Electronic Supplementary Material (ESI) for ChemComm.

Mn-Salen Catalysed Benzylic C-H Activation for the Synthesis of Aryl [^{18}F]CF_3-containing PET probes

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SUPPORTING INFORMATION

1. General experimental procedures, materials and instrumentation

All reactions were performed under anhydrous conditions and an atmosphere of nitrogen in flame-dried glassware unless otherwise stated. Yields refer to chromatographically and spectroscopically (^{1}H-NMR) homogenous materials.

Solvents and reagents: All solvents were purified and dried according to standard methods prior to use. All chemicals were handled in accordance with COSHH regulations as directed by the HSE (UK). All reagents were used as commercially supplied.

Flash chromatography (FC) was always performed on silica gel (Merck Kieselgel 60 F_{254} 320-400 mesh) according to the method of W. C. Still, unless otherwise stated. Thin Layer Chromatography (TLC) was performed on Merck aluminium-backed plated pre-coated with silica (0.2 mm, 60 F_{254}) which were visualised either by quenching of ultraviolet fluorescence (λ = 254 and 366 nm) or by charring with 10% $KMnO_4$ in 1M H_2SO_4. ^{1}H NMR spectra: These were recorded at 400 MHz on a Bruker AV-400 or on a Bruker AV-500 instrument. Chemical shifts (δ_H) are quoted in parts per million (ppm), referenced to the appropriate residual solvent peak in ^{1}H nmr. Coupling constants (*J*) are reported to the nearest 0.5 Hz. ^{13}C NMR spectra: These were recorded at 100 MHz on a Bruker AV-400 instrument. Mass spectra: Low resolution mass spectra (*m/z*) were recorded on either a VG platform II or VG AutoSpec spectrometers, with only molecular ions (M^+, MH^+, MNa^+, MK^+, MNH_4^+) and major peaks being reported with intensities quoted as percentages of the base peak.

[^{18}F]Fluoride was produced by a cyclotron (GE PETrace) using the $^{18}O(p,n)^{18}F$ nuclear reaction with 16.4 MeV proton irradiation of an enriched [^{18}O]H_2O target.

Analytical reverse-phase HPLC was carried out on an Agilent 1200 instrument using a Phenomenex Gemini C18 column (150 mm x 4.6 mm) with a gradient of acetonitrile and water or acetonitrile containing 0.1 % TFA and water containing 0.1 % TFA at 1 ml/min. All wavelengths for UV were measured at 254 nm. Laura 3 software was used for processing all HPLC chromatograms.

HPLC Methods –

(A) Flow-rate: 1 ml/min; Gradient: 0 mins: 95% MeCN with 0.1% TFA/5% H_2O; 5 mins: 95% MeCN with 0.1% TFA/5% H_2O; 15 mins: 5% MeCN with 0.1% TFA/95% H_2O; 17 mins: 5% MeCN with 0.1% TFA/95% H_2O; 20 mins: 95% MeCN with 0.1% TFA/5% H_2O.
(B) Flow-rate: 1 ml/min; Gradient: 0 mins: 95% MeCN with 0.1% TFA/5% H_2O; 2 mins: 0 mins: 95% MeCN with 0.1% TFA/5% H_2O; 12 mins: 5% MeCN with 0.1% TFA/95% H_2O; 17 mins: 5% MeCN with 0.1% TFA/95% H_2O; 20 mins: 95% MeCN with 0.1% TFA/5% H_2O.
(C) Flow-rate: 1 ml/min; Isocratic 0-20 mins: 30% MeCN with 0.1% TFA/70% H_2O.

2. Synthesis of unlabelled compounds

Compounds **3a-e** have been synthesised previously.[1-3] Compounds **3f-j** (and their associated precursors **2f-j**) were commercially available from Sigma-Aldrich Ltd.

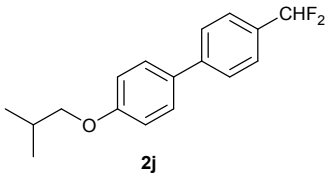
General method for the synthesis of ^{19}F reference compounds: Compound **2a** (115 mg, 0.8 mmol) was dissolved in MeCN (10 ml) and to that solution, AgOTf (411 mg, 1.6 mmol), catalyst **1** (100 mg, 20 mol%), 18-crown-6 (633 mg, 2.4 mmol) and CsF (186 mg, 3.2 mmol) were added. After 5 minutes stirring at 60^oC under N_2, PhIO (704 mg, 3.2 mmol) was added portionwise to the reaction mixture over 30 minutes at 5 minute intervals. The reaction was then cooled to room temperature and concentrated *in vacuo* before being purified by silica flash column chromatography (100% petrol 40-60) to afford the desired product **3a** as an oil (37 mg, 27 % yield).

General procedure for Suzuki coupling

To a stirred solution of 4-isobutoxyphenylboronic acid (194 mg, 1.0 mmol) and 4-bromobenzofluoride (1.1 mmol) in DMF (6 mL) was added potassium phosphate (523 mg, 3.0 mmol) and Tetrakis(triphenylphosphine)palladium(0) (58 mg, 0.05 mmol), and the resultant mixture was heated to 80 °C for 4 h. The mixture was allowed to cool to room temperature, and was diluted with H_2O. The product was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with H_2O (2 x 20 mL) and brine (2 x 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield an off-white solid as crude.

The product was purified by flash column chromatography eluting with 100% petroleum ether to yield the pure product as white plates (0.4 mmol, 40 % yield).

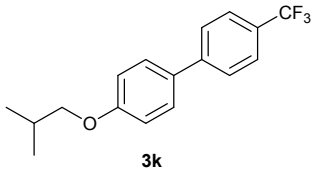
4-(2-Methylpropoxy)-4'-(difluoromethyl)biphenyl (2k)



2j

δ_H (400 MHz, $CDCl_3$) 7.64 (d, *J* = 8.3 Hz, 2H), 7.53 (m, 4H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.69 (t, *J* = 56.6 Hz, 1H), 3.78 (d, *J* = 6.5 Hz, 2H), 2.13 (dq, *J* = 13.3, 6.8 Hz, 1H), 1.06 (d, *J* = 6.7 Hz, 6H). δ_C (100 MHz, $CDCl_3$) 159.4, 143.4 (t, *J* = 2.0 Hz), 132.5 (t, *J* = 22.5 Hz), 128.2 (2C), 127.7, 126.9 (2C), 126.0 (t, *J* = 6.0 Hz, 2C) 115.0, 114.8 (t, *J* = 238 Hz), 74.6, 28.3, 19.3 (2C). δ_F (400 MHz, $CDCl_3$) -110.04, -110.19. HRMS (CI^+) *m*/*z* calcd for $C_{17}H_{18}OF$, 257.1342 (M^+- F), *found* 257.1348.

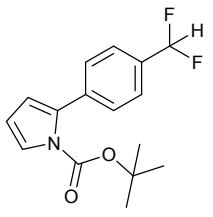
4-(2-Methylpropoxy)-4'-(trifluoromethyl)biphenyl (3k)



3k

δ_H (400 MHz, $CDCl_3$) 7.68 – 7.62 (m, 4H), 7.53 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 3.78 (d, *J* = 6.5 Hz, 2H), 2.12 (dq, *J* = 13.3, 6.7 Hz, 1H), 1.06 (d, *J* = 6.7 Hz, 6H). δ_C (100 MHz, $CDCl_3$) 159.6, 144.3 (d, *J* = 1.8 Hz), 131.9, 128.6 (q, *J* = 32 Hz), 128.3 (2C), 126.8 (2C), 125.7 (q, *J* = 4 Hz, 2C), 124.4 (q, *J* = 272 Hz), 115.0 (2C), 74.6, 28.3, 19.3 (2C). δ_F (400 MHz, $CDCl_3$) -62.31. HRMS (CI^+) *m*/*z* calcd for $C_{17}H_{18}OF_3$, 295.1310 (M^+), *found* 295.1304.

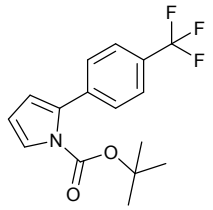
***tert*-Butyl 2-[4-(difluoromethyl)phenyl]-1*H*-pyrrole-1-carboxylate (2l)**



δ_H (400 MHz, $CDCl_3$) 7.34 – 7.45 (m, 4H), 7.30 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.60 (t, *J* = 56.5 Hz, 1H), 6.13 – 6.19 (m, 2H), 1.30 (s, 9H). δ_C (100 MHz, $CDCl_3$) 149.2, 138.1, 136.9, 133.5 (d, *J* = 91 Hz), 129.4, 127.3, 124.9 (t, *J* = 6 Hz), 123.1, 117.1, 114.9, 113.6 (d, *J* = 238 Hz),

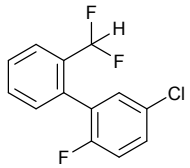
110.8, 106.0. δ_F (400 MHz, $CDCl_3$) -110.39, -110.54. HRMS (EI^+) *m*/*z* calcd for $C_{16}H_{17}NO_2F_2$, 293.1227 (M^+), *found* 293.1216.

tert-Butyl 2-[4-(trifluoromethyl)phenyl]-1*H*-pyrrole-1-carboxylate (3l)



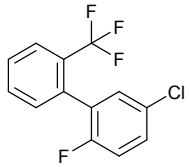
δ_H (400 MHz, $CDCl_3$) 7.46 (dd, *J* = 56.7, 7.4 Hz, 4H), 7.31 (dd, *J* = 3.0, 2.1 Hz, 2H), 6.14 – 6.20 (m, 3H), 1.31 (s, 9H). δ_C (100 MHz, $CDCl_3$) 149.1, 137.9 (d, J = 2 Hz), 134.4, 133.5, 129.3, 129.1 (d, *J* = 36 Hz), 127.6, 124.5 (q, *J* = 4 Hz), 123.4, 122.7 (d, *J* = 40 Hz), 115.5, 110.9, 84.1, 27.6. δ_F (400 MHz, $CDCl_3$) -62.45, -117.11, -120.51. HRMS (EI^+) *m*/*z* calcd for $C_{16}H_{16}NO_2F_3$, 311.1133 (M^+), *found* 311.1141.

5-Chloro-2'-(difluoromethyl)-2-fluorobiphenyl (2m)



δ_H (400 MHz, $CDCl_3$) 7.67-7.73 (m, 1H), 7.45-7.51 (m, 2H), 7.30 (ddd, *J* = 7.1, 4.4, 2.7 Hz, 1H), 7.20-7.25 (m, 2H), 7.05 (t, *J* = 8.8 Hz), 6.44 (t, *J* = 54.8 Hz, 1H). δ_C (100 MHz, $CDCl_3$) 132.8 (d, *J* = 22), 131.5, 131.1, 130.7, 129.9, 129.1, 125.81, 125.75, 117.0 (d, *J* = 24 Hz), 112.9. δ_F (400 MHz, $CDCl_3$) -110.0 (d, *J* = 305 Hz), -114.1 (d, *J* = 303 Hz), -117.9. HRMS (EI^+) *m*/*z* calcd for $C_{13}H_8ClF_3$, 256.0267 (M^+), *found* 256.0269.

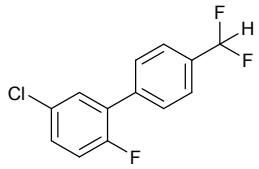
5-Chloro-2-fluoro-2'-(trifluoromethyl)biphenyl (3n)



δ_H (400 MHz, $CDCl_3$) 7.70 (d, *J* = 8.1 Hz, 1H), 7.48 (dt, *J* = 24.7, 7.6 Hz, 1H), 7.24-7.29 (m, 2H), 7.16-7.19 (m, 1H), 6.97-7.07 (m, 2H). δ_C (100 MHz, $CDCl_3$) 158.4 (d, *J* = 251 Hz), 131.9, 131.5, 131.1 (d, *J* = 2.9 Hz), 130.2 (d, *J* = 4.4 Hz), 129.8 (d, *J* = 8.1 Hz), 129.3 (d, *J* = 3.7 Hz), 128.6, 126.3 (d, *J* = 5.1 Hz), 123.8 (d, *J* = 16.9 Hz), 122.4, 117.3 (dd, *J* = 16.9, 6.6

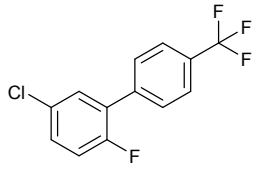
Hz), 116.0 (d, J = 24.2 Hz). δ_F (400 MHz, $CDCl_3$) -59.0, -117.9. HRMS (EI^+) m/z calcd for $C_{13}H_7ClF_4$, 274.0172 (M^+), *found* 274.0170.

5-Chloro-4'-(difluoromethyl)-2-fluorobiphenyl (2n)



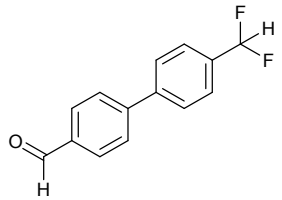
δ_H (400 MHz, $CDCl_3$) 7.61 (m, 4H), 7.42 (dd, J = 6.6, 2.7 Hz, 1H), 7.31 (ddd, J = 8.8, 4.2, 2.7 Hz, 1H), 7.12 (dd, J = 9.9, 8.8 Hz, 1H), 6.70 (t, J = 56.4 Hz, 1H). δ_C (100 MHz, $CDCl_3$) 137.0, 135.9, 134.1 (d, J = 22 Hz), 130.3 (d, J = 3 Hz), 129.6, 129.4, 129.3 (t, J = 2 Hz), 125.9 (t, J = 6 Hz), 117.6 (d, J = 25 Hz), 116.8, 114.5. δ_F (400 MHz, $CDCl_3$) -110.89, -111.04, -120.59. HRMS (EI^+) m/z calcd for $C_{13}H_8ClF_3$, 256.0267 (M^+), *found* 256.0262.

5-Chloro-2-fluoro-4'-(trifluoromethyl)biphenyl (3n)



δ_H (400 MHz, $CDCl_3$) 7.61 – 7.74 (m, 2H), 7.42 (dd, J = 6.6, 2.6 Hz, 1H), 7.34 – 7.39 (m, 2H), 7.03 – 7.20 (m, 2H). δ_C (100 MHz, $CDCl_3$) 158.2 (d, J = 25 Hz), 131.0 (t, J = 3 Hz), 130.3 (d, J = 4 Hz), 130.2 (t, J = 4 Hz), 129.6, 129.2 (d, J = 3 Hz), 125.6 (d, J = 4 Hz), 123.8 (d, J = 11 Hz), 117.8, 117.3 (ddd, J = 17, 10, 7 Hz). δ_F (400 MHz, $CDCl_3$) -62.64, -117.11, -120.51. HRMS (EI^+) m/z calcd for $C_{13}H_7ClF_4$, 274.0172 (M^+), *found* 274.0167.

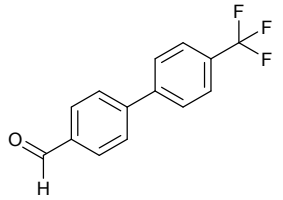
4-(Formyl)-4'-(difluoromethyl)biphenyl (2o)



δ_H (400 MHz, $CDCl_3$) 10.0 (s, 1H), 7.91 (d, J = 8.5 Hz, 2H), 7.69 (d, J = 8.1 Hz, 2H), 7.64 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 8.1 Hz, 2H), 6.64 (t, J = 56.2 Hz). δ_C (100 MHz, $CDCl_3$) 191.8, 171.1, 146.1, 142.2, 135.7, 134.6, 134.4, 127.9, 127.7, 126.3 (t, J = 5.9 Hz), 116.8, 114.5,

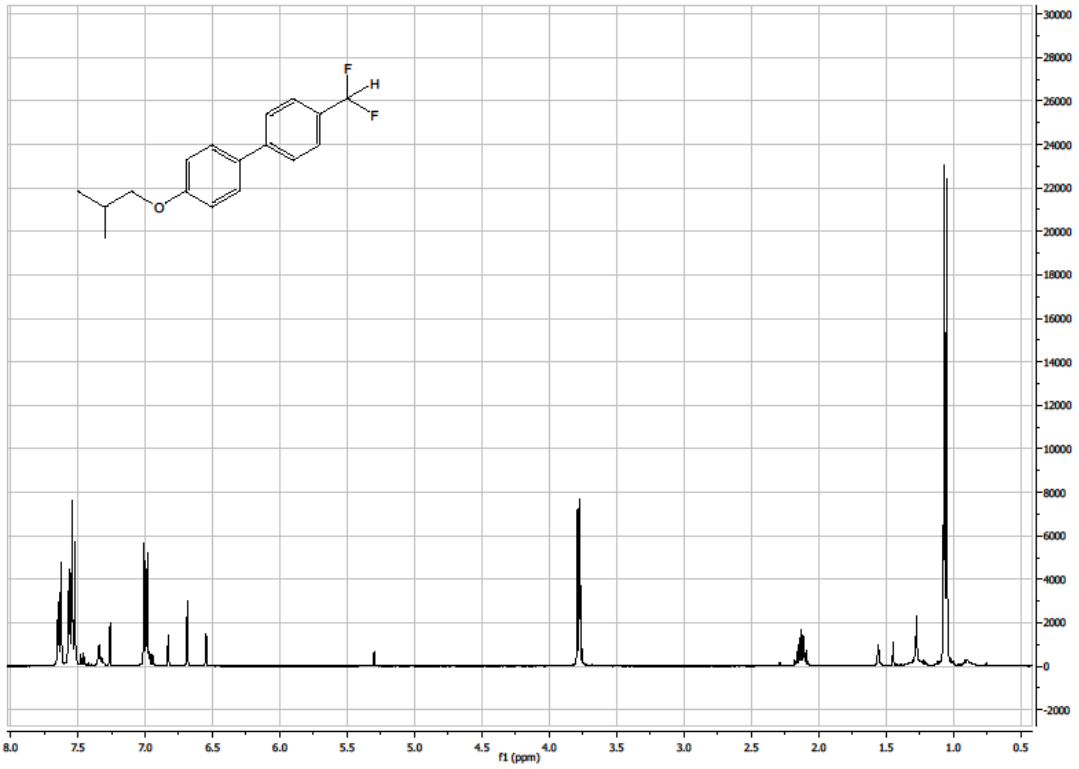
112.0. δ_F (400 MHz, $CDCl_3$) -110.83, -110.98. HRMS (EI^+) *m/z* calcd for $C_{14}H_{10}F_2O$, 232.0700 (M^+), *found* 232.0700.

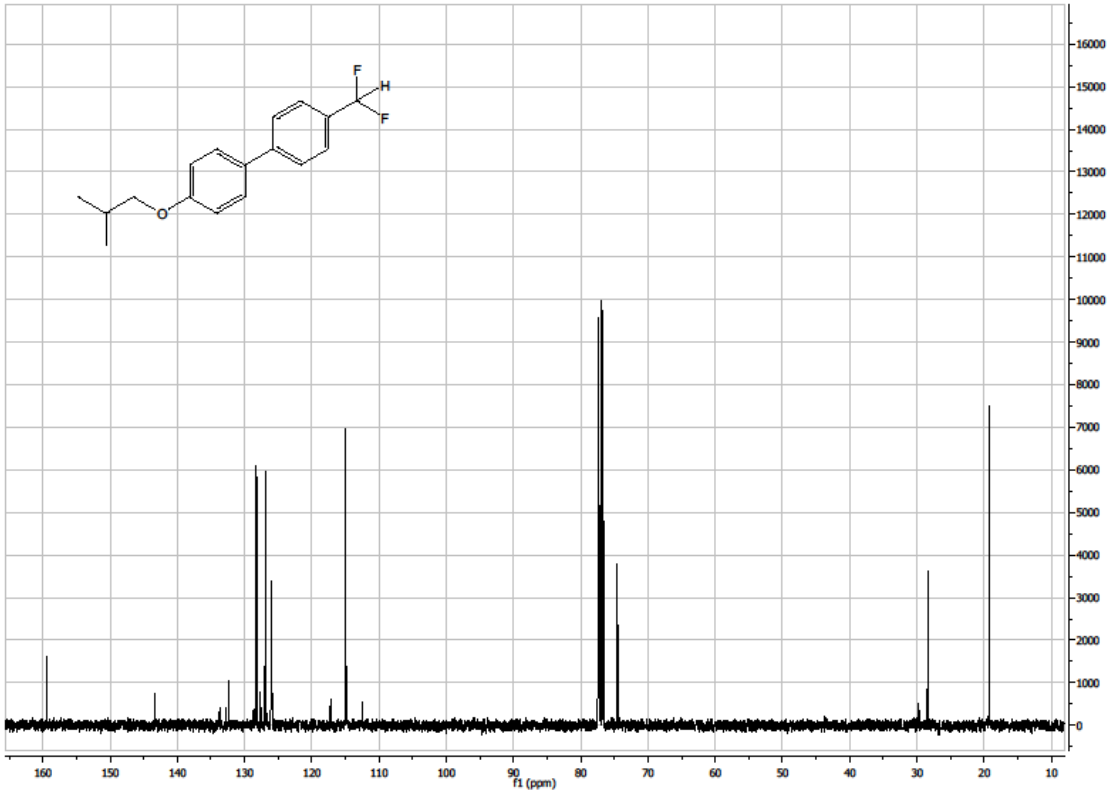
4-(Formyl)-4'-(trifluoromethyl)biphenyl (3o)



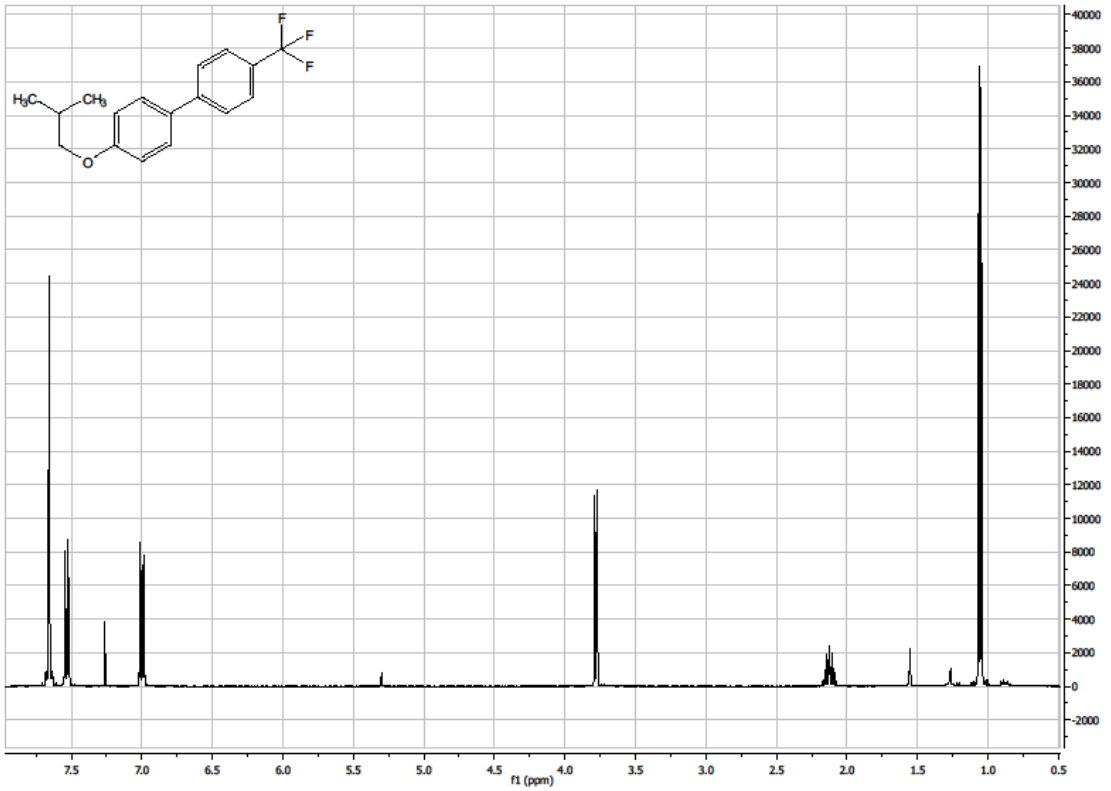
δ_H (400 MHz, $CDCl_3$) 10.0 (s, 1H), 7.91 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.1 Hz, 2H). δ_C (100 MHz, $CDCl_3$) 191.7, 145.6, 143.3, 135.9, 130.4, 130.3, 127.9, 127.7, 126.0 (d, *J* = 3.7 Hz), 125.9. δ_F (400 MHz, $CDCl_3$) -62.60. HRMS (EI^+) *m/z* calcd for $C_{14}H_9F_3O$, 250.0605 (M^+), *found* 250.0610.

3. Nmr of relevant compounds






F
H
F
O
-110.04
-110.19
f1 (ppm)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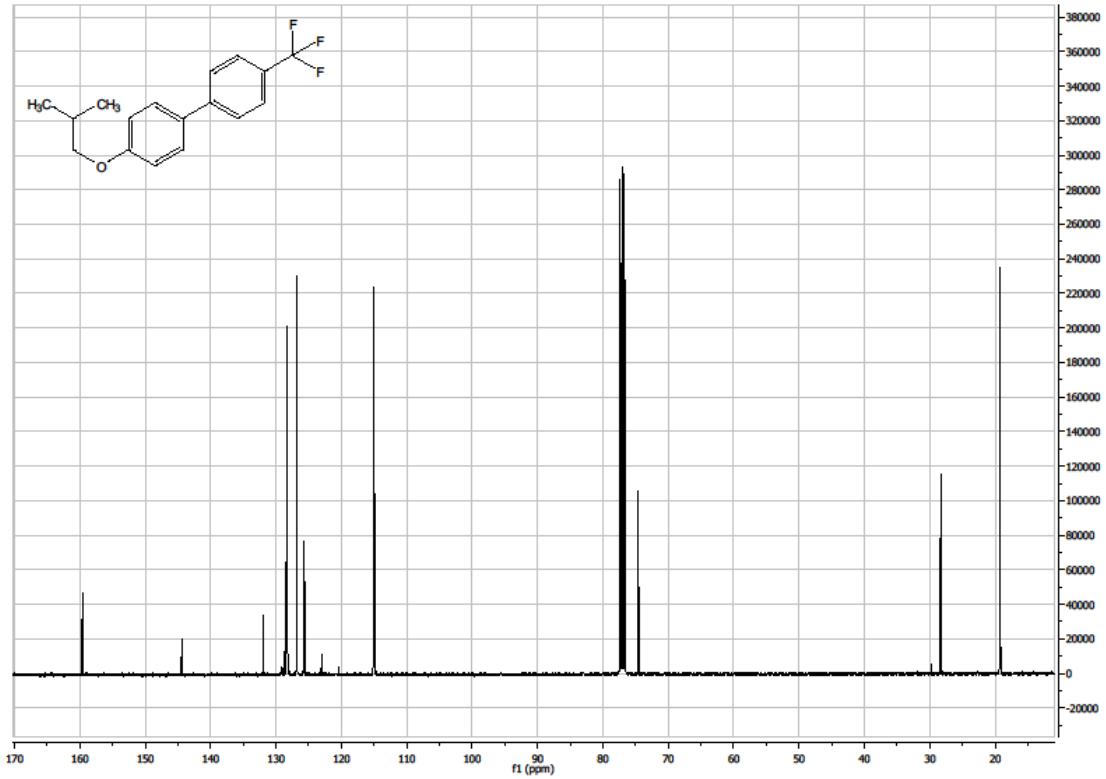
F
F
H3C
CH3
O
f1 (ppm)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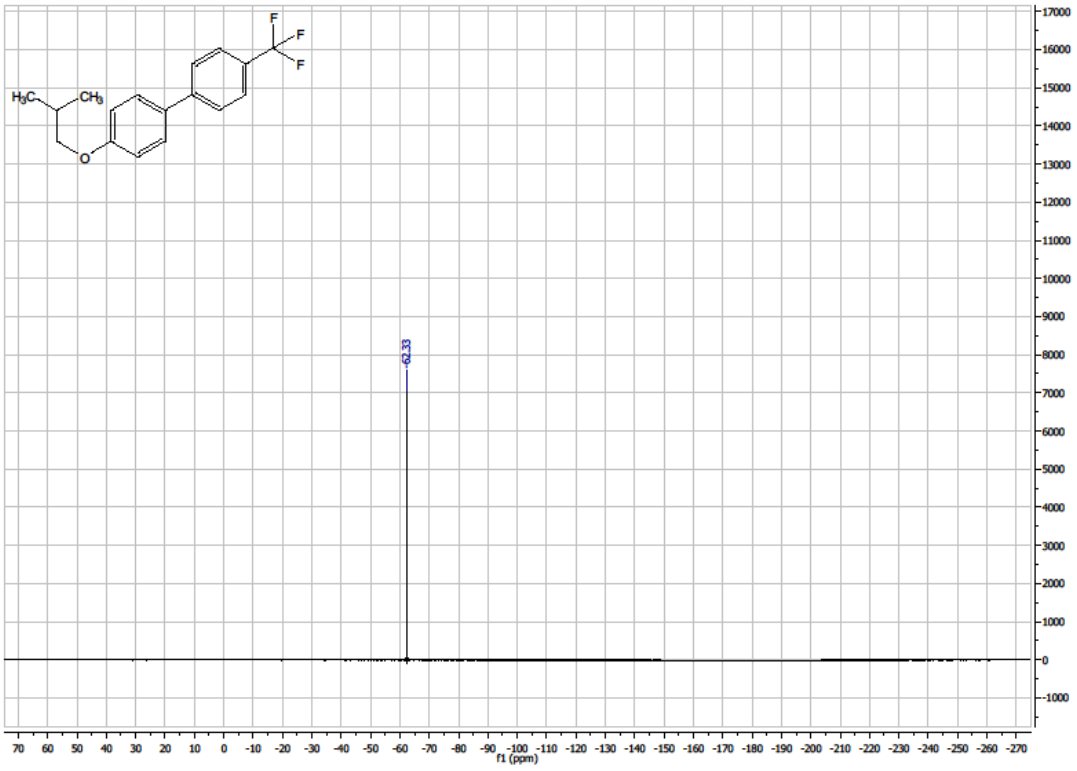
F
F
H3C
CH3
O
f1 (ppm)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H3C
CH3
O
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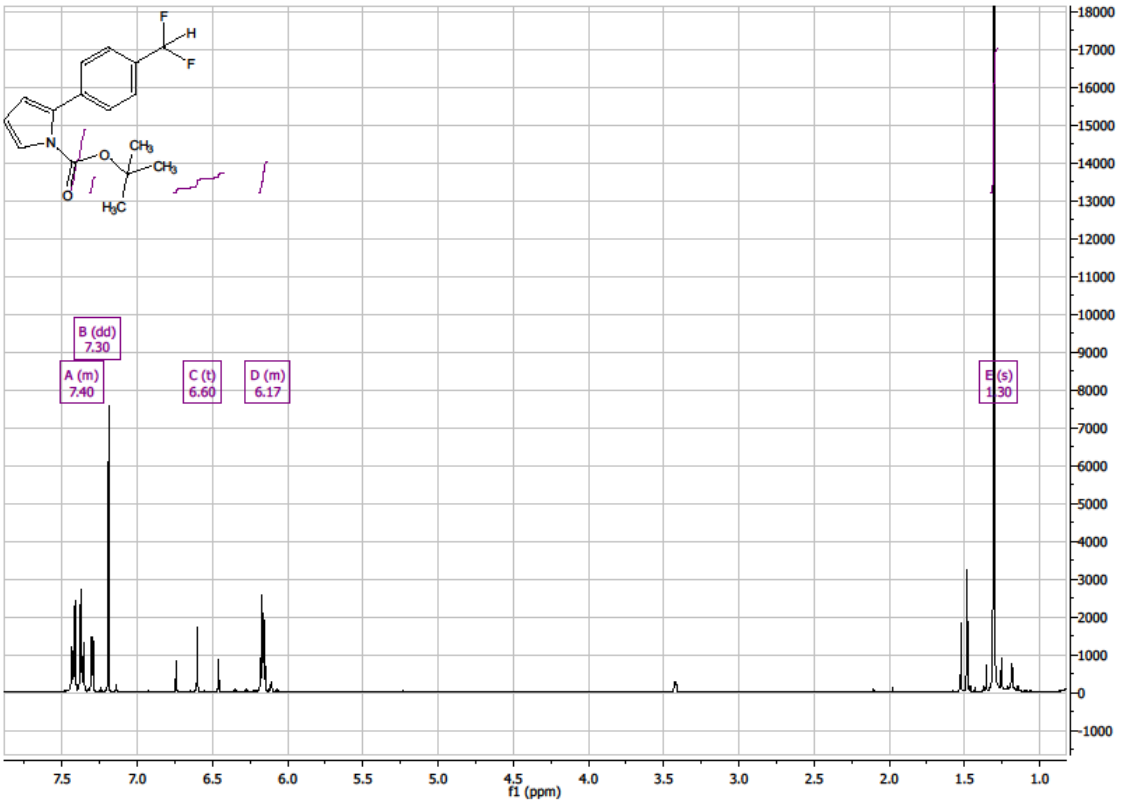
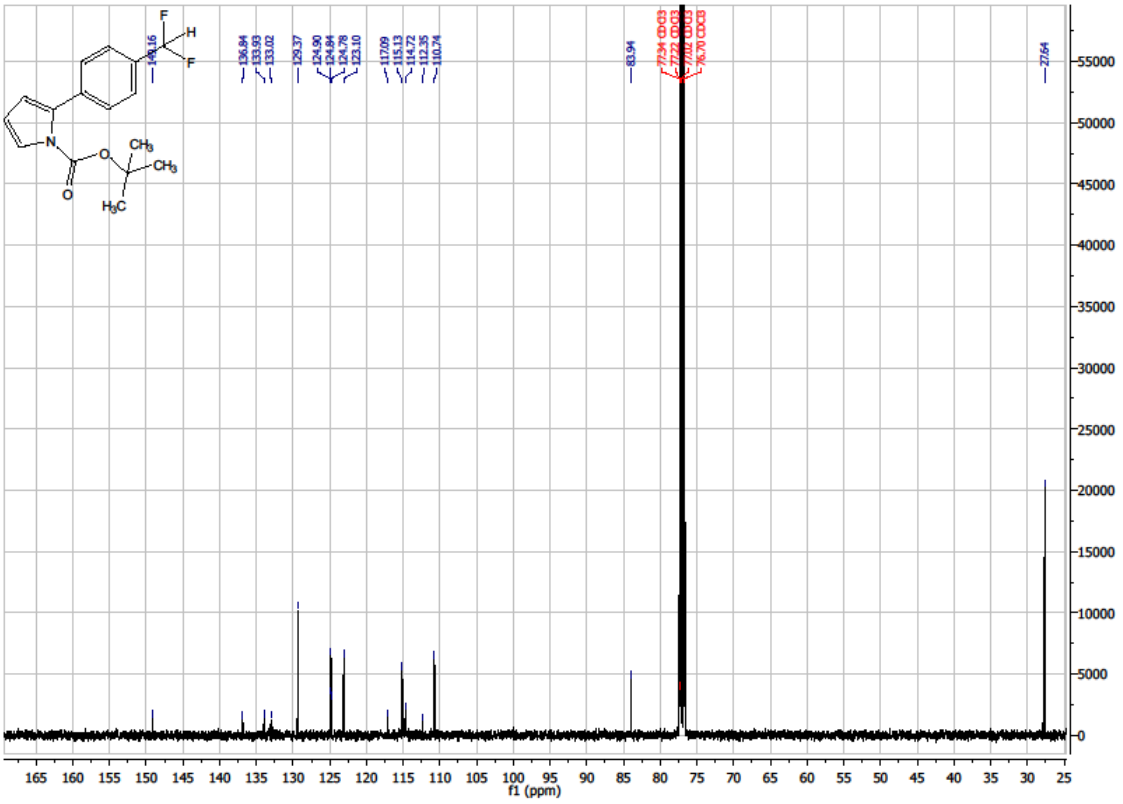
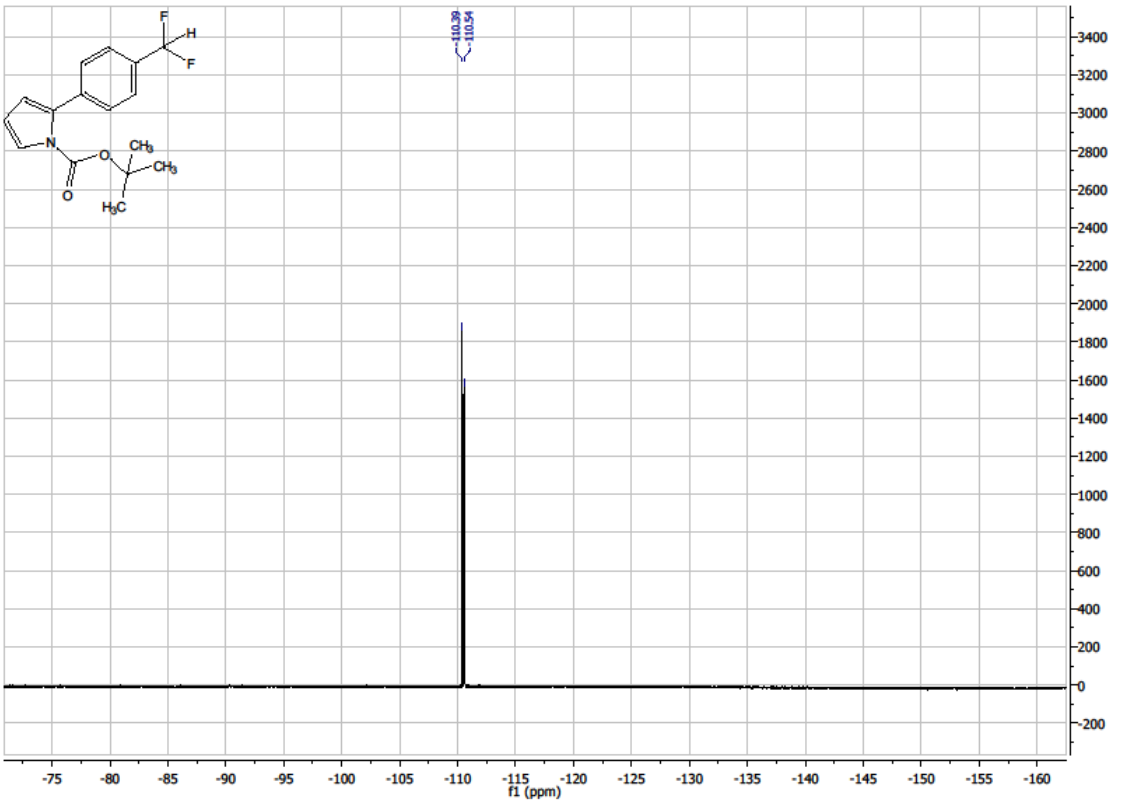
f1 (ppm)


B (dd)
7.30
A (m)
7.40
C (t)
6.60
D (m)
6.17
E (s)
1.30
f1 (ppm)


f1 (ppm)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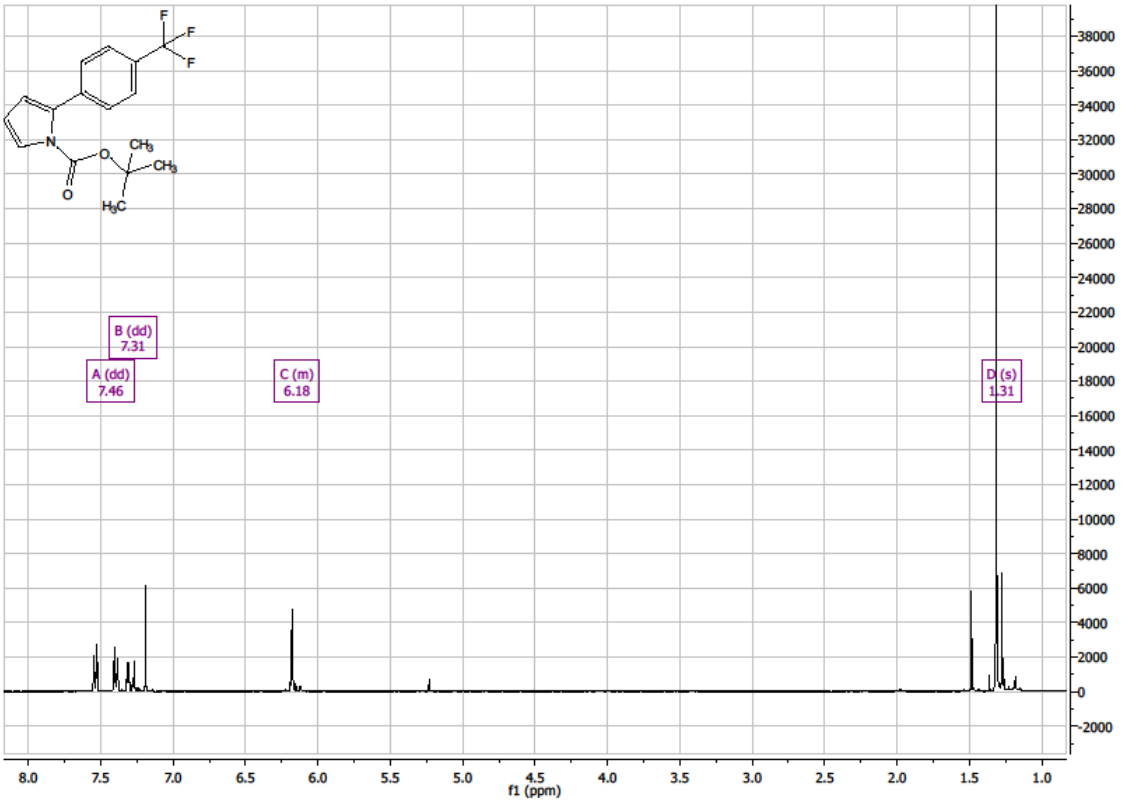
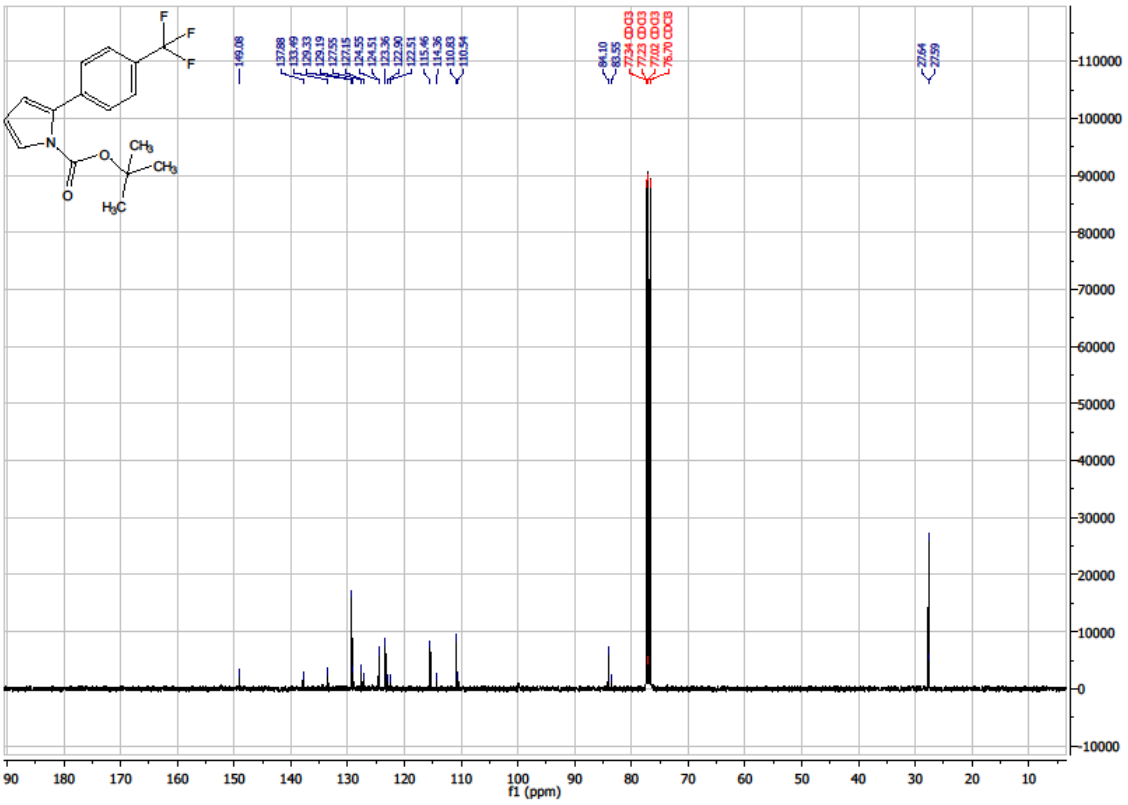
H
F
N
O
O
CH3
CH3
H3C
-110.39
-110.54
f1 (ppm)


F
F
F
N
O
O
CH3
CH3
H3C
B (dd)
7.31
A (dd)
7.46
C (m)
6.18
D (s)
1.31
f1 (ppm)


F
F
F
N
O
O
CH3
CH3
H3C
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137.88
133.49
129.33
129.19
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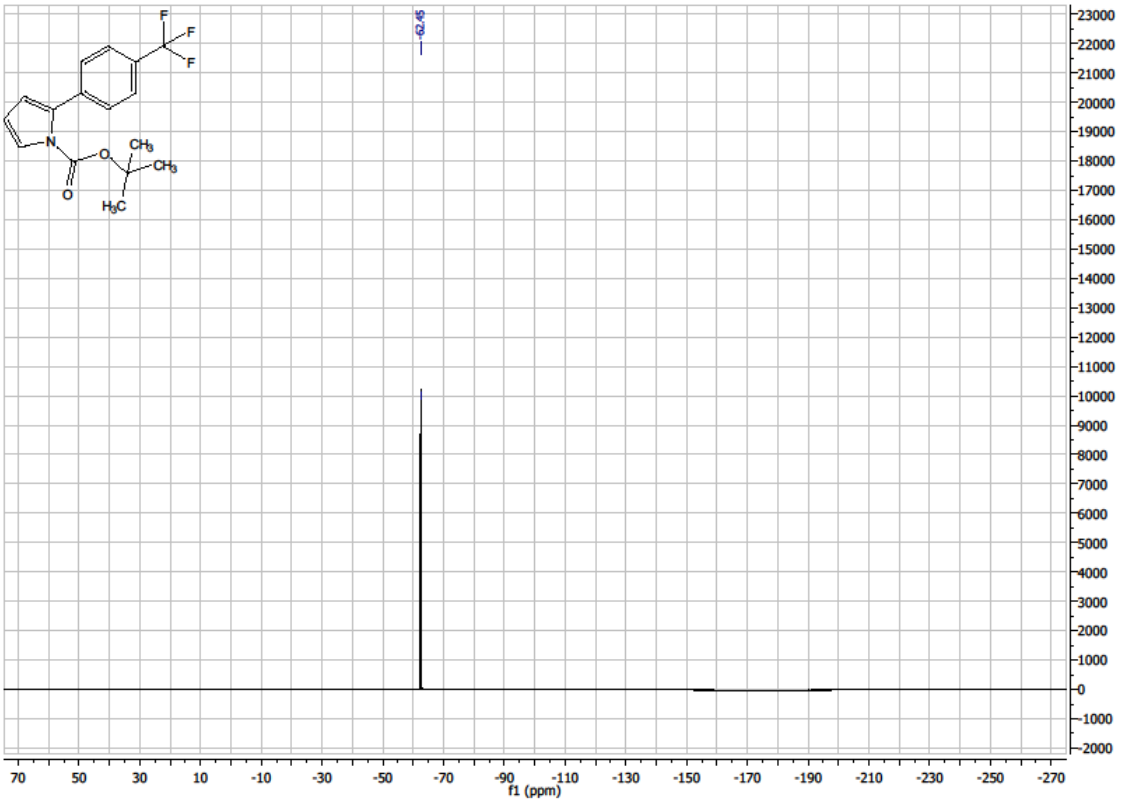
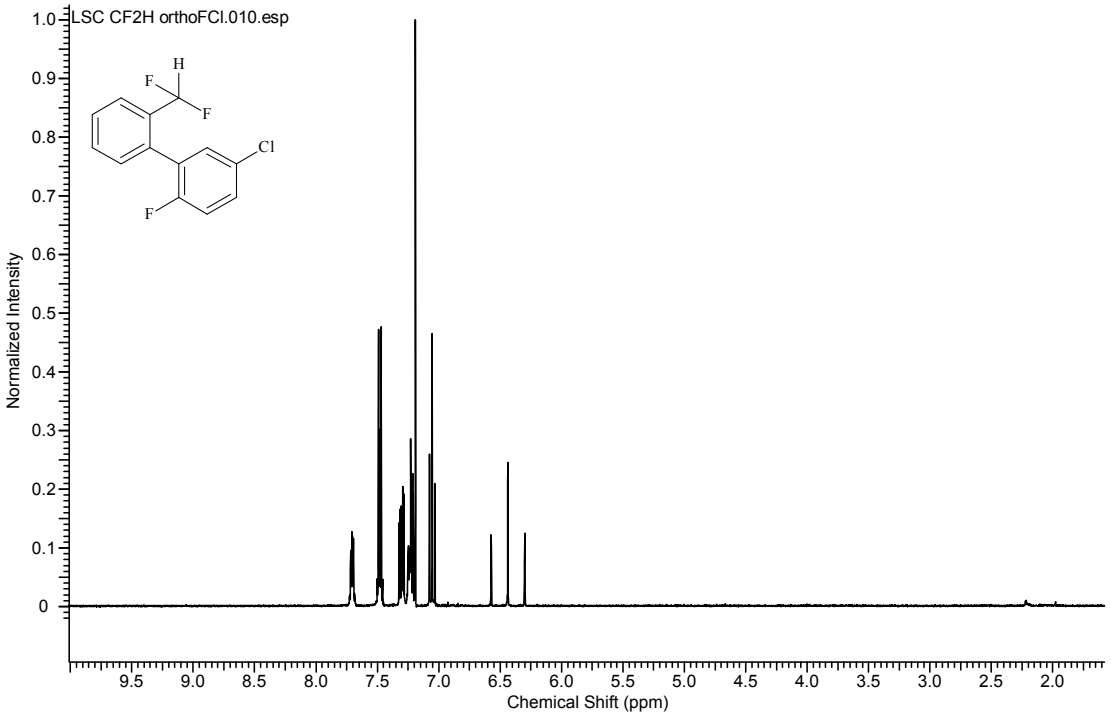
127.15
124.55
124.51
123.36
122.90
122.51
115.46
114.36
110.83
110.54
84.10
83.55
77.24 CDCl3
77.23 CDCl3
77.02 CDCl3
76.70 CDCl3
27.64
27.59
f1 (ppm)


F
F
F
N
O
O
CH3
CH3
H3C
-62.45
f1 (ppm)


LSC CF2H orthoFCl.010.esp
H
F
F
Cl
F
Normalized Intensity
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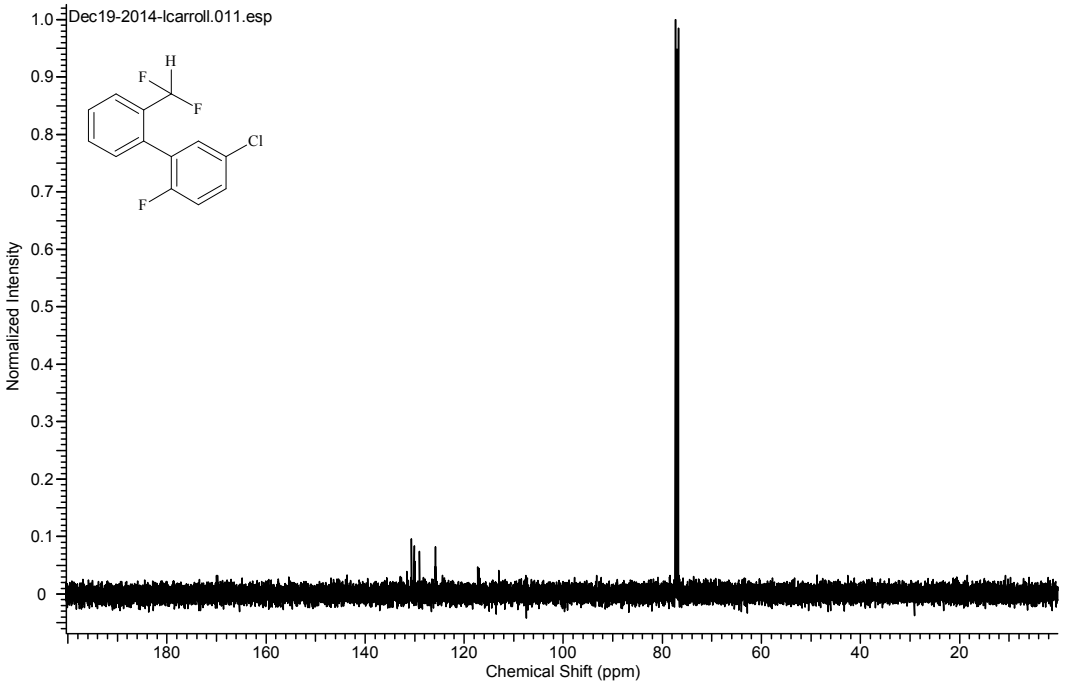
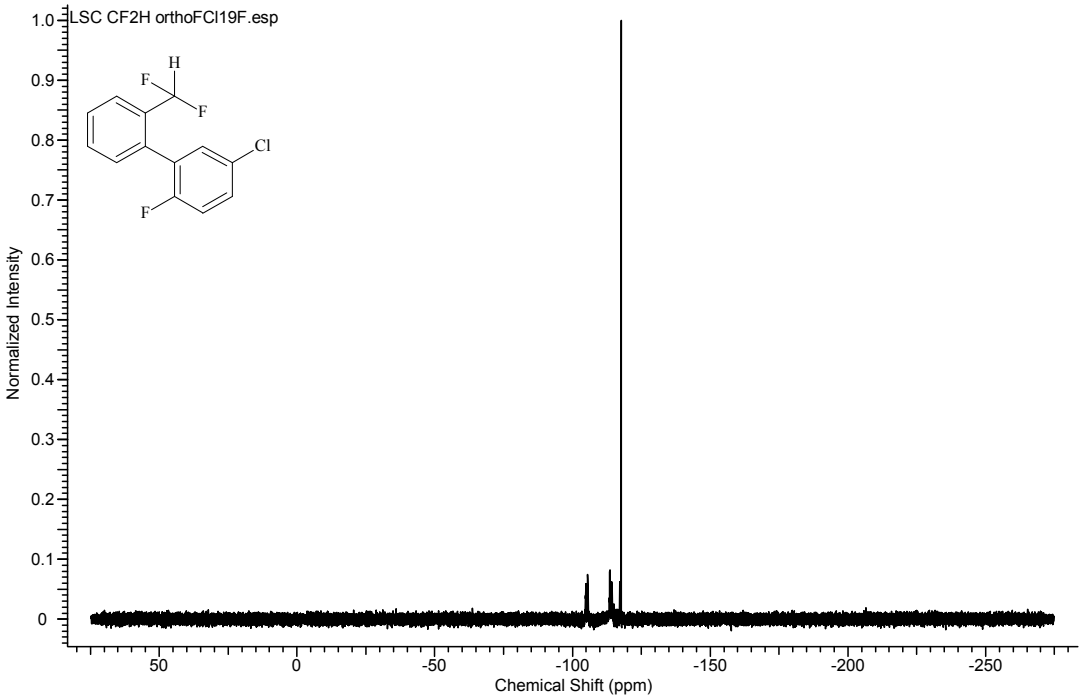
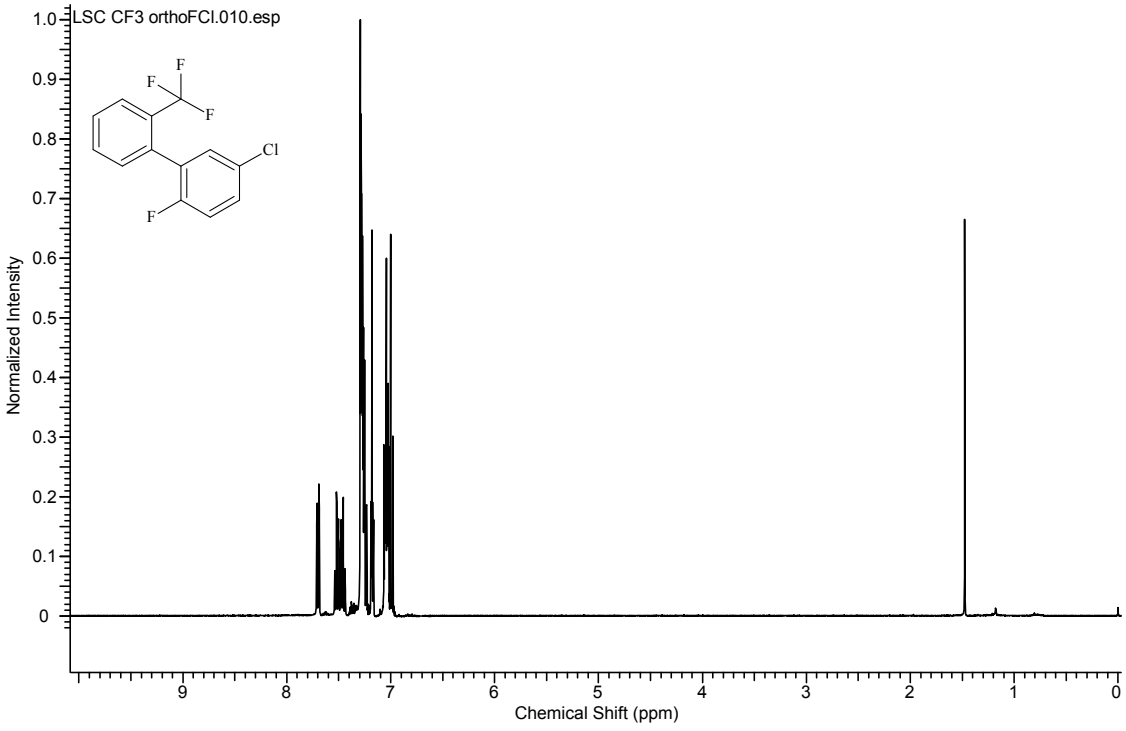
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
Chemical Shift (ppm)


Dec19-2014-lcarroll.011.esp
H
F
F
Cl
F
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
180
160
140
120
100
80
60
40
20
Chemical Shift (ppm)


LSC CF2H orthoFCl19F.esp
H
F
F
Cl
F
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
50
0
-50
-100
-150
-200
-250
Chemical Shift (ppm)


LSC CF3 orthoFCl.010.esp
F
F
F
Cl
F
Normalized Intensity
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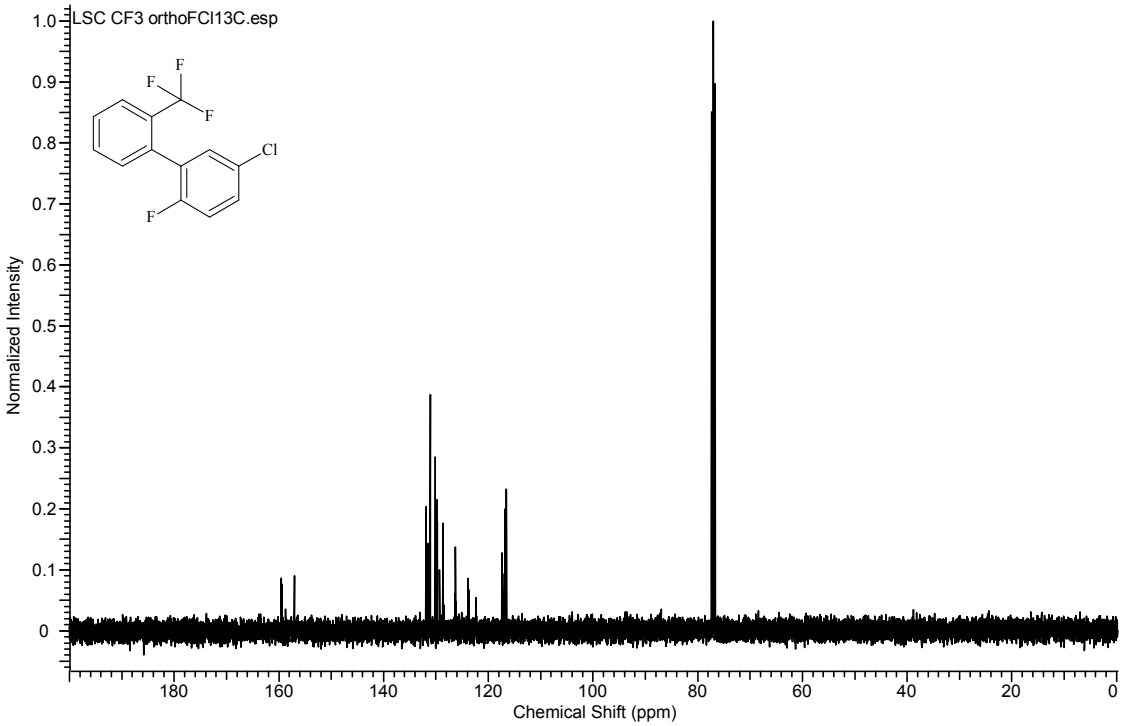
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


LSC CF3 orthoFCl13C.esp
F
F
F
Cl
F
Normalized Intensity
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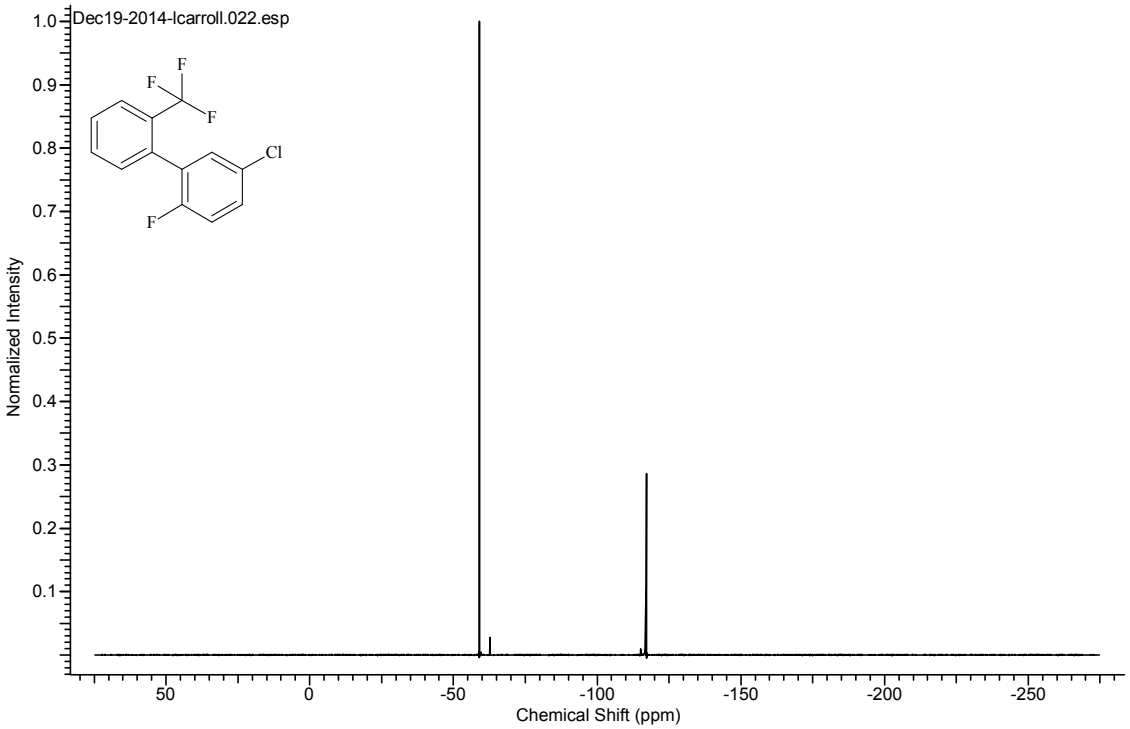
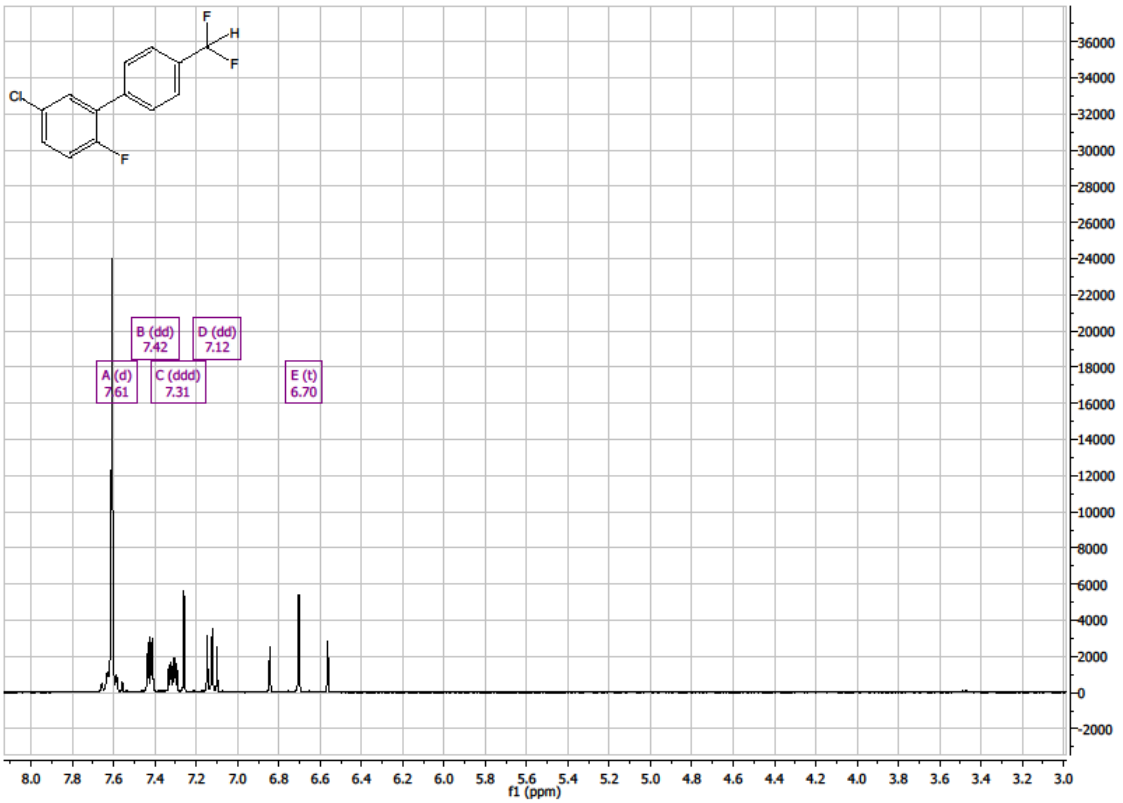
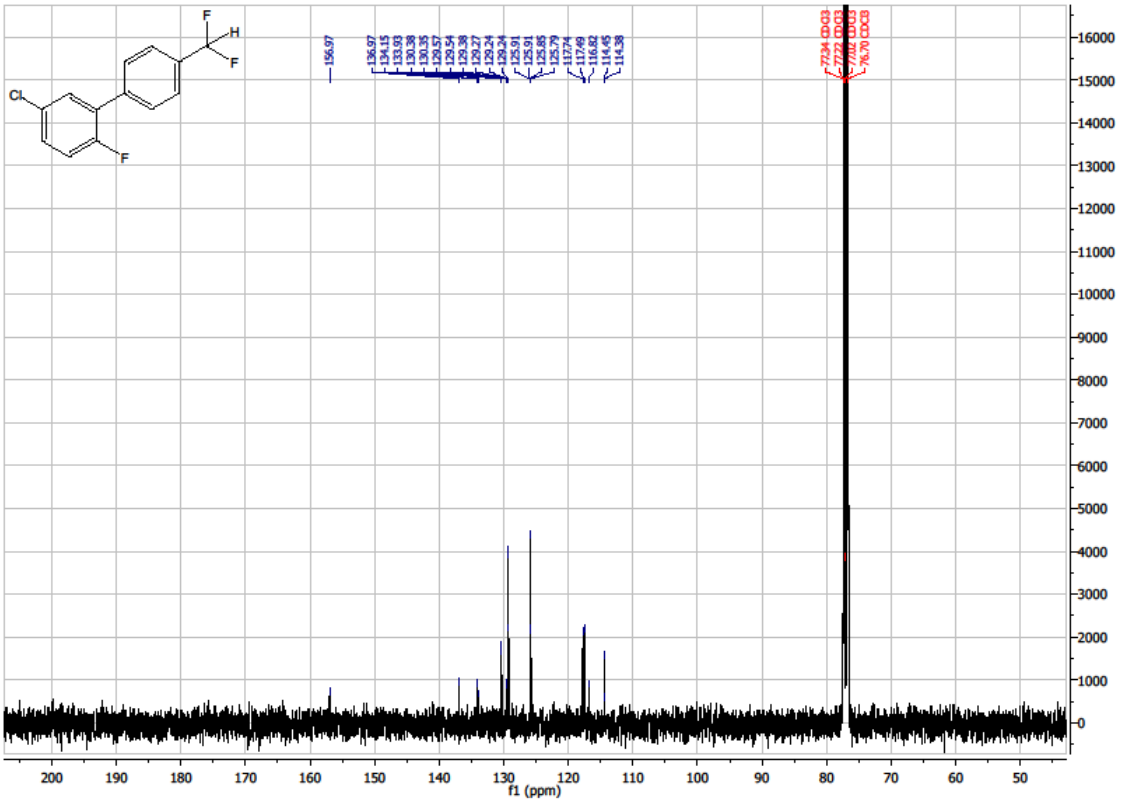
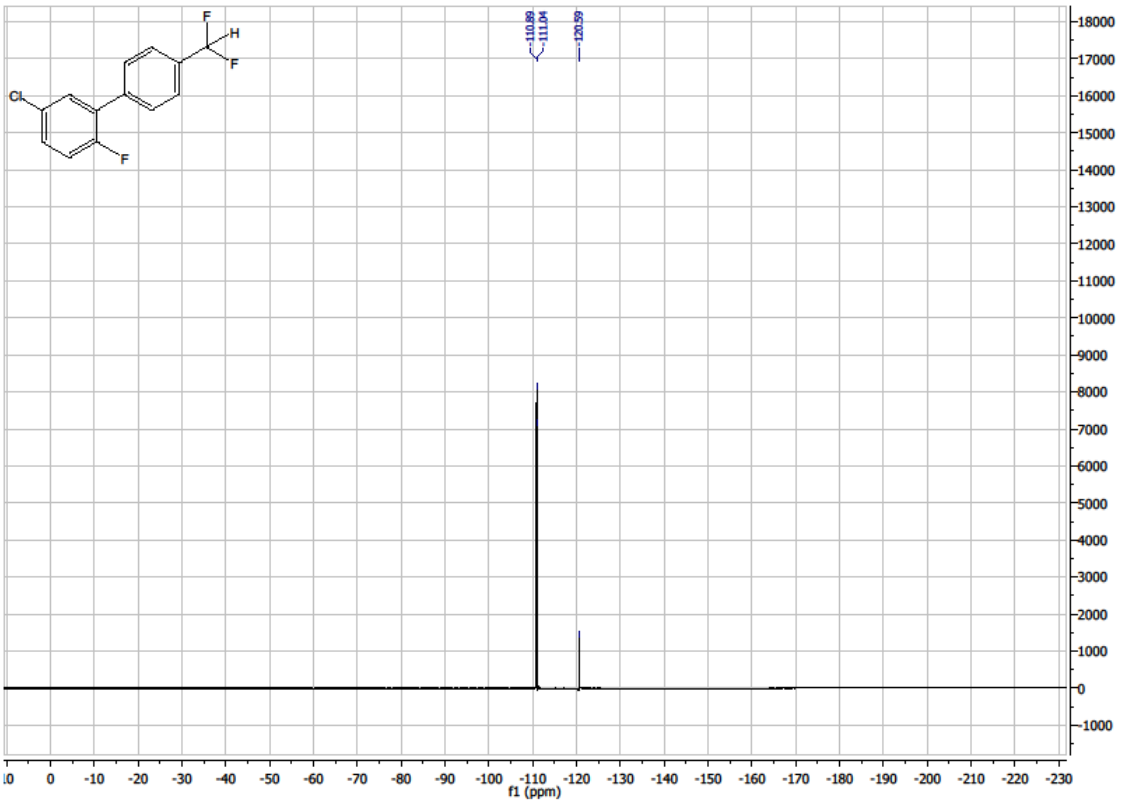
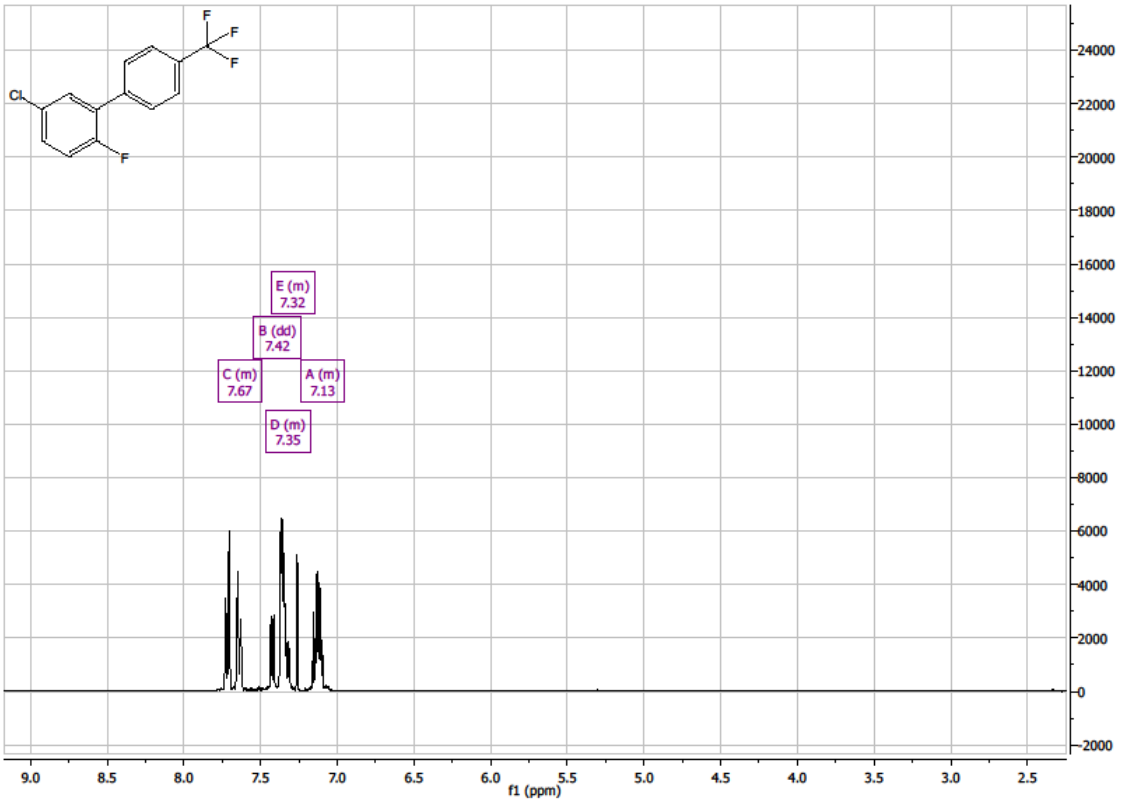
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

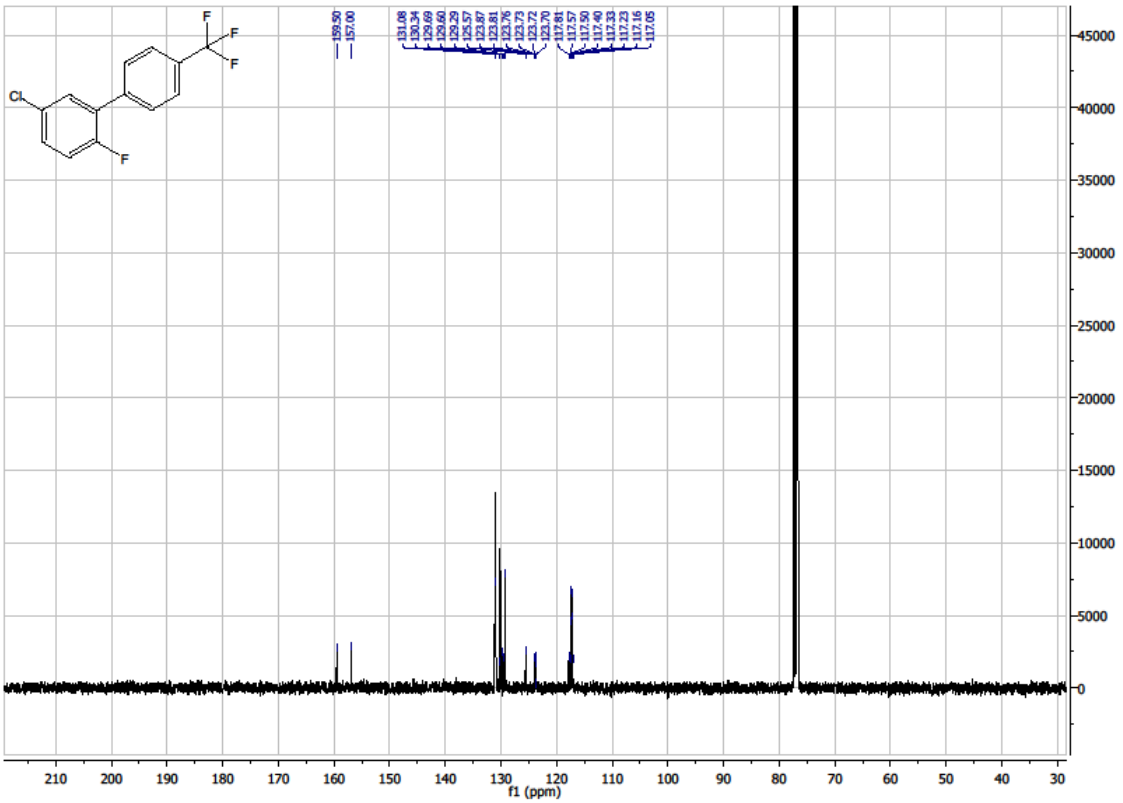

Dec19-2014-lcarroll.022.esp
F
F
F
Cl
F
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
50
0
-50
-100
-150
-200
-250
Chemical Shift (ppm)

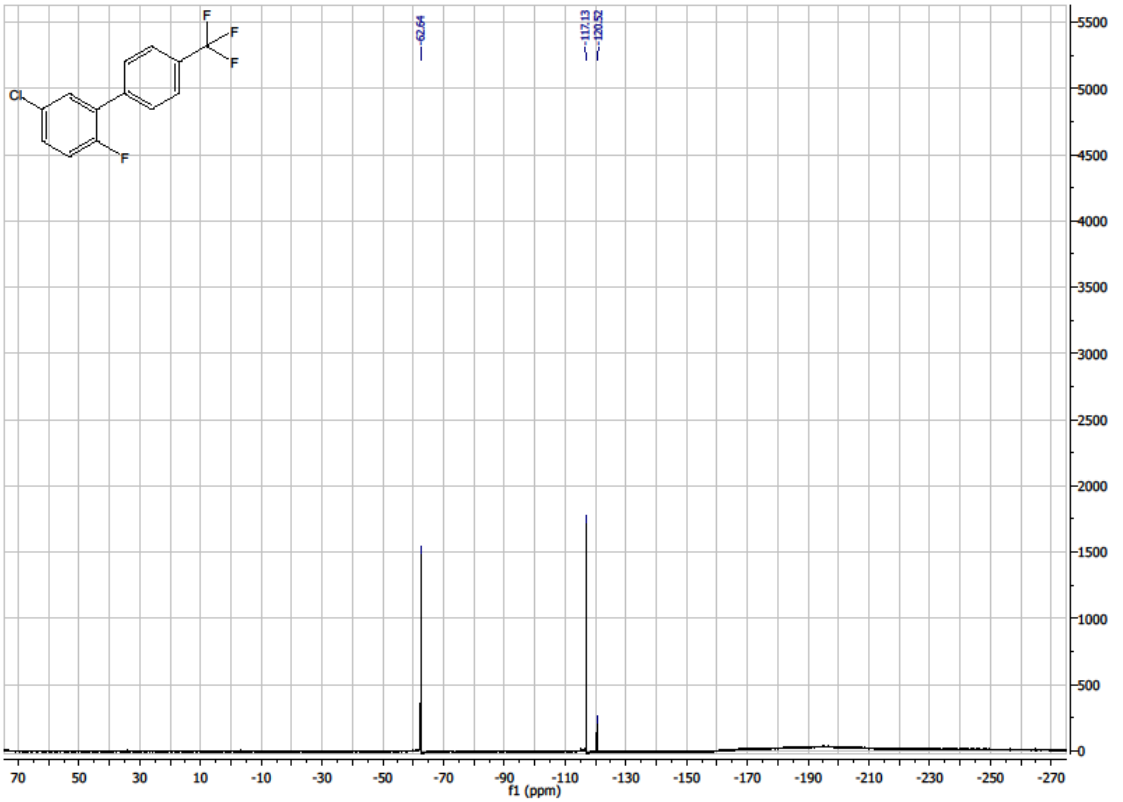

F
H
F
Cl
F
B (dd)
7.42
D (dd)
7.12
A (d)
7.61
C (ddd)
7.31
E (t)
6.70
f1 (ppm)

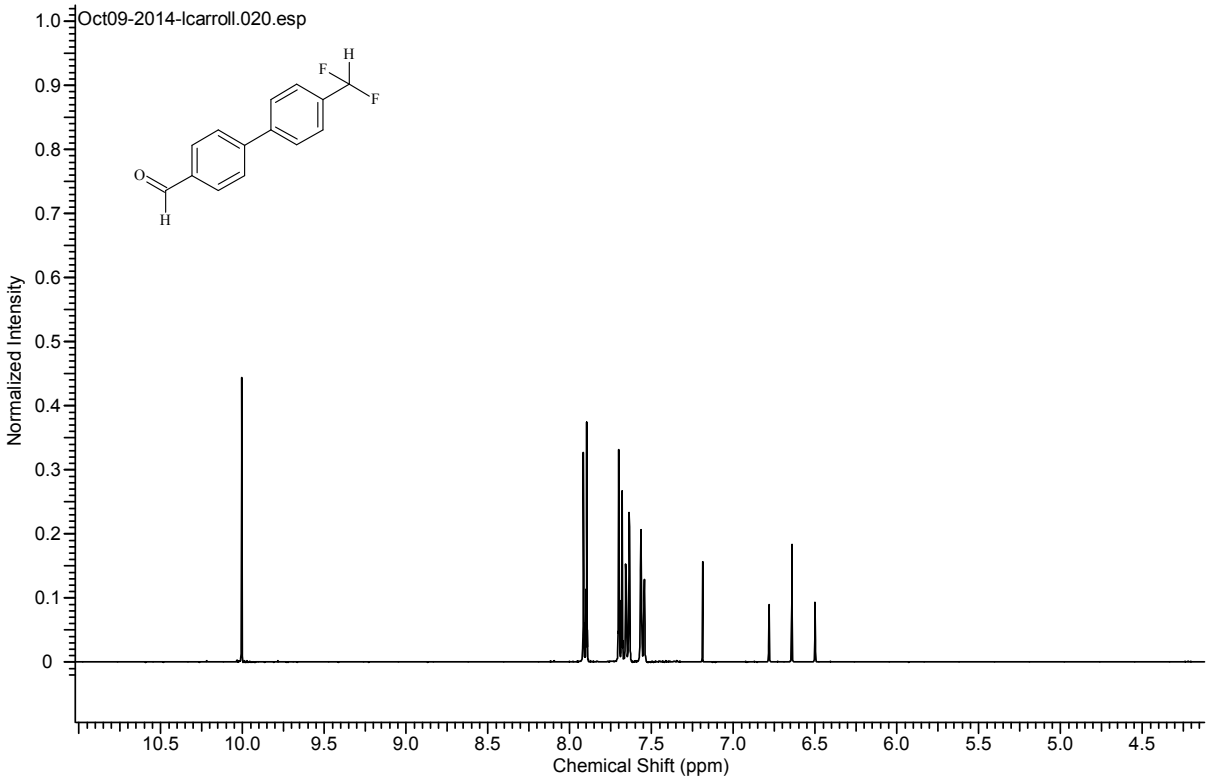

F
H
F
Cl
F
156.97
136.97
134.15
133.93
130.38
130.35
129.57
129.54
129.38
129.27
129.24
125.91
125.91
125.85
125.79
117.74
117.49
116.82
114.45
114.38
7734 CDCl3
7722 CDCl3
7710 CDCl3
76.70 CDCl3
f1 (ppm)

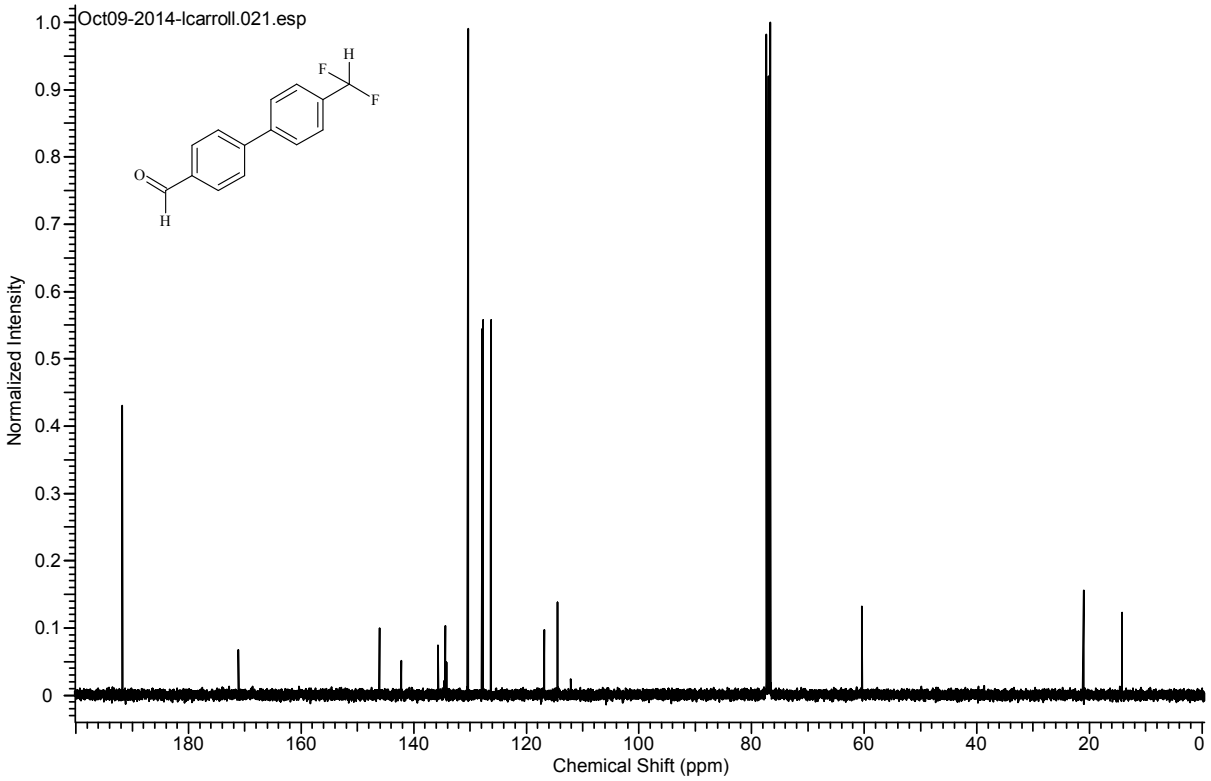

F
H
F
Cl
F
-110.89
-111.04
-120.59
f1 (ppm)

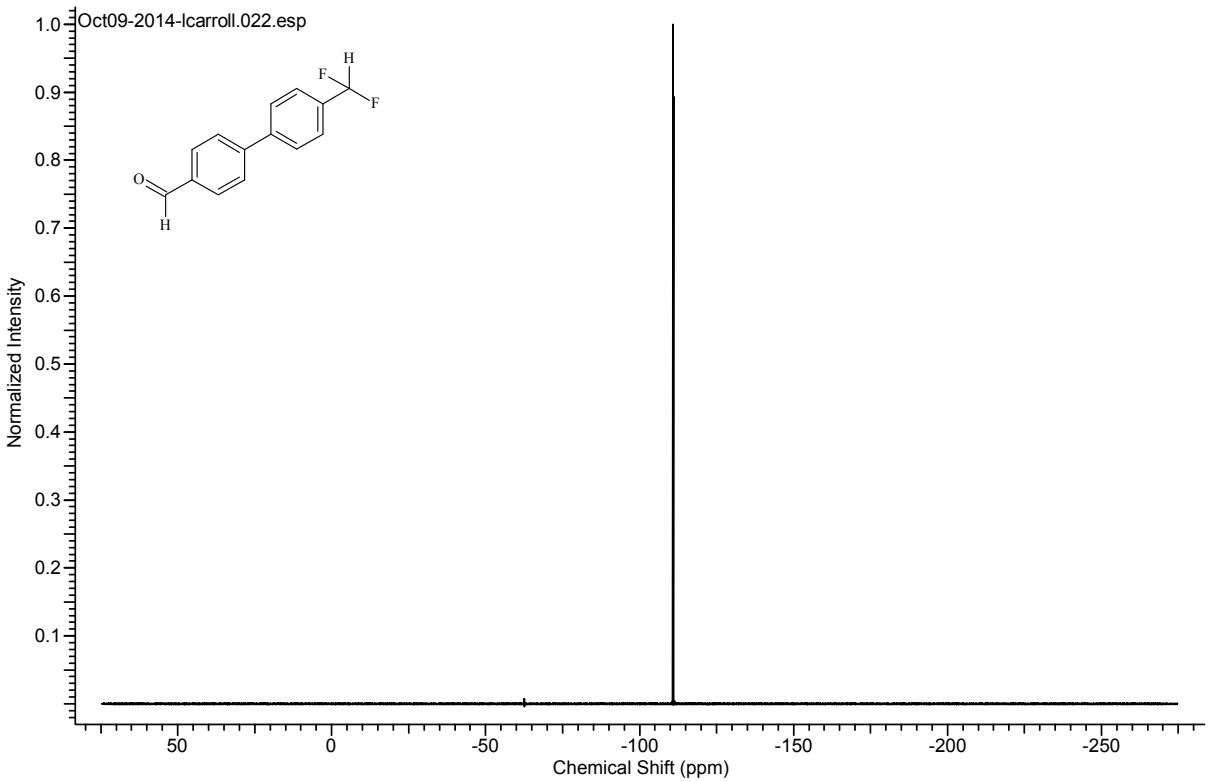

F
F
F
Cl
F
E (m)
7.32
B (dd)
7.42
C (m)
7.67
A (m)
7.13
D (m)
7.35
f1 (ppm)

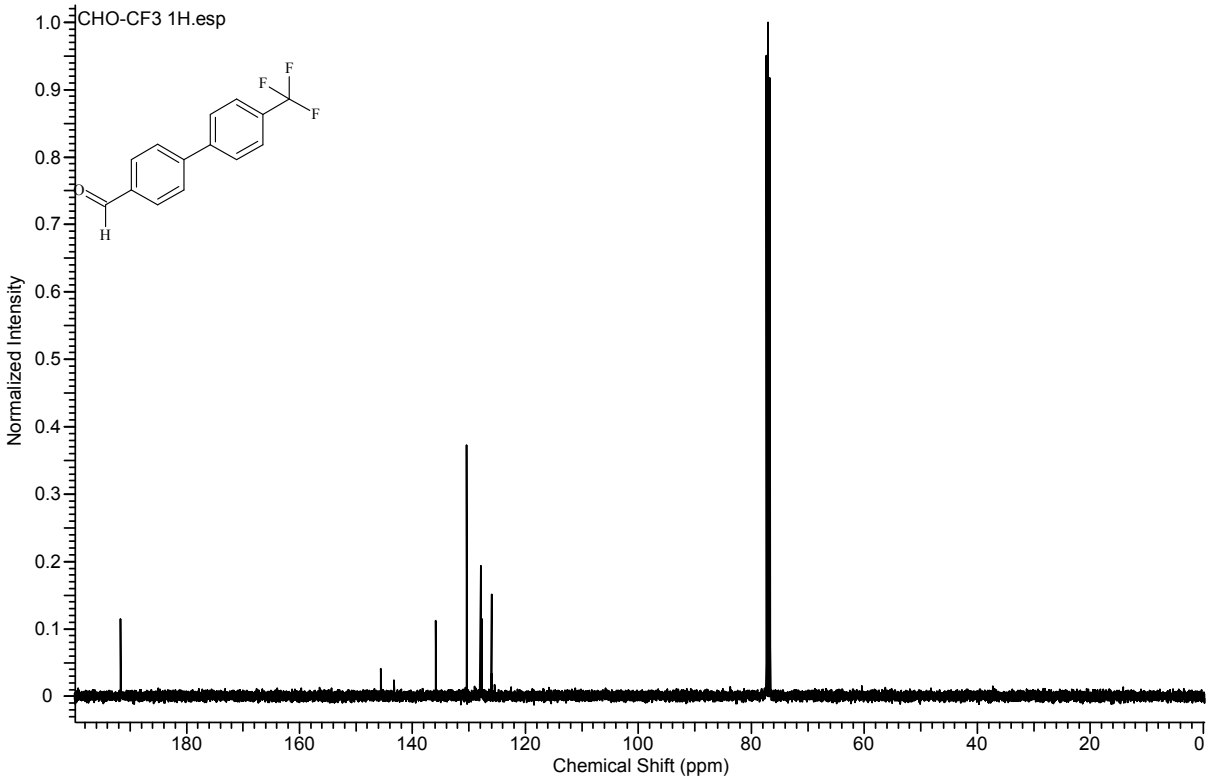

F
F
F
Cl
F
159.50
157.00
131.08
130.34
129.69
129.60
129.29
125.57
123.87
123.81
123.76
123.73
123.72
123.70
117.81
117.57
117.50
117.40
117.33
117.23
117.16
117.05
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
f1 (ppm)

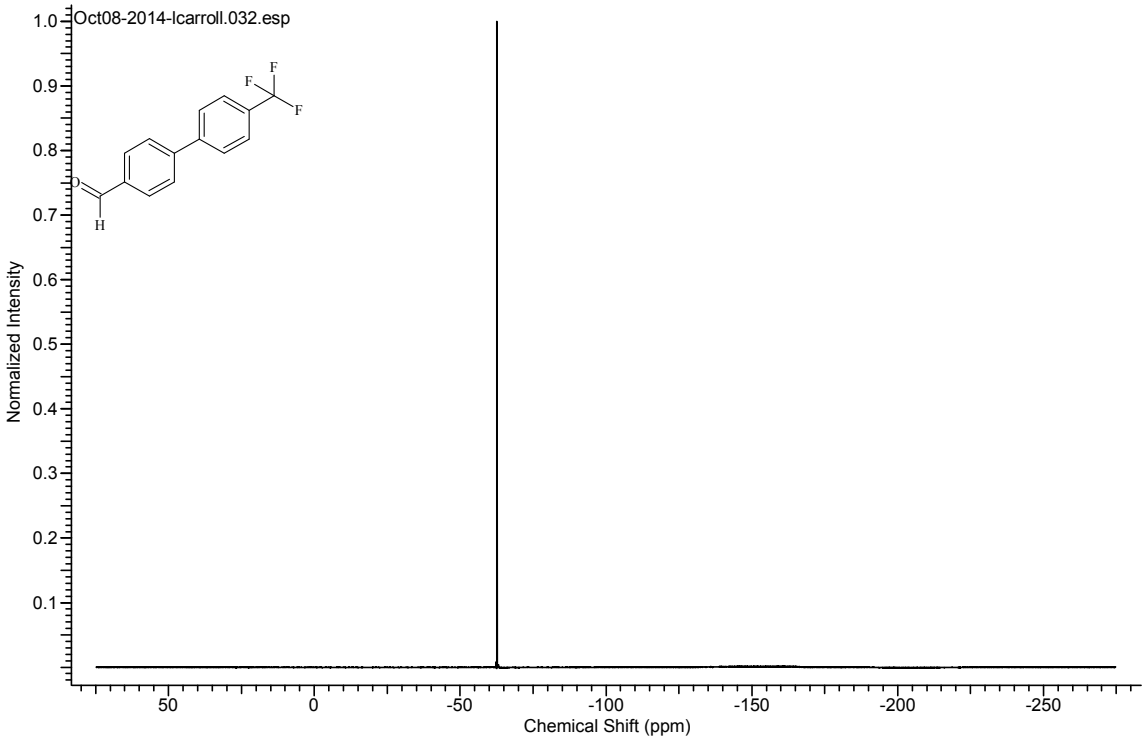

F
F
F
Cl
F
-62.64
-117.13
-120.52
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
70
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
-250
-270
f1 (ppm)


Oct09-2014-lcarroll.020.esp
Normalized Intensity
Chemical Shift (ppm)


Oct09-2014-lcarroll.021.esp
Normalized Intensity
Chemical Shift (ppm)


Oct09-2014-lcarroll.022.esp
Normalized Intensity
Chemical Shift (ppm)

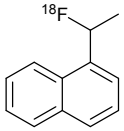

CHO-CF3 1H.esp
Normalized Intensity
Chemical Shift (ppm)


Oct08-2014-lcarroll.032.esp
F
F
F
O
H
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
Normalized Intensity
50
0
-50
-100
-150
-200
-250
Chemical Shift (ppm)

4. ^{18}F radiochemistry

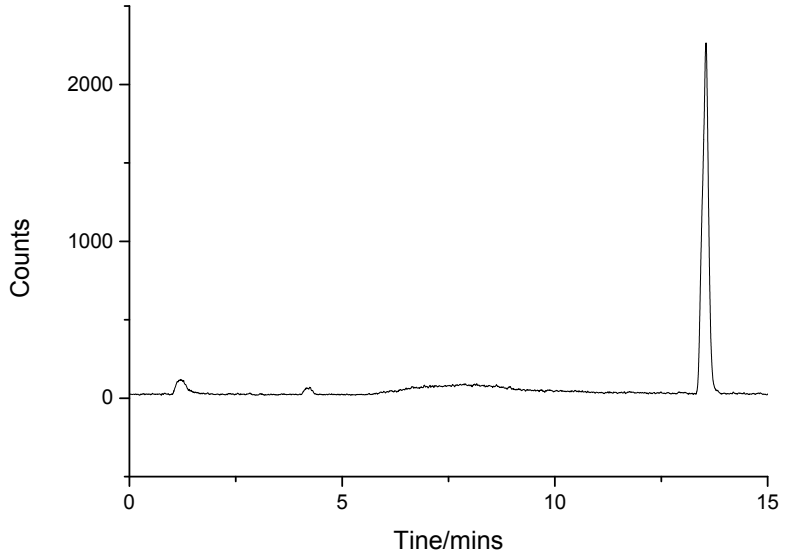
Typical one-pot procedure: 1-Ethylnapthelene (**2a**) (3 μl) was added to 100 μl of MeCN containing 3 mg of **1** and 3 mg of AgOTf. Subsequently, [^{18}F]fluoride (containing 18-crown-6 (7 mg) and K_2CO_3 (2 mg), dried azeotropically with MeCN and re-dissolved in MeCN (1 ml); 100 μl) was added and the reaction mixture was warmed to 60^{o}C for 5 minutes. PhIO was then added over 20 minutes (12 mg, 4 x 3 mg portions) before the reaction was left for a final 5 minutes. A sample was taken and diluted with MeCN:H_2O (1:1, 1 ml) before the reaction was analysed by analytical HPLC, giving a radiochemical incorporation of 75 %, with a total synthesis time of 50 minutes from EOB.

5. Analytical HPLC traces of ^{18}F radiochemical reactions

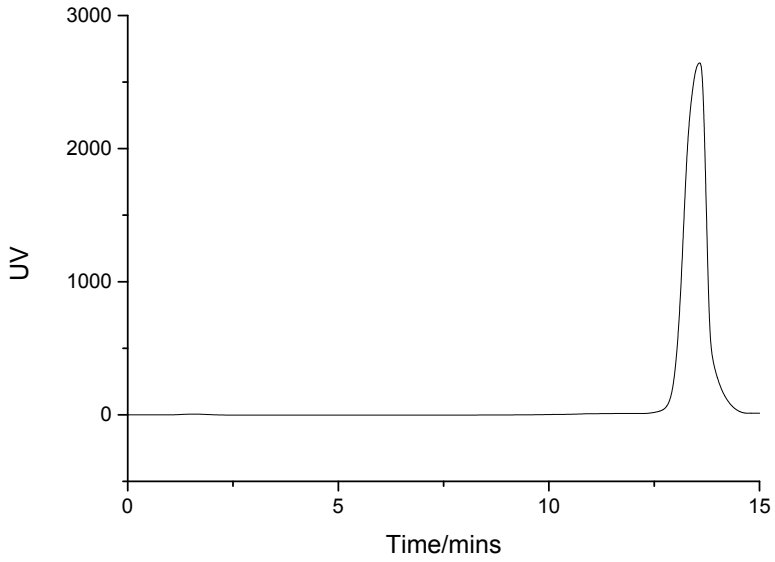


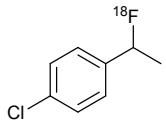
[^{18}F]3a

HPLC method A, RC Trace – 72 ± 3 %, n = 4, R_t = 13.7 minutes



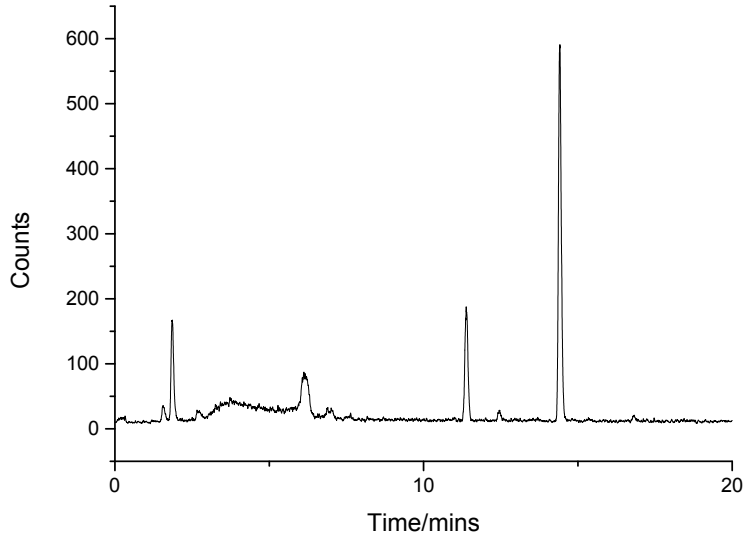
UV Cold Reference



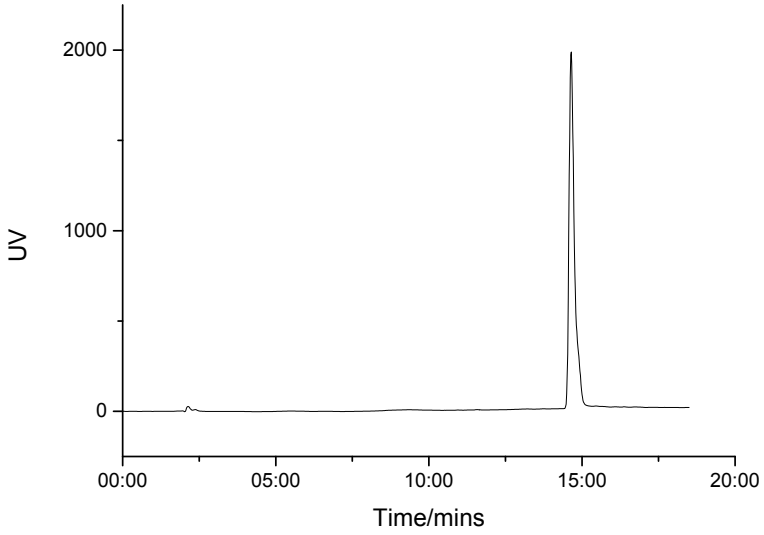


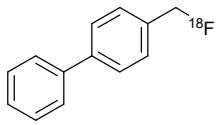
[^{18}F]3b

HPLC method A, RC Trace – 45 ± 4 %, n = 4, R_t = 14.4 minutes



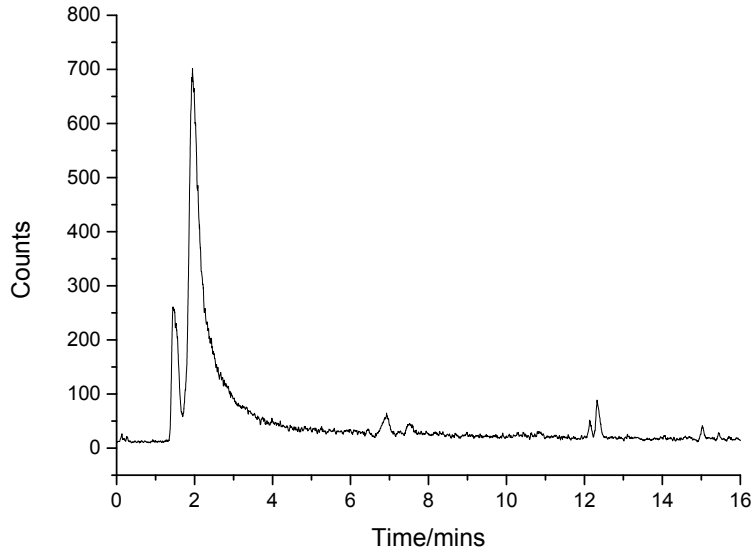
UV Cold Reference



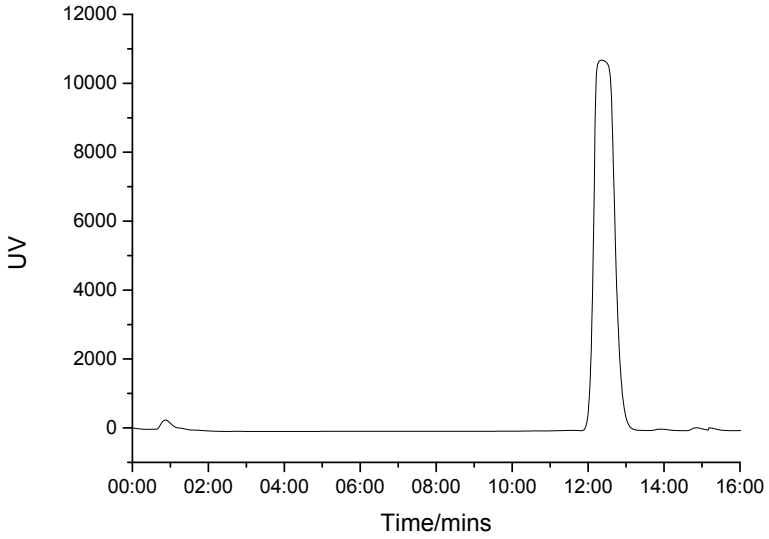


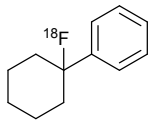
[^{18}F]3c

HPLC method A, RC Trace – 3 ± 1 %, n = 4, R_t = 12.3 minutes



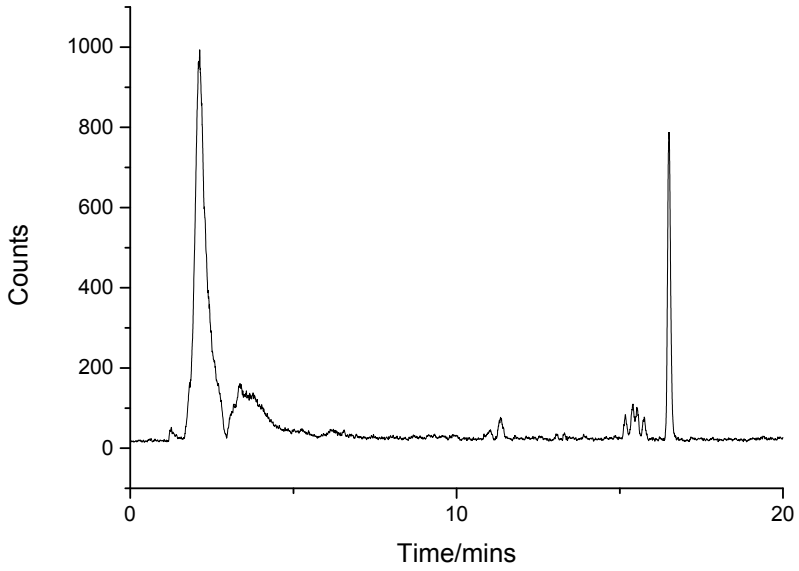
UV Cold Reference



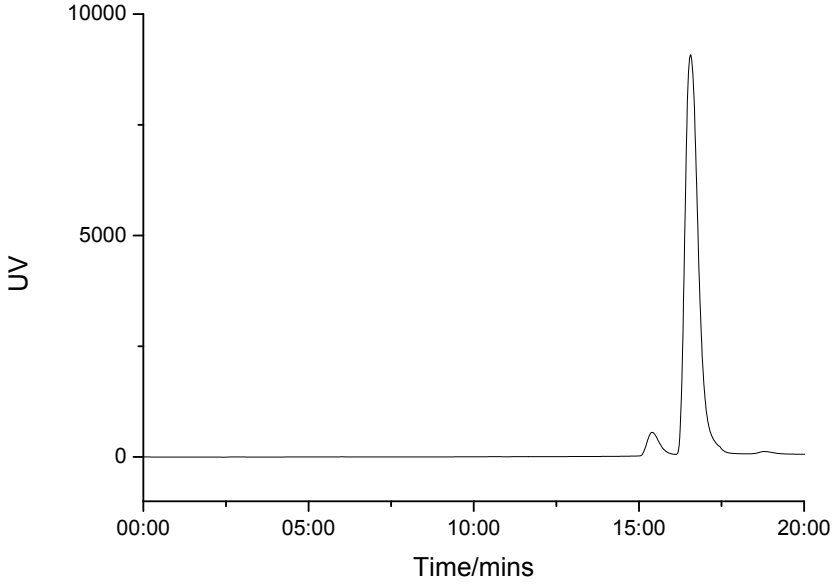


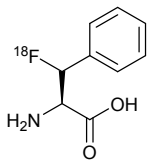
[^{18}F]3d

HPLC method A, RC Trace – 14 ± 2 %, n = 4, R_t = 16.5 minutes



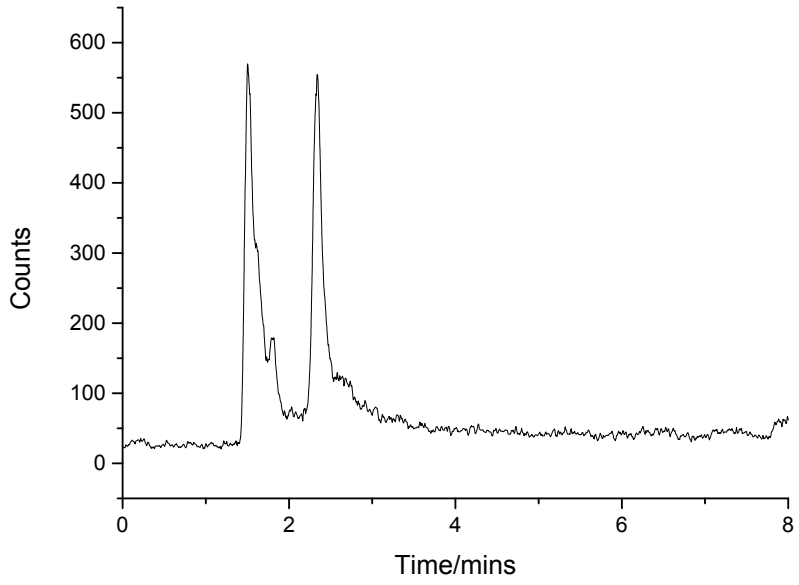
UV Cold Reference



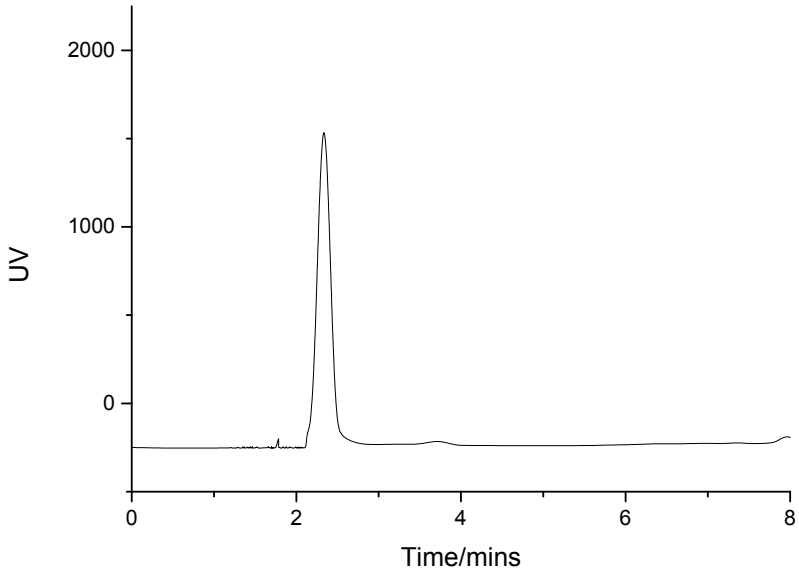


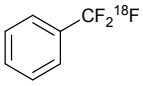
[^{18}F]3e

HPLC method A, RC Trace – 52 %, n = 4, R_t = 2.6 minutes



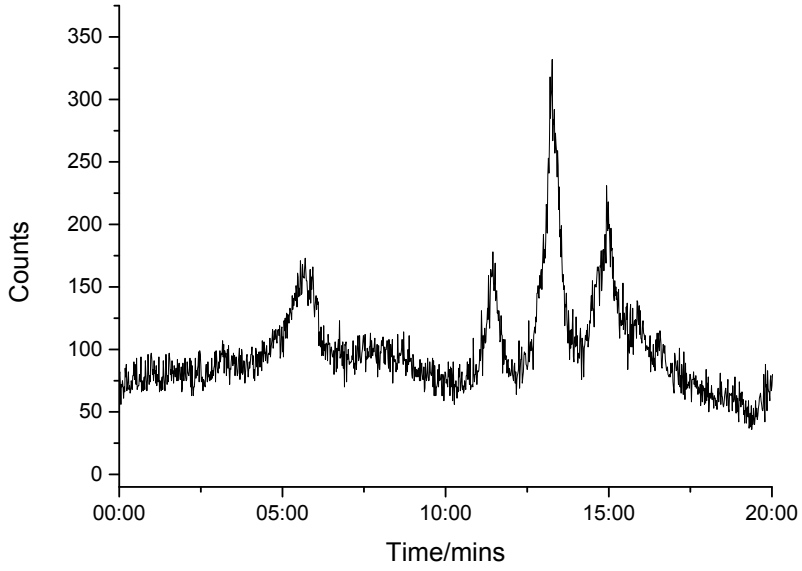
UV Cold reference



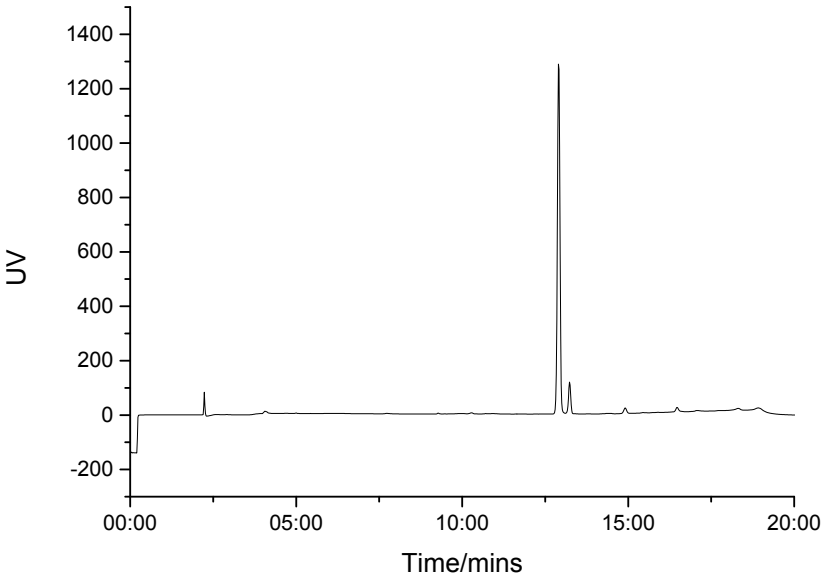


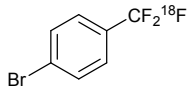
[^{18}F]3f

HPLC method A, RC Trace – 27 ± 4 %, n = 3, R_t = 13.1 minutes



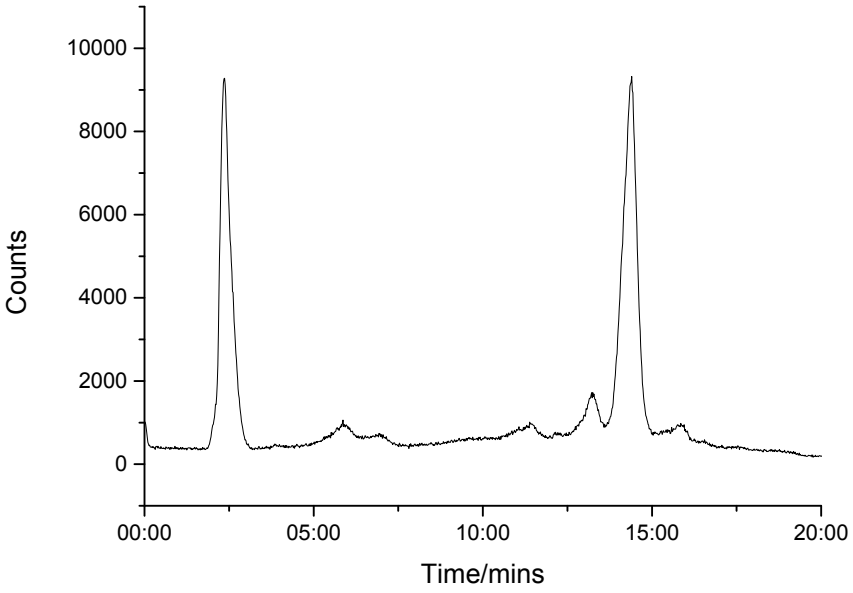
UV Cold Reference



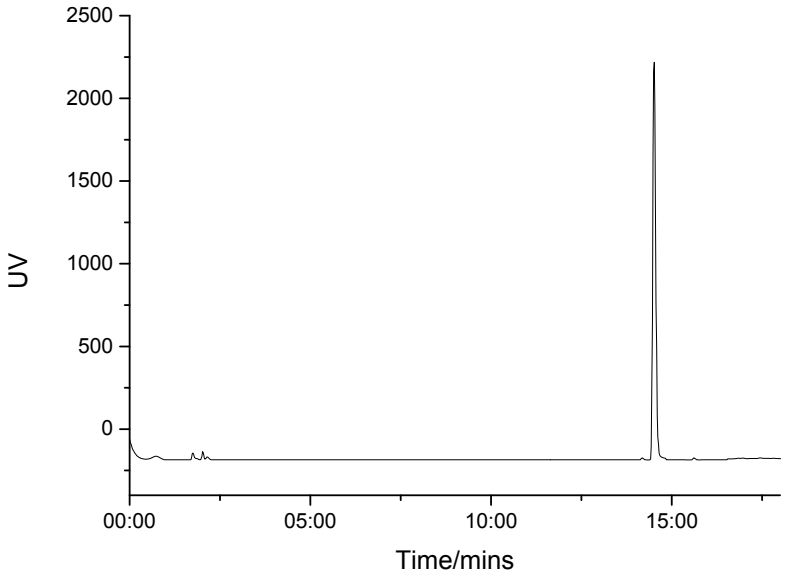


[^{18}F]3g

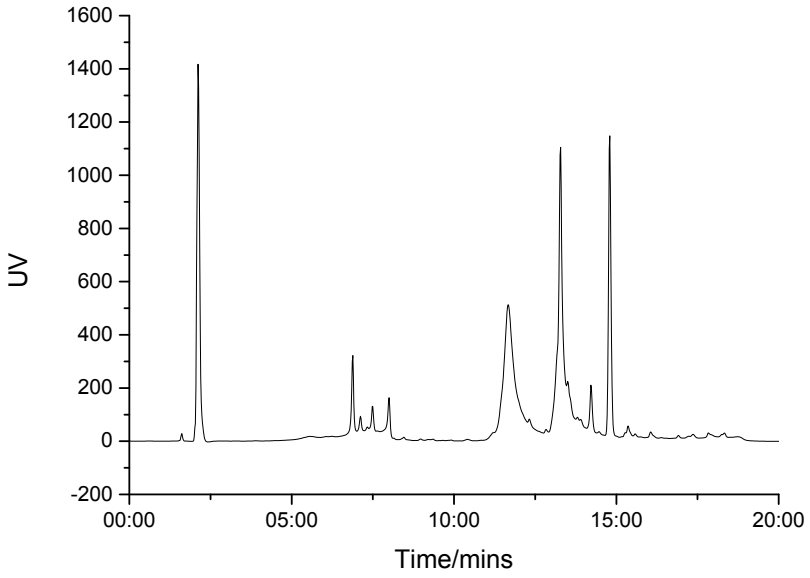
HPLC method A, RC Trace – 44 ± 3 %, n = 4, R_t = 14.3 minutes

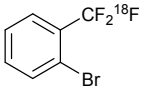


UV Cold reference



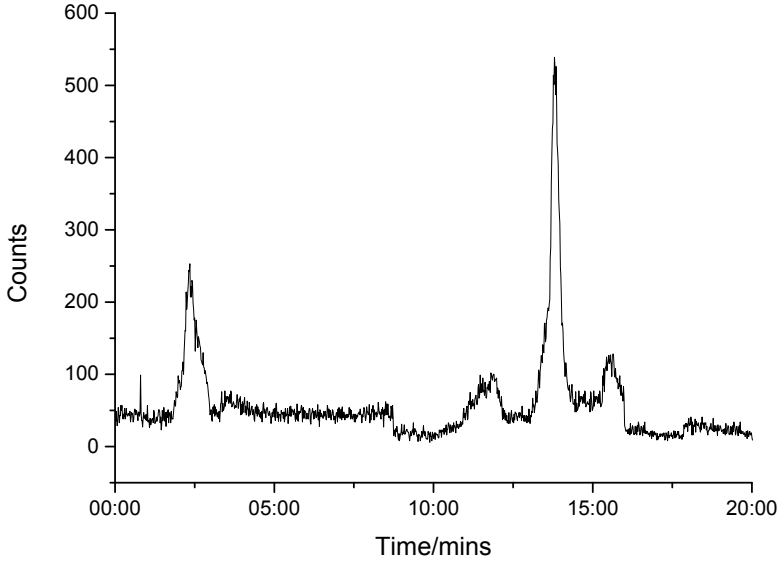
Co-Injection of Reference into reaction mixture



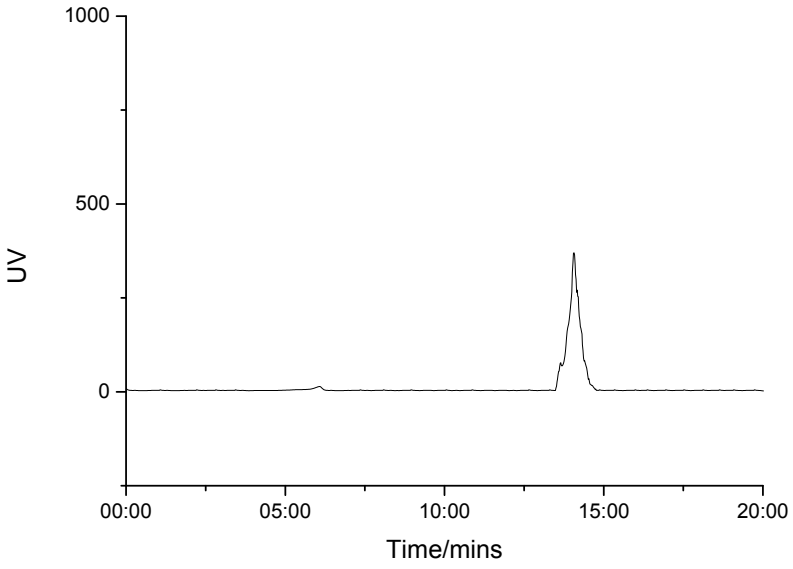


[^{18}F]3h

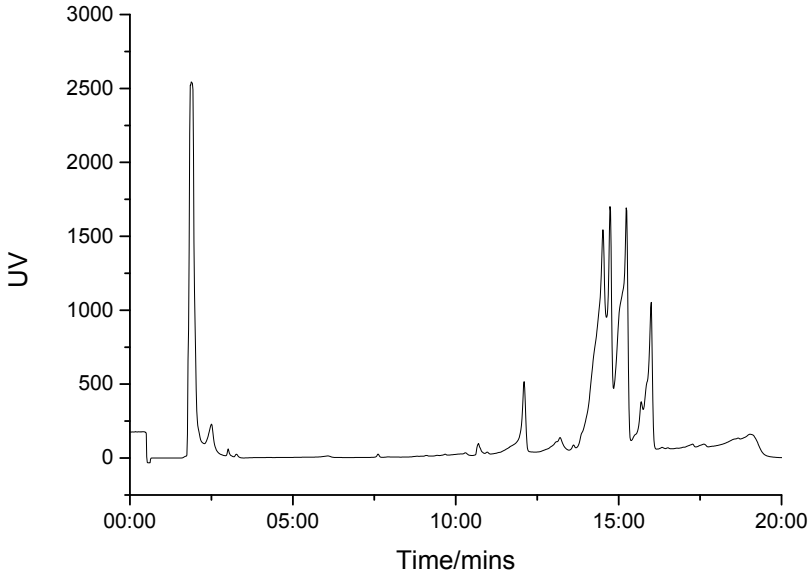
HPLC method A, RC Trace – 54 ± 2 %, n = 4, R_t = 14.0 minutes

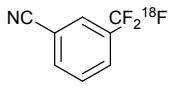


UV Cold Reference



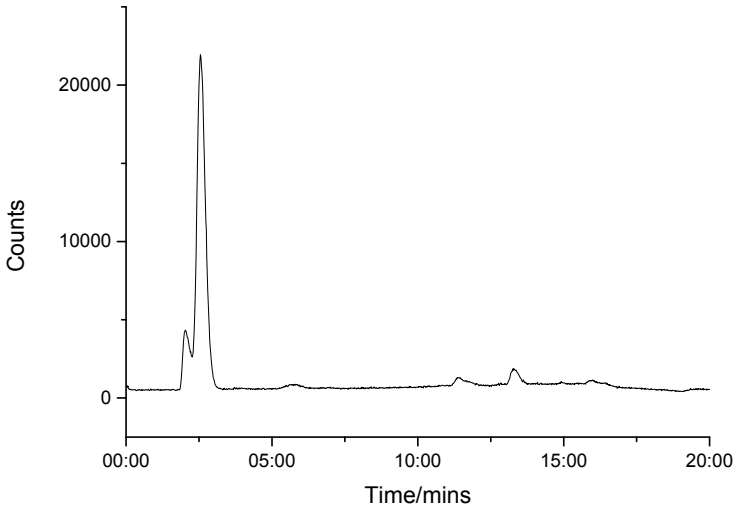
Co-Injection of Reference into reaction mixture



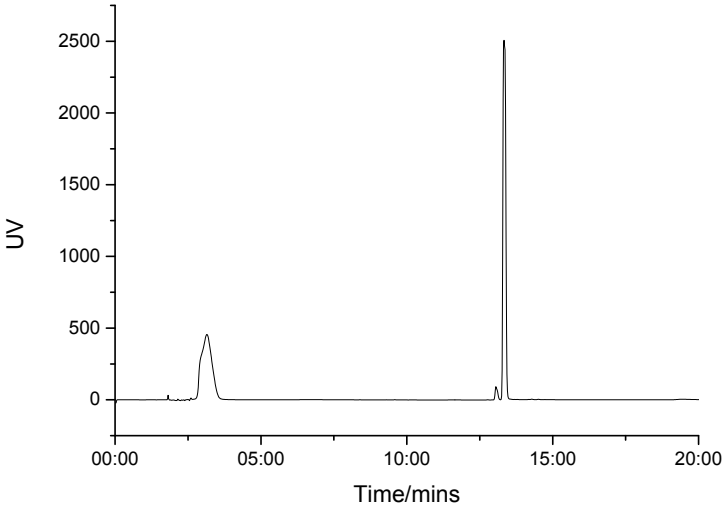


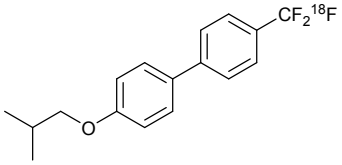
[^{18}F]3j

HPLC method A, RC Trace – 8 ± 2 %, n = 3, R_t = 13.4 minutes



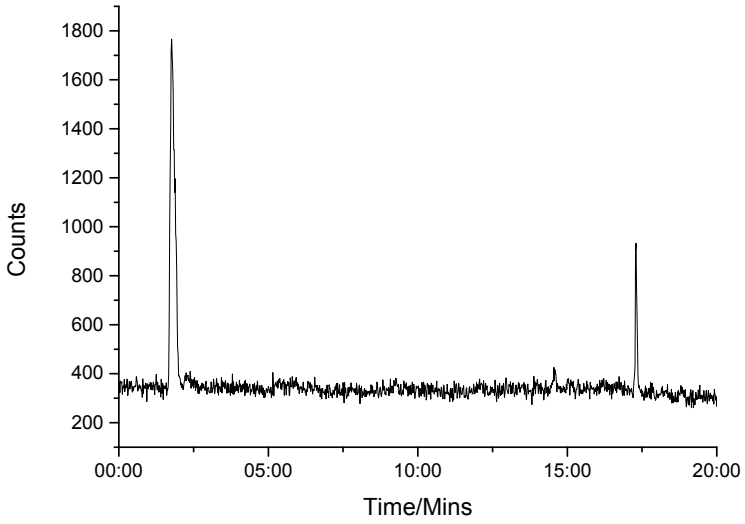
UV cold reference



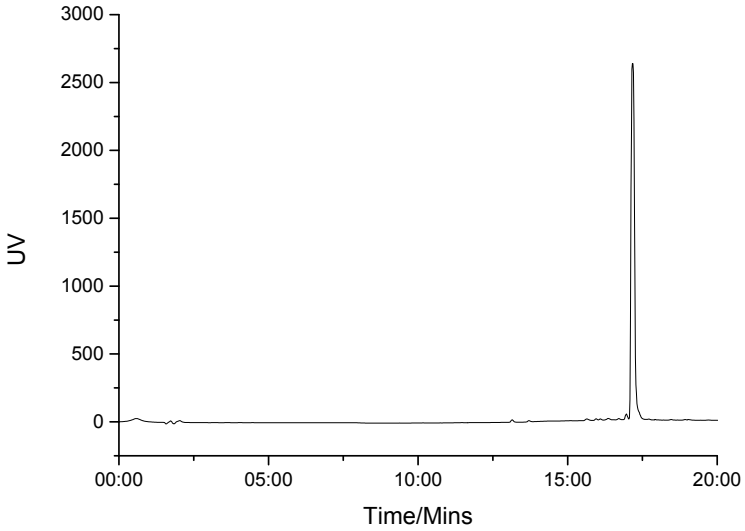


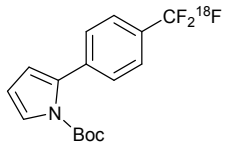
[^{18}F]3k

HPLC method A, RC Trace – 19 ± 3 %, n = 4, R_t = 17.2 minutes



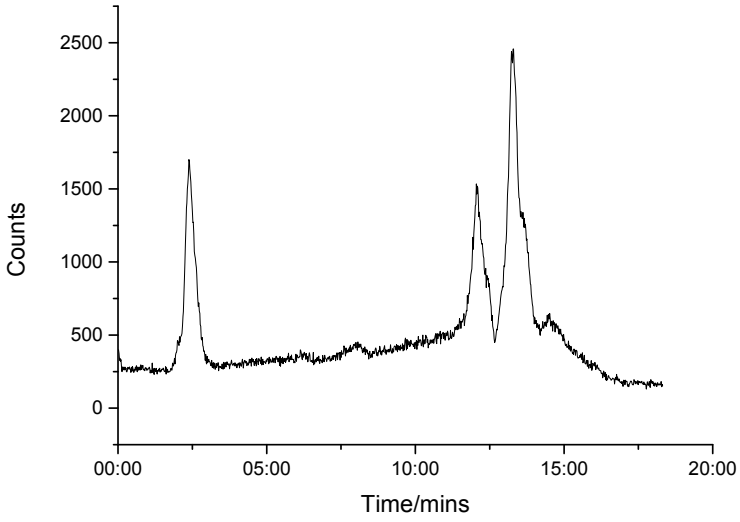
UV cold reference



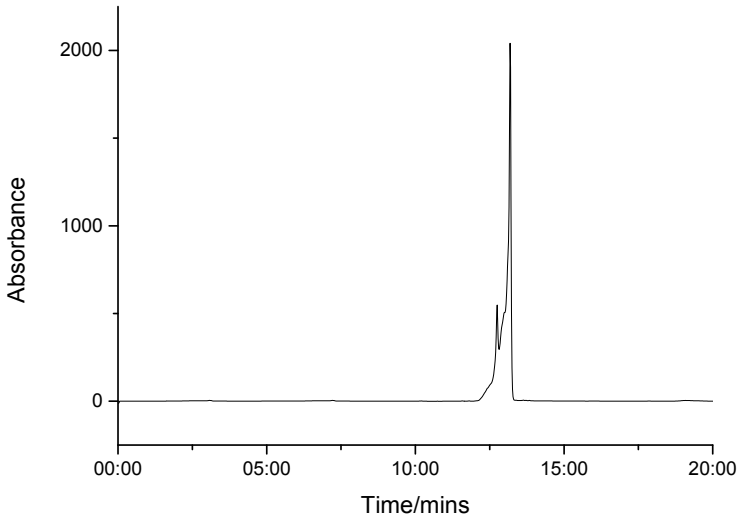


[^{18}F]3l

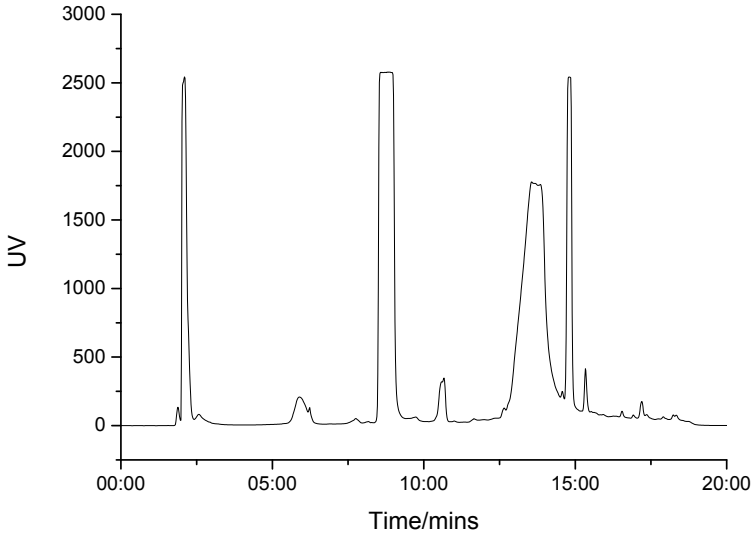
HPLC method B, RC Trace – 42 ± 8 %, n = 3, R_t = 13.2 minutes

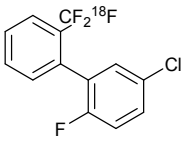


UV Cold reference



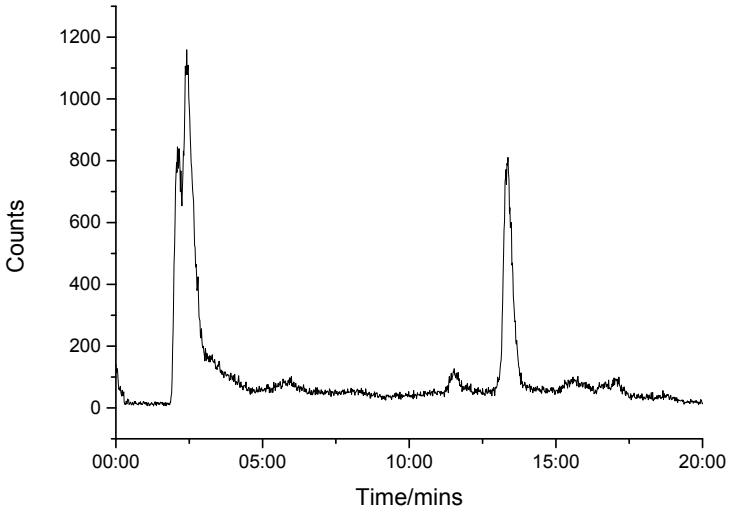
Co-Injection of Reference into reaction mixture



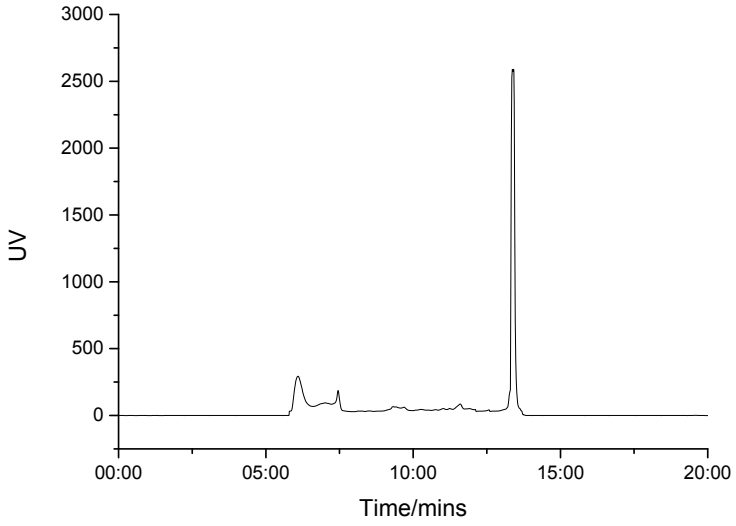


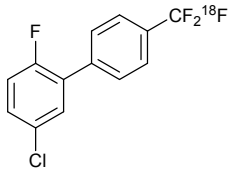
[^{18}F]3m

HPLC method B, RC Trace – 36 ± 4 %, n = 3, R_t = 13.2 minutes



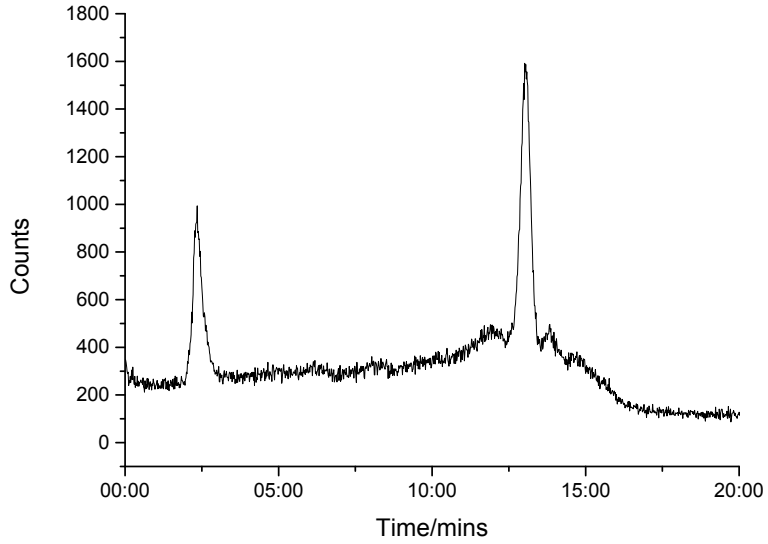
UV Cold Reference



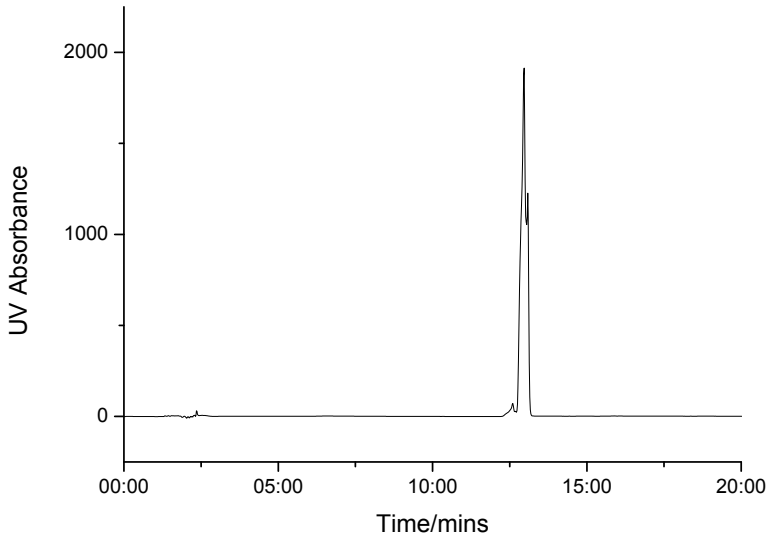


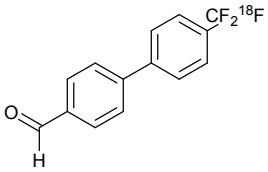
[^{18}F]3n

HPLC method B, RC Trace - 61± 5 %, n = 3, R_t = 12.9 minutes



UV Cold Reference

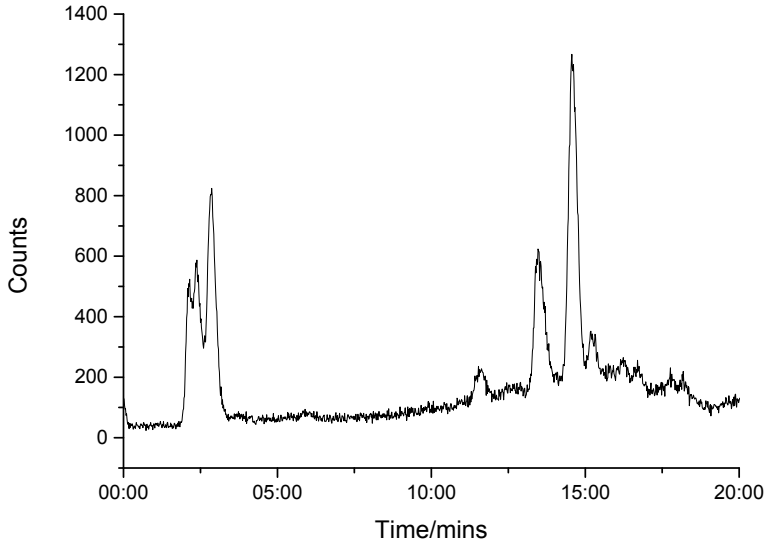




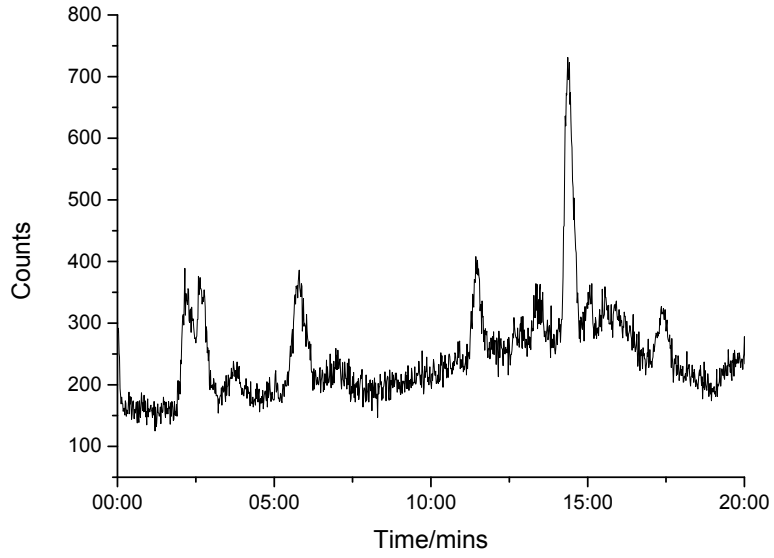
[^{18}F]3o

HPLC method B, RC Trace – 34 ± 2 %, n = 3, R_t = 14.5 minutes

Via prosthetic labelling (note: **[^{18}F]g** is present at 13.2 minutes using this HPLC method)



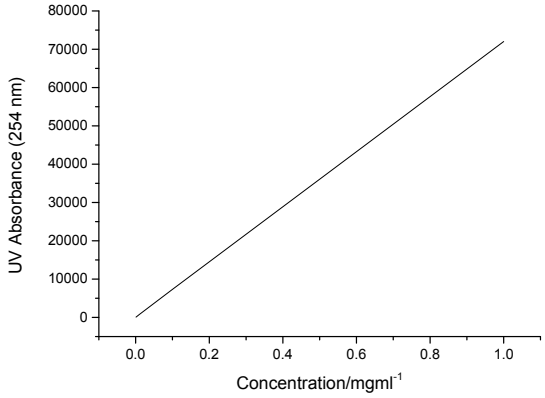
Via 1-step oxidative labelling



6. Specific Activity Calibration

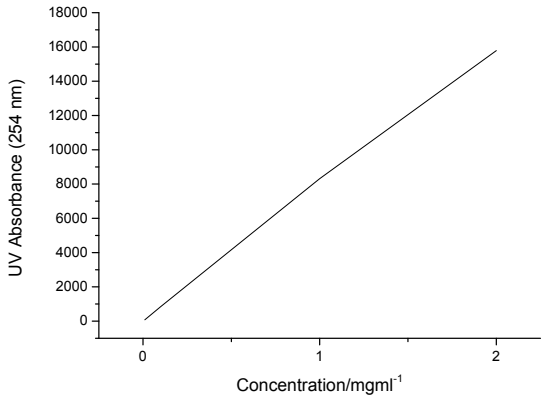
For 3a:

Concentration mg/ml	UV Absorbance
1	72015
0.1	7312
0.001	768
0.0001	71



For 3i:

Concentration mg/ml	UV Absorbance
2	15785
1	8312
0.1	844
0.01	79



Specific activity was measured as follows –

370 MBq of [^{18}F]fluoride was dried under standard conditions in the presence of 18-crown-6 (7 mg) and K_2CO_3 (2 mg) by azeotropic distillation with MeCN twice, followed by re-dissolving in 300 µl of dry MeCN. To this, 1-ethylnapthelene (**2a**) (3 µl) was added to 100 µl of MeCN containing 3 mg of **1** and 3 mg of AgOTf, and the reaction mixture was heated to 60^{o}C for 5 minutes. PhIO was then added over 20 minutes (12 mg, 4 x 3 mg portions) before the reaction was left for a final 5 minutes. This was then diluted and purified by semi-prep HPLC (Gradient A, 3 ml/min, 150 x 10 C18 Gemini) with the product collected (87 MBq). This was subsequently analysed by analytical HPLC (Gradient A, 1 ml/min, 150 x 4.6 C18 Gemini), and the UV absorbance compared to that of the calibration carried out.

7. ICP Measurement

The ICP sample was collected from the reaction to form **[^{18}F]3a**, with a starting activity of 200 MBq. The reaction was carried out as described previously, and was purified by a modified form of HPLC method A (flow-rate = 3 ml/min, as opposed to 1 ml/min in the usual method A) on a C18 250 mm x 10 mm Ultracarb semi-preparative HPLC column. A small fraction of the collected peak (> 10 µl from 3 ml) was re-injected for confirmation of the

product, with the majority allowed to decay (10 half-lives) before being sent for analysis at the University of Sheffield.

8. References

1. Liu, W. and J.T. Groves, *Manganese-Catalyzed Oxidative Benzylic C–H Fluorination by Fluoride Ions.* Angewandte Chemie International Edition, 2013. **52**(23): p. 6024-6027.
2. Lee, K.-C.L., Sang-Yoon; Choe, Yearn-Seong; Chi, Dae-Yoon; , *Metabolic Stability of [18F]Fluoroalkylbiphenyls.* Bulletin of the Korean Chemical Society, 2004. **25**(8): p. 1225-1230.
3. Kollonitsch, J., S. Marburg, and L.M. Perkins, *Fluorodehydroxylation, a novel method for synthesis of fluoroamines and fluoroamino acids.* The Journal of Organic Chemistry, 1979. **44**(5): p. 771-777.