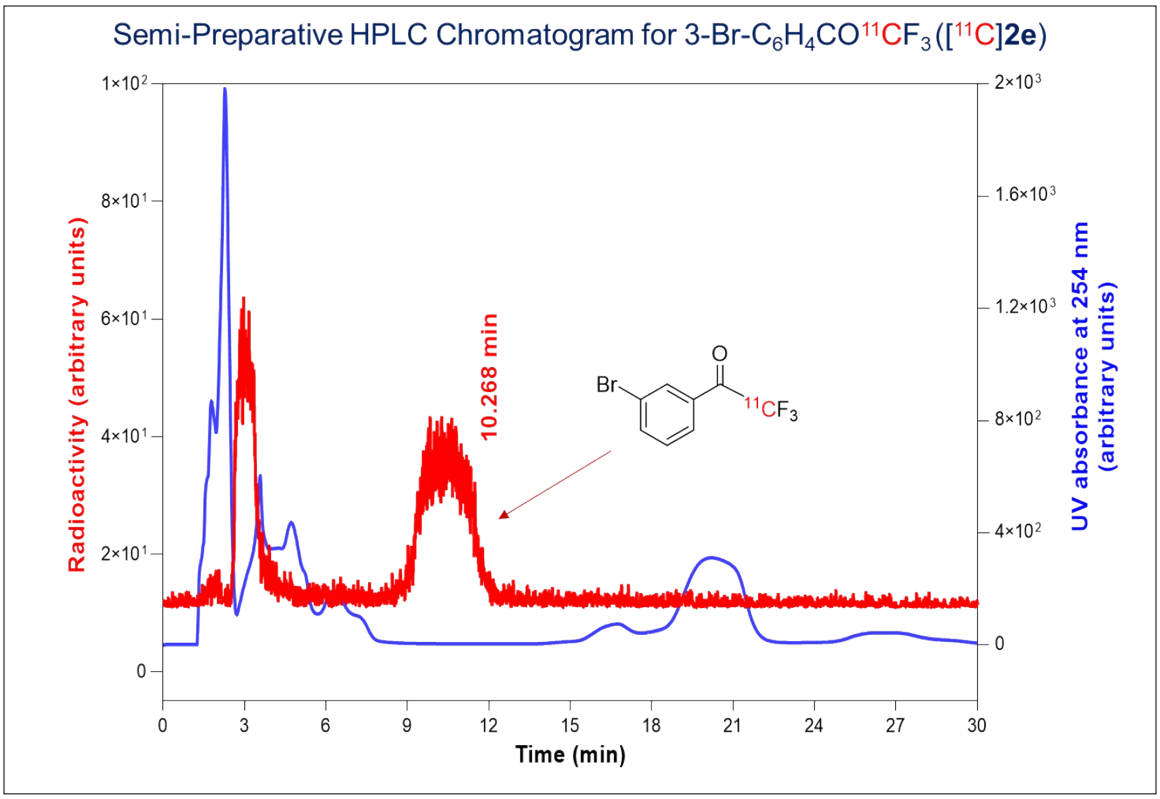
Semi-Preparative HPLC Chromatogram for [^{11}C]2e

HPLC Conditions:

Column: XTerra RP_{18}, 10 μm, 7.8 × 300 mm, i.d.; Waters Corp.

Mobile Phase: 35% MeCN (B)–65% H_2O (A), isocratic, 6.0 mL/min flow rate.

Detection: Absorbance at 254 nm.



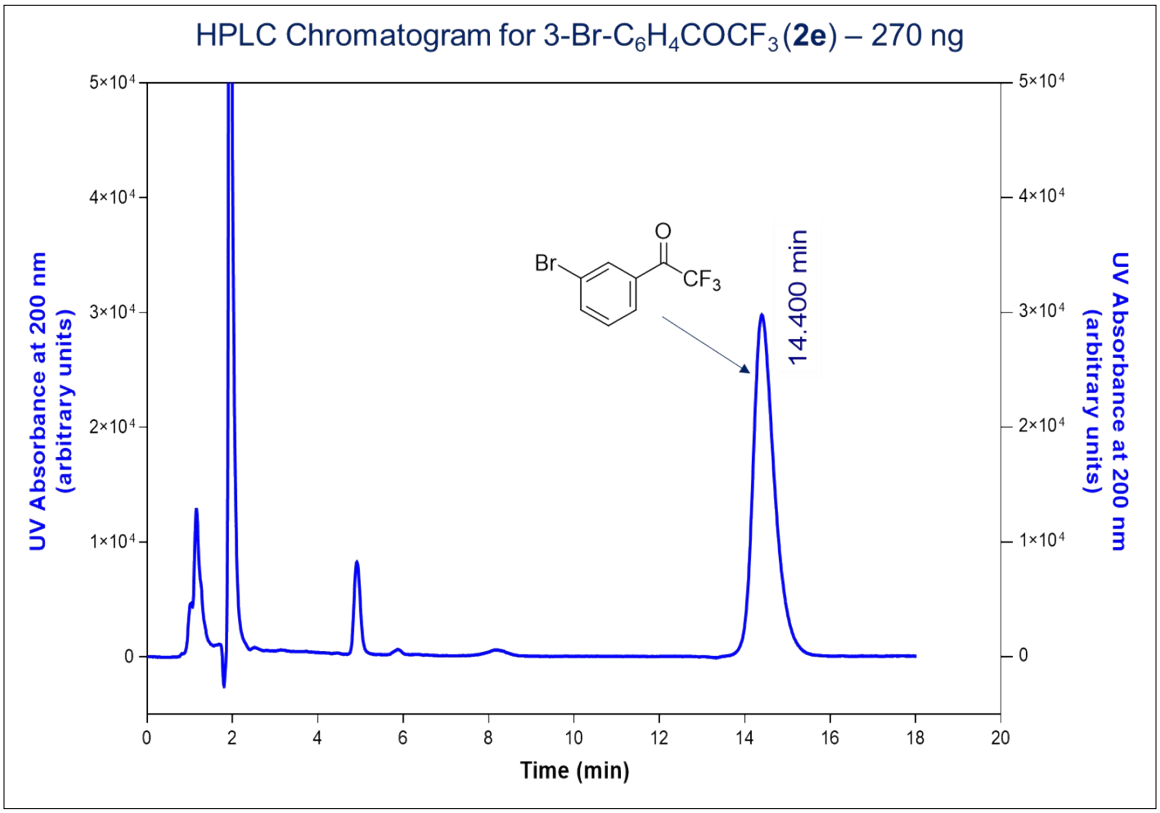
Analytical HPLC Chromatogram for 2e

HPLC Conditions:

Column: XTerra RP_{18}, 5 μm, 4.6 × 250 mm, i.d.; Waters Corp.

Mobile Phase: 35% MeCN (B)–65% H_2O (A), isocratic, 1.5 mL/min flow rate.

Detection: Absorbance at 200 nm.



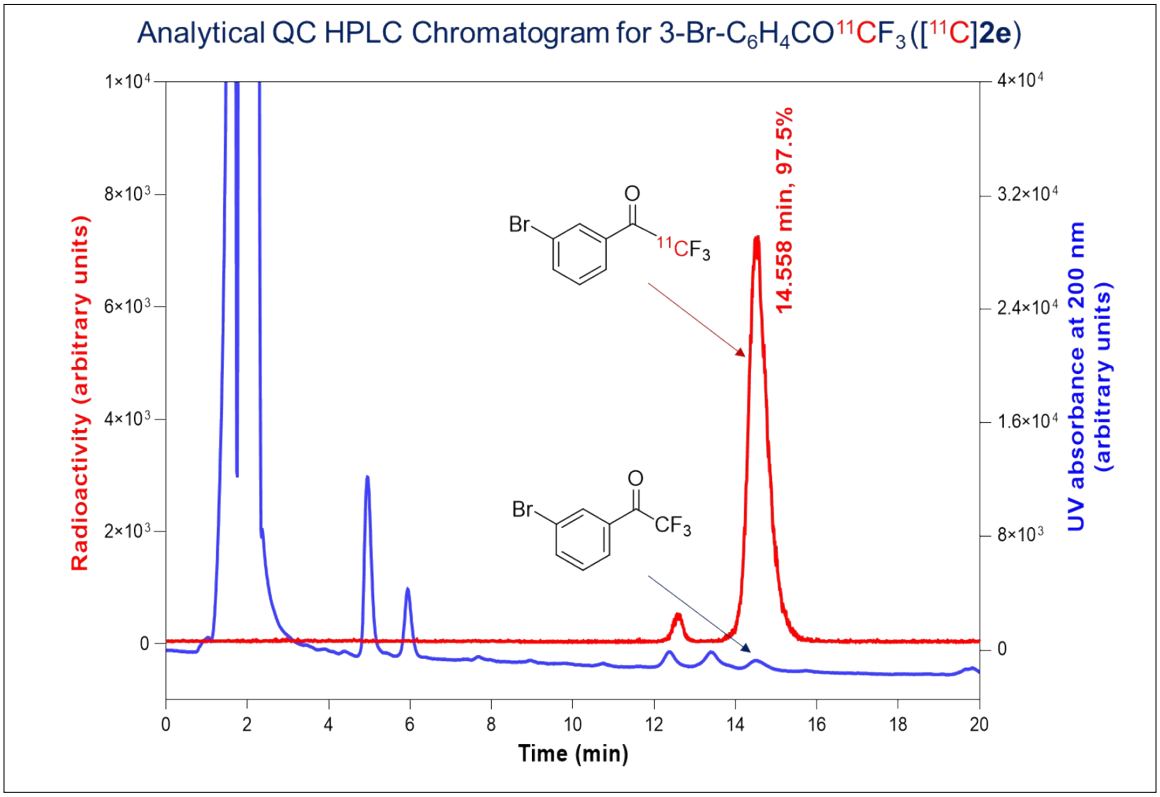
Analytical QC HPLC Chromatogram for [^{11}C]2e

HPLC Conditions:

Column: XTerra RP_{18}, 5 μm, 4.6 × 250 mm, i.d.; Waters Corp.

Mobile Phase: 35% MeCN (B)–65% H_2O (A), isocratic, 1.5 mL/min flow rate.

Detection: Absorbance at 200 nm.



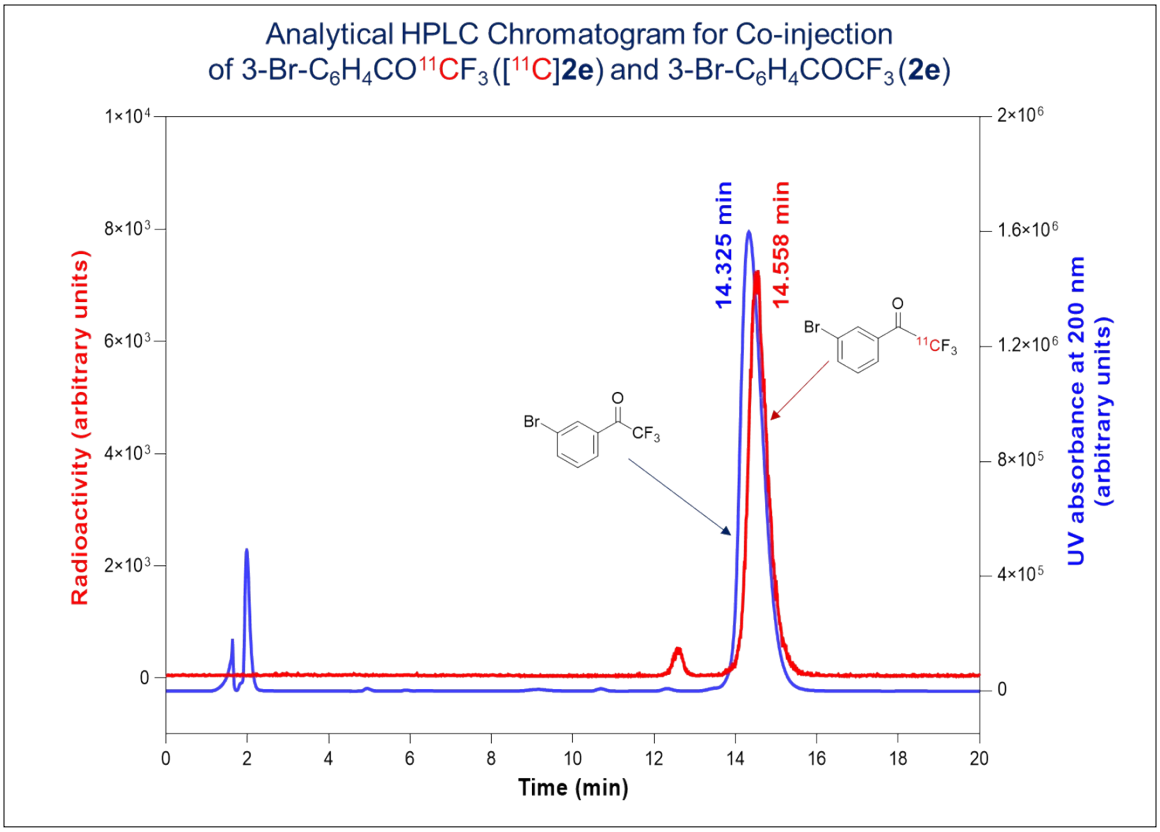
Analytical HPLC Chromatogram for Co-injection of [^{11}C]2e and 2e

HPLC Conditions:

Column: XTerra RP_{18}, 5 μm, 4.6 × 250 mm, i.d.; Waters Corp.

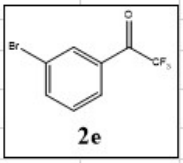
Mobile Phase: 35% MeCN (B)–65% H_2O (A), isocratic, 1.5 mL/min flow rate.

Detection: Absorbance at 200 nm.



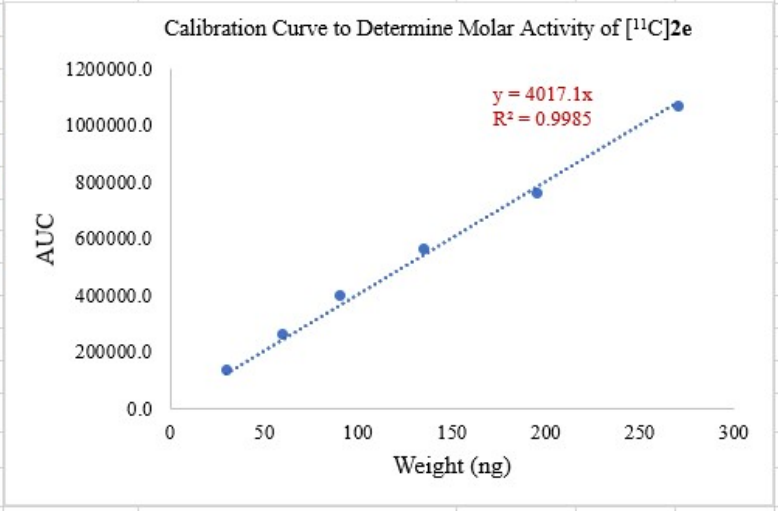
Calibration Curve and Molar Activity (A_m) Calculation for [^{11}C]2e

Stock solution: 1 mg of **2e** in 10 mL acetonitrile:			0.1 mg/mL		
Solution for injection: 300 μ L stock diluted to 10 mL in 1:1 MeCN–water:			0.003 mg/mL		
Analytical HPLC column: XTerra, RP_{18}, 5 μ, 250 x 4.6 mm (i.d. Waters Corp.)					
Mobile phase: 35%B (MeCN)–65%A (H_2O), isocratic, 1.5 mL/min, 200 nm UV					



2e

Weight (ng)	**AUC**
30	138095.0
60	261300.0
90	401724.0
135	562293.0
195	761180.0
270	1070755.0
MW of **2e** (g/mol):	253.02
QC area under the curve (AUC, 200 nm)	15584.00
Injected activity (μ Ci)	20.80
Mass (ng) = AUC / slope	3.88
Molar mass (nmol) = mass (ng) / MW	0.015
Molar activity (A_m) (mCi/μ mol)	1356.60
Molar activity (A_m) (GBq/μ mol) at EOS	**50.19**
Molar activity (A_m) (GBq/μ mol) at EOB	379.00



MW of **2e** (g/mol):	253.02			
QC area under the curve (AUC, 200 nm)	22007.00			
Injected activity (μ Ci)	36.30			
Mass (ng) = AUC / slope	5.48	**Average A_m (GBq/μmol) at EOS**	**SD (n = 2)**	
Molar mass (nmol) = mass (ng) / MW	0.022	**60 min after EOB**		
Molar activity (A_m) (mCi/μ mol)	1676.54			
Molar activity (A_m) (GBq/μ mol) at EOS	**62.03**	**56.11**	**5.92**	
Molar activity (A_m) (GBq/μ mol) at EOB	495.00			