Cu-Mediated C–H ^{18}F-Fluorination of Electron-Rich (Het-ero)Arenes

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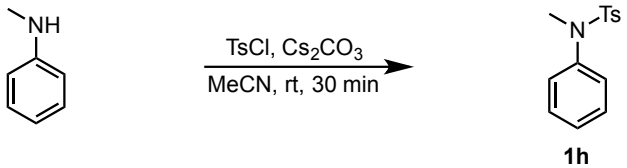
I. General Considerations, Methods, and Materials

^{1}H NMR spectra were obtained on a Varian MR400 (400.52 MHz for ^{1}H; 376.87 MHz for ^{19}F), a Varian vnmrs 500 (500.01 MHz for ^{1}H; 470.56 MHz for ^{19}F), a Varian vnmrs 700 (699.76 MHz for ^{1}H; 175.95 MHz for ^{13}C), or a Varian Inova 500 (499.90 MHz for ^{1}H) spectrometer. Chemical shifts are reported in parts per million (ppm) and referenced to the residual solvent peak ($CDCl_3$: ^{1}H: δ = 7.26 ppm, ^{13}C: δ = 77.16 ppm; DMSO-d_6: ^{1}H: δ = 2.50 ppm, ^{13}C: δ = 39.52 ppm; CD_3OD: ^{1}H: δ = 3.30 ppm, ^{13}C: δ = 49.00 ppm; CD_3CN: ^{1}H: δ = 1.94 ppm). ^{19}F NMR spectra are referenced to standard trichlorofluoromethane ($CFCl_3$: δ = 0.00 ppm for ^{19}F). NMR spectra were recorded at room temperature unless otherwise noted. The abbreviations for ^{1}H and ^{19}F multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), pentet (p) heptet (hept), doublet of doublet (dd), doublet of doublet of doublet (ddd), doublet of triplet (dt), doublet of doublet of triplet (ddt), triplet of doublet (td), pentet of doublet (pd), broad singlet (bs) and multiplet (m). Coupling constants (*J*) are reported in hertz (Hz). Melting points were determined with a Mel-Temp 3.0 (Laboratory Devices, Inc) and are uncorrected. High-resolution mass spectra were recorded on a Micromass AutoSpec Ultima Magnetic Sector mass spectrometer. Infrared spectroscopy was performed on a Perkin-Elmer Spectrum BX FT-IR spectrometer, and peaks are reported in cm^{-1}. Thin layer chromatography (TLC) was perfomed on Macherey-Nagel GmbH & Co. precoated TLC-plates SIL G-25 UV_{254} (0.25 mm silica gel with fluorescent indicator UV_{254}). Flash column chromatography was conducted using a Biotage Isolera One system with SNAP Ultra column cartridges.

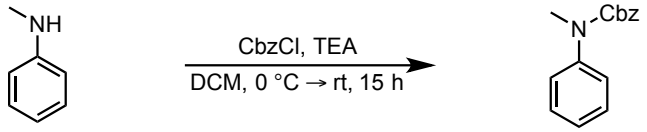
Commercial reagents and solvents were used as received unless otherwise noted. Anhydrous acetonitrile, *N*-methyl aniline, cesium carbonate, potassium carbonate, anisole, 4-fluoroanisole, methyl 2-methoxybenzoate, 1,3-dimethoxybenzene, *o*-xylene, spray-dried potassium fluoride, and benzyl bromide were obtained from Sigma Aldrich. *p*-Toluenesulfonyl chloride, methyl 5-fluoro-2-hydroxybenzoate, benzyl phenyl ether, 18-crown-6, and benzyl chloroformate were obtained from Acros. Anhydrous dichloromethane was obtained from Acros and was stored over activated molecular sieves. Toluene and magnesium sulfate were obtained from Fisher Chemical. Iodine, *p*-toluenesulfonic acid monohydride, 4-fluoro-*N*-methylaniline, 1-fluoro-2,4-dimethoxybenzene, 1-phenyl-2-pyrrolidinone, 2,2,2-trifluoroethanol, dimethyl carbonate, and triethylamine were obtained from Alfa Aesar. Anhydrous *N*,*N*'-dimethylformamide was obtained from Alfa Aesar and was stored over activated molecular sieves. 4-Fluorotoluene, 2-fluoroanisole, and 4-fluoro-*o*-xylene were obtained from Matrix Scientific. *m*-Chloroperoxybenzoic acid (85%) was obtained from AK Scientific. 5-Fluoro-2,3-dihydrobenzofuran was obtained from Apollo Scientific. Anhydrous diethyl ether was obtained from EMD Millipore Corporation. 2-Bromoanisole, 2-bromo-4-fluoroanisole, 2,3-dihydrobenzofuran, 1-(4-fluorophenyl)-2-pyrrolidinone, 3-methylthiophene, 1,3-dimethyluracil, 3-chloro-6,11-dihydro-6-methyl-5,5,11-trioxodibenzo[c,f][1,2]thiazepine, fluorouracil, *N*-Fluoro-*N*'-chloromethyltriethylenediamine bis(tetrafluoroborate) (SelectFluor) and 4-benzyloxyfluorobenzene were obtained from Oakwood Products. Nimesulide, 4-(3,5-dimethylpyrazol-1-yl)benzonitrile, and methyl 1-methylpyrrole-2-carboxylate were obtained from Combi-Blocks. 1,3,5-Trimethylbenzene was obtained from TCI America. 3-Fluoroanisole and 2,6-diisopropylphenol were obtained from Ark Pharm, Inc. DMSO-d_6, CD_3OD, $CDCl_3$ were obtained from Cambridge Isotope Laboratories. Copper(II) trifluoromethanesulfonate was obtained from Strem. Ethyl acetate (EtOAc), hexanes (Hex), methanol (MeOH) and dichloromethane (DCM) for column chromatography were obtained from VWR International.

II. Synthesis and Characterization of Starting Materials



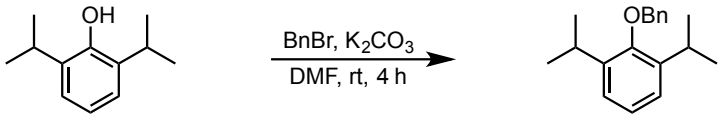
1h

***N*,4-Dimethyl-*N*-phenylbenzenesulfonamide (1h)**. A previously reported procedure was used for the synthesis of **1h** from *N*-methyl aniline.[1] Recrystallization from MeOH led to the isolation of **1h** as a white solid (1.08 g, 45% yield, mp 92-93 °C). ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.43 (d, J = 7.9 Hz, 2H), 7.33-7.21 (multiple peaks, 5H), 7.13-7.06 (m, 2H), 3.16 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 143.6, 141.6, 133.4, 129.4, 128.8, 127.9, 127.3, 126.6, 38.1, 21.6; FT-IR 1594.9, 1491.0, 1342.2, 1170.1, 1063.0, 866.8 cm^{-1}; HRMS *m*/*z* calculated for $C_{14}H_{16}NO_2S$ [M+H]$^+$: 262.0897, found 262.0896.



1i

Benzyl methyl(phenyl)carbamate (1i). To a 50 mL round bottom flask equipped with a magnetic stir bar were added *N*-methyl aniline (1.0 mL, 9.2 mmol, 1.0 equiv) and benzyl chloroformate (1.6 mL, 11 mmol, 1.2 equiv) in DCM (18 mL) under a nitrogen atmosphere. The mixture was cooled to 0 °C using an ice bath and triethylamine (1.9 mL, 14 mmol, 1.5 equiv) was added dropwise. The mixture was stirred for 15 h at room temperature. Upon completion, the mixture was diluted with DCM (5.0 mL) and washed with water (3 x 25 mL) and brine (25 mL). The organic phase was dried with magnesium sulfate and concentrated *in vacuo*. Purification by silica gel flash chromatography (25 g Biotage SNAP-Ultra silica column, gradient from 0% to 3% EtOAc:Hex) led to the isolation of **1i** as a colorless oil (860 mg, 39% yield), R_f = 0.16 (10% EtOAc:Hex, visualized by 254 nm light and PMA stain), which was stored in the freezer until use. ^{1}H NMR (700 MHz, DMSO-d_6, 90 °C) δ 7.39-7.33 (multiple peaks, 4H), 7.33-7.27 (multiple peaks, 5H), 7.22 (t, J = 7.3 Hz, 1H), 5.13 (s, 2H), 3.27 (s, 3H); ^{13}C NMR (176 MHz, DMSO-d_6, 90 °C) δ 154.2, 142.8, 136.4, 128.2, 127.8, 127.2, 126.9, 125.3, 125.1, 66.1, 36.9; ^{13}C NMR (176 MHz, $CDCl_3$, room temperature) δ 155.5, 143.3, 136.7, 128.9, 128.5, 128.0, 127.7, 126.2, 67.3, 37.9; FT-IR 1694.2, 1595.0, 1422.9, 1298.6, 1150.8, 1002.7, 913.8 cm^{-1}; HRMS *m*/*z* calculated for $C_{15}H_{16}NO_2$ [M+H]$^+$: 242.1176, found 242.1176.

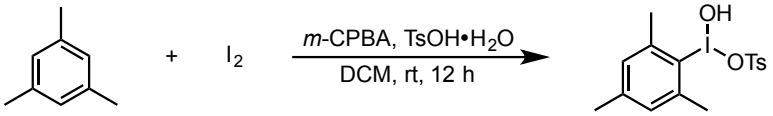


1p

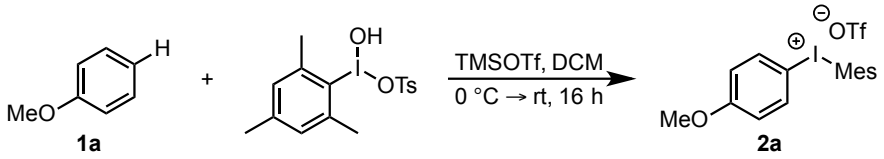
2-(Benzyloxy)-1,3-diisopropylbenzene (1p). To a 25 mL round bottom flask equipped with a magnetic stir bar was added 2,6-diisopropylphenol (1.0 mL, 5.6 mmol, 1.0 equiv) in DMF (8.0 mL) under a nitrogen atmosphere. To the mixture were added K_2CO_3 (1.6 g, 11 mmol, 2.0 equiv) and benzyl bromide (1.0 mL, 8.4 mmol, 1.5 equiv). The mixture was stirred for 4 h at room temperature before being quenched with H_2O (20 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organics were washed with H_2O (7 x 10 mL) and brine (10 mL), dried with magnesium sulfate, and concentrated *in vacuo*. Purification by silica gel flash chromatography (0% to 10% Et_2O:Hex) led to the isolation of **1p** as a colorless oil (330 mg, 22% yield), R_f = 0.53 (9:1 Hex:Et_2O, visualized by 254 nm light and phosphomolybdic acid (PMA) stain). ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.54-7.47 (m, 2H), 7.43 (m, 2H), 7.39-7.33 (m, 1H), 7.17-7.11 (multiple peaks, 3H), 4.81 (s, 2H), 3.40 (hept, J = 6.9 Hz, 2H), 1.25 (d, J = 6.9 Hz, 12H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 153.3, 142.1, 137.9, 128.7, 128.0, 127.5, 124.9, 124.2, 76.5, 26.7, 24.3; FT-IR 1454.9, 1255.1, 1181.1, 1098.1, 1017.4, 759.0 cm^{-1}; HRMS *m*/*z* calculated for $C_{19}H_{25}O$ [M+H]$^+$: 269.1900, found 269.1893.

1q

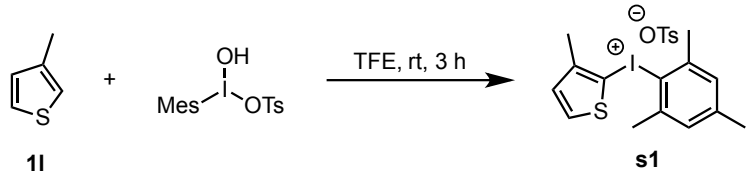
***N*-Benzyl-*N*-(4-nitro-2-phenoxyphenyl)methanesulfonamide (1q)**. To a 25 mL round bottom flask equipped with a magnetic stir bar was added nimesulide (1.0 g, 3.2 mmol, 1.0 equiv) in DMF (5.0 mL) under a nitrogen atmosphere. To the mixture were added K_2CO_3 (900 mg, 6.5 mmol, 2.0 equiv) and benzyl bromide (0.58 mL, 4.9 mmol, 1.5 equiv). The mixture was stirred for 4 h at room temperature before being quenched with H_2O (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organics were washed with H_2O (7 x 10 mL) and brine (10 mL), then dried with magnesium sulfate and concentrated *in vacuo*. Recrystallization from EtOH led to the isolation of **1q** as a white solid (1.13 g, 88% yield, mp 126-128 °C). ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.78 (dd, J = 8.7, 2.5 Hz, 1H), 7.57 (d, J = 2.5 Hz, 1H), 7.49 (t, J = 8.0 Hz, 2H), 7.36-7.27 (multiple peaks, 7H), 7.08 (d, J = 8.0 Hz, 2H), 4.92 (s, 2H), 3.09 (s, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 155.5, 154.2, 148.0, 135.5, 134.5, 134.2, 130.9, 128.8, 128.8, 128.3, 126.0, 120.0, 117.7, 112.2, 54.0, 40.5; FT-IR 1586.5, 1512.7, 1486.0, 1323.6, 1202.2, 1063.3 cm^{-1}; HRMS *m*/*z* calculated for $C_{20}H_{19}N_2O_5SNa$ $[M+H]^+$: 399.1009, found 399.1007.



Hydroxy(mesityl)-λ^3-iodaneyl 4-methylbenzenesulfonate. A previously reported procedure was used for the synthesis of MesI(OH)OTs from 1,3,5-trimethylbenzene.[2] To a 250 mL round bottom flask equipped with a stir bar was added iodine (2.3 g, 9.0 mmol, 0.50 equiv) in DCM (60 mL). To the stirring solution were added 1,3,5-trimethylbenzene (2.5 mL, 18 mmol, 1.0 equiv), *m*-CPBA (80%, 5.8 g, 27 mmol, 1.5 equiv), and TsOH•H_2O (3.4 g, 18 mmol, 1.0 equiv). The solution was stirred at room temperature for 12 h, before being concentrated *in vacuo*. To the residue was added diethyl ether (75 mL), and the mixture was stirred at room temperature for an additional 30 min. The precipitate was collected by filtration and dried to afford MesI(OH)OTs as a white solid (6.41 g, 82% yield, mp 105-106 °C). The ^{1}H and ^{13}C NMR spectroscopic data match those previously reported in the literature.[2-3]



Mesityl(4-methoxyphenyl)iodonium trifluoromethanesulfonate (2a). To a solution of MesI(OH)OTs (430 mg, 1.0 mmol, 1.0 equiv) in DCM (4.0 mL) in a 20 mL vial equipped with a stir bar was added arene **1a** (0.11 mL, 1.0 mmol, 1.0 equiv). The stirring solution was cooled to 0 °C and trimethylsilyl trifluoromethanesulfonate (TMSOTf) (0.18 mL, 1.0 mmol, 1.0 equiv) was added dropwise. The solution was warmed to room temperature and stirred for 18 h. The solution was concentrated under a stream of nitrogen, and Et_2O was added to precipitate the diaryliodonium salt. The mixture was stirred for 30 min before the diaryliodonium salt was collected by filtration, washed with Et_2O, and dried under vacuum, leading to the isolation of **2a** as a grey solid (314 mg, 63% yield), which was stored in the freezer until use. ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.64 (d, J = 9.1 Hz, 2H), 7.09 (s, 2H), 6.93 (d, J = 9.1 Hz, 2H), 3.82 (s, 3H), 2.64 (s, 6H), 2.35 (s, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 162.7, 144.5, 142.3, 135.5, 130.5, 121.2, 118.2, 100.1, 55.9, 27.2, 21.2; ^{19}F NMR (377 MHz, $CDCl_3$) δ –78.8 (s, 3F); FT-IR 1572.3, 1486.1, 1239.6, 1176.8, 1022.7, 824.8 cm^{-1}; HRMS *m*/*z* calculated for $C_{16}H_{18}OI$ $[M]^+$: 353.0397, found 353.0399.

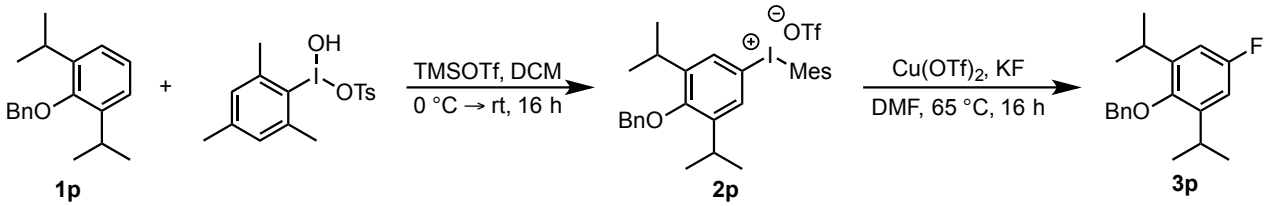


Mesityl(3-methylthiophen-2-yl)iodonium 4-methylbenzenesulfonate (s1). A previously reported procedure was used for the synthesis of **s1** from 3-methylthiophene.[4] To a solution of MesI(OH)OTs (700

mg, 1.6 mmol, 1.0 equiv) in 2,2,2-trifluoroethanol (TFE) (8.0 mL) in a 20 mL vial equipped with a stir bar was added of arene **1l** (0.16 mL, 1.0 mmol, 1.0 equiv). The solution was stirred for 3 h at room temperature. To the solution was added MeOH (5 mL) before the reaction mixture was concentrated *in vacuo*. To the residue was added diethyl ether (10 mL), and the mixture stirred at room temperature for 30 min. The precipitate was collected by filtration and dried to afford **s1** as a grey solid (619 mg, 75% yield), which was stored in the freezer until use. ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.60-7.51 (multiple peaks, 3H), 7.05 (d, *J* = 8.0 Hz, 2H), 7.01 (s, 2H), 6.93 (d, *J* = 5.4 Hz, 1H), 2.71 (s, 6H), 2.51 (s, 3H), 2.34-2.29 (multiple peaks, 6H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 147.5, 143.8, 142.5, 141.4, 139.5, 135.0, 130.2, 130.1, 128.6, 126.9, 126.0, 96.3, 27.4, 21.5, 21.2, 17.9. FT-IR 1456.1, 1374.6, 1229.0, 1153.2, 1007.7, 819.8 cm^{-1}; HRMS *m/z* calculated for $C_{14}H_{16}SI$ [M]$^+$: 343.0012, found 343.0015.

III. Synthesis and Characterization of Authetic Samples of Fluorinated Arenes

A. General Procedure for the Synthesis of Fluorinated Arenes

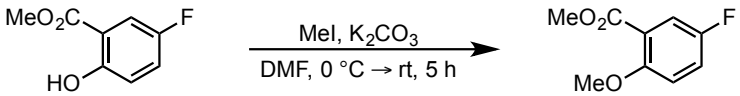


1p **2p** **3p**

To a solution of MesI(OH)OTs (240 mg, 0.56 mmol, 1.0 equiv) in DCM (2.2 mL) in a 20 mL vial equipped with a stir bar was added **1p** (150 mg, 0.56 mmol, 1.0 equiv). The stirring solution was cooled to 0 °C and trimethylsilyl trifluoromethanesulfonate (TMSOTf) (0.10 mL, 0.56 mmol, 1.0 equiv) was added dropwise. The solution was warmed to room temperature and stirred for 18 h. The solution was concentrated under a stream of nitrogen, and Et_2O was added to precipitate the diaryliodonium salt. The mixture was stirred for 30 min before the diaryliodonium salt was collected by filtration, washed with Et_2O, dried under vacuum, and stored for use in subsequent fluorination reactions without any further purification.

In a glovebox, to a 20 mL vial equipped with a stir bar were added diaryliodonium salt **2p** (660 mg, 1.0 mmol, 1.0 equiv), $Cu(OTf)_2$ (72 mg, 0.20 mmol, 20 mol %), KF (64 mg, 1.1 mmol, 1.1 equiv), and anhydrous DMF (10 mL). The reaction vial was sealed with a Teflon-lined cap, and the reaction was heated in an aluminum block at 65 °C for 16 h. After completion, the reaction was cooled to room temperature, quenched with saturated $NaHCO_3$, and extracted with pentane (3 x 15 mL). The combined organics were washed with H_2O (7 x 20 mL), dried with magnesium sulfate, concentrated *in vacuo*, and purified by silica gel flash chromatography.

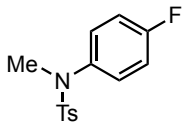
B. Synthesis and Characterization of 3d, 3h-3i, 3m-3q



3d

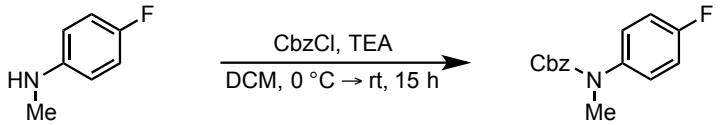
Methyl 5-fluoro-2-methoxybenzoate (3d). To a 25 mL round bottom flask equipped with a magnetic stir bar was added methyl 5-fluoro-2-hydroxybenzoate (500 mg, 2.9 mmol, 1.0 equiv) in DMF (5.3 mL) under a nitrogen atmosphere. The mixture was cooled to 0 °C using an ice bath, and potassium carbonate (610 mg, 4.4 mmol, 1.5 equiv) was added followed by the dropwise addition of iodomethane (0.22 mL, 3.5 mmol, 1.2 equiv). The mixture was stirred for 5 h at room temperature. Upon completion the mixture was quenched with water (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organics were washed with water (3 x 10 mL) and brine (10 mL) before being dried with magnesium sulfate, and concentrated *in vacuo*. Purification by silica gel flash chromatography (10 g Biotage SNAP-

Ultra silica column, 5% EtOAc:pentane) led to the isolation of **3d** as a colorless oil (401 mg, 74% yield), R_f = 0.12 (10% EtOAc:Hex, visualized by 254 nm light and PMA stain). ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 8.7, 3.2 Hz, 1H), 7.17 (ddd, *J* = 9.1, 7.5, 3.2 Hz, 1H), 6.92 (dd, *J* = 9.1, 4.2 Hz, 1H), 3.92-3.86 (multiple peaks, 6H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 165.6 (d, *J* = 2.4 Hz), 156.2 (d, *J* = 240.0 Hz), 155.6 (d, *J* = 2.1 Hz), 120.9 (d, *J* = 7.0 Hz), 120.0 (d, *J* = 22.9 Hz), 118.2 (d, *J* = 24.7 Hz), 113.5 (d, *J* = 7.7 Hz), 56.7, 52.3; ^{19}F NMR (377 MHz, $CDCl_3$) δ –124.3 (m, 1F). FT-IR 1731.4, 1495.8, 1435.8, 1305.9, 1242.7, 1177.6, 1071.7 cm^{-1}; HRMS *m/z* calculated for $C_9H_{10}FO_3$ $[M+H]^+$: 185.0608, found 185.0604.



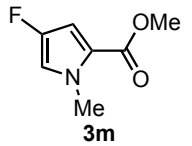
3h

***N*-(4-Fluorophenyl)-*N*,4-dimethylbenzenesulfonamide (3h).** The general procedure was followed using diaryliodonium salt **2h** (270 mg, 0.41 mmol, 1.0 equiv), $Cu(OTf)_2$ (30 mg, 0.08 mmol, 20 mol %), and KF (26 mg, 0.45 mmol, 1.1 equiv) in anhydrous DMF (4.1 mL). Purification by silica gel flash chromatography (50 g Biotage SNAP-Ultra silica column, step gradient from 0% to 5% to 10% to 20% EtOAc:Hex) led to the isolation of **3h** as a white solid (24 mg, 21% yield, mp 85-86 °C), R_f = 0.26 (4:1 Hex:EtOAc, visualized by 254 nm light and PMA stain). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.8 Hz, 2H), 7.25 (d, *J* = 7.8 Hz, 2H), 7.05 (dd, *J* = 8.7, 4.9 Hz, 2H), 6.98 (app. t, *J* = 8.7 Hz, 2H), 3.14 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 161.7 (d, *J* = 247.4 Hz), 143.9, 137.7 (d, *J* = 3.1 Hz), 133.4, 129.6, 128.6 (d, *J* = 8.6 Hz), 128.1, 115.8 (d, *J* = 22.7 Hz), 38.4, 21.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ –114.7 (m, 1F); FT-IR 1598.9, 1497.4, 1344.3, 1189.9, 1063.5, 873.8 cm^{-1}; HRMS *m/z* calculated for $C_{14}H_{15}NSO_2F$ $[M+H]^+$: 280.0802, found 280.0799.



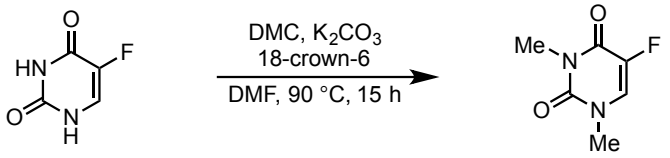
3i

Benzyl (4-fluorophenyl)(methyl)carbamate (3i). To a 25 mL round bottom flask equipped with a magnetic stir bar were added 4-fluoro-*N*-methylaniline (0.50 mL, 4.2 mmol, 1.0 equiv) and benzyl chloroformate (0.71 mL, 5.0 mmol, 1.2 equiv) in DCM (8.4 mL) under a nitrogen atmosphere. The mixture was cooled to 0 °C using an ice bath and triethylamine (0.87 mL, 6.3 mmol, 1.5 equiv) was added dropwise. The mixture was stirred for 15 h at room temperature. Upon completion, the mixture was diluted with DCM (2 mL) and washed with water (3 x 15 mL) and brine (15 mL). The organic phase was dried with magnesium sulfate and concentrated *in vacuo*. Purification by silica gel flash chromatography (25 g Biotage SNAP-Ultra silica column, 3% EtOAc:Hex) led to the isolation of **3i** as a colorless oil (394 mg, 36% yield), R_f = 0.12 (10% EtOAc:Hex, visualized by 254 nm light and PMA stain). ^{1}H NMR (400 MHz, DMSO-d_6, 90 °C) δ 7.39-7.26 (multiple peaks, 7H), 7.16 (t, *J* = 8.8 Hz, 2H), 5.11 (s, 2H), 3.04 (s, 3H); ^{13}C NMR (176 MHz, DMSO-d_6, 90 °C) δ 159.6 (d, *J* = 243.1 Hz), 154.3, 139.1, 136.3, 127.8, 127.2, 127.2, 126.9, 114.9 (d, *J* = 22.5 Hz), 66.2, 37.1; ^{13}C NMR (176 MHz, $CDCl_3$, room temperature) δ 160.7 (d, *J* = 246.1 Hz), 155.4, 139.2, 136.5, 128.4, 128.0, 127.7 (bs), 115.6 (d, *J* = 22.6 Hz), 67.3, 37.9 (bs); ^{19}F NMR (376 MHz, DMSO-d_6, 90 °C) δ –116.6 (m, 1F); FT-IR 1699.5, 1508.7, 1345.9, 1218.4, 1146.9, 1011.5 cm^{-1}; HRMS *m/z* calculated for $C_{15}H_{15}NO_2F$ $[M+H]^+$: 260.1081, found 260.1081.



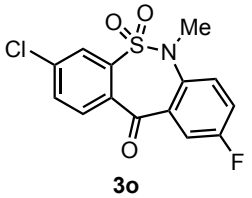
3m

Methyl 4-fluoro-1-methyl-1*H*-pyrrole-2-carboxylate (3m). The general procedure was followed using diaryliodonium salt **2m** (490 mg, 0.92 mmol, 1.0 equiv), $Cu(OTf)_2$ (65 mg, 0.18 mmol, 20 mol %), and KF (59 mg, 1.01 mmol, 1.1 equiv) in anhydrous DMF (9.2 mL). The desired product was purified by silica gel flash chromatography (10 g Biotage SNAP-Ultra silica column, 3% EtOAc:Hex) affording **3m** as a colorless oil (12 mg, 8% yield), R_f = 0.35 (4:1 Hex:EtOAc, visualized by 254 nm light and PMA stain). ^{1}H NMR (401 MHz, $CDCl_3$) δ 6.59 (d, *J* = 2.2 Hz, 1H), 6.57 (dd, *J* = 3.5, 2.2 Hz, 1H), 3.87 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 161.5 (d, *J* = 3.1 Hz), 150.0 (d, *J* = 240.1 Hz), 118.6, 114.1 (d, *J* = 27.6 Hz), 103.8 (d, *J* = 14.9 Hz), 51.4, 37.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ –165.7 (d, *J* = 3.4 Hz, 1F); FT-IR 1699.7, 1435.6, 1322.1, 1244.0, 1107.7, 1054.9 cm^{-1}; HRMS *m*/*z* calculated for $C_7H_8NO_2F$ $[M]^+$: 157.0539, found 157.0534. Of note, the ^{1}H, ^{13}C and ^{19}F NMR spectroscopic data did not match those previously reported in the literature for methyl 5-fluoro-1-methyl-1*H*-pyrrole-2-carboxylate.[5]



3n

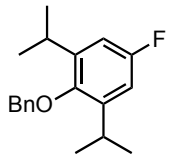
5-Fluoro-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (3n). A previously reported procedure was used for the synthesis of **3n** from fluorouracil.[6] To a 100 mL round bottom flask equipped with a magnetic stir bar and a reflux condenser were added powdered K_2CO_3 (3.2 g, 23 mmol, 3.0 equiv), 18-crown-6 (410 mg, 1.5 mmol, 20 mol %), and dimethyl carbonate (7.8 mL, 92 mmol, 12 equiv) in DMF (30 mL). To the mixture was added fluorouracil (1.0 g, 7.7 mmol, 1.0 equiv) in one portion. The mixture was stirred for 15 h at 90 °C. After completion, the reaction was cooled to room temperature and quenched with H_2O (50 mL). The solution was extracted with DCM (3 x 50 mL). The combined organics were washed with H_2O (7 x 50 mL), brine (50 mL), then dried with magnesium sulfate and concentrated *in vacuo*. Purification by silica gel flash chromatography (10 g Biotage SNAP-Ultra silica column, gradient from 0% to 100% EtOAc:Hex) led to the isolation of **3n** as a white solid (250 mg, 21% yield, mp 128-129 °C), R_f = 0.06 (50% EtOAc:Hex, visualized by 254 nm light and PMA stain). ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.23 (d, *J* = 5.0 Hz, 1H), 3.40 (s, 3H), 3.39 (s, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 157.5 (d, *J* = 25.0 Hz), 150.3, 139.9 (d, *J* = 233.8 Hz), 127.5 (d, *J* = 32.5 Hz), 37.1, 28.4 (d, *J* = 1.4 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ –167.3 (m, 1F); FT-IR 1703.4, 1651.9, 1428.5, 1326.7, 1275.3, 1083.2, 1057.8 cm^{-1}; HRMS *m*/*z* calculated for $C_6H_8N_2O_2F$ $[M+H]^+$: 159.0564, found 159.0562.



3o

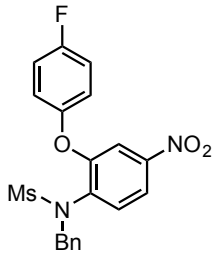
3-Chloro-9-fluoro-6-methyldibenzo[*c*,*f*][1,2]thiazepin-11(6*H*)-one 5,5-dioxide (3o). The general procedure was followed using diaryliodonium salt **2o** (200 mg, 0.28 mmol, 1.0 equiv), $Cu(OTf)_2$ (21 mg, 0.06 mmol, 20 mol %), and KF (18 mg, 0.31 mmol, 1.1 equiv) in anhydrous DMF (2.8 mL). Purification by silica gel flash chromatography (50 g Biotage SNAP-Ultra silica column, step gradient from 0% to 5% to 10% to 20% EtOAc:Hex) led to the isolation of **3o** as a white solid (52 mg, 57% yield, mp 185-186 °C), R_f = 0.24 (4:1 Hex:EtOAc, visualized by 254 nm light). ^{1}H NMR (400 MHz, CD_3CN) δ 7.94 (d, *J* = 2.1 Hz, 1H), 7.92 (app. ddd, *J* = 9.9, 2.8, 0.5 Hz, 1H), 7.90 (app. d, *J* = 8.3 Hz, 1H), 7.81 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.53 (app. ddd, *J* = 9.0, 5.0, 0.5 Hz, 1H), 7.49 (app. ddd, *J* = 9.0, 7.0, 2.8 Hz, 1H), 3.28 (s, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 188.0 (d, *J* = 1.6 Hz), 160.6 (d, *J* = 248.3 Hz), 139.4, 138.6, 137.5 (d, *J* = 3.0 Hz), 133.8, 133.5, 133.1 (d, *J* = 6.6 Hz), 132.3, 127.4 (d, *J* = 8.0 Hz), 126.0, 122.4 (d, *J* = 23.4 Hz), 118.3 (d, *J* = 24.9 Hz), 39.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ –115.4 (m, 1F); FT-IR 1642.1,

1580.1, 1487.2, 1403.1, 1353.9, 1165.0, 1050.8, 991.7 cm^{-1}; HRMS *m/z* calculated for $C_{14}H_{10}NSO_3ClF$ $[M+H]^+$: 326.0048, found 326.0051.



3p

2-(Benzyloxy)-5-fluoro-1,3-diisopropylbenzene (3p). The general procedure was followed using diaryliodonium salt **2p** (660 mg, 1.0 mmol, 1.0 equiv), $Cu(OTf)_2$ (72 mg, 0.20 mmol, 20 mol %), and KF (64 mg, 1.1 mmol, 1.1 equiv) in anhydrous DMF (10 mL). Purification by silica gel flash chromatography (10 g Biotage SNAP-Ultra silica column, gradient from 0% to 10% EtOAc:Hex) led to the isolation of **3p** as a colorless oil (139 mg, 49% yield), R_f = 0.62 (10% EtOAc:Hex, visualized by 254 nm light and PMA stain). ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.1 Hz, 2H), 7.42 (t, *J* = 7.1 Hz, 2H), 7.36 (t, *J* = 7.1 Hz, 1H), 6.79 (d, *J* = 9.5 Hz, 2H), 4.77 (s, 2H), 3.37 (pd, *J* = 6.8, 1.1 Hz, 2H), 1.22 (d, *J* = 6.8 Hz, 12H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 160.1 (d, *J* = 240.9 Hz), 149.1 (d, *J* = 2.6 Hz), 144.1 (d, *J* = 7.1 Hz), 137.6, 128.7, 128.2, 127.5, 110.7 (d, *J* = 22.7 Hz), 76.7, 27.1, 24.1; ^{19}F NMR (377 MHz, $CDCl_3$) δ –118.2 (m, 1F); FT-IR 1596.3, 1442.1, 1331.5, 1181.6, 964.1 cm^{-1}; HRMS *m/z* calculated for $C_{19}H_{23}OF$ $[M]^+$: 286.1733, found 286.1740.

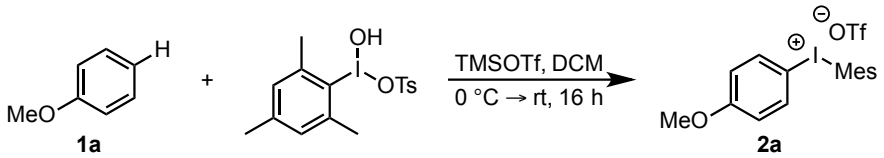


3q

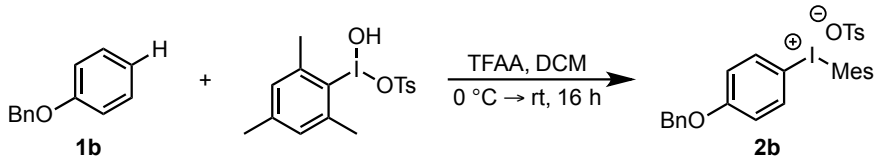
***N*-Benzyl-*N*-(2-(4-fluorophenoxy)-4-nitrophenyl)methanesulfonamide (3q)**. The general procedure was followed using diaryliodonium salt **2q** (840 mg, 1.1 mmol, 1.0 equiv), $Cu(OTf)_2$ (76 mg, 0.21 mmol, 20 mol %), and KF (67 mg, 1.2 mmol, 1.1 equiv) in anhydrous DMF (11 mL). Purification by silica gel flash chromatography (10 g Biotage SNAP-Ultra silica column, gradient from 0% to 50% EtOAc:Hex) led to the isolation of a nearly inseparable 0.67:1.0 mixture of *N*-Benzyl-*N*-(4-nitro-2-phenoxyphenyl)methanesulfonamide (**1q**) and **3q** (171 mg, 39% yield of **3q**). The desired product could be separated by repeated column chromatography (10 g Biotage SNAP-Ultra silica column, 10% EtOAc:Hex) affording **3q** as a white solid, mp 128-129 °C, R_f = 0.36 (1:1 Hex:EtOAc, visualized by 254 nm light and PMA stain). ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.51 (d, *J* = 2.5 Hz, 1H), 7.34 (d, *J* = 8.7 Hz, 1H), 7.31-7.27 (multiple peaks, 5H), 7.22-7.13 (m, 2H), 7.04 (dd, *J* = 9.1, 4.3 Hz, 2H), 4.91 (s, 2H), 3.10 (s, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 160.4 (d, *J* = 245.8 Hz), 155.9, 150.1 (d, *J* = 2.8 Hz), 148.1, 135.4, 134.2, 128.9 (three overlapping carbons), 128.5, 121.9 (d, *J* = 8.5 Hz), 117.9, 117.7 (d, *J* = 23.6 Hz), 111.8, 54.2, 40.7; ^{19}F NMR (377 MHz, $CDCl_3$) δ –116.9 (m, 1F); FT-IR 1739.7, 1525.5, 1522.2, 1344.9, 1208.6, 1153.9 cm^{-1}; HRMS *m/z* calculated for $C_{20}H_{17}N_2SO_5FNa$ $[M+Na]^+$: 439.0734, found 439.0727.

IV. Regioisomer Assignment of mesityl(aryl)iodonium salts

A. General Procedures for the Synthesis of mesityl(aryl)iodonium salts

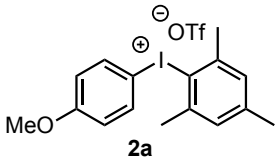


General Procedure A: To a solution of MesI(OH)OTs (43 mg, 0.10 mmol, 1.0 equiv) in DCM (0.40 mL) in a 4 mL vial equipped with a stir bar was added arene **1a** (11 µL, 0.10 mmol, 1.0 equiv). The stirring solution was cooled to 0 °C, and trimethylsilyl trifluoromethanesulfonate (TMSOTf) (18 µL, 0.10 mmol, 1.0 equiv) was added dropwise. The solution was warmed to room temperature and stirred for 18 h. The solution was concentrated under a stream of nitrogen, and Et_2O was added to precipitate the diaryliodonium salt. The mixture was stirred for 30 min before the diaryliodonium salt was collected by filtration, washed with Et_2O, dried under vacuum, and analyzed by ^1H NMR for regioisomer identification.



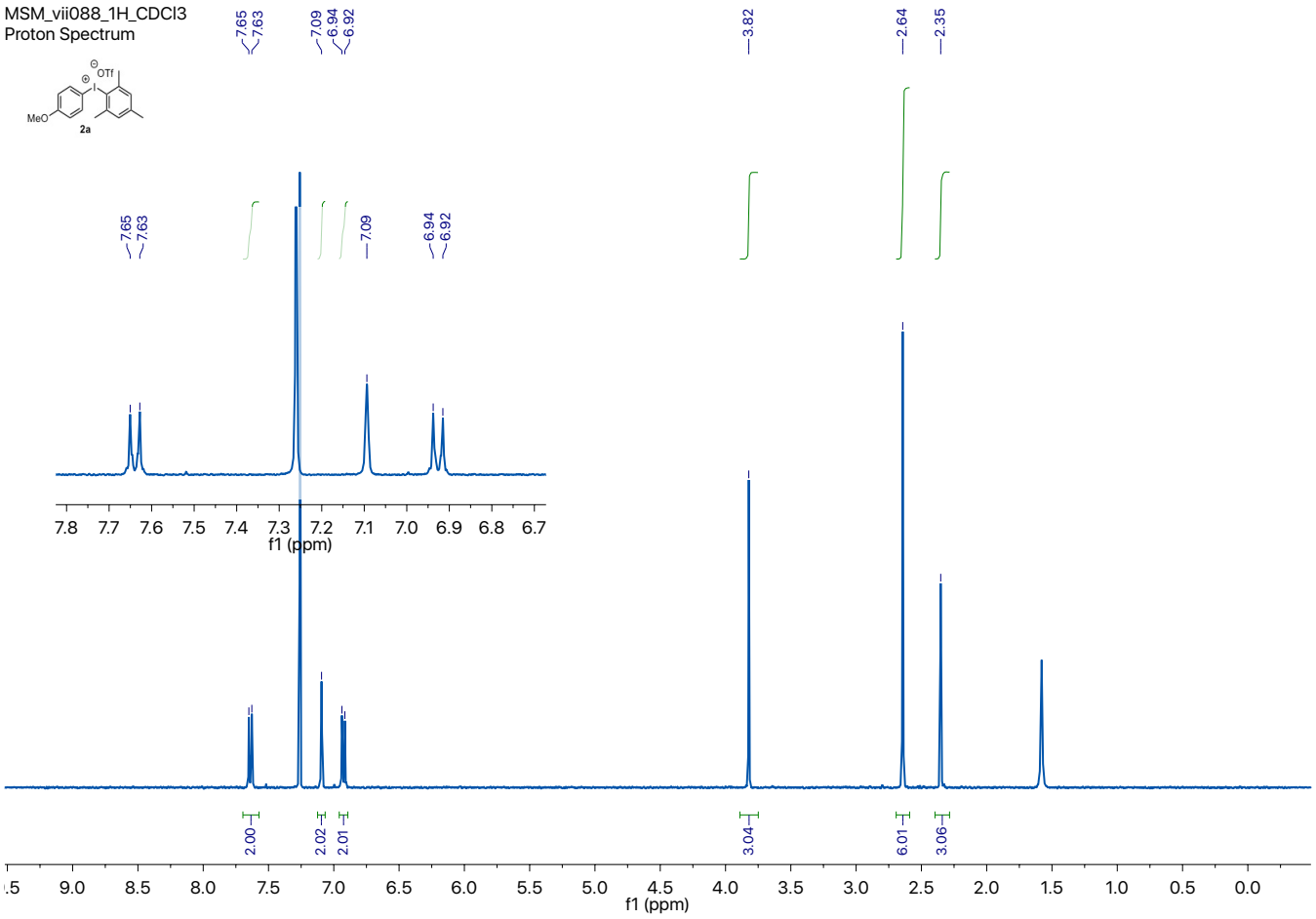
General Procedure B: To a solution of MesI(OH)OTs (43 mg, 0.10 mmol, 1.0 equiv) in DCM (0.40 mL) in a 4 mL vial equipped with a stir bar was added arene **1b** (11 µL, 0.10 mmol, 1.0 equiv). The stirring solution was cooled to 0 °C, and trifluoroacetic anhydride (TFAA) (14 µL, 0.10 mmol, 1.0 equiv) was added dropwise. The solution was warmed to room temperature and stirred for 18 h. The solution was concentrated under a stream of nitrogen, and Et_2O was added to precipitate the diaryliodonium salt. The mixture was stirred for 30 min before the diaryliodonium salt was collected by filtration, washed with Et_2O, dried under vacuum, and analyzed by ^1H NMR for regioisomer identification.

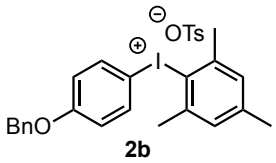
B. Regioisomer Assignment of 2a-2q



2a

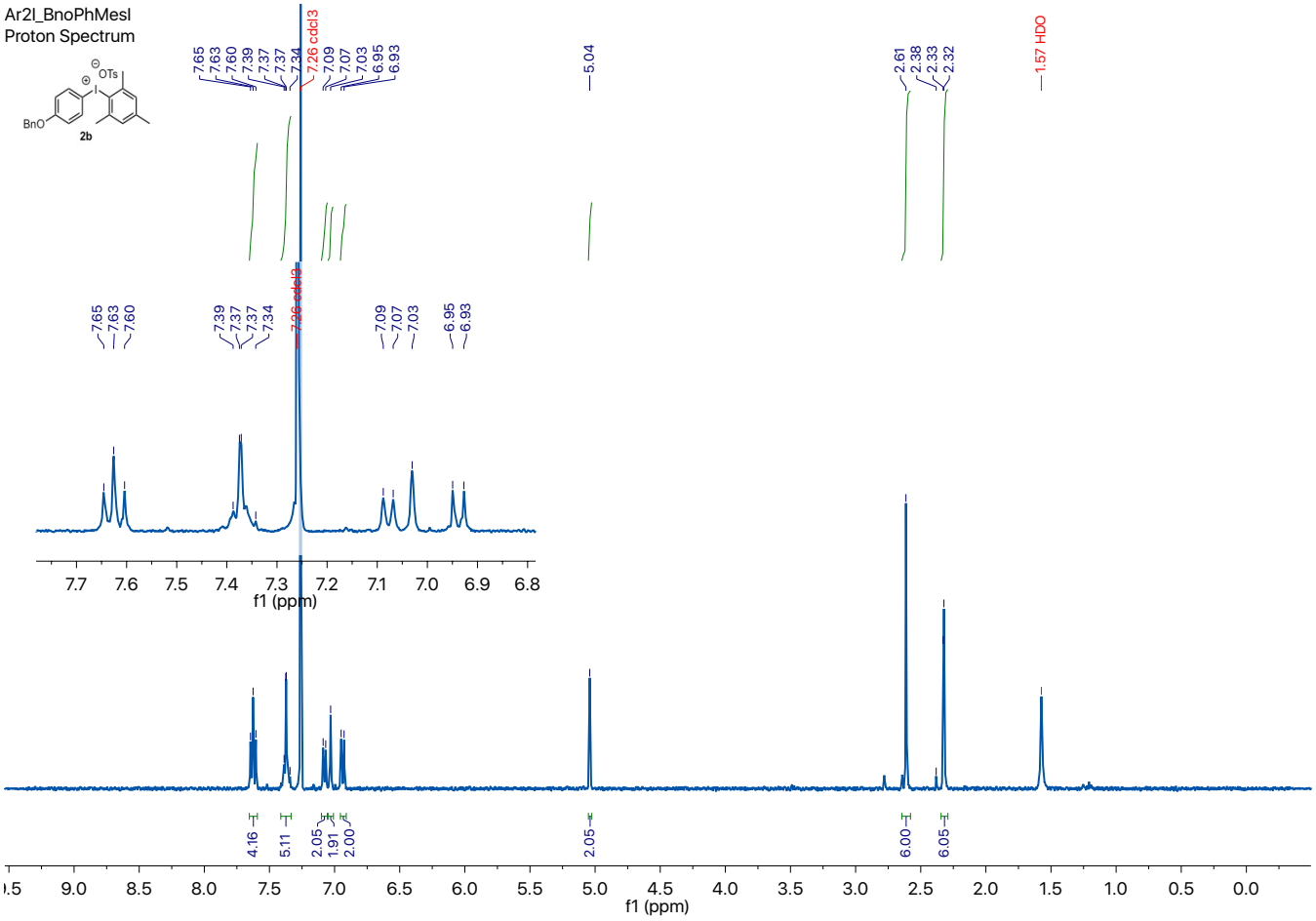
Mesityl(4-methoxyphenyl)iodonium trifluoromethanesulfonate (2a). General procedure A was followed. ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.64 (d, J = 9.1 Hz, 2H), 7.09 (s, 2H), 6.93 (d, J = 9.1 Hz, 2H), 3.82 (s, 3H), 2.64 (s, 6H), 2.35 (s, 3H).

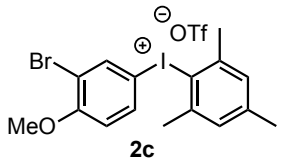




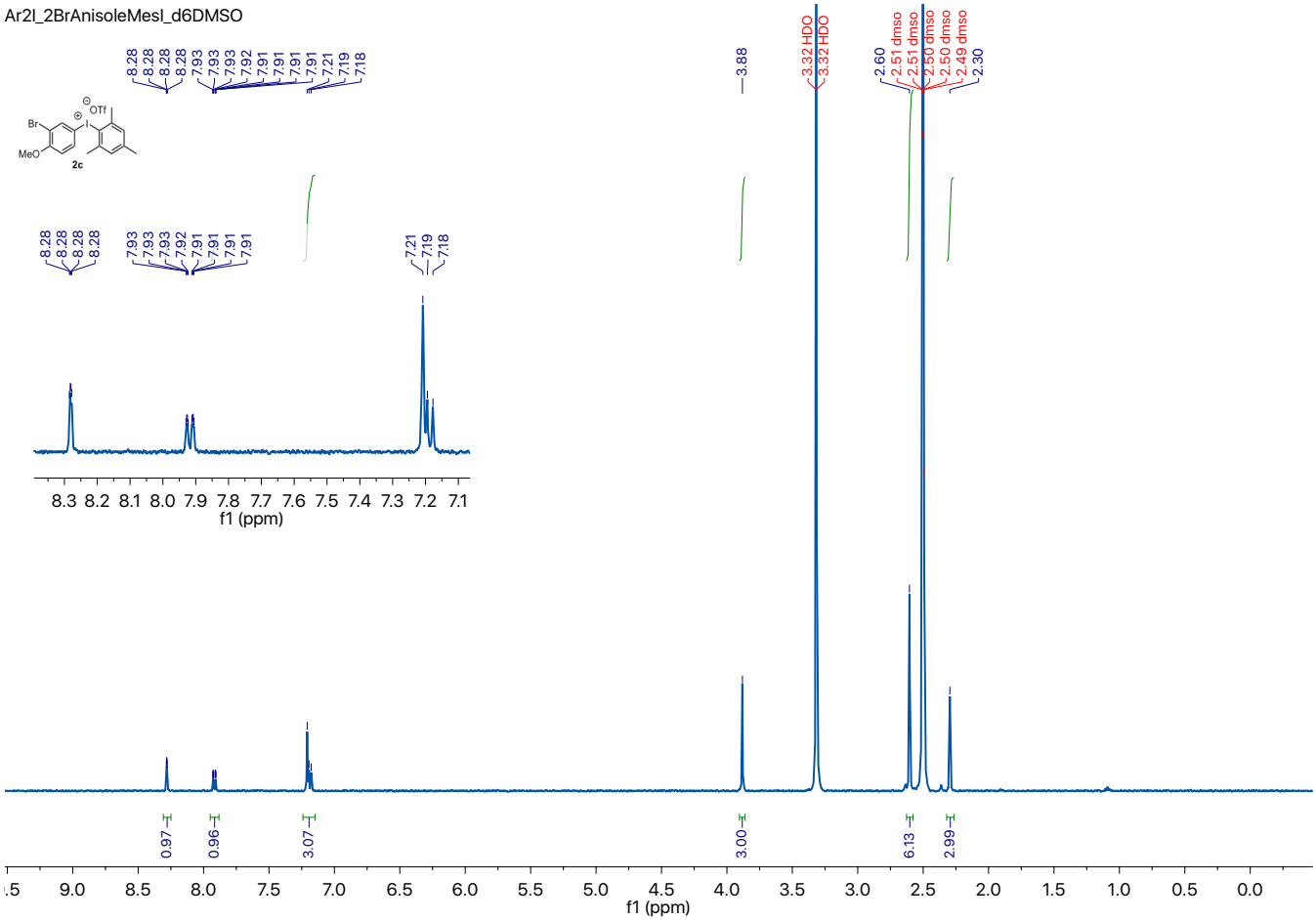
2b

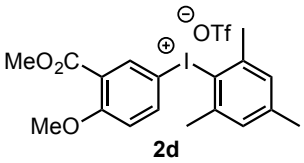
(4-(Benzyloxy)phenyl)(mesityl)iodonium 4-methylbenzenesulfonate (2b). General procedure B was followed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.59 (multiple peaks, 4H), 7.42-7.32 (multiple peaks, 5H), 7.08 (d, J = 7.9 Hz, 2H), 7.03 (s, 2H), 6.94 (d, J = 9.0 Hz, 2H), 5.04 (s, 2H), 2.61 (s, 6H), 2.35-2.30 (multiple peaks, 6H).





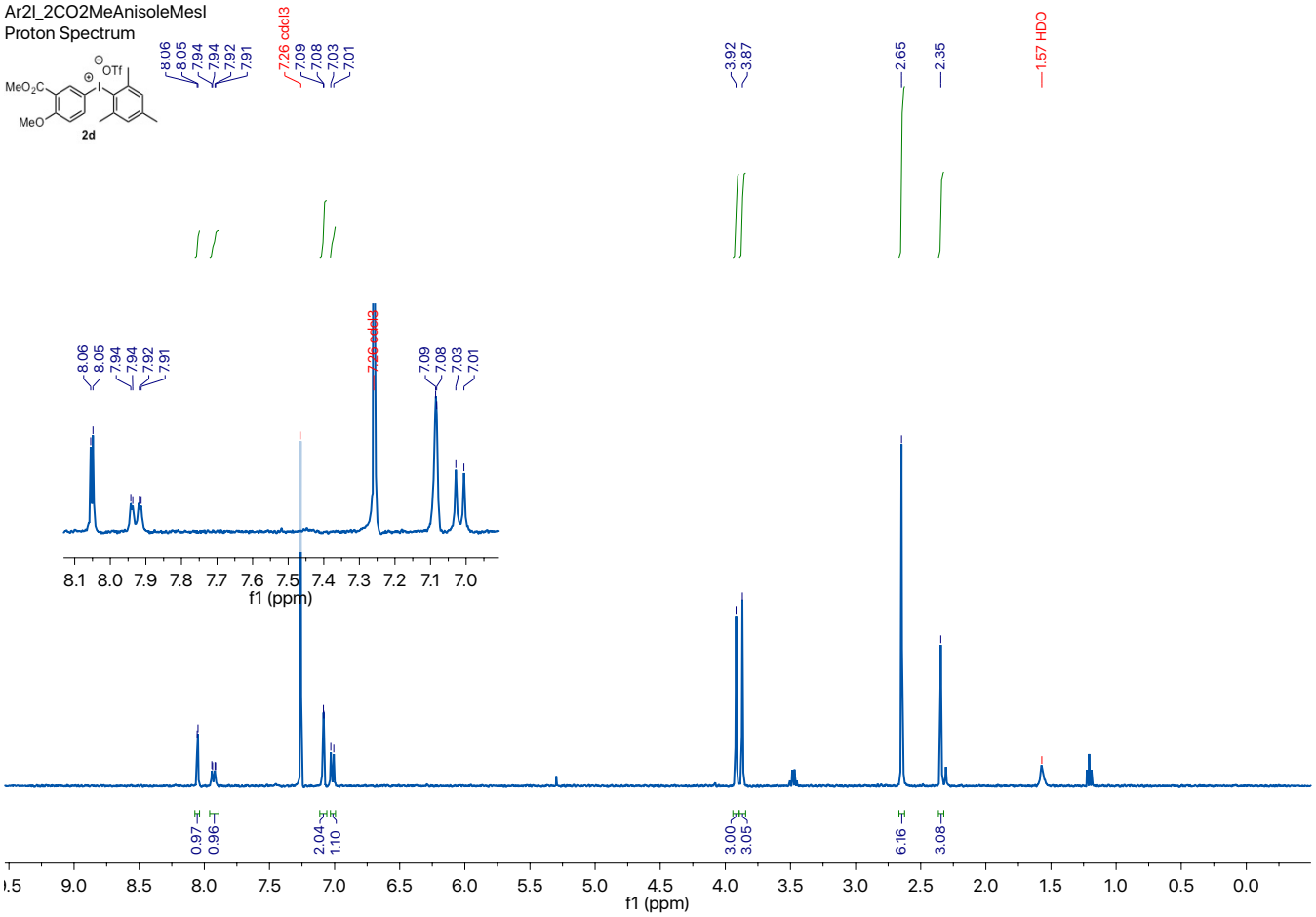
(3-Bromo-4-methoxyphenyl)(mesityl)iodonium trifluoromethanesulfonate (2c). General procedure A was followed. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.28 (dd, J = 2.3, 1.1 Hz, 1H), 7.92 (ddd, J = 8.9, 2.3, 1.1 Hz, 1H), 7.24-7.15 (multiple peaks, 3H), 3.88 (s, 3H), 2.60 (s, 6H), 2.30 (s, 3H).

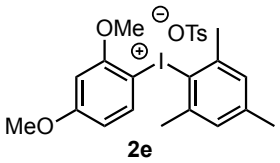




2d

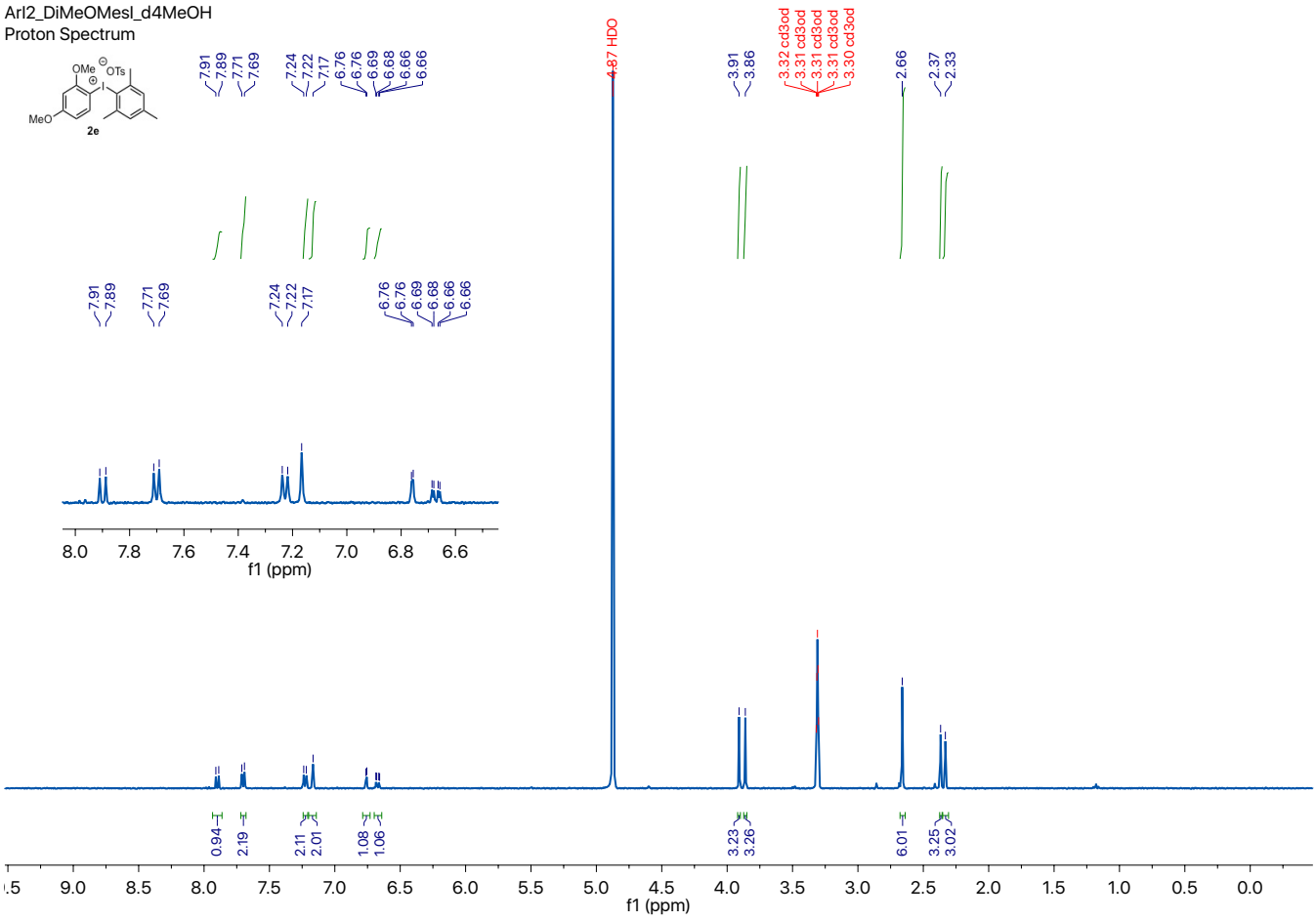
(4-Methoxy-3-(methoxycarbonyl)phenyl)(mesityl)iodonium trifluoromethanesulfonate (2d). General procedure A was followed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 2.3 Hz, 1H), 7.93 (dd, J = 9.3, 2.3 Hz, 1H), 7.08 (s, 2H), 7.02 (d, J = 9.3 Hz, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 2.65 (s, 6H), 2.35 (s, 3H).

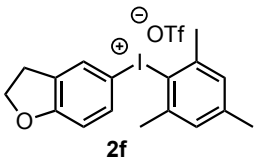




2e

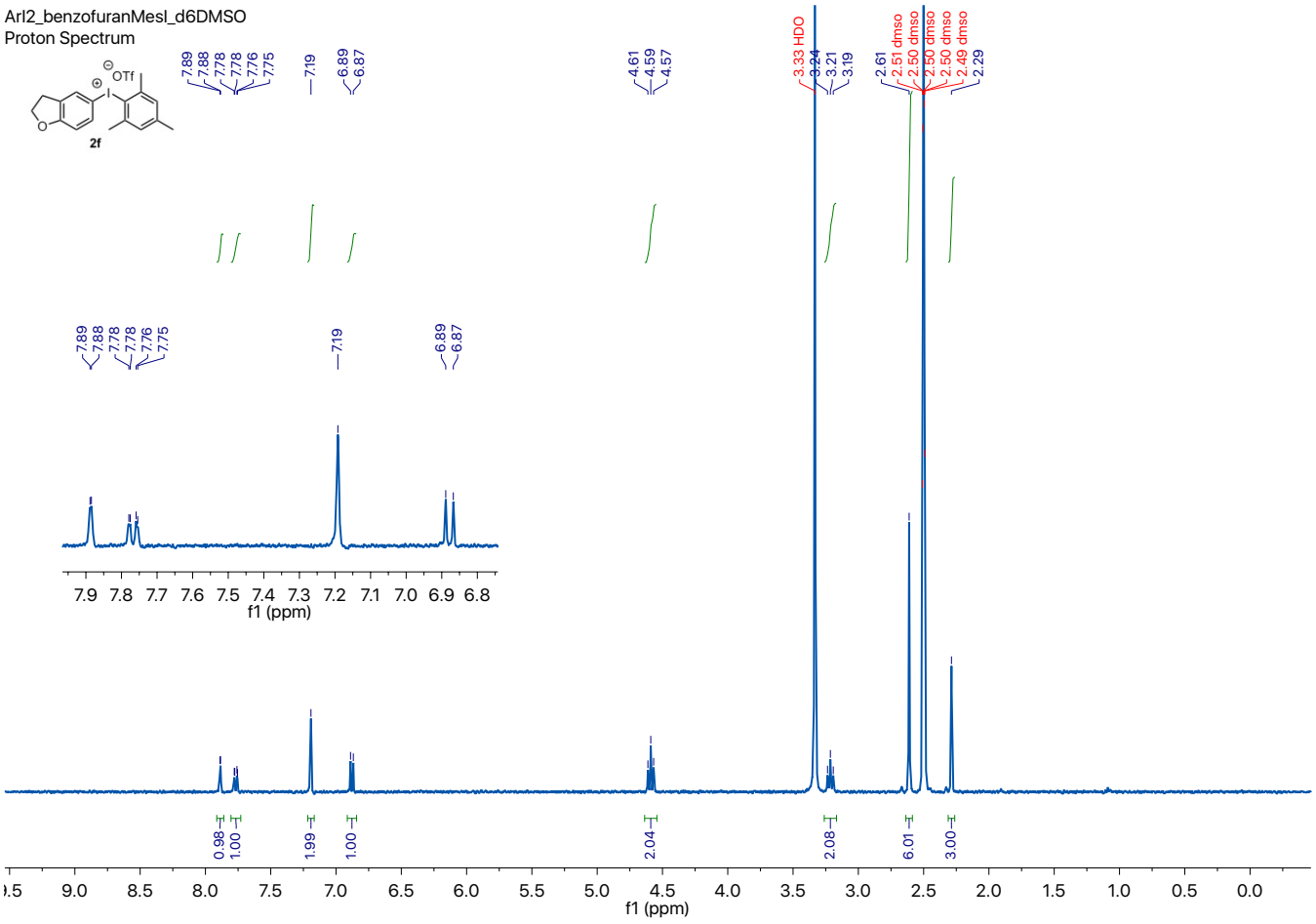
(2,4-Dimethoxyphenyl)(mesityl)iodonium 4-methylbenzenesulfonate (2e). General procedure B was followed. ^{1}H NMR (401 MHz, CD_3OD) δ 7.90 (d, *J* = 8.9 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.17 (s, 2H), 6.76 (d, *J* = 2.6 Hz, 1H), 6.67 (dd, *J* = 8.9, 2.6 Hz, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 2.66 (s, 6H), 2.37 (s, 3H), 2.33 (s, 3H).

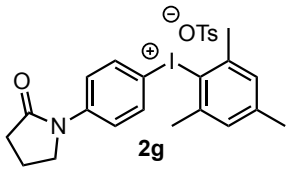




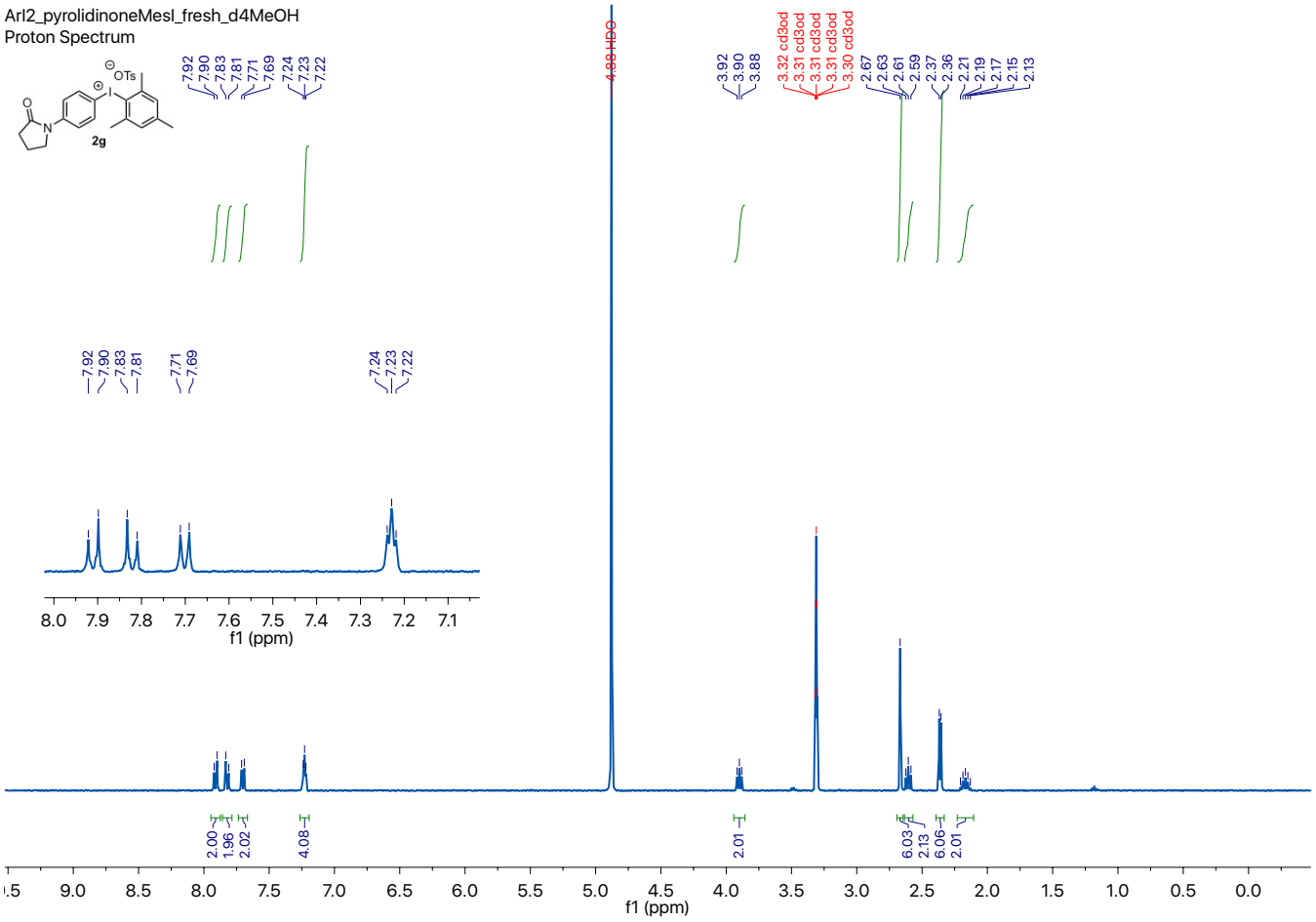
2f

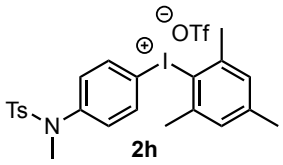
(2,3-Dihydrobenzofuran-5-yl)(mesityl)iodonium trifluoromethanesulfonate (2f). General procedure A was followed. ^{1}H NMR (401 MHz, DMSO-d_6) δ 7.89 (d, J = 1.7 Hz, 1H), 7.77 (dd, J = 8.4, 1.7 Hz, 1H), 7.19 (s, 2H), 6.88 (d, J = 8.4 Hz, 1H), 4.59 (t, J = 8.8 Hz, 2H), 3.21 (t, J = 8.8 Hz, 2H), 2.61 (s, 6H), 2.29 (s, 3H).



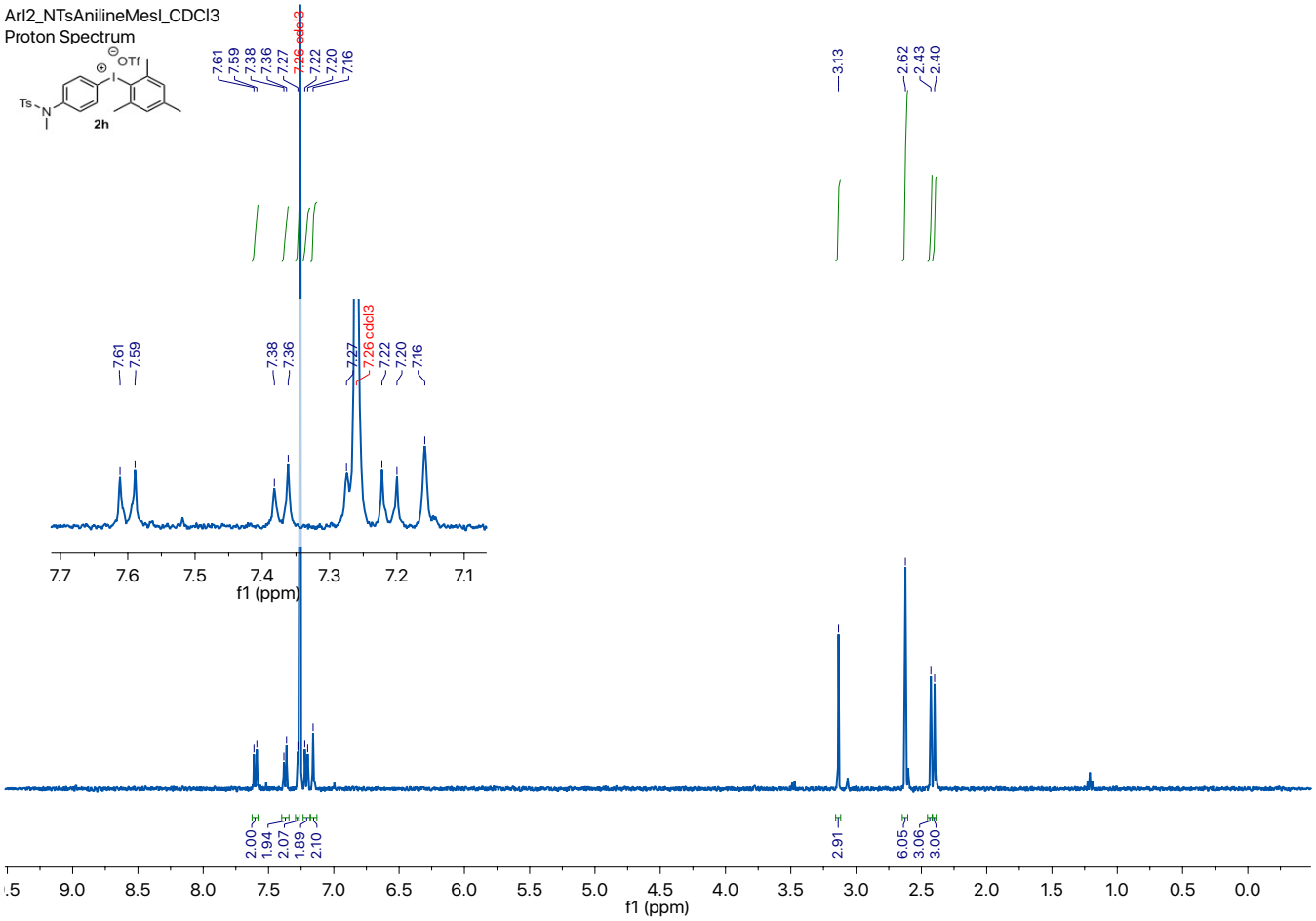


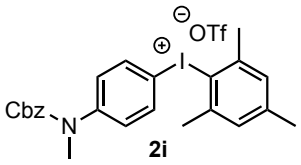
(4-(2-Oxopyrrolidin-1-yl)phenyl)(mesityl)iodonium 4-methylbenzenesulfonate (2g). General procedure B was followed. ^{1}H NMR (401 MHz, CD_3OD) δ 7.91 (d, J = 9.1 Hz, 2H), 7.82 (d, J = 9.1 Hz, 2H), 7.70 (d, J = 8.1 Hz, 2H), 7.25-7.21 (multiple peaks, 4H), 3.90 (t, J = 7.1 Hz, 2H), 2.67 (s, 6H), 2.61 (t, J = 8.1 Hz, 2H), 2.39-2.33 (multiple peaks, 6H), 2.17 (p, J = 7.6 Hz, 2H).



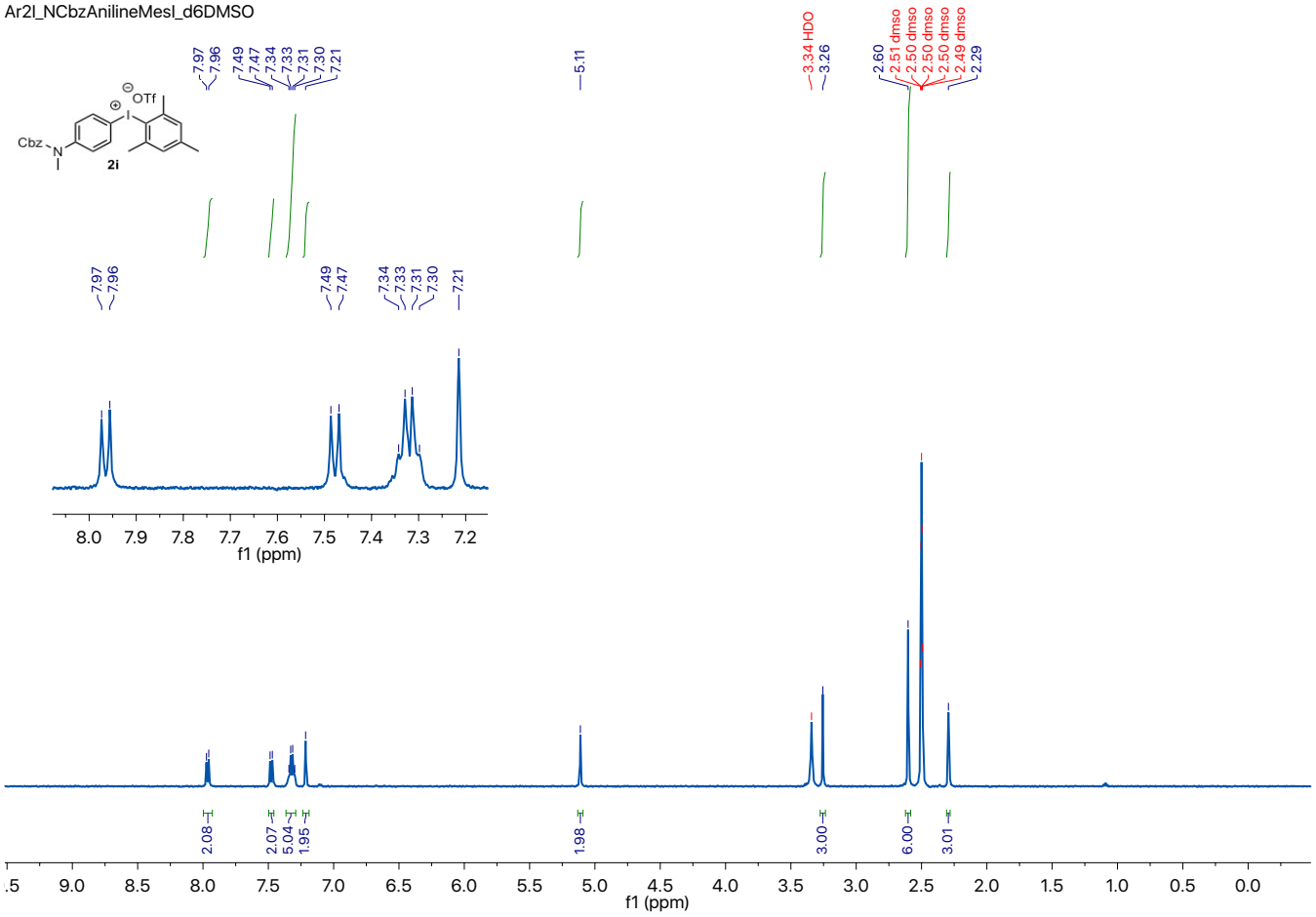


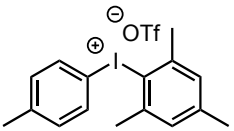
(4-((*N*,4-Dimethylphenyl)sulfonamido)phenyl)(mesityl)iodonium trifluoromethanesulfonate (2h). General procedure A was followed. ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.9 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.30-7.26 (m, 2H), 7.21 (d, *J* = 8.9 Hz, 2H), 7.16 (s, 2H), 3.13 (s, 3H), 2.62 (s, 6H), 2.43 (s, 3H), 2.40 (s, 3H).





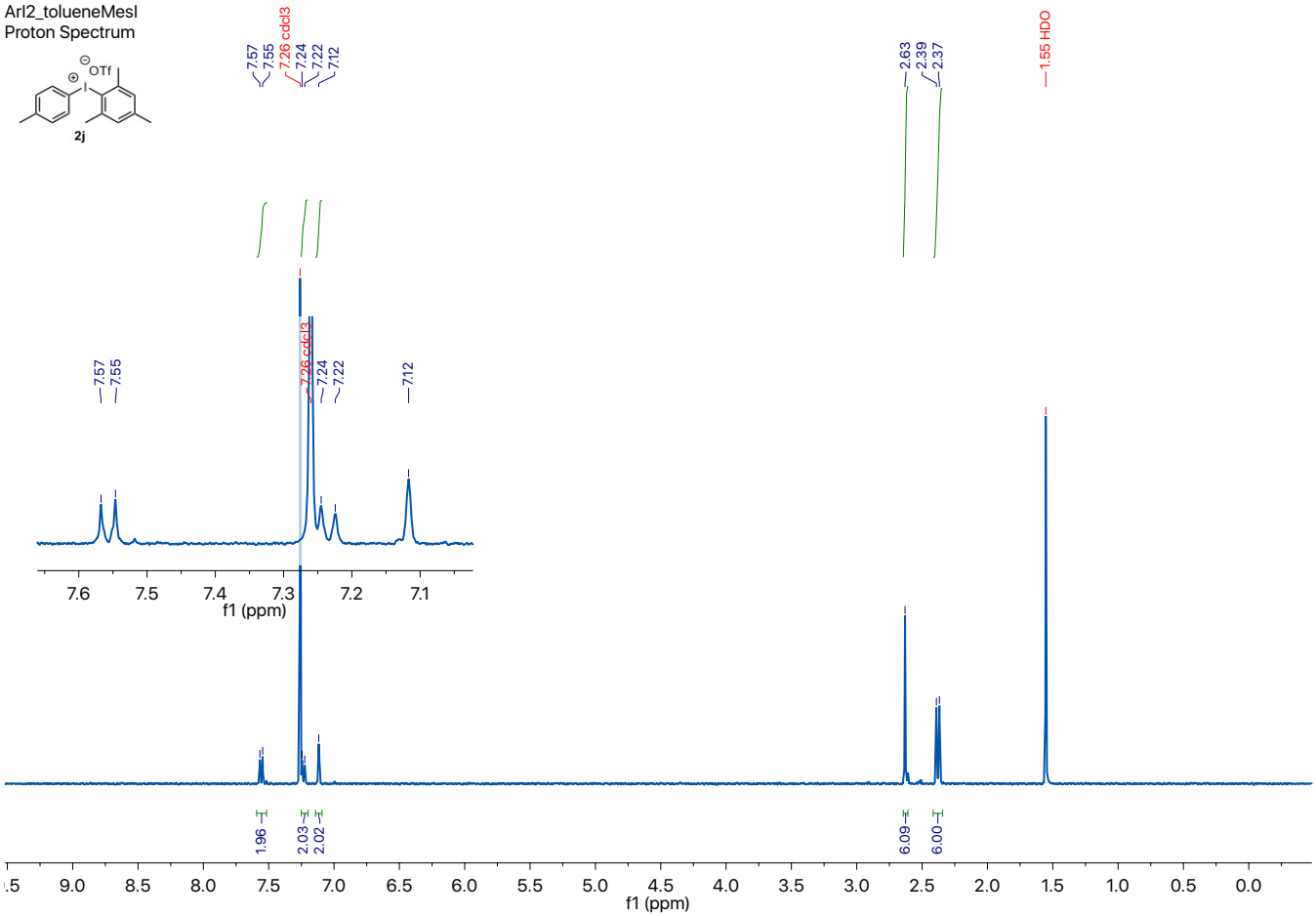
(*p*-Tolyl)(mesityl)iodonium trifluoromethanesulfonate (2i). General procedure A was followed. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.96 (d, J = 8.7 Hz, 2H), 7.48 (d, J = 8.7 Hz, 2H), 7.36-7.28 (multiple peaks, 5H), 7.21 (s, 2H), 5.11 (s, 2H), 3.26 (s, 3H), 2.60 (s, 6H), 2.29 (s, 3H).

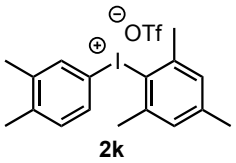




2j

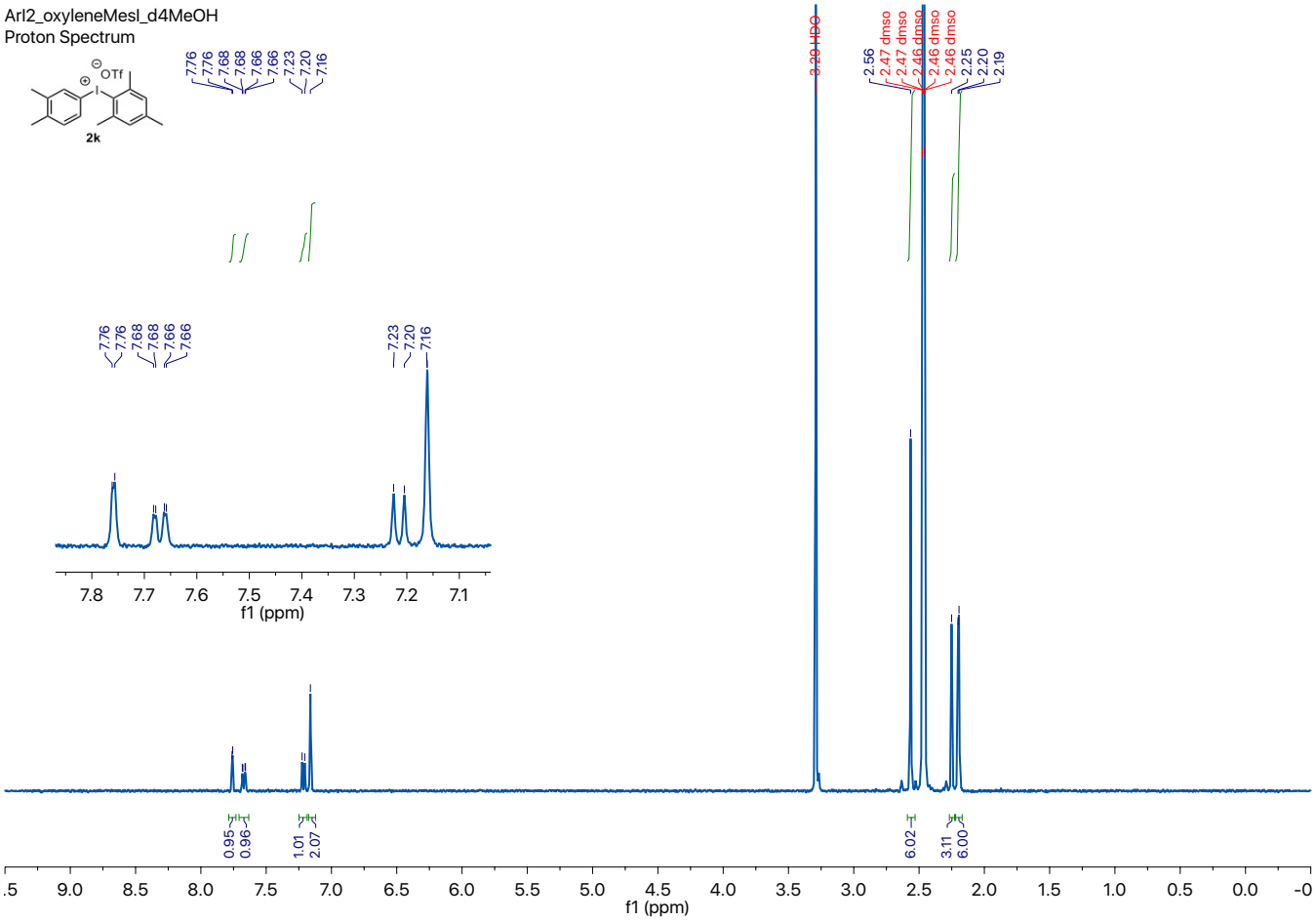
(4-(((Benzyloxy)carbonyl)(methyl)amino)phenyl)(mesityl)iodonium trifluoromethanesulfonate (2j). General procedure A was followed. ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.56 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 7.12 (s, 2H), 2.63 (s, 6H), 2.42-2.34 (multiple peaks, 6H).

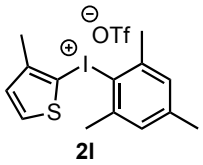




2k

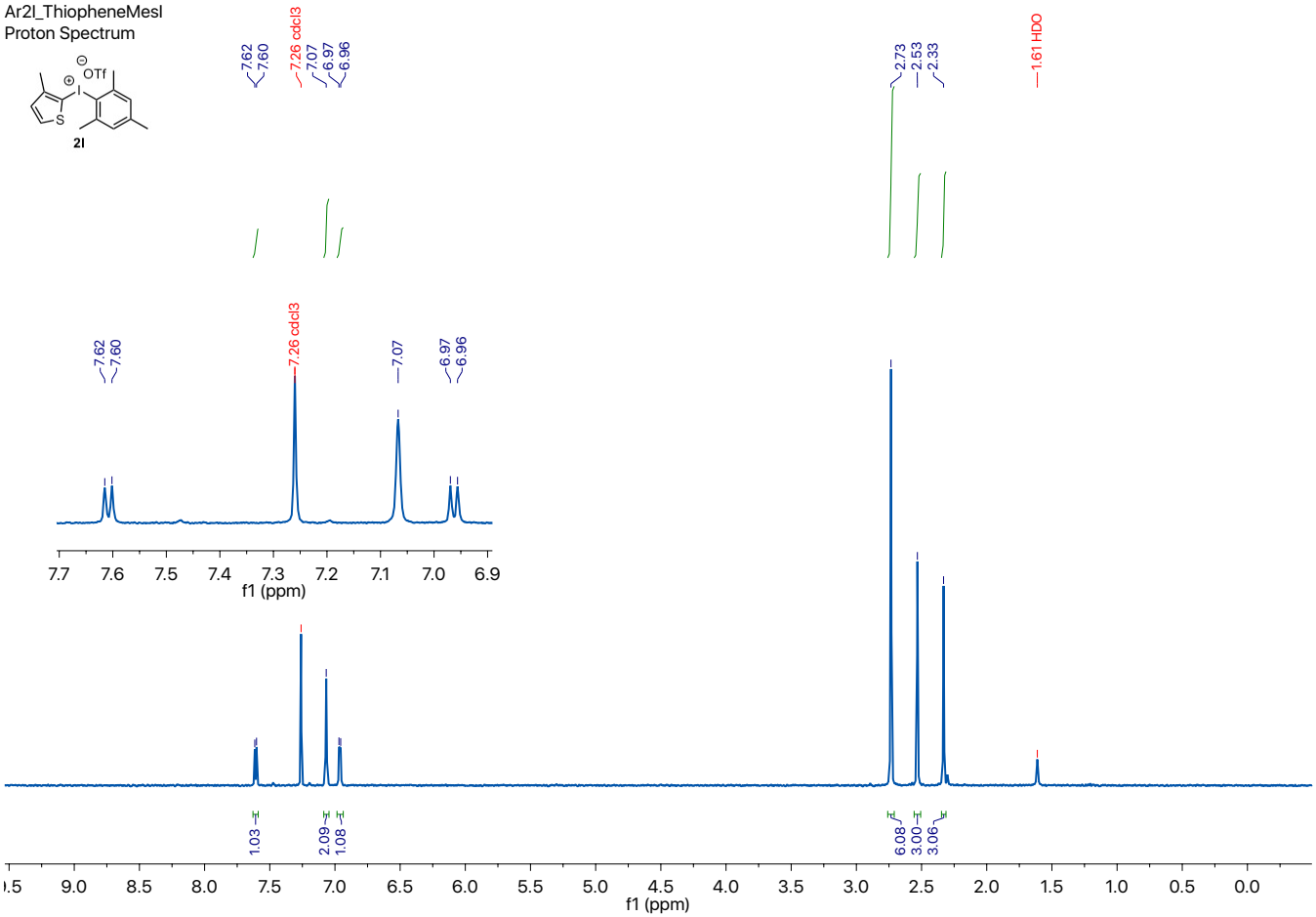
(4-((*N*,4-Dimethylphenyl)sulfonamido)phenyl)(mesityl)iodonium trifluoromethanesulfonate (2k). General procedure A was followed. ^{1}H NMR (401 MHz, DMSO-d_6) δ 7.76 (d, J = 2.0 Hz, 1H), 7.67 (dd, J = 8.2, 2.0 Hz, 1H), 7.21 (d, J = 8.2 Hz, 1H), 7.16 (s, 2H), 2.56 (s, 6H), 2.25 (s, 4H), 2.22-2.17 (multiple peaks, 6H).

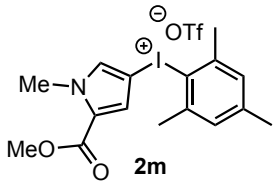




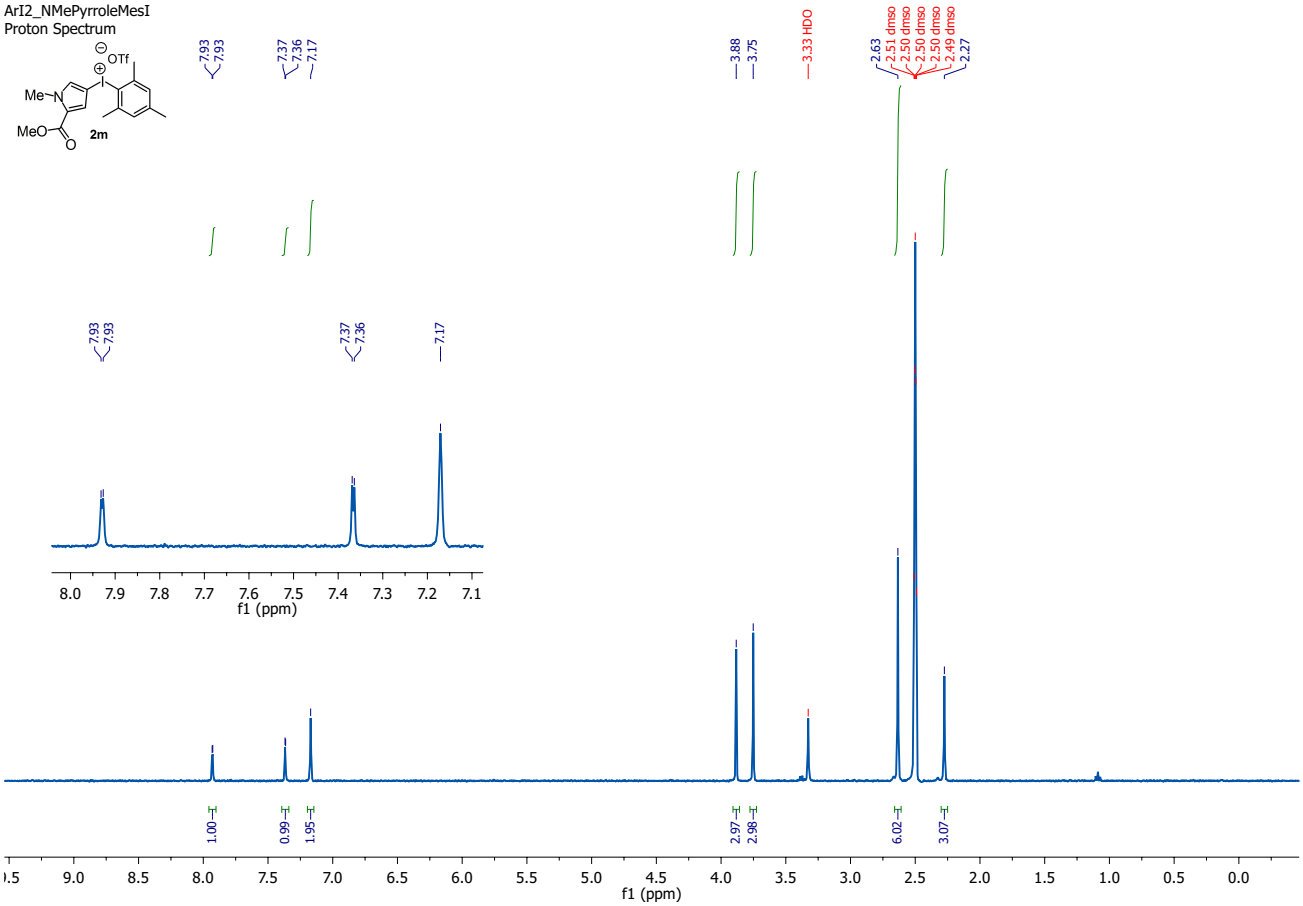
2l

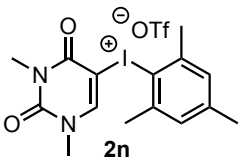
(3-Methylthiophen-2-yl)(mesityl)iodonium trifluoromethanesulfonate (2l). General procedure A was followed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 5.4 Hz, 1H), 7.07 (s, 2H), 6.96 (d, J = 5.4 Hz, 1H), 2.73 (s, 6H), 2.53 (s, 3H), 2.33 (s, 3H).



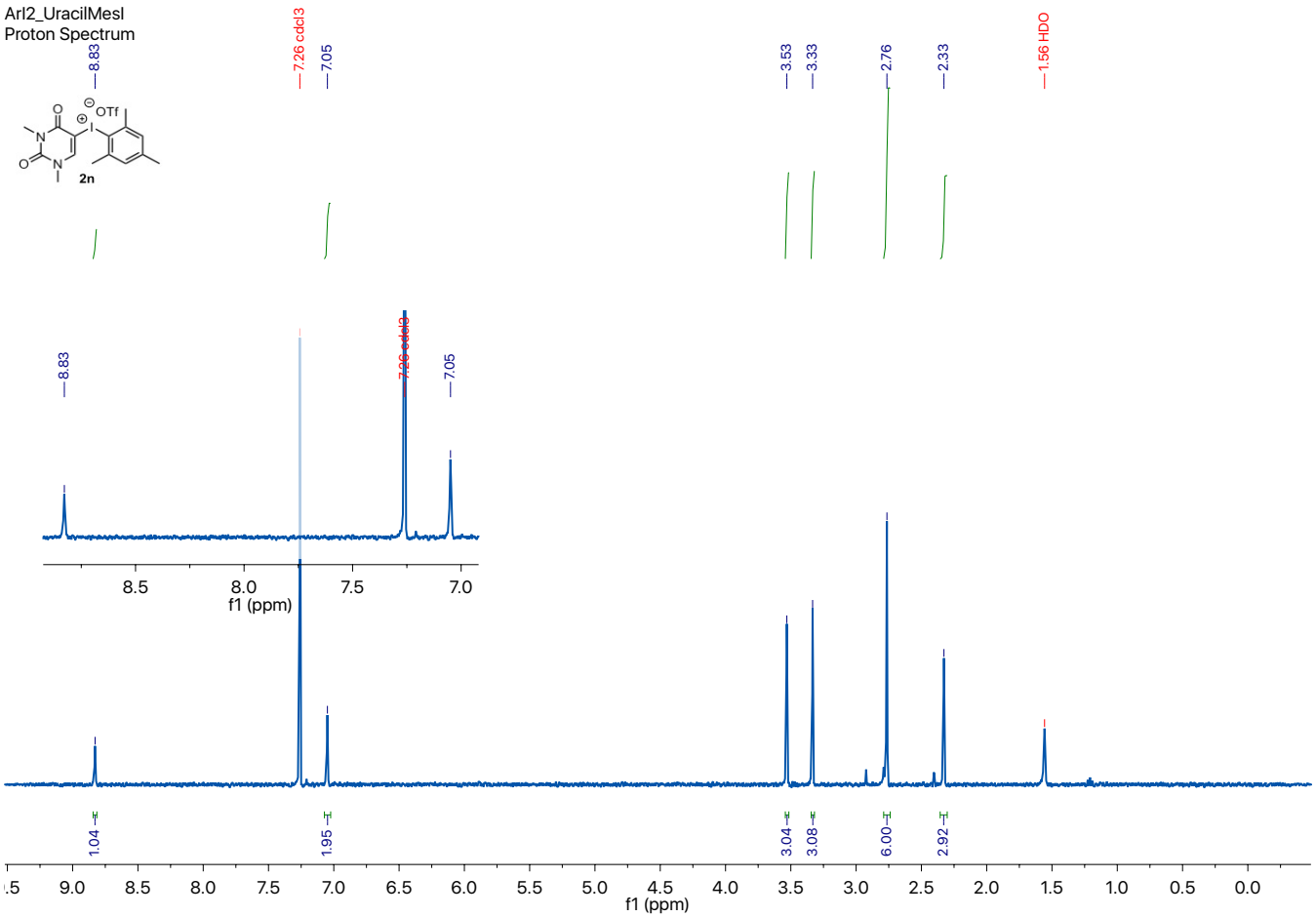


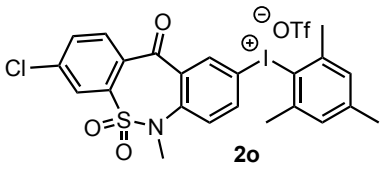
(4-(Methoxycarbonyl)-1-methyl-1*H*-pyrrol-2-yl)(mesityl)iodonium trifluoromethanesulfonate (2m). General procedure A was followed. ^{1}H NMR (401 MHz, DMSO-d_6) δ 7.93 (d, J = 1.9 Hz, 1H), 7.37 (d, J = 1.9 Hz, 1H), 7.17 (s, 2H), 3.88 (s, 3H), 3.75 (s, 3H), 2.63 (s, 6H), 2.27 (s, 3H).



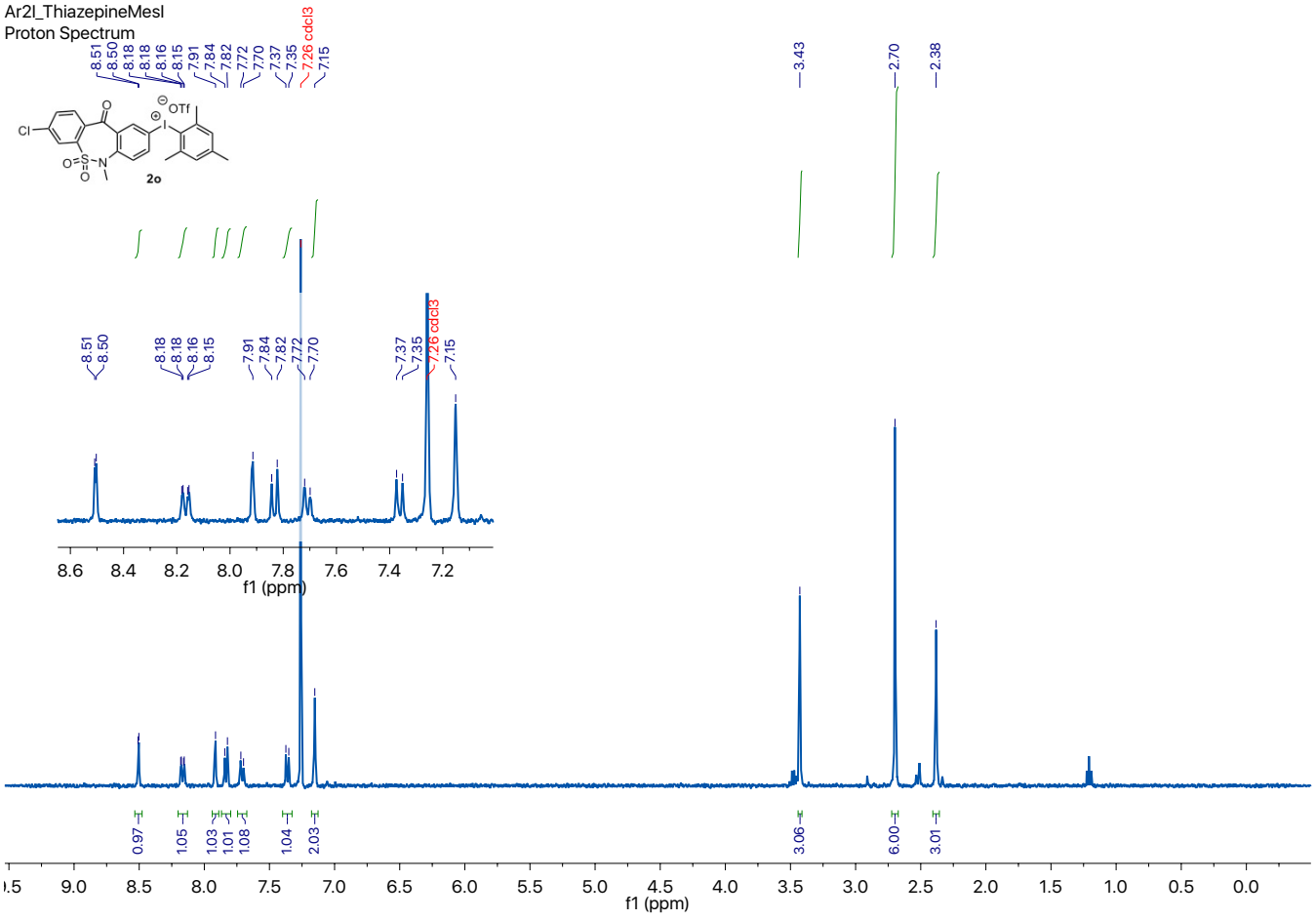


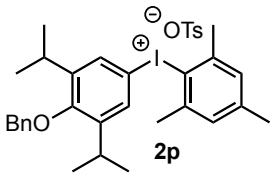
(1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)(mesityl)iodonium trifluoromethanesulfonate (2n). General procedure A was followed. ^{1}H NMR (401 MHz, $CDCl_3$) δ 8.83 (s, 1H), 7.05 (s, 2H), 3.53 (s, 3H), 3.33 (s, 3H), 2.76 (s, 6H), 2.33 (s, 3H).



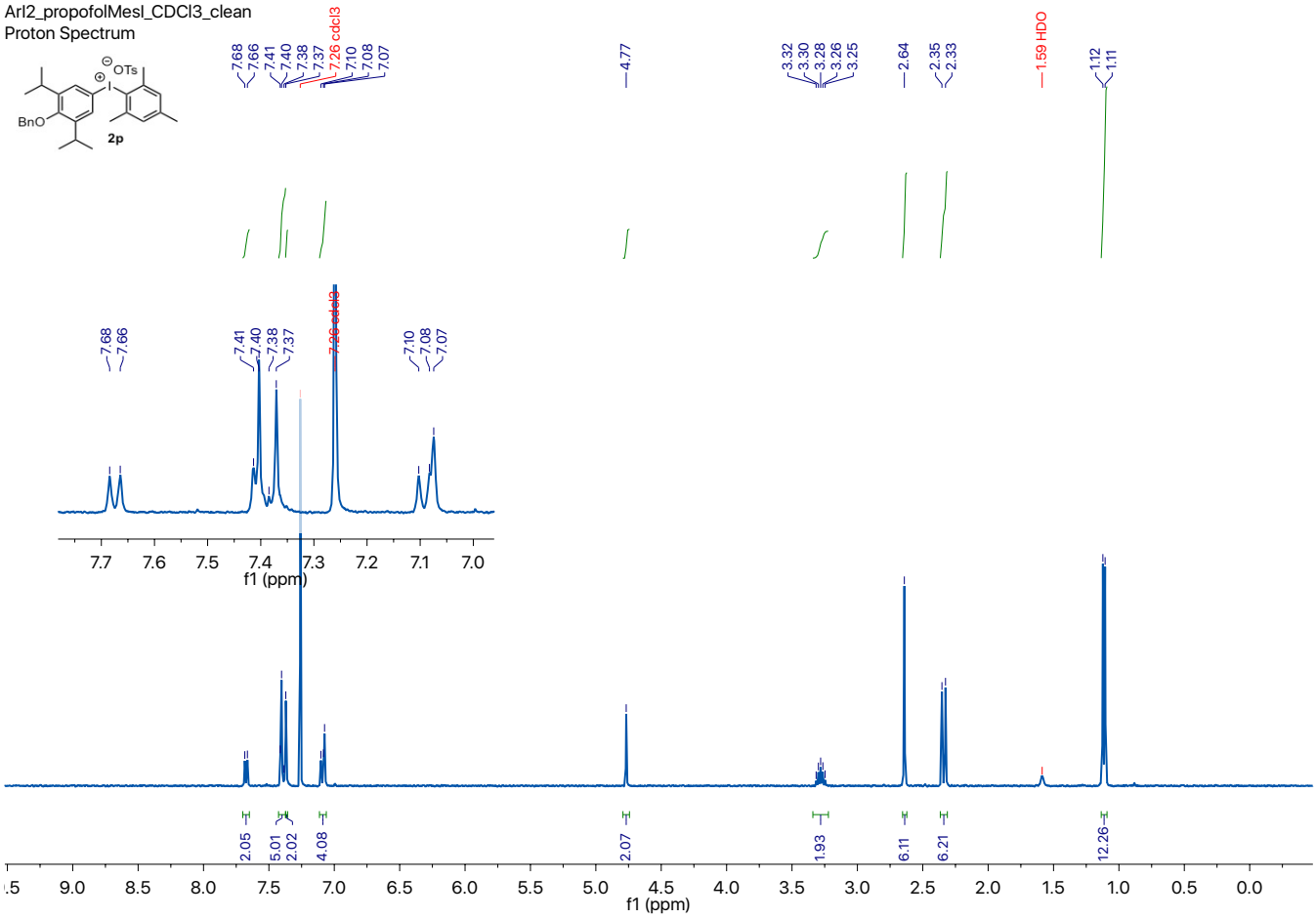


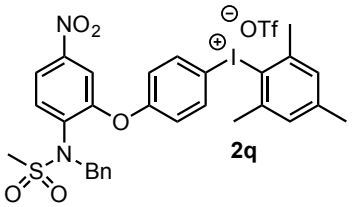
(3-Chloro-6-methyl-5,5-dioxido-11-oxo-6,11-dihydrodibenzo[*c*,*f*][1,2]thiazepin-9-yl)(mesityl)iodonium trifluoromethanesulfonate (2o). General procedure A was followed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 2.1 Hz, 1H), 8.17 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.91 (s, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.36 (d, *J* = 8.9 Hz, 1H), 7.15 (s, 2H), 3.43 (s, 3H), 2.70 (s, 6H), 2.38 (s, 3H).



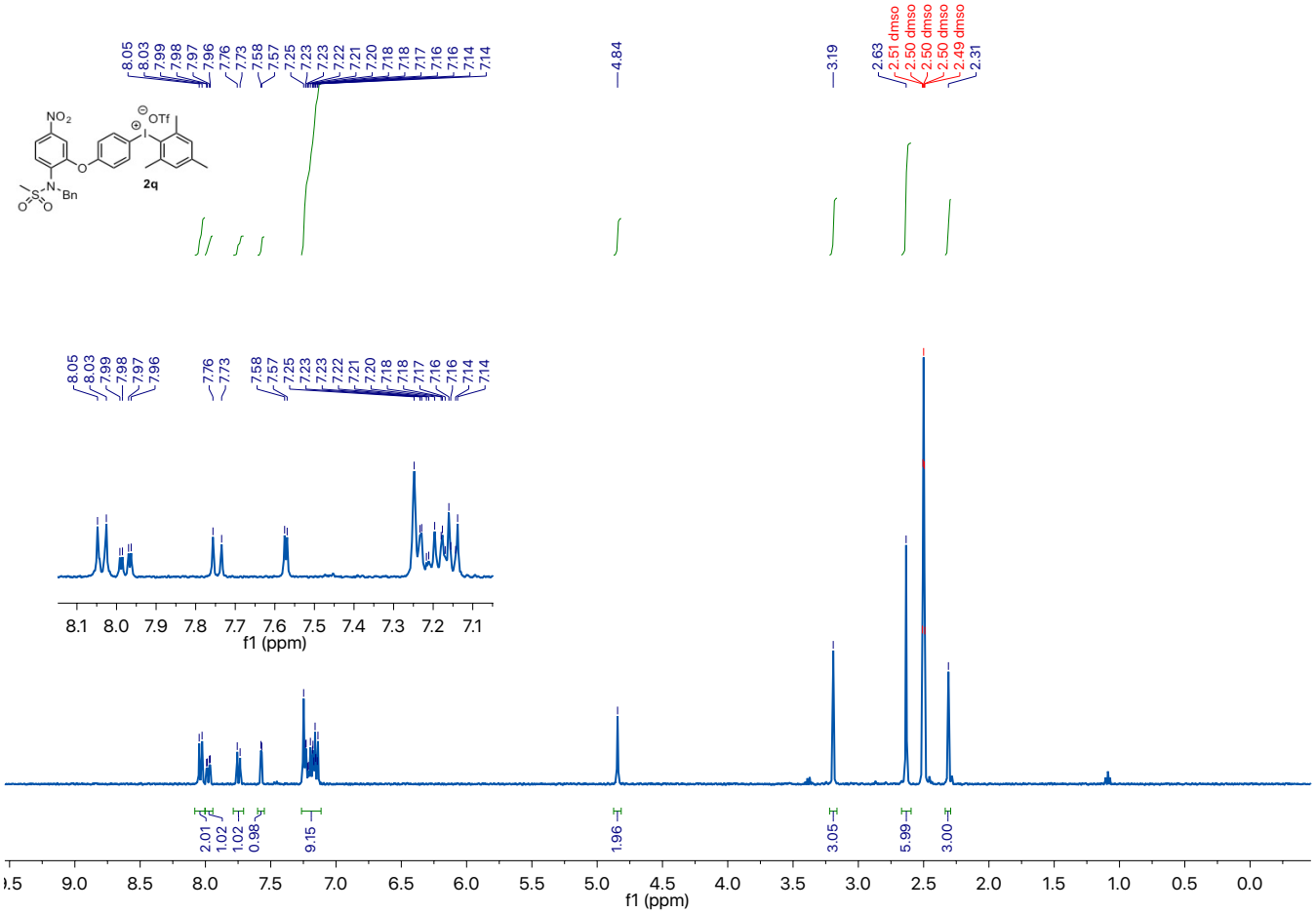


(4-(Benzyloxy)-3,5-diisopropylphenyl)(mesityl)iodonium 4-methylbenzenesulfonate (2p). General procedure A was followed. ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.67 (d, J = 8.0 Hz, 2H), 7.43-7.38 (multiple peaks, 5H), 7.37 (s, 2H), 7.13-7.05 (multiple peaks, 4H), 4.77 (s, 2H), 3.28 (p, J = 6.9 Hz, 2H), 2.64 (s, 6H), 2.35 (s, 3H), 2.33 (s, 3H), 1.11 (d, J = 6.9 Hz, 12H).





(4-(2-(*N*-Benzylmethylsulfonamido)-5-nitrophenoxy)phenyl)(mesityl)iodonium trifluoromethanesulfonate (2q). General procedure A was followed. ^{1}H NMR (401 MHz, DMSO-d_6) δ 8.04 (d, J = 8.9 Hz, 2H), 7.98 (dd, J = 8.8, 2.6 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.57 (d, J = 2.6 Hz, 1H), 7.26-7.11 (multiple peaks, 9H), 4.84 (s, 2H), 3.19 (s, 3H), 2.63 (s, 6H), 2.31 (s, 3H).



V. Radiochemistry

A. General Considerations, Methods, and Materials

Anhydrous potassium carbonate, 18-crown-6, tetrakis(acetonitrile)copper(I) triflate, trimethylsilyl triflate, and trifluoroacetic acid were obtained from Sigma Aldrich. Anhydrous acetonitrile, anhydrous DCM, and anhydrous N,N-dimethylformamide were obtained from Acros Organics. HPLC grade acetonitrile, ammonium acetate and anisole were obtained from Fisher Chemical. Ethanol was purchased from American Reagent. Potassium triflate was obtained from Oakwood Chemical. N,N-Diisopropylethylamine was obtained from Sigma Aldrich and was distilled from potassium hydroxide before use and stored under argon. Sterile 0.9% saline and sterile water for injection were purchased from Hospira. Ultrapure water was obtained from a Millipore MilliQ Gradient A10 system. Sterile vials were purchased from Hollister-Stier.

QMA-light Sep-Paks were purchased form Waters Corporation, and were flushed with 10 ml ethanol, followed by 10 mL of water, followed by 10 mL of 0.5 M aqueous sodium bicarbonate solution or 0.5 M aqueous potassium triflate solution as specified below, followed by 10 mL of water before use. Sep-Pak C18 1cc Vac cartridges were purchased from Waters Corporation, and were flushed with 10 ml ethanol, followed by 10 mL of water before use.

Glass backed thin layer chromatography (TLC) plates coated with silica gel $60F_{254}$ were used for radio-TLC analysis and were purchased from EMD-Millipore. Radio-TLC analysis was performed using a Bioscan AR 2000 Radio-TLC scanner (Ekert and Ziegler).

Activity in vials was counted using a CRC-15 (Capintec) detector, calibrated for fluorine-18.

High performance liquid chromatography (HPLC) was performed using a Shimadzu LC-2010A HT system, or a Shimadzu LC system (SCL-10Avp controller, SIL-10AF injector, SPD-10Avp UV detector, LC-DADvp FCV-10ALvp pump system, DGU-14A degasser and CTO-10A5vp column oven) equipped with a Bioscan B-FC-1000 radiation detector in series. A 0.2 min offset was applied to all traces below to account for the detectors being in series. The following set of HPLC conditions were used, as specified below:

HPLC Condition A: Column: Phenomenex Luna 5 µm C18(2) 100 Å 150 mm x 4.6 mm
Flow Rate: 2 $mL.min^{-1}$
Solvent A: H_20+0.1% trifluoroacetic acid
Solvent B: MeCN
Grad/isocrat: 0-3 min, 5% B; 3-20 min, linear gradient, 5-95%B; 20-30 min, 5% B

HPLC Condition B: Column: Phenomenex Luna 5 µm C18(2) 100 Å 150 mm x 4.6 mm
Flow Rate: 2 $mL.min^{-1}$
Solvent A: H_20+0.1% trifluoroacetic acid
Solvent B: MeCN
Grad/isocrat: 0-5 min, linear gradient, 5-60%B; 5-20 min, linear gradient, 60-95%B; 20-25 min, 95%B; 25-35 min, 5% B

HPLC Condition C: Column: Phenomenex Synergi 4 µm Hydro-RP 80 Å 150 mm x 4.6 mm
Flow Rate: 2 $mL.min^{-1}$
Solvent A: 20 mM NH_4OAc in H_20, pH 7.4
Solvent B: MeCN

Grad/isocrat: 0-3 min, 0% B; 3-20 min, linear gradient, 0-20%B; 20-25 min, linear gradient, 20-95%B; 25-30 min, 95%B; 30-40 min, 0% B

HPLC Condition D: Column: Phenomenex Kinetex 5 µm PFP 100 Å 250 mm x 4.6 mm
Flow Rate: 2 mL.min^{-1}
Solvent A: 50% MeCN in H_2O, 20 mM NH_4OAc, pH 4.5
Grad/isocrat: isocratic, 12 min

HPLC Condition E: Column: Phenomenex Luna 5 µm C18(2) 100 Å 150 mm x 4.6 mm
Flow Rate: 2 mL.min^{-1}
Solvent A: 35% MeCN in H_2O, 10 mM NH_4OAc, pH 4.5
Grad/isocrat: isocratic, 15 min

B. Radiosynthesis of ^{18}F-labeled Arenes

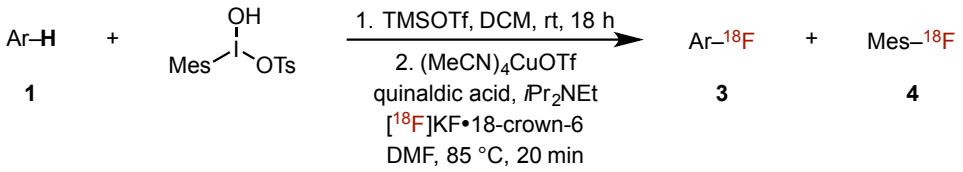
i. Potassium [^{18}F]fluoride for manual reactions

Potassium [^{18}F]fluoride preparation was conducted on a TRACERLab FX_{FN} or TRACERLab FX_{NPro} (General Electric, GE) automated radiochemistry synthesis module. Before [^{18}F]fluoride delivery, ports in the module were charged under ambient atmosphere as follows:

- Port 1: K_2CO_3 (3.5 mg) in H_2O (0.5 mL)
- Port 2: 18-crown-6 (15 mg) in MeCN (1 mL)
- Port 5: DMF (7.5 mL)

[^{18}F]Fluoride was produced via the $^{18}O(p,n)^{18}F$ reaction by proton irradiation (40 µA, 2-5 min) of an [^{18}O]H_2O containing target in a GE PETTrace cyclotron. The [^{18}F]fluoride (ca. 120-300 mCi) was swept to the synthesis module in a bolus of [^{18}O]H_2O by stream of argon. The aqueous solution of [^{18}F]fluoride was passed through a QMA-light Sep-Pak cartridge ($NaHCO_3$ preconditioning) to trap [^{18}F]fluoride before elution into the reactor vessel with a solution of K_2CO_3 in H_2O (contents of Port 1). To this, a solution of 18-crown-6 in MeCN (contents of Port 2) was added, and the mixture azeotropically dried by heating the reaction vessel to 100 °C and drawing vacuum (ca. 1 kPa) for 5 min, followed by simultaneous vacuum draw and argon stream for a further 6 minutes. The dried [^{18}F]KF•18-crown-6•K_2CO_3 complex was cooled to 50 °C before addition of DMF (contents of Port 5). The mixture was stirred for 5 min before being transferred out of the reactor under Ar pressure into a sterile vial to yield a solution of [^{18}F]KF•18-crown-6•K_2CO_3 (30-100 mCi) in DMF. 100 µL aliquots of this solution were then used for manual methodology experiments.

ii. Optimized General Procedure for the Synthesis of [^{18}F]Fluoroarenes



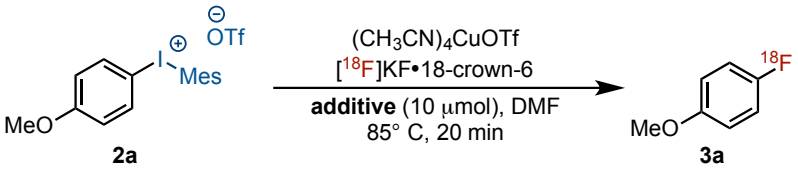
To a solution of MesI(OH)OTs (43 mg, 0.10 mmol, 1.0 equiv) in anhydrous DCM (0.40 mL) in a 4 mL vial equipped with a stir bar was added arene (0.10 mmol, 1.0 equiv). The stirring solution was cooled to 0 °C, and trimethylsilyl trifluoromethanesulfonate (TMSOTf) (18 µL (0.10 mmol, 1.0 equiv) was added dropwise. The solution was warmed to room temperature and stirred for 18 h before being used as a stock solution (0.25 M) of diaryliodonium in subsequent radiofluorination reactions.

To a 4 mL vial were added anhydrous dimethylformamide (DMF) (800 μL), diaryliodonium stock solution (40 μL, 10 μmol), and *N*,*N*-diisopropylethylamine (*i*Pr_2NEt) (3.5 μL, 20 μmol). The solution was agitated with a vortex mixer and aged for 10 min at room temperature. Under an ambient atmosphere, tetrakis(acetonitrile)copper(I) trifluoromethanesulfonate ($(MeCN)_4CuOTf$) (100 μL of a 100 mM solution, 10 μmol) and quinaldic acid (10 μmol) in DMF were added to the diaryliodonium/*i*Pr_2NEt solution. The reaction vial was sealed with a PTFE/Silicone septum cap and a 100 μL aliquot of [^{18}F]KF•18-crown-6•K_2CO_3 complex in DMF (typically 60-800 μCi, prepared as described above) was added to the reaction vial via syringe.[1] The reaction was heated in an aluminum block at 85 °C for 20 min. After 20 min, the reaction was removed from the heat and allowed to cool to room temperature. Radiochemical conversions (RCCs) were obtained by radio-TLC analysis (2-5 μL aliquots) using a 50:50 hexanes-ethyl acetate eluent,[2] and are not reported to reflect losses during [^{18}F]KF•18-crown-6•K_2CO_3 preparation.

Radiochemical conversions (RCCs) were determined by dividing the integrated area under the fluoroarene peak on radio-TLC by the total integrated area of all peaks on the radio-TLC trace. The identity of the [^{18}F]fluoroarene was verified using radio-HPLC (10-50 μL aliquots) and comparing samples to those that were spiked with a sample the authentic [^{19}F]fluoroarene product. The ratio of [^{18}F]fluoroarene to [^{18}F]fluoromesitylene and other byproducts was obtained by dividing the integrated area under the [^{18}F]fluoroarene or [^{18}F]fluoromesitylene peak on HPLC by the total integrated area of all peaks, excluding the peak observed from [^{18}F]fluoride.

iii. Summary of Reaction Optimization Studies

a. Evaluation of additives for the radiofluorination of isolated 4-$MeOC_6H_4$-I-MesOTf (2a)[a]



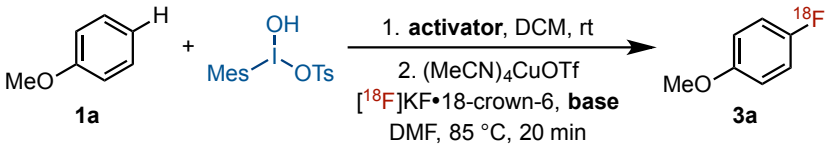
entry	additive	RCC (%)
1	none	46 ± 9 (*n* = 4)
2	AcOH	13 ± 4 (*n* = 4)
3	TFA	8 ± 4 (*n* = 4)
4	H_2O	45 ± 7 (*n* = 4)
5	quinaldic acid	62 ± 5 (*n* = 3)
6	quinaldic acid, *i*Pr_2NEt (10 μmol)	85 ± 2 (*n* = 3)

[a] Manual synthesis conditions: 4-$MeOC_6H_4$-I-MesOTf (**2a**) (10 μmol), $(MeCN)_4CuOTf$ (10 μmol), [^{18}F]KF•18-crown-6•K_2CO_3 complex in DMF (100 μL, 80-1200 μCi), **additive** (10 μmol), total volume 1.0 mL. Acetic acid (AcoH), trifluoroacetic acid (TFA).

[1] Typically, 4-12 reactions were set up in parallel. As a consequence, the exact times that the mixtures remain at room temperature prior to the addition of [^{18}F]fluoride varies between runs, and between days. The RCCs however appear insensitive to this variation as reflected in the small standard deviations observed

[2] Radio-TLCs for volatile products (eg. 4-fluoroanisole and 2-fluoro-4-methylthiophene) were counted immediately after developing, before the plate had dried completely

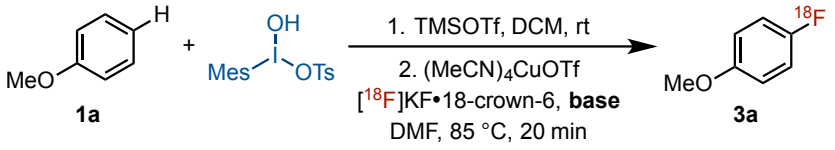
b. Optimization of the C(sp^2)–H radiofluorination of anisole (1a)[a]



entry	activator	base	RCC 3a[b] (%)
1	$TsOH•H_2O$	–	27 ± 4 (*n* = 4)
2	$TsOH•H_2O$	*i*Pr_2NEt (20 μmol)	61 ± 8 (*n* = 9)
3	TFAA	–	1 ± 1 (*n* = 3)
4	TFAA	*i*Pr_2NEt (4.0 equiv)	13 ± 2 (*n* = 3)
5	TMSOTf	–	5 ± 2 (*n* = 5)
6	TMSOTf	*i*Pr_2NEt (10 μmol)	58 ± 0.4 (*n* = 3)
7	TMSOTf	*i*Pr_2NEt (20 μmol)	78 ± 4 (*n* = 3)
8[c,d]	TMSOTf	*i*Pr_2NEt (20 μmol)	87 ± 4 (*n* = 13)
9[e]	TMSOTf	*i*Pr_2NEt (20 μmol)	00 ± 0 (*n* = 3)

[a] Manual synthesis conditions: 1. Anisole (**1a**) (10 μmol), MesI(OH)OTs (10 μmol), **activator** (10 μmol), DCM (40 μL); 2. $(MeCN)_4CuOTf$ (10 μmol), [^{18}F]KF•18-crown-6•K_2CO_3 complex in DMF (100 μL, 80-1200 μCi), total volume 1.0 mL. [b] Radiochemical conversion was determined by radio-TLC (average of *n* runs). The identity of 4-[^{18}F]fluoroanisole (**3a**) was confirmed by HPLC. [c] Quinaldic acid (10 μmol) was included in step 2. [d] 98:2 selectivity (**3a**:[^{18}F]fluoromesitylene) detected by radio-HPLC. [e] $(MeCN)_4CuOTf$ was omitted. Tosylic acid (TsOH), trifluoroacetic anhydride (TFAA), trimethylsilyl trifluoromethanesulfonate (TMSOTf).

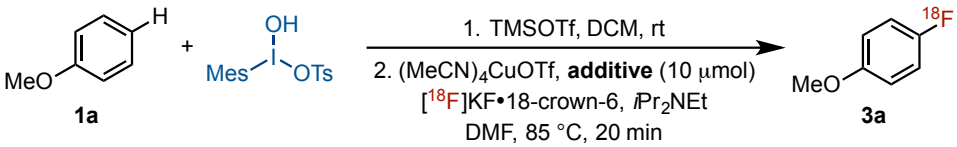
c. Base evaluation studies[a]



entry	base	μmol	RCC (%)
1	*i*Pr_2NEt	10	58 ± 0.4 (*n* = 3)
2	*i*Pr_2NEt	20	78 ± 4 (*n* = 3)
3	Et_3N	10	44 ± 11 (*n* = 5)
4	Et_3N	20	78 ± 7 (*n* = 4)
5	pyridine	10	6 ± 2 (*n* = 3)
6	pyridine	20	5 ± 1 (*n* = 3)
7	K_2CO_3	10	43 ± 8 (*n* = 3)
8	K_2CO_3	20	31 ± 7 (*n* = 3)

[a] Manual synthesis conditions: 1. Anisole (**1a**) (10 μmol), MesI(OH)OTs (10 μmol), TMSOTf (10 μmol), DCM (40 μL); 2. $(MeCN)_4CuOTf$ (10 μmol), [^{18}F]KF•18-crown-6•K_2CO_3 complex in DMF (100 μL, 80-1200 μCi), **base** (*x* μmol), total volume 1.0 mL.

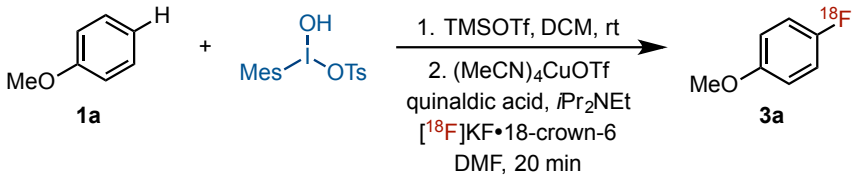
d. Additive evaluation studies[a]



entry	**additive**	RCC (%)
1	TMEDA	85 ± 5 (*n* = 3)
2	Quinox	48 ± 7 (*n* = 3)
3	bpy	88 ± 9 (*n* = 7)
4	picolinic acid	87 ± 4 (*n* = 4)
5	quinaldic acid	87 ± 4 (*n* = 13)
6[b]	quinaldic acid	87 ± 2 (*n* = 3)

[a] Manual synthesis conditions: 1. Anisole (**1a**) (10 µmol), MesI(OH)OTs (10 µmol), TMSOTf (10 µmol), DCM (40 µL); 2. $(MeCN)_4CuOTf$ (10 µmol), *i*Pr_2NEt (20 µmol), [^{18}F]KF•18-crown-6•K_2CO_3 complex in DMF (100 µL, 80-1200 µCi), **additive** (10 µmol), total volume 1.0 mL. [b] *i*Pr_2NEt (25 µmol). Tetramethylethylenediamine (TMEDA), 2-(4,5-dihydro-2-oxazolyl)quinoline (Quinox), 2,2'-bipyridine (bpy).

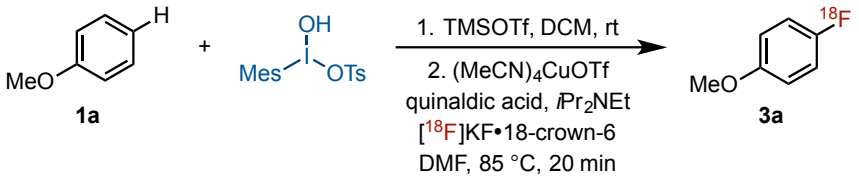
e. Temperature evaluation studies[a]



entry	**Temperature (°C)**	RCC (%)
1	65	81 ± 14 (*n* = 6)
2[b]	85	87 ± 4 (*n* = 13)
3[c]	105	90 ± 6 (*n* = 5)

[a] Manual synthesis conditions: 1. Anisole (**1a**) (10 µmol), MesI(OH)OTs (10 µmol), TMSOTf (10 µmol), DCM (40 µL); 2. $(MeCN)_4CuOTf$ (10 µmol), *i*Pr_2NEt (20 µmol), [^{18}F]KF•18-crown-6•K_2CO_3 complex in DMF (100 µL, 80-1200 µCi), quinaldic acid (10 µmol), total volume 1.0 mL. [b] 98:2 selectivity (**3a**:[^{18}F]fluoromesitylene) detected by radio-HPLC. [c] 98:2 selectivity (**3a**:[^{18}F]fluoromesitylene) detected by radio-HPLC

f. Reaction time point evaluation[a]

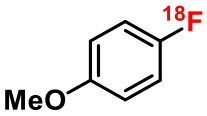


entry	**Time (min)**	RCC (%)
1	5	86 ± 1 (*n* = 3)
2	10	86 ± 1 (*n* = 3)
3	15	89 ± 1 (*n* =3)
4	20	87 ± 4 (*n* = 13)
5	30	89 ± 1 (*n* = 3)

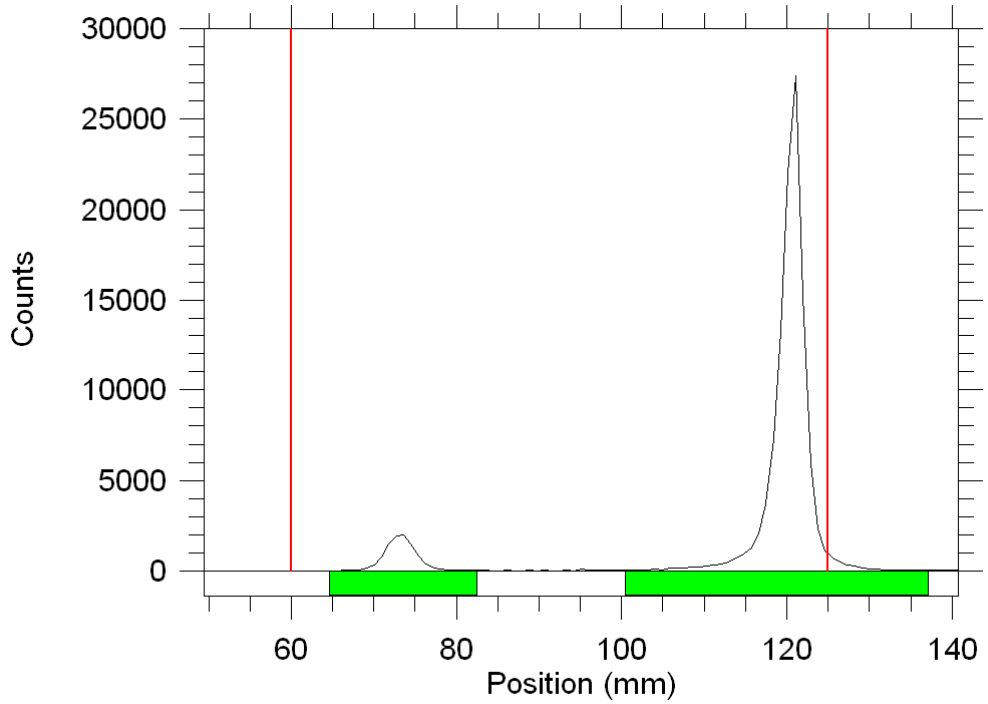
[a] Manual synthesis conditions: 1. Anisole (**1a**) (10 µmol), MesI(OH)OTs (10 µmol), TMSOTf (10 µmol), DCM (40 µL); 2. $(MeCN)_4CuOTf$ (10 µmol), *i*Pr_2NEt (20 µmol), [^{18}F]KF•18-crown-6•K_2CO_3 complex in DMF (100 µL, 80-1200 µCi), quinaldic acid (10 µmol), total volume 1.0 mL.

iv. Radio-HPLC/Radio-TLC Analysis for ^{18}F-labeled Arenes

a. 4-[^{18}F]Fluoroanisole (3a)



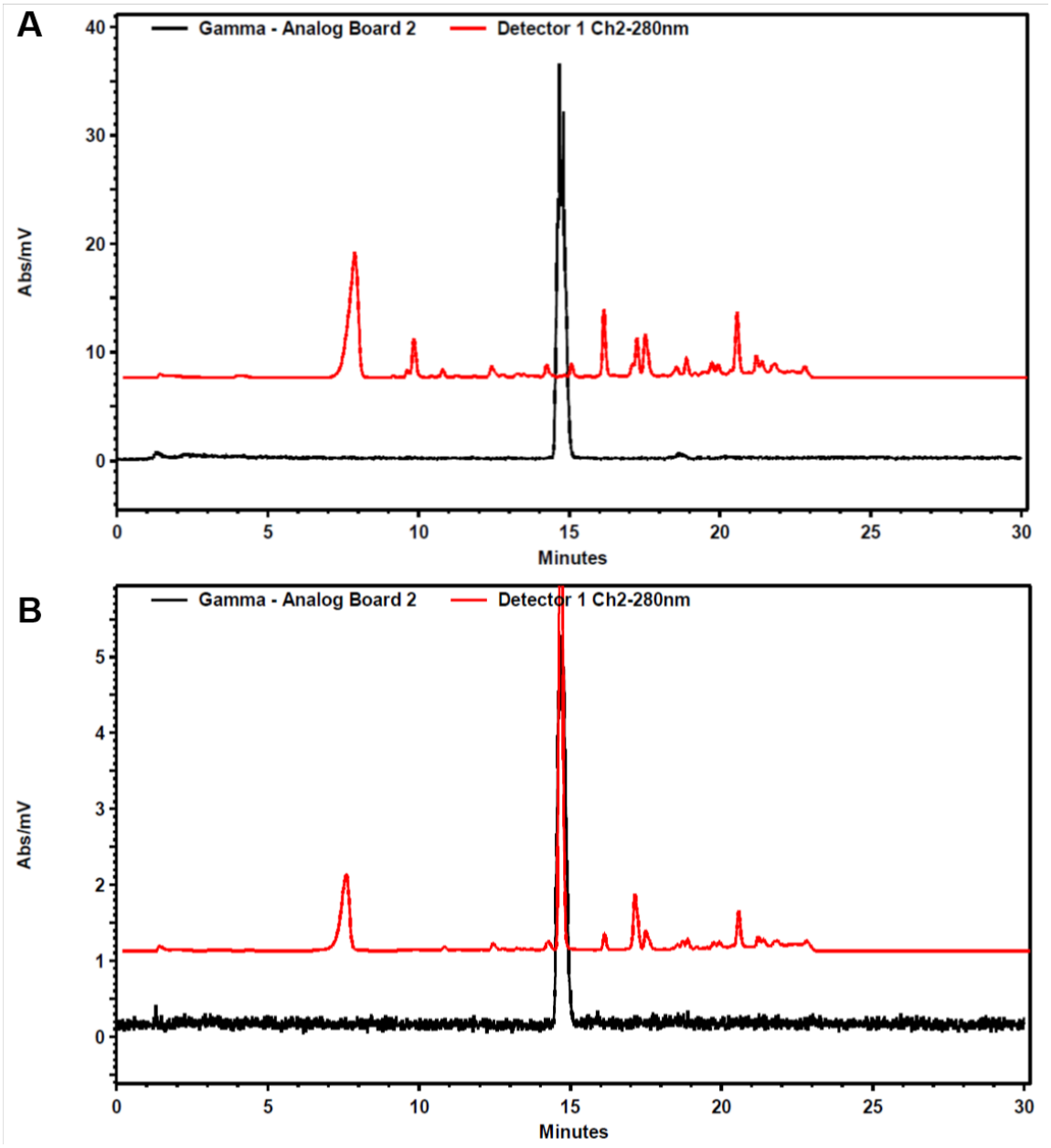
Radio-TLC eluent: 50% EtOAc in hexanes



Raw RCCs (%): 89, 94, 93, 90, 88, 81, 80, 85, 93, 85, 87, 87, 85. Average: 87 ± 4%. Selectivity: 98:2 (**3a**:**4**). RCC corrected for presence of **4**: 85 ± 4% (n = 13).

In the absence of quinaldic acid - Raw RCCs (%): 82, 77, 74. Average: 78 ± 4%. Selectivity: 98:2 (**3a**:**4**). RCC corrected for presence of **4**: 76 ± 4% (n = 13).

HPLC conditions: Condition A
A: 4-[^{18}F]Fluoroanisole **3a** reaction gamma trace overlaid with UV trace at 280 nm
B: 4-[^{18}F]Fluoroanisole **3a** reaction gamma trace overlaid with UV trace at 280 nm spiked with 4-fluoroanisole

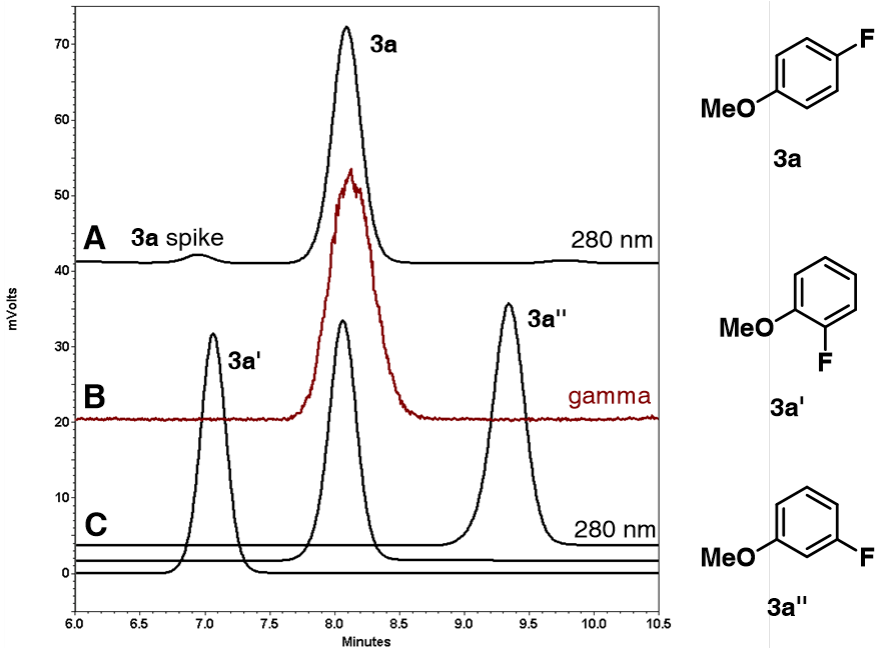


The site-selectivity of the reaction of anisole was determined by radio-HPLC analysis via comparison to authentic standards of the three possible isomers.

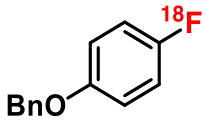
HPLC conditions: Condition E
Overlaid HPLC chromatograms for the one-pot radiofluorination of **1a**.

A: UV-HPLC chromatogram of the crude reaction mixture spiked with 4-fluoroanisole **3a** at 280 nm.
B: Radio-HPLC chromatogram of the crude reaction mixture.

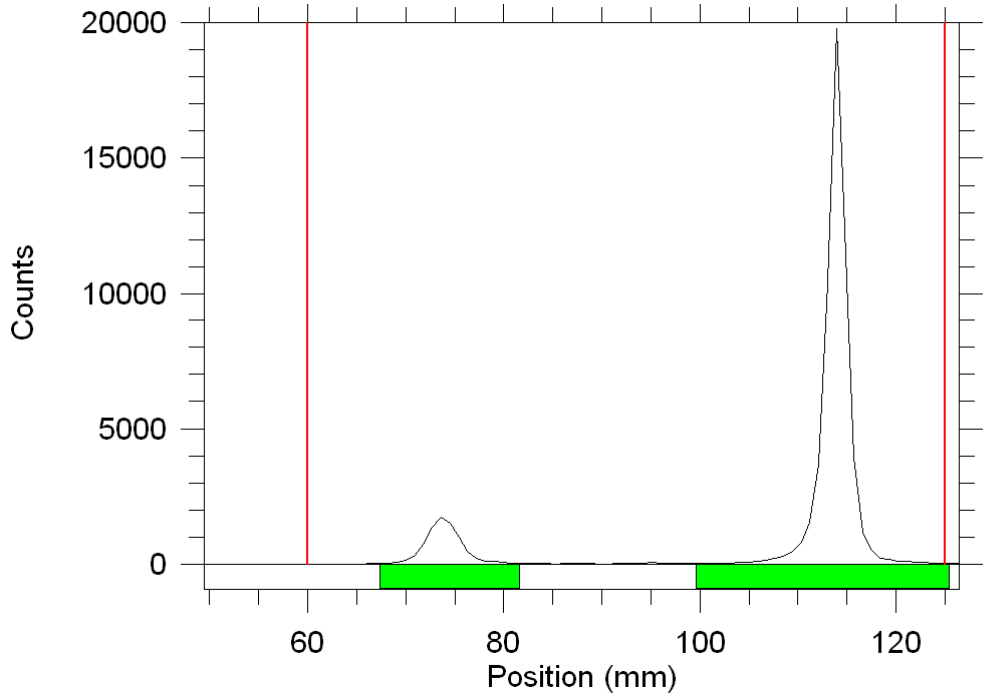
C: UV-HPLC chromatograms of authentic samples of possible fluoroanisole isomers at 280 nm



b. Benzyl 4-[^{18}F]fluorophenyl ether (3b)[3]



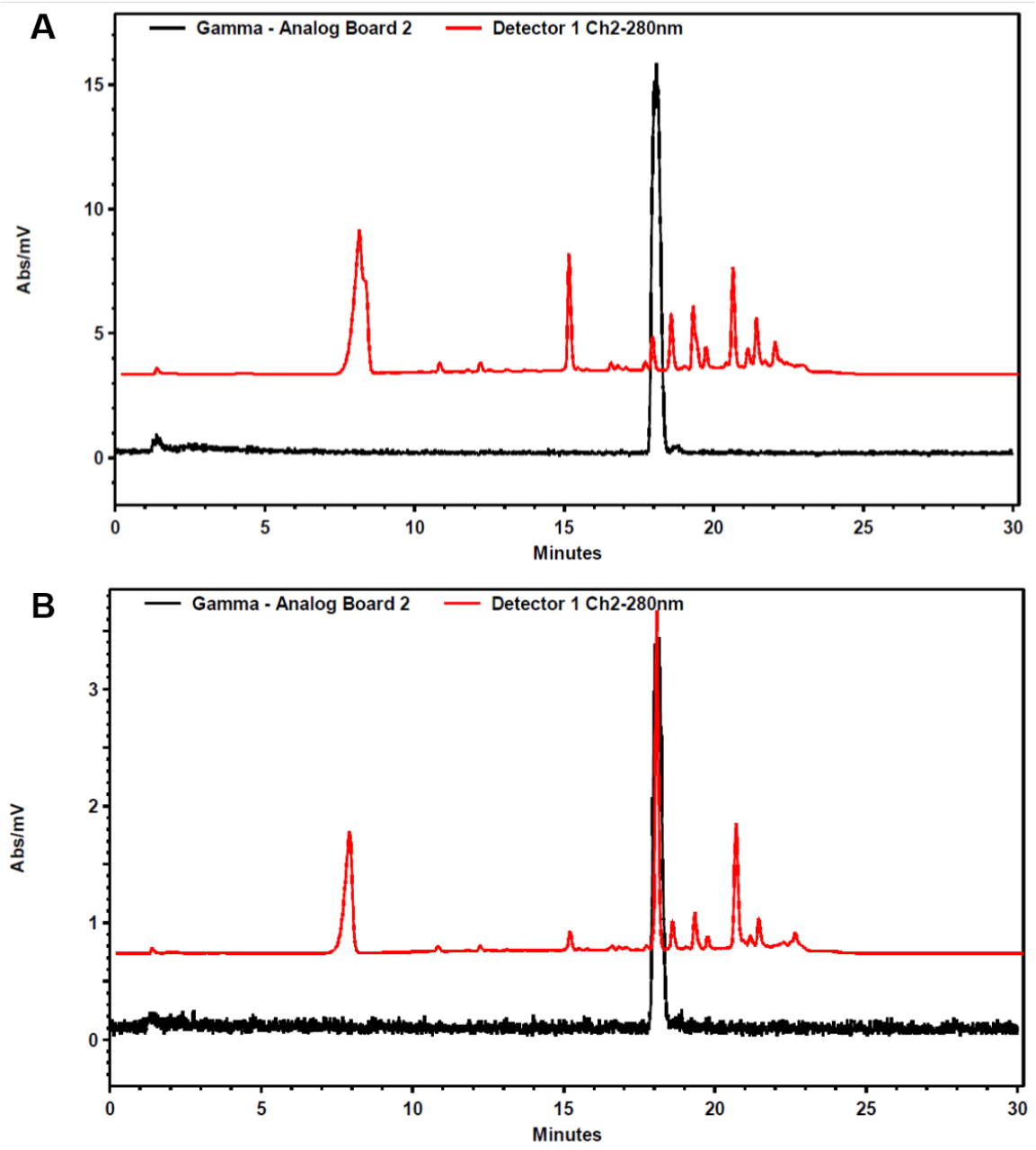
Radio-TLC eluent: 50% EtOAc in hexanes



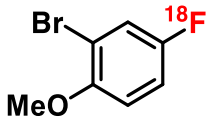
Raw RCCs (%): 87, 92, 93, 91. Average: 90 ± 3%. Selectivity: 98:2 (**3b**:**4**). RCC corrected for presence of **4**: 88 ± 3% (n = 4).

[3] The general procedure was followed using 9.0 μL (0.10 mmol, 1.0 equiv) TMSOTf.

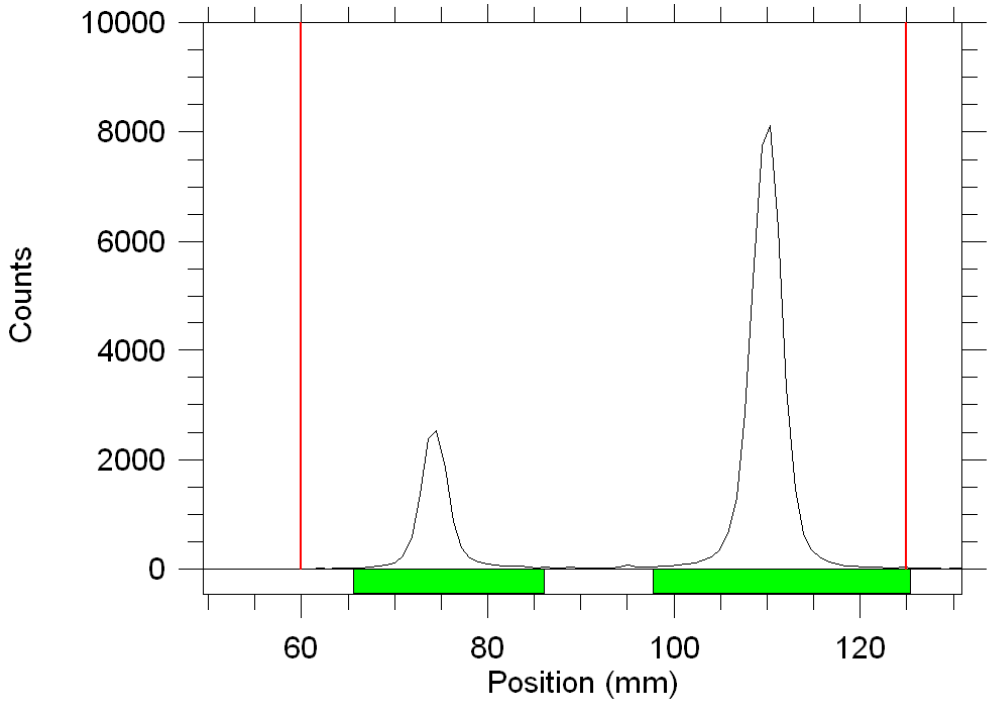
HPLC conditions: Condition A
A: Benzyl 4-[^{18}F]fluorophenyl ether **3b** reaction gamma trace overlaid with UV trace at 280 nm
B: Benzyl 4-[^{18}F]fluorophenyl ether **3b** reaction gamma trace overlaid with UV trace at 280 nm spiked with benzyl 4-fluorophenyl ether **3b**



c. 2-Bromo-4-[^{18}F]fluoroanisole (3c)

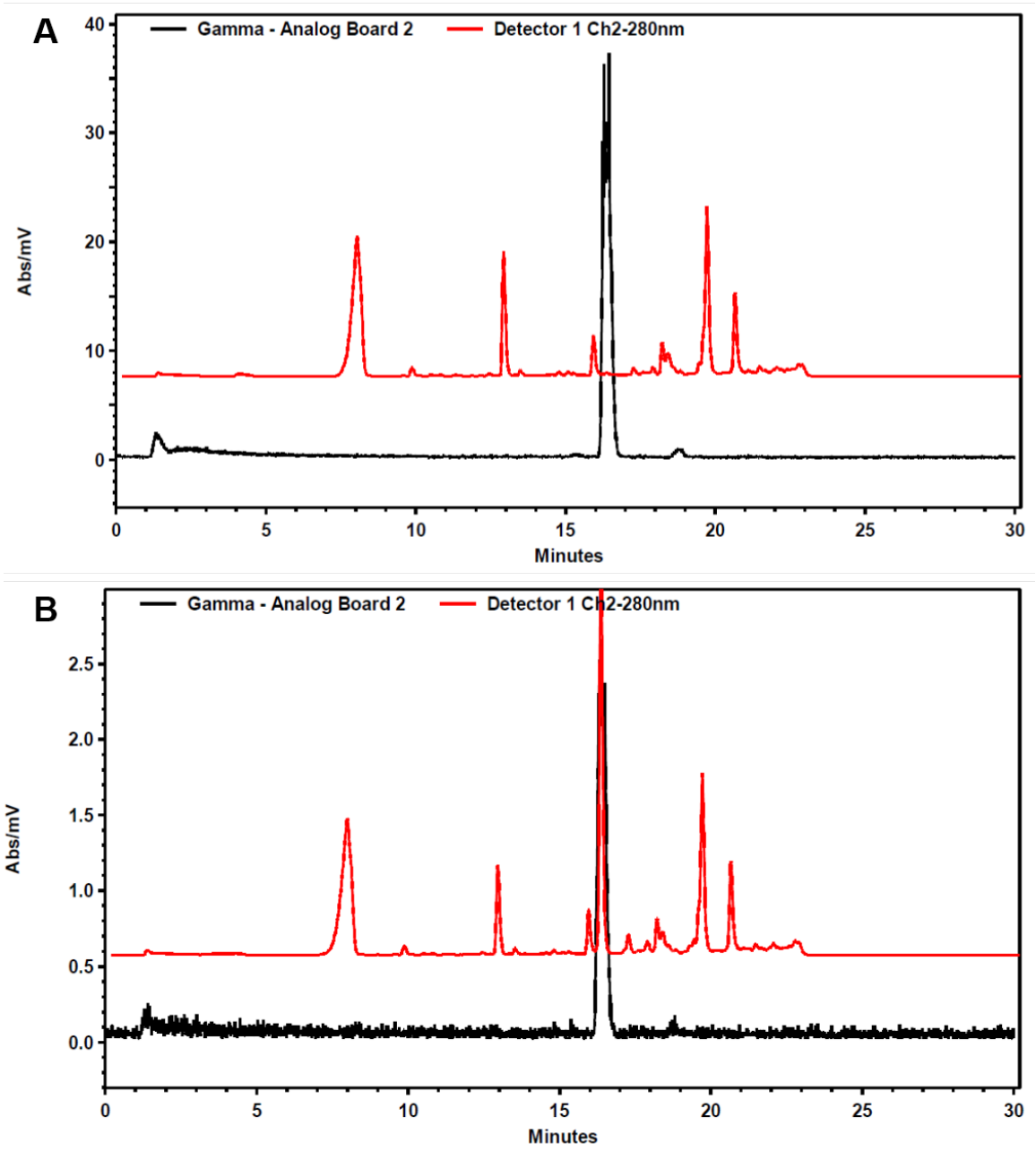


Radio-TLC eluent: 50% EtOAc in hexanes

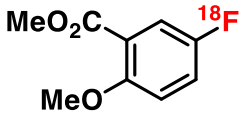


Raw RCCs (%): 87, 83, 87, 78. Average: 84 ± 4%. Selectivity: 97:3 (**3c**:**4**). RCC corrected for presence of **4**: 81 ± 4% (n = 4).

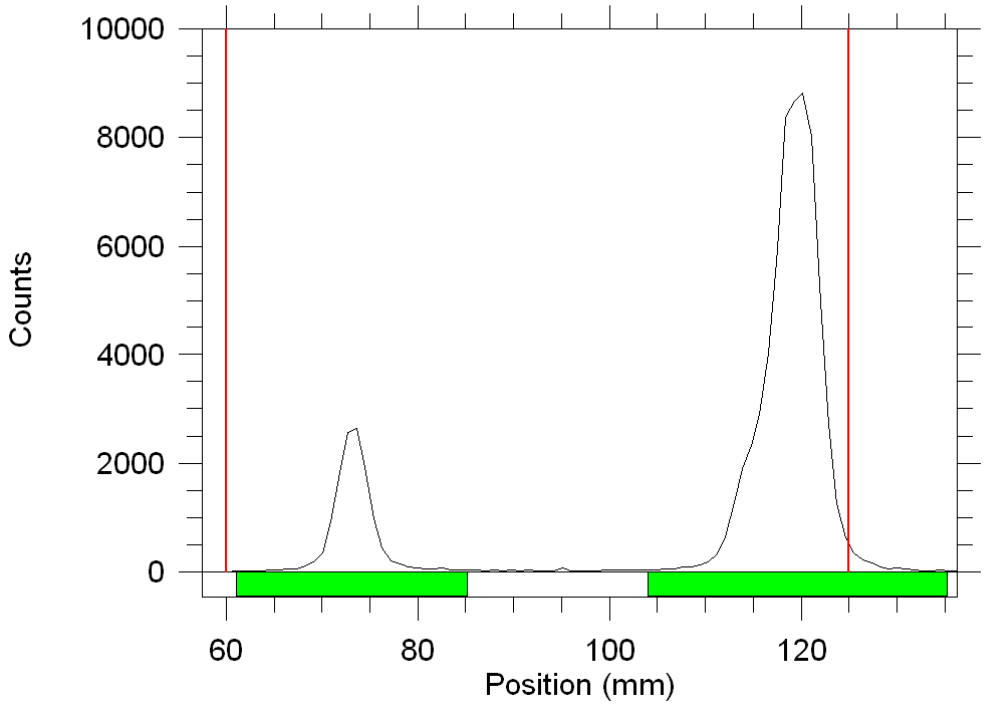
HPLC conditions: Condition A
A: 2-Bromo-4-[^{18}F]fluoroanisole **3c** reaction gamma trace overlaid with UV trace at 280 nm
B: 2-Bromo-4-[^{18}F]fluoroanisole **3c** reaction gamma trace overlaid with UV trace at 280 nm spiked with 2-bromo-4-fluoroanisole **3c**



d. Methyl 5-[^{18}F]fluoro-2-methoxybenzoate (3d)[4]



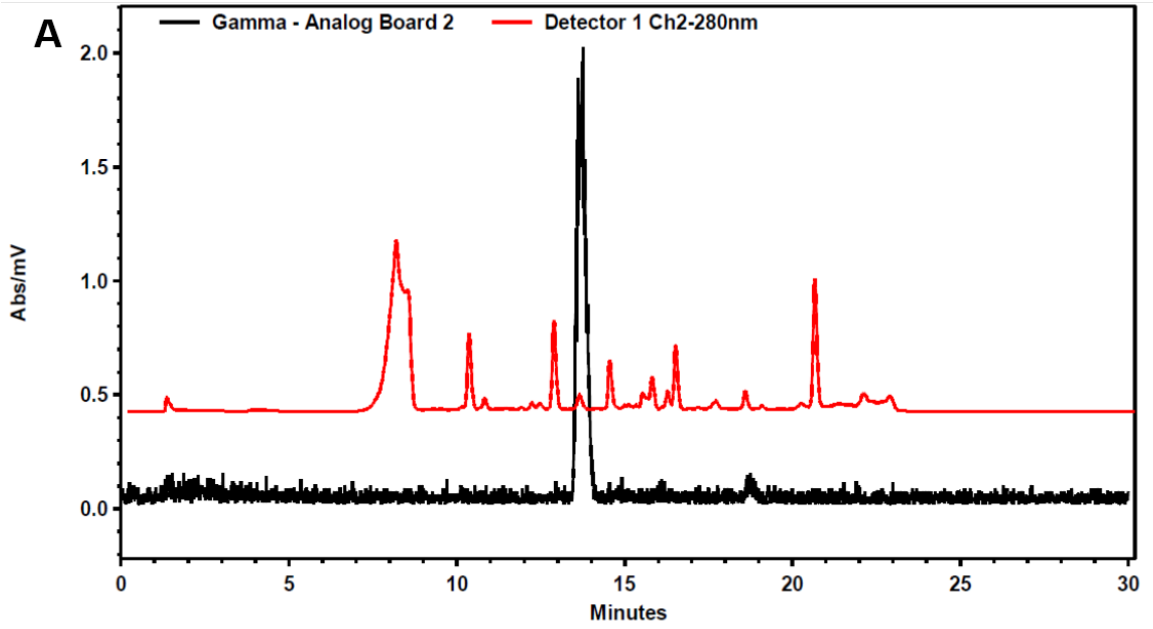
Radio-TLC eluent: 50% EtOAc in hexanes

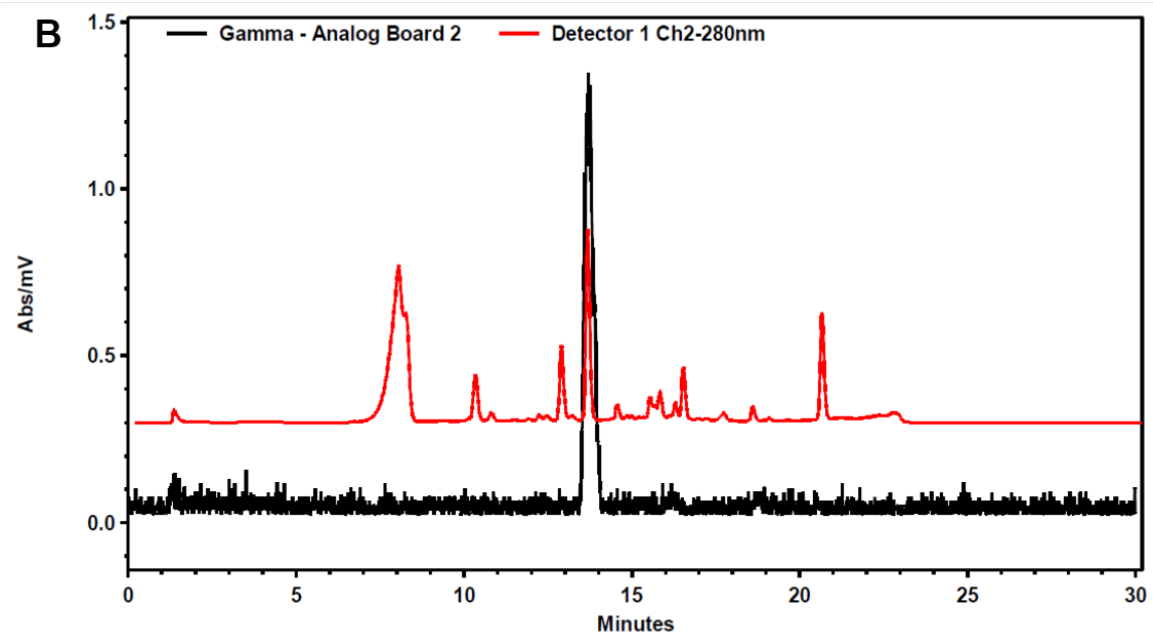


Raw RCCs (%): 84, 88, 86, 90. Average: 87 ± 3%. Selectivity: 95:5 (**3d**:**4**). RCC corrected for presence of **4**: 83 ± 3% (n = 4).

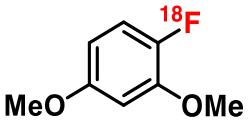
[4] The general procedure was followed using 9.0 μL (0.10 mmol, 1.0 equiv) TMSOTf.

HPLC conditions: Condition A
A: Methyl 5-[^{18}F]fluoro-2-methoxybenzoate **3d** reaction gamma trace overlaid with UV trace at 280 nm
B: Methyl 5-[^{18}F]fluoro-2-methoxybenzoate **3d** reaction gamma trace overlaid with UV trace at 280 nm spiked with methyl 5-fluoro-2-methoxybenzoate **3d**

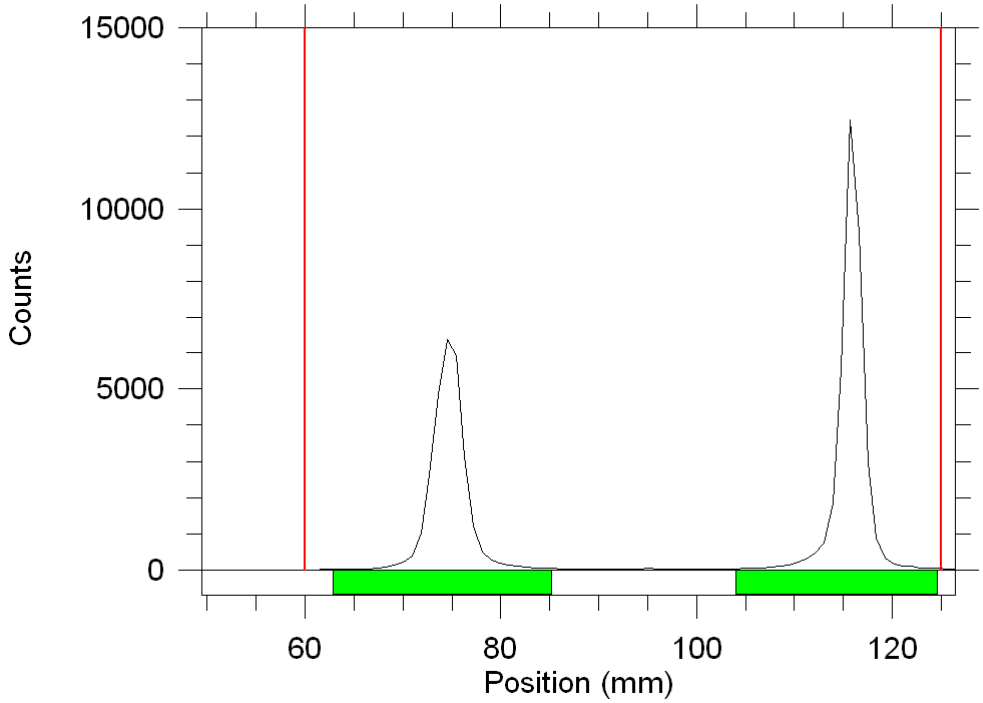




e. 1-[^{18}F]Fluoro-2,4-dimethoxybenzene (3e)

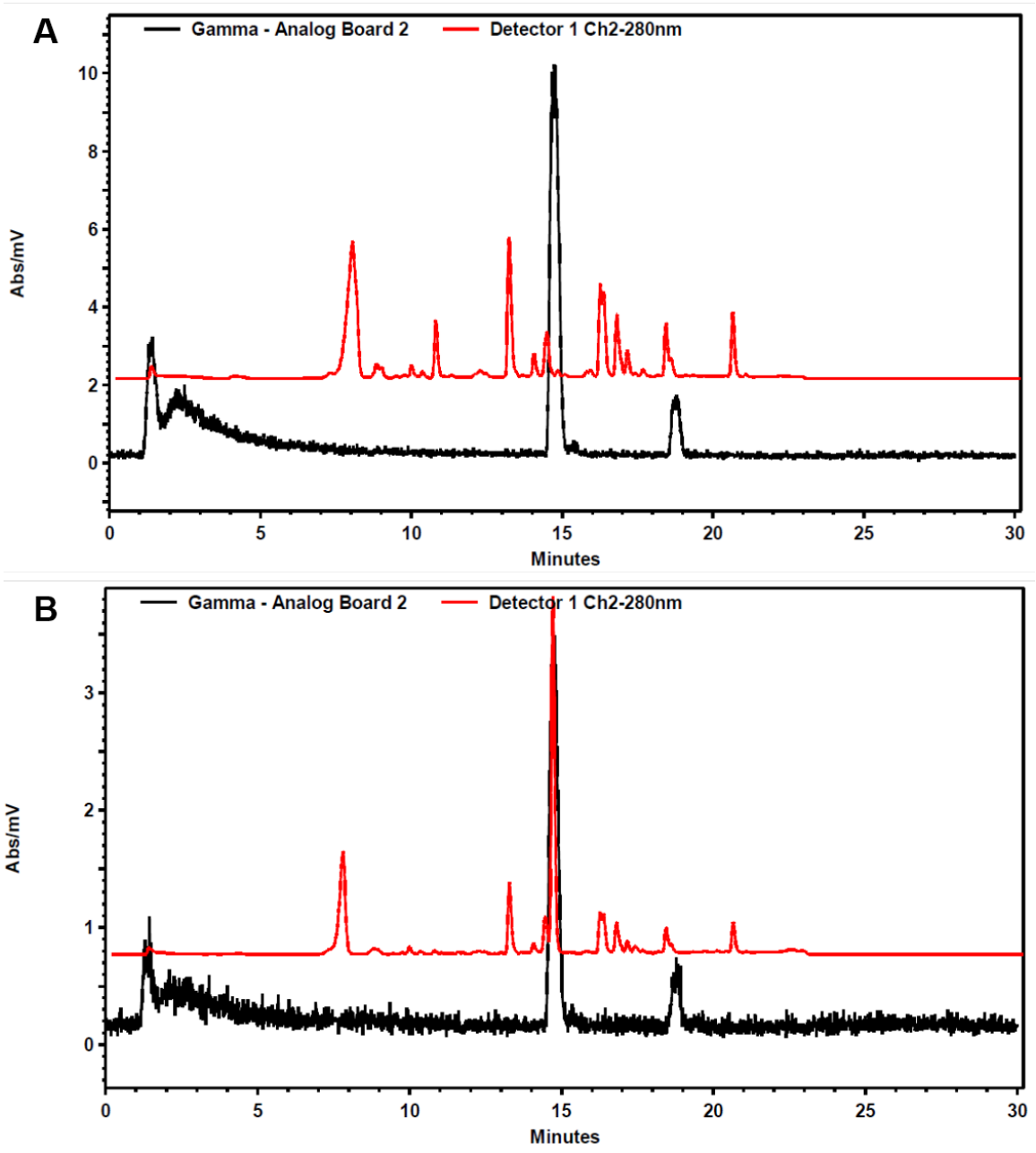


Radio-TLC eluent: 50% EtOAc in hexanes

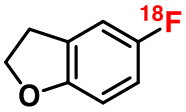


Raw RCCs (%): 62, 62, 70, 70, 72, 64, 57, 64. Average: 65 ± 5%. Selectivity: 88:12 (**3e**:**4**). RCC corrected for presence of **4**: 57 ± 4% (*n* = 8).

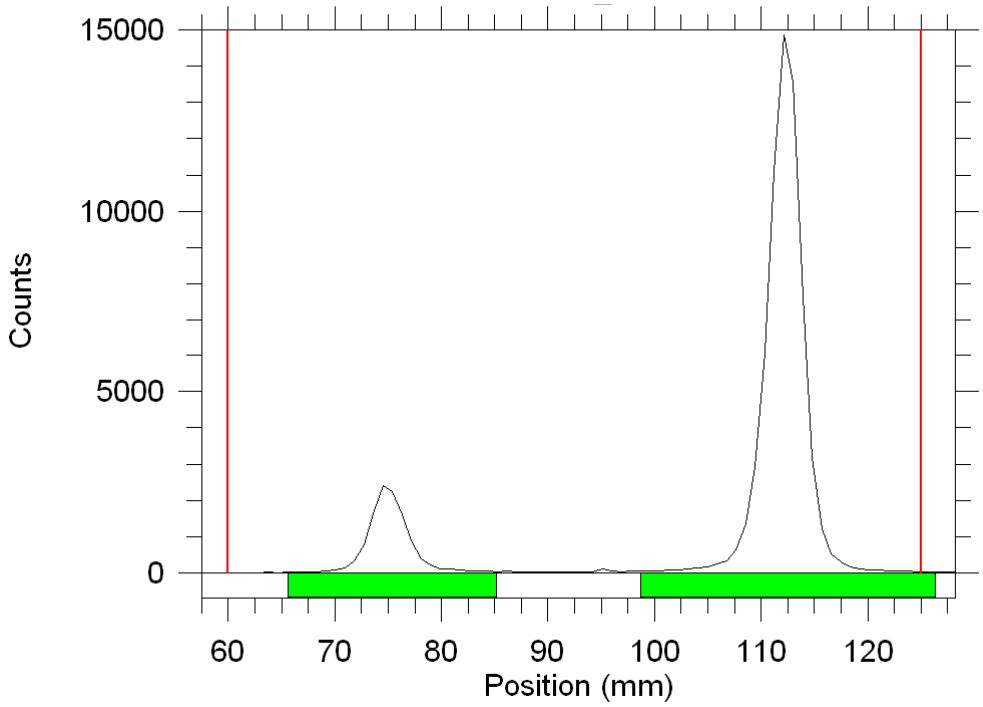
HPLC conditions: Condition A
A: 1-[^{18}F]Fluoro-2,4-dimethoxybenzene **3e** reaction gamma trace overlaid with UV trace at 280 nm
B: 1-[^{18}F]Fluoro-2,4-dimethoxybenzene **3e** reaction gamma trace overlaid with UV trace at 280 nm spiked with 1-[^{18}F]Fluoro-2,4-dimethoxybenzene **3e**



f. 5-[^{18}F]Fluoro-2,3-dihydrobenzofuran (3f)

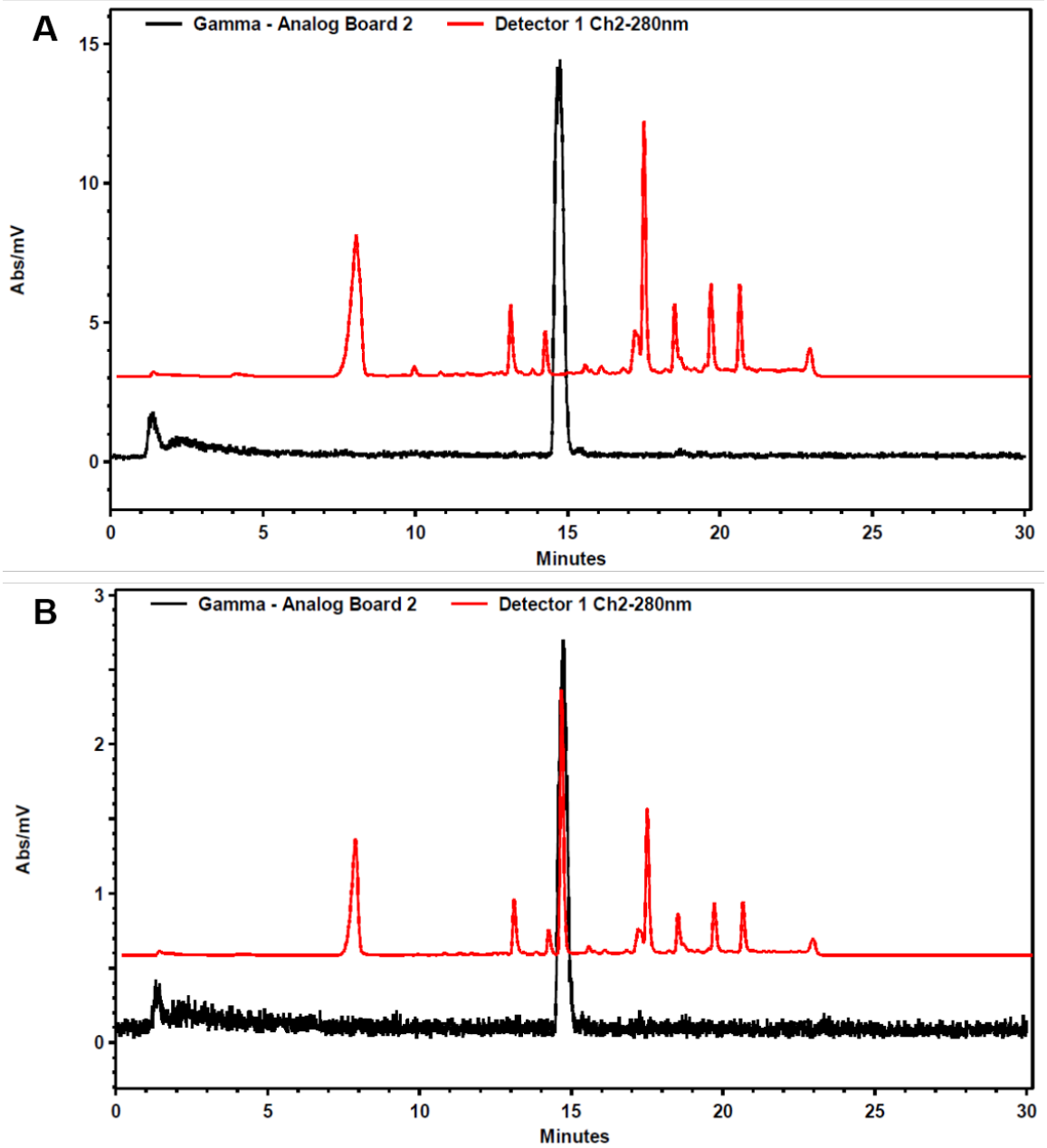


Radio-TLC eluent: 50% EtOAc in hexanes

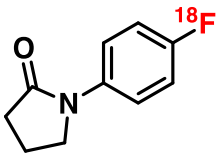


Raw RCCs (%): 82, 82, 74, 85, 80. Average: 81 ± 4%. Selectivity: 98:2 (**3f**:**4**). RCC corrected for presence of **4**: 79 ± 4% (*n* = 5).

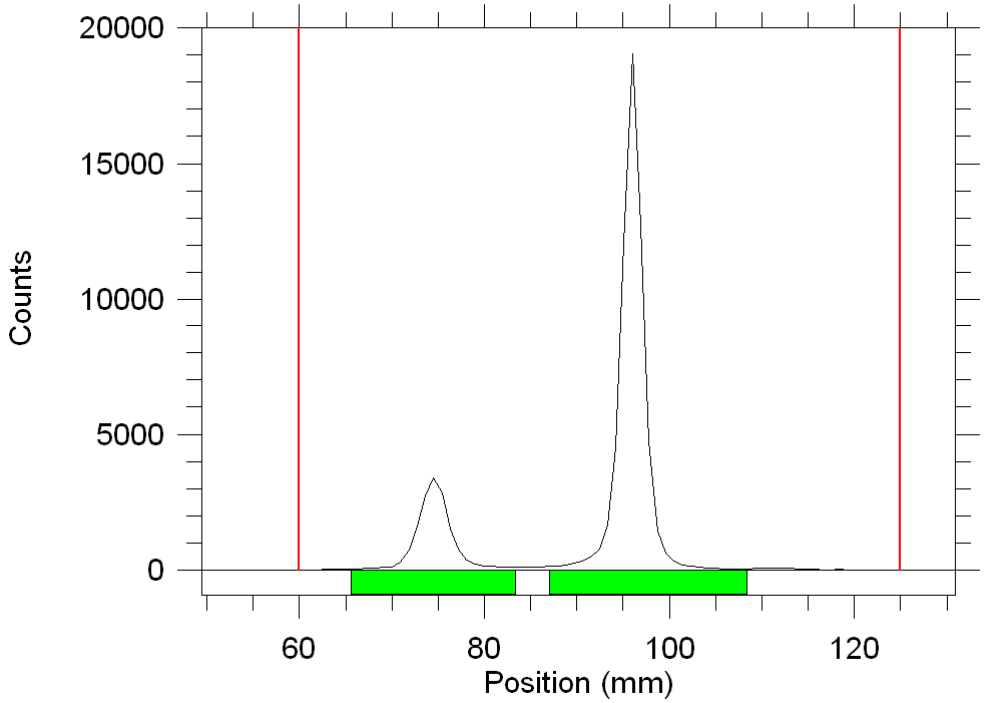
HPLC conditions: Gradient Condition A
A: 5-[^{18}F]Fluoro-2,3-dihydrobenzofuran **3f** reaction gamma trace overlaid with UV trace at 280 nm
B: 5-[^{18}F]Fluoro-2,3-dihydrobenzofuran **3f** reaction gamma trace overlaid with UV trace at 280 nm spiked with 5-fluoro-2,3-dihydrobenzofuran **3f**



g. *N*-(4-[^{18}F]fluorphenyl)pyrrolidine-2-one (3g)

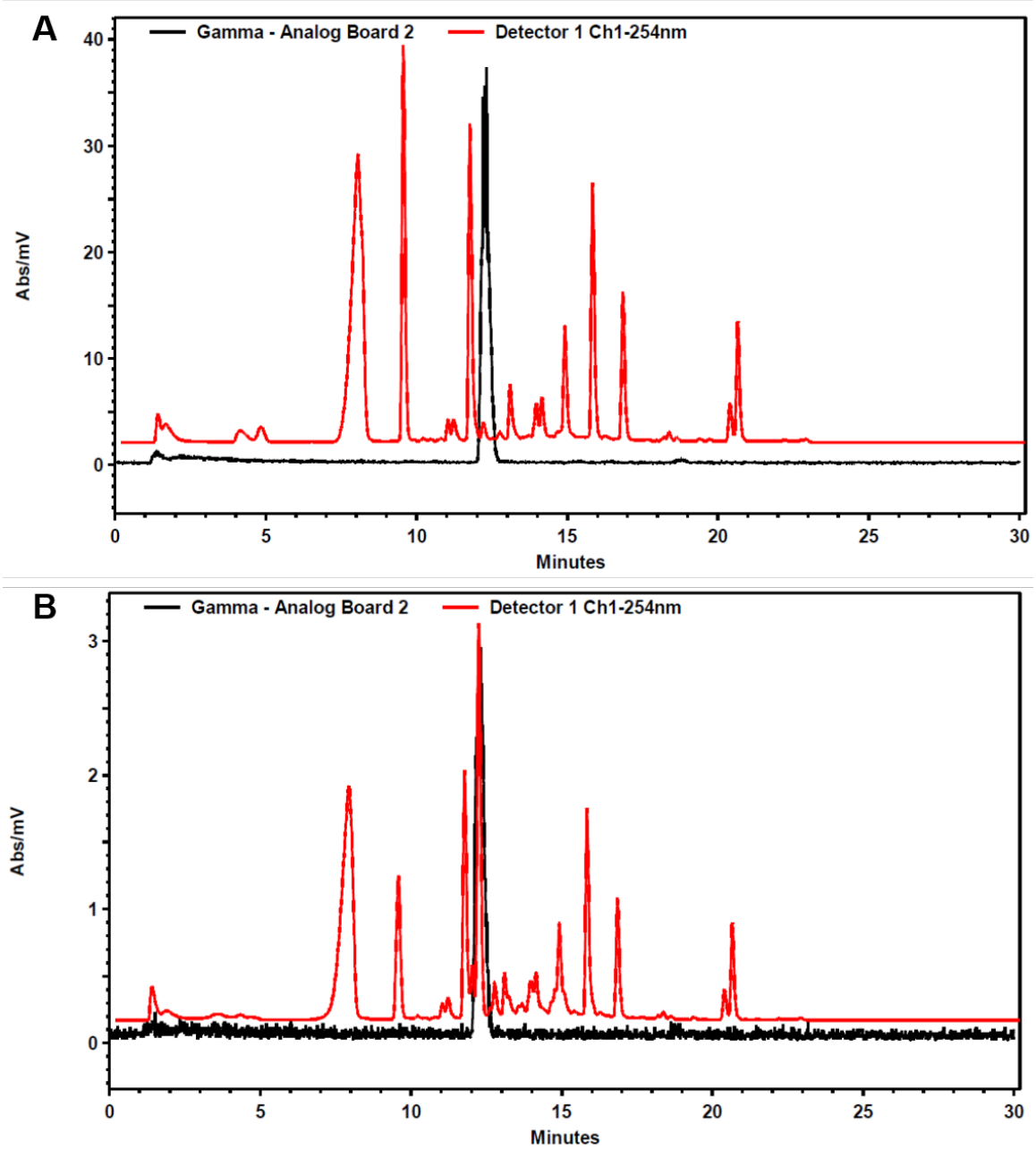


Radio-TLC eluent: 50% EtOAc in hexanes

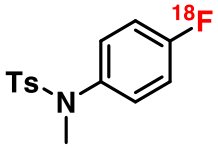


Raw RCCs (%): 92, 87, 75, 80, 82, 87. Average: 84 ± 6%. Selectivity: 97:3 (**3g**:**4**). RCC corrected for presence of **4**: 81 ± 6% (n = 6).

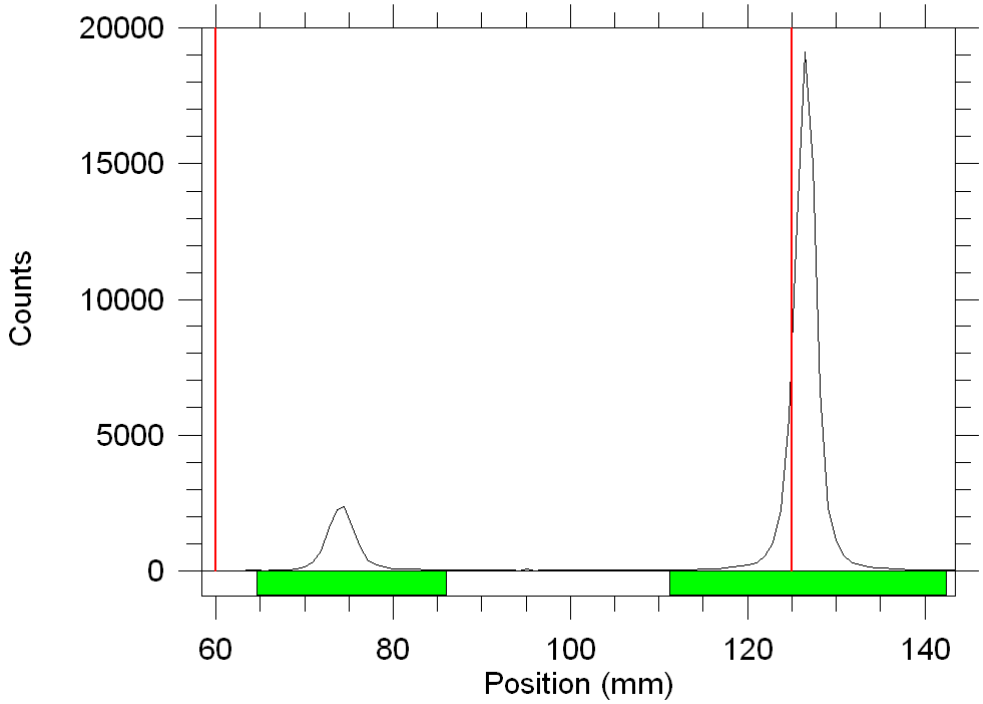
HPLC conditions: Gradient Condition A
A: *N*-(4-[^{18}F]fluorphenyl)pyrrolidine-2-one **3g** reaction gamma trace overlaid with UV trace at 254 nm
B: *N*-(4-[^{18}F]fluorphenyl)pyrrolidine-2-one **3g** reaction gamma trace overlaid with UV trace at 254 nm spiked with *N*-(4-fluorphenyl)pyrrolidine-2-one **3g**



h. 4-[^{18}F]Fluoro-*N*-methyl-*N*-tosylaniline (3h)[5]



Radio-TLC eluent: 50% EtOAc in hexanes

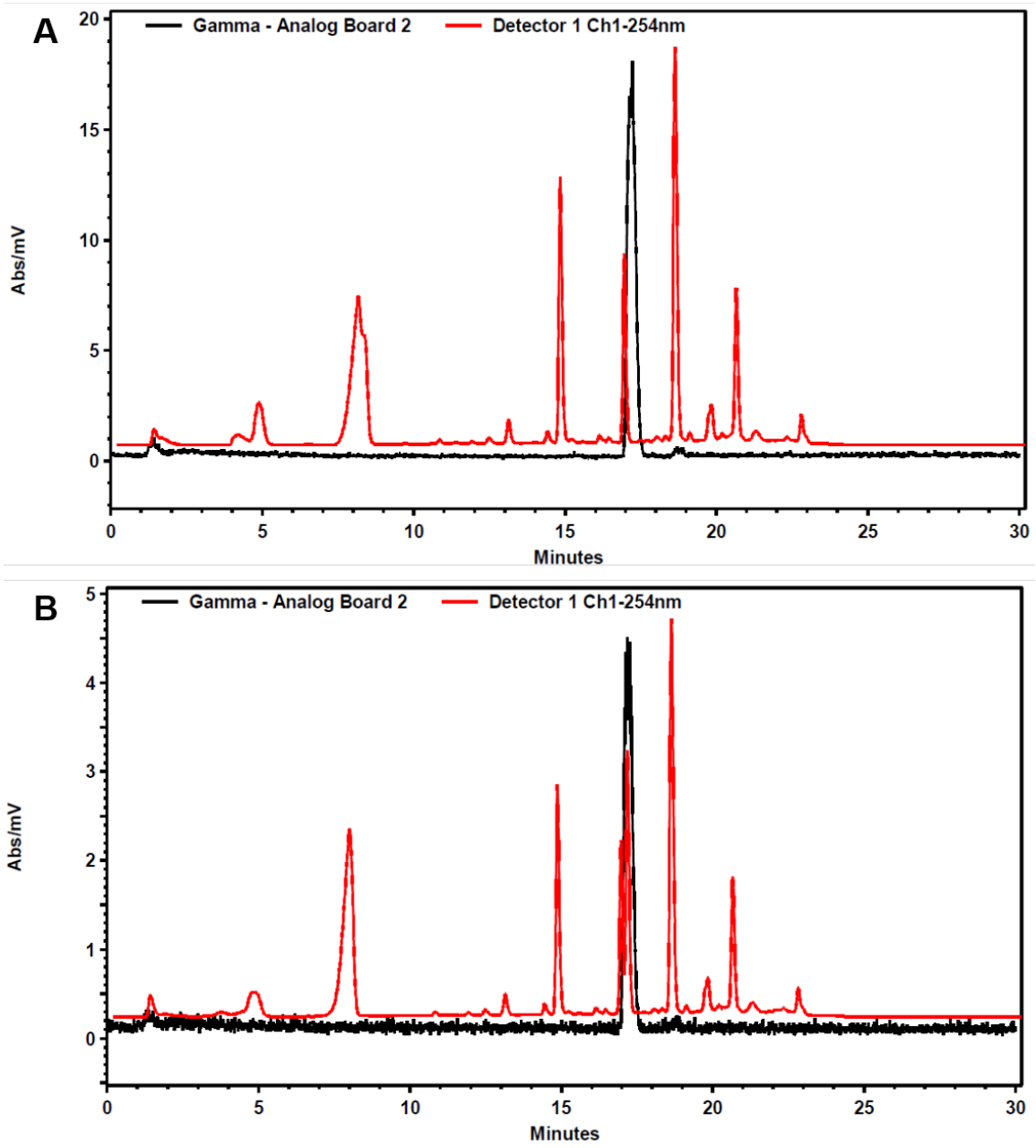


Raw RCCs (%): 86, 83, 84, 85, 86. Average: 85 ± 2%. Selectivity: 98:2 (**3h**:**4**). RCC corrected for presence of **4**: 83 ± 1% (*n* = 5).

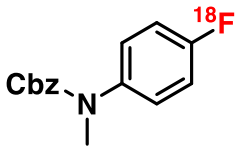
In the absence of quinaldic acid - Raw RCCs (%): 53, 63, 59, 41. Average: 59 ± 10%. Selectivity: 95:5 (**3h**:**4**). RCC corrected for presence of **4**: 56 ± 10% (*n* = 4).

[5] The general procedure was followed using 9.0 μL (0.10 mmol, 1.0 equiv) TMSOTf.

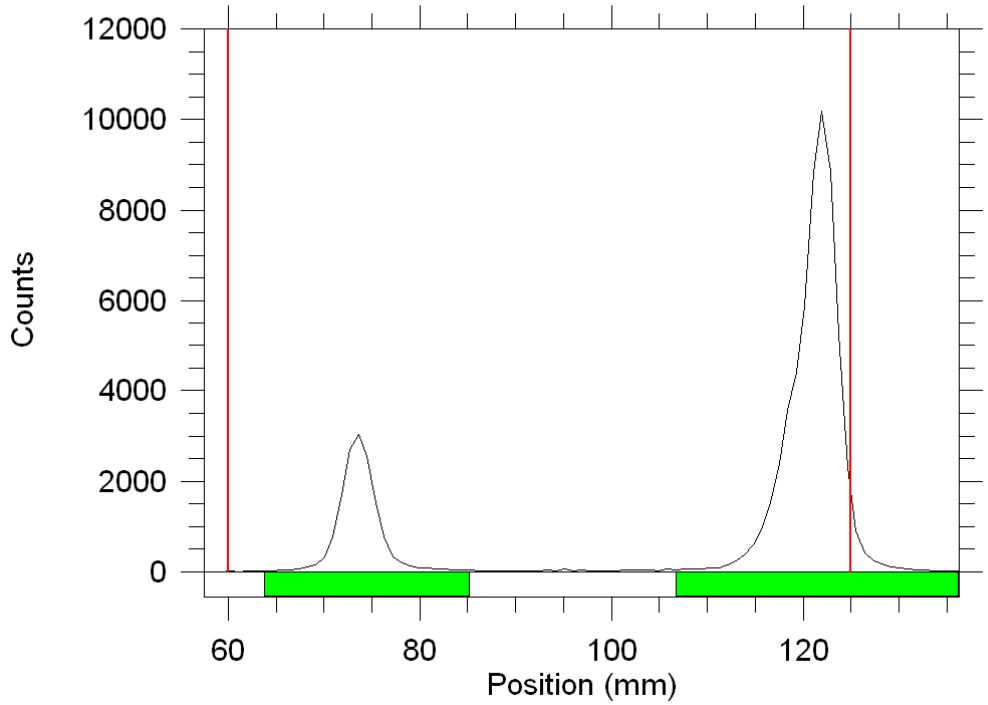
HPLC conditions: Condition A
A: 4-[^{18}F]fluoro-*N*-methyl-*N*-tosylaniline **3h** reaction gamma trace overlaid with UV trace at 254 nm
B: 4-[^{18}F]fluoro-*N*-methyl-*N*-tosylaniline **3h** reaction gamma trace overlaid with UV trace at 254 nm spiked with 4-fluoro-*N*-methyl-*N*-tosylaniline **3h**



i. *N*-Carboxybenzyl-4-[^{18}F]fluoro-*N*-methylaniline (3i)[6]



Radio-TLC eluent: 50% EtOAc in hexanes



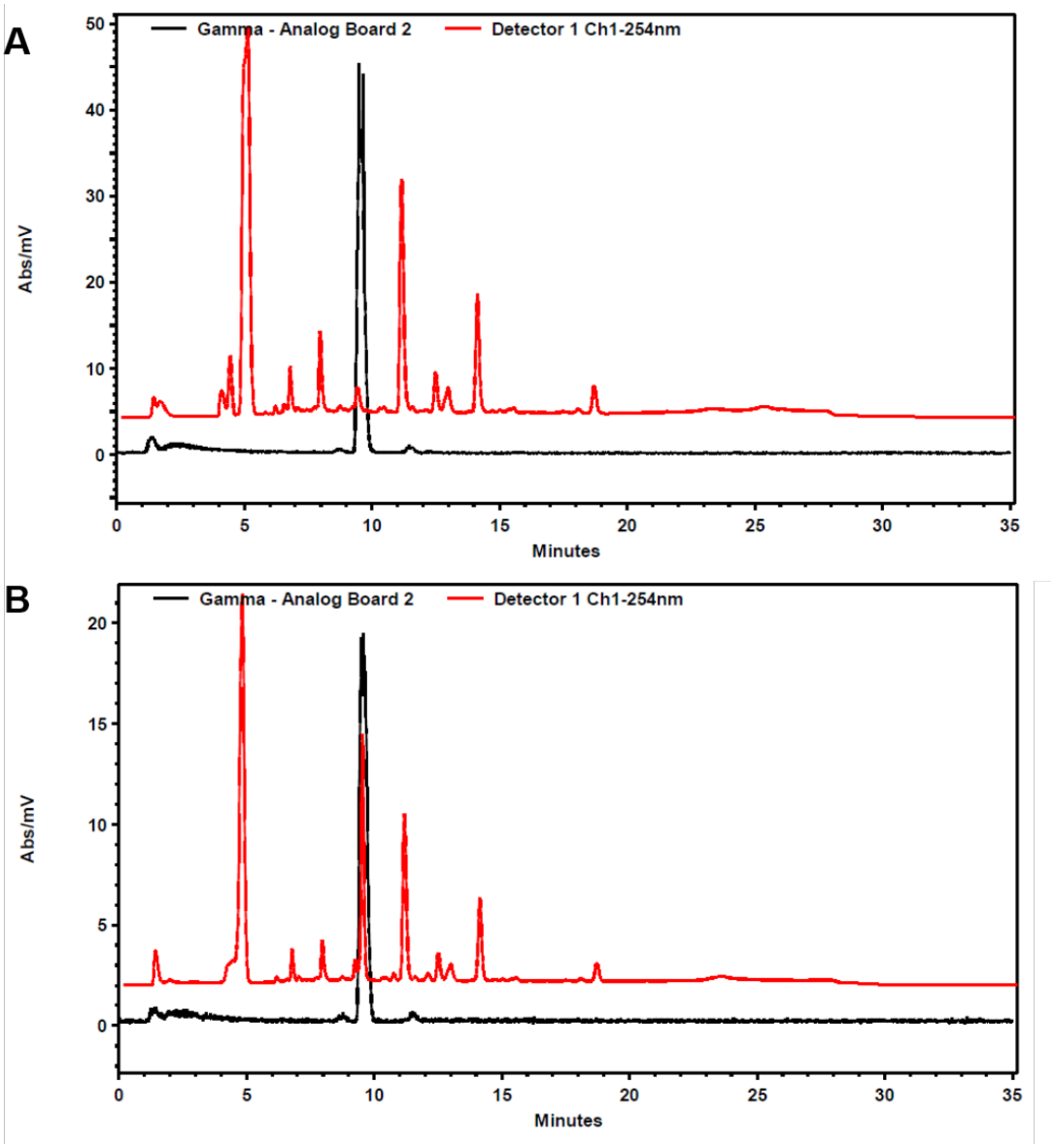
Raw RCCs (%): 81, 77, 77, 77. Average: 78 ± 2%. Selectivity: >99:1 (**3i**:**4**). RCC corrected for presence of **4**: 78 ± 2% (n = 4).

[6] The general procedure was followed using 9.0 μL (0.10 mmol, 1.0 equiv) TMSOTf.

HPLC conditions: Condition B

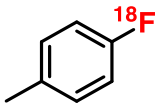
A: *N*-Carboxybenzyl-4-[^{18}F]fluoro-*N*-methylaniline **3i** reaction gamma trace overlaid with UV trace at 254 nm

B: *N*-Carboxybenzyl-4-[^{18}F]fluoro-*N*-methylaniline **3i** reaction gamma trace overlaid with UV trace at 254 nm spiked with *N*-Carboxybenzyl-4-fluoro-*N*-methylaniline **3i**[7]

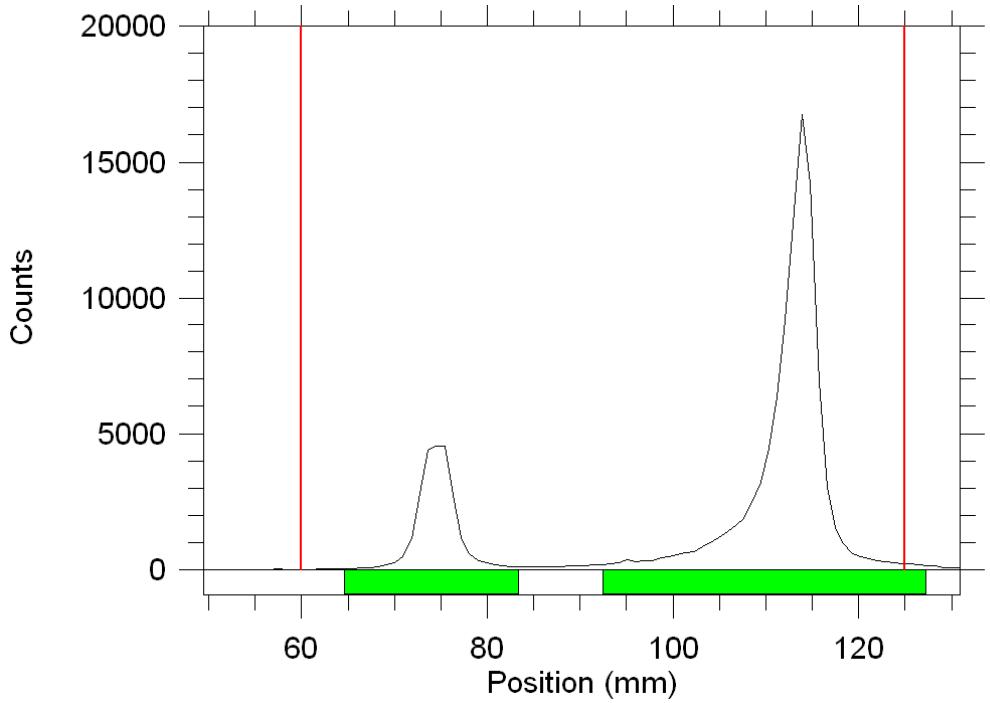


[7] The Rad peak at ca. 8.5 min corresponds to an unknown byproduct believed to originate from unreacted TMSOTf and/or TMSOTs, see control studies below.

j. 4-[^{18}F]Fluorotoluene (3j)

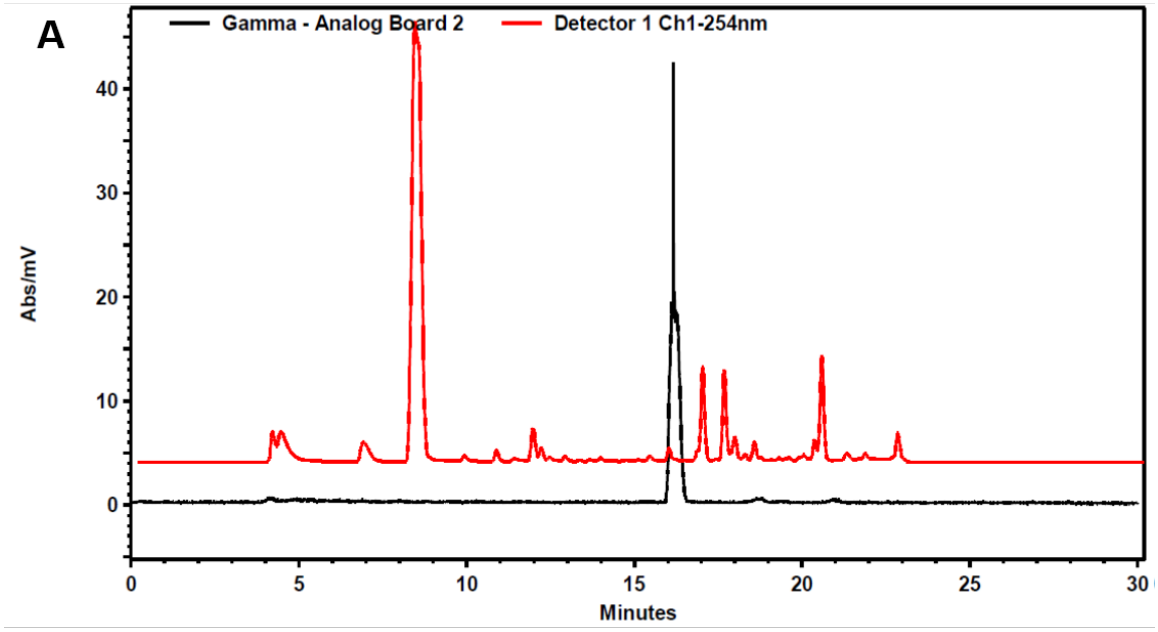


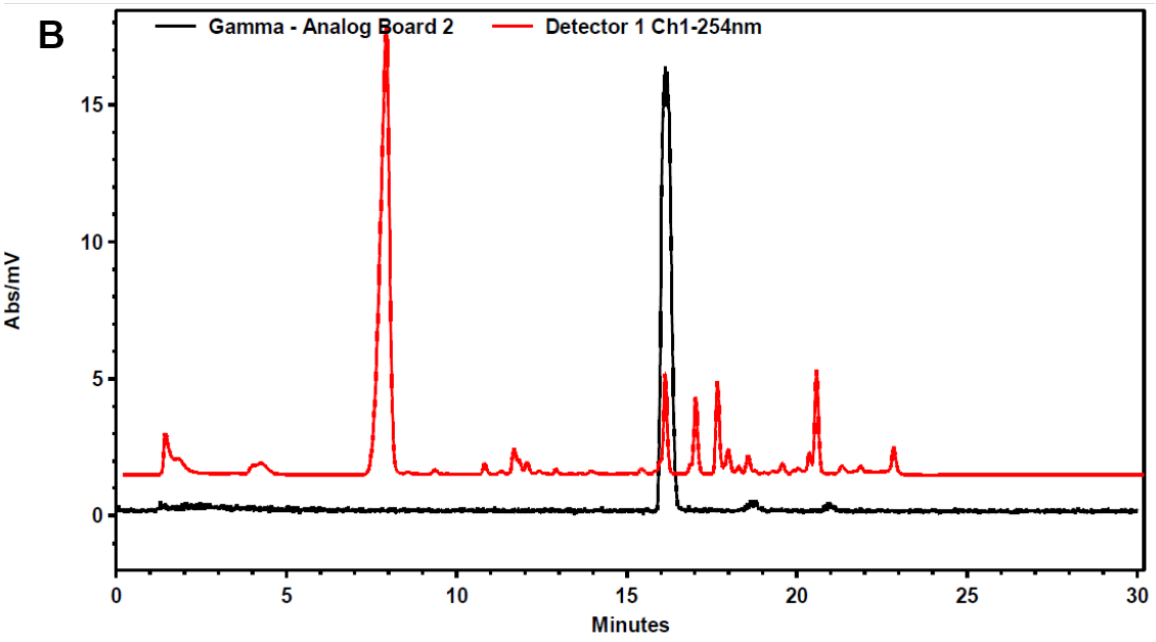
Radio-TLC eluent: 50% EtOAc in hexanes



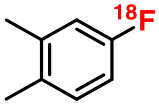
Raw RCCs (%): 84, 92, 82, 81. Average: 85 ± 5%. Selectivity: 98:2 (**3j**:**4**). RCC corrected for presence of **4**: 83 ± 5% (n = 4).

HPLC conditions: Gradient Condition A
A: 4-[^{18}F]Fluorotoluene **3j** reaction gamma trace overlaid with UV trace at 254 nm
B: 4-[^{18}F]Fluorotoluene **3j** reaction gamma trace overlaid with UV trace at 254 nm spiked with 4-fluorotoluene **3j**

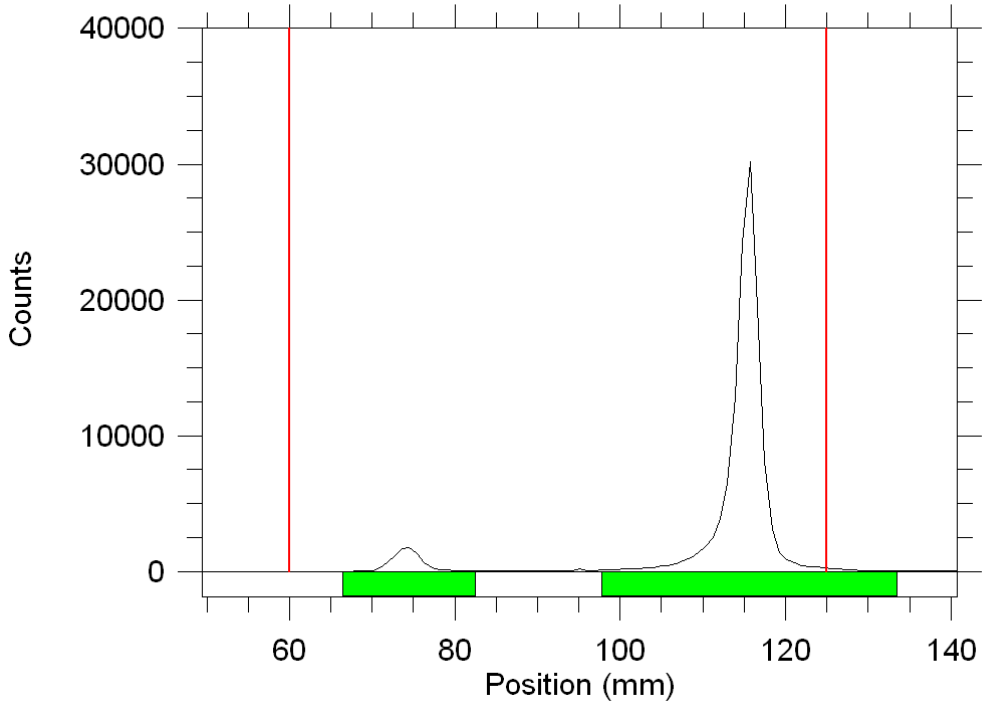




k. 4-[^{18}F]Fluoro-*o*-xylene (3k)

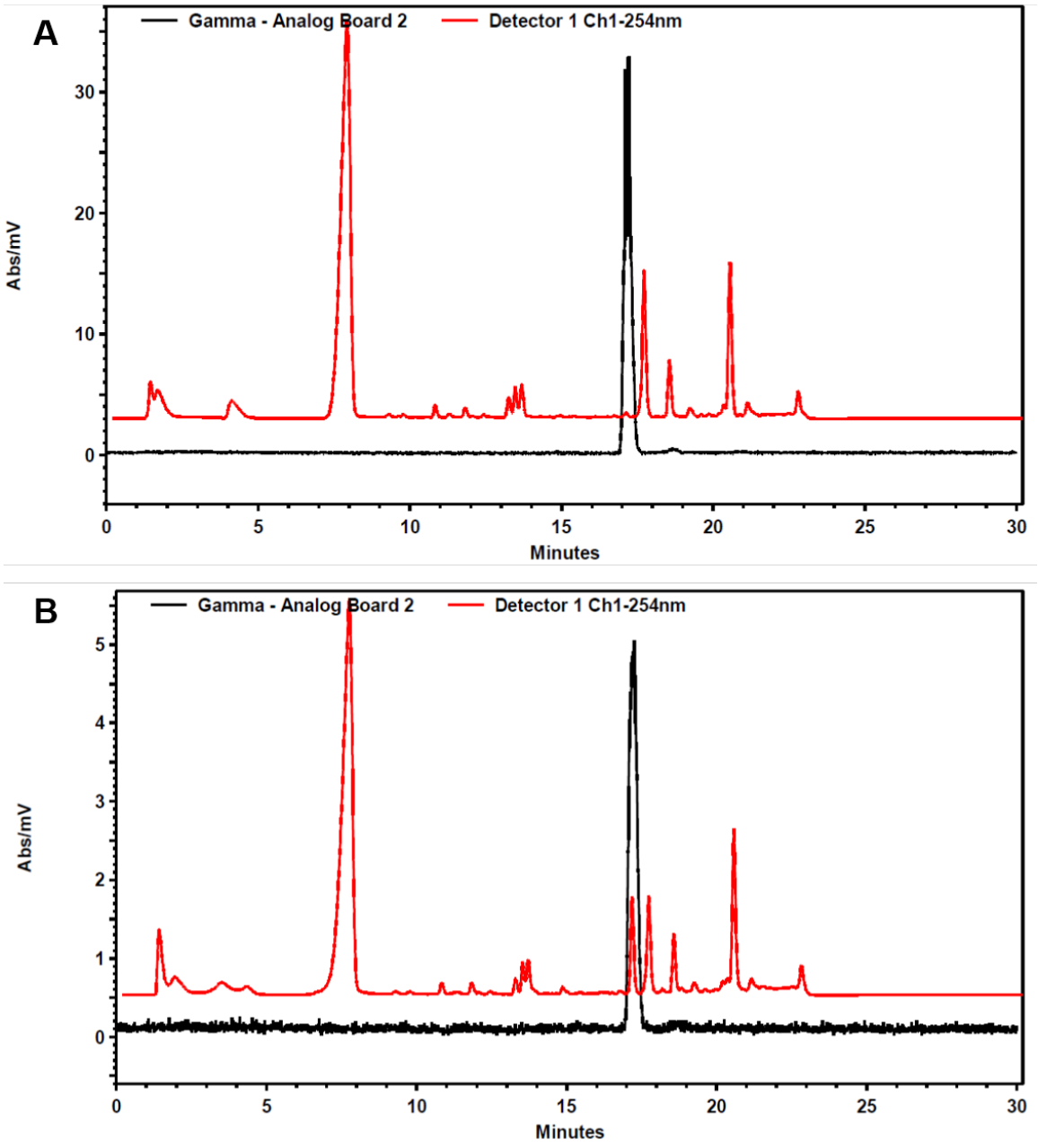


Radio-TLC eluent: 50% EtOAc in hexanes

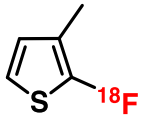


Raw RCCs (%): 87, 91, 90, 94. Average: 90 ± 3%. Selectivity: 98:2 (**3k**:**4**). RCC corrected for presence of **4**: 88 ± 3% (n = 4).

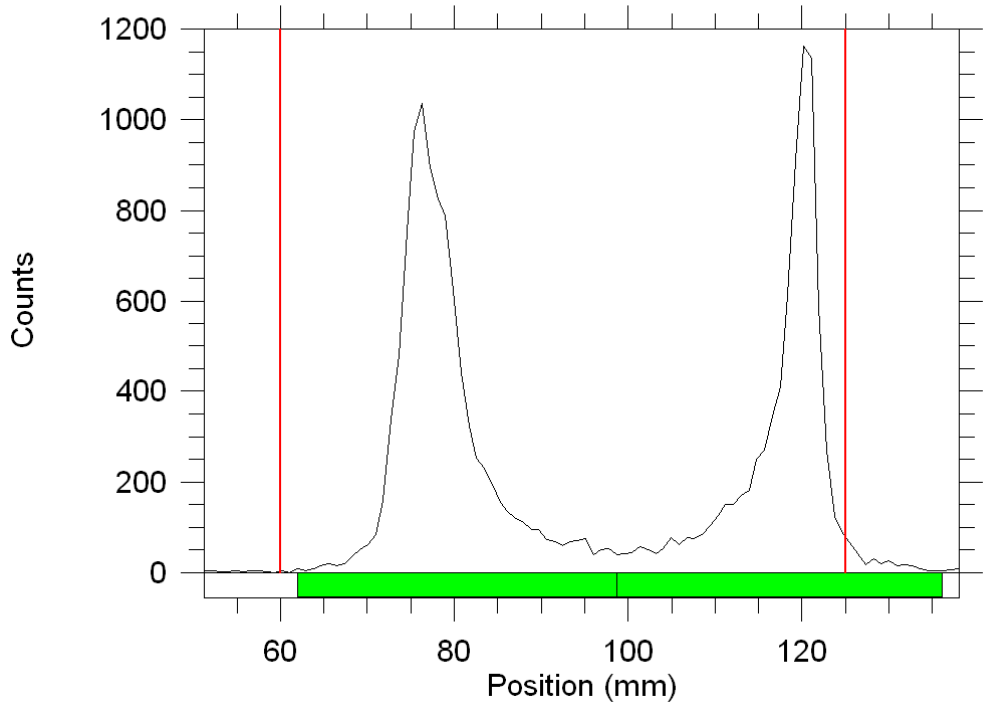
HPLC conditions: Condition A
A: 4-[^{18}F]Fluoro-*o*-xylene **3k** reaction gamma trace overlaid with UV trace at 254 nm
B: 4-[^{18}F]Fluoro-*o*-xylene **3k** reaction gamma trace overlaid with UV trace at 254 nm spiked with 4-fluoro-*o*-xylene **3k**



l. 2-[^{18}F]Fluoro-3-methylthiophene (3l)[8]



Radio-TLC eluent: 50% EtOAc in hexanes



Raw RCCs (%): 26, 45, 27, 28, 36, 36, 43, 58, 53, 36. Average: 40 ± 11%. Selectivity: 62:38 (**3l**:byproducts). RCC corrected for presence of **4** and unknown byproduct (see below, ca. 21 min HPLC gamma trace): 25 ± 7% (n = 11).

In the absence of quinaldic acid - Raw RCCs (%): 30, 26, 28. Average: 28 ± 2%. Selectivity: 68:32 (**3l**:**4**). RCC corrected for presence of **4**: 19 ± 1% (n = 3).

[8] The general procedure was followed with 105 °C heating of the radiofluorination.

HPLC conditions: Gradient Condition A

A: 2-[^{18}F]Fluoro-4-methylthiophene **3l** reaction gamma trace overlaid with UV trace at 254 nm prepared from the isolated diaryliodonium salt **s1**.[9] 2-[^{18}F]Fluoro-4-methylthiophene **3l** is observed with a retention time of 16.3 min, while the peak at 18.9 min corresponds to [^{18}F]fluoromesitylene.

B: 2-[^{18}F]Fluoro-4-methylthiophene **3l** reaction gamma trace overlaid with UV trace at 254 nm prepared using the in situ approach from the C-H precursor. 2-[^{18}F]Fluoro-4-methylthiophene **3l** is observed with a retention time of 16.3 min, while the peak at 18.9 min corresponds to [^{18}F]fluoromesitylene. The peak at retention time 15.3 min is an unknown by-product.[10]

C: 2-[^{18}F]Fluoro-4-methylthiophene **3l** reaction gamma trace overlaid with UV trace at 254 nm spiked with 2-[^{18}F]Fluoro-4-methylthiophene **3l** produced from isolated diaryliodonium salt **3l**. Overlap of the two peaks at 16.3 min is observed.

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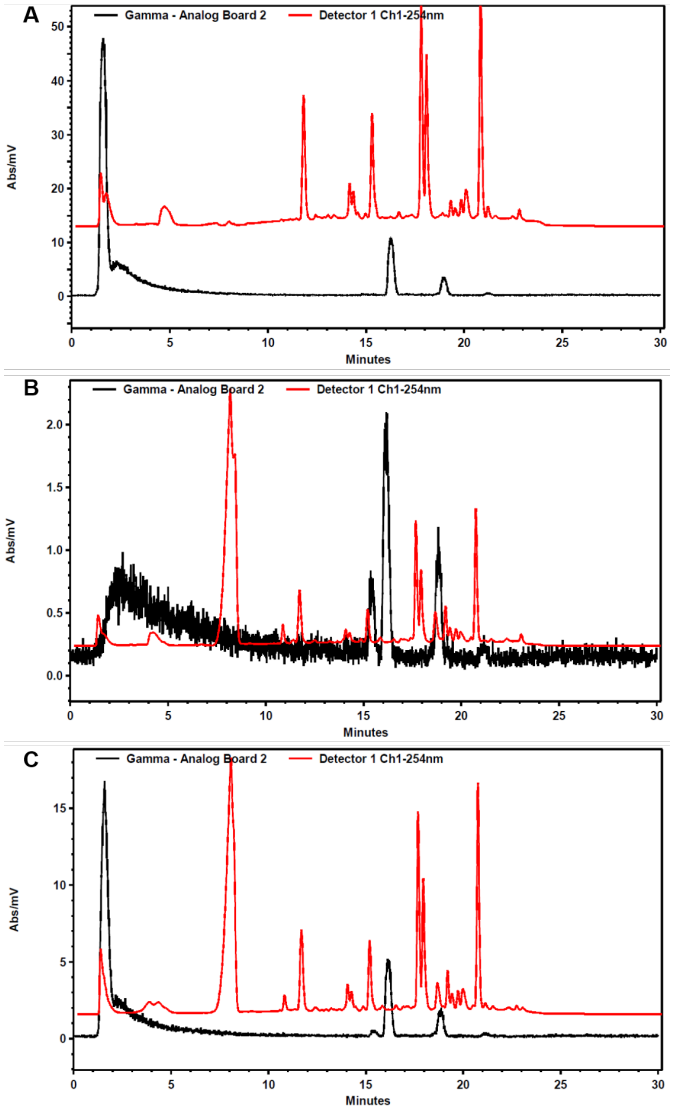
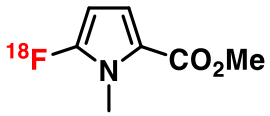
[9] The radiofluorination of **s1** was carried out in accordance with a previously reported method.[7] To a 4 mL vial were added 2.6 mg **s1** (6.0 μmol), 2.3 mg tetrakis(acetonitrile)copper(I) trifluoromethanesulfonate ((MeCN)$_4$CuOTf) (6 μmol), and 500 μL anhydrous dimethylformamide (DMF). The reaction vial was sealed with a PTFE/Silicone septum cap and a 250 μL aliquot of [^{18}F]KF·18-crown-6·K_2CO_3 complex in DMF (typically 60-800 μCi, prepared as described above) was added to the reaction vial via syringe. The reaction was heated in an aluminum block at 85 °C for 20 min. After 20 min, the reaction was removed from heat and allowed to cool to room temperature. Radiochemical conversions (RCCs) were obtained by radio-TLC analysis (2-5 µL aliquots) using a 50:50 hexanes-ethyl acetate eluent, and are not reported to reflect losses during [^{18}F]KF·18-crown-6·K_2CO_3 preparation. Raw RCCs (%): 11, 11. Average: 11% (*n* = 2). Selectivity: 75:25 (**3l**:**4**). A sample of the product mixture was analyzed using radio-HPLC (10-50 µL aliquots). The sample was used as a spike to verify the identity of **3l** in the C–H radiofluorination.

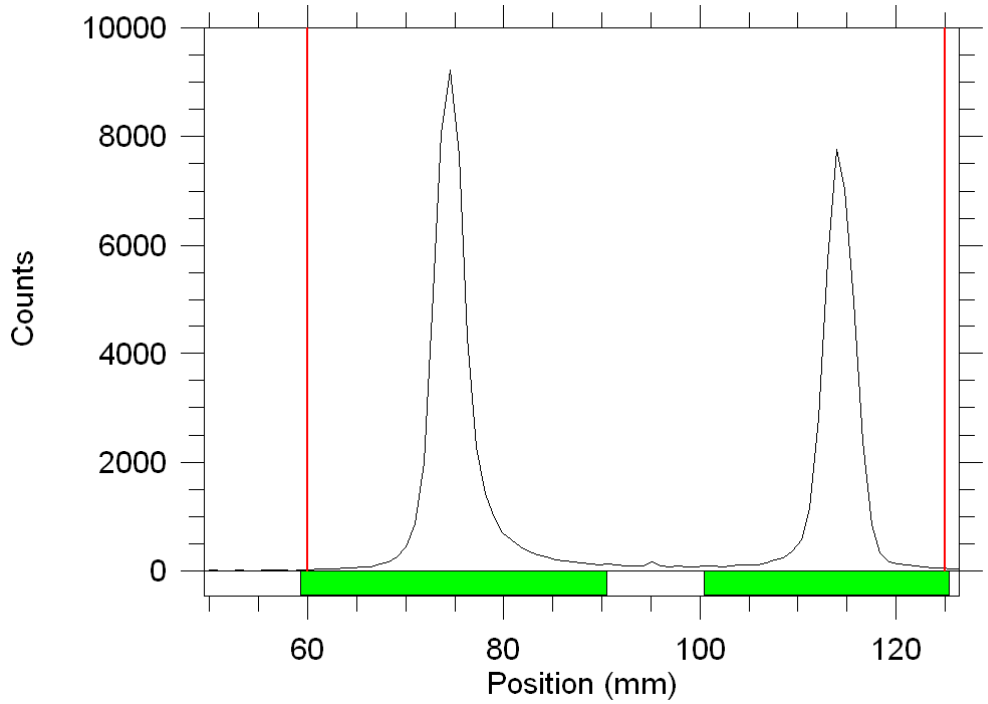
[10] The Rad peak at ca. 15.3 min corresponds to an unknown byproduct believed to originate from unreacted TMSOTf and/or TMSOTs, see control studies below. The Rad peak at ca. 21 min corresponds to an extremely non-polar unknown byproduct also observed for **3m** and **3o**.


A
Gamma - Analog Board 2
Detector 1 Ch1-254nm
Abs/mV
Minutes
B
Gamma - Analog Board 2
Detector 1 Ch1-254nm
Abs/mV
Minutes
C
Gamma - Analog Board 2
Detector 1 Ch1-254nm
Abs/mV
Minutes

m. Methyl 5-[^{18}F]fluoro-*N*-methylpyrrole-2-carboxylate (3m)[11]



Radio-TLC eluent: 50% EtOAc in hexanes



Raw RCCs (%): 34, 36, 34. Average: 35 ± 1%. Selectivity: 73:27 (**3m**:**4**). RCC corrected for presence of **4**: 25 ± 1% (n = 3).

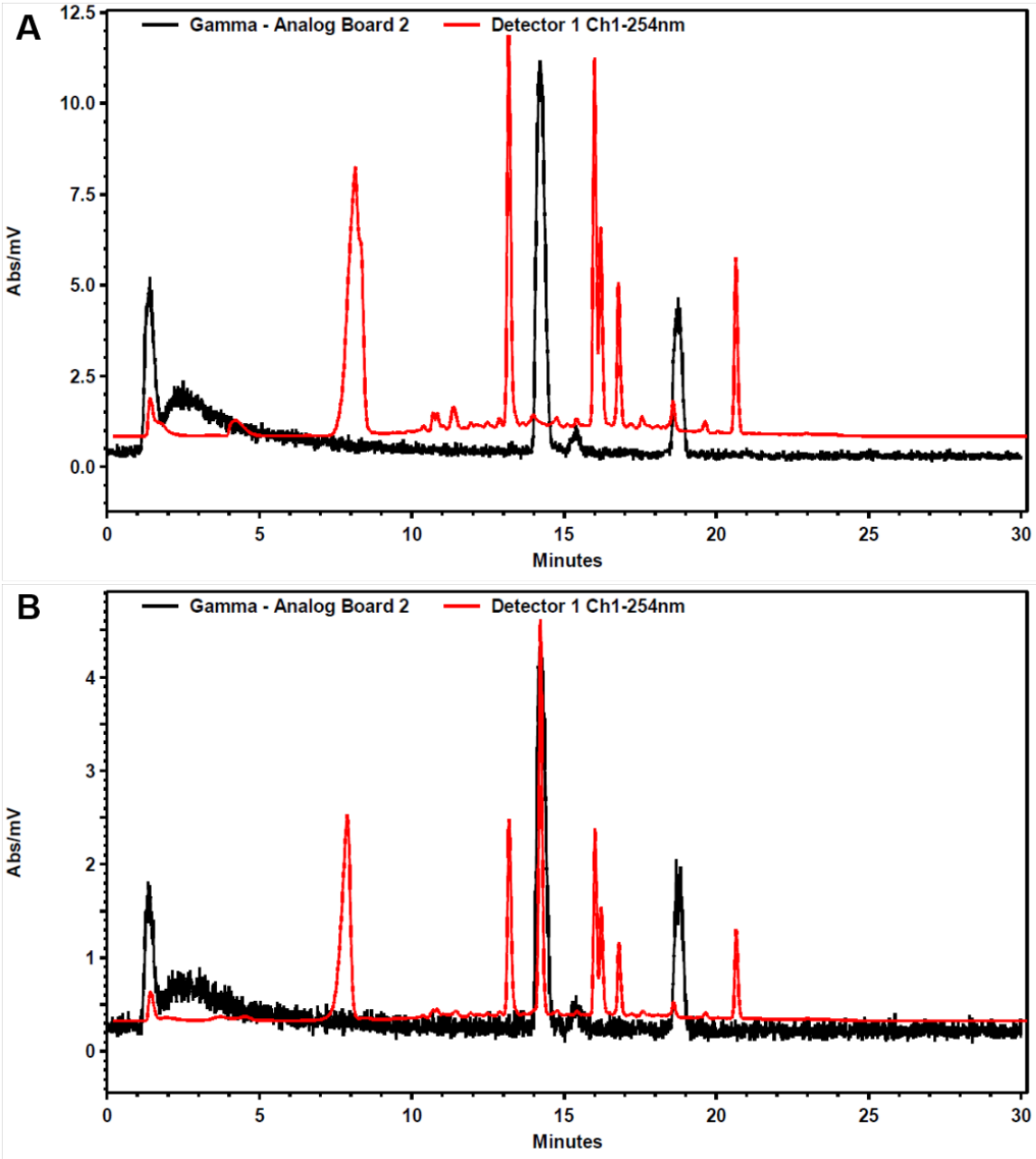
In the absence of quinaldic acid - Raw RCCs (%): 12, 13, 13, 10. Average: 12 ± 1%. Selectivity: 69:31 (**3m**:**4**). RCC corrected for presence of **4**: 8 ± 1% (n = 4).

[11] The general procedure was followed using 9.0 μL (0.10 mmol, 1.0 equiv) TMSOTf and with 105 °C heating of the radiofluorination.

HPLC conditions: Condition A

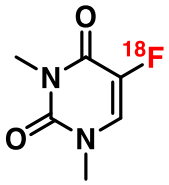
A: Methyl 5-[^{18}F]fluoro-*N*-methylpyrrole-2-carboxylate **3m** reaction gamma trace overlaid with UV trace at 254 nm[12]

B: Methyl 5-[^{18}F]fluoro-*N*-methylpyrrole-2-carboxylate **3m** reaction gamma trace overlaid with UV trace at 254 nm spiked with methyl 5-fluoro-*N*-methylpyrrole-2-carboxylate **3m** (t_R 14.3 min). The peak with t_R 18.8 min in the gamma trace is [^{18}F]fluoromesitylene.

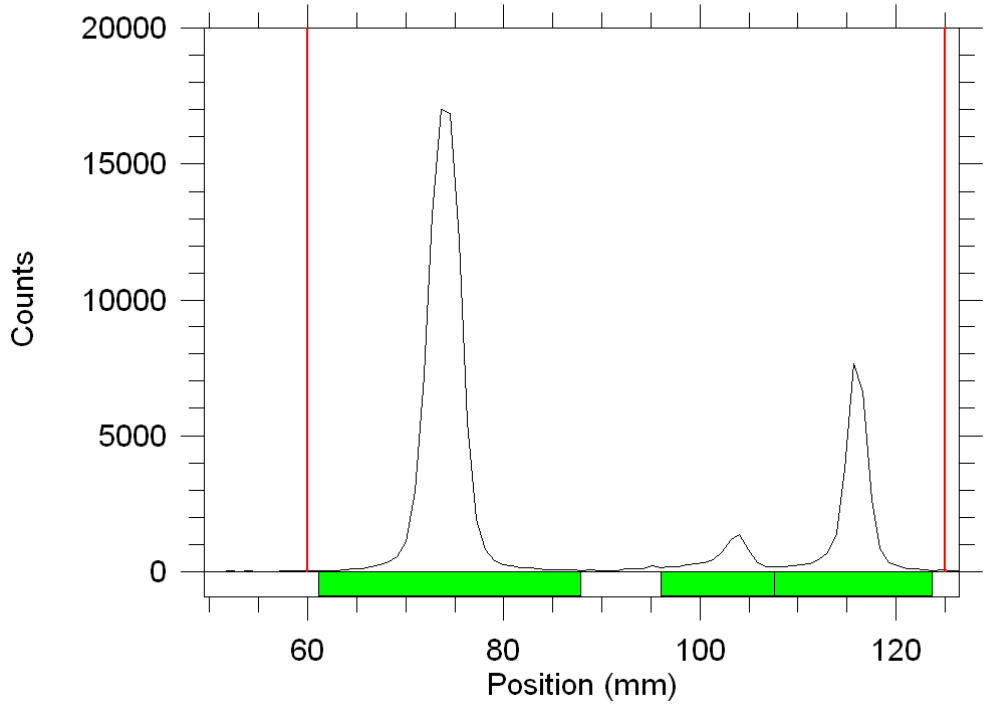


[12] The Rad peak at ca. 15.3 min corresponds to an unknown byproduct believed to originate from unreacted TMSOTf and/or TMSOTs, see control studies below.

n. *N*,*N*′-Dimethyl-5-[^{18}F]fluorouracil (3n)[13]



Radio-TLC eluent: 50% EtOAc in hexanes

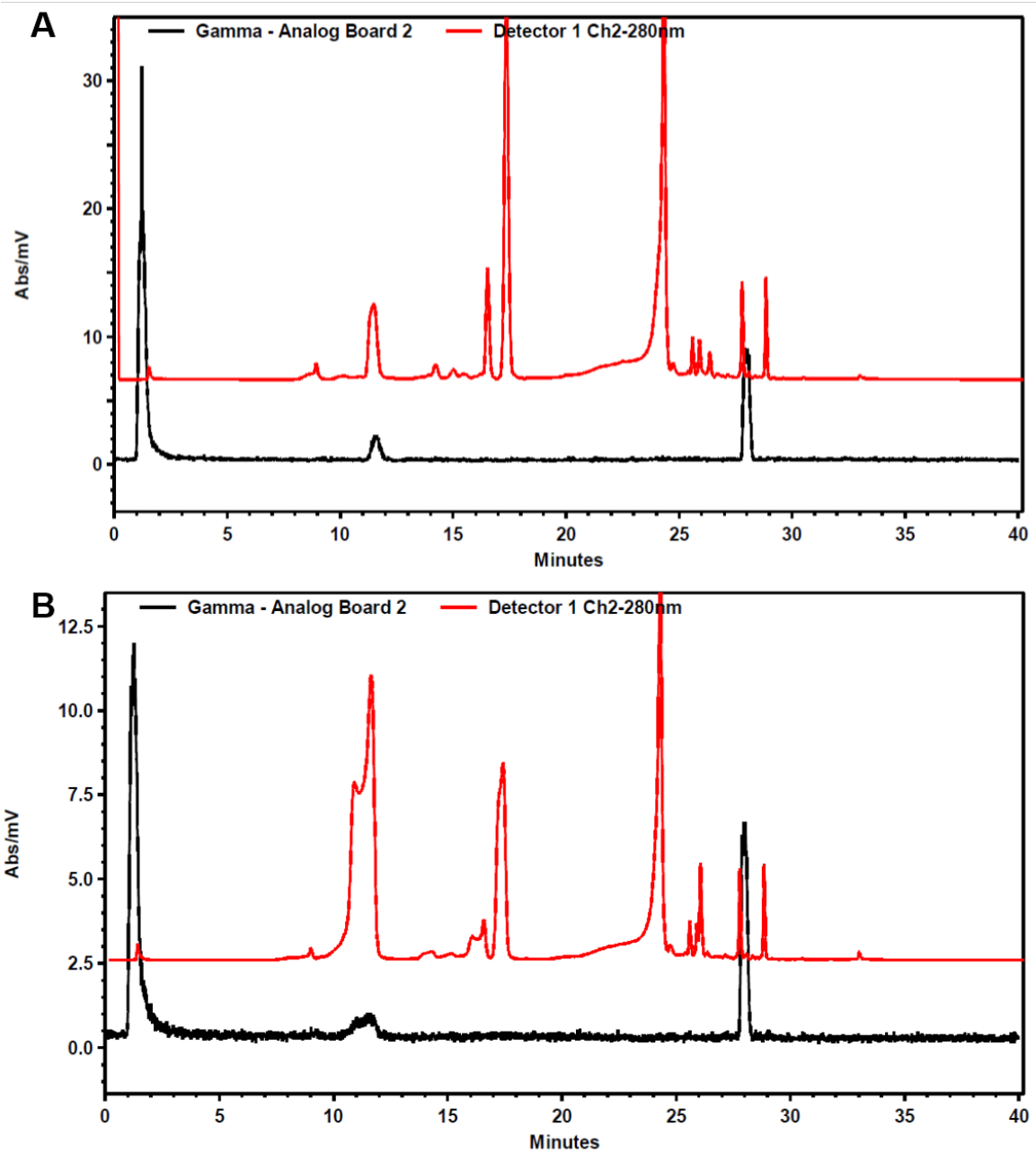


Raw RCCs (%): 37, 39, 38, 40. Average: 38 ± 1%. Selectivity: 25:75 (**3n**:**4**). RCC corrected for presence of **4**: 10 ± 1% (*n* = 4).

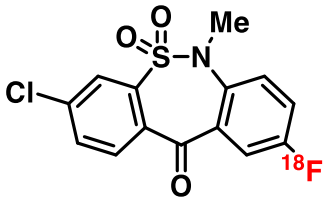
In the absence of quinaldic acid - Raw RCCs (%): 22, 23, 22, 11. Average: 20 ± 6%. Selectivity: 24:76 (**3n**:**4**). RCC corrected for presence of **4**: 5 ± 1% (*n* = 4).

[13] The general procedure was followed using 9.0 μL (0.10 mmol, 1.0 equiv) TMSOTf and with 105 °C heating of the radiofluorination.

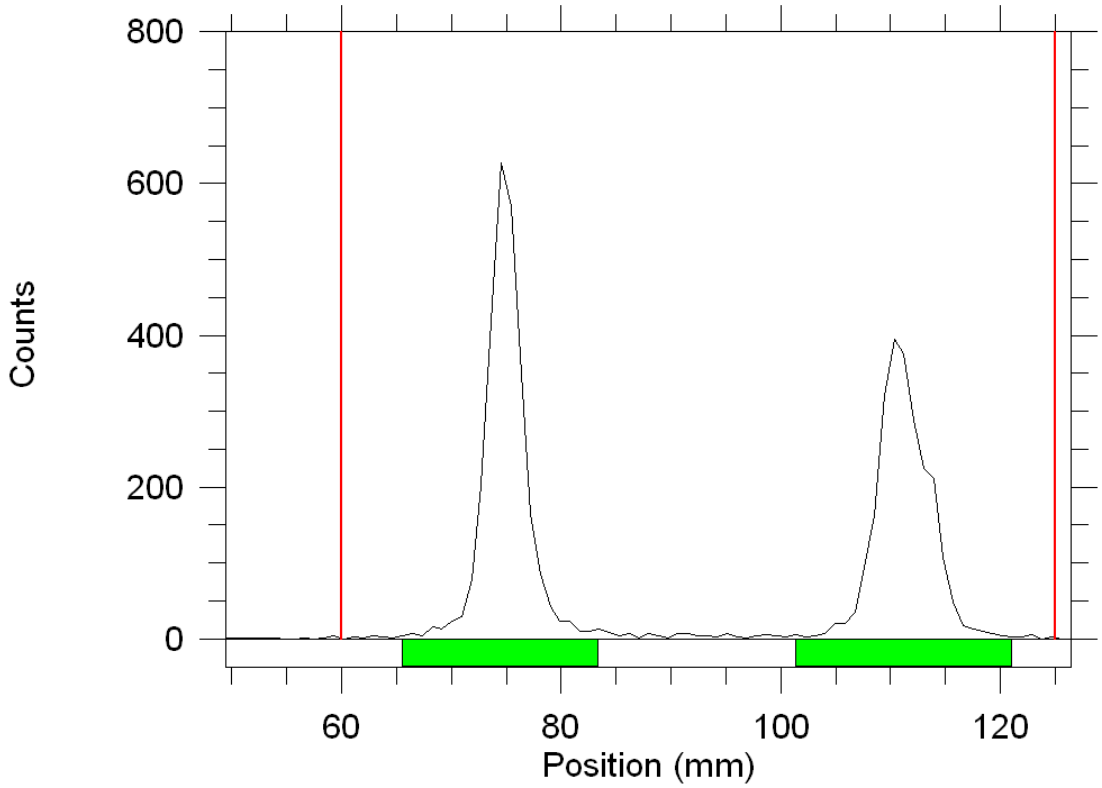
HPLC conditions: Condition C
A: *N*,*N*′-Dimethyl-5-[^{18}F]fluorouracil **3n** reaction gamma trace overlaid with UV trace at 280 nm.
B: *N*,*N*′-Dimethyl-5-[^{18}F]fluorouracil **3n** reaction gamma trace overlaid with UV trace at 280 nm spiked with *N*,*N*′-dimethyl-5-fluorouracil **3n** (t_R 11.7 min). The peak with t_R 28.0 min in the gamma trace is [^{18}F]fluoromesitylene.



o. 3-Chloro-9-[^{18}F]fluoro-6-methyldibenzo[*c*,*f*][1,2]thiazepin-11(6*H*)-one 5,5-dioxide (3o)



Radio-TLC eluent: 50% EtOAc in hexanes



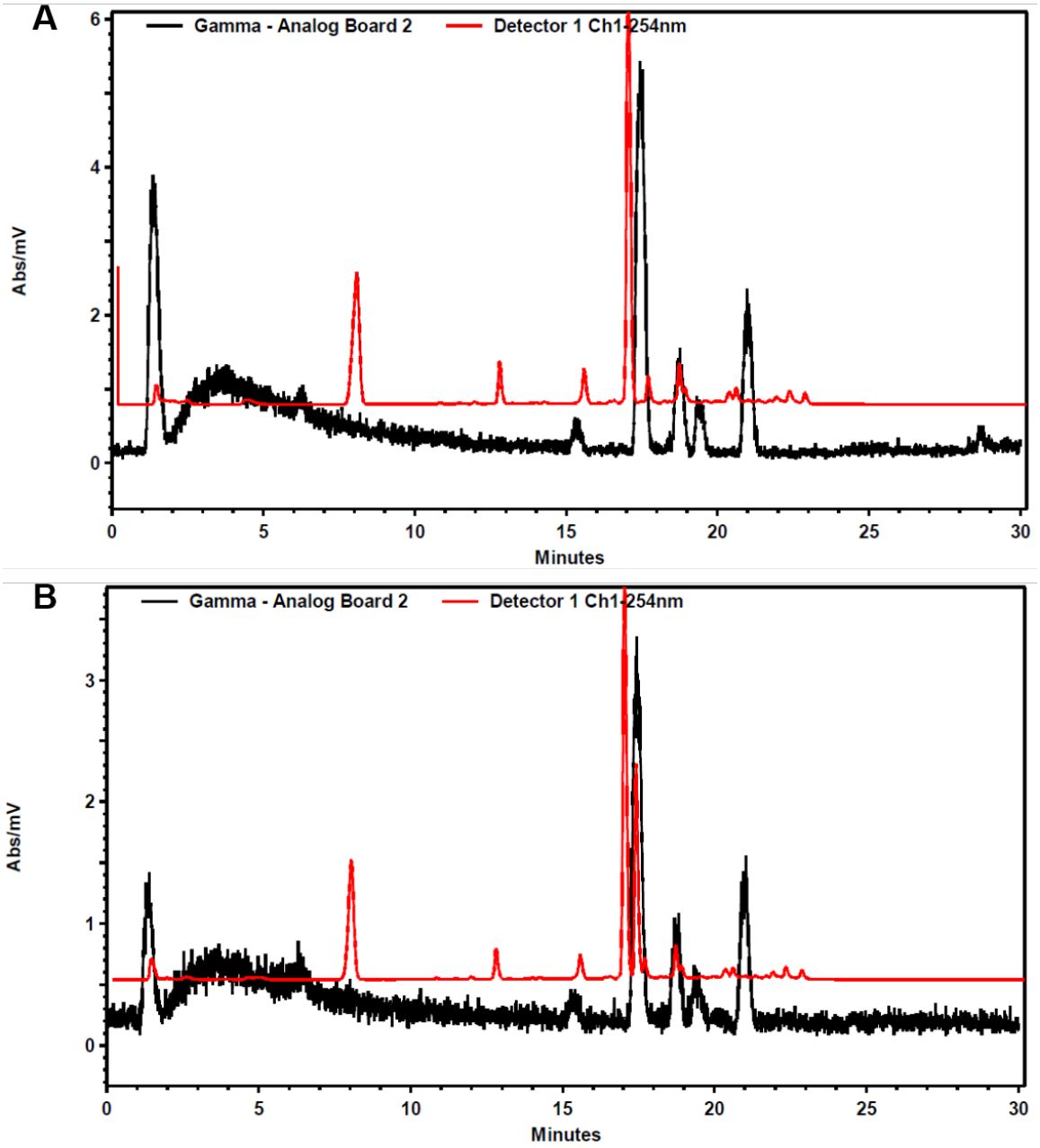
Raw RCCs (%): 32, 46, 43, 27, 19. Average: 33 ± 11%. Selectivity: 53:47 (**3o**:byproducts). RCC corrected for presence of **4** and unknown byproduct (see below, ca. 21 min HPLC gamma trace): 18 ± 6% (n = 5).

In the absence of quinaldic acid - Raw RCCs (%): 25, 28, 25, 20. Average: 25 ± 3%. Selectivity: 66:33 (**3o**:byproducts). RCC corrected for presence of **4** and unknown byproduct (see below, ~21 min HPLC gamma trace): 17 ± 2% (n = 4).

HPLC conditions: Gradient Condition A

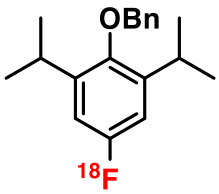
A: 3-Chloro-9-[^{18}F]fluoro-6-methyldibenzo[*c*,*f*][1,2]thiazepin-11(6*H*)-one 5,5-dioxide **3o** reaction gamma trace overlaid with UV trace at 254 nm[14]

B: 3-Chloro-9-[^{18}F]fluoro-6-methyldibenzo[*c*,*f*][1,2]thiazepin-11(6*H*)-one 5,5-dioxide **3o** reaction gamma trace overlaid with UV trace at 254 nm spiked with 3-Chloro-9-fluoro-6-methyldibenzo[*c*,*f*][1,2]thiazepin-11(6*H*)-one 5,5-dioxide **3o**

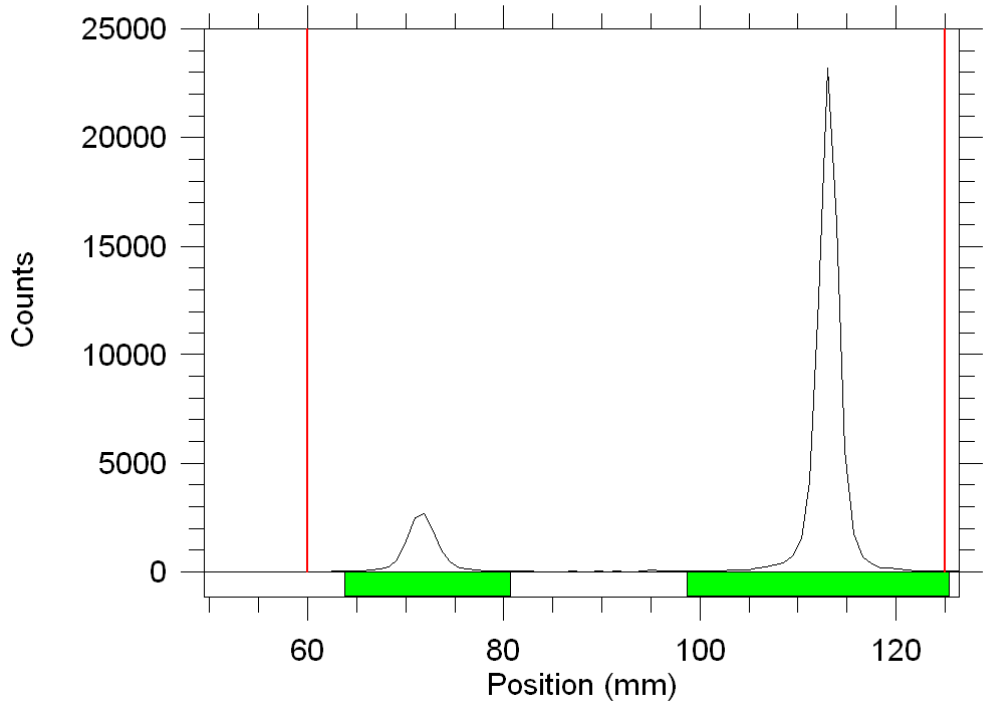


[14] The Rad peaks at ca. 15.3 and 19.5 min corresponds to unknown byproducts believed to originate from unreacted TMSOTf and/or TMSOTs, see control studies below. The Rad peak at ca. 21 min corresponds to an extremely non-polar unknown byproduct also observed for **3l**.

p. *O*-Benzyl-4-[^{18}F]fluoropropofol (3p)

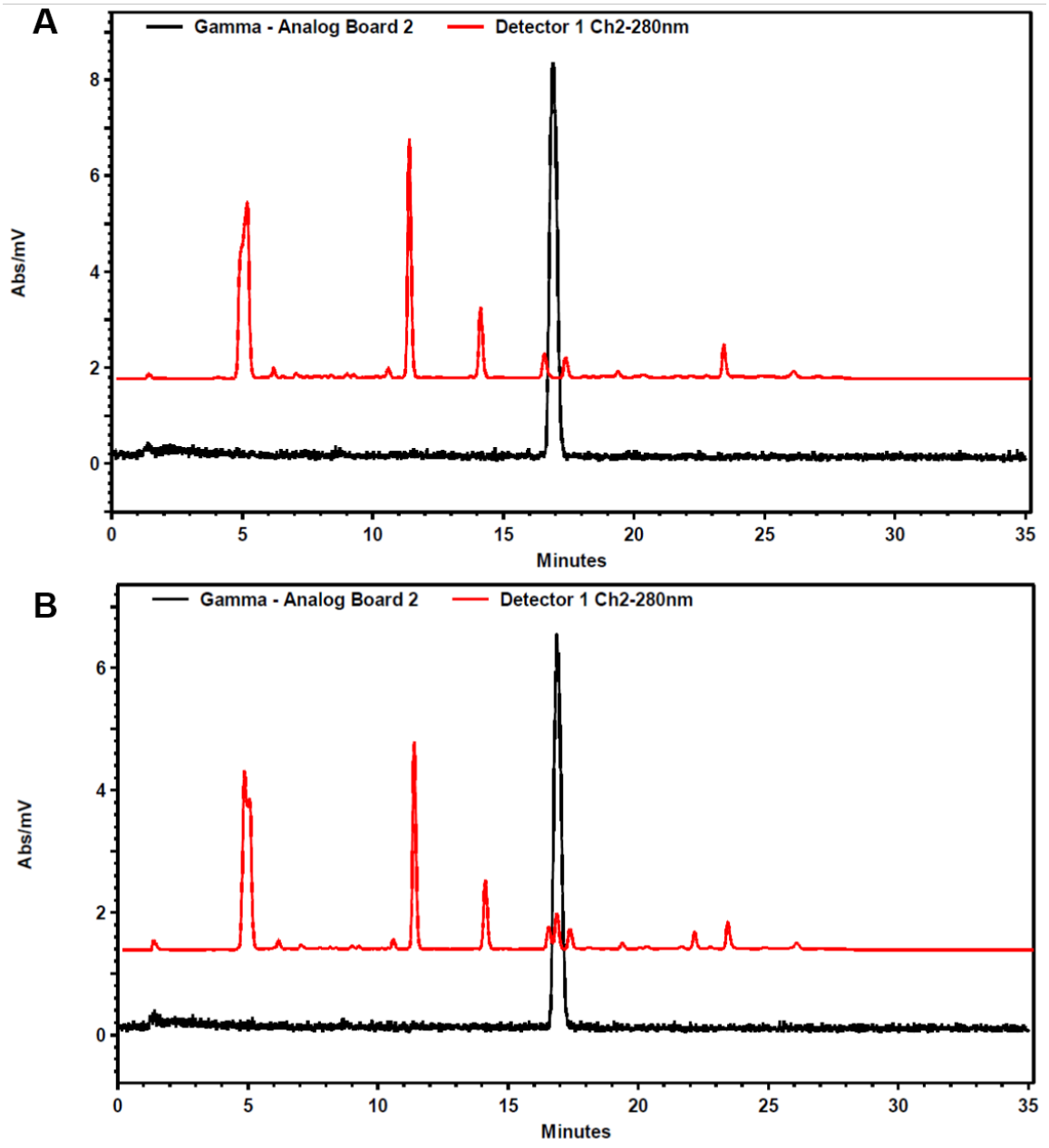


Radio-TLC eluent: 50% EtOAc in hexanes

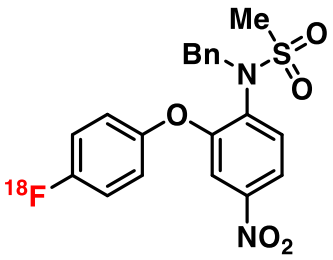


Raw RCCs (%): 85, 85, 90, 85, 87. Average: 87 ± 2%. Selectivity: >99:1 (**3p**:**4**). RCC corrected for presence of **4**: 87 ± 2% (n = 5).

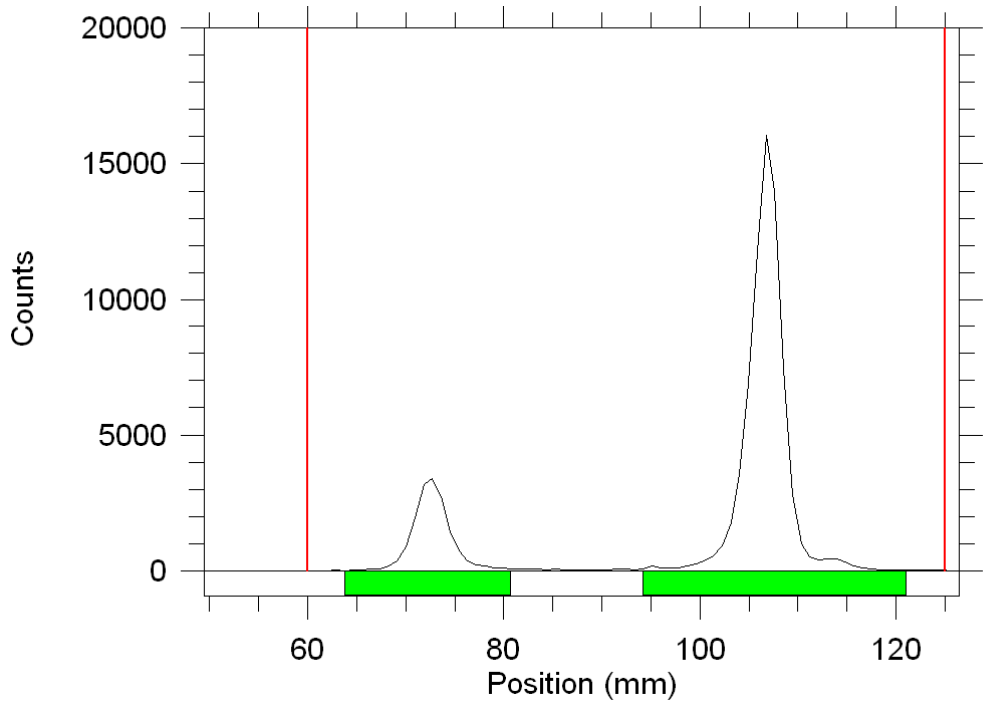
HPLC conditions: Condition B
A: *O*-Benzyl-4-[^{18}F]fluoropropofol **3p** reaction gamma trace overlaid with UV trace at 280 nm
B: *O*-Benzyl-4-[^{18}F]fluoropropofol **3p** reaction gamma trace overlaid with UV trace at 280 nm spiked with *O*-benzyl-4-fluoropropofol **3p**



q. *N*-Benzyl-4-[^{18}F]fluoronimesulide (3q)



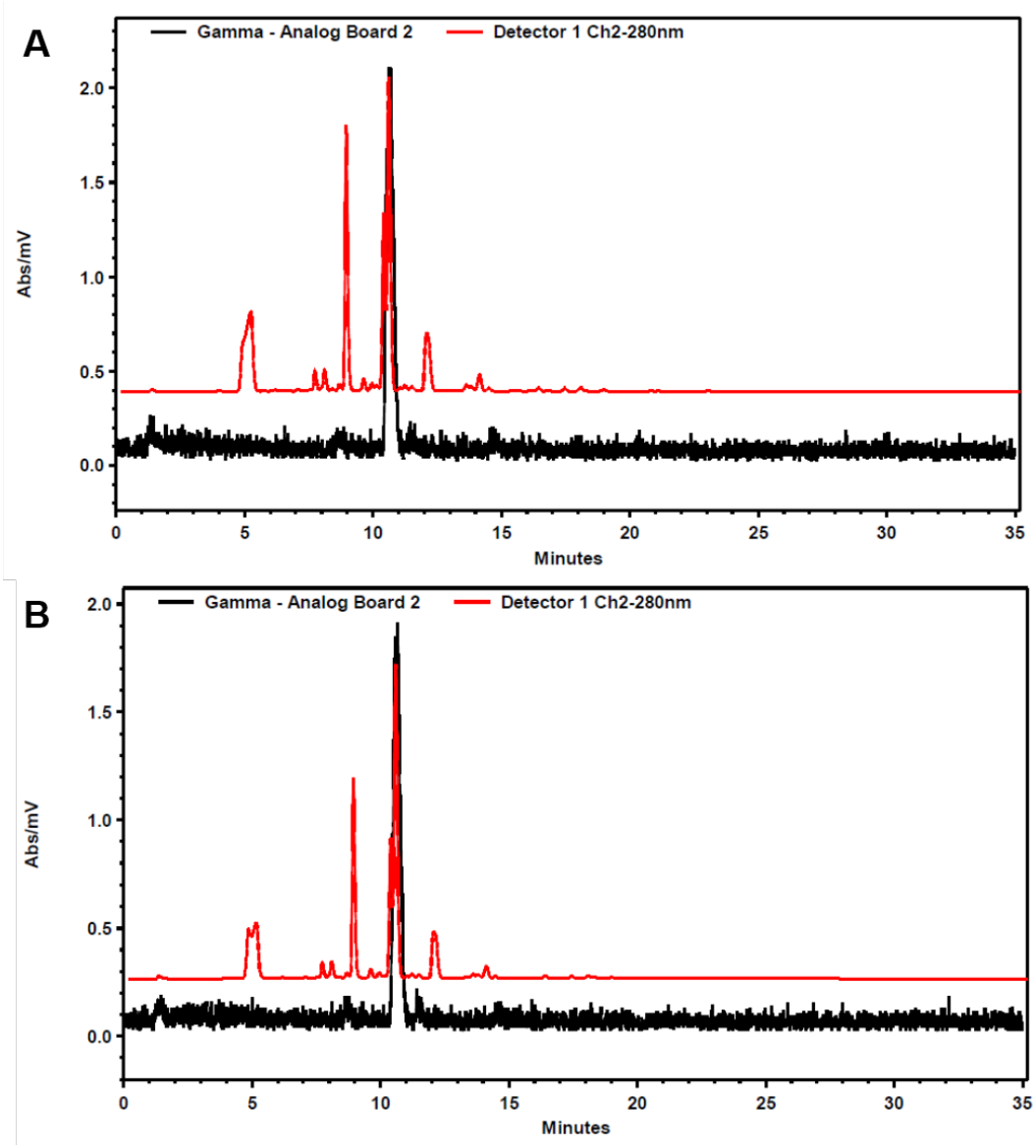
Radio-TLC eluent: 50% EtOAc in hexanes



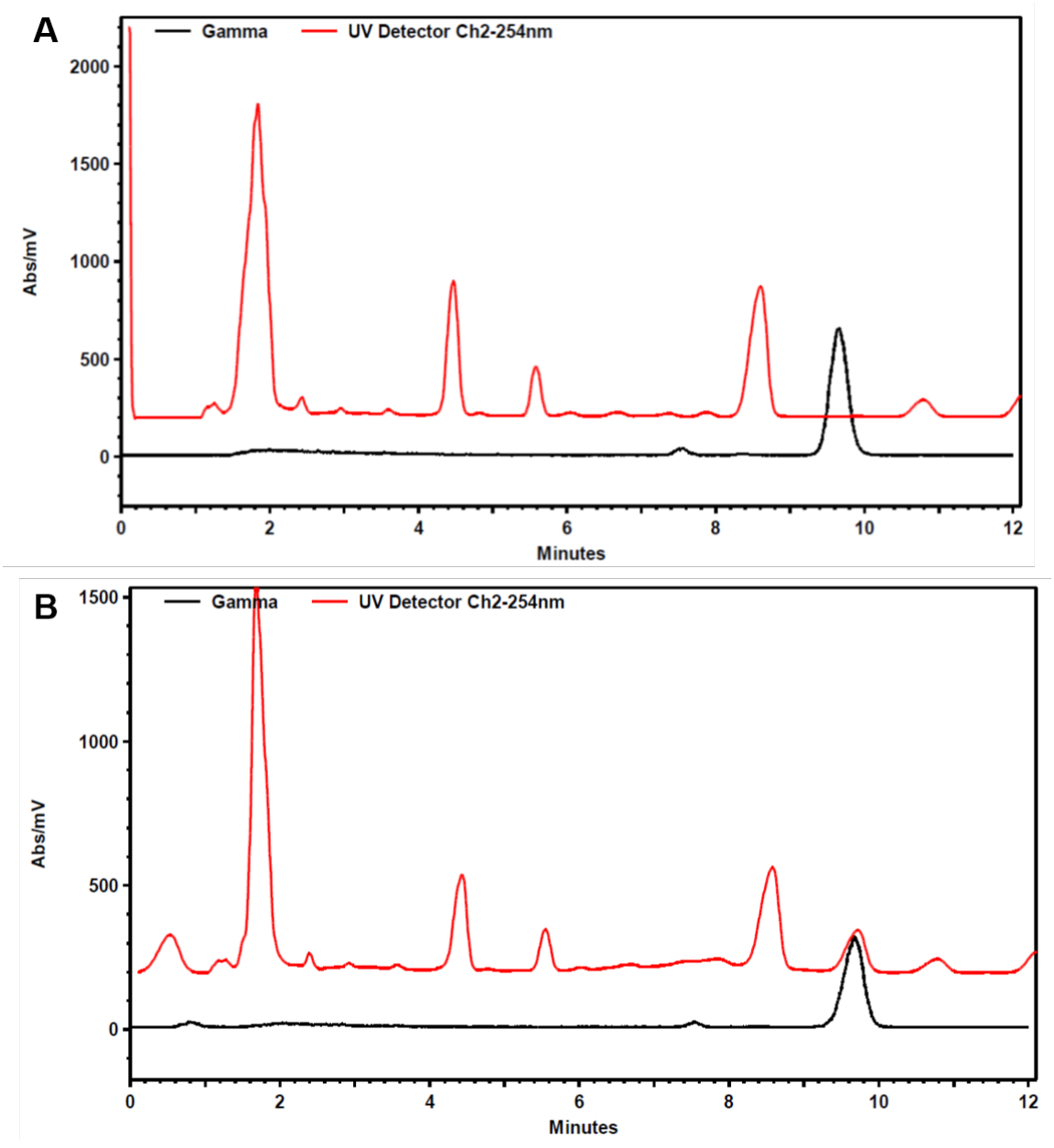
Raw RCCs (%): 79, 81, 89, 90, 87, 85, 79. Average: 84 ± 5%. Selectivity: 96:4 (**3q**:**4**). RCC corrected for presence of **4**: 81 ± 5% (n = 7).

In the absence of quinaldic acid - Raw RCCs (%): 54, 56, 58, 57. Average: 56 ± 2%. Selectivity: 97:3 (**3q**:**4**). RCC corrected for presence of **4**: 54 ± 2% (n = 4).

HPLC conditions: Condition B
A: *N*-Benzyl-4-[^{18}F]fluoronimesulide **3q** reaction gamma trace overlaid with UV trace at 280 nm
B: *N*-Benzyl-4-[^{18}F]fluoronimesulide **3q** reaction gamma trace overlaid with UV trace at 280 nm, after spiking with *N*-benzyl-4-fluoronimesulide **3q**



HPLC conditions: Condition D
A: *N*-Benzyl-4-[^{18}F]fluoronimesulide **3q** reaction gamma trace overlaid with UV trace at 254 nm
B: *N*-Benzyl-4-[^{18}F]fluoronimesulide **3q** reaction gamma trace overlaid with UV trace at 254 nm, after spiking with *N*-benzyl-4-fluoronimesulide **3q**



C. Automated Radiosynthesis of ^{18}F-labeled Arenes

i. Automated Synthesis of 4-[^{18}F]Fluoroanisole (3a)

To a solution of MesI(OH)OTs (43 mg, 0.10 mmol, 1.0 equiv) anhydrous DCM (0.40 mL) in a 4 mL vial equipped with a stir bar was added anisole (11 μL, 0.10 mmol, 1.0 equiv). The stirring solution was cooled to 0 °C and trimethylsilyl trifluoromethanesulfonate (TMSOTf) (18 μL, 0.10 mmol, 1.0 equiv) was added dropwise. The solution was warmed to room temperature and stirred for 18 h before being used as a stock solution (0.25 M) of diaryliodonium in the subsequent radiofluorination reaction.

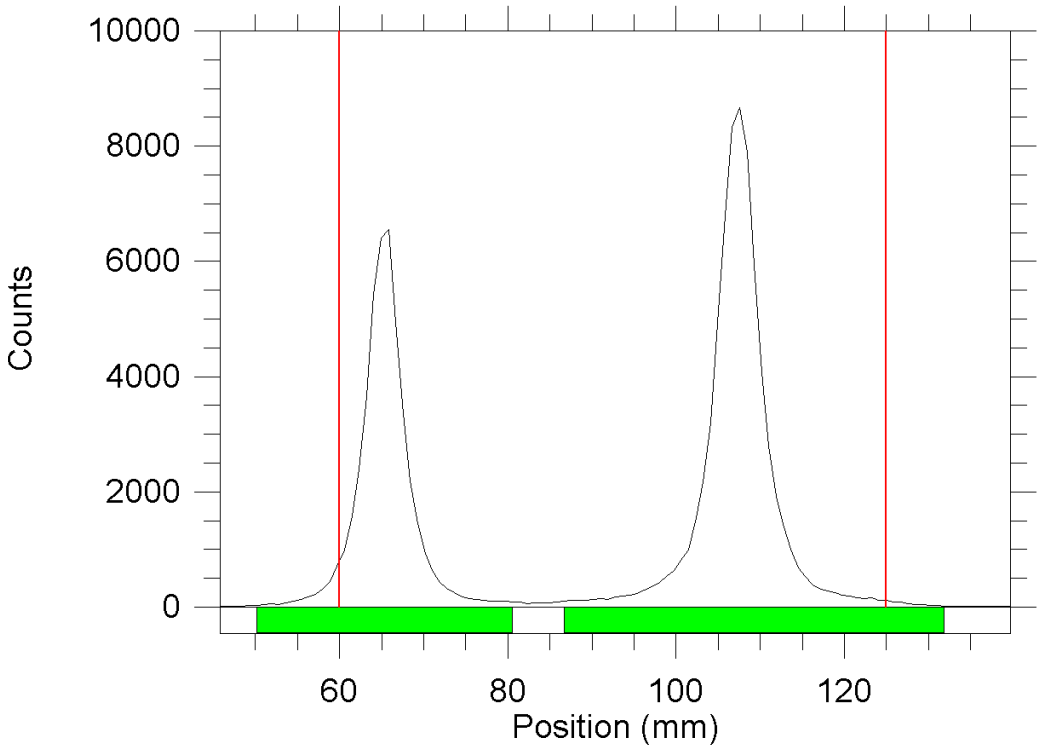
Automated syntheses were conducted on a GE TRACERLab FX_{FN} automated radiochemistry synthesis module. Before [^{18}F]fluoride delivery, ports in the module were charged under ambient atmosphere as follows:

- Port 1: KOTf (5 mg) and K_2CO_3 (50 μg) in H_2O (0.5 mL)
- Port 2: 18-crown-6 (15 mg) in MeCN (1.0 mL)
- Port 3: $(MeCN)_4CuOTf$ (3.7 mg, 10 μmol, 1.0 equiv) and quinaldic acid (1.7 mg, 10 μmol, 1.0 equiv) in DMF (0.5 mL)
- Port 4: diaryliodonium stock solution (see above) in DCM (40 μL, 10 μmol, 1.0 equiv) and diisopropylethylamine (3.5 μL, 20 μmol, 2.0 equiv) in DMF (0.5 mL)
- Port 5: DMF (3.0 mL)
- Port 6: DMF (3.0 mL).

[^{18}F]Fluoride (ca. 1500 mCi) was produced in a GE PETTrace cyclotron as described above for the manual reactions and swept to the synthesis module in a bolus of [^{18}O]H_2O by stream of argon. The aqueous solution of [^{18}F]fluoride was passed through a pre-conditioned QMA-light cartridge (Sep-Pak, potassium triflate preconditioning) to trap [^{18}F]fluoride, before the [^{18}F]fluoride was eluted into the reactor vessel with a solution of KOTf in H_2O (contents of Port 1). To this, a solution of 18-crown-6 in MeCN (contents of Port 2) was added, and the mixture azeotropically dried by heating the reaction vessel to 100 °C and drawing vacuum (ca. 1 kPa) for 5 minutes, followed by simultaneous vacuum draw and argon stream for an additional 6 minutes. The dried [^{18}F]KF•18-crown-6•KOTf complex (ca. 750 mCi) was cooled to 50 °C before addition of $(MeCN)_4CuOTf$ and quinaldic acid in DMF (contents of Port 3). The mixture was stirred for 3 min before addition of diaryliodonium stock solution and diisopropylethylamine in DMF (contents of Port 4). The reaction vessel was sealed and heated to 85 °C, and held at this temperature for 30 min before being cooled to 50 °C, diluted with DMF (contents of Port 5) and transferred out of the reactor under argon pressure into a vented sterile vial. The reactor was then rinsed with a further measure of DMF (contents of Port 6), and this too transferred to the sterile vial to yield a mixture of 4-[^{18}F]fluoroanisole (**3a**) and unreacted [^{18}F]KF (total 300-400 mCi) in 7 mL of DMF.

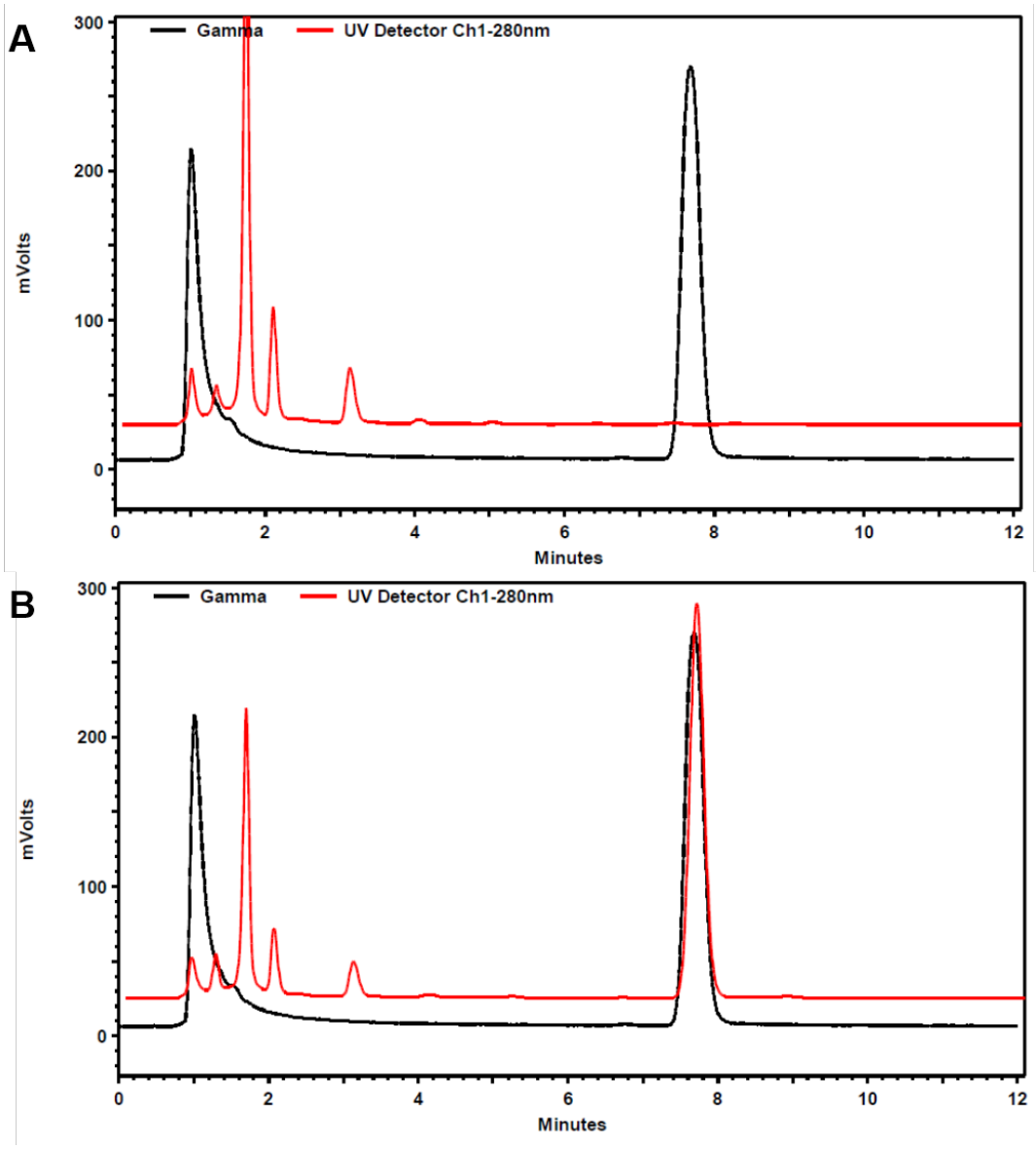
Radiochemical conversions (RCCs) were obtained by radio-TLC analysis (2-5 μL aliquots) using a 50:50 hexanes-ethyl acetate eluent, and are not reported to reflect losses of radioactivity during [^{18}F]KF•18-crown-6•K_2CO_3 preparation or radioactivity remaining in the reactor after transfers (c.a 250 mCi). Radiochemical conversions (RCCs) were determined by dividing the integrated area under the fluoroarene peak on radio-TLC by the total integrated area of all peaks on the radio-TLC trace. RCC was found to be 56 ± 4 % (n=4).

Radio-TLC eluent: 50% EtOAc in hexanes



An aliquot (200 µmol) removed for HPLC analysis using HPLC Condition E., which confirmed the product's identity as 4-[^{18}F]fluoroanisole (**3a**).

HPLC conditions: Condition E
A: 4-[^{18}F]Fluoroanisole **3a** reaction gamma trace overlaid with UV trace at 280nm
B: 4-[^{18}F]Fluoroanisole **3a** reaction gamma trace overlaid with UV trace at 280nm spiked with 4-fluoroanisole



The specific activity of the 4-[^{18}F]fluoroanisole (**3a**) was determined as follows. After the diluted reaction mixture was transferred from the hot-cell to a vial, the total activity in the vial ([^{18}F]fluoride+4-[^{18}F]fluoroanisole) was counted using a CAPINTEC (CRC-15R) well counter, and the RCC of the reaction (ratio of ([^{18}F]fluoride to 4-[^{18}F]fluoroanisole) was determined by analysis of a small aliquot (2-5 μL) of the mixture by the radio-TLC method described above. The activity of the product (4-[^{18}F]fluoroanisole only) in the vial was determined by multiplication of the total activity in the product vial by the RCC, which, after division by the total volume of the solution, yields a concentration of activity (Ci•mL^{-1}).

An aliquot of known volume of this sample was then analyzed by HPLC using HPLC Condition E, and the area of the UV peak corresponding to the 4-[^{18}F]fluoroanisole was determined. The molar concentration (mol•L^{-1}) of the product in the sample was then determined by linear regression analysis against a standard curve generated from injection of identical volumes of solutions of known concentration of the 4-fluoroanisole. Division of the concentration of activity for the 4-[^{18}F]fluoroanisole (Ci•mL^{-1}) by the molar concentration of the product (mol•L^{-1}) gives the end of synthesis (EOS) specific activity (Ci•mmol^{-1}). EOS specific activity was found to be 2700 ± 1900 Ci•mmol^{-1} (n = 4).

ii. Automated Synthesis of *N*-Benzyl-4-[^{18}F]fluoronimesulide (3q)

To a solution of MesI(OH)OTs (43 mg, 0.10 mmol, 1.0 equiv) in anhydrous DCM (0.40 mL) in a 4 mL vial equipped with a stir bar was added *N*-benzylnimesulide (40 mg, 0.10 mmol, 1.0 equiv). The stirring solution was cooled to 0 °C and trimethylsilyl trifluoromethanesulfonate (TMSOTf) (18 μL, 0.10 mmol, 1.0 equiv) was added dropwise. The solution was warmed to room temperature and stirred for 18 h before being used as a stock solution (0.25 M) of diaryliodonium in the subsequent radiofluorination reaction.

Automated syntheses were conducted on a GE TRACERLab FX$_{FN}$ automated radiochemistry synthesis module. Before [^{18}F]fluoride delivery, ports in the module were charged under ambient atmosphere as follows

- Port 1: KOTf (5 mg) and K_2CO_3 (50 μg) in H_2O (0.5 mL)
- Port 2: 18-crown-6 (15 mg) in MeCN (1.0 mL)
- Port 3: $(MeCN)_4CuOTf$ (3.7 mg, 10 μmol, 1.0 equiv) and quinaldic acid (1.7 mg, 10 μmol, 1.0 equiv) in DMF (0.5 mL)
- Port 4: diaryliodonium stock solution (see above) in DCM (40 μL, 10 μmol, 1.0 equiv) and diisopropylethylamine (3.5 μL, 20 μmol, 2.0 equiv) in DMF (0.5 mL)
- Port 6: 50% MeCN in H_2O, 20 mM NH_4OAc, pH 4.5 (2 mL)
- Port 7: 0.9% isotonic sterile saline solution (9.5 mL)
- Port 8: EtOH (0.5 mL)
- Port 9: sterile water (10 mL)
- Dilution flask: MilliQ water (50 mL).

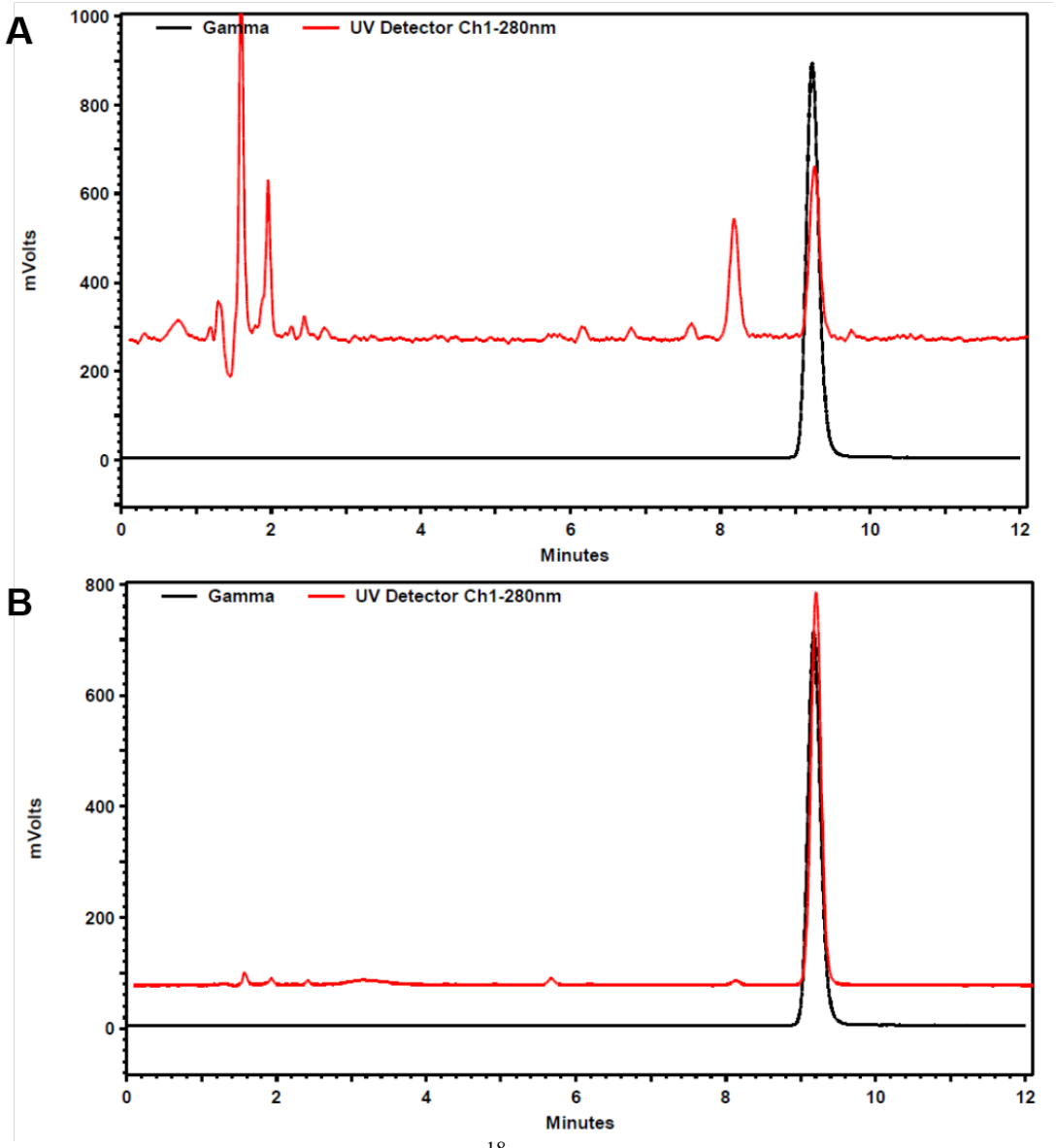
[^{18}F]Fluoride (ca. 1500 mCi) was produced in a GE PETTrace cyclotron as described above for the manual reactions and swept to the synthesis module in a bolus of [^{18}O]H_2O by stream of argon. The aqueous solution of [^{18}F]fluoride was passed through a pre-conditioned QMA-light cartridge (Sep-Pak, potassium triflate preconditioning) to trap [^{18}F]fluoride, before the [^{18}F]fluoride was eluted into the reactor vessel with a solution of KOTf in H_2O (contents of Port 1). To this, a solution of 18-crown-6 in MeCN (contents of Port 2) was added, and the mixture azeotropically dried by heating the reaction vessel to 100 °C and drawing vacuum (ca. 1 kPa) for 5 minutes, followed by simultaneous vacuum draw and argon stream for an additional 6 minutes. The dried [^{18}F]KF•18-crown-6•KOTf complex (ca. 900 mCi) was cooled to 50 °C before addition of $(MeCN)_4CuOTf$ and quinaldic acid in DMF (contents of

Port 3). The mixture was stirred for 3 min before addition of diaryliodonium stock solution and diisopropylethylamine in DMF (contents of Port 4). The reaction vessel was sealed and heated to 85 °C, and held at this temperature for 30 min before being cooled to 50 °C, diluted with HPLC buffer (contents of Port 6) and transferred out of the reactor under argon pressure into an intermediate vial (ca. 180 mCi remains in the reactor), before being loaded onto the HPLC sample loop.

Purification was performed using semi-preparative HPLC using a Phenomenex Luna 5 μm PFP (2)100 Å 250 mm x 10 mm column, at 4 $mL.min^{-1}$ with 50% MeCN in H_2O, 20 mM NH_4OAc, pH 4.5 as mobile phase and the gamma peak eluting at 28.5-30.5 min was collected and diluted into 50 mL of water (contents of the dilution flask). The solution was then passed through a Sep-Pak C18 1cc Vac, the cartridge washed with sterile water (contents of Port 9), before the product was eluted into a collection vial with ethanol (contents of Port 8). The Sep-Pak C18 1cc Vac was then flushed with isotonic saline (contents of Port 7), and this too transferred to the collection vial. The resultant product solution was then transferred to a sterile vial for analysis. Total synthesis time was c.a 109 min. Activity in the product vial was counted (41 ± 31 mCi, n = 3), representing 2.8 ± 1.9% non-decay corrected radiochemical yield (RCY) of the final product.

An aliquot (200 μmol) removed for HPLC analysis using HPLC Condition D., which confirmed the product's identity as *N*-benzyl-4-[^{18}F]fluoronimesulide (**3q**).

HPLC conditions: Condition D
A: *N*-Benzyl-4-[^{18}F]fluoronimesulide **3q** reaction gamma trace overlaid with UV trace at 280 nm
B: *N*-Benzyl-4-[^{18}F]fluoronimesulide **3q** reaction gamma trace overlaid with UV trace at 280 nm, after spiking with *N*-benzyl-4-fluoronimesulide **3q**

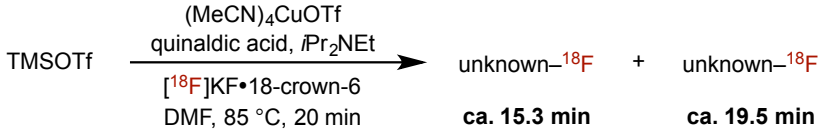


The specific activity of the *N*-benzyl-4-[^{18}F]fluoronimesulide (**3q**) was determined as follows. A 20 µL aliquot was analyzed by HPLC using HPLC Condition D, and the area of the UV peak (280 nm) corresponding to the *N*-benzyl-4-fluoronimesulide (t_R = 9.2 min) was determined. The molar concentration (mol•L^{-1}) of *N*-benzyl-4-fluoronimesulide in the sample was then determined by linear regression analysis against a standard curve generated from injection of identical volumes of solutions of known concentration of *N*-benzyl-4-fluoronimesulide. The concentration of activity was determined by dividing the total activity by the volume of the solution (10 mL), and division of the concentration of activity for the *N*-benzyl-4-[^{18}F]fluoronimesulide (**3q**) (Ci•mL^{-1}) by the molar concentration of the product (mol•L^{-1}) gives the end of synthesis (EOS) specific activity (Ci•mmol^{-1}). EOS specific activity was found to be 2840 ± 690 Ci•mmol^{-1} (n = 3).

In the UV chromatogram of the isolated product, the presence of *N*-benzylnimesulide (**1q**) (CH-precursor for the fluorination) was also observed (t_R = 8.2 min). The molar quantity of *N*-benzylnimesulide (**1q**) was determined by linear regression analysis against a standard curve generated from injection of identical volumes of solutions of known concentration of *N*-benzylnimesulide. The effective specific activity of the product was then determined using the sum of the molar concentration

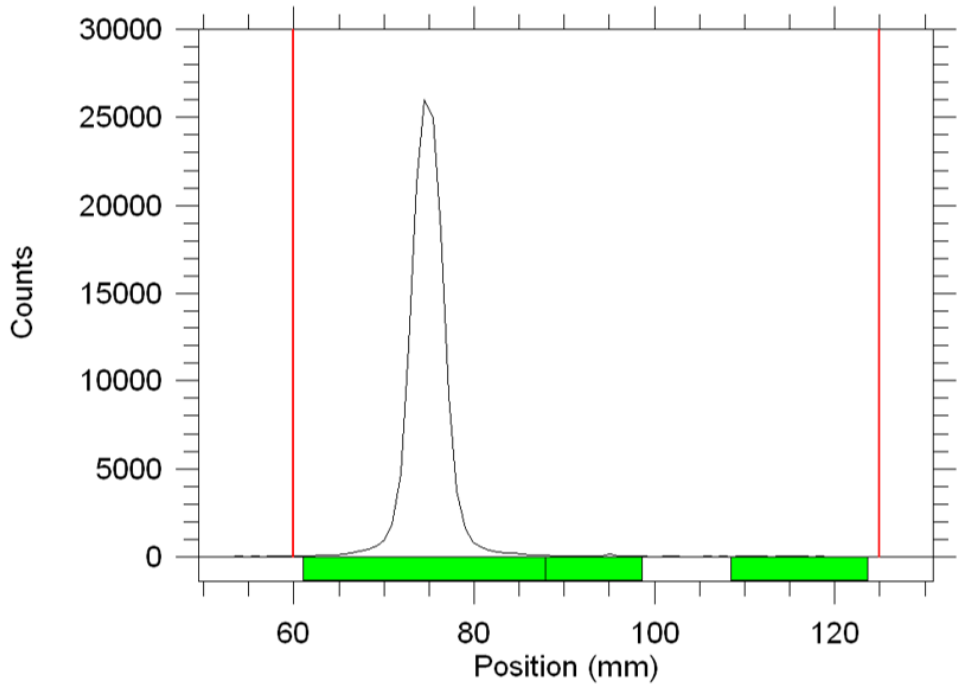
of the C–H entity and the C–F entity. EOS effective specific activity was found to be 1500 ± 820 Ci•mmol^{-1} (n = 3).

D. Control Experiments

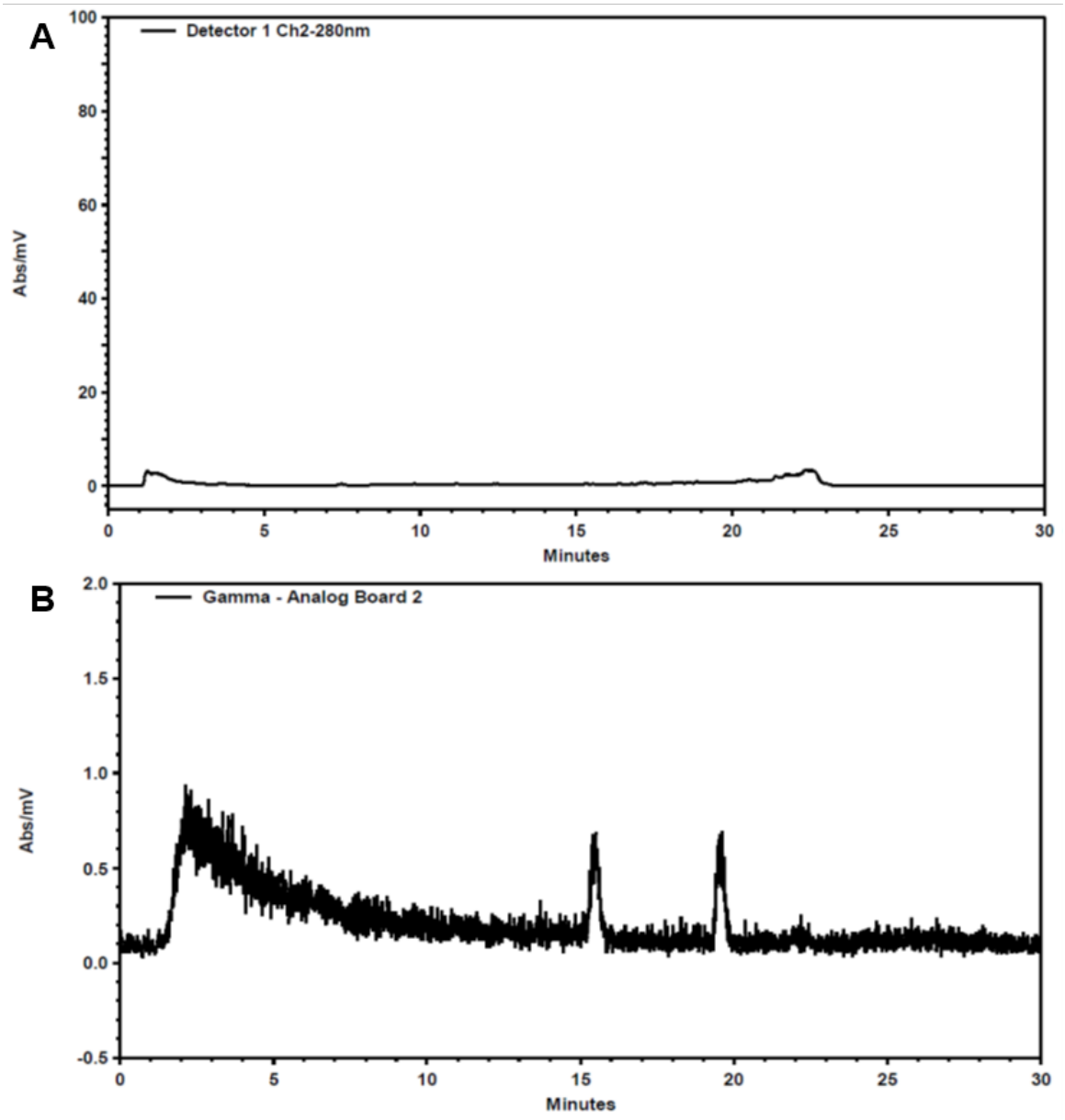


To a 4 mL vial were added anhydrous dimethylformamide (DMF) (800 µL), TMSOTf (1.8 µL, 10 µmol), and *N*,*N*-diisopropylethylamine (*i*Pr$_2$NEt) (3.5 µL, 20 µmol). The solution was agitated with a vortex mixer and aged for 10 min at room temperature. Under an ambient atmosphere, tetrakis(acetonitrile)copper(I) trifluoromethanesulfonate ((MeCN)$_4$CuOTf) (100 µL of a 100 mM solution, 10 µmol) and quinaldic acid (10 µmol) in DMF was added to the diaryliodonium/*i*Pr$_2$NEt solution. The reaction vial was sealed with a PTFE/Silicone septum cap and a 100 µL aliquot of [^{18}F]KF•18-crown-6•K_2CO_3 complex in DMF (typically 60-800 µCi, prepared as described above) was added to the reaction vial via syringe. The reaction was heated in an aluminum block at 85 °C for 20 min. After 20 min, the reaction was removed from heat and allowed to cool to room temperature. Radiochemical conversion (RCC) was obtained by radio-TLC analysis (2-5 µL aliquots) using a 50:50 hexanes-ethyl acetate eluent, and are not reported to reflect losses during [^{18}F]KF•18-crown-6•K_2CO_3 preparation. The samples were further analyzed using radio-HPLC (10-50 µL aliquots). While a 0% RCC was observed by radio-TLC, unknown byproducts were observed in the gamma trace of radio-HPLC at ca. 15.3 and 19.5 min.

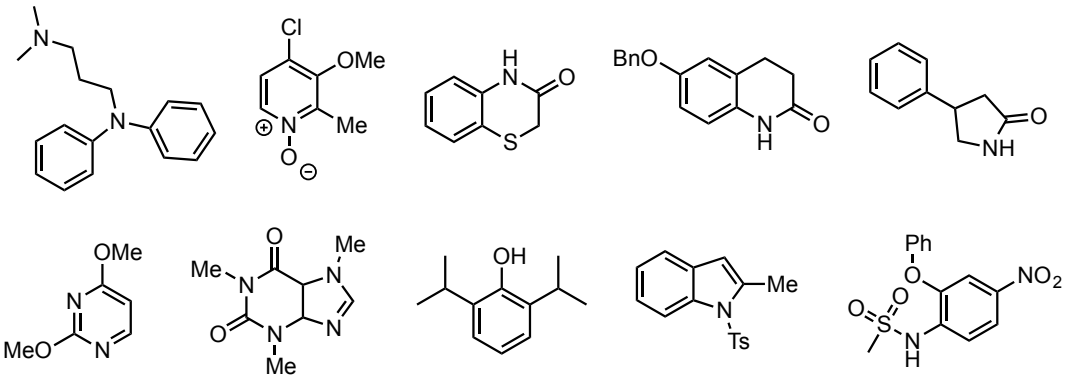
Radio-TLC eluent: 50% EtOAc in hexanes



HPLC conditions: Condition A
A: UV trace at 280 nm of a control reaction between TMSOTf and [^{18}F]KF•18-crown-6•K_2CO_3
B: Gamma trace of a control reaction between TMSOTf and [^{18}F]KF•18-crown-6•K_2CO_3



E. Unreactive or Non-Compatible Substrates



VI. References

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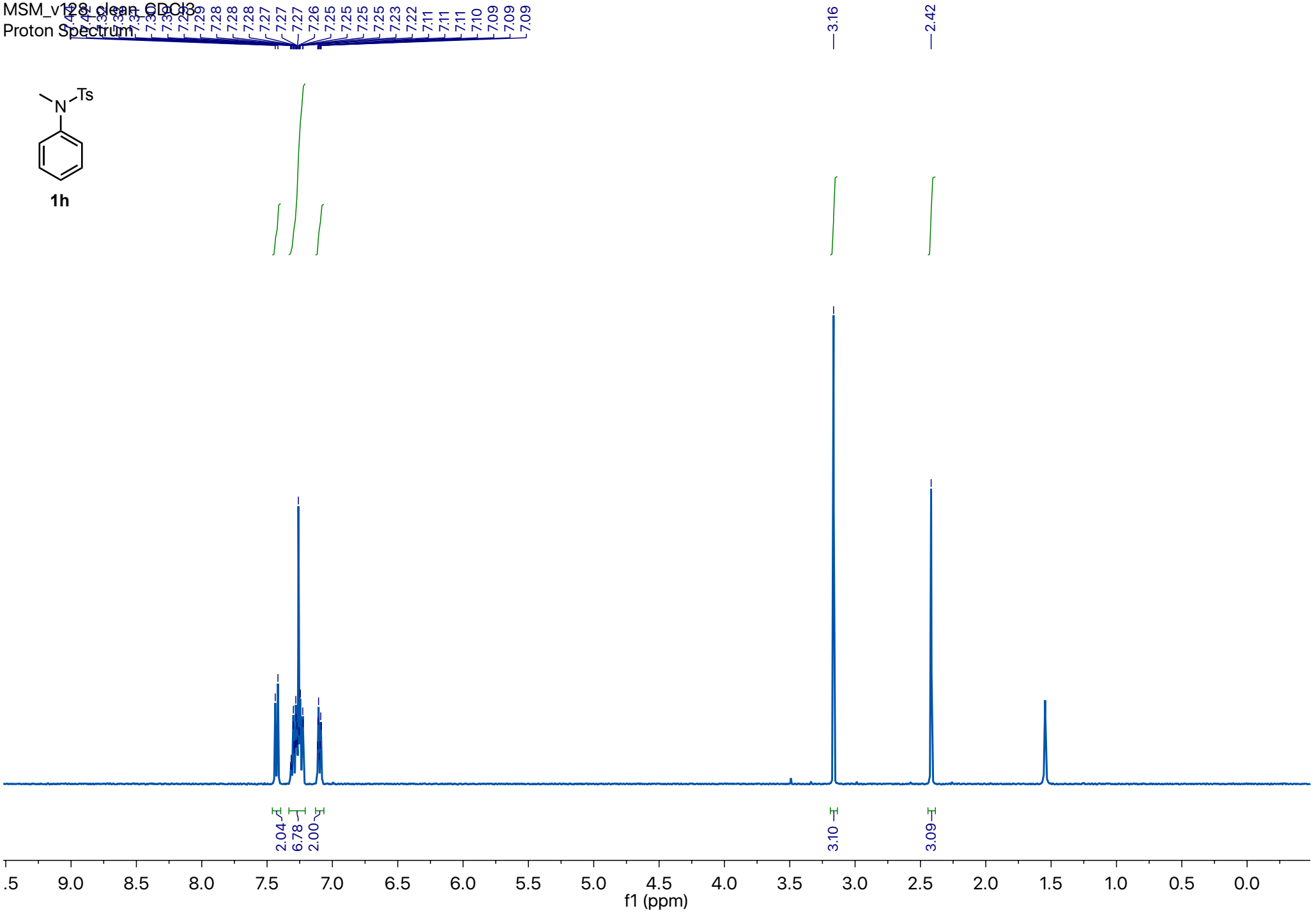
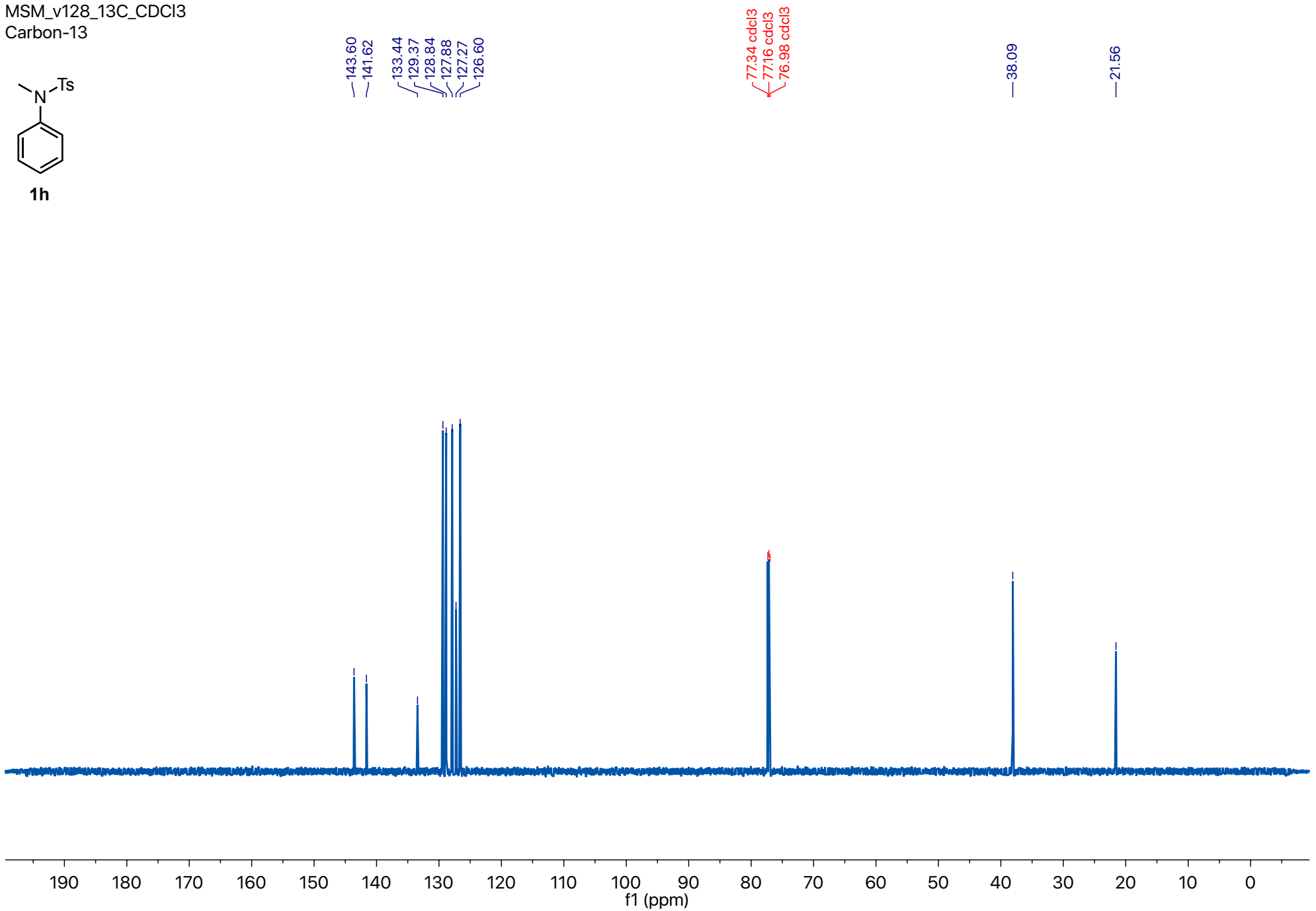
VII. NMR Spectra

^{1}H NMR (401 MHz, $CDCl_3$)

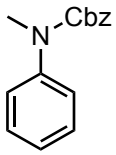


^{13}C NMR (176 MHz, $CDCl_3$)



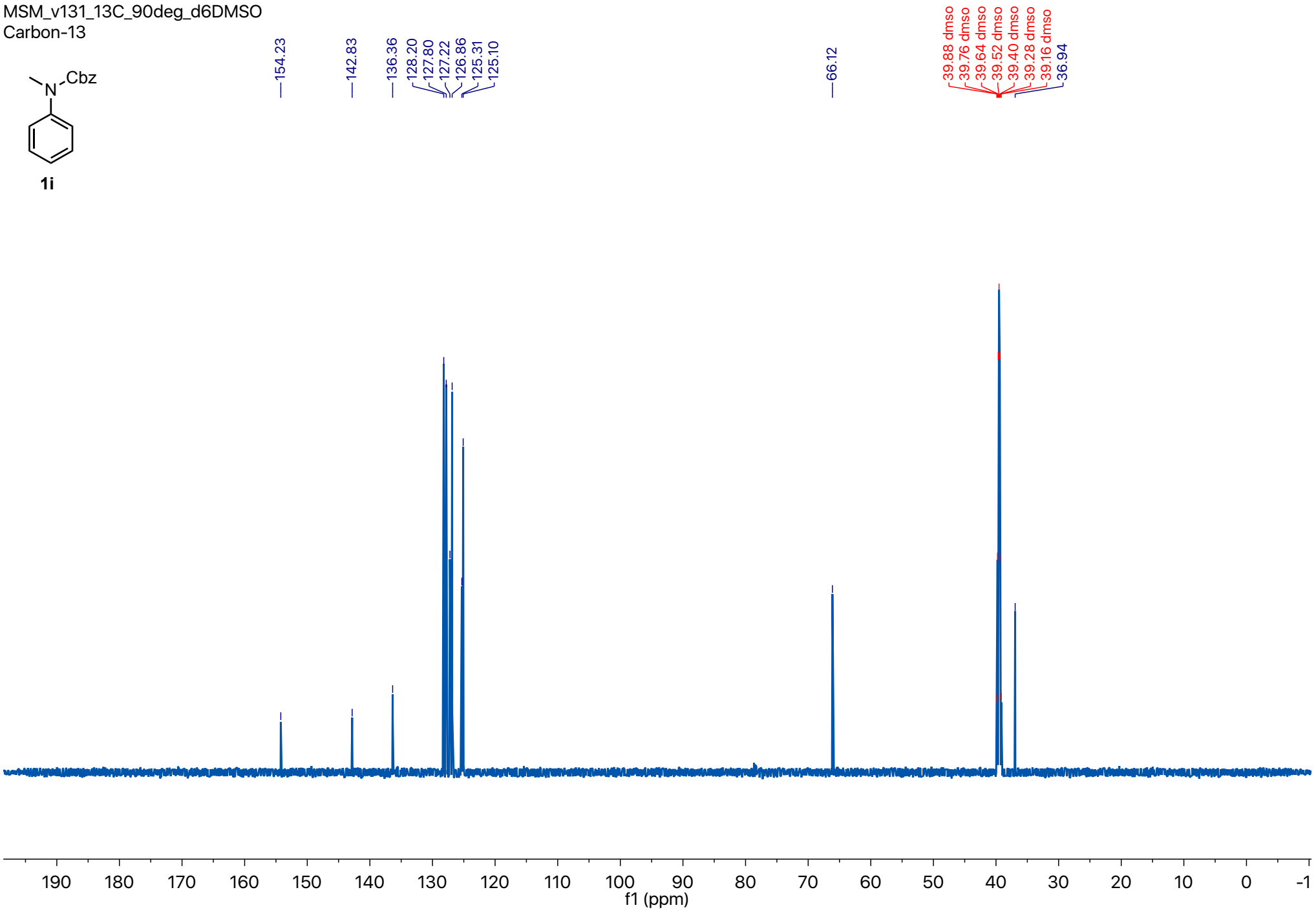
^{1}H NMR (700 MHz, d_6-DMSO)

MSM_v131_1H_90deg_d6DMSO
Proton Spectrum



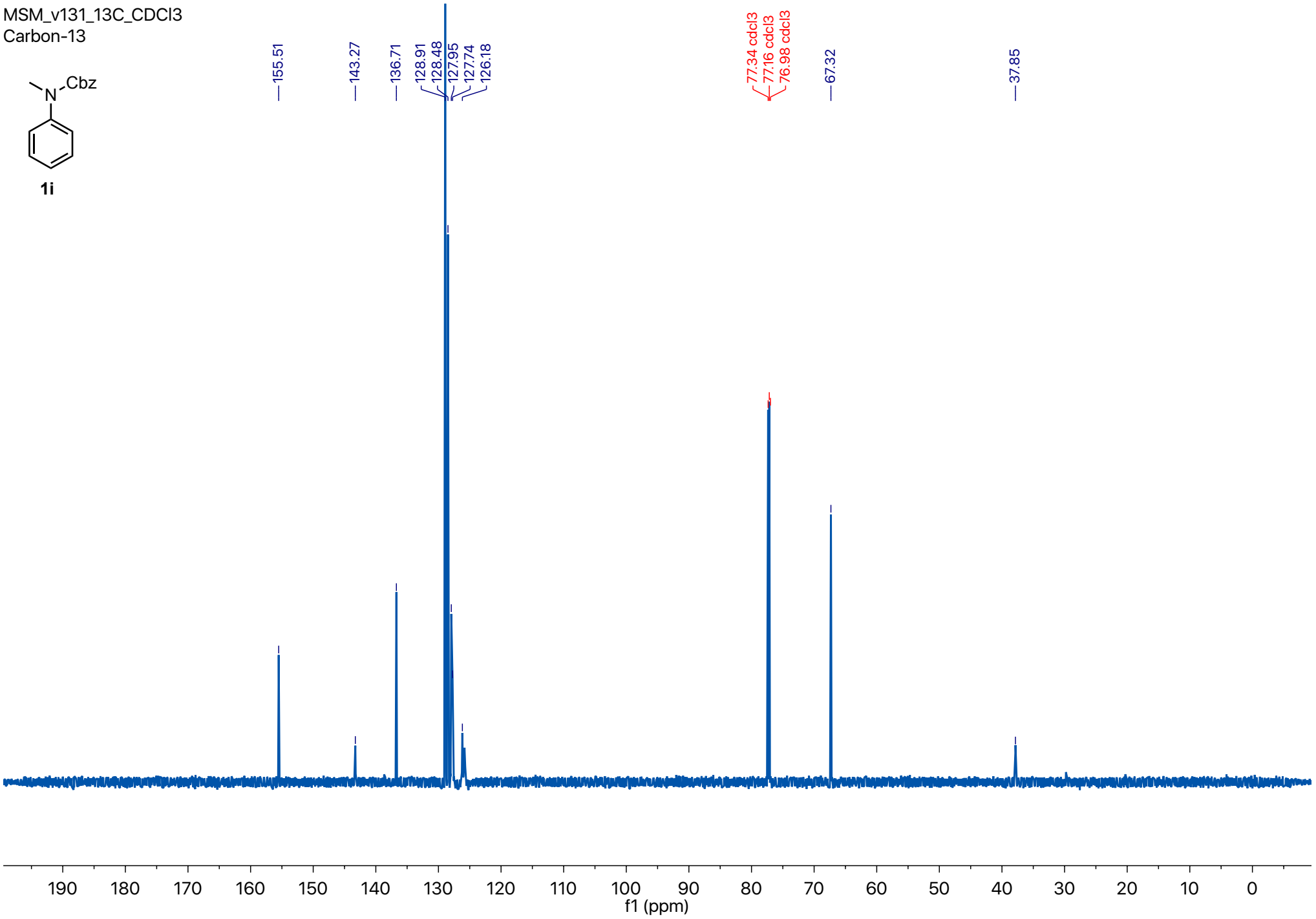
1i

^{13}C NMR (176 MHz, d_6-DMSO)

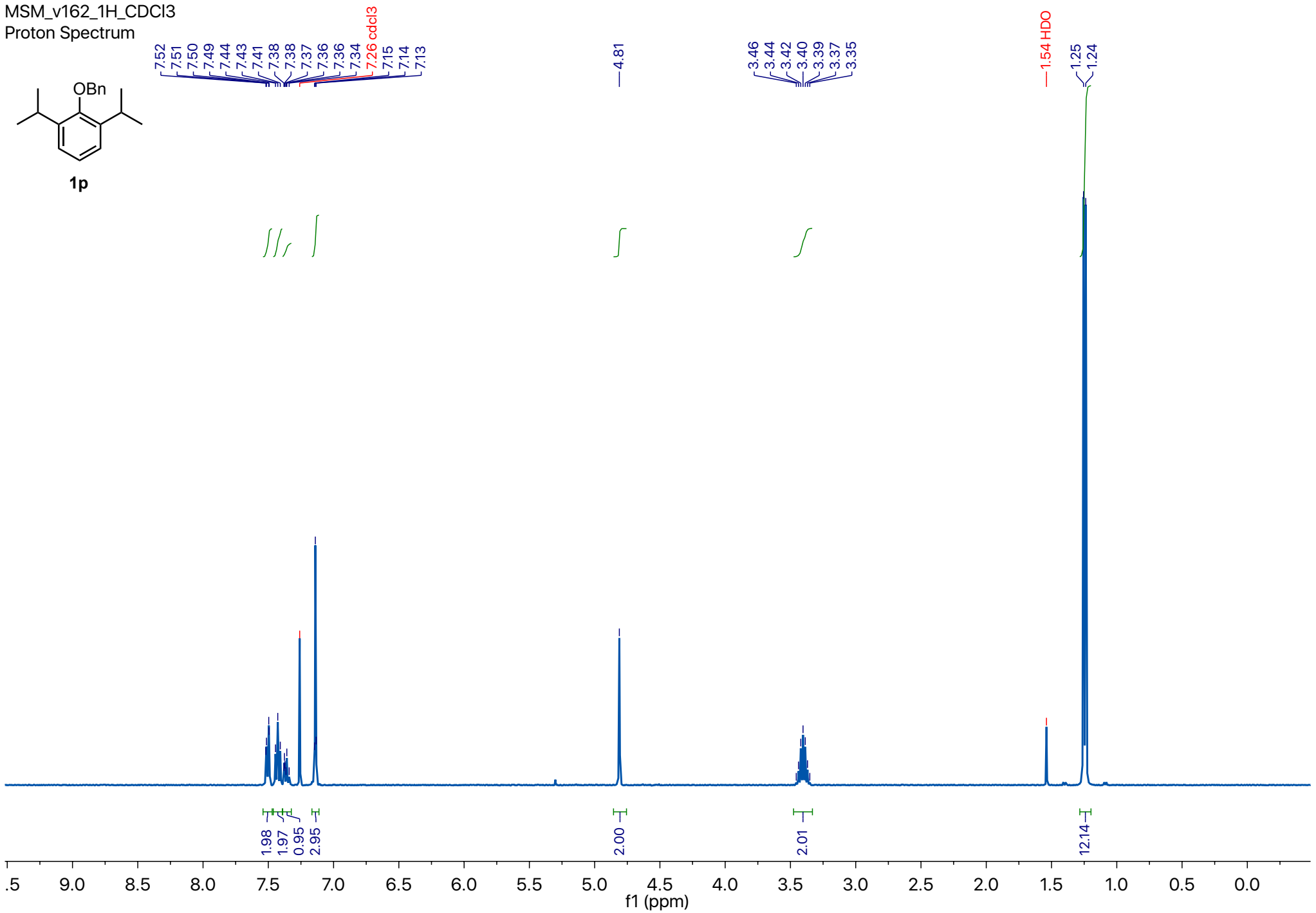


1i

^{13}C NMR (176 MHz, $CDCl_3$)

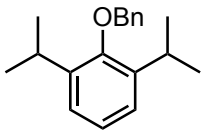


^{1}H NMR (401 MHz, $CDCl_3$)



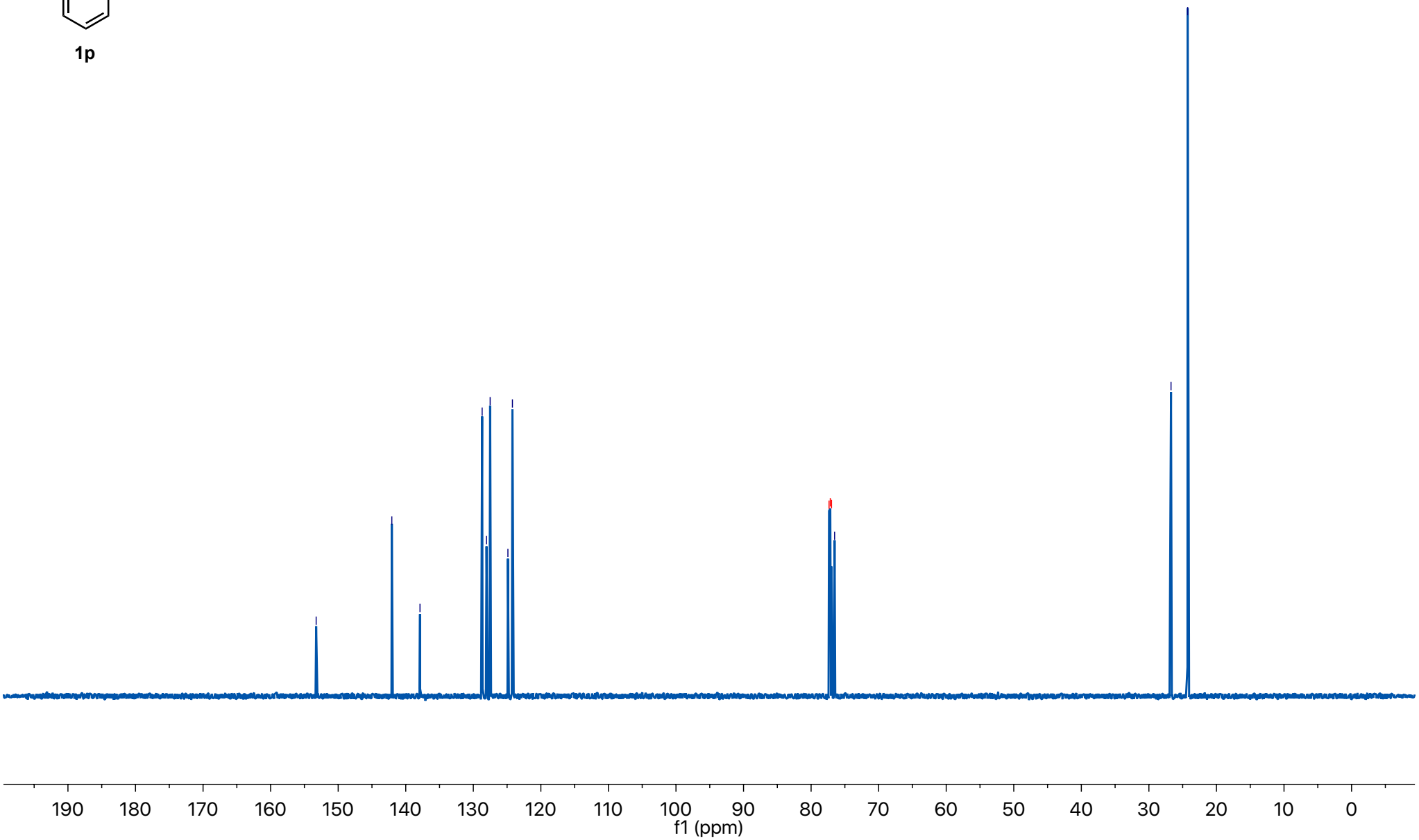
^{13}C NMR (176 MHz, $CDCl_3$)

MSM_v162_13C_CDCl3
Carbon-13

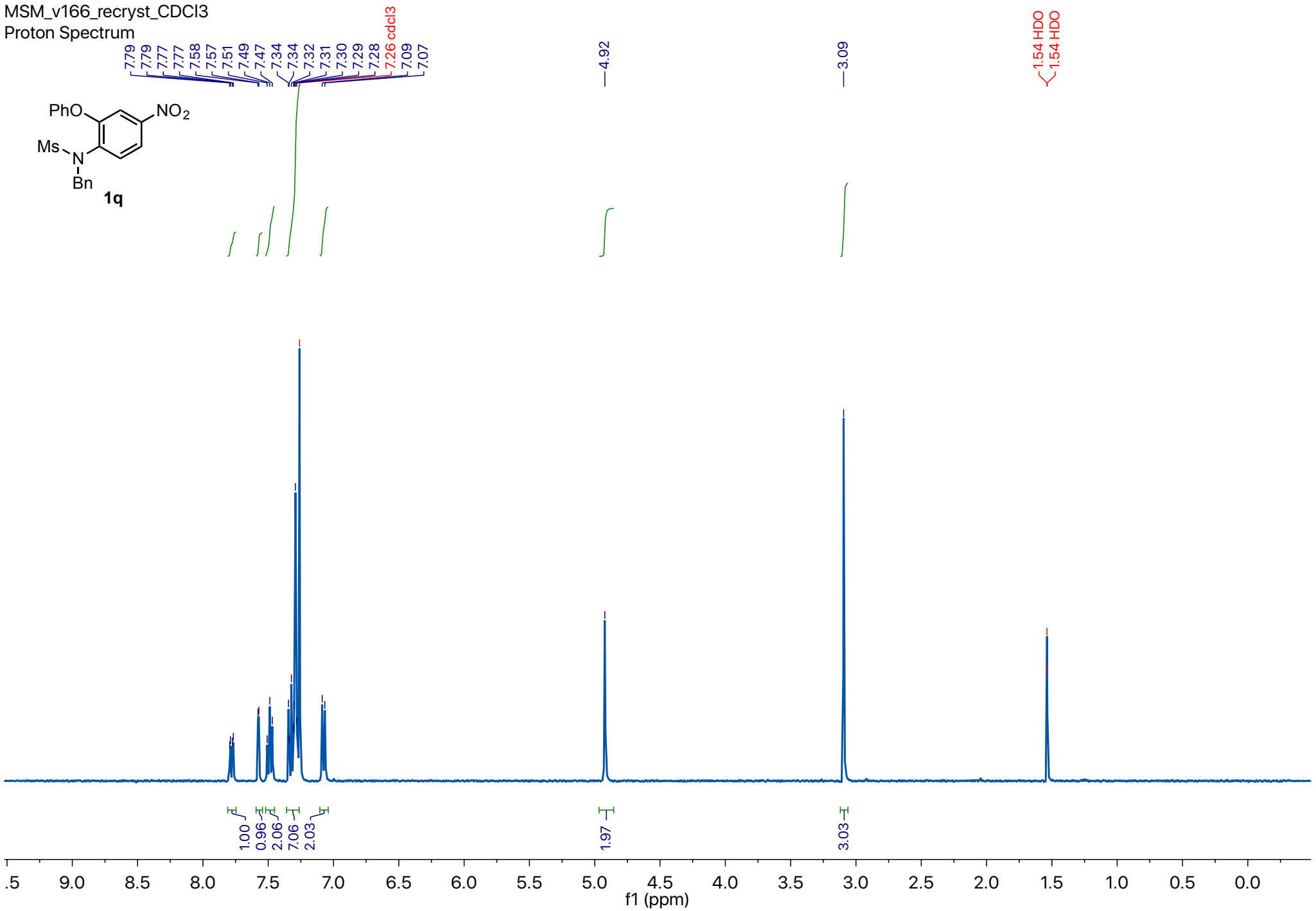


1p

153.26
142.06
137.89
128.69
128.04
127.51
124.88
124.21
77.34 cdcl3
77.16 cdcl3
76.98 cdcl3
76.52
26.73
24.26

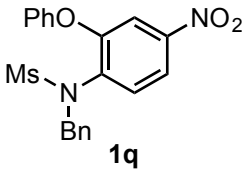


^{1}H NMR (401 MHz, $CDCl_3$)



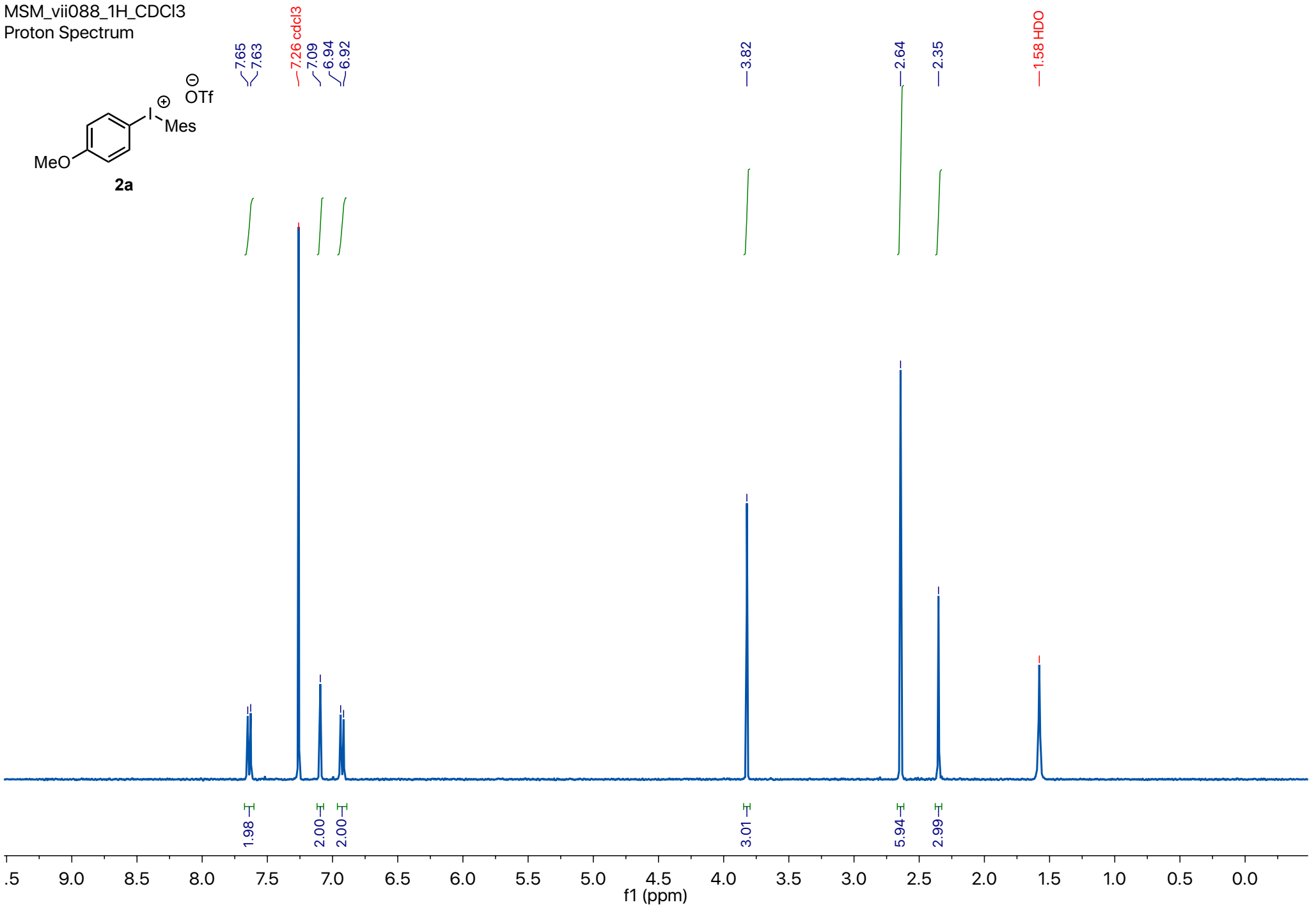
^{13}C NMR (176 MHz, $CDCl_3$)

MSM_v166_13C_CDCl3
Carbon-13

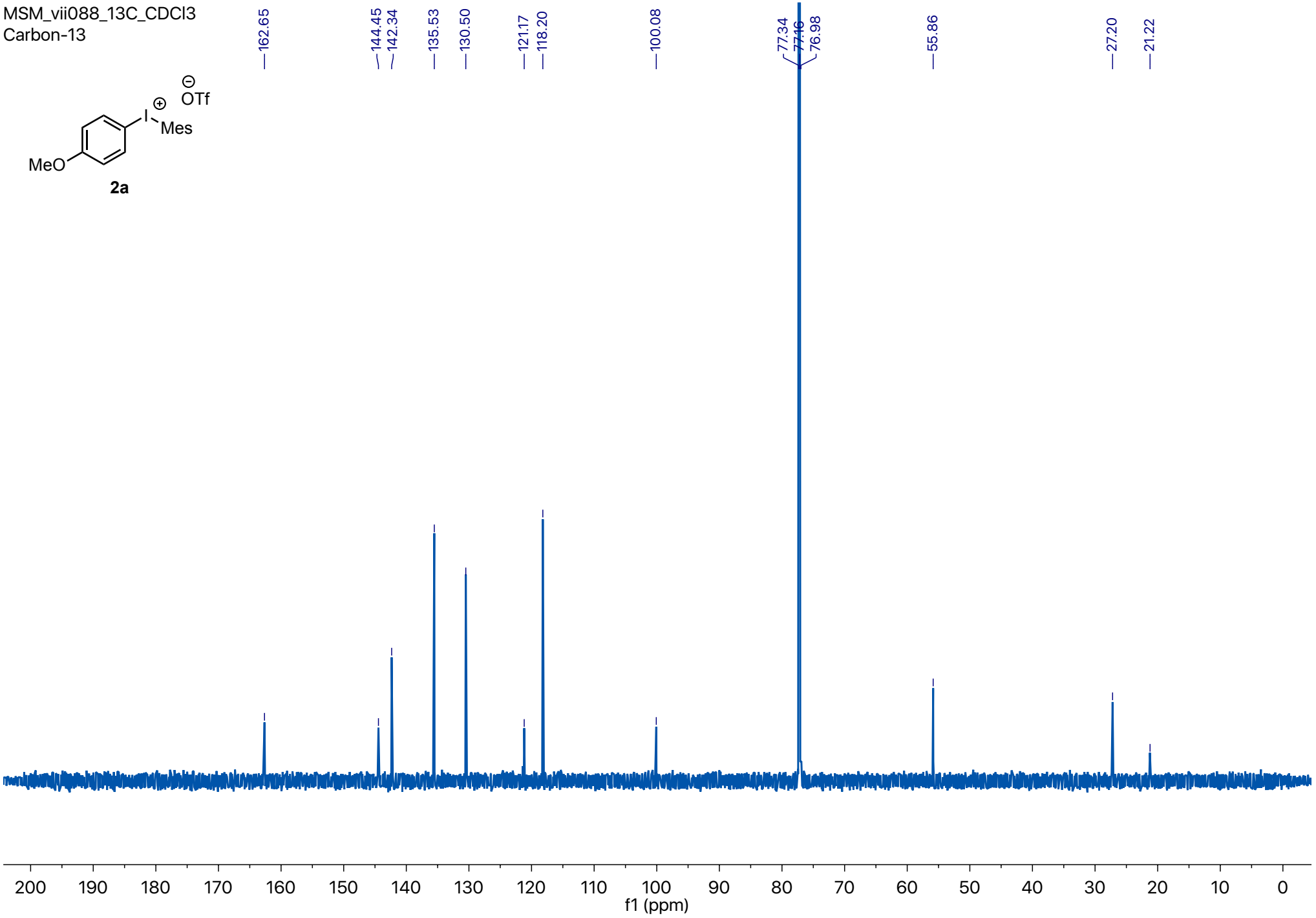


1q

^{1}H NMR (401 MHz, $CDCl_3$)

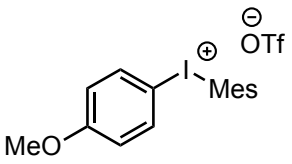


^{13}C NMR (176 MHz, $CDCl_3$)



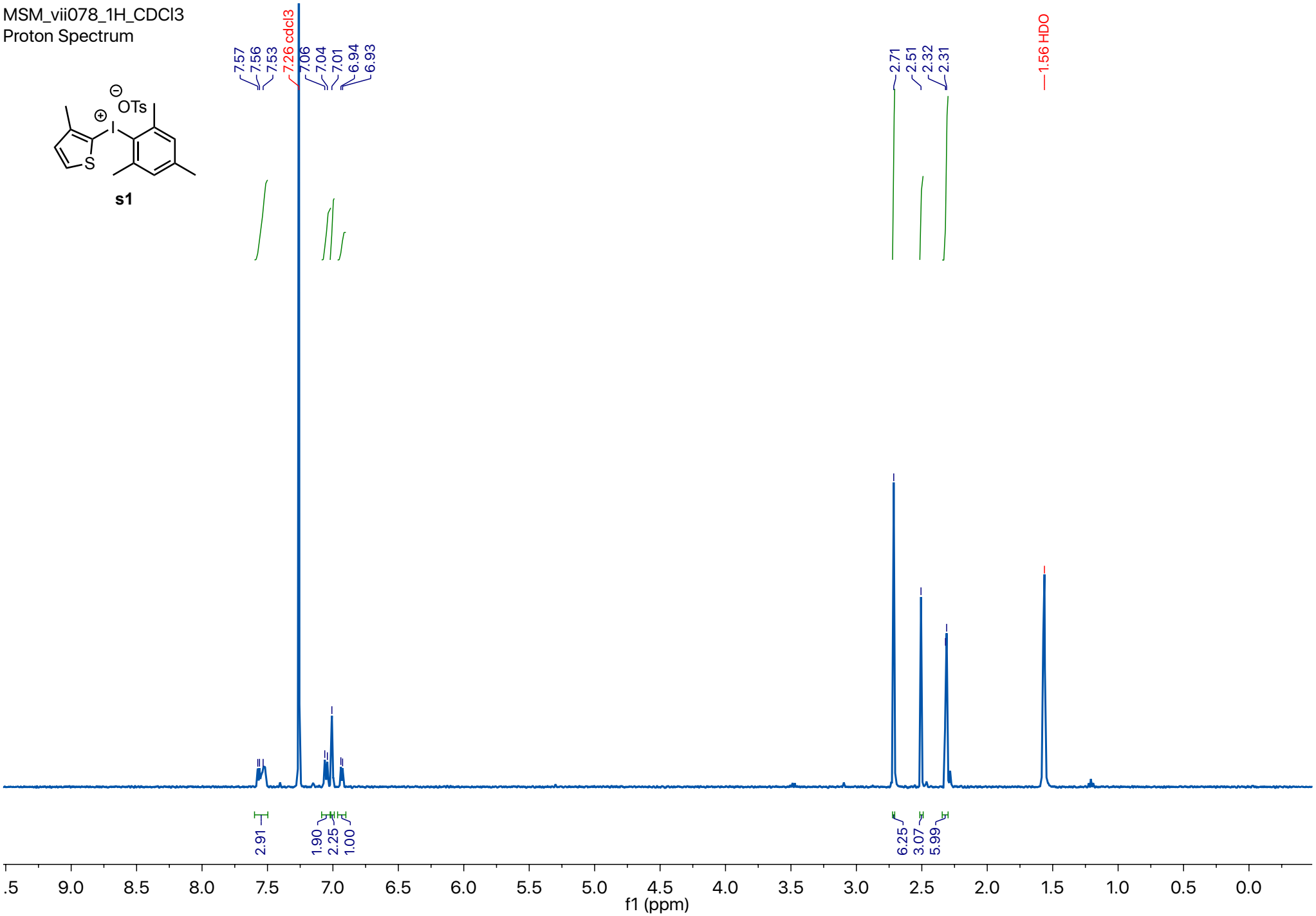
^{19}F NMR (377 MHz, $CDCl_3$)

MSM_vii088_19F_CDCl3
STANDARD FLUORINE PARAMETERS



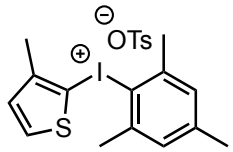
2a

^{1}H NMR (401 MHz, $CDCl_3$)



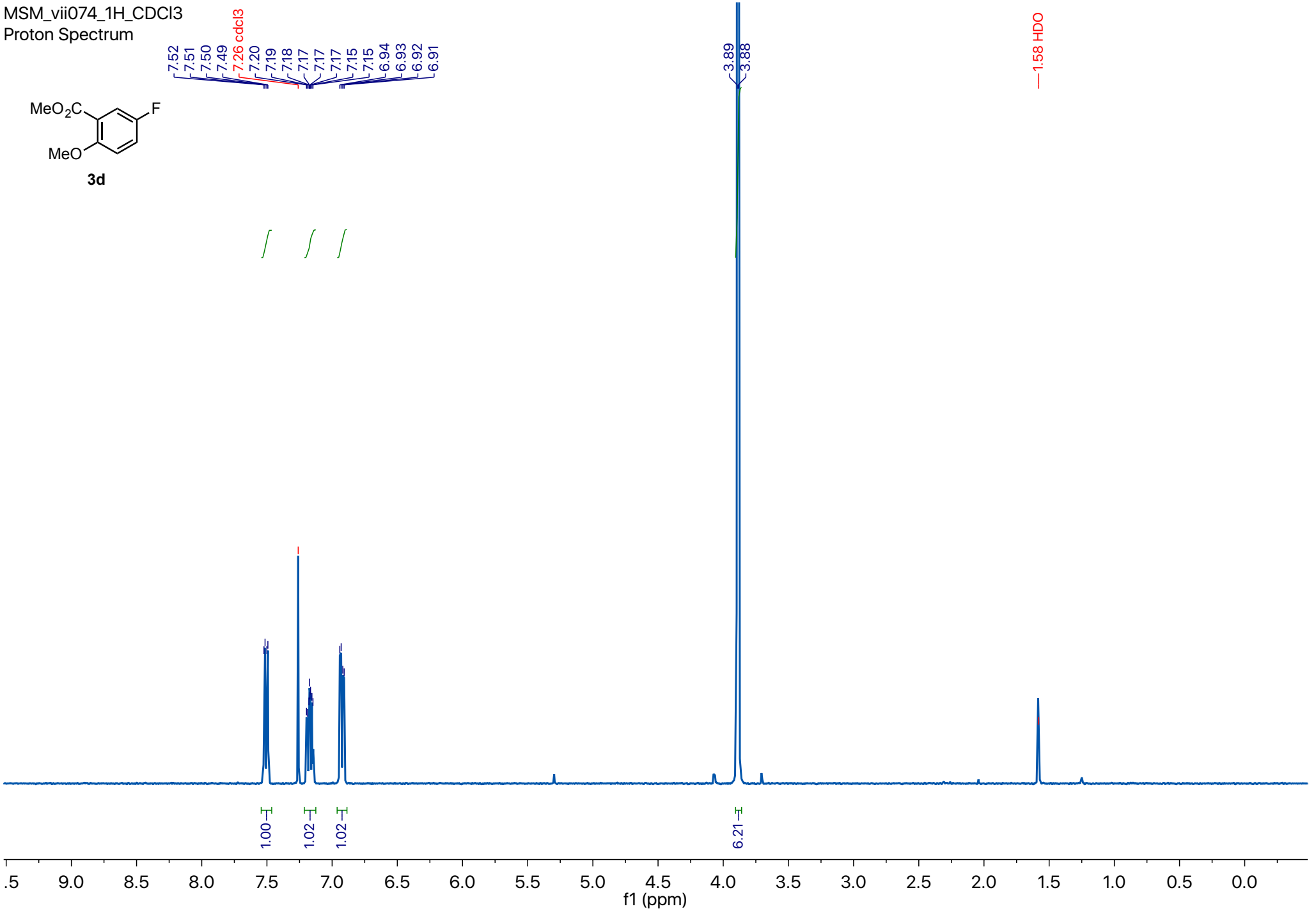
^{13}C NMR (176 MHz, $CDCl_3$)

MSM_vii078_13C_CDCl3
Carbon-13



s1

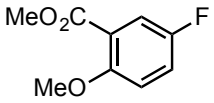
^{1}H NMR (401 MHz, $CDCl_3$)



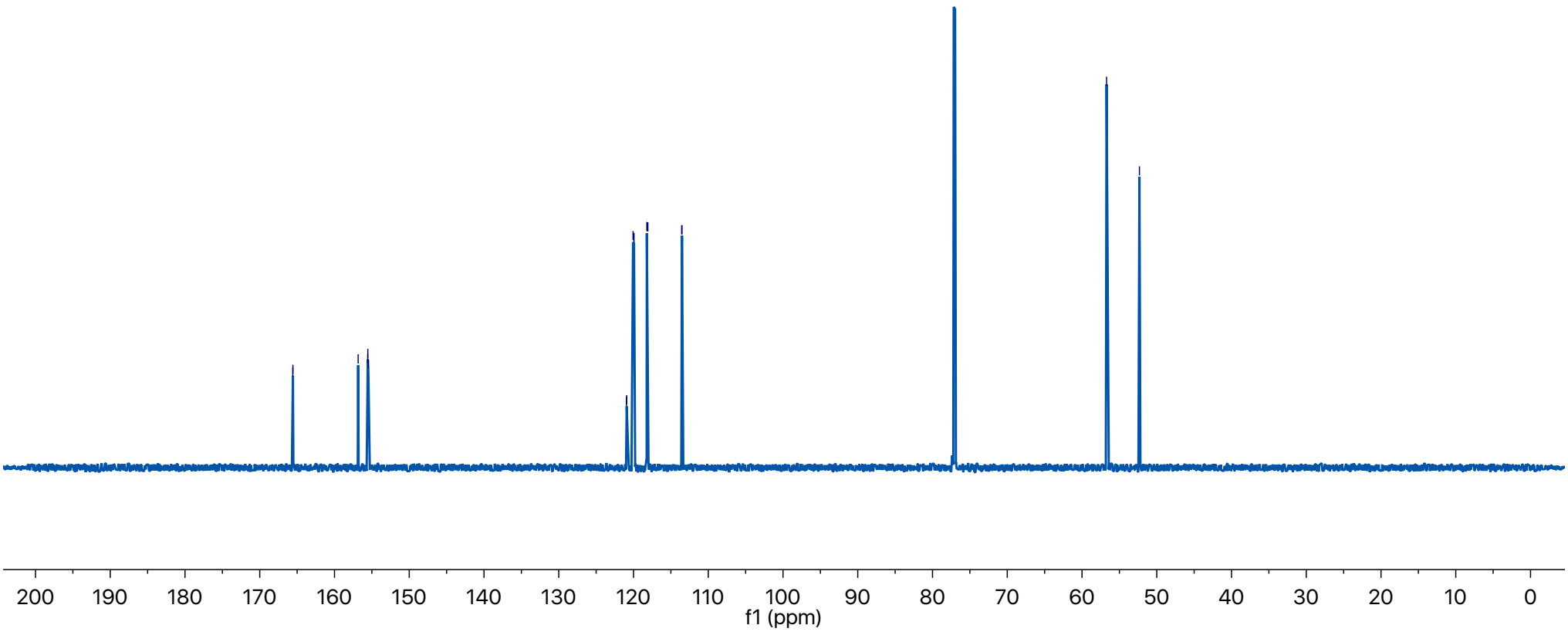
^{13}C NMR (176 MHz, $CDCl_3$)

MSM_vii074_13C_CDCl3
Carbon-13

165.58
165.56
156.84
155.56
155.54
155.47
120.95
120.91
120.06
119.93
118.22
118.08
113.56
113.51
56.71
52.32

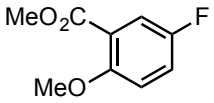


3d



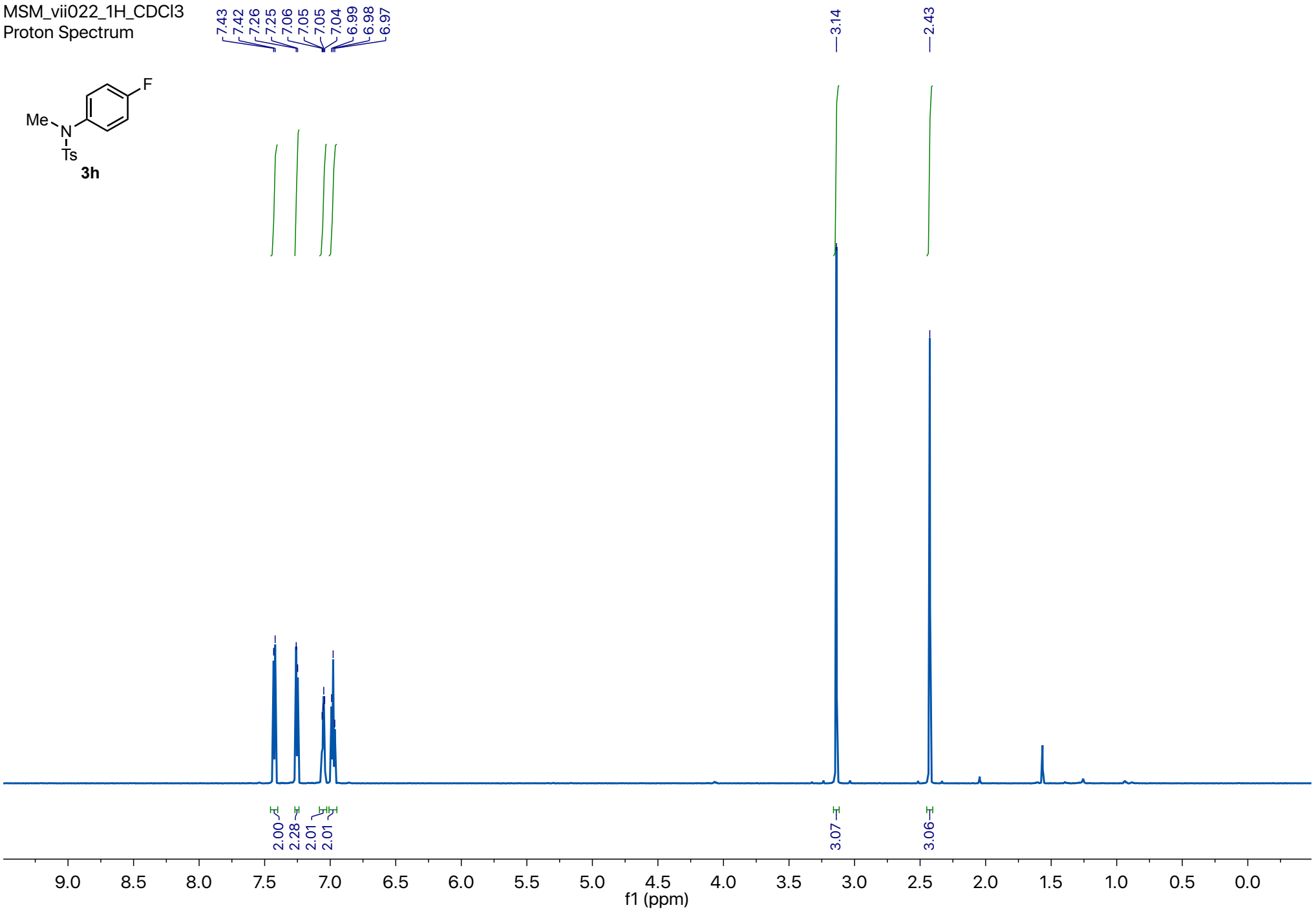
^{19}F NMR (377 MHz, $CDCl_3$)

MSM_vii074_19F_CDCl3
STANDARD FLUORINE PARAMETERS

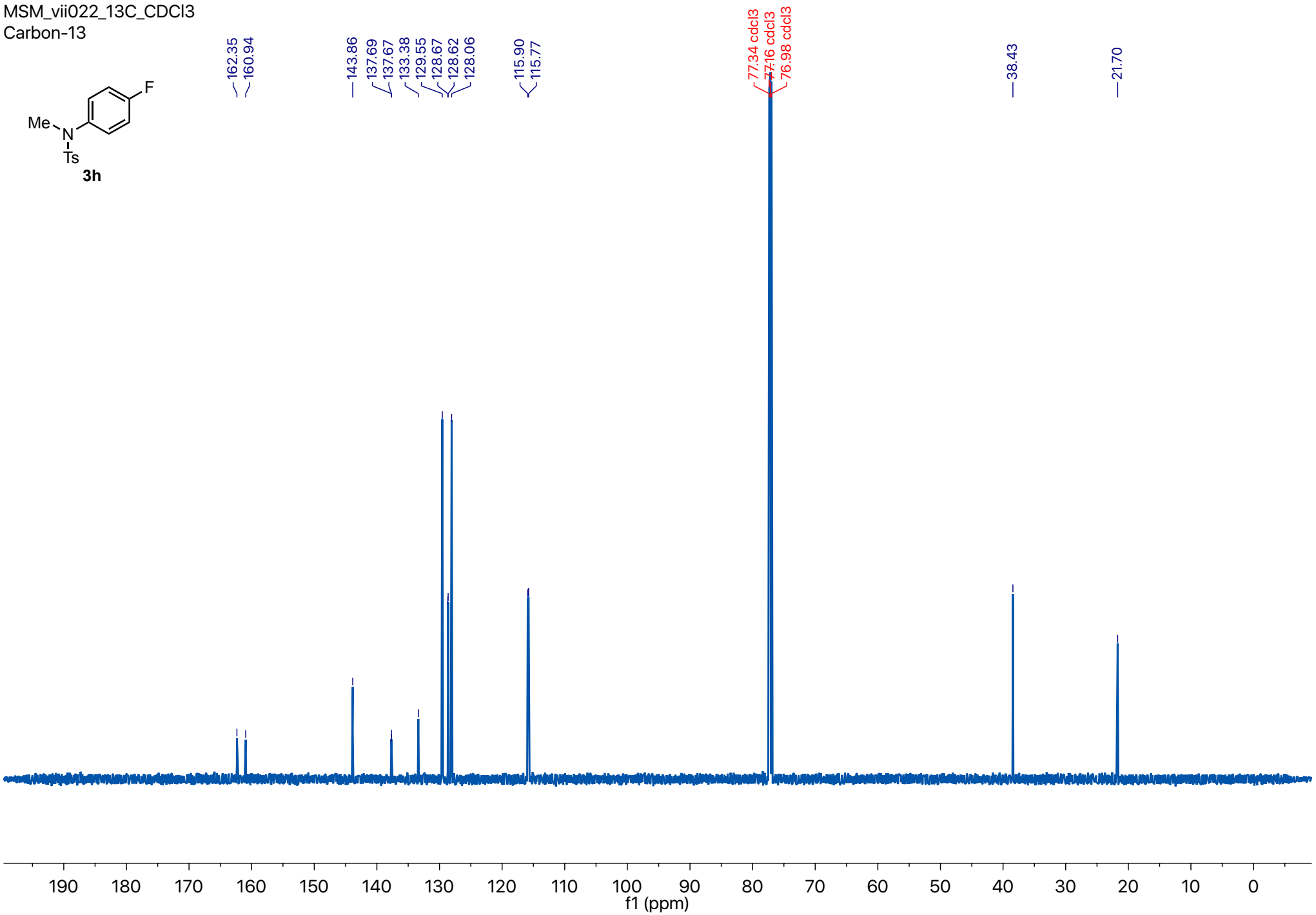


3d

^{1}H NMR (700 MHz, $CDCl_3$)

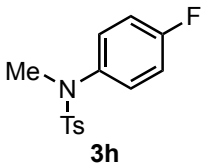


^{13}C NMR (176 MHz, $CDCl_3$)



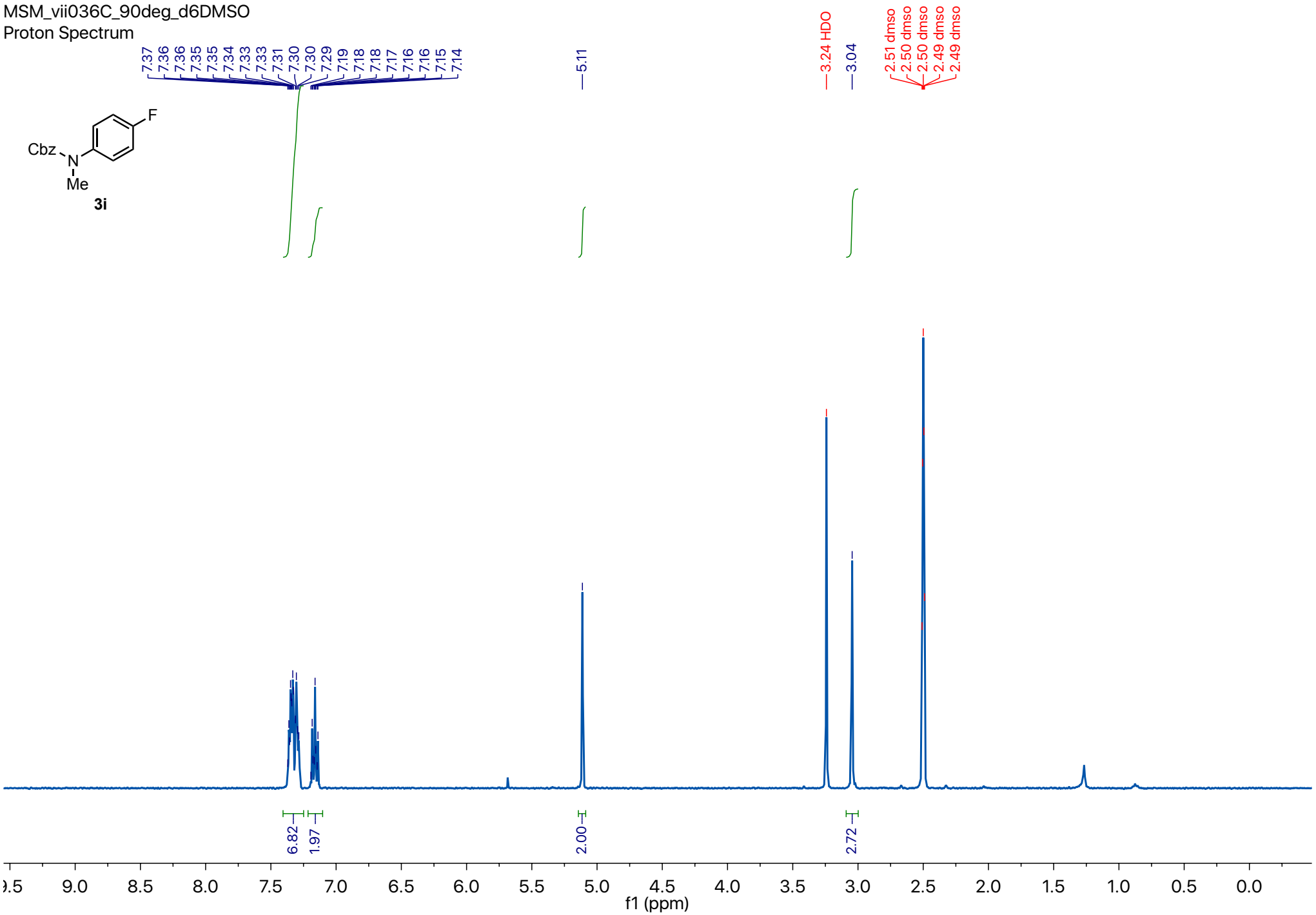
^{19}F NMR (376 MHz, $CDCl_3$)

MSM_vii022_19F_CDCl3
Fluorine-19



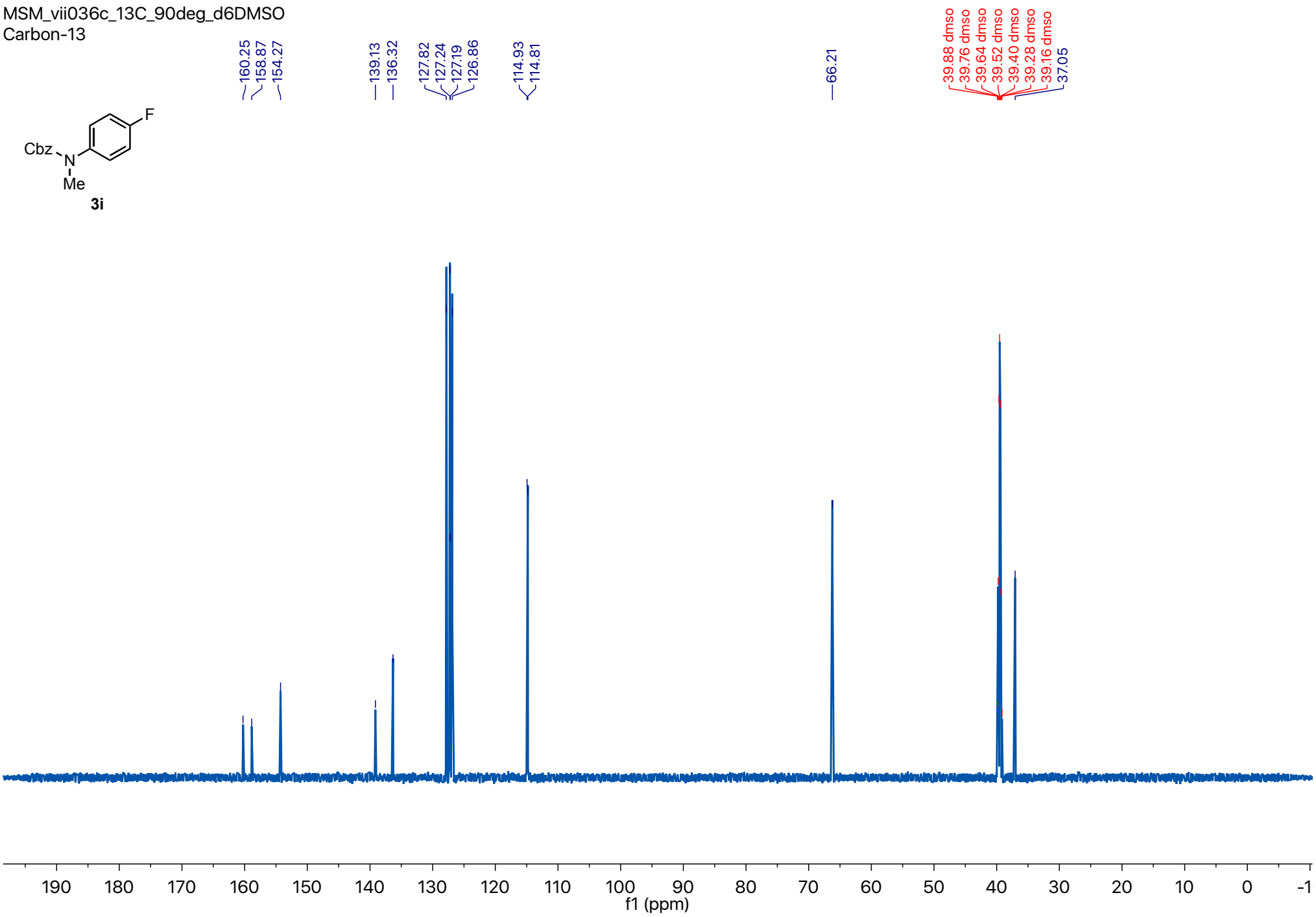
3h

^{1}H NMR (400 MHz, d_6-DMSO)



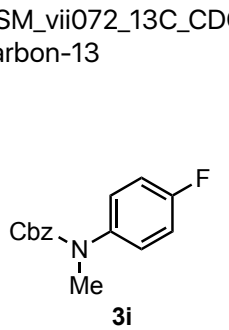
^{13}C NMR (176 MHz, d_6-DMSO)

MSM_vii036c_13C_90deg_d6DMSO
Carbon-13



^{13}C NMR (176 MHz, $CDCl_3$)

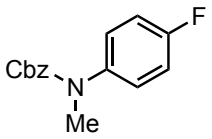
MSM_vii072_13C_CDCl3
Carbon-13



3i

^{19}F NMR (376 MHz, d_6-DMSO)

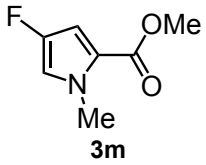
MSM_vii036C_90deg_d6DMSO
Fluorine-19



3i

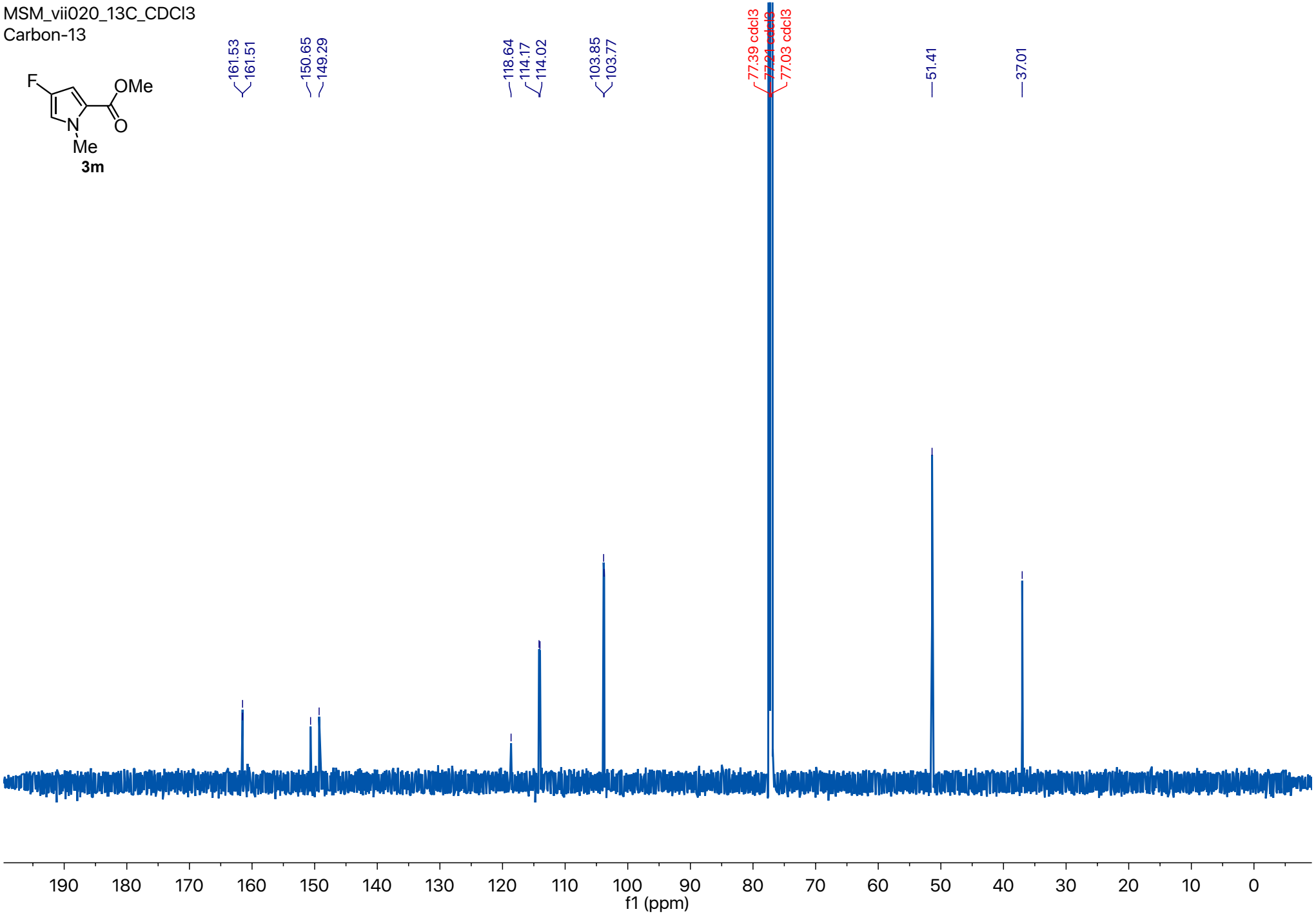
^{1}H NMR (401 MHz, $CDCl_3$)

MSM_vii020_1H_CDCl3
Proton Spectrum



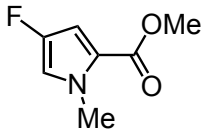
3m

^{13}C NMR (176 MHz, $CDCl_3$)



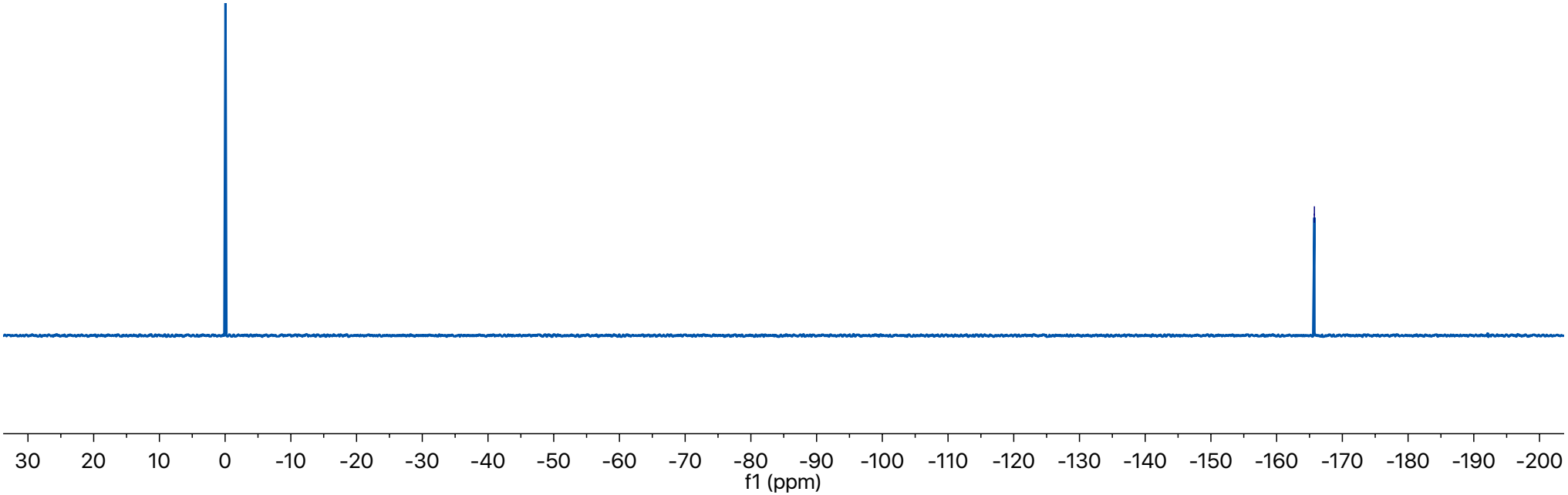
^{19}F NMR (376 MHz, $CDCl_3$)

MSM_vii020_19F_CDCl3
Fluorine-19



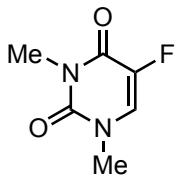
3m

-165.74
-165.74



^{1}H NMR (401 MHz, $CDCl_3$)

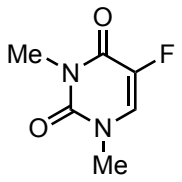
MSM_vii070_1H_CDCl3
Proton Spectrum



3n

^{13}C NMR (176 MHz, $CDCl_3$)

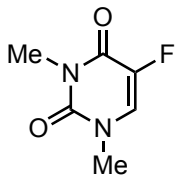
MSM_vii070_13C_CDCl3
Carbon-13



3n

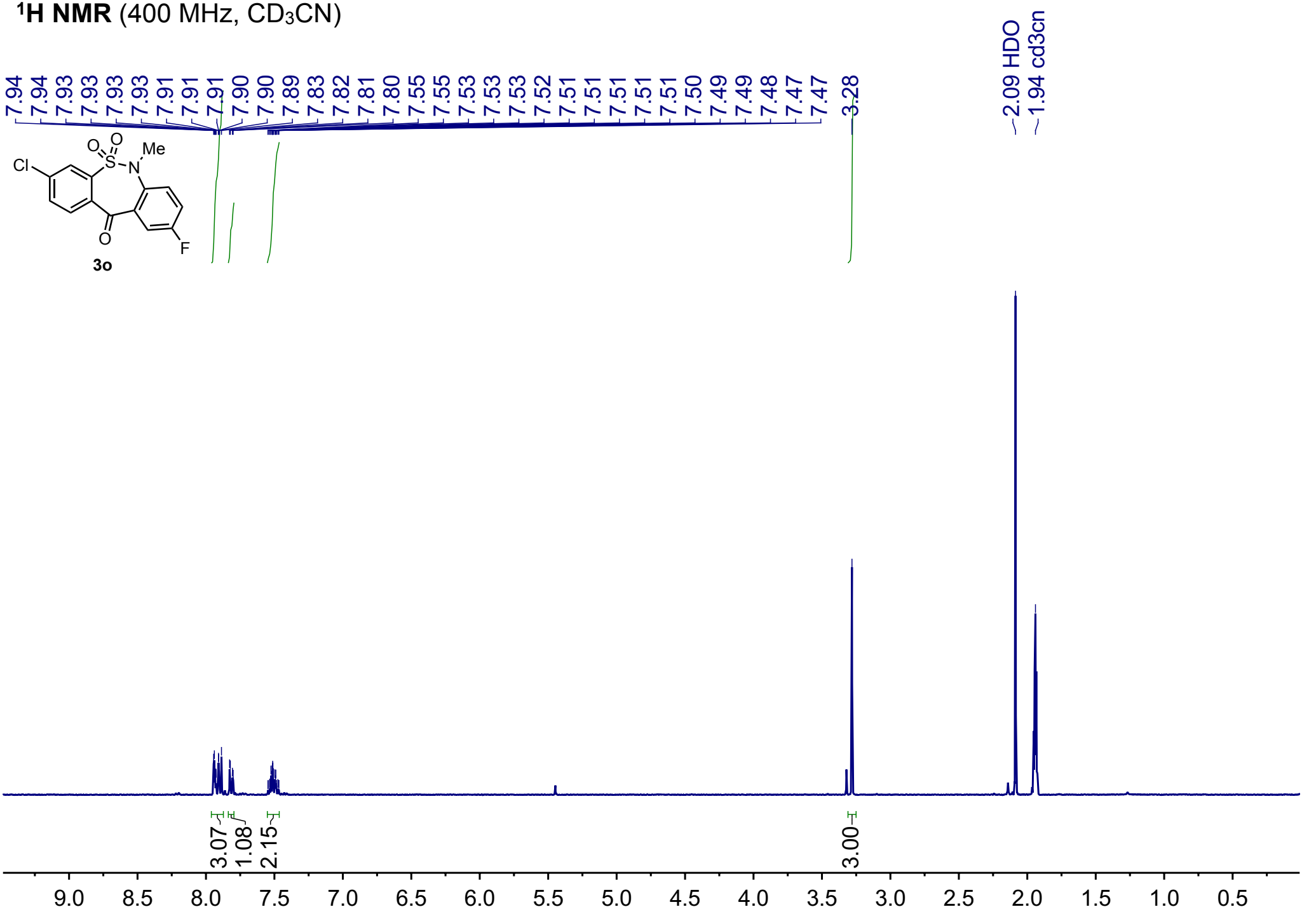
^{19}F NMR (377 MHz, $CDCl_3$)

MSM_vii070_19F_CDCl3
STANDARD FLUORINE PARAMETERS

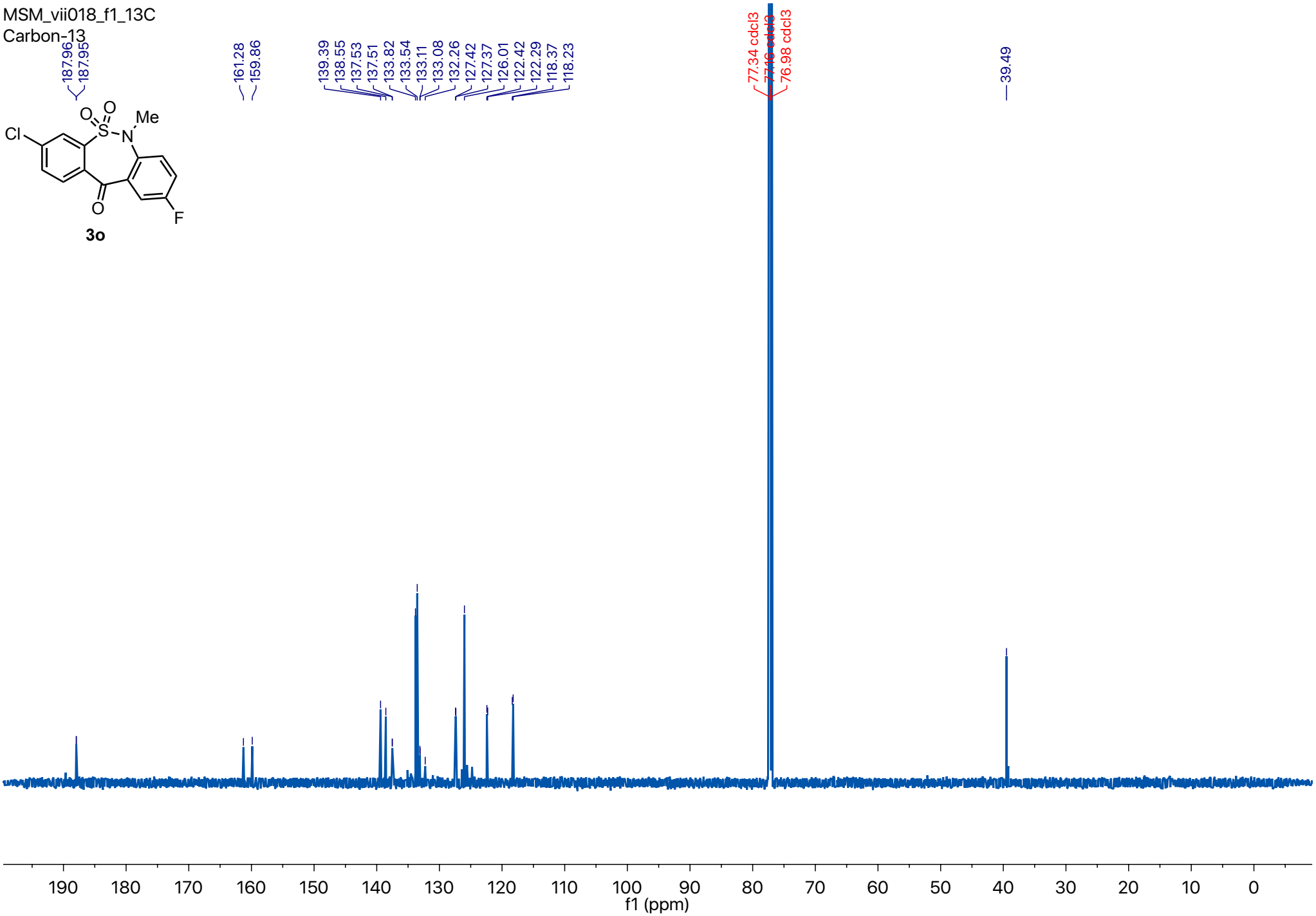


3n

^{1}H NMR (400 MHz, CD_3CN)

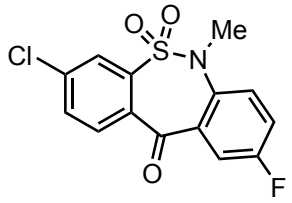


^{13}C NMR (176 MHz, $CDCl_3$)

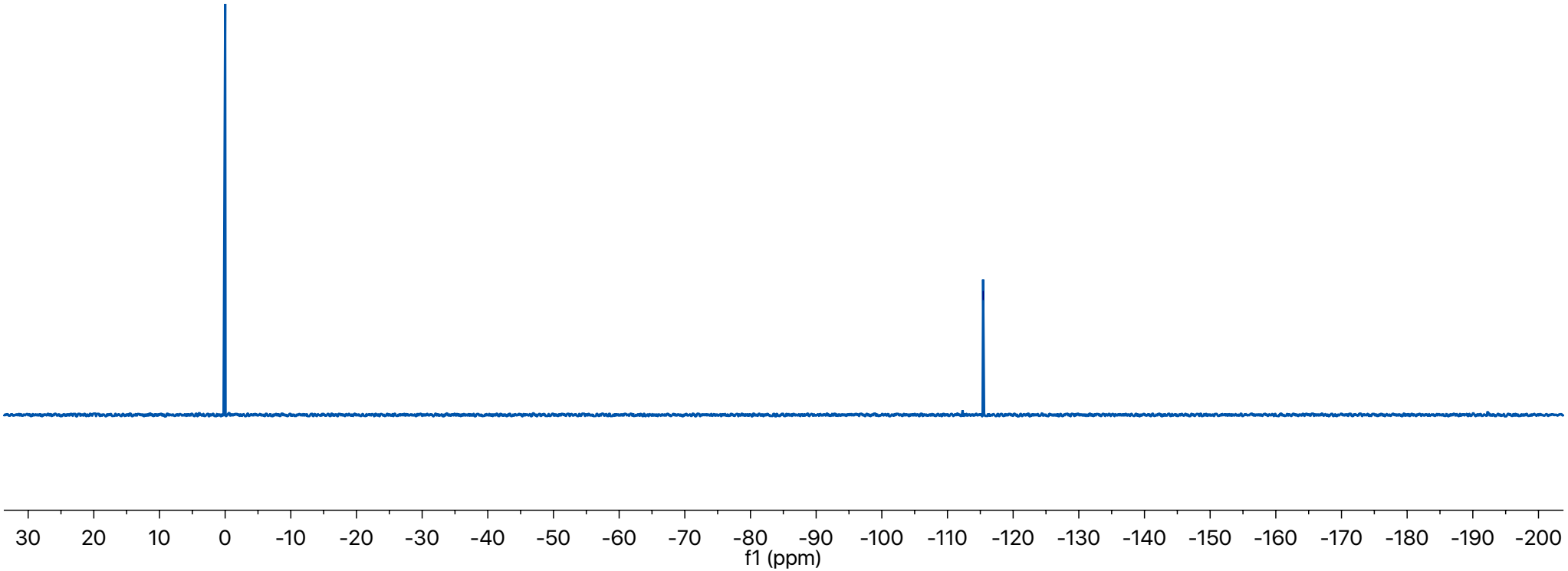


^{19}F NMR (376 MHz, $CDCl_3$)

MSM_vii018_19F_CDCl3
Fluorine-19

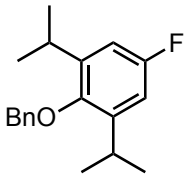


3o



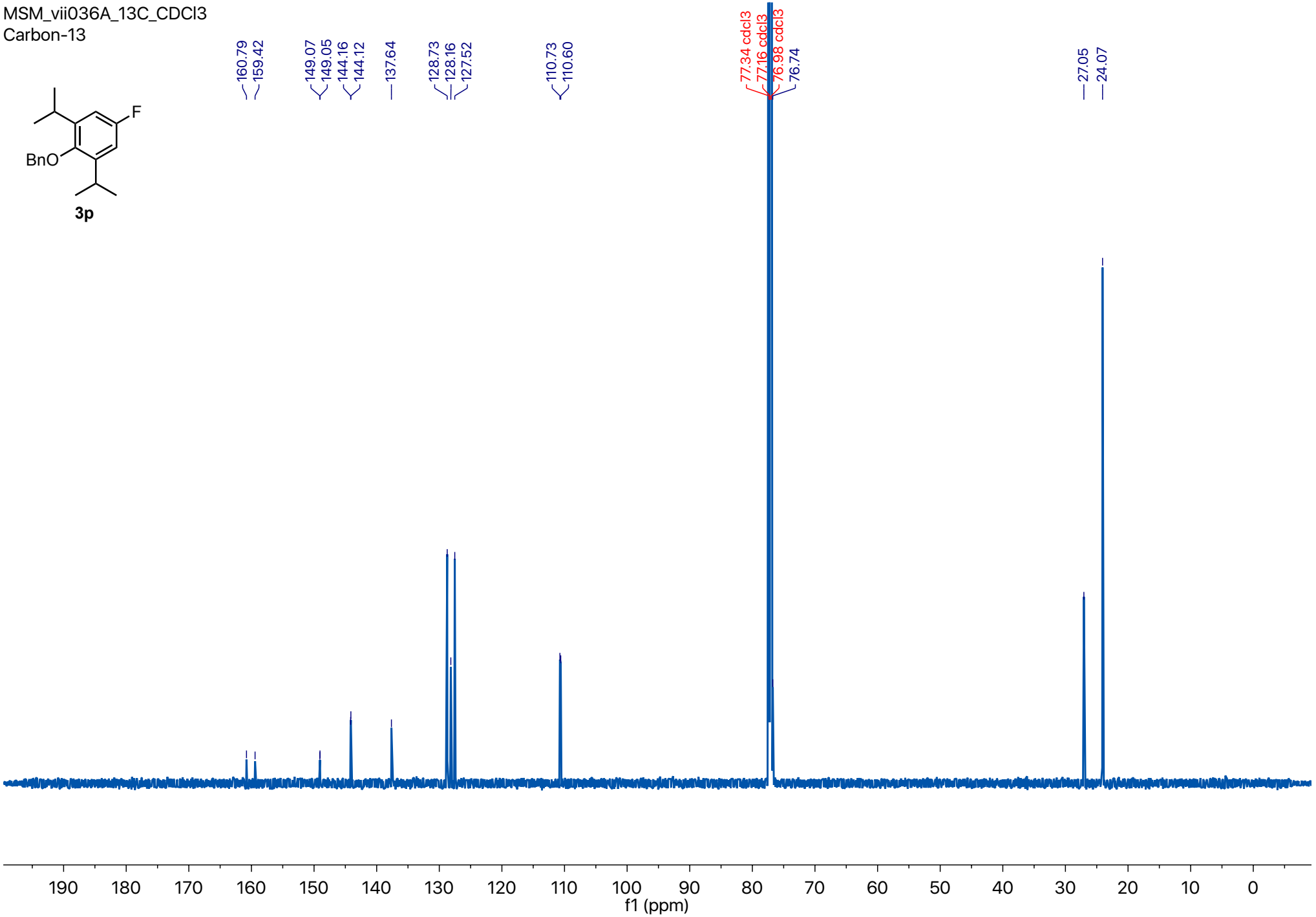
^{1}H NMR (401 MHz, $CDCl_3$)

MSM_vii036A_1H_CDCl3
Proton Spectrum



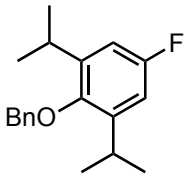
3p

^{13}C NMR (176 MHz, $CDCl_3$)



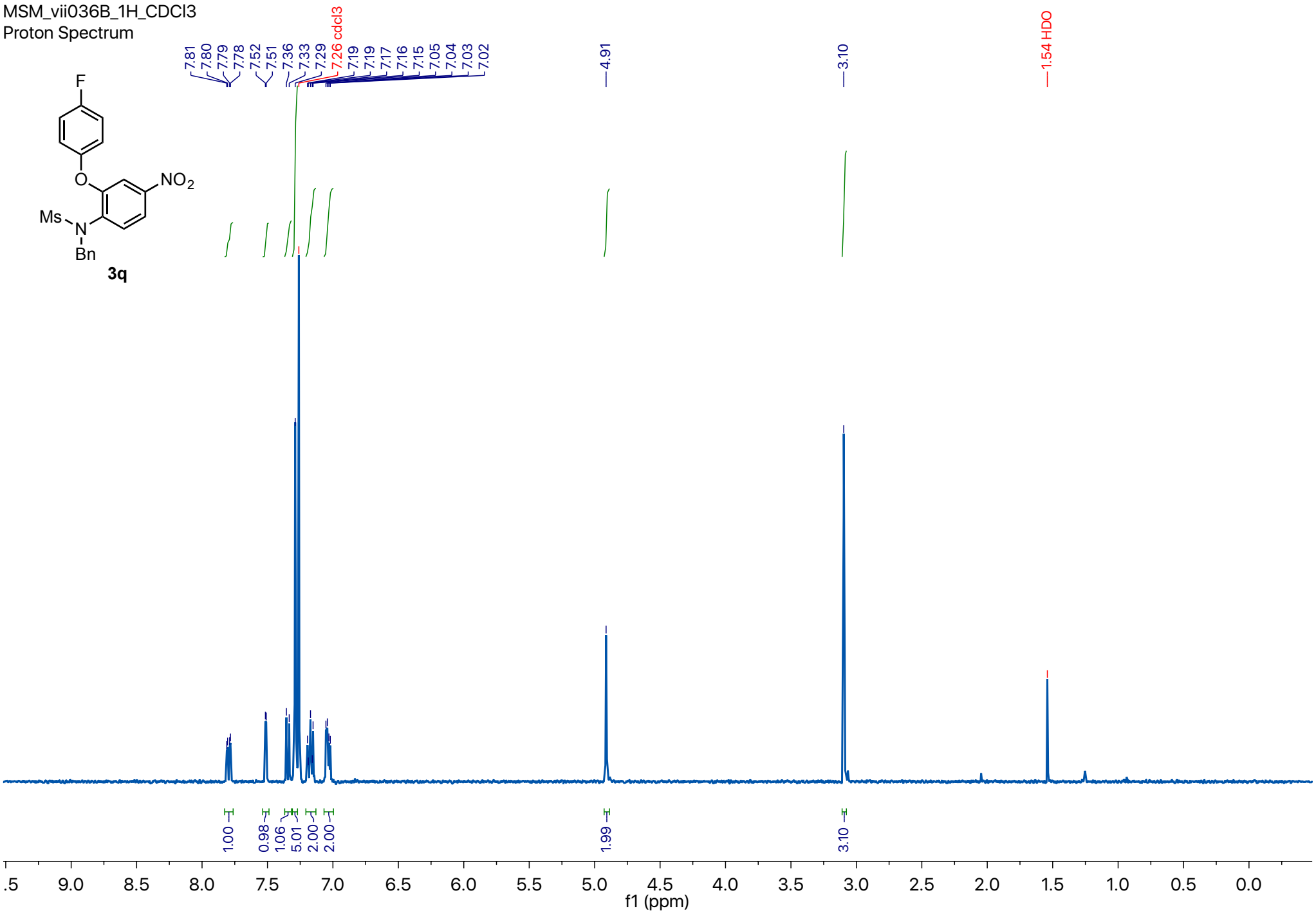
^{19}F NMR (377 MHz, $CDCl_3$)

MSM_vii036A_19F_CDCl3
STANDARD FLUORINE PARAMETERS

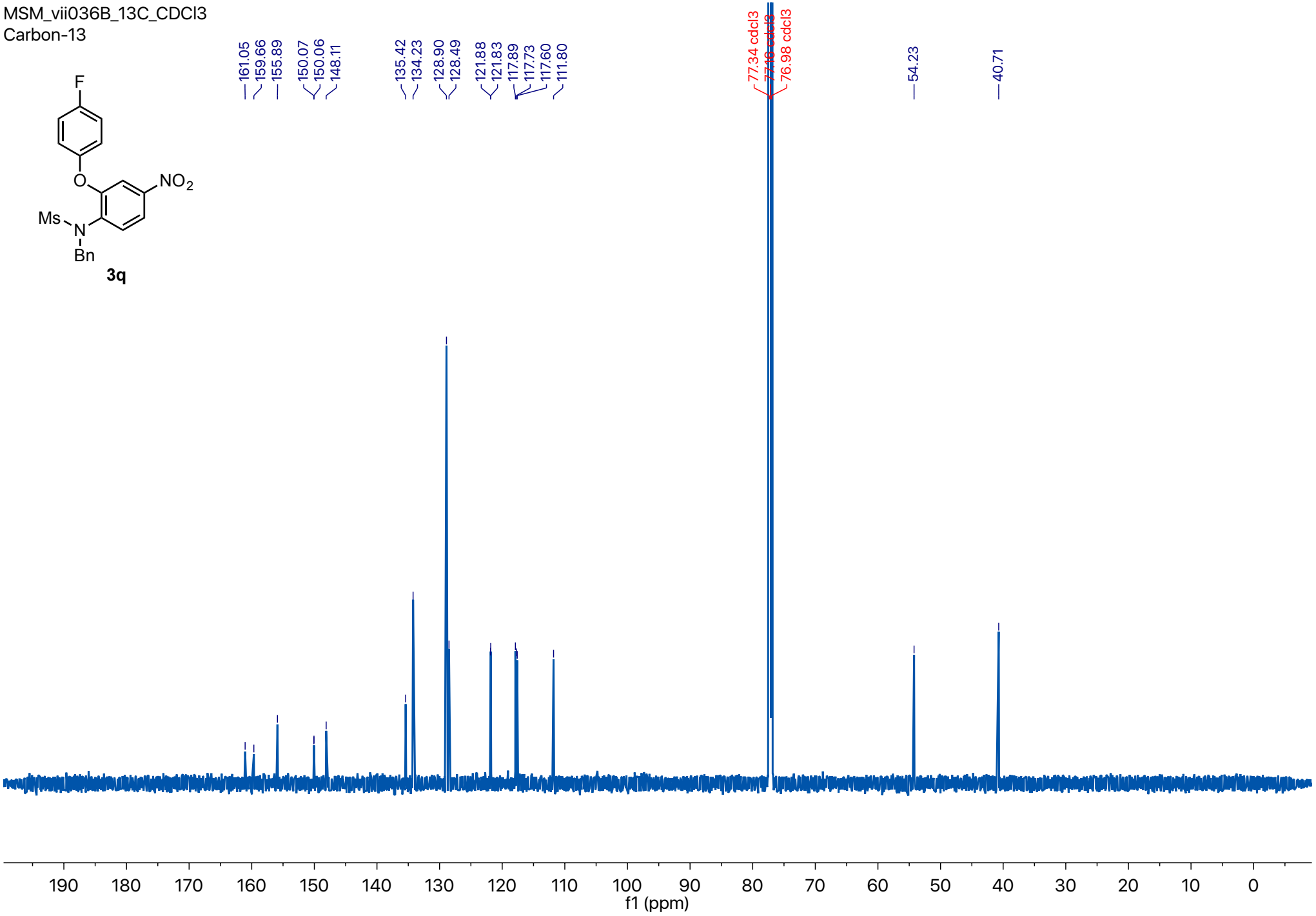


3p

^{1}H NMR (401 MHz, $CDCl_3$)



^{13}C NMR (176 MHz, $CDCl_3$)



^{19}F NMR (377 MHz, $CDCl_3$)