Supplementary Information for:

Convergent ^{18}F-Radiosynthesis: A New Dimension for Radiolabelling

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Table of Contents

1. Precursors and Reference Compounds

1.1 General Information

Unless otherwise stated, ^{1}H NMR spectra were recorded on Bruker DPX200, AV400, DPX400 or AVC500 spectrometers. ^{13}C NMR spectra were recorded on Bruker AV400 or AVC500 spectrometers fitted with a ^{13}C cryoprobe. ^{19}F NMR spectra were recorded on a Bruker AV400 spectrometer. ^{1}H and ^{13}C NMR spectra are reported as chemical shifts (δ) in parts per million (ppm) relative to the solvent peak using the Bruker internal referencing procedure (edlock). ^{19}F NMR spectra are referenced relative to $CFCl_3$ in $CDCl_3$. Scalar coupling constants (*J*) are reported in units of hertz (Hz).

High resolution mass spectra (HRMS, *m/z*) were recorded on a Bruker MicroTOF spectrometer using positive (ESI^+) or negative electrospray ionization (ESI^-).

Infrared spectra were recorded using a Bruker Tensor 27 FT-IR spectrometer either on NaCl discs as a thin film in a solution in dichloromethane or in a KBr pellet which is prepared by grinding the solid sample with solid KBr and applying great pressure to the dry mixture. Absorptions are reported in wavenumbers (cm^{-1}) and only peaks of interest are included.

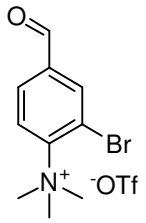
Melting points of solids were measured on either a Griffin or Phillip Harris apparatus and were uncorrected.

All reactions were performed in flame-dried apparatus with magnetic stirring under an inert atmosphere. All solvents were dried on a column of alumina prior to use. Flash column chromatography was performed over Merck silica gel C60 (40-60 μm) using eluent systems as described for each experiment.

The characterization data for Biginelli products **2a**[1] and **2c**[2] agreed with literature values.

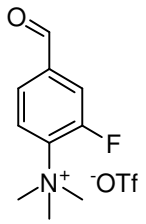
1.2 Experimental Procedures and Characterization Data

2-Bromo-4-formyl-*N*,*N*,*N*-trimethylanilinium trifluoromethanesulfonate (7b)



3-Bromo-4-(dimethylamino)benzaldehyde[3] (114 mg, 0.5 mmol) was dissolved in dichloromethane (8 mL). Methyl trifluoromethanesulfonate (62 μL, 0.55 mmol) was added and the reaction was stirred at room temperature overnight. The crude reaction mixture was concentrated at room temperature to a volume of 4 mL before being poured carefully into cold diethyl ether (20 mL). A precipitate appeared which was filtered and dried *in vacuo*. Recrystallization from dichloromethane/diethyl ether afforded the pure product as a light brown solid (71 mg, 0.18 mmol, 36% yield). **^{1}H NMR (500 MHz, $(CD_3)_2CO$)**: ppm 10.17 (s, 1 H), 8.51-8.54 (m, 2 H), 8.23-8.25 (m, 1 H), 4.21 (s, 9 H); **^{13}C NMR (100 MHz, $(CD_3)_2CO$)**: ppm 190.9, 147.8, 139.5, 138.2, 131.0, 128.4, 126.1, 115.6, 57.2; **HRMS** (ESI^+, *m/z*) $C_{10}H_{13}BrNO^+$ ($[M\text{-}OTf]^+$) *calc*. 242.0175, *found* 242.0177; **IR:** 3051, 2987, 2305, 1698, 1422; **m.p.**=176 °C (decomposition observed).

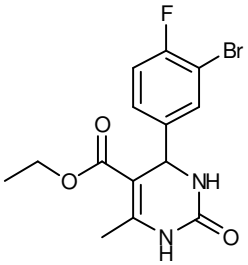
2-Fluoro-4-formyl-*N*,*N*,*N*-trimethylanilinium trifluoromethanesulfonate (7c)



3-Fluoro-4-(dimethylamino)benzaldehyde (334 mg, 2.0 mmol) was dissolved in dichloromethane (15 mL). Methyl trifluoromethanesulfonate (280 μL, 2.4 mmol) was added and the reaction mixture was stirred at room temperature overnight. The crude mixture was concentrated *in vacuo* at room temperature to a volume of 4 mL before being poured carefully into cold diethyl ether (20 mL). A precipitate appeared which was filtered and dried *in vacuo*. Recrystallization from dichloromethane/diethyl ether afforded the pure product as a pale yellow solid (172 mg, 0.52 mmol, 26% yield). **^{1}H**

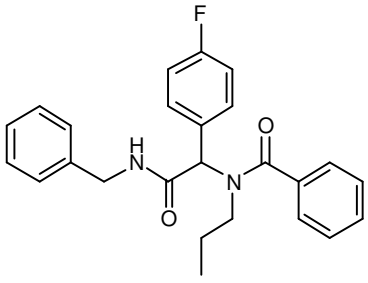
NMR (500 MHz, $(CD_3)_2CO$): ppm 10.18 (d, *J* = 1.9 Hz, 1 H), 8.41 (dd, *J* = 8.5, 8.2 Hz, 1 H), 8.09 (dd, *J* = 8.4, 1.6 Hz, 1 H), 8.09 (dd, *J* = 9.3, 1.4 Hz, 1 H), 4.08 (s, 9 H); **^{13}C NMR (125 MHz, $(CD_3)_2CO$)**: ppm 191.0, 156.4 (d, *J* = 253.7 Hz), 140.9 (d, *J* = 6.7 Hz), 138.3 (d, *J* = 6.7 Hz), 127.8 (d, *J* = 2.9 Hz), 125.2, 122.3 (q, *J* = 322.3 Hz), 119.4 (d, *J* = 22.9 Hz), 57.6 (d, *J* = 5.7 Hz); **^{19}F NMR (377 MHz, $(CD_3)_2CO$)**: ppm -110.4, -78.9; **HRMS** (ESI^+, *m/z*) $C_{10}H_{13}FNO^+$ ($[M\text{-}OTf]^+$) *calc*.182.0976, *found* 182.0982; **IR:** 3056, 2988, 2306, 1707, 1594, 1500, 1435; **m.p.**=58 °C (decomposition observed).

Ethyl 4-(3-bromo-4-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2b)



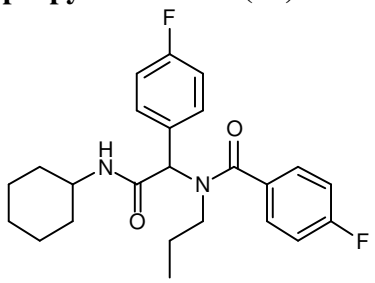
3-Bromo-4-fluorobenzaldehyde (101 mg, 0.5 mmol) was added to ethyl acetoacetate (96 µL, 0.75 mmol), urea (30 mg, 0.5 mmol) and ytterbium(III) trifluoromethanesulfonate (31 mg, 10 mol%) in acetonitrile (0.5 mL). The vial was sealed and the reaction mixture was stirred at 100°C for 5 hours. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (50% ethyl acetate in hexane, R_f=0.2) to give the pure product as a white solid (160 mg, 0.45 mmol, 90% yield). **^{1}H NMR (400 MHz, $(CD_3)_2SO$)**: ppm 9.31 (br. s., 1 H), 7.80 (br. s., 1 H), 7.49 (dd, *J* = 6.7, 2.1 Hz, 1 H), 7.35 (dd, *J* = 8.8, 8.6 Hz, 1 H), 7.26 (ddd, *J* = 8.6, 4.8, 2.3 Hz, 1 H), 5.15 (d, *J* = 3.3 Hz, 1 H), 3.92-4.06 (m, 2 H), 2.25 (s, 3 H), 1.09 (t, *J* = 7.1 Hz, 3 H); **^{13}C NMR (125 MHz, $(CD_3)_2SO$)**: ppm 165.1, 157.4 (d, *J* = 244.1 Hz), 151.8, 149.1, 143.0 (d, *J* = 3.8 Hz), 131.3, 127.6 (d, *J* = 7.6 Hz), 116.9 (d, *J* = 22.9 Hz), 107.6 (d, *J* = 21.0 Hz), 98.5, 59.3, 53.1, 17.8, 14.0; **^{19}F NMR (377 MHz, $CDCl_3$)**: ppm -110.4; **HRMS** (ESI^+, *m/z*) $C_{14}H_{15}BrFN_2O_3^+$ ($[M+H]^+$) *calc.* 357.0245, *found* 357.0245; **IR**: 3055, 2987, 2306, 1703, 1422; **m.p.** = 194 °C.

***N*-[2-(Benzylamino)-1-(4-fluorophenyl)-2-oxoethyl]-*N*-propylbenzamide (3a)**



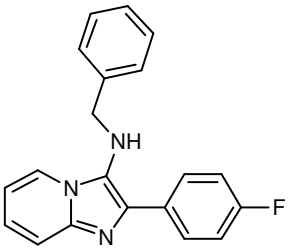
4-Fluorobenzaldehyde (54 µL, 0.5 mmol), benzyl isocyanide (66 µL, 0.5 mmol), 1-propylamine (41 µL, 0.5 mmol) and benzoic acid (61 mg, 0.5 mmol) were mixed in ethanol (1 ml) and stirred for 48 hours at room temperature. After removal of solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (33% ethyl acetate in hexane, R_f=0.3) to give the pure product as a white solid (138 mg, 0.36 mmol, 78% yield). **^{1}H NMR (200MHz, $CDCl_3$)**: ppm 6.98-7.58 (m, 14 H), 6.61 (br. s, 1 H), 5.71 (br. s, 1 H), 4.52 (d, *J* = 5.9 Hz, 2 H), 3.15-3.38 (m, 2 H), 0.90-1.55 (m, 2 H), 0.49-0.56 (m, 3 H); **^{13}C NMR (125MHz, $CDCl_3$)**: ppm 172.8, 169.5, 162.6 (d, *J* = 248.0 Hz), 137.9, 136.3, 131.1 (d, *J* = 4.0 Hz), 130.9 (d, *J* = 7.6 Hz), 129.7, 128.6, 128.5, 127.7, 127.5, 126.5, 115.8 (d, *J* = 21.0 Hz), 62.9, 50.8, 43.7, 22.7, 11.0; **^{19}F NMR (377 MHz, $CDCl_3$)**: ppm -113.0; **HRMS** (ESI^+, *m/z*) $C_{25}H_{25}FN_2NaO_2^+$ ($[M+Na]^+$) *calc*. 427.1792, *found* 427.1780; **IR:** 3055, 2986, 2306, 1682, 1628, 1510, 1421; **m.p.** = 142 °C.

_N_-[2-(Cyclohexylamino)-1-(4-fluorophenyl)-2-oxoethyl]-4-fluoro-_N_-propylbenzamide (3b)



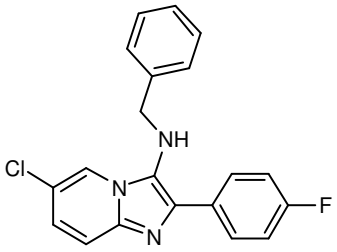
4-Fluorobenzaldehyde (54 µL, 0.5 mmol), cyclohexyl isocyanide (62 µL, 0.5 mmol), 1-propylamine (41 µL, 0.5 mmol) and 4-fluorobenzoic acid (70 mg, 0.5 mmol) were mixed in ethanol (1 mL) and stirred for 48 hours at room temperature. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (50% ethyl acetate in hexane, R_f=0.5) to give the pure product as a white solid (124 mg, 0.30 mmol, 61% yield). **^{1}H NMR (500 MHz, $CDCl_3$)**: ppm 7.45 (dd, *J* = 8.5, 5.4 Hz, 4 H), 7.10 (dt, *J* = 11.0, 8.7 Hz, 4 H), 6.17 (br. s, 1 H), 5.64 (br. s, 1 H), 3.78-3.92 (m, 1 H), 3.24 (dd, *J* = 10.1, 5.4 Hz, 2 H), 1.87-2.01 (m, 2 H), 1.70 (td, *J* = 8.4, 3.9 Hz, 2 H), 1.61 (dd, *J* = 9.0, 3.9 Hz, 1 H), 1.33-1.46 (m, 3 H), 1.03-1.23 (m, 4 H), 0.57 (br. s, 3 H); **^{13}C NMR (125 MHz, $CDCl_3$)**: ppm 171.9, 168.5, 163.3 (d, *J* = 249.8 Hz), 162.6 (d, *J* = 248.9 Hz), 132.5 (d, *J* = 2.9 Hz), 131.3 (d, *J* = 2.9 Hz), 130.9 (d, *J* = 7.6 Hz), 128.8 (d, *J* = 7.6 Hz), 115.8 (d, *J* = 21.0 Hz), 115.7 (d, *J* = 21.0 Hz), 63.0, 51.8, 48.6, 32.8, 25.4, 24.7, 24.6, 22.6, 11.1; **^{19}F NMR (377 MHz, $CDCl_3$)**: ppm -113.0, -110.1; **HRMS** (ESI^+, *m/z*) $C_{24}H_{28}F_2N_2NaO_2^+$ ($[M+Na]^+$) *calc*. 437.2011, *found* 437.2001; **IR:** 3055, 2987, 2306, 1422; **m.p.** = 184 °C.

N-Benzyl-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridin-3-amine (4a)



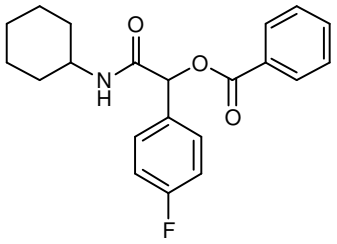
Benzyl isocyanide (70 µL, 0.58 mmol) was added to a solution of 4-fluorobenzaldehyde (81 µL, 0.75 mmol) and 2-aminopyridine (47 mg, 0.5 mmol) in methanol (1 mL). Scandium(III) trifluoromethanesulfonate (12 mg, 25 µmol, 5 mol%) was then added and the reaction was stirred at room temperature for 24 hours. The mixture was diluted with dichloromethane (5 mL) and quenched with water (5 mL). The layers were separated and the organic fraction was washed with saturated aqueous glutamic acid solution (5 mL, pH 10) and brine (5 mL). After drying over anhydrous sodium sulfate and filtration, the solvents were removed *in vacuo*. Recrystallization from dichloromethane/hexane afforded the product as an orange/brown solid (116 mg, 0.37 mmol, 73% yield). **^{1}H NMR (400 MHz, $CDCl_3$)**: ppm 7.94-7.99 (m, 3 H), 7.54-7.57 (m, 1 H), 7.27-7.36 (m, 5 H), 7.10-7.17 (m, 3 H), 6.76 (m, 1 H), 4.19 (d, *J* = 6.1 Hz, 2 H), 3.43 (t, *J* = 6.1 Hz, 1 H); **^{13}C NMR (125 MHz, $CDCl_3$)**: ppm 162.3 (d, *J* = 247.0 Hz), 141.1, 138.8, 134.8, 129.6 (d, *J* = 2.9 Hz), 128.8, 128.7, 128.1, 127.7, 125.2, 124.7, 122.4, 117.0, 115.6 (d, *J* = 21.0 Hz), 112.1, 52.3; **^{19}F NMR (377 MHz, $CDCl_3$)**: ppm -114.5; **HRMS** (ESI^+, *m/z*) $C_{20}H_{17}FN_3^+$ ($[M+H]^+$) *calc.* 318.1401, *found* 318.1400; **IR:** 3054, 2987, 2306, 1422; **m.p.** = 109 ºC.

N-Benzyl-6-chloro-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridin-3-amine (4b)



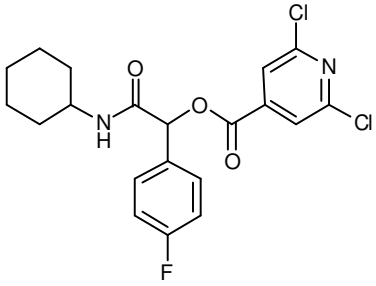
Benzyl isocyanide (70 µL, 0.58 mmol) was added to a solution of 4-fluorobenzaldehyde (81 µL, 0.75 mmol) and 2-amino-5-chloropyridine (64 mg, 0.5 mmol) in methanol (1 mL). Scandium(III) trifluoromethane-sulfonate (12 mg, 25 µmol, 5 mol%) was then added and the reaction was stirred at room temperature for 24 hours. The mixture was diluted with dichloromethane (5 mL) and quenched with water (5 mL). The layers were separated and the organic fraction was washed with saturated glutamic acid solution (5 mL, pH 10) and brine (5 mL). After drying over anhydrous sodium sulfate and filtration, the solvents were removed *in vacuo*. Recrystallization from dichloromethane/hexane afforded the product as a pale yellow solid (112 mg, 0.32 mmol, 62% yield). **^{1}H NMR (400 MHz, $CDCl_3$)**: ppm 7.89-7.96 (m, 3 H), 7.45-7.48 (m, 1 H), 7.27-7.36 (m, 5 H), 7.06-7.16 (m, 3 H), 4.17 (d, *J* = 5.8 Hz, 2 H), 3.47 (t, *J* = 5.8 Hz, 1 H); **^{13}C NMR (125 MHz, $CDCl_3$)**: ppm 162.4 (d, *J* = 247.0 Hz), 139.6, 138.5, 136.5, 129.6 (d, *J* = 2.9 Hz), 128.8, 128.7, 128.2, 127.9, 125.7, 125.6, 120.4, 120.4, 117.6, 115.6 (d, *J* = 21.9 Hz), 52.4; **^{19}F NMR (377 MHz, $CDCl_3$)**: ppm -113.9; **HRMS** (ESI^+, *m/z*) $C_{20}H_{15}ClFN_3Na^+$ ($[M+Na]^+$) *calc.* 374.0831, *found* 374.0830; **IR**: 3055, 2983, 2333, 1422; **m.p.** = 178 ºC.

2-(Cyclohexylamino)-1-(4-fluorophenyl)-2-oxoethyl benzoate (5a)



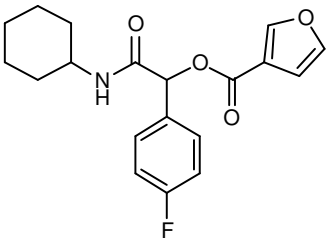
4-Fluorobenzaldehyde (107 µL, 1.0 mmol), benzoic acid (146 mg, 1.2 mmol) and cyclohexyl isocyanide (124 µL, 1.0 mmol) were added to an aqueous solution of LiCl (4M, 5 mL). The mixture was stirred at room temperature for 8 hours. Dichloromethane was added (20 mL) and the layers were separated. The aqueous phase was washed with dichloromethane (10 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. Flash column chromatography on silica gel (20% ethyl acetate in hexane, R_f=0.3) afforded the pure product as a white solid (350 mg, 0.98 mmol, 98% yield). **^{1}H NMR (400 MHz, $CDCl_3$)**: ppm 8.09 (dd, *J* = 8.6, 1.3 Hz, 2 H), 7.60-7.66 (m, 1 H), 7.46-7.55 (m, 4 H), 7.07 (t, *J* = 8.7 Hz, 2 H), 6.29 (s, 1 H), 6.14 (d, *J* = 8.1 Hz, 1 H), 3.77-3.89 (m, 1 H), 1.86-1.99 (m, 2 H), 1.57-1.76 (m, 3 H), 1.30-1.43 (m, 2 H), 1.08-1.26 (m, 3 H); **^{13}C NMR (100 MHz, $CDCl_3$)**: ppm 167.2, 164.8, 163.0 (d, *J* = 248.0 Hz), 133.7, 131.7 (d, *J* = 2.9 Hz), 129.8, 129.3 (d, *J* = 8.6 Hz), 129.1, 128.7, 115.6 (d, *J* = 21.9 Hz), 75.1, 48.3, 33.0, 32.8, 25.4, 24.7, 24.7; **^{19}F NMR (377 MHz, $CDCl_3$)**: ppm -112.5; **HRMS** (ESI^+, *m/z*) $C_{21}H_{22}FNNaO_3^+$ ($[M+Na]^+$) *calc.*378.1476, *found* 378.1471; **IR**: 3267, 3099, 2993, 1724, 1654, 1117; **m.p.** = 190 °C.

2-(Cyclohexylamino)-1-(4-fluorophenyl)-2-oxoethyl 2,6-dichloroisonicotinate (5b)



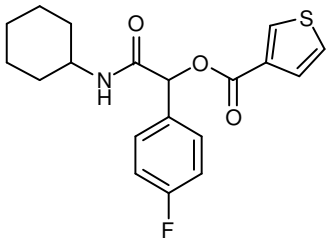
4-Fluorobenzaldehyde (107 µL, 1.0 mmol), 2,4-dichloropyridin-4-carboxylic acid (230 mg, 1.2 mmol) and cyclohexyl isocyanide (124 µL, 1.0 mmol) were added to an aqueous solution of LiCl (4M, 5 mL). The mixture was stirred at room temperature for 8 hours. Dichloromethane was added (20 mL) and the layers were separated. The aqueous phase was washed with dichloromethane (10 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. Flash column chromatography on silica gel (20% ethyl acetate in hexane, R_f=0.3) afforded the product as a white solid (270 mg, 0.63 mmol, 63% yield). **^{1}H NMR (500 MHz, $CDCl_3$)**: ppm 8.22 (d, *J* = 8.2 Hz, 1 H), 7.49 (dd, *J* = 8.7, 5.2 Hz, 2 H), 7.39 (d, *J* = 8.2 Hz, 1 H), 7.08 (t, *J* = 8.7 Hz, 2 H), 6.37 (d, *J* = 7.9 Hz, 1 H), 6.25 (s, 1 H), 3.73-3.89 (m, 1 H), 1.88-1.98 (m, 2 H), 1.70 (td, *J* = 8.0, 3.8 Hz, 2 H), 1.62 (ddd, *J* = 12.8, 3.6, 3.5 Hz, 1 H), 1.31-1.42 (m, 2 H), 1.10-1.24 (m, 3 H); **^{13}C NMR (125 MHz, $CDCl_3$)**: ppm 166.4, 163.2 (d, *J* = 248.9 Hz), 162.2 , 153.6, 149.0, 143.5, 130.9 (d, *J* = 3.8 Hz), 129.7 (d, *J* = 8.6 Hz), 124.6, 123.3, 115.9 (d, *J* = 21.9 Hz), 76.6, 48.5, 32.9, 32.8, 25.3, 24.6; **^{19}F NMR (377 MHz, $CDCl_3$)**: ppm -111.6; **HRMS** (ESI^+, *m/z*) $C_{20}H_{19}Cl_2FN_2NaO_3^+$ ($[M+Na]^+$) *calc.* 447.0649, *found* 447.0643; **IR**: 3253, 3090, 1744, 1650, 1139, 1054; **m.p.** = 174 °C.

2-(Cyclohexylamino)-1-(4-fluorophenyl)-2-oxoethyl 3-furoate (5c)



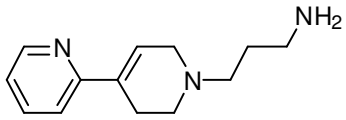
4-Fluorobenzaldehyde (107 µL, 1.0 mmol), 3-furoic acid (134 mg, 1.2 mmol) and cyclohexyl isocyanide (124 µL, 1.0 mmol) were added to an aqueous solution of LiCl (4M, 5 mL). The mixture was stirred at room temperature for 8 hours. Dichloromethane was added (20 mL) and the layers were separated. The aqueous phase was washed with dichloromethane (10 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. Flash column chromatography on silica gel (20% ethyl acetate in hexane, R_f=0.4) afforded the product as a white solid (300 mg, 0.88 mmol, 88% yield). **^{1}H NMR (400 MHz, $CDCl_3$)**: ppm 8.11 (m, 1 H), 7.44-7.49 (m, 3 H), 7.03-7.08 (m, 2 H), 6.70-6.78 (m, 1 H), 6.20 (d, *J* = 8.1 Hz, 1 H), 3.76-3.86 (m, 1 H), 1.84-1.98 (m, 2 H), 1.56-1.74 (m, 3 H), 1.30-1.41 (m, 2 H), 1.11-1.22 (m, 3 H); **^{13}C NMR (125 MHz, $CDCl_3$)**: ppm 167.0, 163.0 (d, *J* = 248.0 Hz), 162.0, 161.2, 148.2, 144.2, 131.5 (d, *J* = 3.8 Hz), 129.3 (d, *J* = 8.6 Hz), 118.4, 115.7 (d, *J* = 21.0 Hz), 109.7, 74.6, 48.3, 32.9, 32.8, 25.4, 24.7, 24.6; **^{19}F NMR (377 MHz, $CDCl_3$)**: ppm -112.4; **HRMS** (ESI^+, *m/z*) $C_{19}H_{20}FNNaO_4^+$ ($[M+Na]^+$) *calc.* 368.1269, *found* 368.1264; **IR**: 3161, 2998, 1478, 1046, 991; **m.p.** = 168 °C.

2-(Cyclohexylamino)-1-(4-fluorophenyl)-2-oxoethyl thiophene-3-carboxylate (5d)



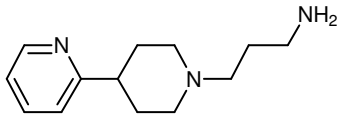
4-Fluorobenzaldehyde (107 µL, 1.0 mmol), thiophene-3-carboxylic acid (146 mg, 1.2 mmol) and cyclohexyl isocyanide (124 µL, 1.0 mmol) were added to an aqueous solution of LiCl (4M, 5 mL). The mixture was stirred at room temperature for 8 hours. Dichloromethane was added (20 mL) and the layers were separated. The aqueous phase was washed with dichloromethane (10 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. Flash column chromatography on silica gel (30% ethyl acetate in hexane, R_f=0.5) afforded the product as a white solid (250 mg, 0.70 mmol, 70% yield). **^{1}H NMR (400 MHz, $CDCl_3$)**: ppm 8.19-8.23 (m, 1 H), 7.57 (dt, *J* = 5.1, 1.3 Hz, 1 H), 7.49 (dd, *J* = 8.2, 5.4 Hz, 2 H), 7.34-7.40 (m, 1 H), 7.07 (t, *J* = 8.3 Hz, 2 H), 6.23 (s, 1 H), 6.08 (d, *J* = 7.8 Hz, 1 H), 3.77-3.89 (m, 1 H), 1.87-1.99 (m, 2 H), 1.57-1.75 (m, 3 H), 1.31-1.43 (m, 2 H), 1.09-1.27 ppm (m, 3 H); **^{13}C NMR (125 MHz, $CDCl_3$)**: ppm 167.1, 163.0 (d, *J* = 247.9 Hz), 160.8, 133.7, 132.4, 131.6 (d, *J* = 3.8 Hz), 129.4 (d, *J* = 7.6 Hz), 127.7, 126.7, 115.7 (d, *J* = 21.9 Hz), 74.9, 48.2, 33.0, 32.8, 25.4, 24.7, 24.6; **^{19}F NMR (377 MHz, $CDCl_3$)**: ppm -112.5; **HRMS** (ESI$^+$, *m/z*) $C_{19}H_{20}FNNaO_3S^+$ ([M+Na]$^+$) *calc.* 384.1040, *f*ound 384.1035; **IR**: 3269, 3091, 1715, 1654, 1158; **m.p.** = 179 °C.

3-(3',6'-Dihydro-2,4'-bipyridin-1'(2'*H*)-yl)propan-1-amine (11)



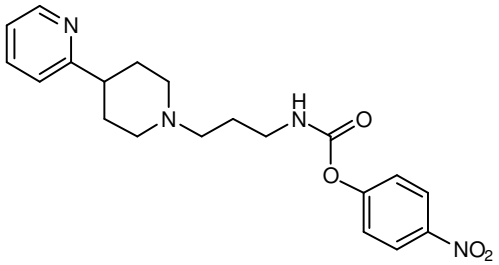
1-(3-Aminopropyl)-2,4'-bipyridinium bromide monohydrobromide[4] (344 mg, 1 mmol) was dissolved in methanol (4 mL) and coolled to 0 °C. Sodium borohydride (151 mg, 4 mmol) was added carefully. The reaction mixture was stirred for 2 hours at 0 °C before being allowed to warm to room temperature overnight. The solvent was removed *in vacuo* and the crude residue was dissolved in diethyl ether (30 mL). After washing with 20% NaOH(aq., 15 mL), the aqueous phase was extracted with diethyl ether (2×30 mL). The combined organic fractions were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford the crude product as a yellow oil. Flash column chromatography on silica gel (10% methanol in dichloromethane with 1% ammonia, R_f=0.2) afforded the pure product as a pale yellow oil (135 mg, 0.68 mmol, 68% yield). **^{1}H NMR (500 MHz, $CDCl_3$)**: ppm 8.56 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1 H), 7.63 (td, *J* = 7.7, 1.9 Hz, 1 H), 7.38 (d, *J* = 10.1 Hz, 1 H), 7.13 (ddd, *J* = 7.5, 4.8, 0.9 Hz, 1 H), 6.64 (ddd, *J* = 3.4, 2.0, 1.8 Hz, 1 H), 3.23 (dd, *J* = 6.3, 2.8 Hz, 2 H), 2.82 (t, *J* = 6.8 Hz, 2 H), 2.73-2.76 (m, 2 H), 2.69-2.71 (m, 2 H), 2.57 (t, *J* = 7.2 Hz, 2 H), 1.71-1.81 (m, 4 H); **^{13}C NMR (125 MHz, $CDCl_3$)**: ppm 157.4, 148.9, 136.3, 135.0, 125.4, 121.8, 119.0, 56.3, 53.4, 50.3, 40.8, 30.4, 26.7; **HRMS** (ESI$^+$, *m/z*) $C_{13}H_{20}N_3^+$ ([M+H]$^+$) *calc*. 218.1652, *found* 218.1655; **IR**: 3385, 2909, 1641, 1632, 1469, 1433, 1384.

3-[4-(Pyridin-2-yl)piperidin-1-yl]propan-1-amine (12)



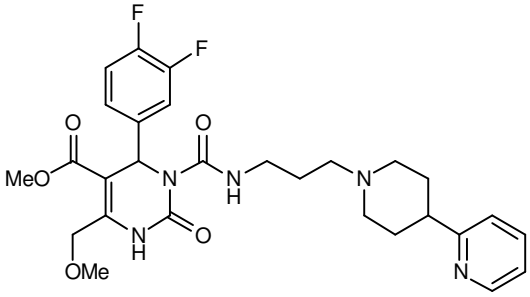
11 (360 mg, 1.8 mmol) and palladium on carbon (36 mg, 10% wt loading) were dissolved in methanol (5 mL). The reaction was purged with hydrogen and stirred overnight at room temperature. The reaction mixture was filtered through Celite® and concentrated *in vacuo*. Flash column chromatography on silica gel (10% methanol in dichloromethane with 1% ammonia, R_f=0.2) afforded the pure product as a pale yellow oil (251 mg, 1.2 mmol, 69% yield). **^{1}H NMR (400 MHz, $CDCl_3$)**: ppm 8.50 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1 H), 7.61 (td, *J* = 7.7, 1.8 Hz, 1 H), 7.18 (dt, *J* = 7.8, 0.9 Hz, 1 H), 7.11 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1 H), 3.04-3.11 (m, 2 H), 2.76 (t, *J* = 6.8 Hz, 2 H), 2.66-2.74 (m, 1 H), 2.43 (t, *J* = 7.2 Hz, 2 H), 2.05 (td, *J* = 11.9, 2.5 Hz, 2 H), 1.90-1.98 (m, 2 H), 1.84 (td, *J* = 12.3, 3.2 Hz, 2 H), 1.68 (tt, *J* = 7.2, 6.8 Hz, 2 H); **^{13}C NMR (125 MHz, $CDCl_3$)**: ppm 165.1, 149.1, 136.4, 121.2, 120.6, 56.8, 54.2, 44.67, 41.0, 32.0, 30.6; **HRMS** (ESI^+, *m/z*) $C_{13}H_{22}N_3^+$ ($[M+H]^+$) *calc*. 220.1808, *found* 220.1810; **IR**: 3357, 2939, 1592, 1474, 1435, 1215, 1125.

4-Nitrophenyl {3-[4-(pyridin-2-yl)piperidin-1-yl]propyl}carbamate (9)



12 (185 mg, 0.84. mmol) was dissolved in dichloromethane (20 mL) and cooled to 0°C. After addition of sodium hydride (60% dispersion in mineral oil, 41 mg, 1 mmol), the mixture was stirred for 1 hour at 0°C. 4-Nitrophenyl chloroformate (205 mg, 1 mmol) was then carefully added and the reaction was stirred for another 1 hour at 0°C. The reaction mixture was filtered through Celite® and concentrated *in vacuo* at room temperature to a volume of 3 mL. The concentrated mixture was then added dropwise to cold diethyl ether (25 mL). A white precipitate was formed which was filtered and washed with diethyl ether. The crude product was dried under vacuum and used directly in the next step without further purification.

Methyl 4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-3-({3-[4-(pyridin-2-yl)piperidin-1-yl]propyl}carbamoyl)-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (10)



Methyl 4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate[4] (62 mg, 0.2 mmol) was dissolved in acetonitrile (1 mL). **9** (77 mg, 0.2 mmol) and potassium carbonate (83 mg, 0.6 mmol) were added and the reaction mixture was stirred for 24 hours at 60°C. After removal of the solvent *in*

vacuo, flash column chromatography column on silica gel (10% methanol in dichloromethane, R_f=0.2) afforded the pure product as a yellow oil (35 mg, 0.06 mmol, 32% yield over two steps); **^{1}H NMR (500 MHz, $CDCl_3$)**: ppm 8.88 (t, *J* = 5.4 Hz, 1 H), 8.52 (dd, *J* = 4.7, 0.9 Hz, 1 H), 7.71 (br. s, 1 H), 7.61 (td, *J* = 7.7, 1.9 Hz, 1 H), 7.16-7.21 (m, 2 H,), 7.05-7.12 (m, 3 H), 6.68 (s, 1 H), 4.68 (s, 2 H), 3.71 (s, 3 H), 3.48 (s, 3 H), 3.41 (qd, *J* = 13.0, 6.6 Hz, 1 H), 3.32 (qd, *J* = 13.0, 6.6 Hz, 1 H), 3.05 (d, *J* = 9.8, 2 H), 2.66-2.76 (m, 1 H), 2.44 (t, *J* = 6.3, 2 H), 2.10 (m, 2 H), 1.83-2.00 (m, 4 H), 1.78 (m, 2 H); **^{13}C NMR (125 MHz, $CDCl_3$)**: ppm 164.9, 164.6, 153.1, 152.3, 150.2 (dd, *J* = 248.9, 12.4 Hz), 149.1, 149.0 (dd, *J* = 248.9, 12.4 Hz), 146.3, 137.5 (t, *J* = 4.3 Hz), 136.5, 123.0 (dd, *J* = 6.7, 3.8 Hz), 121.3, 120.6, 117.3 (d, *J* = 11.2 Hz), 116.1 (d, *J* = 18.1 Hz), 101.3, 68.1, 59.2, 56.1, 54.0, 52.9, 51.7, 44.4, 39.2, 31.7, 26.6; **^{19}F NMR (377 MHz, $CDCl_3$)**: ppm -138.4, -136.8; **HRMS** (ESI^+, *m/z*) $C_{28}H_{34}F_2N_5O_5^+$ ($[M+H]^+$) *calc*. 558.2523, *found* 558.2531; **IR**: 3316, 2941, 1714, 1648, 1518, 1436, 1395.

2. Radiochemistry

2.1 General Information

Radiolabelling experiments was performed in a customized automated radiochemical apparatus purchased from SCINTOMICS and controlled by Scintomics Control Center version 5.03.053.

[^{18}F]Fluoride was produced at the cyclotron of PETNET Solutions at Mont Vernon Hospital (UK) *via* the ^{18}O(p,n)^{18}F reaction (1-2 GBq, 1-5 mL). [^{18}F]Fluoride was separated from ^{18}O-enriched-water using anion exchange cartridges supplied by Synthra (^{18}F-Separation, 45 mg, activated by water (3 mL)) and eluted with a solution of Kryptofix® 222 (15 mg) and potassium carbonate (3 mg) in acetonitrile/water (4:1, 1 mL). The complex was dried under a gentle stream of nitrogen at 120 ^{o}C with successive addition of acetonitrile (3×0.5 mL). The resulting K^{18}F/Kryptofix® 222 complex was dissolved in an anhydrous solvent for use in nucleophilic radiofluorination reactions.

Solid-Phase-Extraction (SPE) was performed on C-18 Sep-Pak cartridges which were purchased from the Waters Corporation and activated by washing with methanol (2 mL) followed by water (2×5 mL). The crude reaction mixture was diluted with water (10-15 times volume) and loaded on a C-18 Sep-Pak cartridge. A further 3 mL of water was passed through and the cartridge was then dried under a gentle stream of nitrogen for 5 minutes. The purified ^{18}F-labeled prosthetic group was eluted from the cartridge with an organic solvent and dispensed into vials for use in 'hot' multicomponent reactions.

Microwave assisted reactions were performed in the cavity of a Model 521 microwave instrument supplied by Resonance Instruments, Inc. with infrared temperature control. Radio-TLC was conducted using Merck silica plates on a Mini-Scan TLC scanner system supplied by LabLogic Systems Ltd. All quoted radiochemical yields (RCYs) are decay corrected.

^{18}F-labeled compounds were identified by comparison of their radioactive HPLC peaks with the UV traces of their non-radioactive reference compounds. Radio-HPLC was conducted on a Gilson HPLC instrument with a NaI-radiodetecter fitted. Unless otherwise stated, the HPLC separations were carried out on a Phenomenex NX 5u C18 column (150×4.60 mm) at room temperature using acetonitrile/water as the mobile phase. The flowing gradients were applied at a flow rate of 1 mL/min:

Gradient A: start with and hold at 10% acetonitrile for 1 minute, linear increase to 30% acetonitrile in 3 minutes, then hold for next 9 minutes before increase to 75% acetonitrile in next 2 minutes, holds for 2 minutes before decrease to 10% acetonitrile.

Gradient B: start with and hold at 10% acetonitrile for 1 minute, linear increase to 45% acetonitrile in 3 minutes, then increase to 55% acetonitrile in next 12 minutes, to 75% acetonitrile in next 3 minutes and hold for 3 minutes before decrease to 10% acetonitrile.

Gradient C: start with and hold at 10% acetonitrile for 1 minute, linear increase to 40% acetonitrile in 3 minutes, then increase to 50% acetonitrile in next 12 minutes, to 75% acetonitrile in next 3 minutes and hold for 3 minutes before decrease to 10% acetonitrile.

Gradient D: start with and hold at 10% acetonitrile for 1 minute, linear increase to 30% acetonitrile in 3 minutes and hold for 6 minutes, then increase to 55% acetonitrile in next 6 minutes and hold for 3 minutes before decrease to 10% acetonitrile.

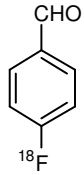
Gradient E: linear increase from 35% acetonitrile to 40% acetonitrile in 10 minutes, then increase to 75% acetonitrile in next 5 minutes, and hold for 15 minutes before decrease to 35% acetonitrile.

Gradient F: linear increase from 5% acetonitrile to 95% acetonitrile in 10 minutes, then hold for next 5 minutes before decrease to 5% acetonitrile.

2.2 Experimental Procedures

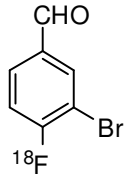
^{18}F-Labeled Prosthetic Groups

4-[^{18}F]Fluorobenzaldehyde ([^{18}F]1a)[5]



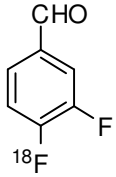
$K^{18}F$/Kryptofix® 222 in dimethyl sulfoxide (0.5 mL) was added to a sealed reaction vial containing **7a** (10 mg) and heated under 50 W microwave irradiation for 100 seconds. The crude reaction mixture was diluted with water (10 mL). Analysis by HPLC ($MeCN/H_2O$ **Gradient A**, 1 mL/min, 20 µL injected) indicated the formation of [^{18}F]**1a** at a retention time of 12.2 min which was consistent with the non-radioactive 4-fluorobenzaldehyde. Analysis by radio-TLC (5% water in acetonitrile) indicated a radiochemical yield of 83% (*n*=3). Purification of [^{18}F]**1a** was achieved by solid-phase-extraction on a C-18 Sep-Pak cartridge in a solution of an organic solvent.

3-Bromo-4-[^{18}F]fluorobenzaldehyde ([^{18}F]1b)



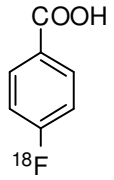
$K^{18}F$/Kryptofix® 222 in acetonitrile (0.3 mL) was added to a sealed reaction vial containing **7b** (10 mg) and heated at 100 °C for 10 minutes. The crude reaction mixture was diluted with water (6 mL). Analysis by HPLC ($MeCN/H_2O$ **Gradient B**, 1 mL/min, 20 µL injected) indicated the formation of [^{18}F]**1b** at a retention time of 10.9 min which was consistent with the non-radioactive 3-bromo-4-fluorobenzaldehyde. Analysis by radio-TLC (5% water in acetonitrile) indicated a radiochemical yield of 90%. Purification of [^{18}F]**1b** was achieved by solid-phase-extraction on a C-18 Sep-Pak cartridge in a solution of 3-methyl-1-butanol.

3,4-[4-^{18}F]Difluorobenzaldehyde ([^{18}F]1c)



Using an experimental batch microfluidic device[6] (Siemens Molecular Imaging), the aqueous [^{18}F]fluoride solution was passed through an strong anion exchanger column (AG1-X8). [^{18}F]Fluoride was eluted into a reaction cavity with a solution of K_2CO_3 (13 µL, 22.5 mg/mL) followed by Kryptofix® 222 (30 µL, 30 mg/mL). The complex was dried under 2 psi N_2 stream at 130 °C. The resulting dry complex of $K^{18}F$/Kryptofix® 222 was used for further nucleophilic ^{18}F-fluorination: **7c** (2 mg) in acetonitrile (40 µL) was added and heated for 4 min at 180 °C. Analysis by HPLC ($MeCN/H_2O$ **Gradient C**, 1 mL/min, 20 µL injected) indicated the formation of **[^{18}F]1c** at a retention time of 9.2 min which was consistent with the non-radioactive 3,4-difluorobenzaldehyde. Elution with water (1 mL) and analysis by radio-TLC (5% water in acetonitrile) indicated a radiochemical yield of 73% (*n*=3). Purification of **[^{18}F]1c** was achieved by solid-phase-extraction on a C-18 Sep-Pak cartridge in a solution of acetonitrile.

4-[^{18}F]Fluorobenzoic acid ([^{18}F]**6**)[7]

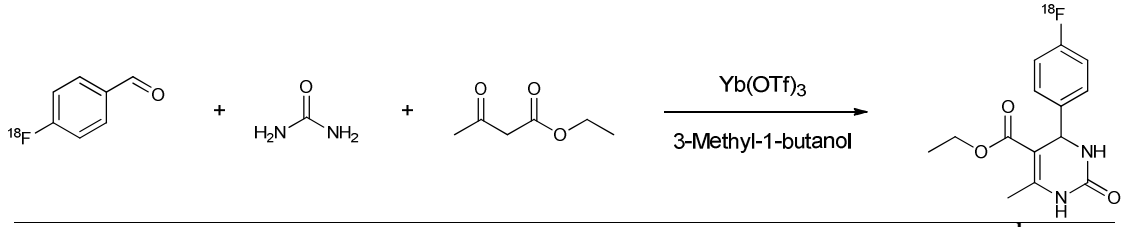


$K^{18}F$/Kryptofix® 222 in acetonitrile (0.3 mL) was added to a sealed reaction vial containing **8** (10 mg) and heated to 120 °C for 15 minutes. Tetrapropylammonium hydroxide (200 µL, 1 M in H_2O) was added to the crude reaction mixture and heated at 120°C for a further 5 minutes. The reaction was then neutralized by stirring with trifluoroacetic acid (200 µL, 1 M in H_2O) at room temperature for 5 minutes. The crude reaction mixture was diluted with water (6 mL). Analysis by HPLC (MeCN/H_2O **Gradient D**, 1 mL/min, 20 µL injected) indicated the formation of [^{18}F]**6** at a retention time of 8.8 min which was consistent with the non-radioactive 4-fluorobenzoic acid. Analysis by radio-TLC (5% H_2O in acetonitrile, R_f=0.5) indicated 56% radiochemistry yield (n=2). Purified [^{18}F]**6** was obtained by solid-phase-extraction on a C-18 Sep-Pak cartridge in a solution of ethanol.

Radio- Biginelli Reaction

Optimization of Radio-Biginelli Reaction

A solution of [^{18}F]**1a** in 3-methyl-1-butanol (200 µL, 5-15 MBq) was dispensed into a sealed vial containing urea, ytterbium(III) trifluoromethanesulfonate and ethyl acetoacetate (6 µL). The mixture was heated before being allowed to cool to room temperature, diluted with methanol (1 mL) and analyzed by radio-TLC. The results for the optimization are shown in Table S.1.

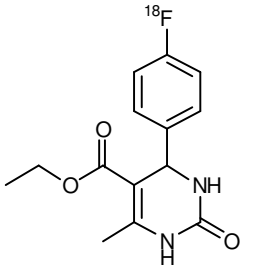


Entry	Temp.[a] (°C)	Time (min)	Urea (mg)	$Yb(OTf)_3$ (mg)	RCY[b] (%)
1	120	20	3	3	29
2	130	10	3	3	43
3	130	15	3	3	34
4	**130**	**20**	**3**	**3**	**66 (*n*=3)**
5	130	30	3	3	44
6	140	10	3	3	62
7	130	20	9	3	54
8	130	20	3	9	44
9	130	20	9	9	15
10	130[c]	20	3	3	44

[a]Conventional heating. [b]Decay corrected. Determined by radio-TLC. [c]Performed under microwave irradiation (50 W).

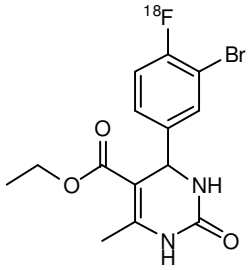
Table S.1 *Optimization of Radio-Biginelli Reaction*

Ethyl 4-(4-[^{18}F]fluorophenyl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate ([^{18}F]2a)



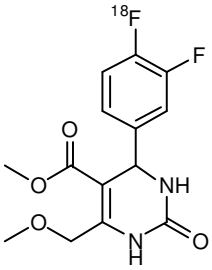
A solution of [^{18}F]**1a** in 3-methyl-1-butanol (200 µL, 5-15 MBq) was dispensed into a sealed vial containing urea (3 mg), ytterbium(III) trifluoromethanesulfonate (3 mg) and ethyl acetoacetate (6 µL). The mixture was heated under vigorous stirring at 130 °C for 20 minutes before being allowed to cool to room temperature and diluted with methanol (1 mL). Analysis by HPLC (MeCN/H_2O **Gradient A**, 1 mL/min, 20 µL injected) indicated 100% consumption of 4-[^{18}F]fluorobenzaldehyde (retention time=12.2 min) with corresponding formation of [^{18}F]**2a** at a retention time of 14.1 min, which was consistent with the 'cold' reference compound. Analysis by radio-TLC (66% ethyl acetate in hexane, R_f=0.3) indicated a radiochemical yield of 66% (*n*=3).

Ethyl-4-(3-bromo-4-[^{18}F]fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate ([^{18}F]2b)



A solution of [^{18}F]**1b** in 3-methyl-1-butanol (200 µL, 8.8 MBq) was dispensed into a sealed vial containing urea (3 mg), ytterbium(III) trifluoromethanesulfonate (3 mg) and ethyl acetoacetate (6 µL). The mixture was heated to 130 ^{o}C for 20 minutes before being allowed to cool to room temperature and diluted with methanol (1 mL). Analysis by HPLC (MeCN/H_2O **Gradient B**, 1 mL/min, 20 µL injected) indicated the formation of [^{18}F]**2b** at a retention time of 8.8 min, which was consistent with the 'cold' reference compound. Analysis by radio-TLC (50% ethyl acetate in hexane, R_f=0.2) indicated a radiochemical yield of 38%.

Methyl 4-(3,4-[4-^{18}F]difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4 tetrahydropyrimidine-5-carboxylate ([^{18}F]2c)

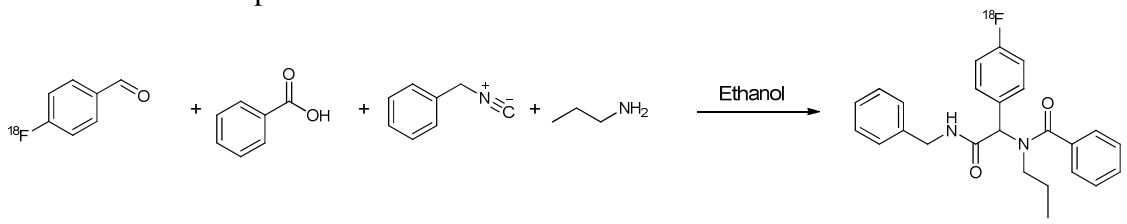


A solution of [^{18}F]**1c** in acetonitrile (200 µL, 9.8 MBq) was dispensed into a sealed vial containing urea (3 mg), ytterbium(III) trifluoromethanesulfonate (3 mg) and methyl 4-methoxy-3-oxobutanoate (6 µL). The mixture was heated to 130 ^{o}C for 30 minutes before being allowed to cool to room temperature. Analysis by HPLC (MeCN/H_2O **Gradient C**, 1 mL/min, 20 µL injected) indicated the formation of **[**^{18}F]**2c** at a retention time of 8.8 min, which was consistent with the 'cold' reference compound. Analysis by radio-TLC (80% ethyl acetate in hexane, R_f=0.3) indicated a radiochemical yield of 25% (*n*=3).

Radio-Ugi Reaction

Optimization of Radio-Ugi Reaction

A solution of [^{18}F]**1a** in ethanol (200 µL, 5-15 MBq) was dispensed into a sealed vial containing benzoic acid, benzyl isocyanide and 1-propylamine. The mixture was heated and stirred before being allowed to cool to room temperature and analyzed by radio-TLC. The results for the optimization are shown in Table S.2.

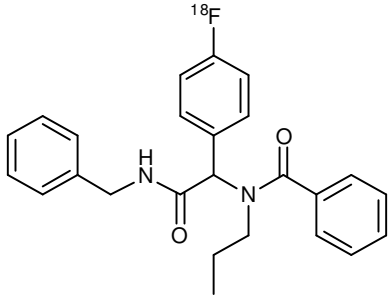


Entry	Temp.[a] (^{o}C)	Time (min)	Benzoic Acid (mg)	Benzyl isocyanide (µL)	1-Propyl amine (µL)	Ethanol (µL)	RCY[b] (%)
1	120	10	3	3	2	500	5
2	120	20	3	3	2	500	10
3	120	30	3	3	2	500	8
4	100	30	3	3	2	500	7
5	130	10	3	3	2	500	5
6	**100**	**30**	**6**	**6**	**4**	**200**	**62 (*n*=3)**
7	120	30	6	6	4	200	59

[a]Conventional heating. [b]Decay corrected. Determined by radio-TLC.

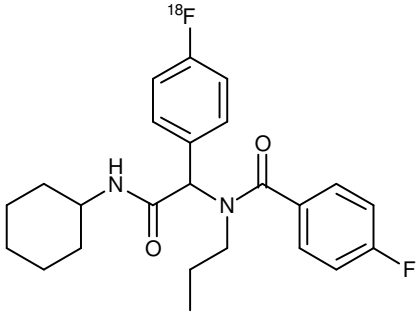
Table S.2 *Optimization of Radio-Ugi Reaction*

N-[2-(Benzylamino)-1-(4-[^{18}F]fluorophenyl)-2-oxoethyl]-*N*-propylbenzamide ([^{18}F]3a)



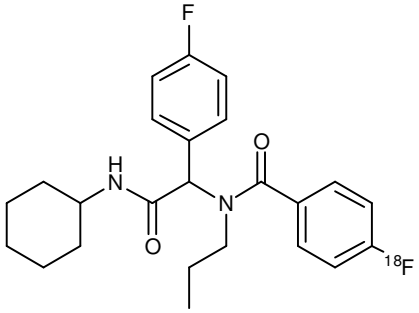
A solution of [^{18}F]**1a** in ethanol (200 µL, 5-15 MBq) was dispensed into a sealed vial containing benzoic acid (6 mg), benzyl isocyanide (6 µL), and 1-propylamine (4 µL). The mixture was heated to 100 ^{o}C and stirred for 30 minutes before being allowed to cool to room temperature. Analysis by HPLC (MeCN/H_2O **Gradient D**, 1 mL/min, 20 µL injected) indicated the formation of [^{18}F]**3a** at a retention time of 16.7 min, which was consistent with the 'cold' reference compound. Analysis by radio-TLC (33% ethyl acetate in hexane, R_f=0.3) indicated a radiochemical yield of 62% (*n*=3).

_N_-[2-(Cyclohexylamino)-1-([4-[^{18}F]fluorophenyl)-2-oxoethyl]-4-fluoro-_N_-propylbenzamide ([^{18}F]3b)



A solution of [^{18}F]**1a** in ethanol (200 µL, 5-15 MBq) was dispensed into a sealed vial containing 4-fluorobenzoic acid (8 mg), cyclohexyl isocyanide (6 µL) and 1-propylamine (4 µL). The mixture was heated to 100 ^{o}C and stirred for 30 minutes before being allowed to cool to room temperature. Analysis by HPLC (MeCN/H_2O **Gradient D**, 1 mL/min, 20 µL injected) indicated the formation of [^{18}F]**3b** at a retention time of 17.2 min, which was consistent with the 'cold' reference compound. Analysis by radio-TLC (20% ethyl acetate in hexane, R_f=0.3) indicated a radiochemical yield of 56% (*n*=2).

_N_-[2-(Cyclohexylamino)-1-(4-[^{18}F]fluorophenyl)-2-oxoethyl]-4-fluoro-_N_-propylbenzamide ([^{18}F]3b)

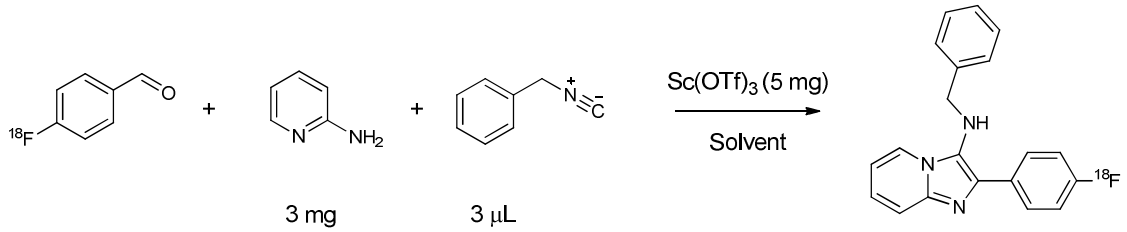


A solution of [^{18}F]**6** in ethanol (200 µL, 6.3 MBq) was dispensed into a sealed vial containing 4-fluorobenzaldehyde (5 µL), cyclohexyl isocyanide (6 µL), 'cold' 4-fluorobenzoic acid (8 mg) and 1-propylamine (4 µL). The mixture was heated at 100 ^{o}C for 30 minutes. Analysis by HPLC (MeCN/H_2O **Gradient D**, 1 mL/min, 20 µL injected) indicated the formation of [^{18}F]**3b** at a retention time of 17.3 min, which was consistent with the 'cold' reference compound. Analysis by radio-TLC (33% ethyl acetate in hexane, R_f=0.5) indicated a radiochemical yield of 10% (*n*=2).

Radio-Groebke-Bienaymé-Blackburn Reaction

Optimization of Radio-Groebke-Bienaymé-Blackburn Reaction

A solution of [^{18}F]**1a** in a solvent (200 µL, 5-15 MBq) was dispensed into a sealed vial containing scandium(III) trifluoromethanesulfonate (5 mg) and 2-aminopyridine (3 mg). A solution of benzyl isocyanide (3 µL) in the solvent (300 µL) was then added *via* syringe. The reaction was heated before being allowed to cool to room temperature, diluted with acetonitrile (1 mL) and analyzed by radio-TLC. The results for the optimization are shown in Table S.3.

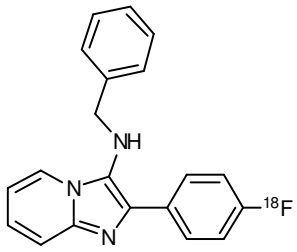


Entry	Temp. (°C)[a]	Time (min)	Solvent (0.5 mL)	RCY (%)[b]
1	100	15	MeCN	3
2	100-120[c]	20	MeCN	8
3	110	15	3-Methyl-1-butanol	31
4	150	15	3-Methyl-1-butanol	73
5	150[d]	15	3-Methyl-1-butanol	64
6	150	30	3-Methyl-1-butanol	80
7	150[e]	15	3-Methyl-1-butanol	81
8	**170**	**15**	**3-Methyl-1-butanol**	**85 (*n*=4)**

[a]Conventional heating. [b]Decay corrected. Determined by radio-TLC. [c]100 °C for 15 minutes followed by 5 minutes at 120 °C. [d]Benzyl isocyanide added prior to [^{18}F]4-fluorobenzaldehyde. [e]Performed under microwave irradiation (50 W).

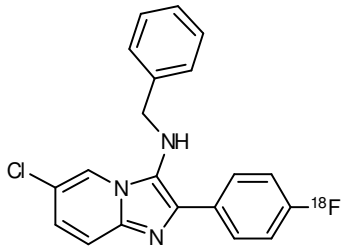
Table S.3 *Optimization of Radio-Groebke-Bienaymé-Blackburn Reaction*

N-Benzyl-2-(4-[^{18}F]fluorophenyl)imidazo[1,2-*a*]pyridin-3-amine ([^{18}F]4a)



A solution of [^{18}F]**1a** in 3-methyl-1-butanol (200 µL, 5-15 MBq) was dispensed into a sealed vial containing scandium(III) trifluoro-methanesulfonate (5 mg) and 2-aminopyridine (3 mg). A solution of benzyl isocyanide (3 µL) in 3-methyl-1-butanol (300 µL) was then added *via* syringe. The reaction was heated at 170 °C for 15 minutes before being allowed to cool to room temperature. The mixture was then diluted with acetonitrile (1 mL). Analysis by radio-HPLC (MeCN/Phosphate Buffer (10mM, pH 7.0) **Gradient E**, 1 mL/min, 20 µL injected) indicated 100% consumption of the [^{18}F]**1a** (retention time=7.5 min) with corresponding formation of [^{18}F]**4a** at a retention time of 16.2 min, which was consistent with the 'cold' reference compound. Radio-TLC (50% ethyl acetate in hexane, R_f=0.2) indicated a radiochemical yield of 85% (*n*=4).

N-Benzyl-6-chloro-2-(4-[^{18}F]fluorophenyl)imidazo[1,2-*a*]pyridin-3-amine ([^{18}F]**4b**)

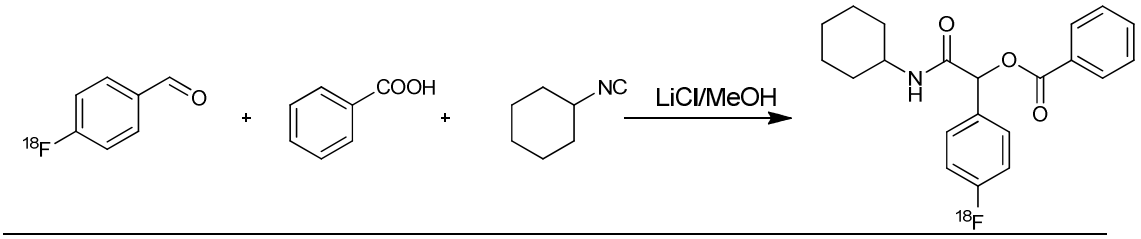


A solution of [^{18}F]**1a** in 3-methyl-1-butanol (200 µL, 5-15 MBq) was dispensed into a sealed vial containing scandium(III) trifluoromethanesulfonate (5 mg) and 2-amino-5-chloropyridine (3 mg). A solution of benzyl isocyanide (3 µL) in 3-methyl-1-butanol (300 µL) was then added *via* syringe. The reaction was heated at 170 ºC for 15 minutes before being allowed to cool to room temperature. The mixture was then diluted with acetonitrile (1 mL). Analysis by radio-HPLC (MeCN/Phosphate Buffer (10mM, pH 7.0) **Gradient E**, 1 mL/min, 20 µL injected) indicated 100% consumption of the [^{18}F]**1a** (retention time=7.5 min) with corresponding formation of [^{18}F]**4b** at a retention time of 18.4 min, which was consistent with the 'cold' reference compound. Radio-TLC (50% ethyl acetate in hexane, R_f=0.4) indicated a radiochemical yield of 76% (*n*=3).

Radio-Passerini Reaction

Optimization of Radio-Passerini Reaction

A solution of 4-[^{18}F]fluorobenzaldehyde ([^{18}F]**1a**) in methanol (100 µL, 5-15 MBq) was dispensed into a sealed vial containing benzoic acid and cyclohexyl isocyanide in an aqueous solution of lithium chloride (4M). The mixture was heated before being allowed to cool to room temperature, diluted with acetonitrile (300 µL) and analyzed by radio-TLC. The results for the optimization are shown in Table S.4.

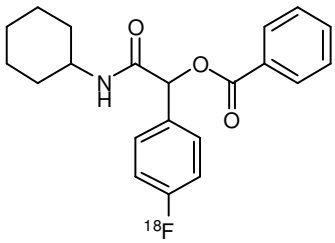


Entry	Temp. (^{o}C)	Time (min)	Benzoic Acid (mg)	Cyclohexyl isocyanide (µL)	4M LiCl (aq.) (µL)	Methanol (µL)	RCY[a] [%]
1	80	30	7	4	0	500	0
2	80	30	7	4	600	100	5
3	100	30	7	4	600	100	3
4	100	30	7	4	300	200	0
5	100	10	7	4	600	100	44
6	100	20	7	4	600	100	56
7	100	30	4	2	600	100	59
8	**100**	**30**	**7**	**4**	**600**	**100**	**65 (*n*=3)**
9	100	30	7	4	700	100	61
10	120	10	7	4	600	100	14
11	120	30	7	4	600	100	32
12	130	30	7	4	600	100	27

[a]Decay-corrected. Determined by radio-TLC

Table S.4 *Optimization of Radio-Passerini Reaction*

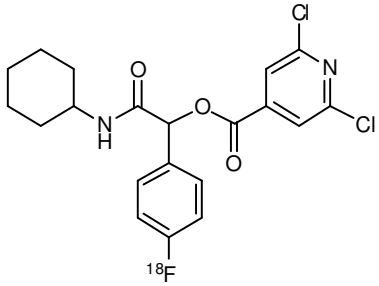
2-(Cyclohexylamino)-1-(4-[^{18}F]fluorophenyl)-2-oxoethylbenzoate ([^{18}F]5a)



A solution of [^{18}F]**1a** in methanol (100 µL, 5-15 MBq) was dispensed into a sealed vial containing benzoic acid (7 mg) and cyclohexyl isocyanide (4 µL) in an aqueous solution of LiCl (4M, 600 µL). The mixture was heated at 100 ^{o}C for 30 minutes before being allowed to cool to room temperature and diluted with acetonitrile (300 µL). Analysis by HPLC (MeCN/H_2O **Gradient F**, 1 mL/min, 20 µL injected)

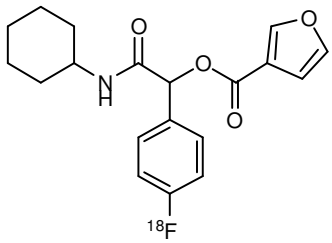
indicated the formation of [^{18}F]**5a** at a retention time of 10.5 minutes, which was consistent with the cold reference compound, in a radiochemical yield of 65% (*n*=3).

2-(Cyclohexylamino)-1-(4-[^{18}F]fluorophenyl)-oxoethyl 2,6-dichloropyridine-4-carboxylate ([^{18}F]5b)



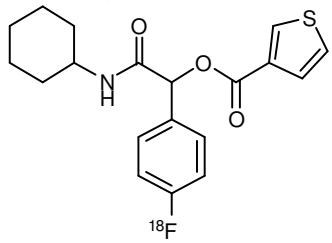
A solution of [^{18}F]**1a** in methanol (100 µL, 5-15 MBq) was dispensed into a sealed vial containing 2,4-dichloropyridin-4-carboxylic acid (7 mg) and cyclohexyl isocyanide (4 µL) in an aqueous solution of LiCl (4M, 600 µL). The mixture was heated at 100 ^{o}C for 30 minutes before being allowed to cool to room temperature and diluted with acetonitrile (300 µL). Analysis by HPLC (MeCN/H_2O **Gradient F**, 1 mL/min, 20 µL injected) indicated the formation of [^{18}F]**5b** at a retention time of 10.8 minutes, which was consistent with the cold reference compound, in a radiochemical yield of 33% (*n*=2).

2-(Cyclohexylamino)-1-(4-[^{18}F]fluorophenyl)-2-oxoethylfuran-3-carboxylate ([^{18}F]5c)



A solution of [^{18}F]**1a** in methanol (100 µL, 5-15 MBq) was dispensed into a sealed vial containing furan-3-carboxylic acid (7 mg) and cyclohexyl isocyanide (4 µL) in an aqueous solution of LiCl (4M, 600 µL). The mixture was heated at 100 ^{o}C for 30 minutes before being allowed to cool to room temperature and diluted with acetonitrile (300 µL). Analysis by HPLC (MeCN/H_2O **Gradient F**, 1 mL/min, 20 µL injected) indicated the formation of [^{18}F]**5c** at a retention time of 9.8 minutes, which was consistent with the cold reference compound, in a radiochemical yield of 28% (*n*=2).

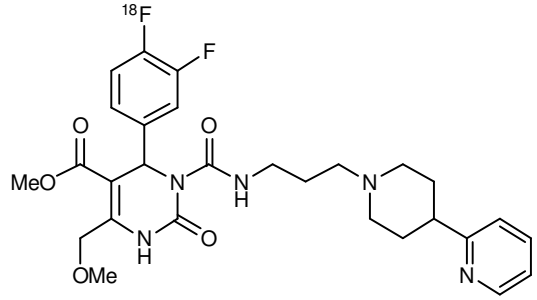
2-(Cyclohexylamino)-1-(4-[^{18}F]fluorophenyl)-2-oxoethylthiophene-3-carboxylate ([^{18}F]5d)



A solution of [^{18}F]**1a**) in methanol (100 µL, 5-15 MBq) was dispensed into a sealed vial containing thiophene-3-carboxylic acid (7 mg) and cyclohexyl isocyanide (4 µL) in an aqueous solution of LiCl (4M, 600 µL). The mixture was heated at 100 ^{o}C for 30 minutes before being allowed to cool to room temperature and diluted with acetonitrile (300 µL). Analysis by HPLC (MeCN/H_2O **Gradient F**, 1 mL/min, 20 µL injected) indicated the formation of [^{18}F]**5d** at a retention time of 10.2 minutes, which was consistent with the cold reference compound, in a radiochemical yield of 32% (*n*=2).

Radiosynthesis of [^{18}F]L771.668

Methyl 4-(3, 4-[4-^{18}F]difluorophenyl)-6-(methoxymethyl)-2-oxo-3-({3-[4-(pyridin-2-yl)piperidin-1-yl]propyl}carbamoyl)-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate ([^{18}F]10)



A solution of **9** (10 mg) and triethylamine (5 µL) in aceronitrile (200 µL) was added to the crude reaction mixture of [^{18}F]**2c** (200 µL, 6.8 MBq) and heated to 130 ^{o}C for 30 minutes before being allowed to cool to room temperature. Analysis by HPLC (MeCN/H_2O **Gradient C**, 1 mL/min, 20 µL injected) indicated the formation of [^{18}F]**10** at a retention time of 5.4 min, which was consistent with the 'cold' reference compound. Analysis by radio-HPLC by integration of peak areas indicated a radiochemical yield of 18% in two steps and a radiochemical yield of 40% for the coupling step. The overall RCY from [^{18}F]fluoride of [^{18}F]**10** is 7% over three steps (75 min overall radiosynthesis time).

2.3 Specific Activity of [^{18}F]1a and [^{18}F]1c

Specific activities of 4-[^{18}F]fluorobenzaldehyde ([^{18}F]**1a**) and 3,4-[4-^{18}F]difluorobenzaldehyde ([^{18}F]**1c**) were measured after nucleophilic radiofluorination of **7a** (2 mg of precursor at 160 ^{o}C for 240 seconds) and **7c** (2 mg of precursor at 200 ^{o}C for 200 seconds) respectively. The reaction mixtures were analyzed by HPLC (MeCN/H_2O, 1 mL/min, 20 µL injected, linear increase from 25% acetonitrle to 30% acetonitrile in 20 minutes). The concentrations of the radioactive compounds were determined using calibration curves obtained by analysis of the UV absorbance (254 nm) of the relevant non-radioactive 4-fluorobenzaldehyde or 3,4-difluorobenzaldehyde.

The specific activity of 4-[^{18}F]fluorobenzaldehyde was 35-90 GBq/µmol (n=3) decay-corrected to the end of synthesis. The specific activity of 3,4-[4-^{18}F]difluorobenzaldehyde was 30-59 GBq/µmol (n=3) decay-corrected to end of synthesis. The specific activities were not measured when UV traces did not allow for the identification of a suitable UV peak (no overlapping impurity) for direct comparison with the corresponding radioactive peak of the labelled products.

The calibration curve (absorbance to concentration) for 4-fluorobenzaldehyde is shown in Figure S.1.

log(Absorbance)=3.78762+0.92427 log(Concentration)
R^2=0.99937
Concentration: mg/mL
Absorbance: AU

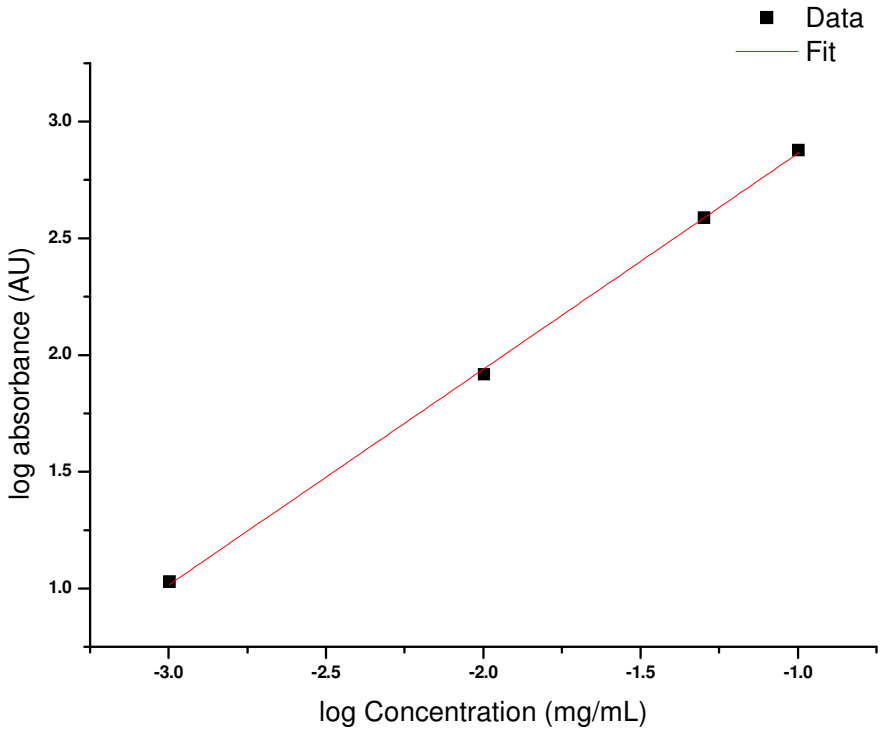


Figure S.1 *Calibration Curve for 4-Fluorobenzaldehyde*

The calibration curve (absorbance to concentration) for 3,4-difluorobenzaldehyde is shown in Figure S.2.

log(Absorbance)=3.64581+0.98808 log(Concentration)
R^2=0.99987
Concentration: mg/mL
Aborbance: AU

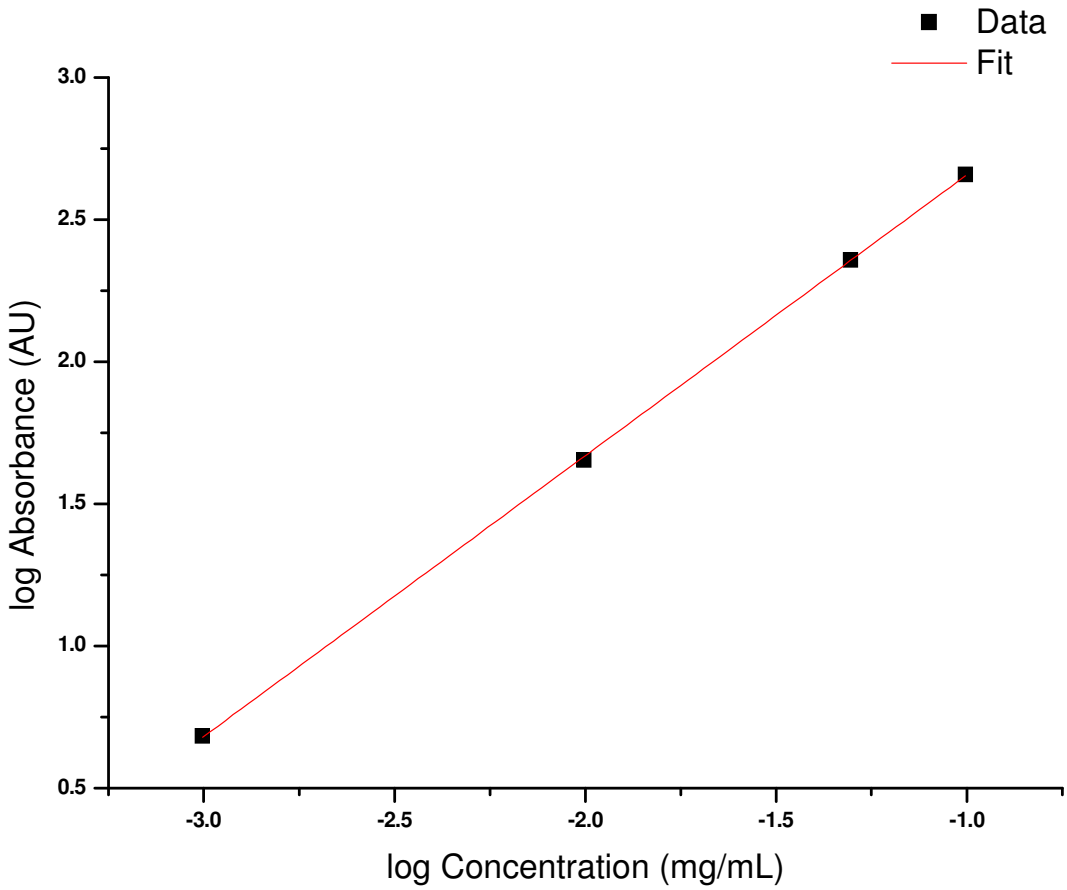


Figure S.2 *Calibration Curve for 3,4-Difluorobenzaldehyde*

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Supplementary Material (ESI) for Chemical Science
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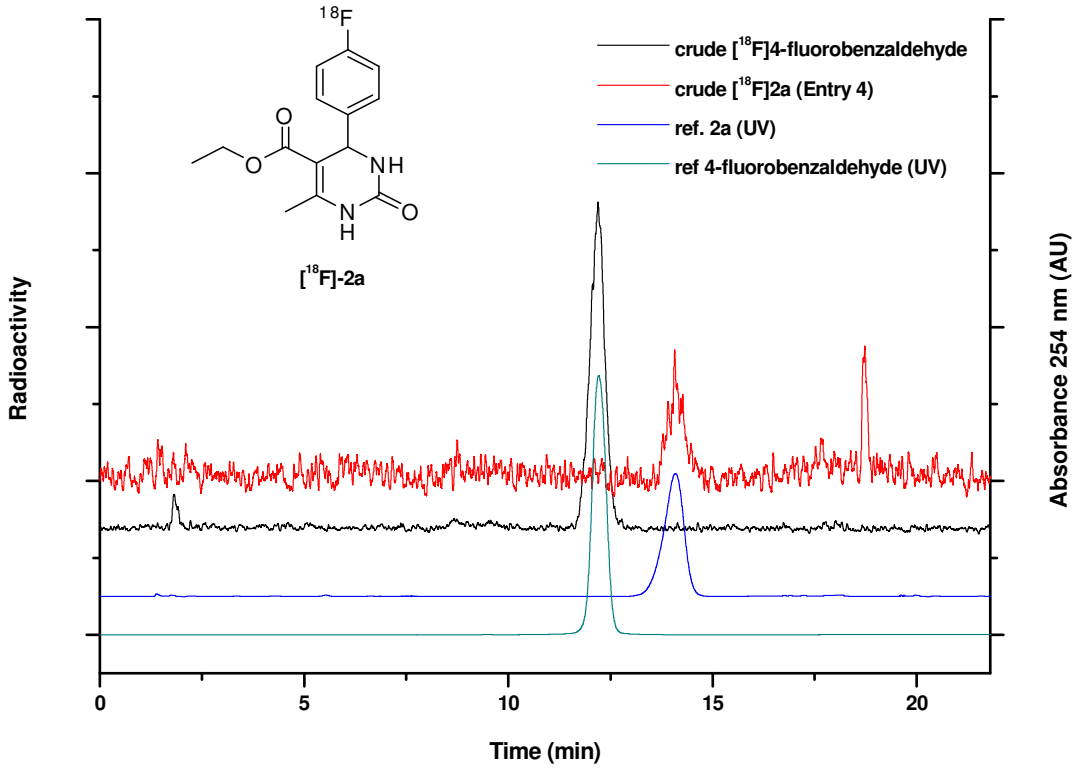
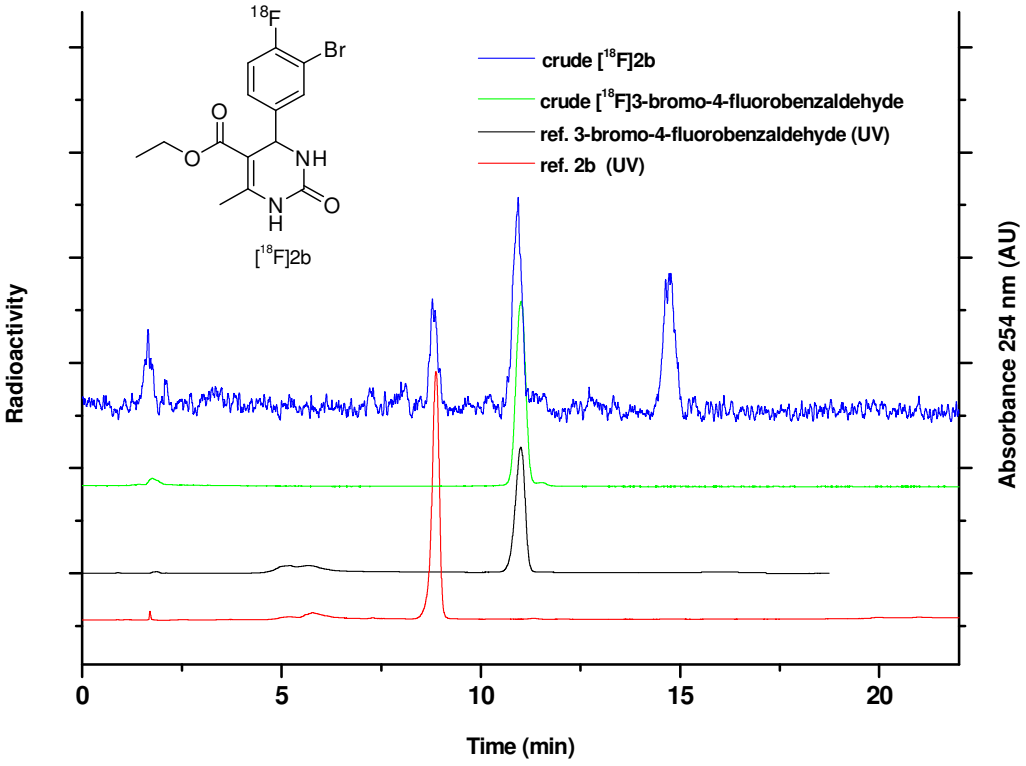
3. HPLC Chromatograms





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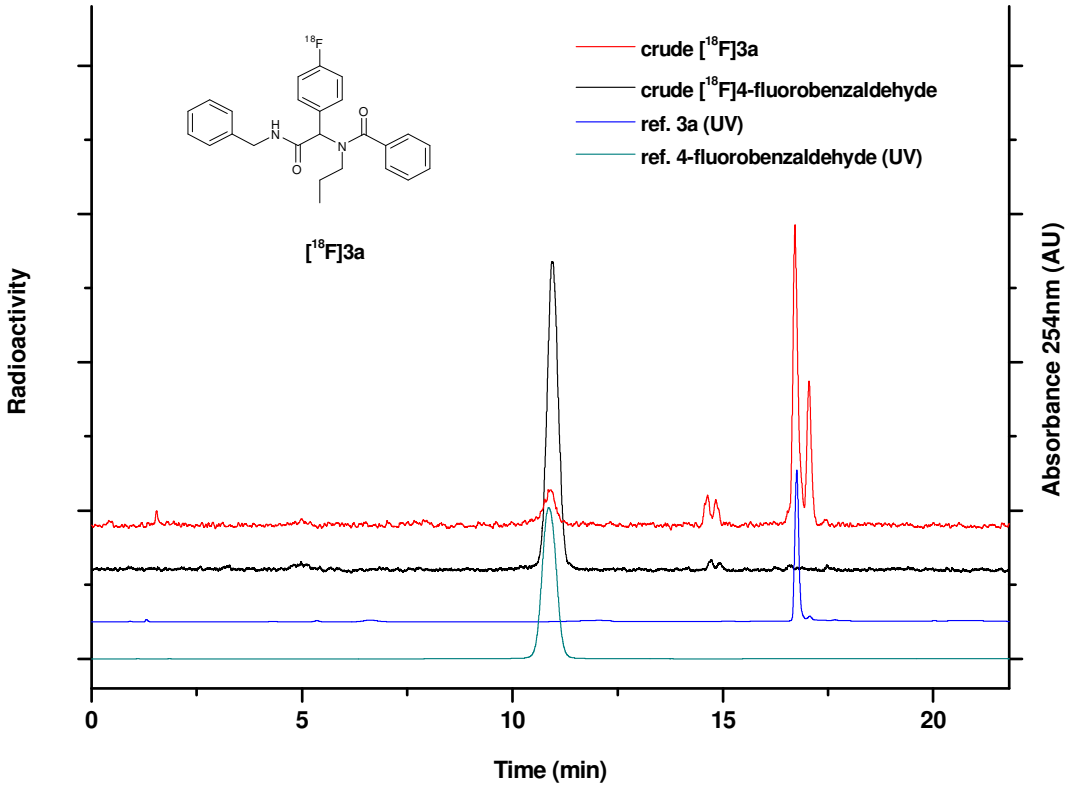

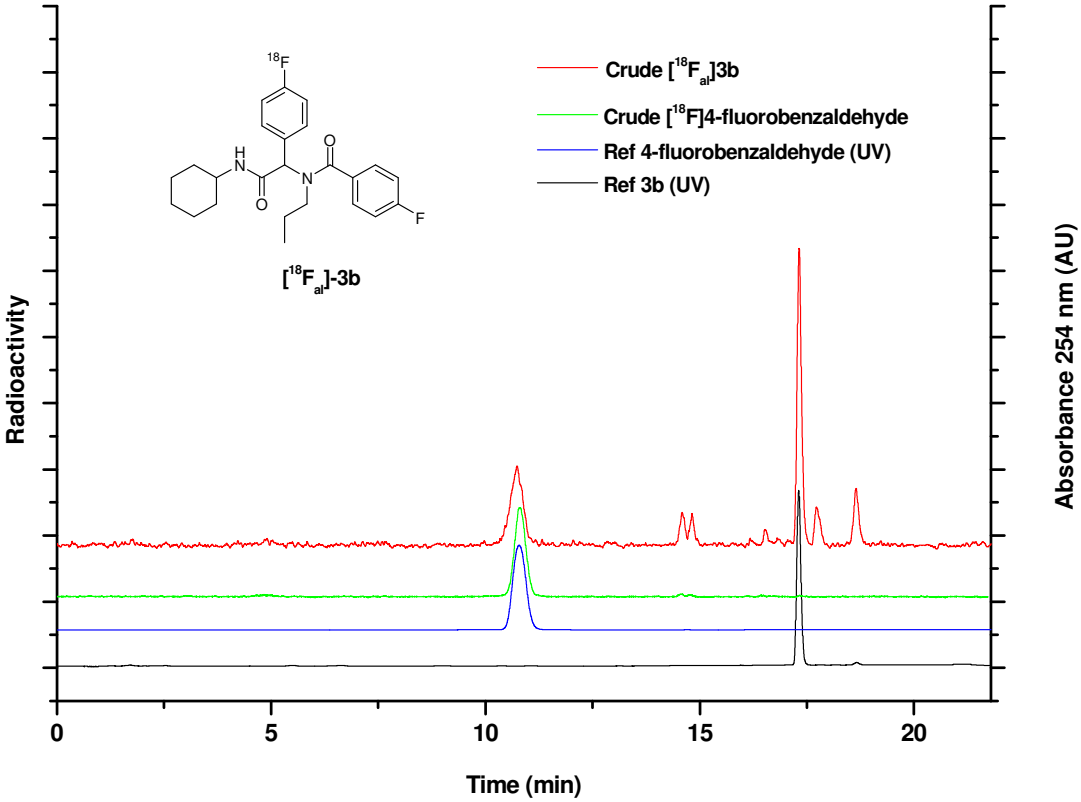

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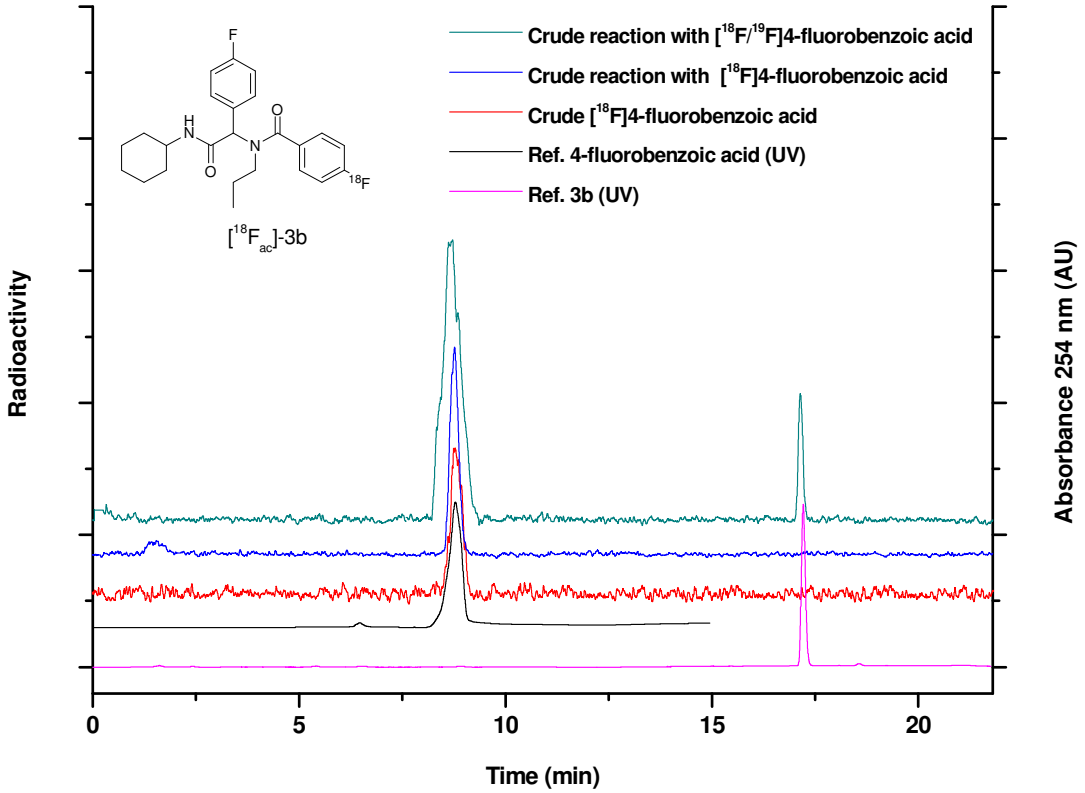
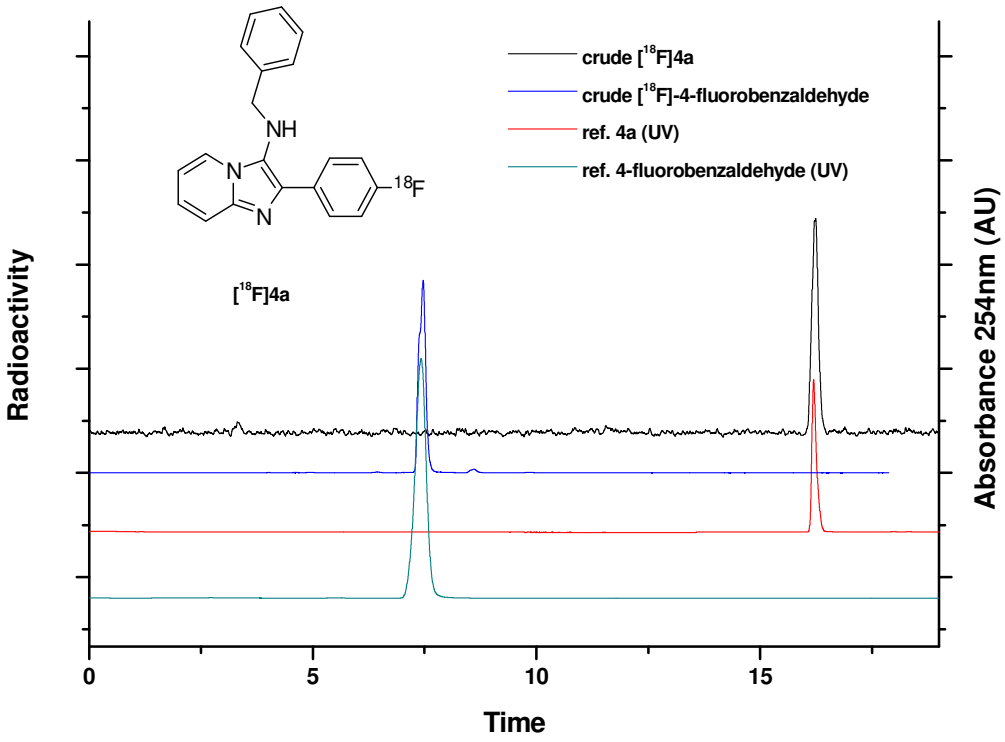
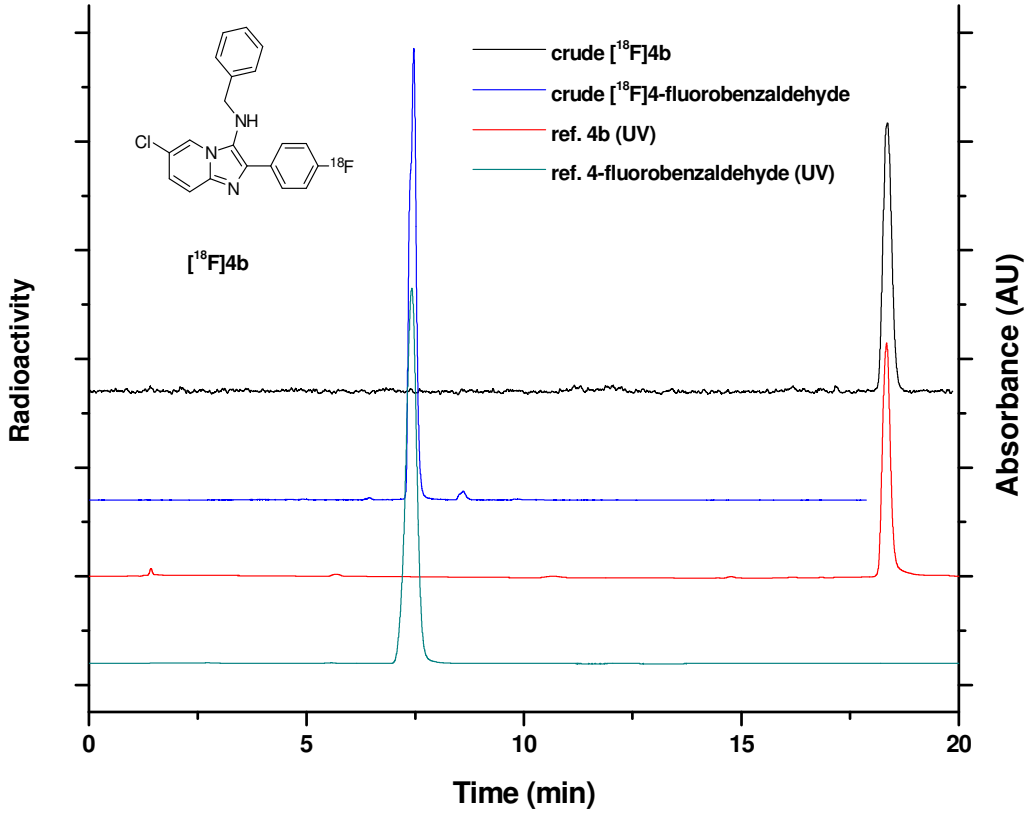
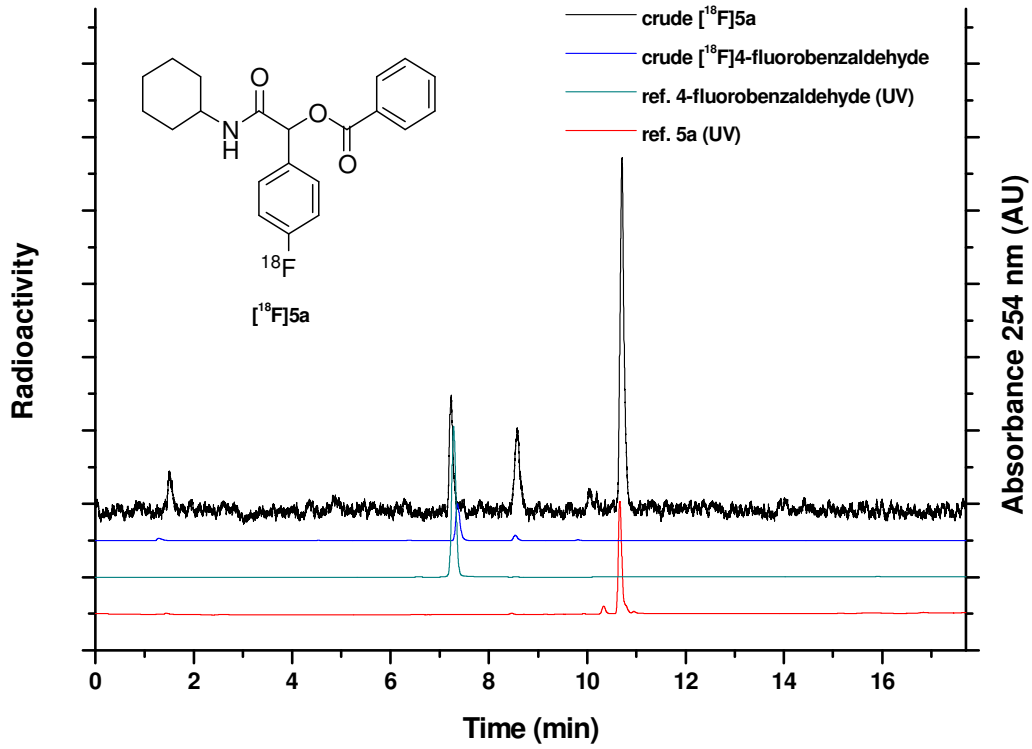
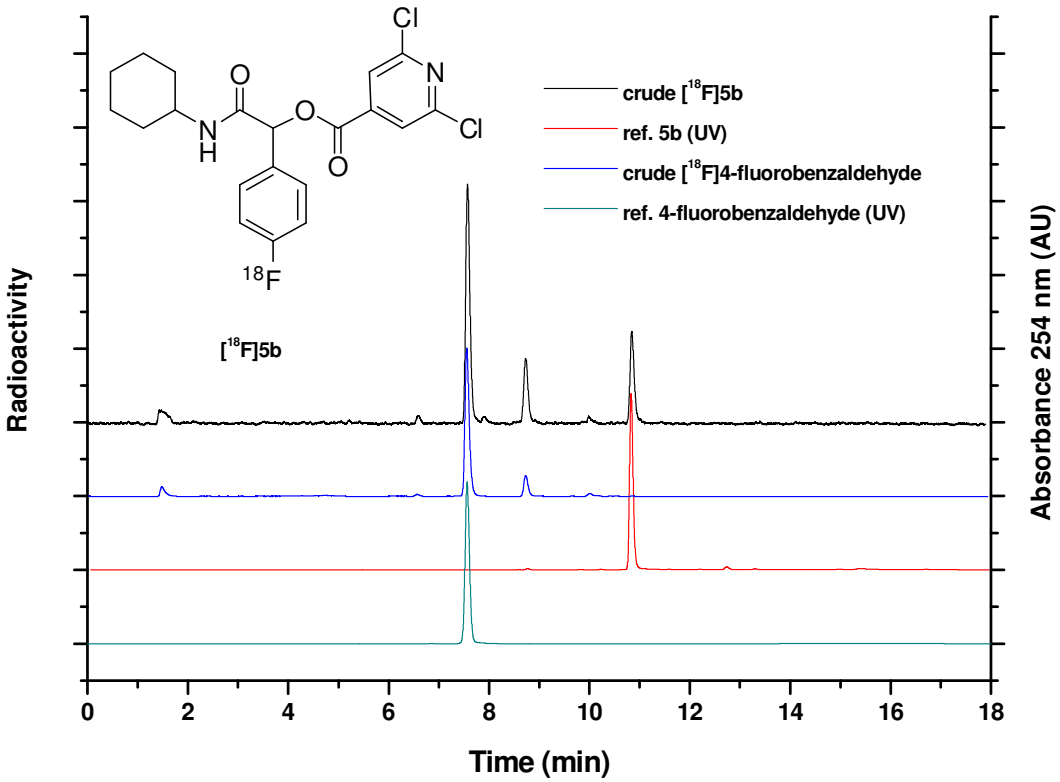
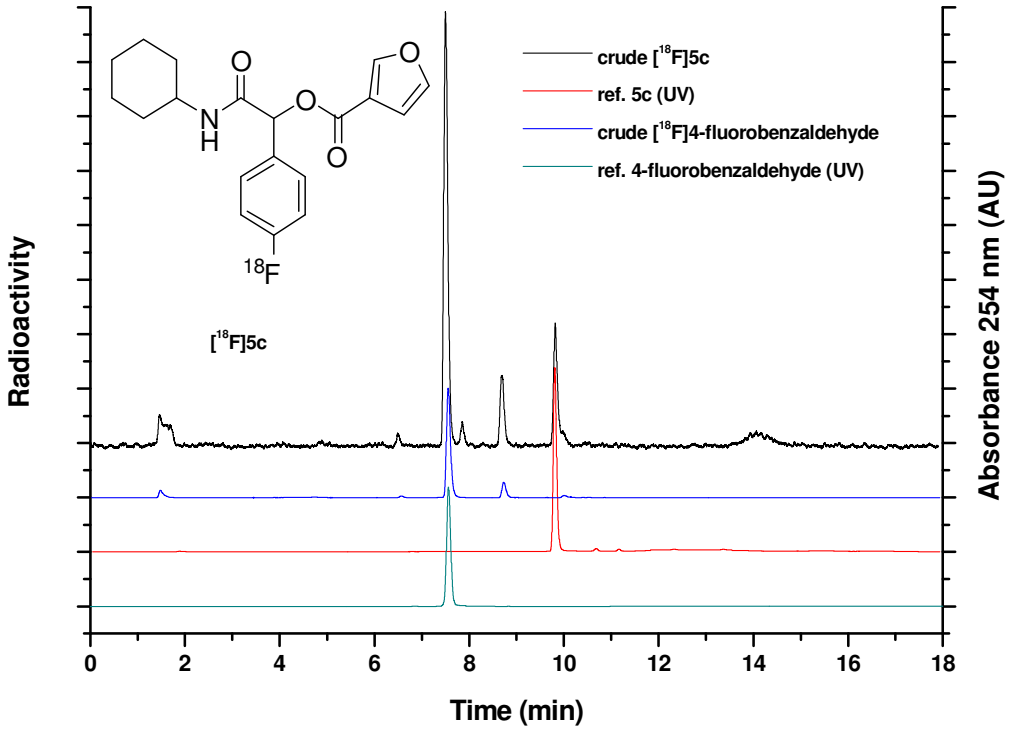


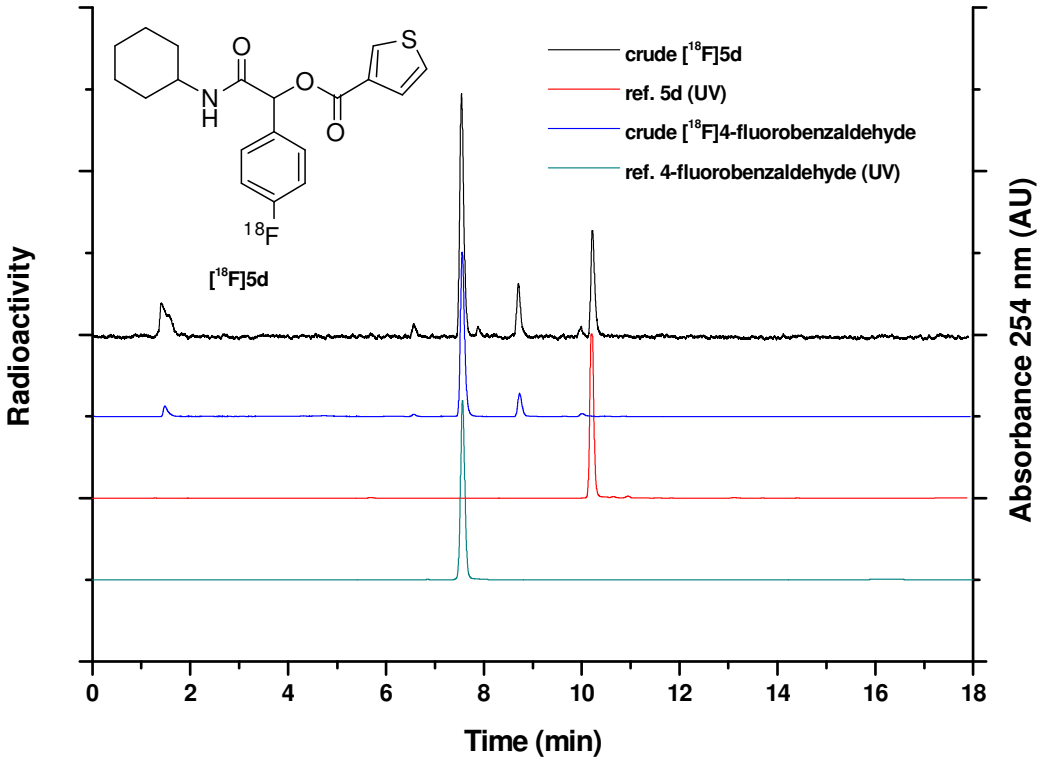


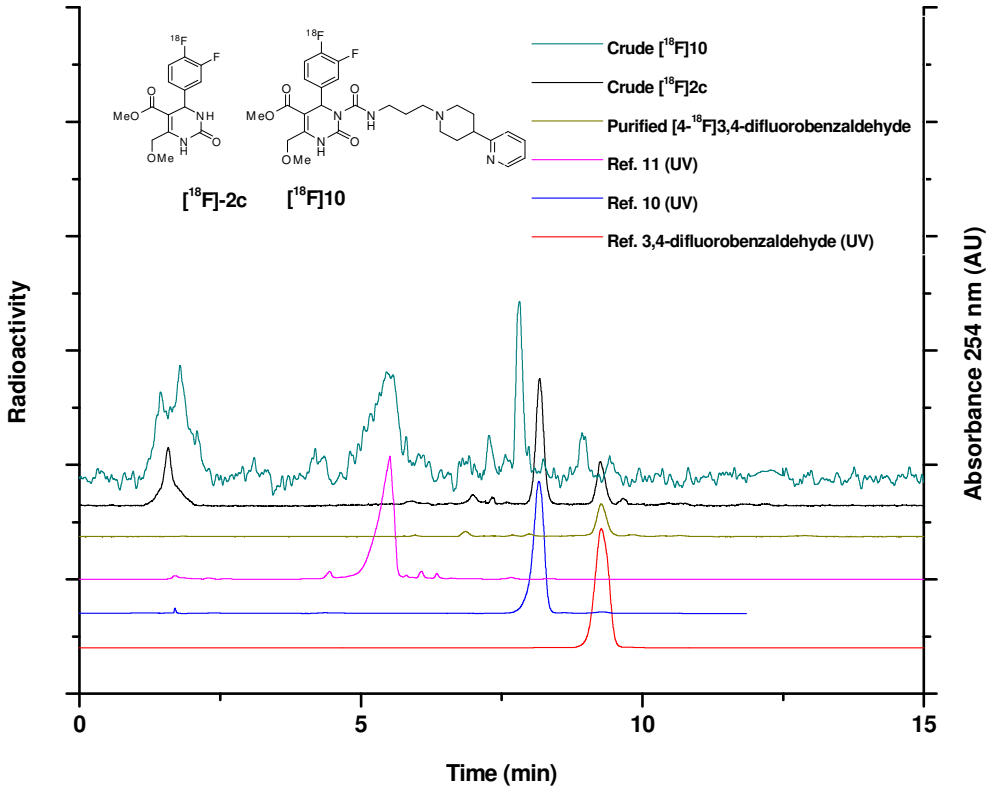

crude [18F]4b
crude [18F]4-fluorobenzaldehyde
ref. 4b (UV)
ref. 4-fluorobenzaldehyde (UV)
NH
Cl
N
N
18F
[18F]4b
Radioactivity
Absorbance (AU)
0
5
10
15
20
Time (min)


crude [18F]5a
crude [18F]4-fluorobenzaldehyde
ref. 4-fluorobenzaldehyde (UV)
ref. 5a (UV)
O
N
H
O
O
18F
[18F]5a
Radioactivity
Absorbance 254 nm (AU)
0
2
4
6
8
10
12
14
16
Time (min)

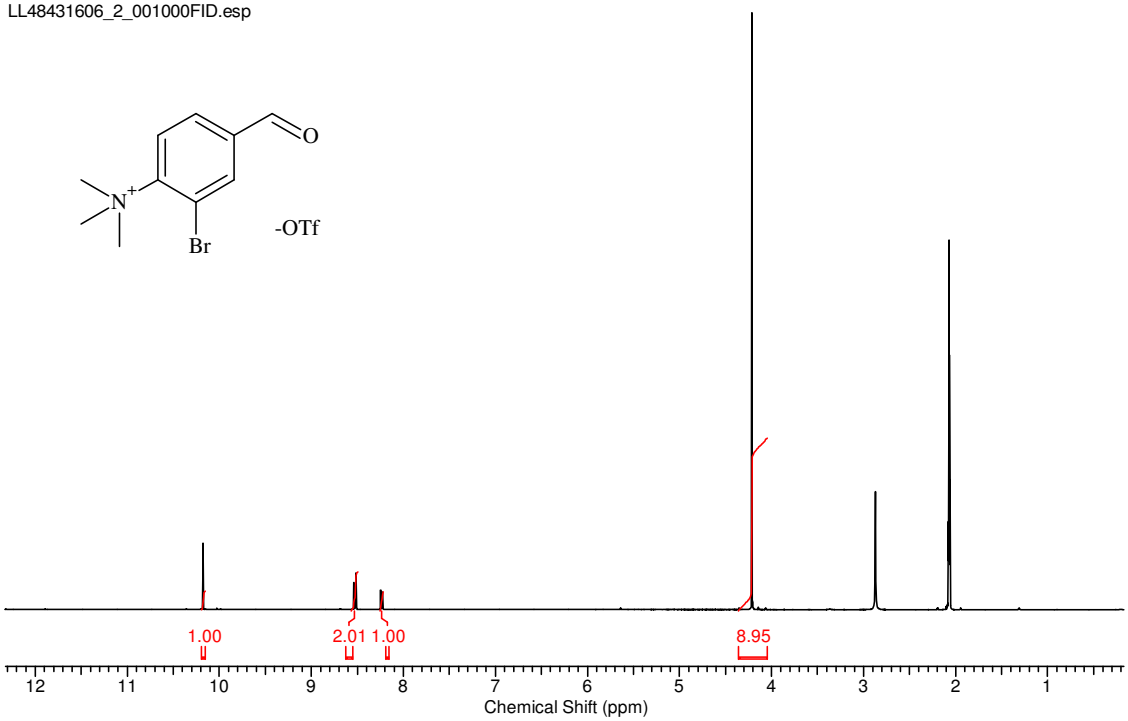

Cl
N
Cl
O
N
H
O
O
^{18}F
[^{18}F]5b
crude [^{18}F]5b
ref. 5b (UV)
crude [^{18}F]4-fluorobenzaldehyde
ref. 4-fluorobenzaldehyde (UV)
Radioactivity
Absorbance 254 nm (AU)
0
2
4
6
8
10
12
14
16
18
Time (min)

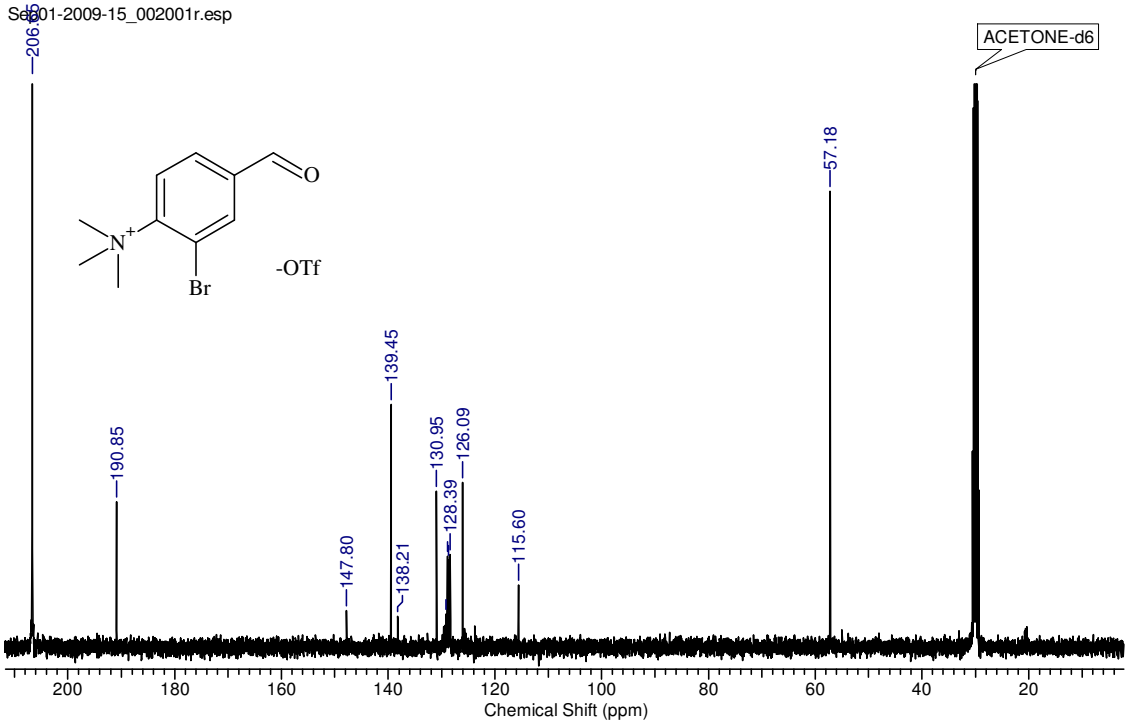

O
O
N
H
O
O
^{18}F
[^{18}F]5c
crude [^{18}F]5c
ref. 5c (UV)
crude [^{18}F]4-fluorobenzaldehyde
ref. 4-fluorobenzaldehyde (UV)
Radioactivity
Absorbance 254 nm (AU)
0
2
4
6
8
10
12
14
16
18
Time (min)


crude [18F]5d
ref. 5d (UV)
crude [18F]4-fluorobenzaldehyde
ref. 4-fluorobenzaldehyde (UV)
[18F]5d
Radioactivity
Absorbance 254 nm (AU)
Time (min)


Crude [18F]10
Crude [18F]2c
Purified [4-18F]3,4-difluorobenzaldehyde
Ref. 11 (UV)
Ref. 10 (UV)
Ref. 3,4-difluorobenzaldehyde (UV)
[18F]-2c
[18F]10
Radioactivity
Absorbance 254 nm (AU)
Time (min)

4. NMR Spectra





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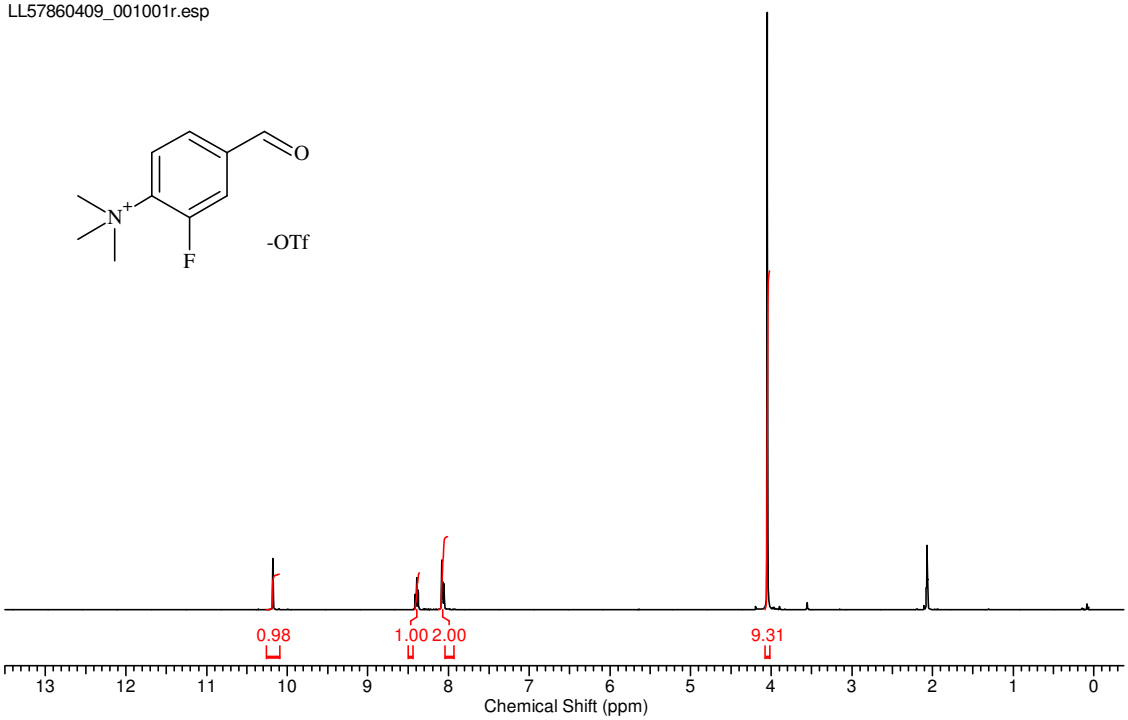

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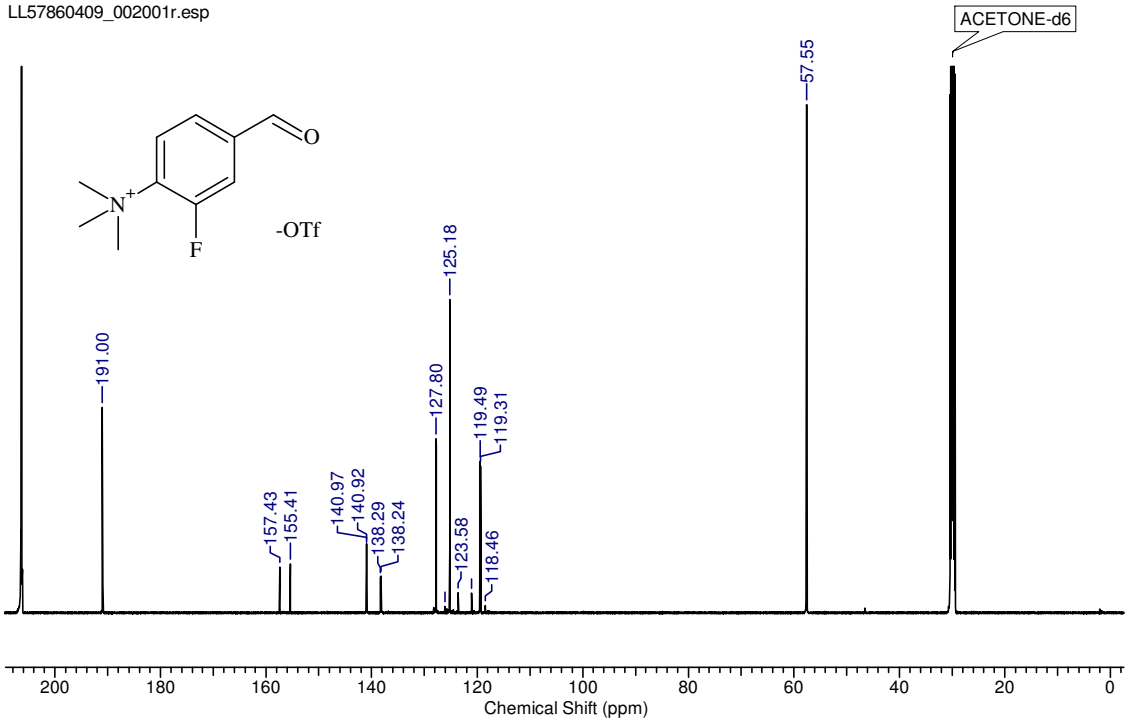

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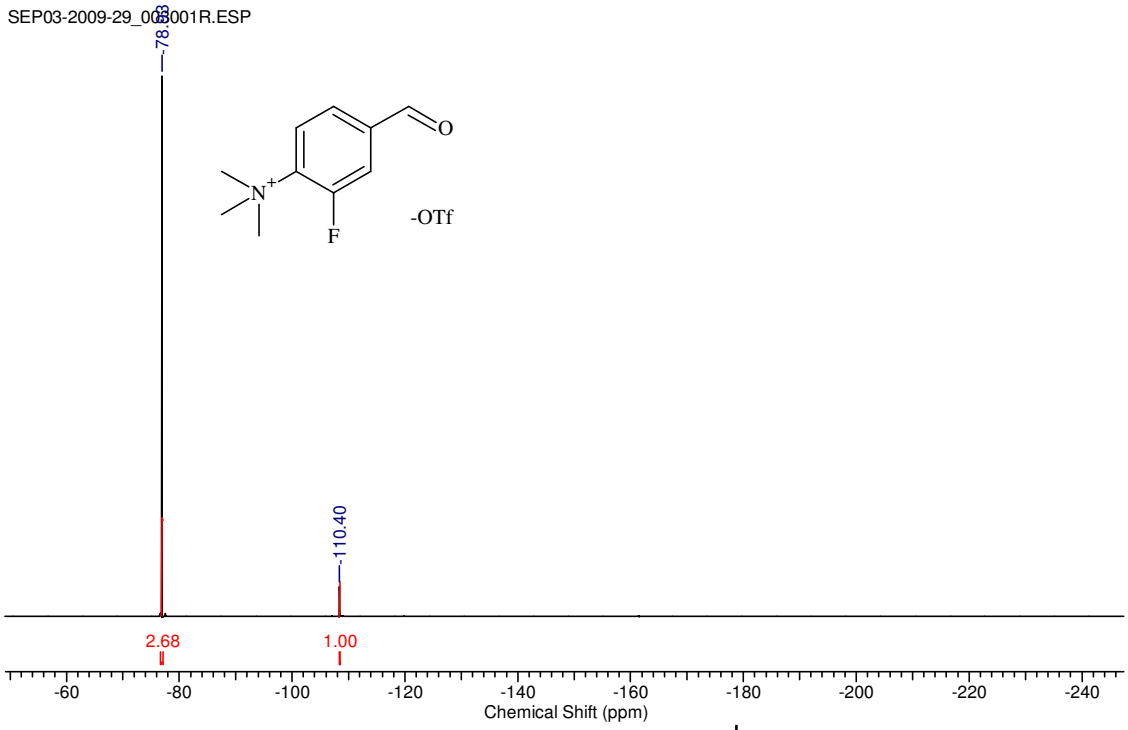

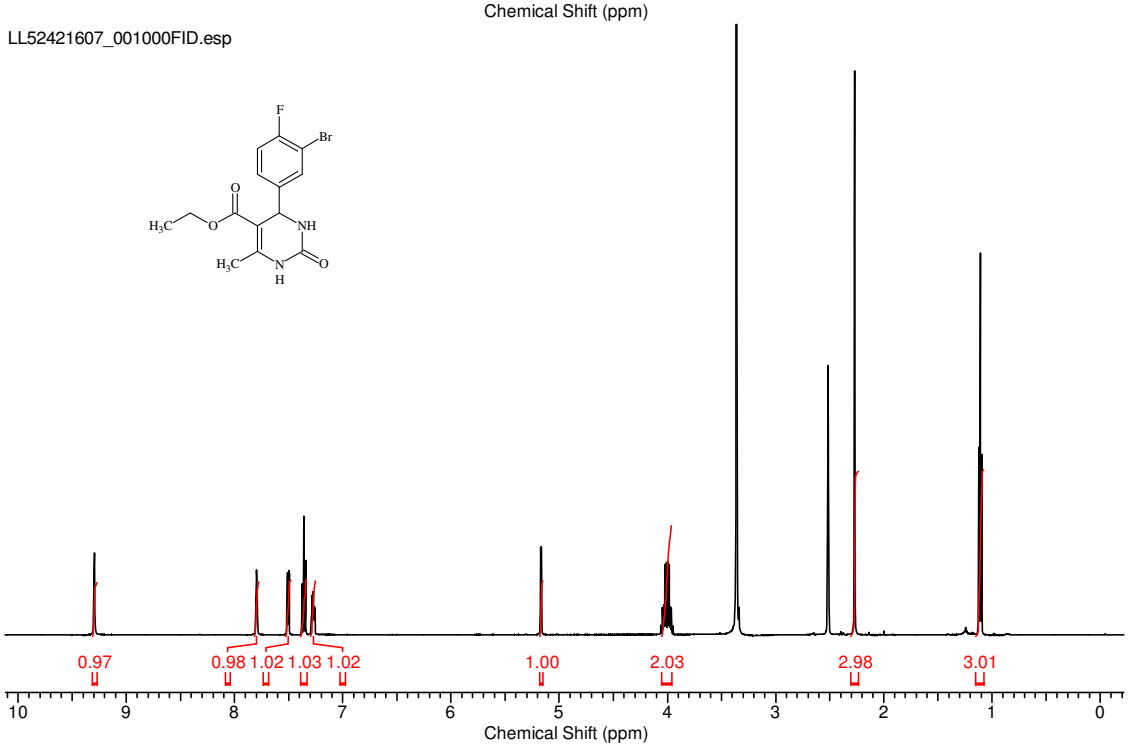

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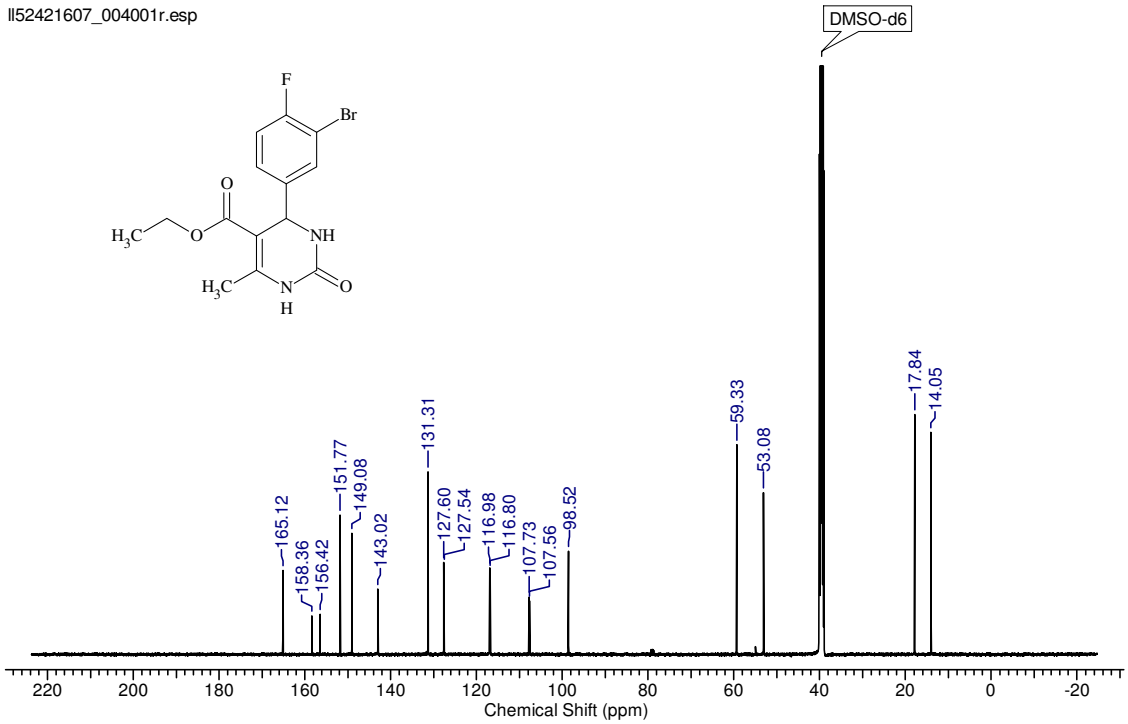

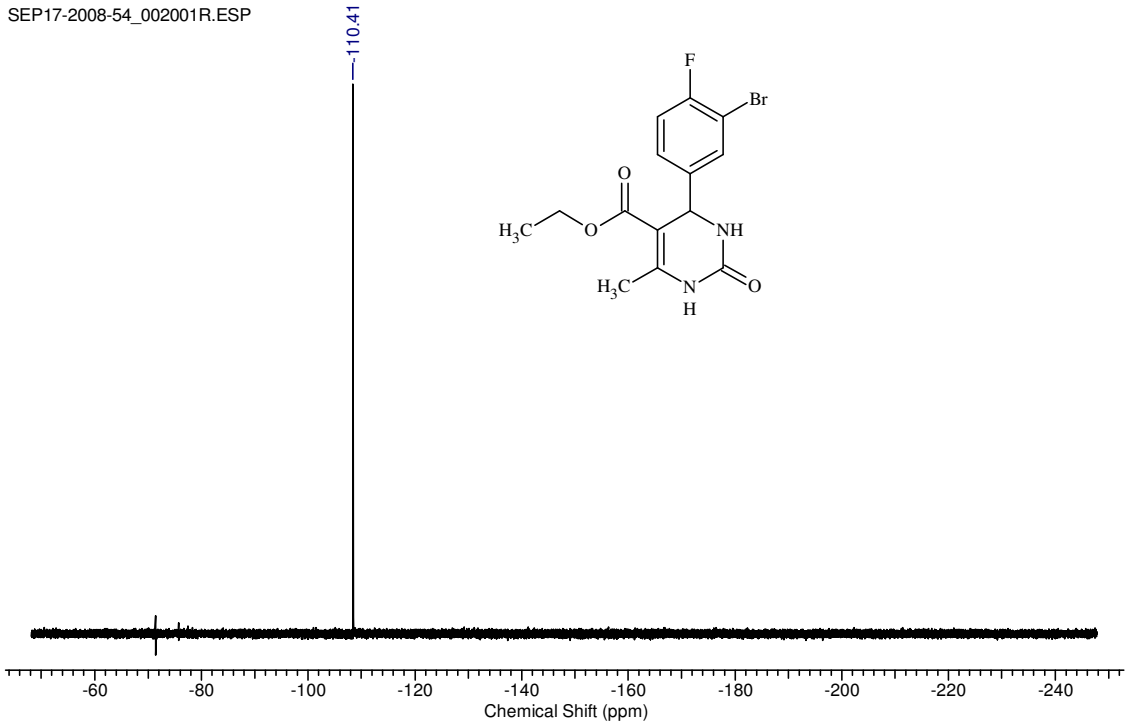

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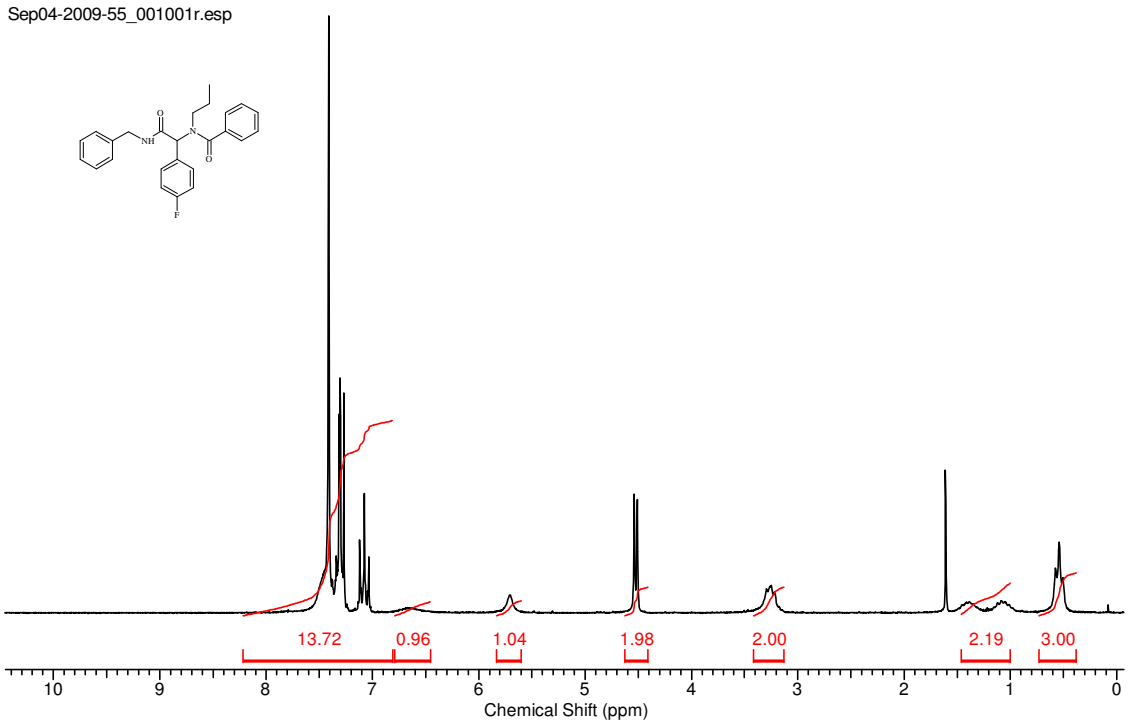

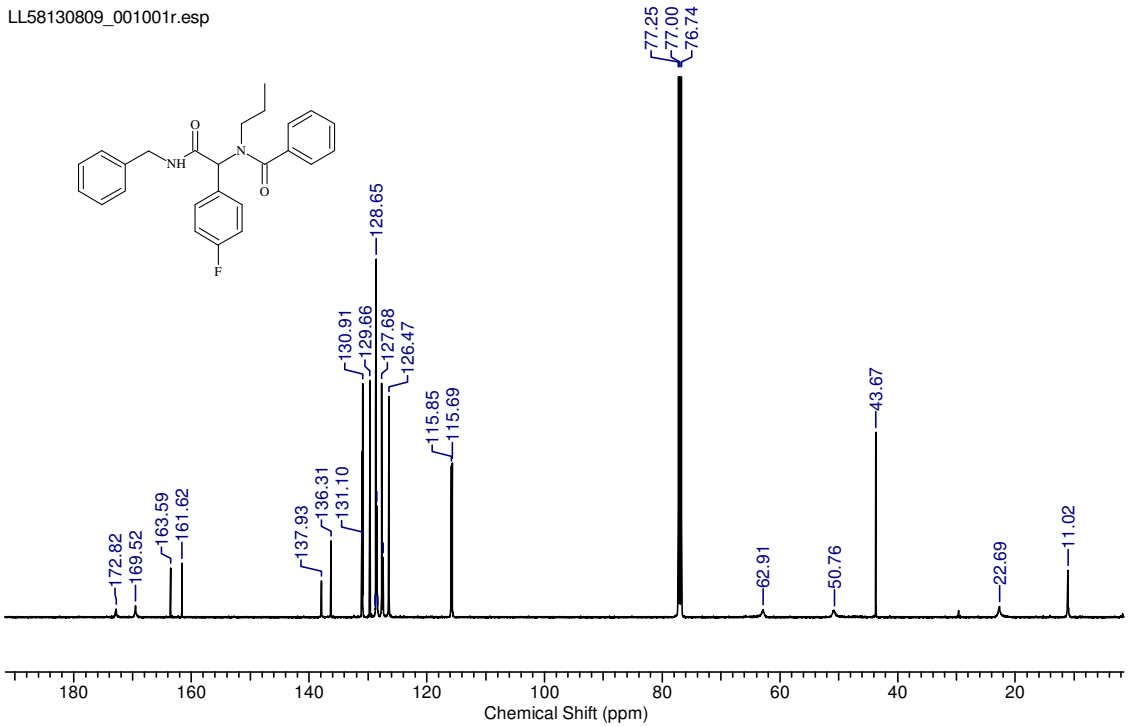

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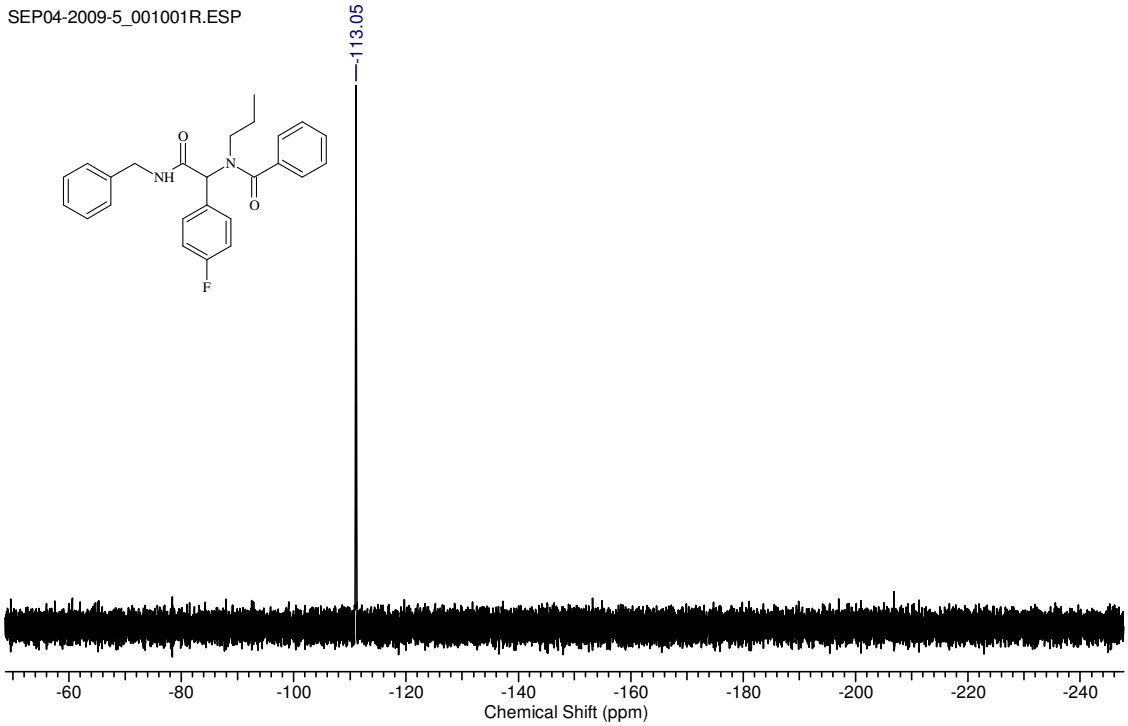

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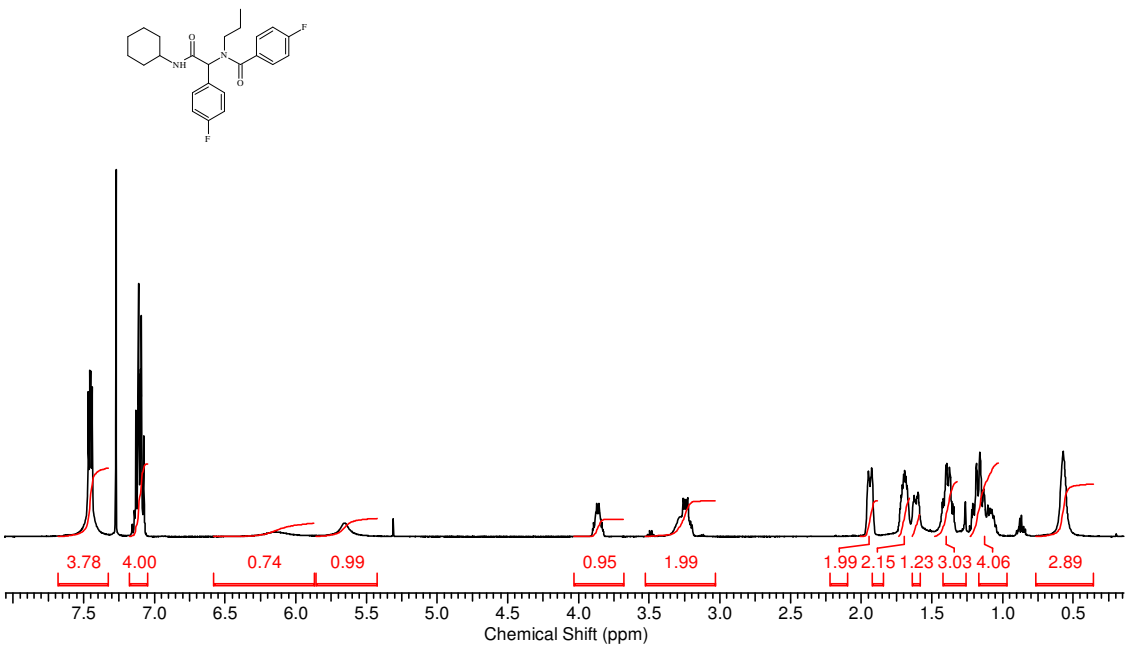

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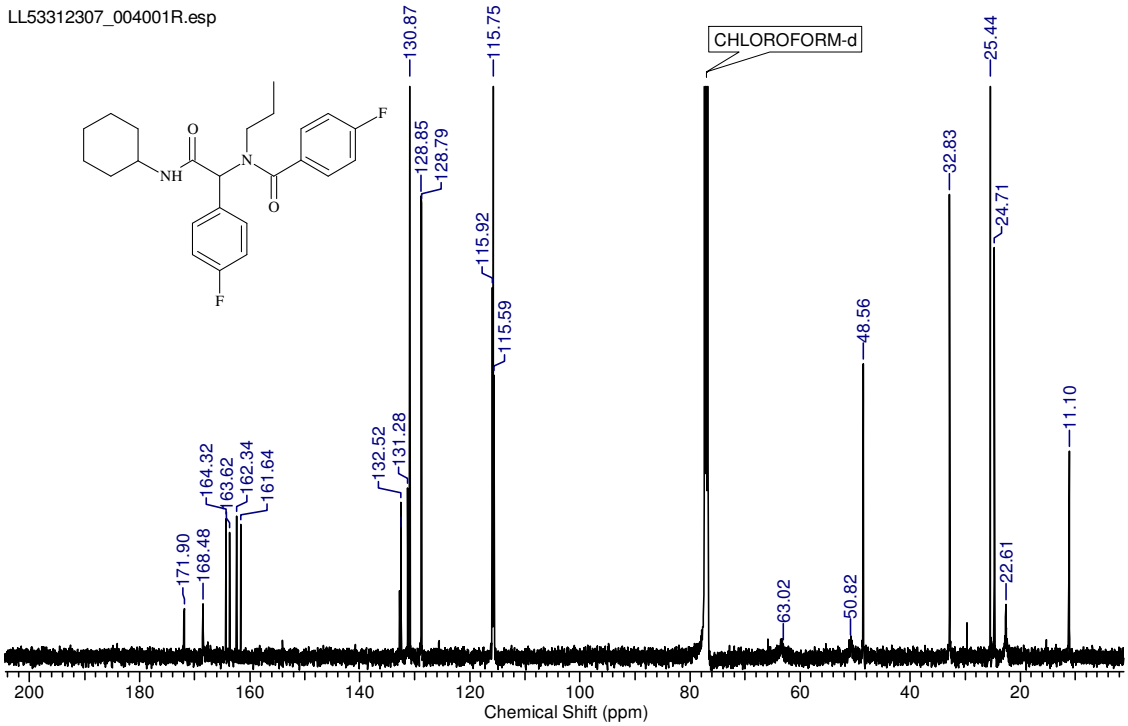

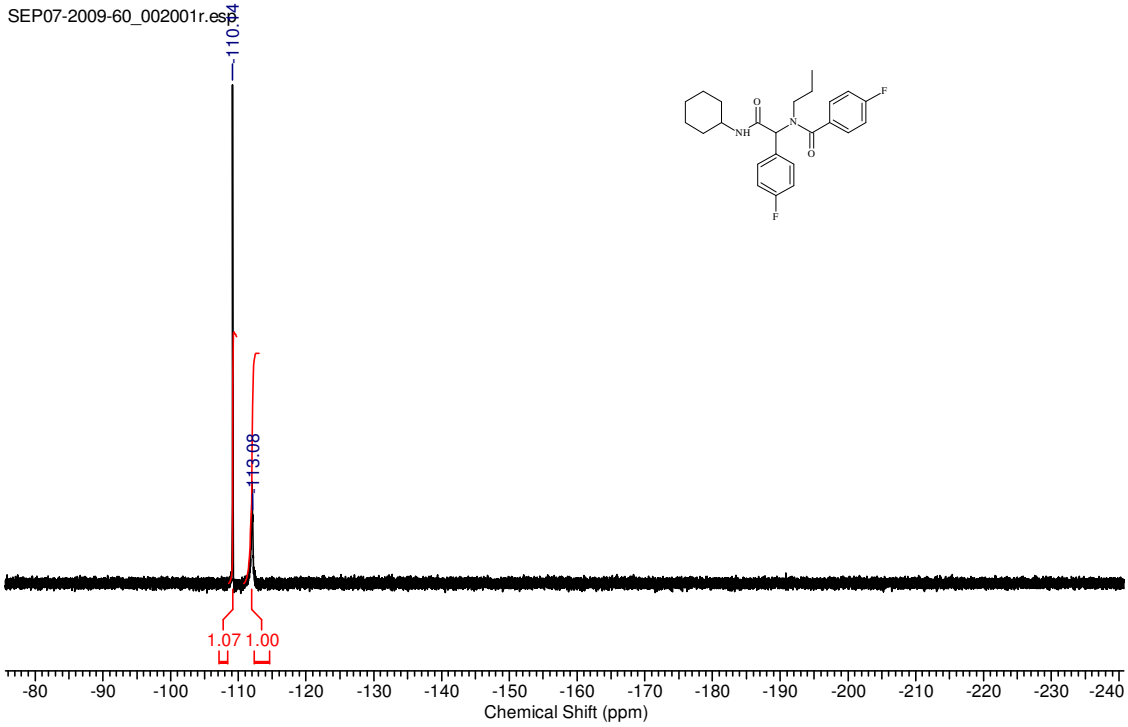

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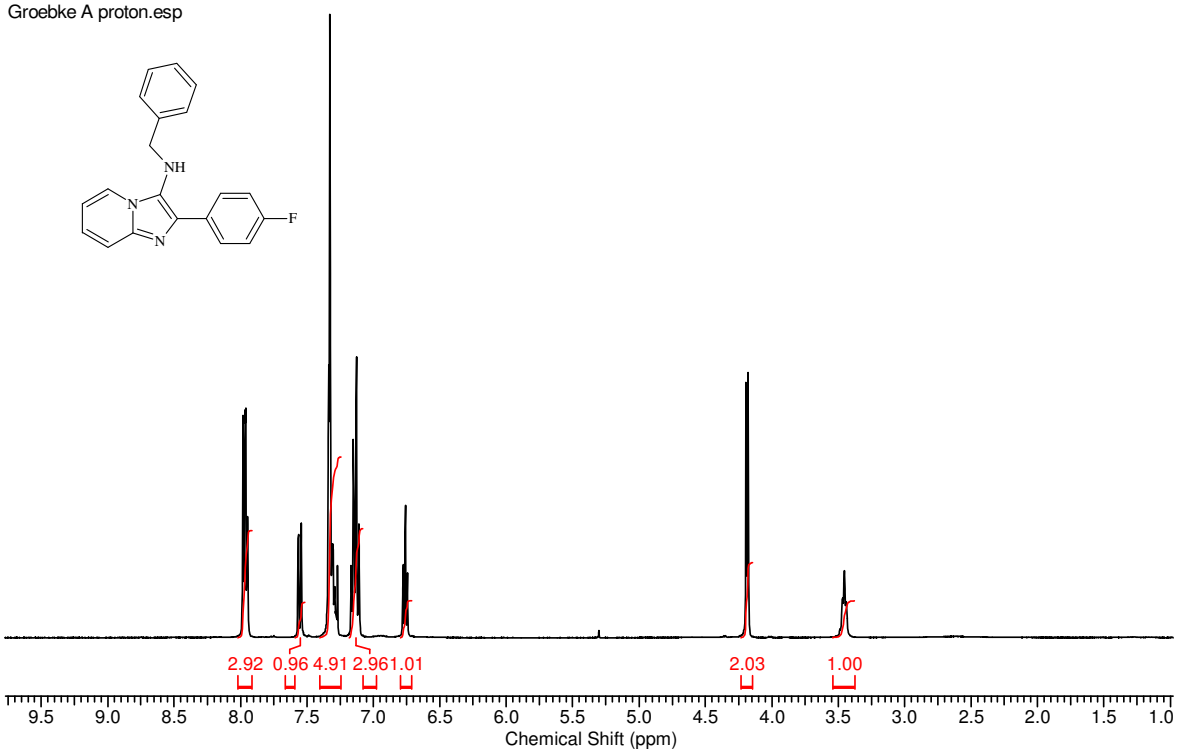

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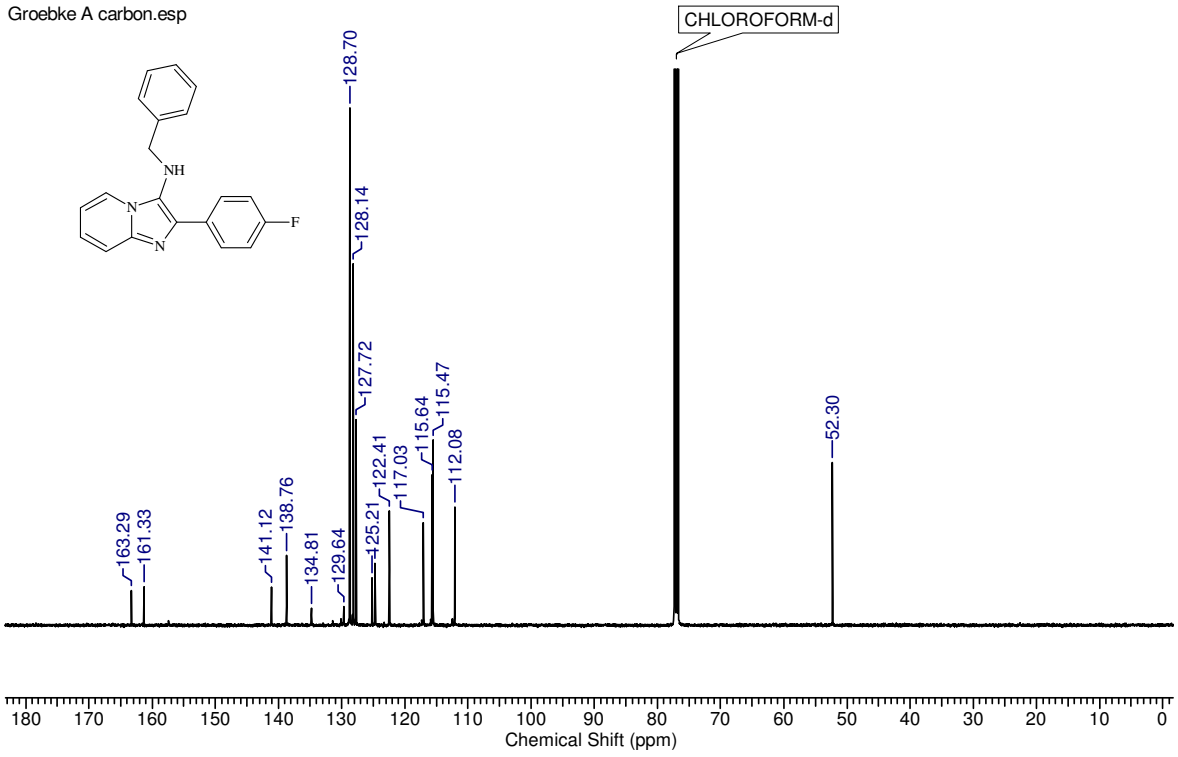

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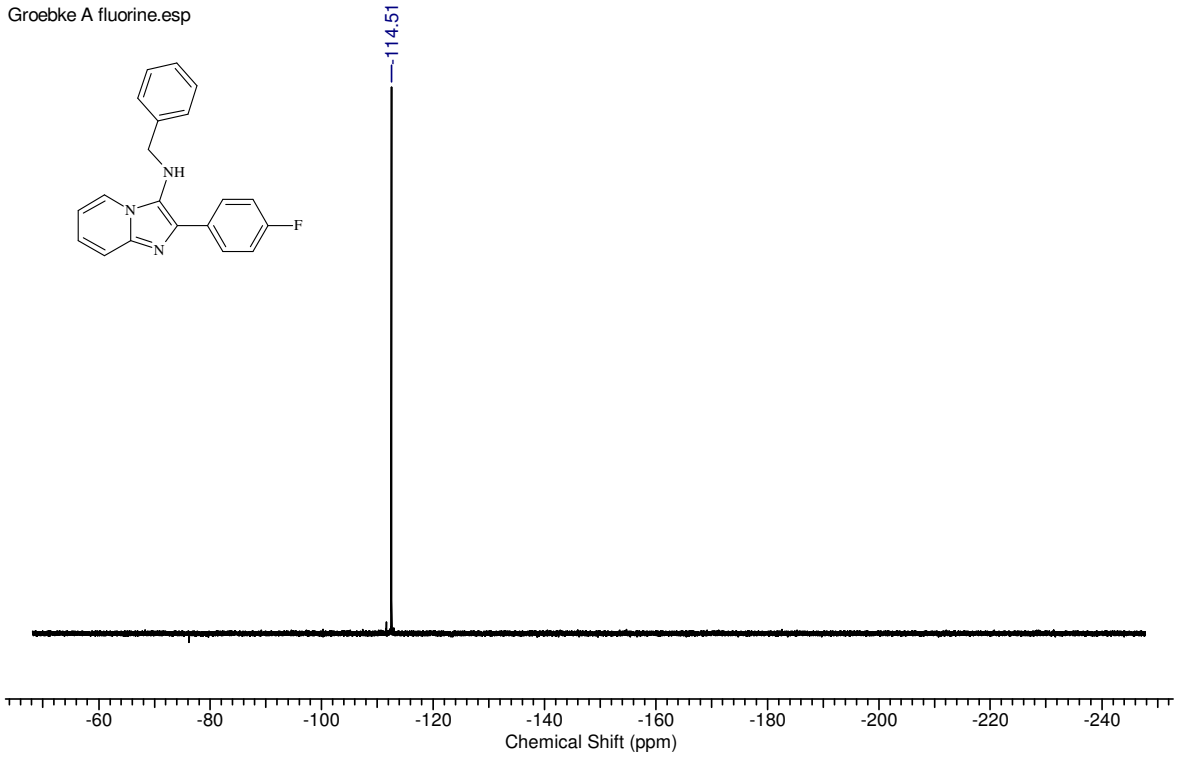

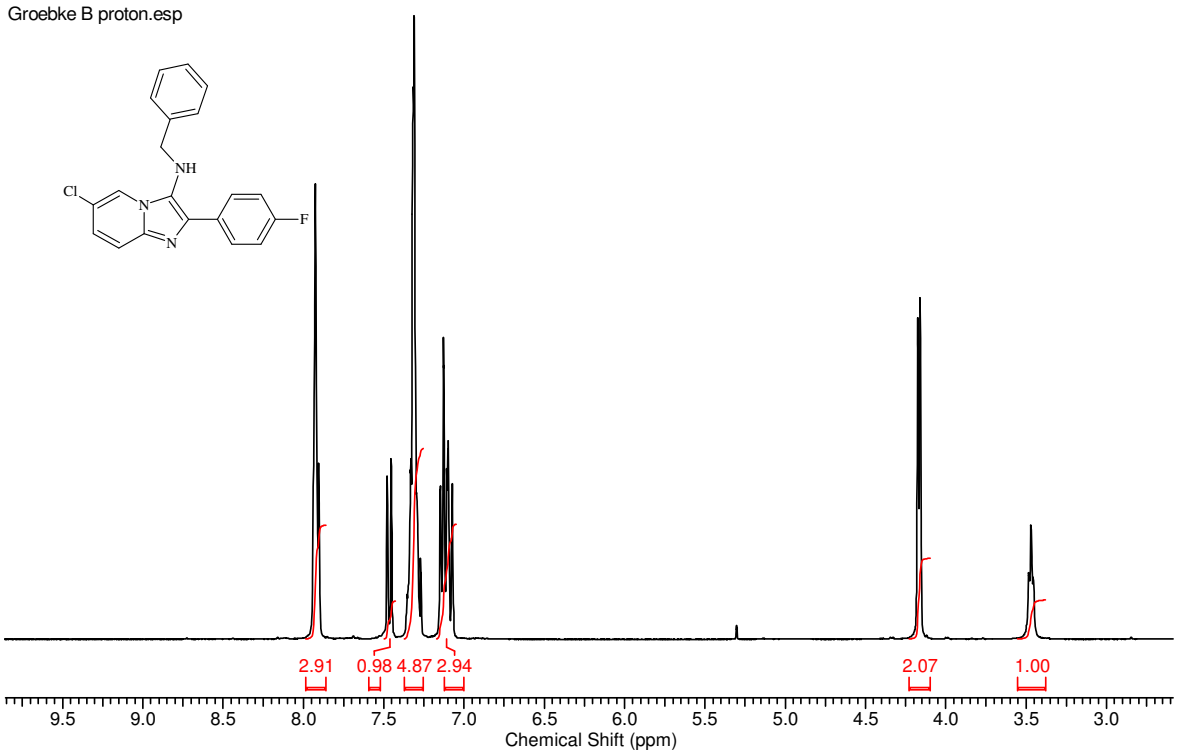

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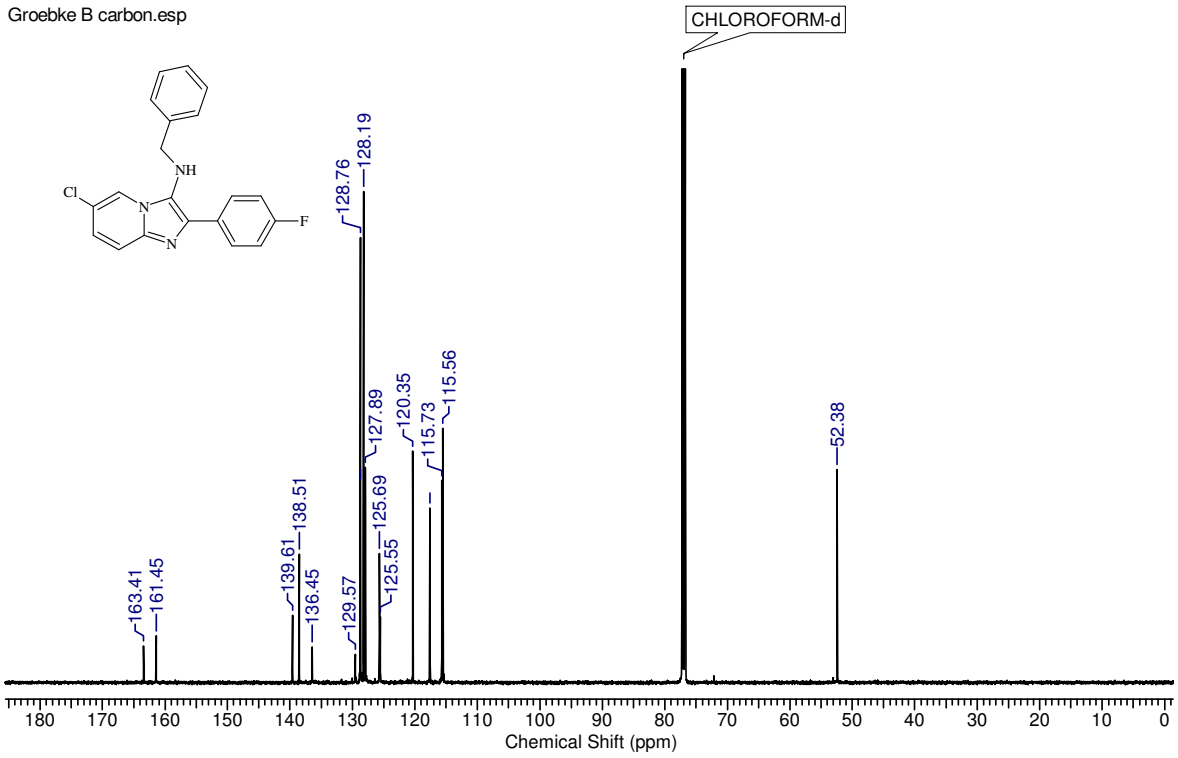

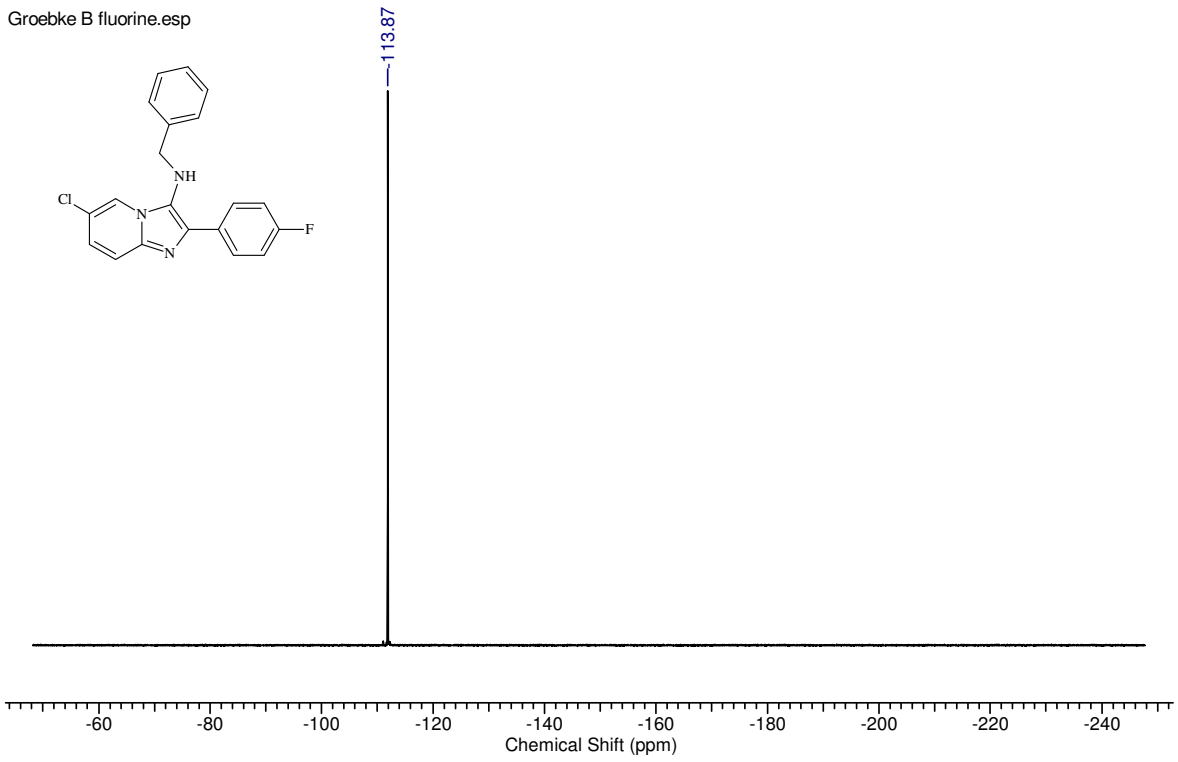

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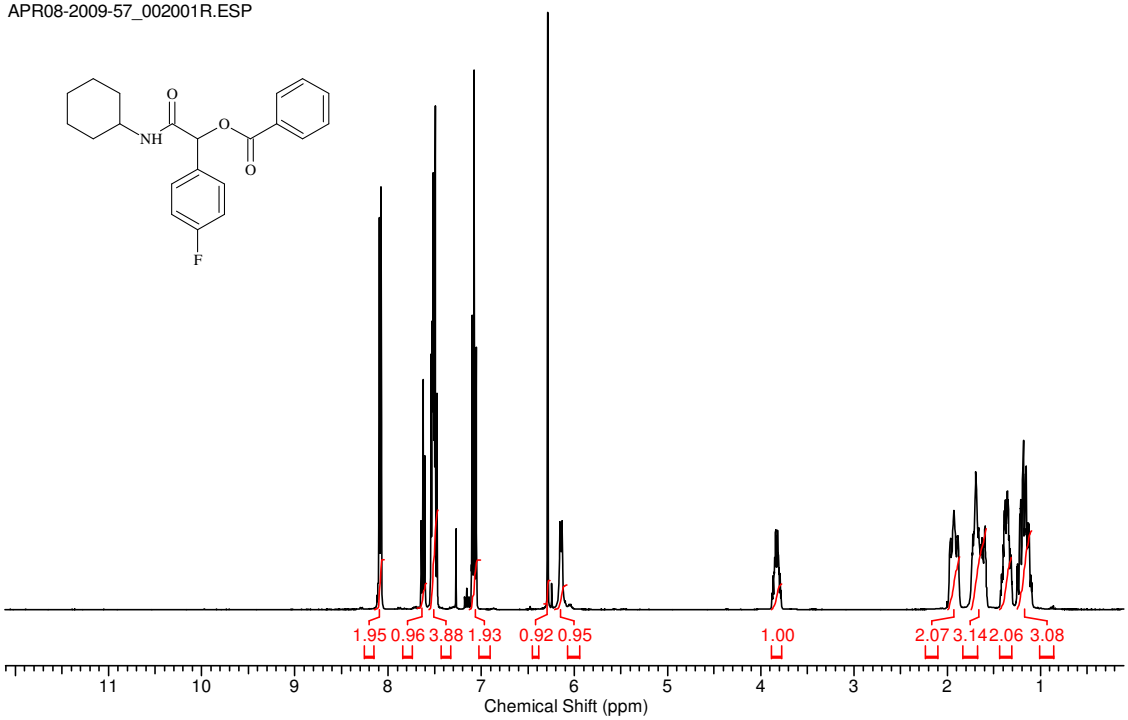

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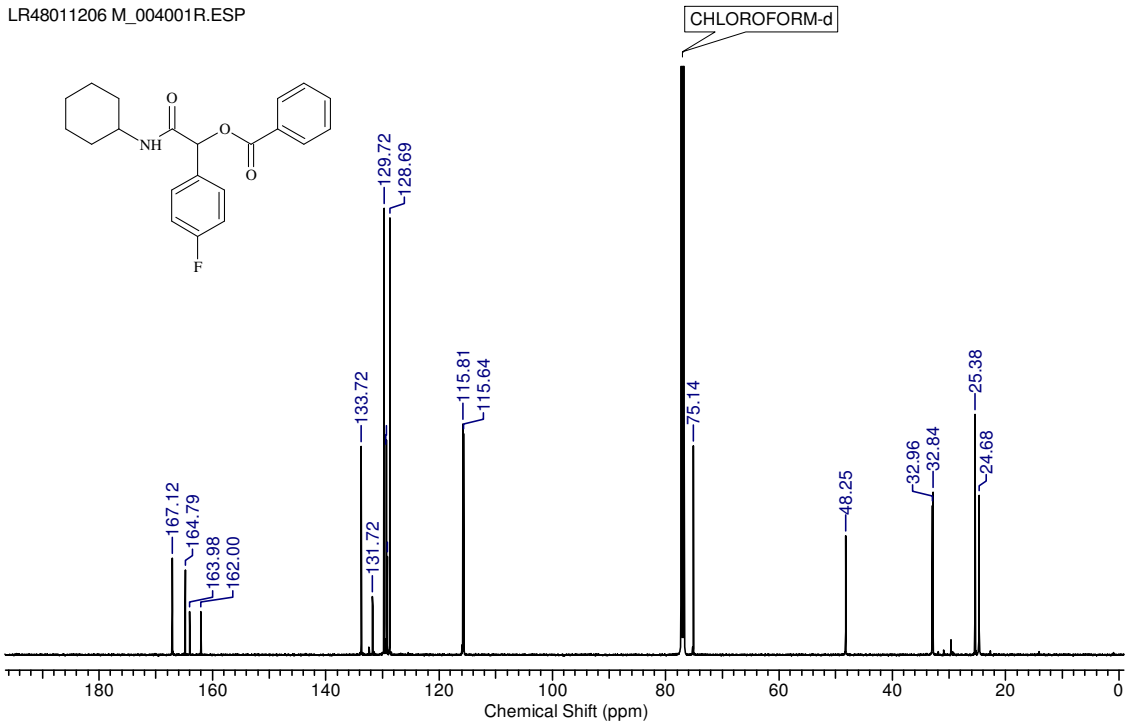

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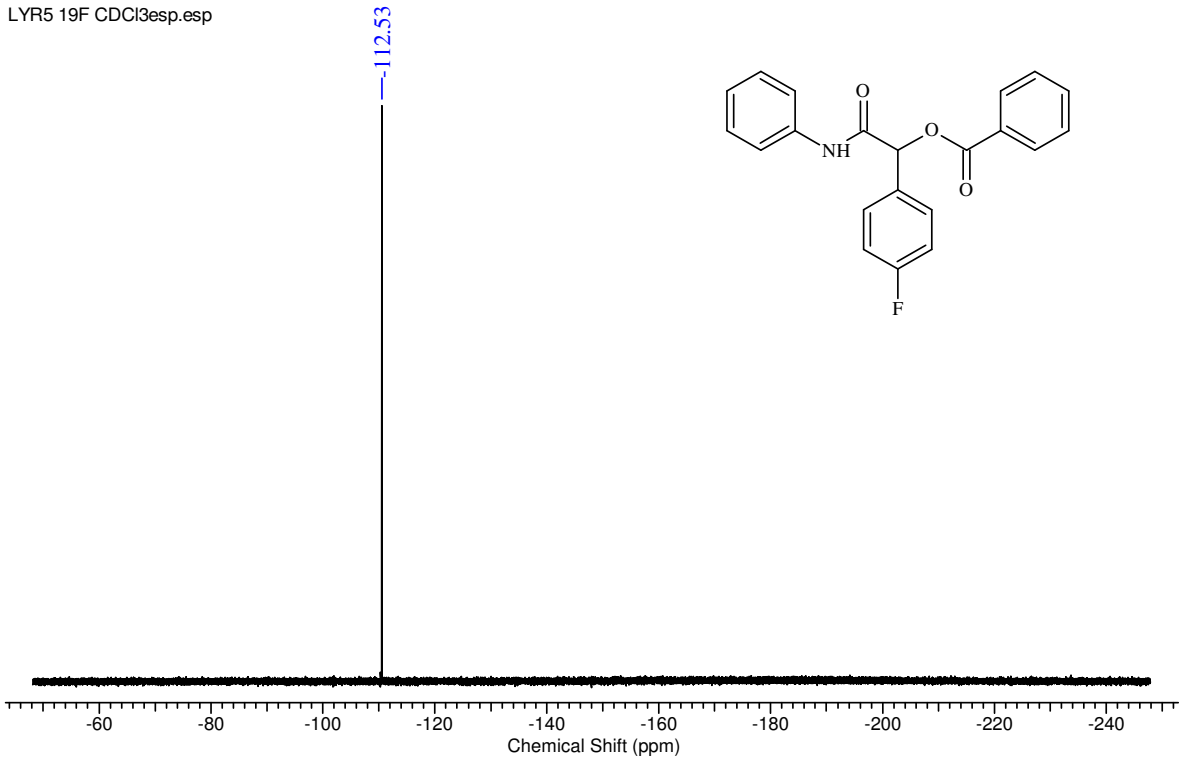

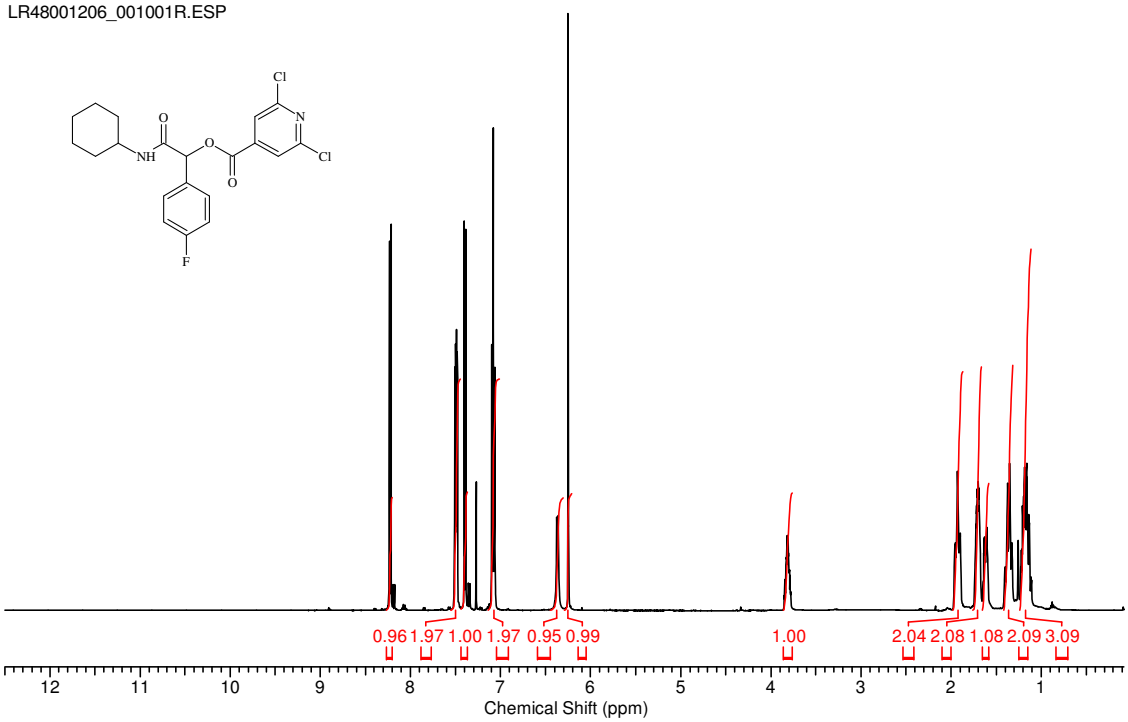

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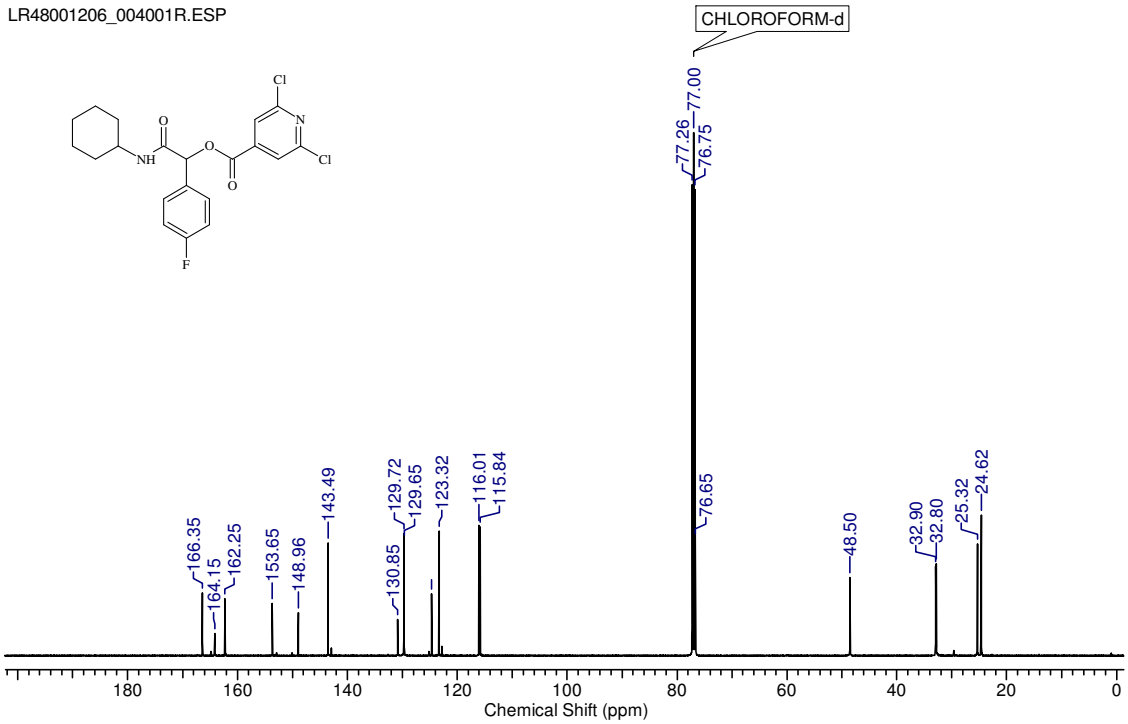

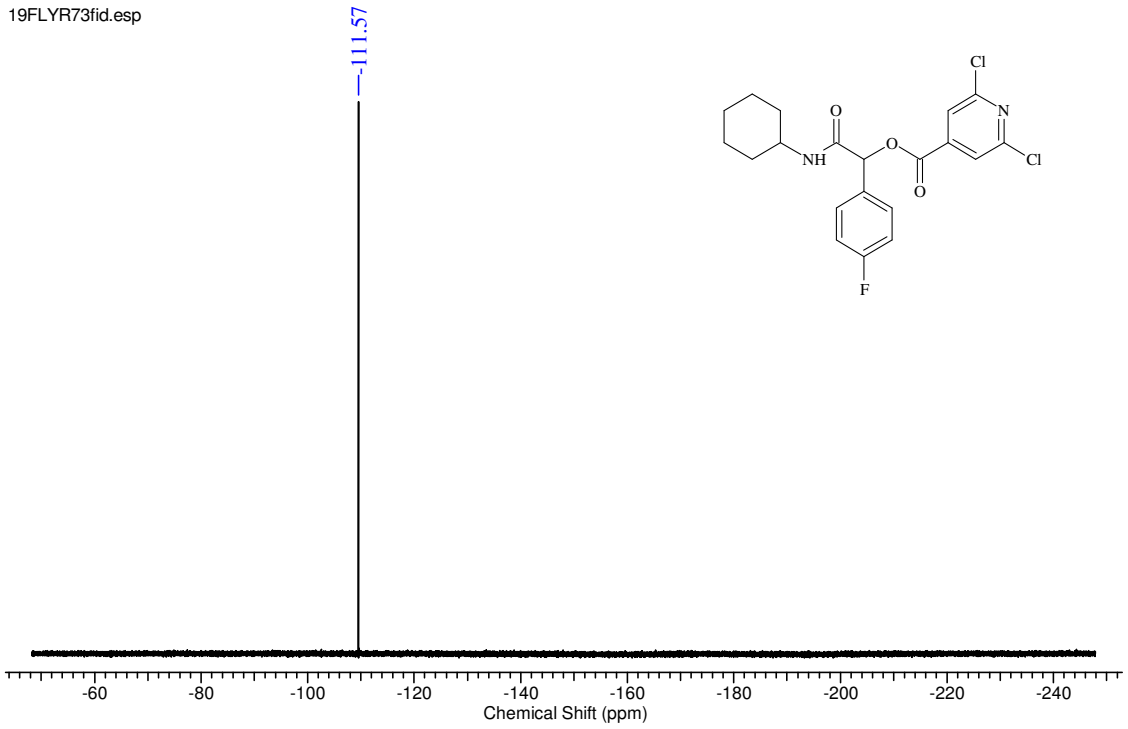

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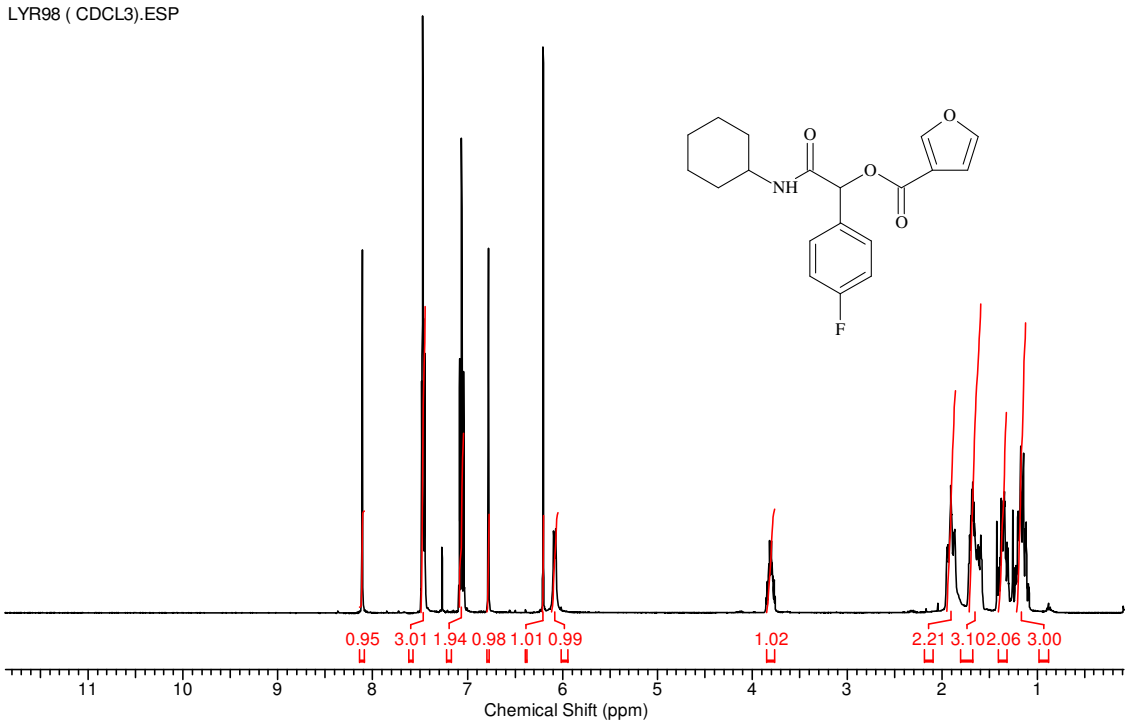

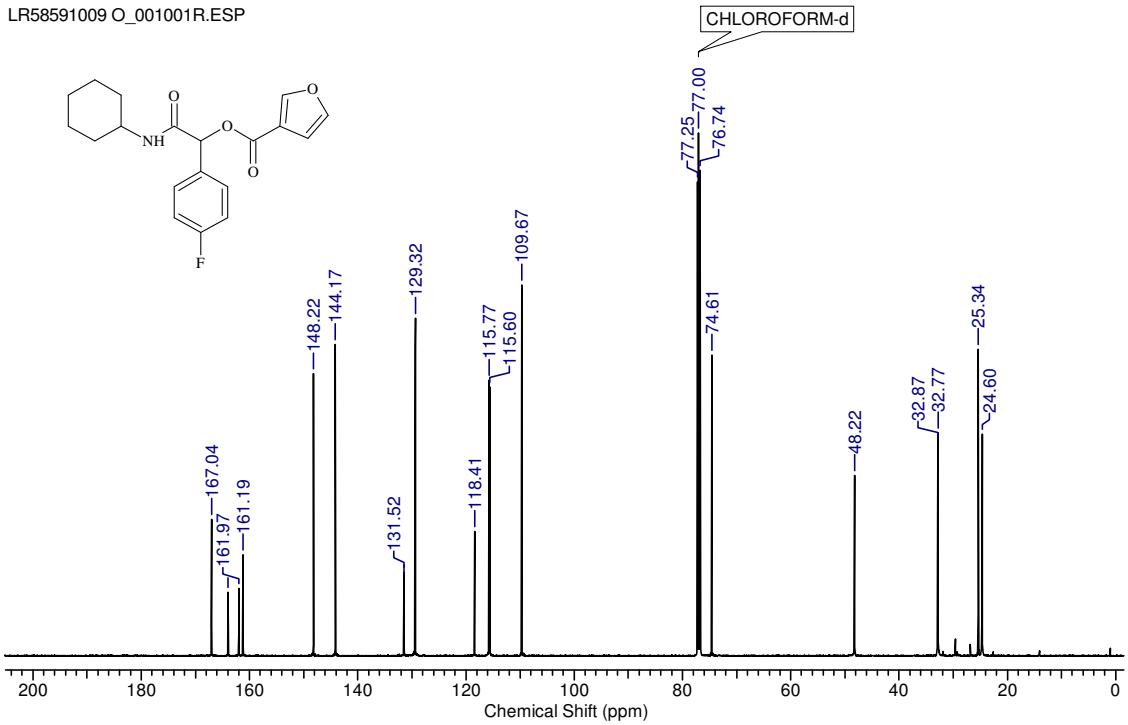

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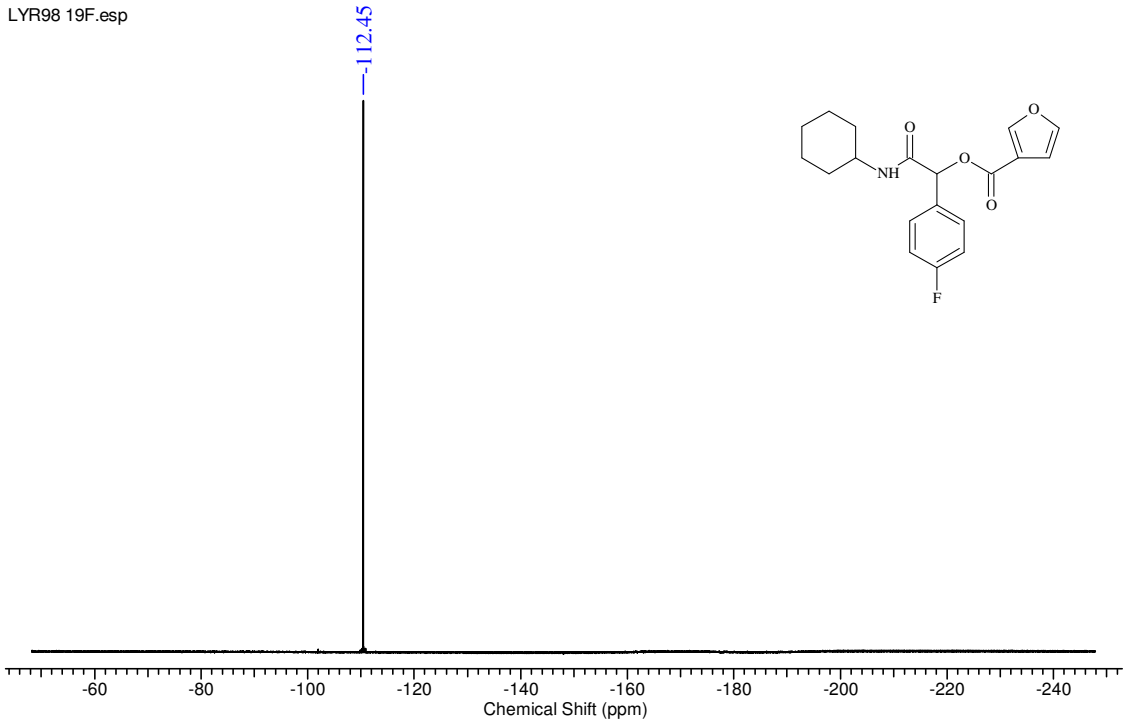

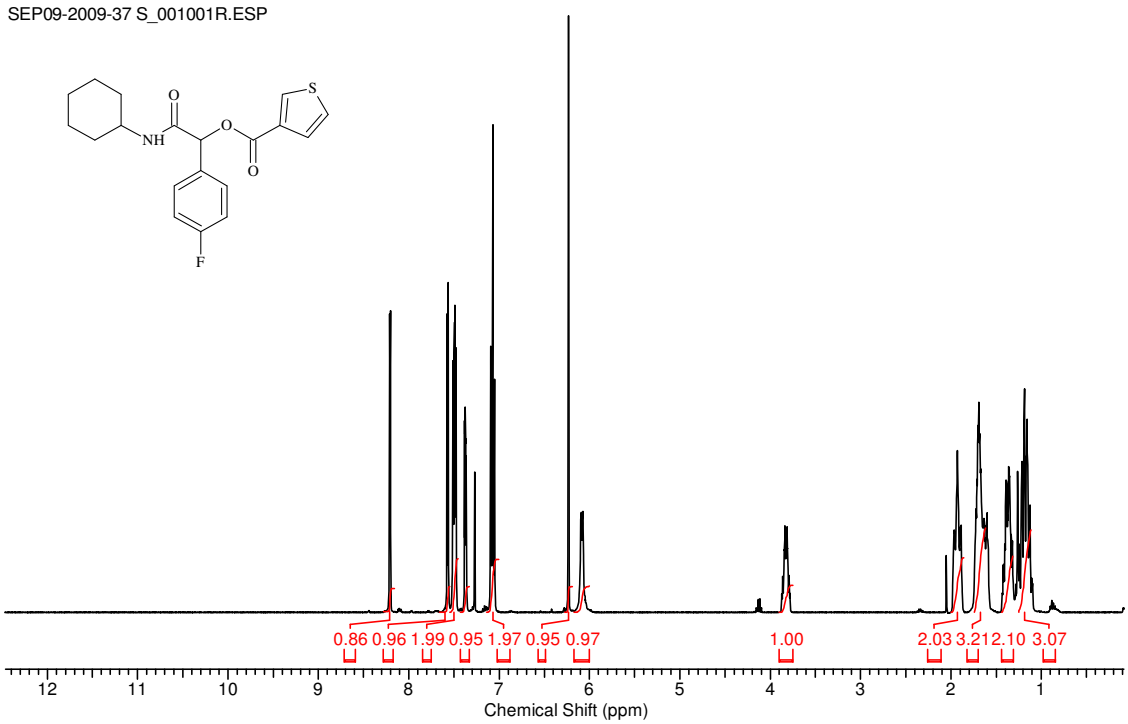

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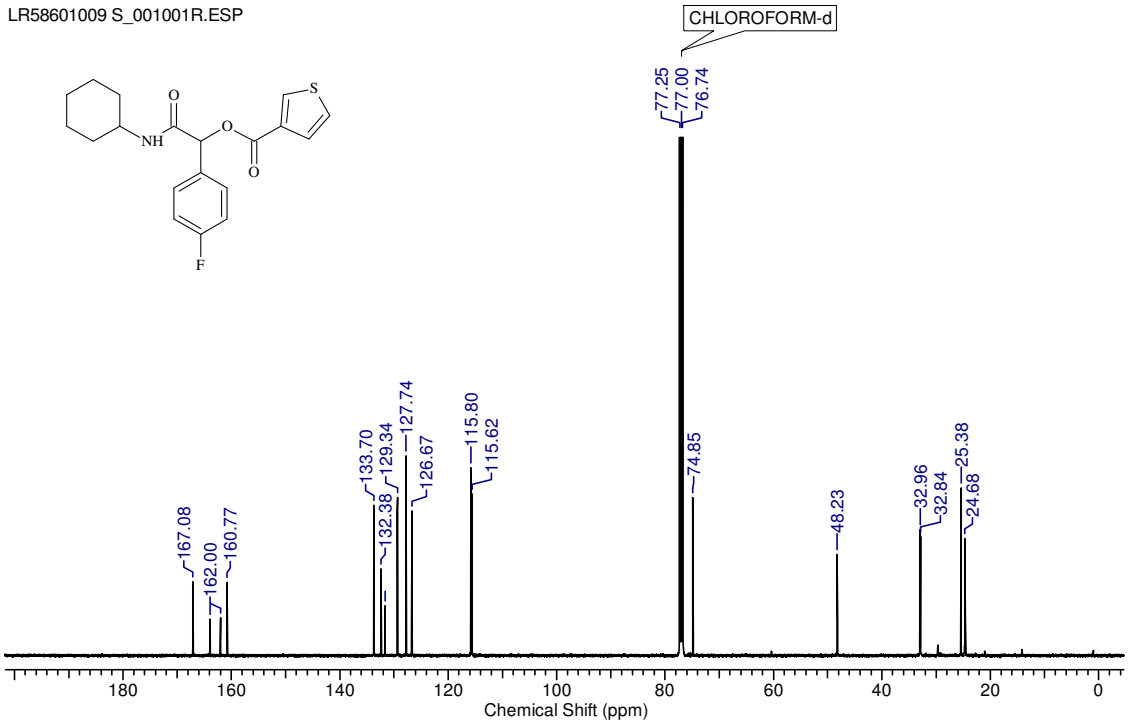

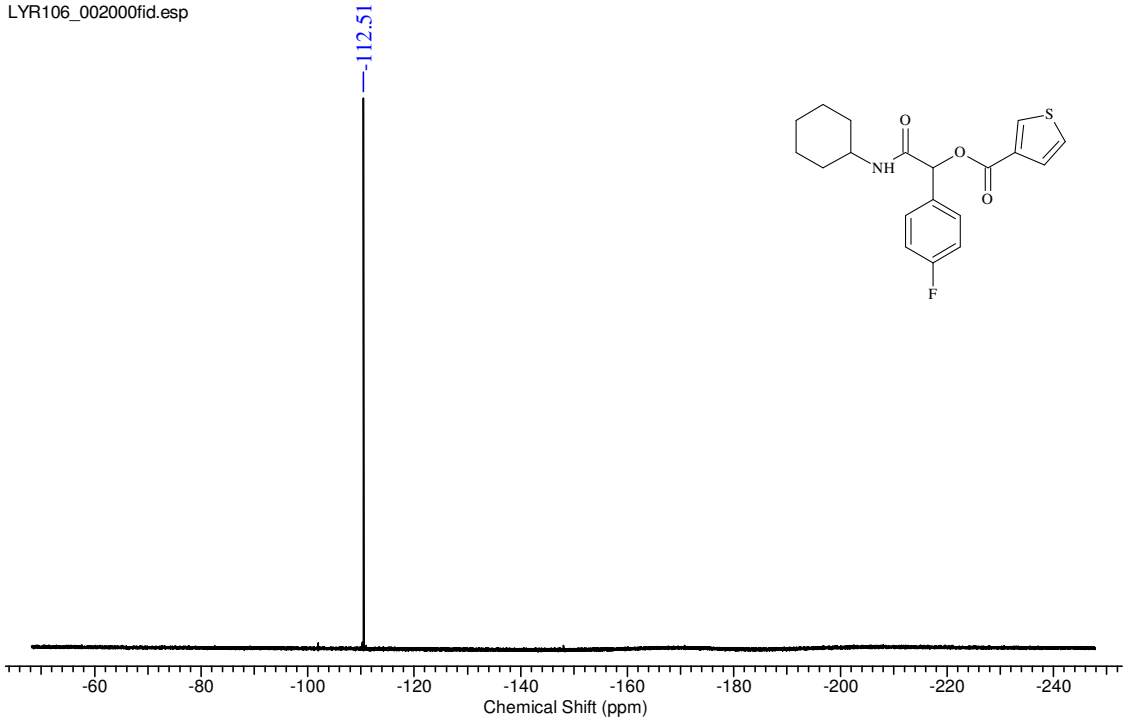

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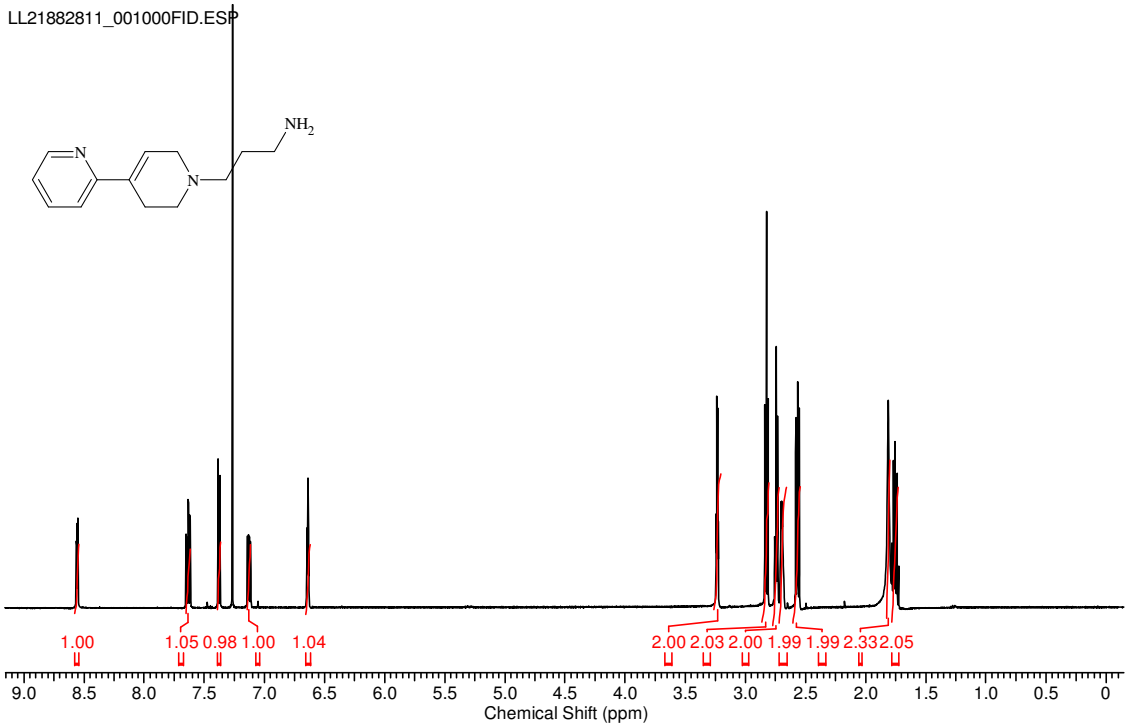

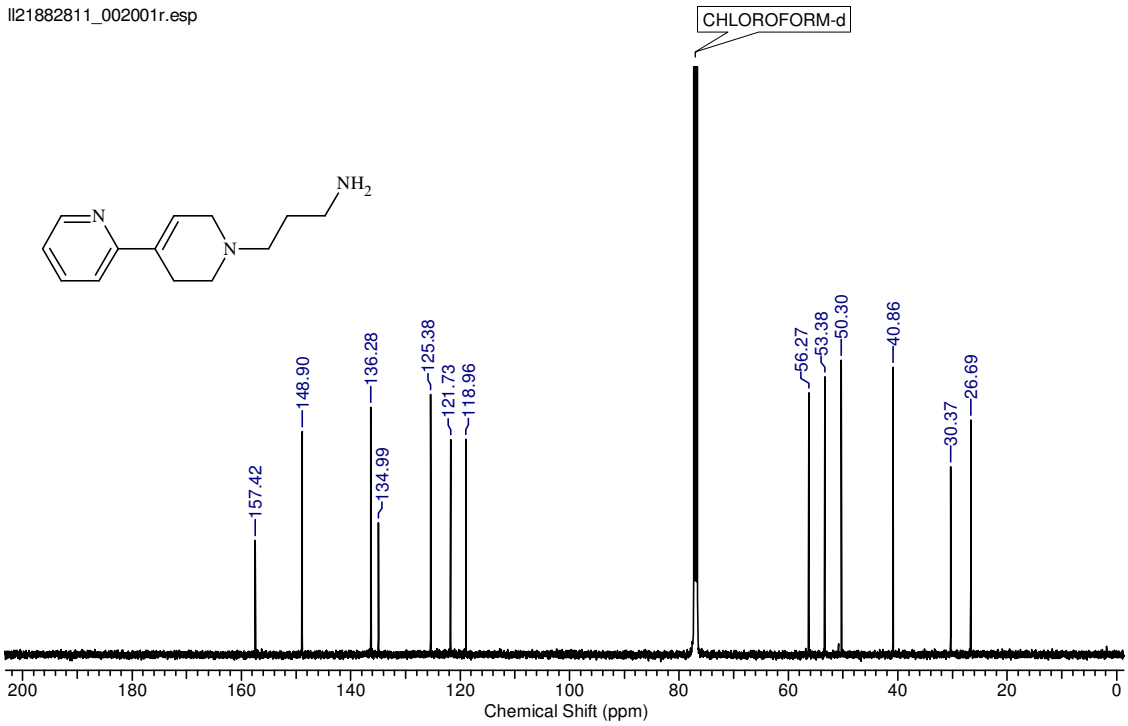

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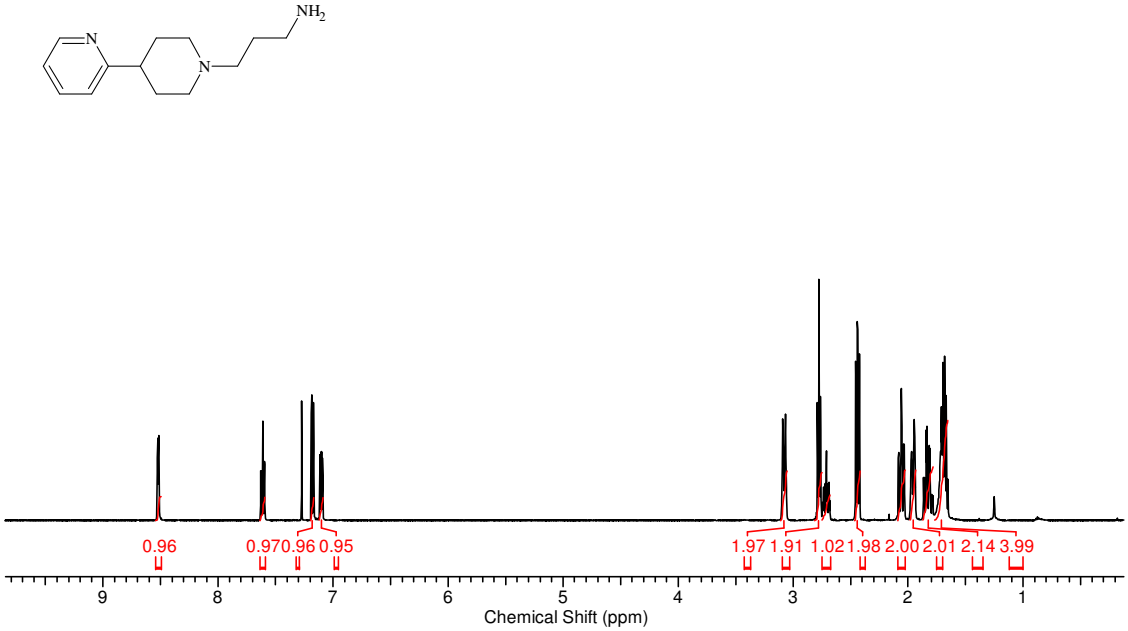

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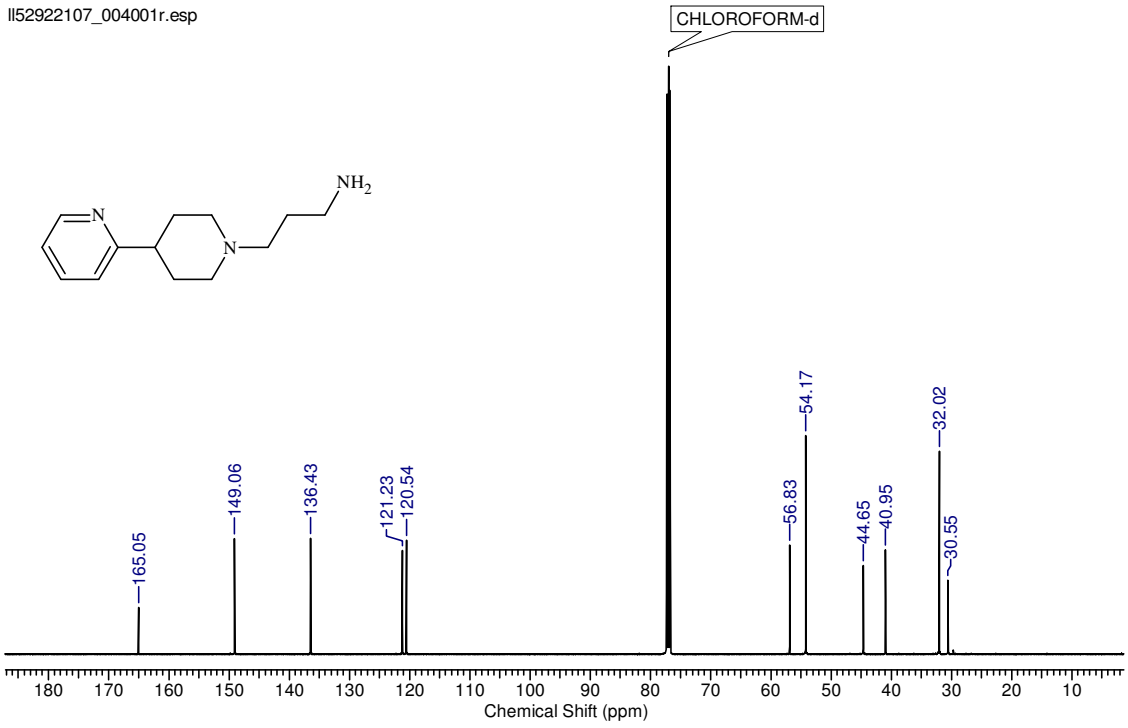

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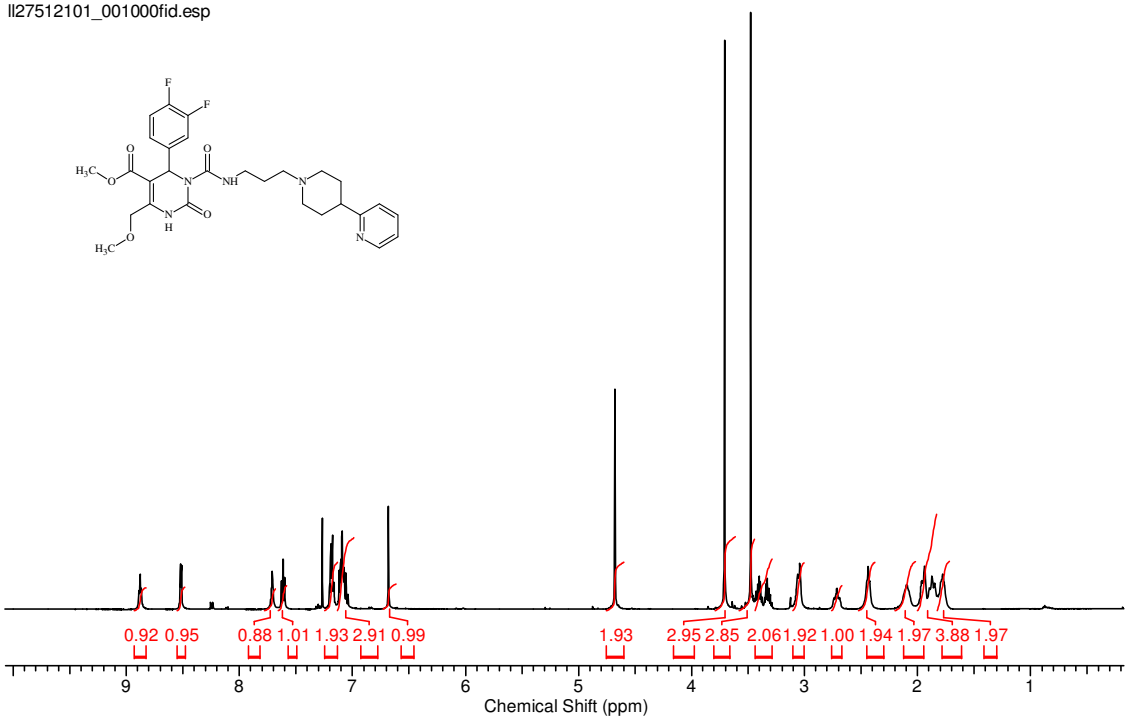

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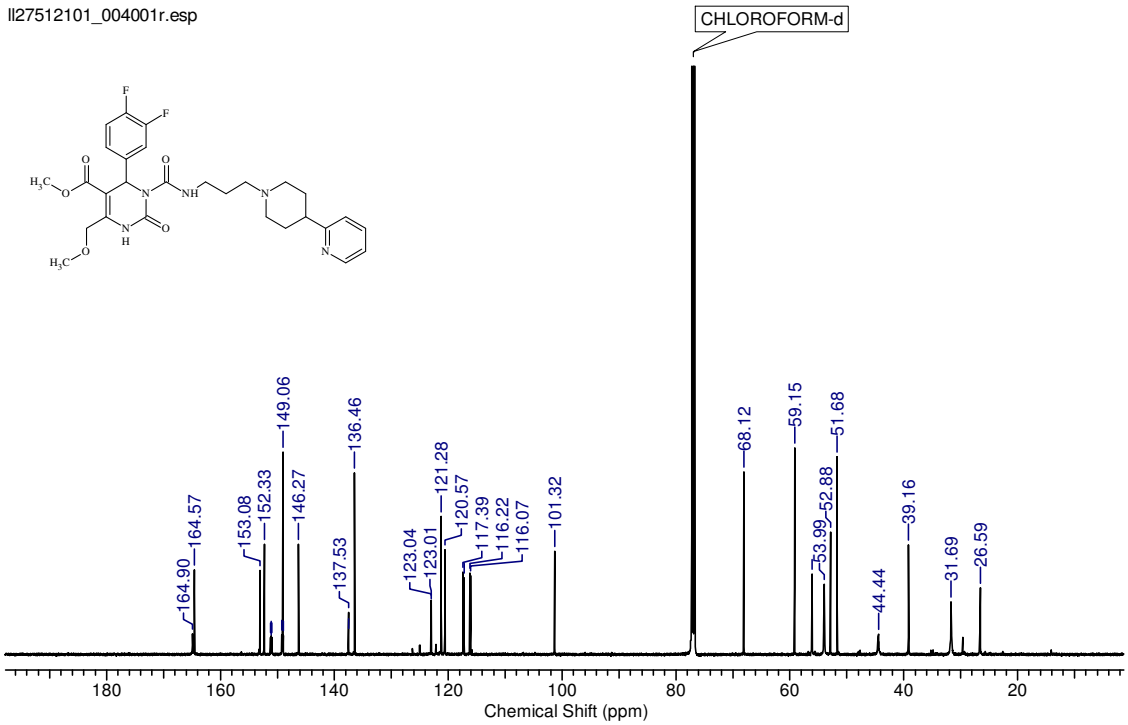

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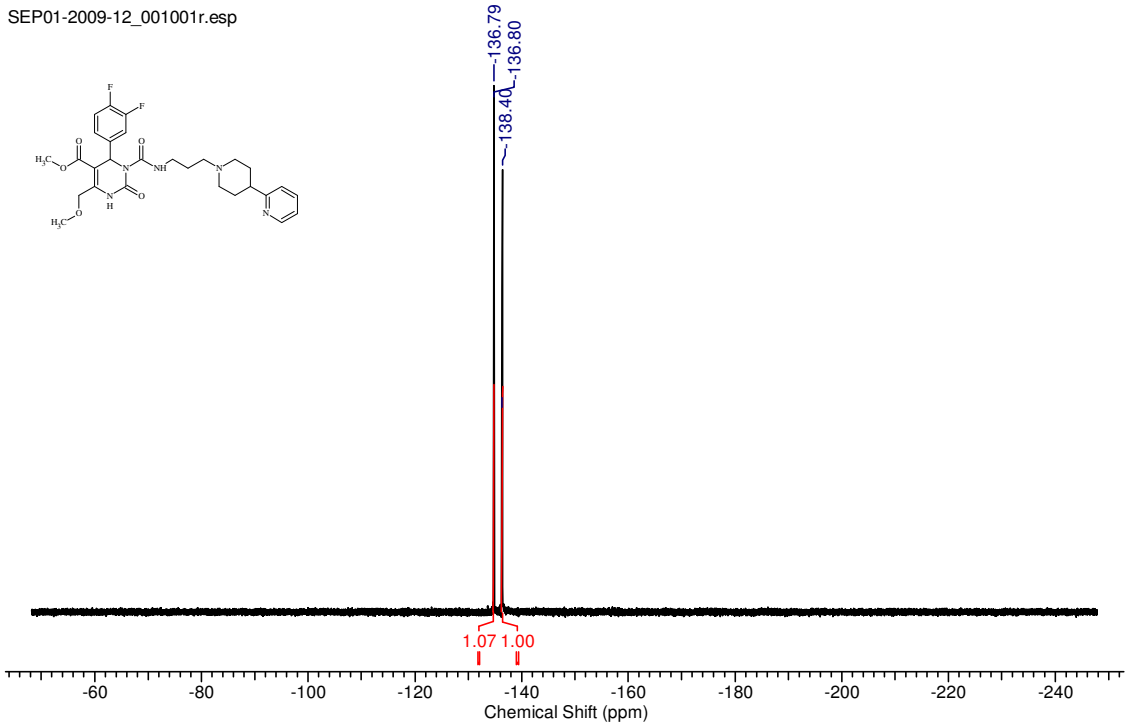

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