Chemoselective acylation of primary amines and amides with potassium acyltrifluoroborates under acidic conditions

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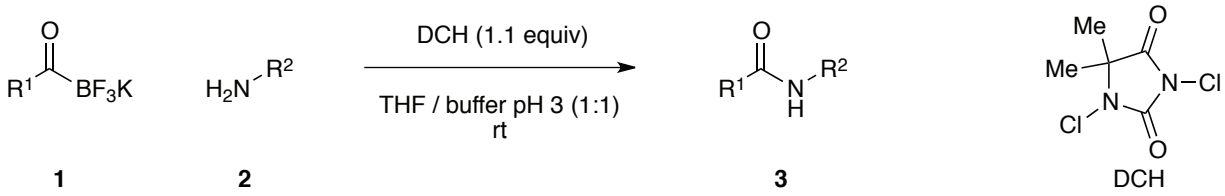
General Information

Reagents were purchased from Acros, Sigma-Aldrich, TCI, Fluka, Fluorochem or ABCR and used without further purification, with the following exceptions. *N*-Chlorosuccinimide (NCS) and 1,3,5-trichloroisocyanuric acid (TCCA) were purchased from Sigma-Aldrich and ABCR respectively, and recrystallized by following the reported procedure.[1] 1,3-Dichloro-5,5-dimethylhydantoin (DCH) was purchased from Fluka and recrystallized from CH_2Cl_2/hexanes (2:1) prior to use. Amines **2k**[2], **2n**[3], **2o**[2] and **S4**[4] and potassium acyltrifluoroborates **1a**[5], **1b-e**[6], **1f-h**[7], **1j**[7], **1k**[8] and **6**[5] were synthesized according to the corresponding literature procedures. Gentamicin C_1 was isolated from the commercial complex (purchased from Apollo, contains gentamicins C_1, C_{1a} and $C_{2a/b}$) by following the reported procedure.[9] *N*−Chloromorpholine was prepared as previously reported.[10]

Thin layer chromatography (TLC) was performed on glass-backed plates pre-coated with silica gel (Merck, Silica Gel 60 F254), which were visualized by fluorescence quenching under UV light or by staining (using ninhydrin or $KMnO_4$ solutions). Flash column chromatography was performed on Silicycle Silica Flash F60 (230–400 Mesh) using a forced flow of air at 0.5–1.0 bar. Melting points (m.p.) were measured on an Electrothermal Mel-Temp melting point apparatus and were uncorrected. NMR spectra were measured on VARIAN Mercury 300 MHz, 75 MHz, Bruker Avance 400 MHz, 100 MHz or Bruker AV-II 600 MHz, 150 MHz. Chemical shifts are expressed in parts per million (ppm) and are referenced to $CDCl_3$ 7.26 ppm, 77.0 ppm; acetone-d_6 2.05 ppm, 29.8 and 206.3 ppm; DMSO-d_6 2.50 ppm, 39.5 ppm; CD_3OD 3.31 ppm, 49.0 ppm. Coupling constants are reported as Hertz (Hz). Splitting patterns are indicated as follows: br, broad; br s, broad singlet; s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; sx, sextet; sp, septet; dd, doublet of doublets; dt, doublet of triplets; td, triplet of doublets; qd, quartet of doublets; ddd, doublet of doublet of doublets; dddd, doublet of doublet of doublet of doublets; tdd, triplet of doublet of doublets; m, multiplet. Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 spectrophotometer and are reported as wavenumber (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter with a 100 mm path length cell operating at the sodium D line (589 nm), at 23-24 ° C and reported as $[\alpha]_D$ (concentration g/100 mL, solvent). High-resolution mass spectra were measured on a Bruker Daltonics maXis ESI– QTOF or Bruker solariX ESI/MALDI–FTICR by the mass spectrometry service of the Laboratorium für Organische Chemie at the ETH Zürich. LC-MS was performed on a Dionex UltiMate 3000 RSLC connected to a Surveyor MSQ Plus mass spectrometer. HPLC (high performance liquid chromatography) was performed on JASCO analytical and preparative instruments. Unless otherwise stated, analytical and preparative reverse-

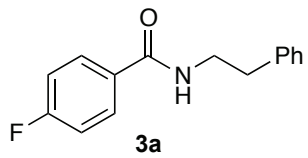
phase HPLC were performed using Shiseido C18 UG120 5 µm (4.6 mm I.D. × 250 mm) and YMC C18 (20 mm I.D. × 250 mm) columns with flow rates 1.0 mL/min and 10 mL/min respectively, using MQ-H_2O with 0.1% TFA (eluent A) and HPLC grade CH_3CN with 0.1% TFA (eluent B). Signals were monitored at 220, 254 and 301 nm. UV-Vis spectra and kinetics measurements were performed on a Thermo NanoDrop 2000c spectrophotometer.

General Procedure 1: Synthesis of Amides from Aliphatic or Aromatic Amines



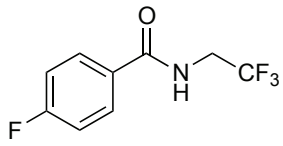
In a round-bottom flask, the corresponding potassium acyltrifluoroborate **1** (0.11 mmol, 1.1 equiv) was dissolved in 1 mL of a 1:1 mixture of THF and aq. buffer pH 3, 25 mM (prepared by dissolving citric acid monohydrate (4.48 g, 21.35 mmol) and trisodium citrate dihydrate (1.07 g, 3.64 mmol) in distilled water (1 L), final pH was adjusted using 0.1 M NaOH and HCl solutions). Amine **2** (0.10 mmol, 1.0 equiv) and 1,3-dichloro-5,5-dimethylhydantoin (DCH, 21.7 mg, 0.11 mmol, 1.1 equiv) were added and the mixture stirred at rt. The solution was quenched with sat. aq. $NaHSO_3$ (0.3 mL), poured into H_2O/brine and extracted with EtOAc (3 x 3 mL). The organic extracts were collected, dried over Na_2SO_4, filtered and evaporated in vacuo. The residue was purified by column chromatography on silica gel to afford the corresponding amide.

***N*-(2-Phenylethyl)-4-fluorobenzamide (3a).**



Prepared by following general procedure 1 for 30 min with potassium 4-fluorobenzoyltrifluoroborate (**1a**, 25.6 mg, 0.11 mmol, 1.1 equiv) and 2-phenethylamine (**2a**, 11.6 µL, 0.10 mmol, 1.0 equiv). The crude material was purified by column chromatography on silica gel (eluting with EtOAc/hexanes = 1:3) to give **3a** as a white solid (22.3 mg, 92%); **m.p.** 117-119 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.72 (dd, *J* = 8.8, 5.3 Hz, 2H, ArH), 7.38-7.34 (m, 2H, ArH), 7.30-7-25 (m, 3H, ArH), 7.1 (t, *J* = 8.6 Hz, 2H, ArH), 6.11 (br s, 1H, NH), 3.74 (dt, *J* = 7.3, 6.3 Hz, 2H, CH_2), 2.96 (t, *J* = 6.9 Hz, 2H, CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.4, 164.7 (d, *J* = 251.6 Hz), 138.8, 130.8 (d, *J* = 3.1 Hz), 129.1 (d, *J* = 8.9 Hz), 128.8, 128.7, 126.7, 115.6 (d, *J* = 21.8 Hz), 41.2, 35.7; **^{19}F NMR** (375 MHz, $CDCl_3$): δ −108.4; **IR** (thin film): v 3348, 3229, 1770, 1735, 1643, 1504, 1355, 1216 cm^{-1}; **ESI-HRMS** calcd for $C_{15}H_{15}FNO$ $[M + H]^+$ 244.1132, found 244.1126.

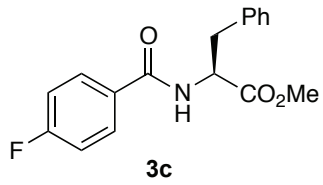
_N_-(2,2,2-Trifluoroethyl)-4-fluorobenzamide (3b).



3b

Prepared by following general procedure 1 for 30 min with potassium 4-fluorobenzoyltrifluoroborate (**1a**, 28.7 mg, 0.13 mmol, 1.3 equiv) and 2,2,2-trifluoroethylamine hydrochloride (**2b**, 13.5 µL, 0.10 mmol, 1.0 equiv). The crude material was purified by column chromatography on silica gel (eluting with EtOAc/hexanes = 1:3) to give **3b** as a white solid (16.3 mg, 74%); **m.p.** 98-100 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.84 (dd, *J* = 8.8, 5.2 Hz, 2H, ArH), 7.15 (td, *J* = 8.5, 1.3 Hz, 2H, ArH), 6.57 (br, 1H, NH), 4.18-4.09 (m, 2H, CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.6,165.1 (d, *J* = 253.3 Hz), 129.6 (d, *J* = 9.1 Hz), 129.3 (d, *J* = 3.2 Hz), 124.1 (q, *J* = 278.4 Hz), 116.9 (d, *J* = 22.0 Hz), 41.1 (q, *J* = 34.8 Hz); **^{19}F NMR** (375 MHz, $CDCl_3$): δ −72.3, −106.7; **IR** (thin film): v 3317, 2923, 1653, 1543, 1505, 1267, 1159 cm^{-1}; **ESI-HRMS** calcd for $C_9H_8F_4NO$ $[M + H]^+$ 222.0537, found 222.0531.

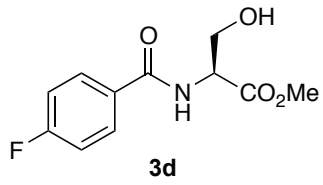
(_S_)-_N_-(4-Fluorobenzoyl)-phenylalanine methyl ester (3c).



3c

Prepared by following general procedure 1 for 1 h with potassium 4-fluorobenzoyltrifluoroborate (**1a**, 25.6 mg, 0.11 mmol, 1.1 equiv) and L-phenylalanine methyl ester hydrochloride (**2c**, 21.6 mg, 0.10 mmol, 1.0 equiv). The crude material was purified by column chromatography on silica gel (eluting with EtOAc/hexanes = 1:2) to give **3c** as a white solid (24.3 mg, 81%); **m.p.** 61-64 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.75 (dd, *J* = 8.8, 5.2 Hz, 2H, ArH), 7.35-7.27 (m, 3H, ArH), 7.16-7.11 (m, 4H, ArH), 6.57 (br, 1H, NH), 5.10 (dt, *J* = 7.6, 5.6 Hz, 1H, CH), 3.78 (s, 3H, CH_3), 3.32 (dd, *J* = 13.9, 5.8 Hz, 1H, CH), 3.25 (dd, *J* = 13.9, 5.4 Hz, 1H, CH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 172.0, 166.1,165.0 (d, *J* = 252.6 Hz), 135.7, 129.9 (d, *J* = 3.1 Hz), 129.4 (d, *J* = 9.0 Hz), 129.3, 128.7, 127.3, 115.8 (d, *J* = 22.0 Hz), 53.6, 52.5, 37.8; **^{19}F NMR** (375 MHz, $CDCl_3$): δ −107.6; **IR** (thin film): v 3309, 3030, 2953, 1745, 1644, 1503, 1229, 1160 cm^{-1}; **ESI-HRMS** calcd for $C_{17}H_{17}FNO_3$ $[M + H]^+$ 302.1187, found 302.1187; **$[\alpha]_D^{25}$**: +89.4 (*c* = 0.22, $CHCl_3$).

(_S_)-_N_-(4-Fluorobenzoyl)-serine methyl ester (3d).

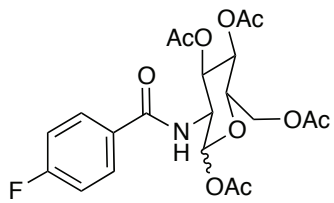


3d

Prepared by following general procedure 1 for 1 h with potassium 4-fluorobenzoyltrifluoroborate (**1a**, 25.6 mg, 0.11 mmol, 1.1 equiv) and L-serine methyl ester hydrochloride (**2d**, 15.6 mg, 0.10 mmol, 1.0 equiv). The crude

material was purified by column chromatography on silica gel (eluting with CH_2Cl_2/MeOH = 100:5) to give **3d** as a white solid (19.3 mg, 80%); **m.p.** 97-99 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.84 (dd, *J* = 8.8, 5.5 Hz, 2H, ArH), 7.12 (t, *J* = 8.7 Hz, 3H, ArH + NH), 4.85 (dt, *J* = 7.2, 3.5 Hz, 1H, CH), 4.09 (dd, *J* = 11.2, 3.8 Hz, 1H, CH), 4.03 (ddd, *J* = 11.2, 3.4, 0.8 Hz, 1H, CH), 3.82 (s, 3H, CH_3), 2.82 (br, 1H, OH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.0, 166.6,165.0 (d, *J* = 252.8 Hz), 129.7, 129.6 (d, *J* = 9.0 Hz), 115.7 (d, *J* = 21.9 Hz), 63.4, 55.2, 52.9; **^{19}F NMR** (375 MHz, $CDCl_3$): δ −107.2; **IR** (thin film): v 3363, 2924, 1741, 1645, 1504, 1230, 1162 cm^{-1}; **ESI-HRMS** calcd for $C_{11}H_{12}FNNaO_4$ $[M + Na]^+$ 264.0643, found 264.0644; **$[\alpha]_D^{25}$**: +39.6 (*c* = 0.32, $CHCl_3$).

2-(4-Fluorobenzamido)-2-deoxy-1,3,4,6-tetra-*O*-acetyl-α/β-D-glucopyranose (3e).

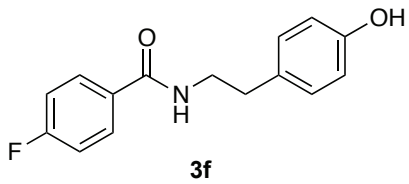


α/β–**3e**

Prepared with potassium 4-fluorobenzoyltrifluoroborate (**1a**, 25.6 mg, 0.11 mmol, 1.1 equiv) and D-glucosamine hydrochloride (**2e**, 21.5 mg, 0.10 mmol, 1.0 equiv) by a modification of general procedure 1. After the reaction was stirred for 1 h at rt and quenched, the aqueous phase containing the product was washed twice with EtOAc and lyophilized. The crude material was resuspended in acetone (5 mL) and Ac_2O (188 µL, 2.0 mmol, 20 equiv) and pyridine (162 µL, 2.0 mmol, 20 equiv) were added at rt. The mixture was stirred for 15 h, quenched with sat. aq. $NaHCO_3$ and extracted with EtOAc (3 x 3 mL). The organic extracts were collected, dried over Na_2SO_4, filtered and evaporated in vacuo. The residue was purified by column chromatography on silica gel (eluting with EtOAc/hexanes = 1:1) to give **3e** as a white solid [31.1 mg, 66% (over 2 steps), mixture of *α* and *β* isomers (α/β ~2:1 ratio, determined by NMR analysis of the reaction crude)]; **α-3e: m.p.** 107-110 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.73 (dd, *J* = 8.8, 5.2 Hz, 2H, ArH), 7.14 (t, *J* = 8.5 Hz, 2H, ArH), 6.35 (d, *J* = 3.7 Hz, 1H, CH), 6.33 (d, *J* = 8.6 Hz, 1H, NH), 5.42-5.29 (m, 2H, CH_2), 4.63 (ddd, *J* = 10.7, 8.5, 3.7 Hz, 1H, CH), 4.31 (dd, *J* = 12.6, 4.2 Hz, 1H, CH), 4.12 (dd, *J* = 12.5, 2.2 Hz, 1H, CH), 4.06 (ddd, *J* = 9.9, 4.1, 2.4 Hz, 1H, CH), 2.19 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.07 (s, 3H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 172.4, 170.8, 169.1, 168.6, 166.1,165.1 (d, *J* = 253.1 Hz), 129.5, 129.3 (d, *J* = 9.1 Hz), 115.9 (d, *J* = 22.0 Hz), 90.5, 70.8, 69.8, 67.3, 61.6, 52.1, 20.9, 20.8, 20.7, 20.6; **^{19}F NMR** (375 MHz, $CDCl_3$): δ −106.7; **IR** (thin film): v 3342, 2962, 1748, 1653, 1505, 1221, 1036 cm^{-1}; **ESI-HRMS** calcd for $C_{21}H_{24}FNNaO_{10}$ $[M + Na]^+$ 492.1267, found 492.1274; **$[\alpha]_D^{25}$**: +87.6 (*c* = 0.69, $CHCl_3$).

β -3e: m.p. 194-196 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.73 (dd, *J* = 8.9, 5.2 Hz, 2H, ArH), 7.09 (t, *J* = 8.6 Hz, 2H, ArH), 6.29 (d, *J* = 9.2 Hz, 1H, NH), 5.80 (d, *J* = 8.7 Hz, 1H, CH), 5.32-5.22 (m, 2H, CH_2), 4.54 (dt, *J* = 10.1, 9.0 Hz, 1H, CH), 4.30 (dd, *J* = 12.4, 4.7 Hz, 1H, CH), 4.16 (dd, *J* = 12.4, 2.3 Hz, 1H, CH), 3.88 (ddd, *J* = 9.6, 4.6, 2.2 Hz, 1H, CH), 2.11 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 1.99 (s, 3H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.5, 170.7, 169.6, 169.2, 166.2,165.0 (d, *J* = 253.0 Hz), 129.7 (d, *J* = 3.2 Hz), 129.3 (d, *J* = 9.1 Hz), 115.9 (d, *J* = 22.0 Hz), 92.9, 73.2, 72.7, 67.6, 61.7, 53.6, 20.9, 20.7, 20.6, 20.6; **^{19}F NMR** (375 MHz, $CDCl_3$): δ −107.1; **IR** (thin film): v 3341, 2958, 1748, 1659, 1503, 1225 cm^{-1}; **ESI-HRMS** calcd for $C_{21}H_{24}FNNaO_{10}$ $[M + Na]^+$ 492.1267, found 492.1273; **$[\alpha]_D^{25}$**: +50.9 (*c* = 0.29, $CHCl_3$).

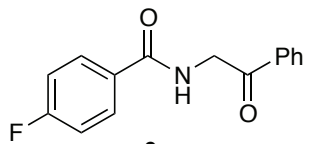
***N*-(2-(4-Hydroxyphenyl)ethyl)-4-fluorobenzamide (3f).**



3f

Prepared by following general procedure 1 for 30 min using potassium 4-fluorobenzoyltrifluoroborate (**1a**, 25.6 mg, 0.11 mmol, 1.1 equiv) and tyramine (**2f**, 13.7 mg, 0.10 mmol, 1.0 equiv). The crude material was purified by column chromatography on silica gel (eluting with CH_2Cl_2/acetone = 10:1, 0.5% AcOH) to give **3f** as a white solid (18.1 mg, 70%); **m.p.** 136-140 °C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 9.18 (s, 1H, OH), 8.55 (t, *J* = 5.6 Hz, 1H, NH), 7.89 (dd, *J* = 8.7, 5.6 Hz, 2H, ArH), 7.29 (t, *J* = 8.9 Hz, 2H, ArH), 7.03 (d, *J* = 8.4 Hz, 2H, ArH), 6.69 (d, *J* = 8.4 Hz, 2H, ArH), 3.44-3.39 (m, 2H, CH_2), 2.73 (dd, *J* = 8.4, 6.6 Hz, 2H, CH_2); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 165.0, 164.2 (d, *J* = 248.2 Hz), 155.6, 131.6 (d, *J* = 2.9 Hz), 130.2 (d, *J* = 9.0 Hz), 129.5, 129.5, 115.6 (d, *J* = 21.6 Hz), 115.1, 41.3, 34.3; **^{19}F NMR** (375 MHz, DMSO-d_6): δ −109.8; **IR** (thin film): v 3285, 2927, 1639, 1503, 1235, 1159 cm^{-1}; **ESI-HRMS** calcd for $C_{15}H_{14}FNNaO_2$ $[M + Na]^+$ 282.0901, found 282.0903.

***N*-(2-Oxo-2-phenylethyl)-4-fluorobenzamide (3g).**

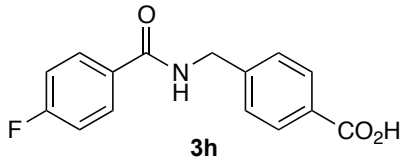


3g

Prepared by following general procedure 1 for 30 min with potassium 4-fluorobenzoyltrifluoroborate (**1a**, 25.6 mg, 0.11 mmol, 1.1 equiv) and 2-aminoacetophenone hydrochloride (**2g**, 17.2 mg, 0.10 mmol, 1.0 equiv). The crude material was purified by column chromatography on silica gel (eluting with EtOAc/hexanes = 1:2) to give **3g** as a white solid (24.5 mg, 95%); **m.p.** 122-126 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.05 (dt, *J* = 8.3, 1.1 Hz, 2H, ArH), 7.92 (dd, *J* = 8.8, 5.2 Hz, 2H, ArH), 7.67 (t, *J* = 7.5 Hz, 1H, ArH), 7.55 (t, *J* = 7.4 Hz, 2H, ArH), 7.32 (br s, 1H, NH), 7.16 (t, *J* = 8.6 Hz, 2H, ArH), 4.97 (dd, *J* = 4.2, 0.7 Hz, 2H, CH_2); **^{13}C NMR**

(100 MHz, $CDCl_3$): δ 196.3, 166.4, 164.9 (d, *J* = 252.2 Hz), 134.3, 134.3, 130.0 (d, *J* = 3.2 Hz), 129.5 (d, *J* = 9.0 Hz), 129.0, 128.0, 115.7 (d, *J* = 21.9 Hz), 46.9; **^{19}F NMR** (375 MHz, $CDCl_3$): δ −107.7; **IR** (thin film): v 3363, 1690, 1635, 1498, 1364, 1224 cm^{-1}; **ESI-HRMS** calcd for $C_{15}H_{13}FNO_2$ $[M + H]^+$ 258.0925, found 258.0740.

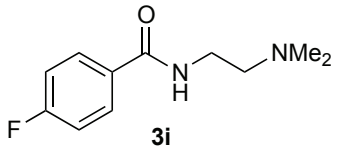
4-(4-Fluorobenzamido)methylbenzoic acid (3h).



3h

Prepared by following general procedure 1 for 1 h using potassium 4-fluorobenzoyltrifluoroborate (**1a**, 25.6 mg, 0.11 mmol, 1.1 equiv) and 4-(aminomethyl)benzoic acid (**2h**, 15.1 mg, 0.10 mmol, 1.0 equiv). The crude material was purified by column chromatography on silica gel (eluting with CH_2Cl_2/MeOH = 100:5, 1% AcOH) to give **3h** as a white solid (21.3 mg, 78%) in >90% purity by NMR. For characterization purposes, the product was further purified by preparative reverse-phase HPLC (YMC C18 column, A/B eluent gradient: 20-95% for 28 min, t_R = 15.7 min); **m.p.** 220-224 °C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 12.86 (br s, 1H, CO_2H), 9.15 (t, *J* = 6.0 Hz, 1H, NH), 7.99 (dd, *J* = 8.9, 5.5 Hz, 2H, ArH), 7.92 (d, *J* = 8.3 Hz, 2H, ArH), 7.43 (d, *J* = 8.3 Hz, 2H, ArH), 7.33 (t, *J* = 8.9 Hz, 2H, ArH), 4.55 (d, *J* = 5.9 Hz, 2H, CH_2); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 167.6, 165.7, 164.4 (d, *J* = 248.6 Hz), 145.2, 131.1 (d, *J* = 2.9 Hz), 130.4 (d, *J* = 9.0 Hz), 129.9, 129.8, 127.6, 115.8 (d, *J* = 21.8 Hz), 43.0; **^{19}F NMR** (375 MHz, DMSO-d_6): δ −109.3; **IR** (thin film): v 3419, 3324, 1682, 1636, 1540, 1504, 1288 cm^{-1}; **ESI-HRMS** calcd for $C_{15}H_{13}FNO_3$ $[M + H]^+$ 274.0874, found 274.0877.

***N*-(2-Dimethylaminoethyl)-4-fluorobenzamide (3i).**

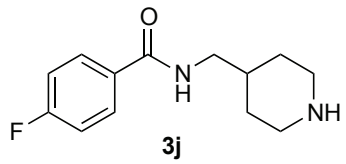


3i

Prepared with potassium 4-fluorobenzoyltrifluoroborate (**1a**, 23 mg, 0.10 mmol, 1.0 equiv), *N,N*-dimethylethylenediamine (**2i**, 13.1 µL, 0.12 mmol, 1.2 equiv). Following addition of $NaHSO_3$, the reaction crude was poured into NaOH 1M, extracted with CH_2Cl_2, washed with H_2O and brine, dried over Na_2SO_4, filtered and evaporated in vacuo. The residue was purified by column chromatography on silica gel (eluting with CH_2Cl_2/MeOH = 100:5, +1% NEt_3) to give **3i** as a yellow oil (14.8 mg, 70%); **^{1}H NMR** (400 MHz, acetone-d_6): δ 7.95 (dd, *J* = 8.7, 5.6 Hz, 2H, ArH), 7.70 (br s, 1H, NH), 7.20 (t, *J* = 8.7 Hz, 2H, ArH), 3.48 (q, *J* = 6.3 Hz, 2H, CH_2), 2.50 (t, *J* = 6.5 Hz, 2H, CH_2), 2.24 (s, 6H, CH_3); **^{13}C NMR** (100 MHz, acetone-d_6): δ 165.3, 164.4 (d, *J* = 251.7 Hz), 131.5 (d, *J* = 3.0 Hz), 129.6 (d, *J* = 8.9 Hz), 115.0 (d, *J* = 21.9 Hz), 58.2, 44.7, 37.4; **^{19}F NMR** (282 MHz,

acetone-d_6): δ −111.4; **IR** (thin film): v 3314, 2945, 2773, 1639, 1547, 1502, 1231, 1159 cm^{-1}; **ESI-HRMS** calcd for $C_{11}H_{16}FN_2O$ $[M + H]^+$ 211.1241, found 211.1243.

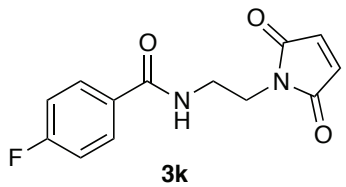
***N*-(Piperidin-4-ylmethyl)-4-fluorobenzamide (3j).**



3j

Prepared with potassium 4-fluorobenzoyltrifluoroborate (**1a**, 29.7 mg, 0.129 mmol, 1.1 equiv), 4-(aminomethyl)piperidine (**2j** 13.4 mg, 0.117 mmol, 1.0 equiv) and NCS (31.3 mg, 0.234 mmol, 2.0 equiv) by a slight modification of general procedure 1. After 30 min stirring at rt, the reaction was quenched with sat. aq. $NaHSO_3$ (0.5 mL), poured into 1M NaOH and extracted with EtOAc (3 x 3 mL). The organic extracts were collected and back-extracted using 1M HCl. (2 x 3 mL). The aqueous extracts were collected, basified with 5M NaOH until pH >12, extracted again with CH_2Cl_2, washed with H_2O and brine, dried over Na_2SO_4, filtered and evaporated in vacuo to give **3j** as a yellowish solid (16.8 mg, 61%); **m.p.** 107-109 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.76 (dd, *J* = 8.8, 5.3 Hz, 2H, ArH), 7.08 (t, *J* = 8.6 Hz, 2H, ArH), 6.33 (s, 1H, NH), 3.31 (t, *J* = 6.2 Hz, 2H, CH_2), 3.08 (d, *J* = 12.6 Hz, 2H, CH), 2.58 (td, *J* = 12.2, 2.4 Hz, 2H, CH), 1.93 (br, 1H, NH), 1.77-1.67 (m, 3H, CH), 1.27-1.14 (m, 2H, CH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.7, 164.7 (d, *J* = 251.7 Hz), 131.0 (d, *J* = 3.1 Hz), 129.3 (d, *J* = 8.9 Hz), 115.7 (d, *J* = 21.9 Hz), 46.4, 46.1, 36.7, 31.2; **^{19}F NMR** (375 MHz, $CDCl_3$): δ −108.4; **IR** (thin film): v 3298, 2924, 1640, 1551, 1504, 1319, 1233, 1159 cm^{-1}; **ESI-HRMS** calcd for $C_{13}H_{18}FN_2O$ $[M + H]^+$ 237.1398, found 237.1402.

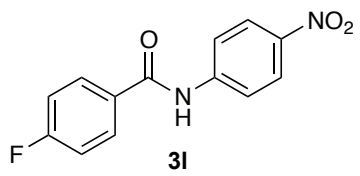
***N*-(2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethyl)-4-fluorobenzamide (3k).**



3k

Prepared by following general procedure 1 for 45 min with potassium 4-fluorobenzoyltrifluoroborate (**1a**, 23.0 mg, 0.10 mmol, 1.0 equiv) and 1-(2-aminoethyl)maleimide trifluoroacetic acid salt (**2k**, 30.5 mg, 0.12 mmol, 1.2 equiv). The crude material was purified by column chromatography on silica gel (eluting with CH_2Cl_2/MeOH = 100:5 + 0.5% AcOH), and recrystallized from EtOAc/hexanes (1:2), filtered and dried in vacuo to give **3k** as a white solid (13.1 mg, 51%); **m.p.** 170-172 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.77 (dd, *J* = 8.8, 5.3 Hz, 2H, ArH), 7.10 (t, *J* = 8.6 Hz, 2H, ArH), 6.74 (s, 2H, CH), 6.66 (br s, 1H, NH), 3.85-3.82 (m, 2H, CH_2), 3.67-3.63 (m, 2H, CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.1, 166.6, 164.8 (d, *J* = 251.8 Hz), 134.3, 130.2 (d, *J* = 3.0 Hz), 129.3 (d, *J* = 8.9 Hz), 115.6 (d, *J* = 21.9 Hz), 40.1, 37.5; **^{19}F NMR** (375 MHz, $CDCl_3$): δ −108.1; **IR** (thin film): v 3335, 3109, 2941, 1707, 1635, 1504, 1405, 1234 cm^{-1}; **ESI-HRMS** calcd for $C_{13}H_{12}FN_2O_3$ $[M + H]^+$ 263.0826, found 263.0829.

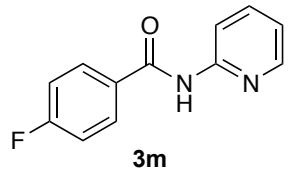
_N_-(4-Nitrophenyl)-4-fluorobenzamide (3l)[11].



3l

Prepared by following general procedure 1 for 1 h with potassium 4-fluorobenzoyltrifluoroborate (**1a**, 23.0 mg, 0.10 mmol, 1.0 equiv), 4-nitroaniline (**2l**, 15.2 mg, 0.11 mmol, 1.1 equiv) and 1,3,5-trichloroisocyanuric acid (TCCA, 8.4 mg, 0.036 mmol, 0.36 equiv) as a replacement for DCH. The crude material was purified by column chromatography on silica gel (eluting with EtOAc/CH_2Cl_2/hexanes = 1:1:3) to give **3l** as a pale yellow solid in >90% purity by NMR (20.8 mg, 80%). For characterization purposes, **3l** was further purified by preparative reverse-phase HPLC (YMC C18 column, gradient of 40-95% MeCN/H_2O + 0.1% TFA for 28 min, t_R = 15.4 min). The spectral data was in accordance with the literature; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 9.2 Hz, 2H, ArH), 8.07 (br s, 1H, NH), 7.91 (dd, *J* = 8.8, 5.1 Hz, 2H, ArH), 7.83 (d, *J* = 9.2 Hz, 2H, ArH), 7.20 (t, *J* = 8.6 Hz, 2H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.3 (d, *J* = 254.4 Hz), 164.7, 143.8, 143.6, 130.1 (d, *J* = 3.2 Hz), 129.6 (d, *J* = 9.1 Hz), 125.2, 119.5, 116.2 (d, *J* = 22.0 Hz); **^{19}F NMR** (375 MHz, $CDCl_3$): δ −105.7.

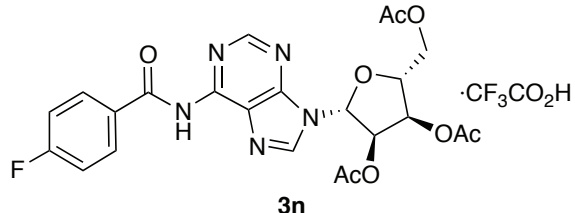
_N_-(2-Pyridyl)-4-fluorobenzamide (3m).



3m

Prepared by following general procedure 1 for 1 h with potassium 4-fluorobenzoyltrifluoroborate (**1a**, 23.0 mg, 0.10 mmol, 1.0 equiv) and 2-aminopyridine (**2m**, 25.2 mg, 0.11 mmol, 1.1 equiv). The crude material was purified by column chromatography on silica gel (eluting with EtOAc/hexanes = 2:5) to give **3m** as a pale yellow solid (15.1 mg, 70%); **m.p.** 115-117 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.76 (br, 1H, NH), 8.36 (d, *J* = 8.4 Hz, 1H, ArH), 8.24 (br s, 1H, ArH), 7.97 (dd, *J* = 8.8, 5.2 Hz, 2H, ArH), 7.76 (t, *J* = 8.3 Hz, 1H, ArH), 7.17 (t, *J* = 8.7 Hz, 2H, ArH), 7.09-7.05 (m, 1H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.0 (d, *J* = 253.4 Hz), 164.7, 151.5, 147.9, 138.5, 130.5 (br), 129.7 (d, *J* = 9.1 Hz), 120.1, 116.0 (d, *J* = 22.0 Hz), 114.2; **^{19}F NMR** (375 MHz, $CDCl_3$): δ −106.7; **IR** (thin film): v 3243, 3070, 2924, 1676, 1504, 1433, 1310, 1231 cm^{-1}; **ESI-HRMS** calcd for $C_{12}H_{10}FN_2O$ $[M + H]^+$ 217.0772, found 217.0775.

1-(6-(4-Fluorobenzamido)-9*H*-purin-9-yl)-1-deoxy-2,3,5-tri-*O*-acetyladenosine trifluoroacetate salt (3n).

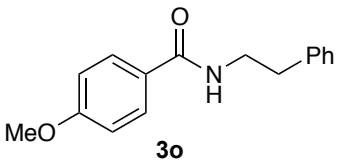


3n

Prepared with potassium 4-fluorobenzoyltrifluoroborate (**1a**, 25.6 mg, 0.11 mmol, 1.1 equiv), adenosine (**2n**,

26.7 mg, 0.10 mmol, 1.0 equiv) and 1,3,5-trichloroisocyanuric acid (TCCA, 9.4 mg, 0.04 mmol, 0.4 equiv) as a replacement for DCH by a modification of general procedure 1. After the reaction was stirred for 2 h at rt and quenched, THF was evaporated in vacuo and the aqueous phase containing the product was lyophilized. The crude material was resuspended in acetone (5 mL), filtered and the solvent evaporated to reduce the volume to ca. 1 mL Ac_2O (500 µL, 5.3 mmol, 53 equiv) and pyridine (250 µL, 1.6 mmol, 16 equiv) were added at rt. The mixture was stirred for 15 h, quenched with sat. aq. $NaHCO_3$, extracted with EtOAc, dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by preparative reverse-phase HPLC (YMC C18 column, gradient of 20-95% MeCN/H_2O + 0.1% TFA for 28 min, t_R = 16.5 min) to give **3n** as a viscous, sticky oil [28.3 mg, 45% (over 2 steps)]; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.26 (br, 2H, NH), 8.76 (s, 1H, ArH), 8.36 (s, 1H, ArH), 8.09 (dd, *J* = 8.8, 5.2 Hz, 2H, ArH), 7.20 (t, *J* = 8 6 Hz, 2H, ArH), 6.28 (d, *J* = 5.4 Hz, 1H, CH), 5.92 (t, *J* = 5.4 Hz, 1H, CH), 5.62 (t, *J* = 5.0 Hz, 1H, CH), 4.49 (q, *J* = 10.7, 8.5, 3.7 Hz, 1H, CH), 4.46-4.38 (m, 2H, CH_2), 2.16 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 2.08 (s, 3H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.3, 169.6, 169.4, 165.8 (d, *J* = 255.1 Hz), 164.2, 161.6 (q, *J* = 40.1 Hz), 152.0, 151.3, 149.4, 142.0, 131.0 (d, *J* = 9.4 Hz), 128.8 (d, *J* = 3.0 Hz), 123.3, 116.0 (d, *J* = 22.2 Hz), 115.2 (q, *J* = 287.6 Hz), 86.6, 80.7, 73.2, 70.6, 62.9, 20.7, 20.5, 20.3; **^{19}F NMR** (375 MHz, $CDCl_3$): δ −76.0, −104.8; **IR** (thin film): v 3113, 1748, 1603, 1504, 1373, 1223 cm^{-1}; **ESI-HRMS** calcd for $C_{23}H_{23}FN_5O_8$ $[M + H]^+$ 516.1525, found 516.1520; **[α]$_D$**: −22.8 (*c* = 1.25, $CHCl_3$).

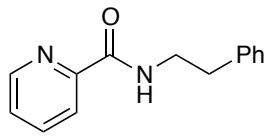
***N*-(2-Phenylethyl)-4-methoxybenzamide (3o)[12].**



3o

Prepared by following general procedure 1 for 30 min with potassium 4-methoxybenzoyltrifluoroborate (**1b**, 24.2 mg, 0.10 mmol, 1.0 equiv) and 2-phenethylamine (**2a**, 13.8 µL, 0.11 mmol, 1.1 equiv). The crude material was purified by column chromatography on silica gel (eluting with EtOAc/hexanes = 1:2) to give **3o** as a white solid (21.4 mg, 84%). The spectral data was in accordance with the literature; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.8 Hz, 2H, ArH), 7.35 (t, *J* = 7.7 Hz, 2H, ArH), 7.27 (t, *J* = 7.3 Hz, 3H, ArH), 6.92 (d, *J* = 8.8 Hz, 2H, ArH), 6.13 (br, 1H, NH), 3.86 (s, 3H, CH_3), 3.73 (q, *J* = 6.6 Hz, 2H, CH_2), 2.95 (t, *J* = 6.9 Hz, 2H, CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 167.0, 162.1, 139.0, 128.8, 128.7, 128.6, 126.9, 126.6, 113.7, 55.4, 41.1, 35.8.

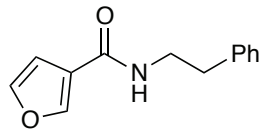
***N*-(2-Phenylethyl)-2-picolinamide (3p)[13].**



3p

Prepared by following general procedure 1 for 1 h with potassium 2-picolinoyltrifluoroborate (**1c,** 21.3 mg, 0.10 mmol, 1.0 equiv) and 2-phenethylamine (**2a**, 13.8 µL, 0.11 mmol, 1.1 equiv). The crude material was purified by column chromatography on silica gel (eluting with EtOAc/hexanes = 2:3) to give **3p** as an oily solid (14.6 mg, 64%). The spectral data was in accordance with the literature; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.52 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H, ArH), 8.20 (dt, *J* = 7.9, 1.1 Hz, 1H, ArH), 8.16 (br s, 1H NH), 7.84 (td, *J* = 7.7, 1.7 Hz, 1H, ArH), 7.41 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, ArH), 7.34-7.29 (m, 1H, ArH), 7.28-7.21 (m, 4H, ArH), 3.74 (q, *J* = 7.2 Hz, 2H, CH_2), 2.95 (t, *J* = 7.3 Hz, 2H, CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.3, 149.9, 148.0, 139.0, 137.3, 128.8, 128.6, 126.5, 126.2, 122.2, 40.8, 36.0.

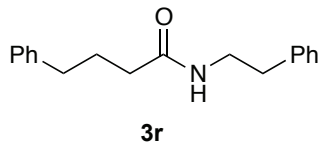
***N*-(2-Phenylethyl)-3-furamide (3q).**



3q

Prepared by following general procedure 1 for 1 h with potassium 3-furoyltrifluoroborate (**1d**, 20.2 mg, 0.10 mmol, 1.0 equiv) and 2-phenethylamine (**2a**, 13.8 µL, 0.11 mmol, 1.1 equiv). The crude material was purified by column chromatography on silica gel (eluting with EtOAc/hexanes = 1:2) to give **3q** as an oily solid (14.6 mg, 64%); **m.p.** 87-89 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.86 (dd, *J* = 0.9, 0.6 Hz, 1H, ArH), 7.40 (t, *J* = 1.8 Hz, 1H, ArH), 7.32 (t, *J* = 7.3 Hz, 2H, ArH), 7.27-7.21 (m, 3H, ArH), 6.53 (m, 1H, ArH), 5.87 (br s, 1H, NH), 3.65 (q, *J* = 6.3 Hz, 2H, CH_2), 2.90 (t, *J* = 6.9 Hz, 2H, CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 162.6, 144.5, 143.7, 138.8, 128.8, 128.7, 126.6, 122.6, 108.2, 40.6, 35.7; **IR** (thin film): v 3317, 2926, 1633, 1537, 1327, 1196, 1160 cm^{-1}; **ESI-HRMS** calcd for $C_{13}H_{14}NO_2$ $[M + H]^+$ 216.1019, found 216.1020.

***N*-(2-Phenylethyl)-4-phenylbutanamide (3r)[14].**

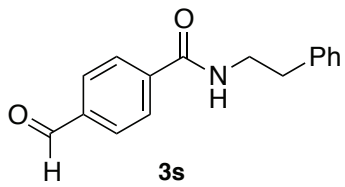


3r

Prepared by following general procedure 1 for 30 min with potassium 4-phenylbutanoyltrifluoroborate (**1e**, 25.4 mg, 0.10 mmol, 1.0 equiv) and 2-phenethylamine (**2a**, 13.8 µL, 0.11 mmol, 1.1 equiv). The crude material was purified by column chromatography on silica gel (eluting with EtOAc/hexanes = 1:3) to give **3r** as a white solid (23.5 mg, 88%). The spectral data was in accordance with the literature; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36-7.16 (m, 10H, ArH), 5.43 (br s, 1H, NH), 3.55 (q, *J* = 6.9 Hz, 2H, CH_2), 2.84 (t, *J* = 6.9 Hz, 2H, CH_2), 2.65 (t, *J* = 7.5 Hz, 2H, CH_2), 2.15 (t, *J* = 7.2 Hz, 2H, CH_2), 1.97 (p, *J* = 7.5 Hz, 2H, CH_2); **^{13}C NMR**

(100 MHz, $CDCl_3$): δ 172.6, 141.5, 138.9, 128.8, 128.7, 128.5, 128.4, 126.5, 125.9, 40.5, 35.9, 35.7, 35.1, 27.1.

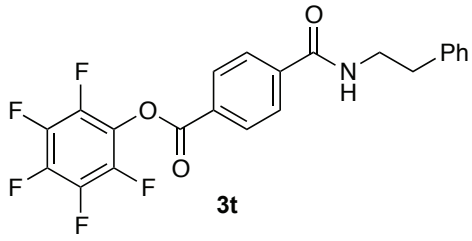
_N_-(2-Phenylethyl)-4-formylbenzamide (3s).



3s

Prepared by following general procedure 1 for 50 min with potassium 4-formylbenzoyltrifluoroborate (**1f**, 24.0 mg, 0.10 mmol, 1.0 equiv) and 2-phenethylamine (**2a**, 13.8 µL, 0.11 mmol, 1.1 equiv). The crude material was purified by column chromatography on silica gel (eluting with EtOAc/hexanes = 2:3) to give **3s** as a white solid (13.6 mg, 54%); **m.p.** 102-104 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.07 (s, 1H CHO), 7.93 (d, *J* = 8.2 Hz, 2H, ArH), 7.85 (d, *J* = 8.2 Hz, 2H, ArH), 7.33 (t, *J* = 7.1 Hz, 2H, ArH), 7.28-7.22 (m, 3H, ArH), 6.29 (br s, 1H, NH), 3.76 (q, *J* = 6.7 Hz, 2H, CH_2), 2.98 (t, *J* = 6.9 Hz, 2H, CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 191.5, 166.4, 139.8, 138.6, 138.2, 129.8, 128.8, 128.8, 127.5, 126.7, 41.3, 35.6; **IR** (thin film): ν 3316, 2925, 1705, 1638, 1543, 1317, 1205 cm^{-1}; **ESI-HRMS** calcd for $C_{16}H_{15}FNNaO_2$ $[M + H]^+$ 276.0995, found 276.1000.

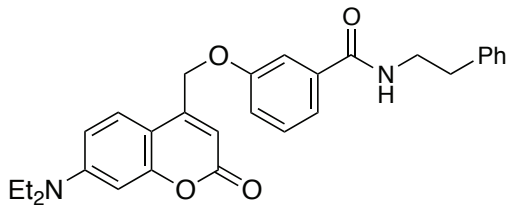
Pentafluorophenyl 4-(_N_-(2-phenylethyl)carbamoyl)benzoate (3t).



3t

Prepared by following general procedure 1 for 50 min with potassium 4-(pentafluorophenoxycarbonyl)benzoyltrifluoroborate (**1g**, 42.2 mg, 0.10 mmol, 1.0 equiv) and 2-phenethylamine (**2a**, 13.8 µL, 0.11 mmol, 1.1 equiv). The crude material was purified by column chromatography on silica gel (eluting with EtOAc/hexanes = 1:3) to give **3t** as a crystalline solid (15.6 mg, 36%); **m.p.** 150-152 °C; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.94 (dd, *J* = 8.9, 5.1 Hz, 2H, ArH), 7.35 (br s, 1H, NH), 7.20 (t, *J* = 8.5 Hz, 2H, ArH); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 166.1, 161.8, 141.3 ({^{19}F}), 140.2, 139.7({^{19}F}), 138.6, 137.9 ({^{19}F}), 131.0, 129.4, 128.8, 128.8, 127.3, 126.8, 125.1({^{19}F}), 41.3, 35.6; **^{19}F NMR** (375 MHz, $CDCl_3$): δ −152.3, −157.4, −162.0; **IR** (thin film): ν 3317, 2924, 1763, 1636, 1520, 1255 cm^{-1}; **ESI-HRMS** calcd for $C_{22}H_{13}F_5NO_3$ $[M - H]^-$ 434.0821, found 434.0810.

3-((7-(Diethylamino)-2-oxo-2_H_-chromen-4-yl)methoxy)-_N_-(2-phenylethyl)benzamide (3u).

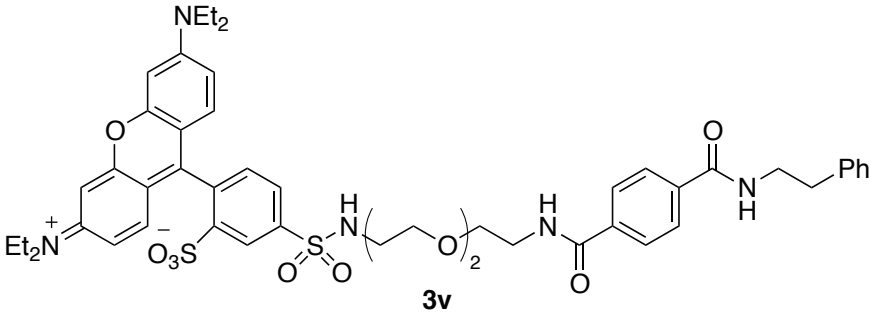


3u

Prepared by a slight modification of general procedure 1. 2-Phenethylamine (**2a**, 15.6 µL, 0.12 mmol, 1.2 equiv) and

DCH (23.6 mg, 0.12 mmol, 1.2 equiv) were dissolved in 2 mL of a 1:1 mixture of THF and aq. buffer pH 3, and stirred for 5 min. Potassium 3-((7-(diethylamino)-2*H*-chromen-2-one)methoxy) benzoyltrifluoroborate (**1h**, 45.6 mg, 0.10 mmol, 1.0 equiv) was added and the mixture stirred for 1 h. The crude material was purified by column chromatography on silica gel (eluting with CH_2Cl_2/MeOH = 100:2) to give **3u** as an orange solid (30.6 mg, 65%); **m.p.** 48-52 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.41 (dd, *J* = 2.6, 1.5 Hz, 1H, ArH), 7.37-7.30 (m, 4H, ArH), 7.27-7.19 (m, 4H, ArH), 7.10 (ddd, *J* = 8.2, 2.7, 1.0 Hz, 1H, ArH), 6.59 (d, *J* = 1.3 Hz, 1H, ArH), 6.53 (d, *J* = 2.5 Hz, 1H, ArH), 6.27 (t, *J* = 1.1 Hz, 1H, NH), 6.17 (t, *J* = 5.6 Hz, 1H, ArH), 5.18 (d, *J* = 1.3 Hz, 2H, CH_2), 3.72 (q, *J* = 6.7 Hz, 2H, CH_2), 3.42 (q, *J* = 7.1 Hz, 4H, CH_2), 2.94 (t, *J* = 6.9 Hz, 2H, CH_2), 1.22 (t, *J* = 7.1 Hz, 6H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 167.2, 162.1, 158.4, 156.5, 150.8, 150.1, 139.0, 136.5, 130.0, 129.0, 128.9, 126.8, 124.6, 119.5, 118.8, 113.1, 108.8, 107.0, 106.2, 98.0, 66.0, 44.9, 41.4, 35.8, 12.6; **IR** (thin film): v 3584, 2971, 2927, 1712, 1604, 1529, 1352 cm^{-1}; **ESI-HRMS** calcd for $C_{29}H_{31}N_2O_4$ $[M + H]^+$ 471.2278, found 471.2276.

2-(6-(Diethylamino)-3-(diethyliminio)-3*H*-xanthen-9-yl)-5-(*N*-(2-(2-(2-(4-(*N*-(2-phenylethyl)carbamoyl)benzamido)ethoxy)ethoxy)ethyl)sulfamoyl)benzenesulfonate (3v).

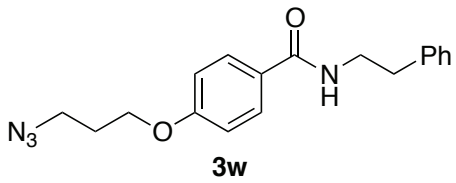


3v

Prepared by a slight modification of general procedure 1. 2-Phenethylamine (**2a**, 7.8 µL, 0.06 mmol, 1.5 equiv) and DCH (11.8 mg, 0.06 mmol, 1.5 equiv) were dissolved in 1 mL of a 1:1 mixture of THF and aq. buffer pH 3, and stirred for 5 min. Potassium 4-(*N*-(2-(2-(2-(4-(6-(diethylamino)-3-(diethyliminio)-3*H*-xanthen-9-yl)-3-sulfonatobenzenesulfonamido)ethoxy)ethoxy)ethyl) carbamoyl)benzoyltrifluoroborate (**1i**, 37.0 mg, 0.04 mmol, 1.0 equiv) was added and the mixture stirred for 1 h. The crude material was purified by column chromatography on silica gel (eluting with CH_2Cl_2/MeOH = 100:8) to give **3v** as a magenta solid (23.3 mg, 62%); **m.p.** 154-157 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.92 (d, *J* = 1.9 Hz, 1H), 8.00 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.81 (s, 3H), 7.72 (t, *J* = 5.5 Hz, 1H), 7.66 (t, *J* = 5.7 Hz, 1H), 7.22-7.15 (m, 6H), 7.12 (t, *J* = 8.6 Hz, 1H), 6.74 (t, *J* = 6.0 Hz, 1H), 6.69 (dd, *J* = 9.6, 2.5 Hz, 2H), 6.46 (d, *J* = 2.5 Hz, 1H), 3.63 (t, *J* = 5.2 Hz, 2H), 3.61-3.55 (m, 6H), 3.52 (q, *J* = 5.3 Hz, 2H), 3.48-3.39 (m, 9H), 3.20 (q, *J* = 5.8 Hz, 2H), 2.79-2.75 (m, 2H), 1.20 (t, *J* = 7.2 Hz, 12H); **^{13}C NMR** (100 MHz,

$CDCl_3$): δ 166.8, 166.6, 158.1, 157.7, 155.5, 147.5, 142.0, 139.7, 136.7, 136.3, 133.9, 133.3, 130.0, 129.0, 128.4, 127.6, 127.5, 127.4, 126.1, 114.3, 113.8, 95.7, 70.7, 70.5, 69.8, 69.5, 46.0, 43.2, 41.7, 40.0, 35.8, 29.8, 12.7; **IR** (thin film): v 3440, 3345, 2928, 1648, 1591, 1416, 1337, 1180, 1076 cm^{-1}; **ESI-HRMS** calcd for $C_{49}H_{58}N_5O_{10}S_2$ $[M + H]^+$ 940.3620, found 940.3608.

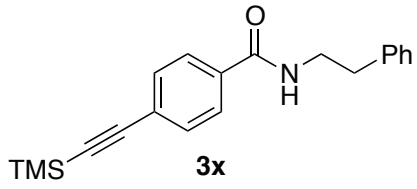
4-(3-Azidopropoxy)-*N*-(2-phenylethyl)benzamide (3w).



3w

Prepared by following general procedure 1 for 50 min with potassium 4-(3-azidopropoxy)benzoyltrifluoroborate (**1j**, 31.1 mg, 0.10 mmol, 1.0 equiv) and 2-phenethylamine (**2a**, 13.8 µL, 0.11 mmol, 1.1 equiv). The crude material was purified by column chromatography on silica gel (eluting with EtOAc/hexanes = 2:3) to give **3w** as a white solid (24.0 mg, 74%); **m.p.** 80-83 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.8 Hz, 2H, ArH), 7.35 (t, *J* = 7.2 Hz, 1H, ArH), 7.29-7.23 (m, 2H, ArH), 6.91 (d, *J* = 8.8 Hz, 2H, ArH), 6.15 (t, *J* = 5.9 Hz, 1H, NH), 4.10 (t, *J* = 6.0 Hz, 2H, CH_2), 3.72 (td, *J* = 6.9, 5.8 Hz, 2H, CH_2), 3.54 (t, *J* = 6.6 Hz, 2H, CH_2), 2.94 (t, *J* = 6.9 Hz, 2H, CH_2), 2.08 (p, *J* = 6.3 Hz, 2H, CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 167.0, 161.3, 139.1, 128.9, 128.8, 128.8, 127.3, 126.7, 114.3, 64.8, 48.2, 41.2, 35.9, 28.8; **IR** (thin film): v 3295, 2942, 2920, 2021, 1607, 1540, 1504, 1300, 1261 cm^{-1}; **ESI-HRMS** calcd for $C_{18}H_{21}N_4O_2$ $[M + H]^+$ 325.1659, found 325.1658.

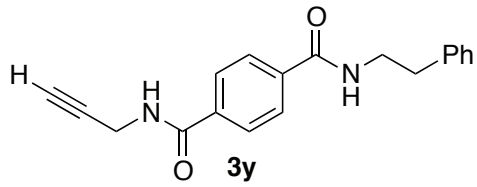
***N*-(2-phenylethyl)-4-(2-trimethylsilylethynyl)benzamide (3x)[14].**



3x

Prepared by following general procedure 1 for 1 h with potassium 4-(2-trimethylsilylethynyl)benzoyltrifluoroborate (**1k**, 30.8 mg, 0.10 mmol, 1.0 equiv) and 2-phenethylamine (**2a**, 15.5 µL, 0.12 mmol, 1.2 equiv). The crude material was purified by preparative TLC (eluting with EtOAc/hexanes = 1:4) to give **3x** as a white solid (22.1 mg, 69%). The spectral data was in accordance with the literature; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.5 Hz, 2H, ArH), 7.48 (d, *J* = 8.5 Hz, 2H, ArH), 7.33 (d, *J* = 7.2 Hz, 2H, ArH), 7.30-7.24 (m, 2H, ArH), 6.14 (br s, 1H, NH), 3.71 (q, *J* = 6.9 Hz, 2H, CH_2), 2.93 (t, *J* = 6.9 Hz, 2H, CH_2), 0.25 (s, 9H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.8, 138.9, 134.3, 132.2, 128.9, 128.9, 126.8, 126.8, 126.5, 104.1, 97.1, 41.3, 35.8, 0.0.

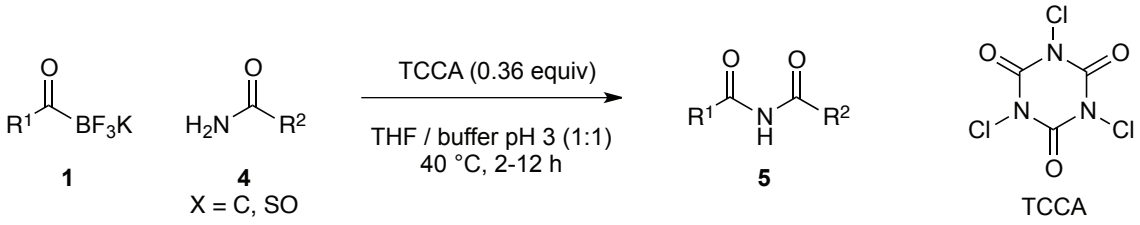
***N*-(2-Phenylethyl)-*N'*-propargylterephthalimide (3y).**



3y

Prepared by following general procedure 1 for 1 h with potassium 4-(*N*-propargylcarbamoyl)benzoyltrifluoroborate (**1l**, 29.2 mg, 0.10 mmol, 1.0 equiv) and 2-phenethylamine (**2a**, 15.5 µL, 0.12 mmol, 1.2 equiv). While stirring the reaction mixture, the product precipitated as a white, insoluble solid. This solid was filtered, washed with H_2O and CH_2Cl_2 and dried in vacuo to give **3y** (24.2 mg, 79%); **m.p.** >210 °C (decomp.); **^{1}H NMR** (400 MHz, DMSO-d_6): δ 9.04 (t, *J* = 5.5 Hz, 1H, NH), 8.69 (t, *J* = 5.6 Hz, 1H, NH), 7.92 (d, *J* = 8.7 Hz, 2H, ArH), 7.88 (d, *J* = 8.7 Hz, 2H, ArH), 7.33-7.17 (m, 5H, ArH), 4.07 (m, 2H, CH_2), 3.53-3.46 (m, 2H, CH_2), 3.13 (t, *J* = 2.5 Hz, 1H, C(sp)H), 2.85 (t, *J* = 7.5 Hz, 2H, CH_2); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 165.4, 165.3, 139.5, 137.0, 135.9, 128.6, 128.3, 127.2, 127.1, 126.1, 81.1, 73.0, 40.9, 35.0, 28.6; **IR** (thin film): v 3284, 2918, 1624, 1546, 1265 cm^{-1}; **ESI-HRMS** calcd for $C_{19}H_{19}N_2O_2$ $[M + H]^+$ 307.1441, found 307.1442.

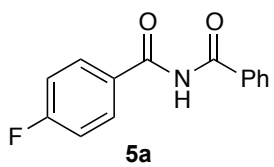
General Procedure 2: Synthesis of Imides from Primary Amides and Sulfonamides



1 **4** X = C, SO **5** TCCA

In a round-bottom flask, potassium acyltrifluoroborate (**1**, 0.11 mmol, 1.1 equiv) was dissolved in 1 mL of a 1:1 mixture of THF and an aq. pH 3 buffer, 25 mM (prepared as described for general procedure 1). The amide or sulfonamide (**4**, 0.10 mmol, 1.0 equiv) and 1,3,5-trichloroisocyanuric acid (TCCA, 8.5 mg, 0.036 mmol, 0.36 equiv) were added sequentially. The mixture was stirred at 40 °C, quenched with saturated $NaHSO_3$ (0.3 mL), poured into H_2O/brine and extracted with EtOAc (3 x 3 mL). The organic extracts were collected, dried over Na_2SO_4, filtered and evaporated in vacuo. The residue was purified by column chromatography on silica gel to afford the imide.

***N*-Benzoyl-4-fluorobenzamide (5a).[15]**

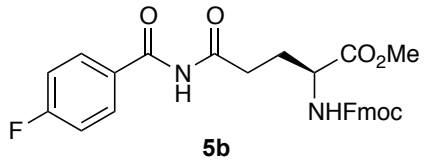


5a

Prepared by following general procedure 2 for 4 h with potassium 4-fluorobenzoyltrifluoroborate (**1a**, 25.6 mg, 0.11 mmol, 1.1 equiv) and benzamide (**4a**, 12.1 mg, 0.10 mmol, 1.0 equiv). The crude material was purified by column

chromatography on silica gel (eluting with CH_2Cl_2/MeOH = 100:4) to give **5a** as a white solid (15.8 mg, 65%). The spectral data was in accordance with the literature; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.01 (br s, 1H, NH), 7.94-7.88 (m, 4H, ArH), 7.64 (t, *J* = 7.5 Hz, 1H, ArH), 7.53 (t, *J* = 7.5 Hz, 2H, ArH), 7.20 (t, *J* = 8.6 Hz, 2H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.5, 165.9, 165.6 (d, *J* = 255.0 Hz), 133.2, 133.1, 130.8 (d, *J* = 9.3 Hz), 129.5 (d, *J* = 3.0 Hz), 128.9, 128.0, 116.0 (d, *J* = 22.1 Hz); **^{19}F NMR** (375 MHz, $CDCl_3$): δ −104.9.

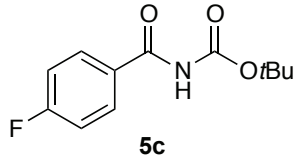
(*S*)-Methyl 2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-5-(4-fluorobenzamido)-5-oxopentanoate (5b).



5b

Prepared by following general procedure 2 for 3 h with potassium 4-fluorobenzoyltrifluoroborate (**1a**, 25.6 mg, 0.11 mmol, 1.1 equiv) and Fmoc-L-glutamine methyl ester (**4b**, 38.3 mg, 0.10 mmol, 1.0 equiv). The crude material was purified by column chromatography on silica gel (eluting with EtOAc/hexanes = 1:2) to give **5b** as a white solid in >90% purity (by NMR) [33.3 mg, 66%]. For characterization purposes, **5b** was further purified by preparative reverse-phase HPLC (YMC C18 column, A/B eluent gradient: 40-95% for 28 min, t_R = 18.6 min); **m.p.** 162-164 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.09 (br, 1H, NH), 7.87 (dd, *J* = 8.9, 5.1 Hz, 2H, ArH), 7.75 (d, *J* = 7.5 Hz, 2H, ArH), 7.58 (d, *J* = 7.5 Hz, 2H, ArH), 7.38 (t, *J* = 7.4 Hz, 2H, ArH), 7.29 (td, *J* = 7.5, 1.2 Hz, 2H, ArH), 7.14 (t, *J* = 8.6 Hz, 2H, ArH), 5.63 (d, *J* = 8.2 Hz, 1H, CH), 4.50 (td, *J* = 8.4, 4.7 Hz, 1H, CH), 4.36 (dd, *J* = 7.3, 2.0 Hz, 2H, CH_2), 4.21 (t, *J* = 7.1 Hz, 1H, CH), 3.77 (s, 3H, CH_3), 3.15-3.01 (m, 2H, CH_2), 2.34 (dq, *J* = 13.1, 6.9 Hz, 1H, CH), 2.08 (dq, *J* = 14.5 7.1 Hz, 1H, CH), 1.84 (br, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 175.2, 172.5, 165.7 (d, *J* = 255.3 Hz), 164.6, 156.1, 143.8, 143.7, 141.3, 130.4 (d, *J* = 9.3 Hz), 128.7 (d, *J* = 3.2 Hz), 127.7, 127.1, 125.1, 120.0, 116.1 (d, *J* = 22.2 Hz), 67.2, 53.2, 52.6, 47.1, 33.5, 27.1; **^{19}F NMR** (375 MHz, $CDCl_3$): δ −104.6; **IR** (thin film): v 3318, 3019, 2952, 1714, 1683, 1477, 1236, 1161 cm^{-1}; **ESI-HRMS** calcd for $C_{28}H_{25}FN_2NaO_6$ $[M + Na]^+$ 527.1589, found 527.1589; **$[\alpha]_D$**: +13.4 (*c* = 1.15, $CHCl_3$).

tert-Butyl *N*-4-fluorobenzoylcarbamate (5c).

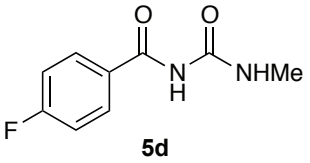


5c

Prepared by following general procedure 2 for 4 h with potassium 4-fluorobenzoyltrifluoroborate (**1a**, 25.6 mg, 0.11 mmol, 1.1 equiv) and *tert*-butyl carbamate (**4c**, 11.7 mg, 0.10 mmol, 1.0 equiv). The crude material was purified by column chromatography on silica gel (eluting with EtOAc/hexanes = 1:3) to give **5c** as a white solid (10.3 mg, 43%); **m.p.** 124-127 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.83 (dd, *J* = 8.7, 5.2 Hz, 3H, ArH + NH),

7.16 (t, *J* = 8.6 Hz, 2H, ArH), 1.56 (s, 9H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.4 (d, *J* = 254.3 Hz), 164.2, 149.5, 130.1 (d, *J* = 9.2 Hz), 129.6 (d, *J* = 3.2 Hz), 116.0 (d, *J* = 22.2 Hz), 83.0, 28.0; **^{19}F NMR** (282 MHz, $CDCl_3$): δ −105.6; **IR** (thin film): v 3270, 2980, 2926, 1749, 1603, 1500, 1220, 1147 cm^{-1}; **ESI-HRMS** calcd for $C_{12}H_{14}FNNaO_3$ $[M + Na]^+$ 262.0850, found 262.0850.

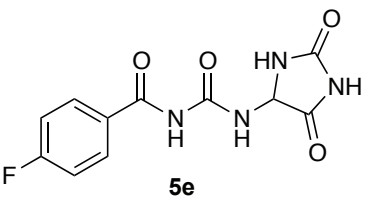
***N*-(4-Fluorobenzoyl)-*N*'-methylurea (5d).**



5d

Prepared by following general procedure 2 for 4 h with potassium 4-fluorobenzoyltrifluoroborate (**1a**, 25.6 mg, 0.11 mmol, 1.1 equiv) and methylurea (**4d**, 7.4 mg, 0.10 mmol, 1.0 equiv). The crude material was purified by column chromatography on silica gel (eluting with EtOAc/hexanes = 1:1) to give **5d** as a white solid (11.7 mg, 60%); **m.p.** 222-226 °C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 10.70 (br s, 1H, NH), 8.49 (q, *J* = 4.9 Hz, 1H, NH), 8.04 (dd, *J* = 9.0, 5.4 Hz, 2H, ArH), 7.33 (t, *J* = 8.7 Hz, 2H, ArH), 2.78 (s, *J* = 4.7 Hz, 3H, CH_3); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 167.4, 165.2 (d, *J* = 250.8 Hz), 154.5, 131.5 (d, *J* = 9.5 Hz), 129.3 (d, *J* = 2.9 Hz), 116.0 (d, *J* = 22.0 Hz), 26.6; **^{19}F NMR** (375 MHz, $CDCl_3$): δ −105.2; **IR** (thin film): v 3332, 1698, 1567, 1280, 1225 cm^{-1}; **ESI-HRMS** calcd for $C_9H_9FN_2NaO_2$ $[M + Na]^+$ 219.0540, found 219.0543.

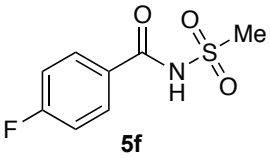
***N*-((2,5-Dioxoimidazolidin-4-yl)carbamoyl)-4-fluorobenzamide (5e).**



5e

Prepared by a modification of general procedure 2 for 4 h with potassium 4-fluorobenzoyltrifluoroborate (**1a**, 25.6 mg, 0.11 mmol, 1.1 equiv), DL-allantoin (**4e**, 31.6 mg, 0.10 mmol, 1.0 equiv) and 1,3-dichloro-5,5-dimethylhydantoin (DCH, 21.7 mg, 0.11 mmol, 1.1 equiv) as a replacement for TCCA. While stirring the reaction mixture, the product precipitated as a white, insoluble solid. This solid was filtered, washed with H_2O and CH_2Cl_2 and dried in vacuo to give **5e** (22.4 mg, 80%); **m.p.** >250 °C (no melting); **^{1}H NMR** (400 MHz, DMSO-d_6): δ 10.95 (s, 1H, NH), 10.73 (s, 1H, NH), 9.23 (d, *J* = 7.1 Hz, 1H, NH), 8.21 (s, 1H, NH), 8.05 (dd, *J* = 8.7, 5.4 Hz, 2H, ArH), 7.36 (t, *J* = 8.6 Hz, 2H, ArH), 5.46 (d, *J* = 7.0 Hz, 1H, CH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 172.9, 167.5, 165.3 (d, *J* = 251.3 Hz), 157.4, 153.3, 131.7 (d, *J* = 9.5 Hz), 129.3 (d, *J* = 2.9 Hz), 116.1 (d, *J* = 22.0 Hz), 62.6; **^{19}F NMR** (282 MHz, DMSO-d_6): δ −106.5; **IR** (thin film): v 3345, 1777, 1698, 1678, 1526, 1434, 1228, 1167 cm^{-1}; **ESI-HRMS** calcd for $C_{11}H_9FN_4NaO_4$ $[M + Na]^+$ 303.0500, found 303.0506.

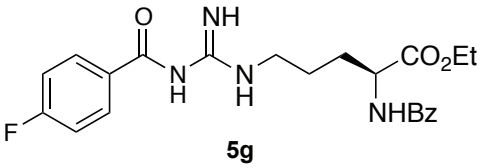
***N*-Methanesulfonyl-4-fluorobenzamide (5f).**



5f

Prepared by following general procedure 2 for 2.5 h at 60 °C with potassium 4-fluorobenzoyltrifluoroborate (**1a**, 25.6 mg, 0.11 mmol, 1.1 equiv) and methanesulfonamide (**4f**, 9.5 mg, 0.10 mmol, 1.0 equiv). The crude material was purified by column chromatography on silica gel (eluting with hexanes/acetone = 3:2 + 0.5% AcOH) to give **5f** as a white solid (14.7 mg, 68%); **m.p.** 178-182 °C; **^{1}H NMR** (400 MHz, acetone-d_6): δ 10.66 (br, 1H, NH), 8.10 (dd, *J* = 8.9, 5.3 Hz, 2H, ArH), 7.31 (t, *J* = 8.8 Hz, 2H, ArH), 3.39 (s, 3H CH_3); **^{13}C NMR** (100 MHz, acetone-d_6): δ 165.6 (d, *J* = 252.2 Hz), 164.9, 131.1 (d, *J* = 9.5 Hz), 128.6 (d, *J* = 2.9 Hz), 115.6 (d, *J* = 22.3 Hz), 40.8; **^{19}F NMR** (375 MHz, acetone-d_6): δ −107.4; **IR** (thin film): v 3252, 1677, 1602, 1443, 1339, 1233, 1157 cm^{-1}; **ESI-HRMS** calcd for $C_8H_7FNO_3S$ $[M - H]^-$ 216.0136, found 216.0139.

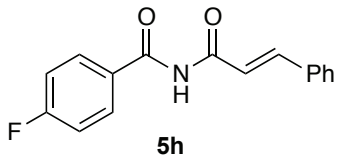
***N*$^\alpha$-benzoyl-*N*$^\omega$-(4-fluorobenzoyl)-L-arginine ethyl ester (5g).**



5g

Prepared by following general procedure 2 for 3 h with potassium 4-fluorobenzoyltrifluoroborate (**1a**, 25.6 mg, 0.11 mmol, 1.1 equiv) and *N*$^\alpha$-benzoyl-L-arginine ethyl ester hydrochloride (**4g**, 102.8 mg, 0.30 mmol, 1.5 equiv). The crude material was purified by column chromatography on silica gel (eluting with CH_2Cl_2/MeOH 100:5, +1% NEt_3) to give **5g** as a white solid in >90% purity (by NMR) [64.1 mg, 75%]. For characterization purposes, **5b** was further purified by preparative reverse-phase HPLC (YMC C18 column, A/B eluent gradient: 20-95% for 28 min, t_R = 15.8 min). The collected fraction was washed with sat. aq. $NaHCO_3$ (to remove CF_3CO_2H), extracted with CH_2Cl_2, dried over Na_2SO_4, filtered and evaporated in vacuo to give **5n** as a crystalline solid; **m. p.** 52-56 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.15 (dd, *J* = 8.5, 5.7 Hz, 2H, ArH), 7.78 (d, *J* = 7.6 Hz, 2H, ArH), 7.56 (d, *J* = 7.4 Hz, 1H, ArH), 7.44 (t, *J* = 7.6 Hz, 2H, ArH), 7.02 (t, *J* = 8.7 Hz, 2H, ArH), 6.98 (d, 1H NH), 4.89-4.79 (m, 1H CH), 4.25 (q, *J* = 7.2 Hz, 2H, CH_2), 3.64-3.52 (m, 1H, CH), 3.21 (br, 1H, CH), 2.07-1.95 (m, 1H, CH), 1.85-1.62 (m, 3H, CH), 1.30 (t, *J* = 7.2 Hz, 2H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 176.0, 172.2, 168.0, 164.8 (d, *J* = 250.5 Hz), 161.3, 134.3, 133.2, 132.3, 131.1 (d, *J* = 8.9 Hz), 128.8, 127.1, 114.7 (d, *J* = 21.5 Hz), 62.1, 51.3, 40.5, 31.1, 25.0, 14.2; **^{19}F NMR** (375 MHz, $CDCl_3$): δ −109.7; **IR** (thin film): v 3329, 2982, 2936, 1734, 1600, 1556, 1353, 1219, 1144 cm^{-1}; **ESI-HRMS** calcd for $C_{22}H_{26}FN_4O_4$ $[M + H]^+$ 429.1933, found 429.1932; **$[\alpha]_D$**: +4.9 (*c* = 1.06, $CHCl_3$).

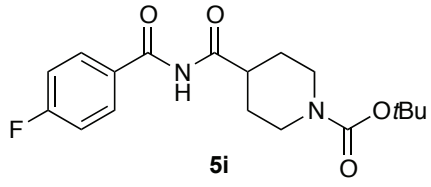
***N*-(*E*)-Cinnamoyl-4-fluorobenzamide (5h).**



5h

Prepared by following general procedure 2 for 3 h with potassium 4-fluorobenzoyltrifluoroborate (**1a**, 23.0 mg, 0.10 mmol, 1.0 equiv) and trans-cinnamamide (**4h**, 16.1 mg, 0.125 mmol, 1.25 equiv). The crude material was purified by column chromatography on silica gel (eluting with EtOAc/hexanes = 1:5 + 0.5% AcOH) to give **5h** as a white solid (15.3 mg, 57%); **m.p.** 179-182 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.84 (br s, 1H, NH), 7.98-7.90 (m, 3H, ArH + CH), 7.81 (d, *J* = 15.7 Hz, 1H, CH), 7.68-7.62 (m, 2H, ArH), 7.44-7.39 (m, 3H, ArH), 7.21 (t, *J* = 8.6 Hz, 2H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 167.7, 165.8 (d, *J* = 255.3 Hz), 164.8, 147.0, 134.5, 130.8, 130.4 (d, *J* = 9.3 Hz), 129.2 (d, *J* = 3.2 Hz), 128.9, 128.7, 119.1, 116.2 (d, *J* = 22.2 Hz); **^{19}F NMR** (375 MHz, $CDCl_3$): δ −104.6; **IR** (thin film): v 3279, 1661, 1611, 1469, 1355, 1248 cm^{-1}**; ESI-HRMS** calcd for $C_{16}H_{12}FNNaO_2$ $[M + Na]^+$ 292.0744, found 292.0745.

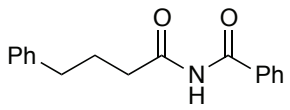
***tert*-Butyl 4-((4-fluorobenzoyl)carbamoyl)piperidine-1-carboxylate (5i).**



5i

Prepared with potassium 4-fluorobenzoyltrifluoroborate (**1a**, 25.6 mg, 0.11 mmol, 1.1 equiv), piperidine-4-carboxamide (**4i**, 12.8 mg, 0.10 mmol, 1.0 equiv) and 1,3,5-trichloroisocyanuric acid (TCCA, 15.3 mg, 0.066 mmol, 0.66 equiv) by a modification of general procedure 2. The reaction was stirred for 3 h at 40 °C and quenched with sat. aq. $NaHSO_3$ (0.6 mL). Sat. aq. $NaHCO_3$ was added until the solution turned slightly basic (pH between 7-8). Boc_2O (340 µL, 1.5 mmol) was added, and the mixture stirred for 1 h at rt, poured into H_2O/brine and extracted with EtOAc (3 x 3 mL). The organic extracts were collected, dried over Na_2SO_4, filtered and evaporated in vacuo. The residue was purified by column chromatography on silica gel (eluting with EtOAc/hexanes = 1:2) to give **3ai** as a white solid [15.6 mg, 44% (over 2 steps)]; **m.p.** 173-175 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.78 (br s, 1H, NH), 7.93 (dd, *J* = 8.9, 5.1 Hz, 2H, ArH), 7.21 (t, *J* = 8.5 Hz, 2H, ArH), 4.28-4.10 (m, 2H, CH_2), 3.61 (tt, *J* = 11.2, 3.6 Hz, 1H, CH), 2.89 (t, *J* = 12.7 Hz, 2H, CH_2), 1.97 (d, *J* = 13.0 Hz, 2H, CH_2), 1.70 (ddd, *J* = 24.5, 12.5, 4.3 Hz, 2H, CH_2), 1.46 (s, 9H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 177.7, 165.8 (d, *J* = 255.6 Hz), 164.3, 154.7, 130.4 (d, *J* = 9.3 Hz), 128.8 (d, *J* = 3.1 Hz), 116.3 (d, *J* = 22.2 Hz), 79.6, 43.1, 42.7, 28.5, 27.9; **^{19}F NMR** (375 MHz, $CDCl_3$): δ −104.5; **IR** (thin film): v 3280, 2975, 2929, 1731, 1692, 1603, 1493, 1240, 1159 cm^{-1}**; ESI-HRMS** calcd for $C_{18}H_{23}FN_2NaO_4$ $[M + Na]^+$ 373.1534, found 373.1540.

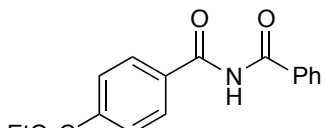
_N_-Benzoyl-4-phenylbutanamide (5j).[16]



5j

Prepared by following general procedure 2 for 3 h with potassium 4-phenylbutanoyltrifluoroborate (**1e**, 25.4 mg, 0.10 mmol, 1.0 equiv) and benzamide (**4a**, 13.3 mg, 0.11 mmol, 1.1 equiv). The crude material was purified by preparative reverse-phase HPLC (YMC C18 column, gradient of 20-95% MeCN/H_2O + 0.1% TFA for 28 min, t_R = 22.2 min) to give **5j** as a white solid (12.0 mg, 45%). The spectral data was in accordance with the literature; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.57 (s, 1H, NH), 7.83 (d, *J* = 7.8 Hz, 2H, ArH), 7.61 (tt, *J* = 7.8, 1.2 Hz, 1H, ArH), 7.50 (t, *J* = 7.8 Hz, 2H, ArH), 7.35-7.19 (m, 5H, ArH), 3.04 (t, *J* = 7.4 Hz, 2H, CH_2), 2.74 (t, *J* = 7.2 Hz, 2H, CH_2), 2.06 (p, *J* = 7.5 Hz, 2H, CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 175.7, 165.4, 141.6, 133.2, 132.8, 129.0, 128.5, 128.4, 127.6, 126.0, 37.0, 35.2, 25.7.

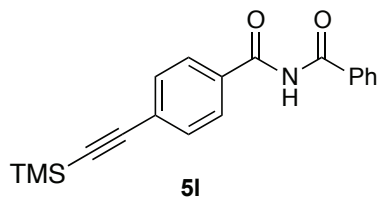
Ethyl 4-(benzoylcarbamoyl)benzoate (5k).[16]



5k

Prepared by following general procedure 2 for 4 h with potassium 4-(ethoxycarbonyl)benzoyltrifluoroborate (**1m**, 28.4 mg, 0.10 mmol, 1.0 equiv) and benzamide (**4a**, 13.3 mg, 0.11 mmol, 1.1 equiv). The crude material was purified by column chromatography on silica gel (eluting with EtOAc/hexanes = 2:3) to give **5k** as a white solid (12.5 mg, 42%). The spectral data was in accordance with the literature; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.17 (s, 1H, NH), 8.11 (d, *J* = 8.0 Hz, 2H, ArH), 7.92-7.85 (m, 3H, ArH), 7.61 (t, *J* = 7.4 Hz, 1H, ArH), 7.49 (t, *J* = 7.6 Hz, 2H, ArH), 4.39 (q, *J* = 7.1 Hz, 2H, CH_2), 1.40 (t, *J* = 7.1 Hz, 3H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.6, 166.3, 165.5, 137.2, 134.2, 133.3, 133.0, 129.9, 128.9, 128.0, 128.0, 61.6, 14.3.

_N_-Benzoyl-4-(2-trimethylsilylethynyl)benzamide (5l).

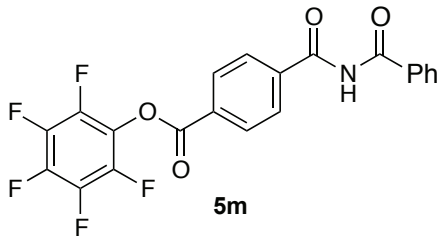


5l

Prepared by following general procedure 2 for 5 h with potassium 4-(2-trimethylsilylethynyl)benzoyltrifluoroborate (**1k**, 30.8 mg, 0.10 mmol, 1.0 equiv), benzamide (**4a**, 15.4 mg, 0.12 mmol, 1.2 equiv) and TCCA (9.3 mg, 0.04 mmol, 0.4 equiv). The crude material was purified by preparative TLC (eluting with EtOAc/hexanes = 1:3) to give **5l** as a viscous oil (18.1 mg, 57%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.99 (s, 1H, NH), 7.86 (d, *J* = 7.6 Hz, 2H, ArH), 7.80 (d, *J* = 8.3 Hz, 2H, ArH), 7.61 (t, *J* = 7.5 Hz, 1H, ArH), 7.56 (d, *J* = 8.4 Hz, 2H, ArH), 7.50 (d, *J* = 7.6 Hz, 2H, ArH), 0.27 (s, 9H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.6, 166.1, 133.4, 133.3, 132.8, 132.4, 129.0, 128.3, 128.1, 128.0, 103.8, 98.6, 0.0**;**

IR (thin film): v 3275, 2959, 2159, 1723, 1604, 1480, 1225 cm^{-1}**; ESI-HRMS** calcd for $C_{19}H_{20}NO_2Si$ $[M + H]^+$ 322.1258, found 322.1264.

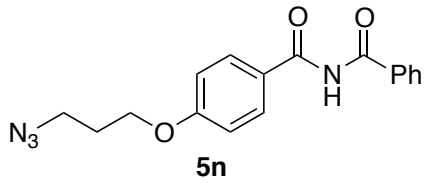
Pentafluorophenyl 4-(*N*-benzoylcarbamoyl)benzoate (5m).



5m

Prepared by following general procedure 2 for 12 h with potassium 4-(pentafluorophenoxycarbonyl)benzoyltrifluoroborate (**1g**, 42.6 mg, 0.10 mmol, 1.0 equiv), benzamide (**4a**, 15.5 mg, 0.12 mmol, 1.2 equiv) and TCCA (11.6 mg, 0.05 mmol, 0.5 equiv). The crude material was purified by column chromatography on silica gel (eluting with EtOAc/hexanes = 1:3 to 2:3) to give **5m** as a viscous oil (22.6 mg, 52%); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.52 (br s, 1H, NH), 8.32 (d, *J* = 8.7 Hz, 2H, ArH), 7.97 (d, *J* = 8.7 Hz, 2H, ArH), 7.90 (dd, *J* = 8.4, 1.2 Hz, 2H, ArH), 7.66 (t, *J* = 7.5 Hz, 1H, ArH), 7.56-7.53 (m, 2H, ArH); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 167.1, 166.0, 161.8, 141.4 ({^{19}F}), 139.9 ({^{19}F}), 139.2, 138.1 ({^{19}F}), 133.8, 132.7, 131.1, 130.6, 129.2, 128.6, 128.1 125.2({^{19}F}); **^{19}F NMR** (375 MHz, $CDCl_3$): δ −152.3, −157.2, −161.9; **IR** (thin film): v 3274, 1764, 1724, 1521, 1481, 1228, 1055 cm^{-1}; **ESI-HRMS** calcd for $C_{21}H_9F_5NO_4$ $[M - H]^-$ 434.0457, found 434.0446.

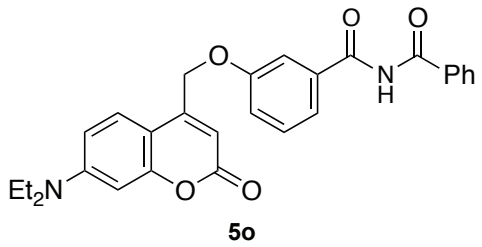
4-(3-Azidopropoxy)-*N*-benzoylbenzamide (5n).



5n

Prepared by following general procedure 2 for 6 h with potassium 4-(3-azidopropoxy)benzoyltrifluoroborate (**1j**, 31.1 mg, 0.10 mmol, 1.0 equiv) and benzamide (**4a**, 15.5 mg, 0.12 mmol, 1.2 equiv). The crude material was purified by preparative TLC (eluting with EtOAc/hexanes = 1:1) to give **5n** as a colourless oil (13.0 mg, 40%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.98 (br s, 1H, NH), 7.89-7.82 (m, 4H, ArH), 7.60 (t, *J* = 7.4 Hz, 1H, ArH), 7.50 (t, *J* = 7.5 Hz, 2H, ArH), 6.97 (d, *J* = 8.7 Hz, 2H, ArH), 4.12 (t, *J* = 5.9 Hz, 2H, CH_2), 3.54 (t, *J* = 6.5 Hz, 2H, CH_2), 2.09 (p, *J* = 6.2 Hz, 2H, CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 167.0, 166.1, 162.9, 133.6, 133.2, 130.5, 129.0, 128.1, 125.6, 114.7, 65.0, 48.2, 28.8; **IR** (thin film): v 3274, 2939, 2099, 1722, 1605, 1469, 1225, 1174 cm^{-1}; **ESI-HRMS** calcd for $C_{17}H_{17}N_4O_3$ $[M + H]^+$ 325.1295, found 325.1289.

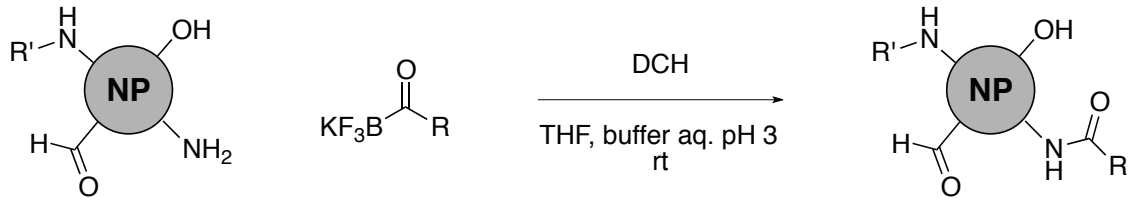
3-((7-(Diethylamino)-2-oxo-2*H*-chromen-4-yl)methoxy)-*N*-benzoylbenzamide (5o).



5o

Prepared by a slight modification of general procedure 1. Benzamide (**4a**, 15.5 mg, 0.12 mmol, 1.2 equiv) and TCCA (14 mg, 0.06 mmol, 0.6 equiv) were dissolved in 2 mL of a 1:1 mixture of THF and aq. buffer pH 3, and stirred for 10 min at rt. Potassium 3-((7-(diethylamino)-2*H*-chromen-2-one)methoxy) benzoyltrifluoroborate (**1h**, 45.6 mg, 0.10 mmol, 1.0 equiv) was added and the mixture stirred for 12 h at 40 °C. The crude material was purified by preparative TLC (eluting with CH_2Cl_2/MeOH = 100:2) to give **5o** as an orange solid (11.7 mg, 25%); **m.p.** 132-136 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.03 (br s, 1H, NH), 7.03 (d, *J* = 8.2 Hz, 2H, ArH), 7.59 (t, *J* = 7.4 Hz, 1H, ArH), 7.51.37-7.40 (m, 5H, ArH), 7.38 (d, *J* = 9.0 Hz, 1H, ArH), 7.23-7.18 (m, 1H, ArH), 6.65 (dd, *J* = 9.0, 2.5 Hz, 1H, ArH), 6.57 (d, *J* = 2.5 Hz, 1H, ArH), 6.28 (br, 1H, ArH), 5.20 (d, *J* = 1.3 Hz, 2H, CH_2), 3.41 (q, *J* = 7.1 Hz, 4H, CH_2), 1.18 (t, *J* = 7.1 Hz, 6H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.6, 166.1, 162.3, 158.5, 156.3, 150.2, 150.1, 135.0, 133.5, 133.2, 130.4, 129.1, 128.1, 124.8, 120.6, 120.6, 114.1, 109.9, 107.5, 107.1, 99.1, 66.0, 45.6, 12.4; **IR** (thin film): v 3263, 2974, 1722, 1603, 1472, 1241, 1199 cm^{-1}; **ESI-HRMS** calcd for $C_{28}H_{27}N_2O_5$ $[M + H]^+$ 471.1914, found 471.1917.

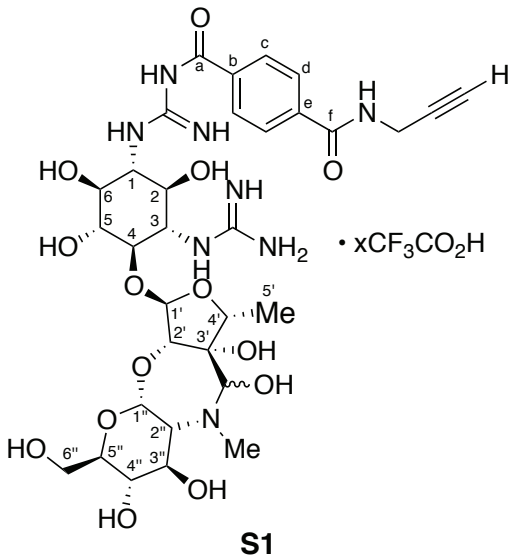
General Procedure 3: Late-stage Labeling of Natural Products



(excess)

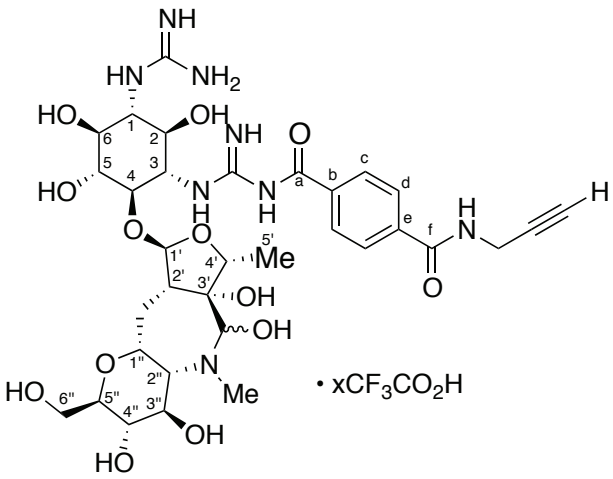
In a round-bottom flask, the corresponding natural product (5.0-10.0 equiv) was dissolved in a mixture of THF and aq. buffer pH 3 (prepared as described in general procedure 1). DCH or NCS (2.0-10.0 equiv) were added and the mixture stirred at rt for 10 min. KAT **1l** or **6** (1.0 equiv) were subsequently added and the solution stirred at rt. The reaction was monitored by analytical HPLC and quenched with sat. aq. $NaHSO_3$. The crude solution was purified by preparative reverse phase HPLC

N^G(C^1/C^3)-(4-(*N*-propargylcarbamoyl)benzoyl)streptomycin trifluoroacetate S1/S2.



S1

+



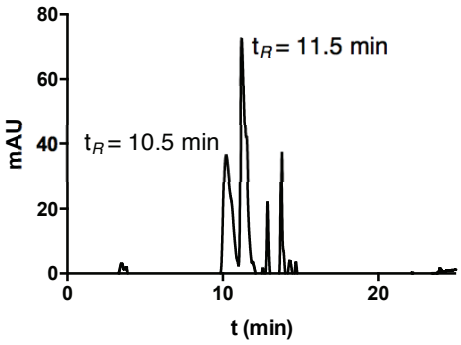
S2

Prepared by following general procedure 3 with streptomycin sesquisulfate (391 mg, 0.50 mmol, 5.0 equiv), KAT **1l** (29.3 mg, 0.10 mmol, 1.0 equiv) and DCH (39.4 mg, 0.20 mmol, 2.0 equiv) in 4 mL of a 1:3 mixture of THF and aq. buffer pH 3, 25 mM (prepared as described in general procedure 1) for 8 h. The solution was purified by preparative reverse phase HPLC (YMC C18 column, A/B eluent gradient: 5-95% for 25 min) to give the title compound as a mixture of four isomers in two main peaks. Based on the chemical shift of guanidine carbons, we have tentatively assigned the main structure of the isolated peaks to **S1** (t_R = 10.5 min, 15.8 mg, ~80% purity, 0.0155 mmol, 15%) and **S2** (t_R = 11.5 min, 14.9 mg, >95% purity, 0.0158 mmol, 17%), each of them containing two inseparable hemiaminal tautomers. From the crude analytical HPLC and MALDI traces (see below), the reaction appeared to be complete, so we attribute the low yields obtained to technical problems during the purification step. **S1: m.p.** >120 °C (decomp.); **1H NMR** (600 MHz, CD3OD): δ 8.17 (m, 4H, Ar^cH), 8.04 (m, 4H, Ar^dH), 5.38-5.31 (m, 4H, $C^{1'}H$, $C^{1''}H$), 4.48 (br s, 1H, $C^{3'}$–C*H*O), 4.45 (br s, 1H, $C^{3'}$–C*H*O), 4.42-4.36 (m, 4H, $C^{2'}H$, $C^{4'}H$), 4.17 (d, *J* = 2.6 Hz, 4H, CH_2C≡C), 3.96-3.88 (m, 4H, C^3H, $C^{6''}H$), 3.80-3.68 (m, 6H, $C^{3''}H$, $C^{5''}H$, C^4H), 3.66-3.59 (m, 4H, C^2H, $C^{6''}H$), 3.56-3.50 (m, 2H, C^5H), 3.44-3.38 (m, 4H, C^1H, C^6H), 2.99-2.93 (m, 2H, $C^{4''}H$), 2.86-2.70 (m, 8H, $C^{2''}$–NCH_3, $C^{2''}H$), 2.63 (t, *J* = 2.5 Hz, 2H, C≡C*H*), 1.25-1.22 (m, 6H, $C^{5'}H_3$); **^{13}C NMR** (151 MHz, CD_3OD): δ 169.3 (C^a), 168.2 (C^f), 163.3 (q, *J* = 34.7 Hz, CF_3CO_2H), 160.5 (C^1–NH*C*(NH)NHR), 157.0 (C^3–NH*C*(NH)NH_2), 140.0 (C^b), 135.7 (C^e), 129.8 (C^c), 129.1 (C^d), 118.2 (q, *J* = 292.9 Hz, CF_3CO_2H), 107.9 ($C^{1'}$), 107.8 ($C^{1'}$), 98.5 ($C^{3'}$–CHO), 98.4 ($C^{3'}$–CHO), 97.0 ($C^{1''}$), 96.8 ($C^{1''}$), 88.4 ($C^{2'}$), 87.4 ($C^{2'}$), 83.2 ($C^{3'}$), 82.6 ($C^{3'}$), 81.1 (C^4), 80.9 (C^4), 80.4 (CH_2C≡C), 78.6 ($C^{4'}$), 78.4 ($C^{4'}$), 75.7 (C^5), 75.5 (C^5), 75.3 ($C^{5''}$), 73.3 (C^6), 72.3 (C≡CH), 72.2 (C^2), 72.1 (C^2), 72.0 ($C^{4''}$), 70.6 ($C^{3''}$), 70.6 ($C^{3''}$), 63.5 ($C^{2''}$), 63.3 ($C^{2''}$), 62.5 ($C^{6''}$), 60.7 (C^1), 59.9 (C^3), 33.0 ($C^{2''}$–NCH_3), 32.6

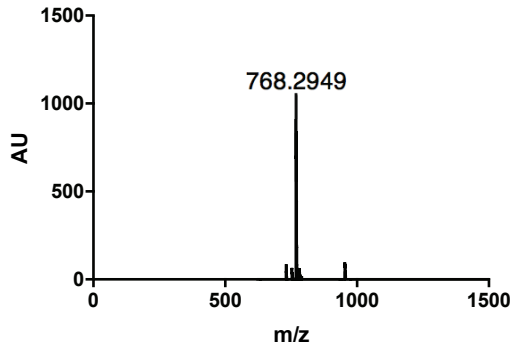
($C^{2''}$–NCH_3), 30.1 (CH_2C≡C), 24.9, 13.2 ($C^{5'}$), 12.9 ($C^{5'}$); **IR** (thin film): v 3322, 2983, 1668, 1206, 1143 cm^{-1}; **ESI-HRMS** calcd for $C_{33}H_{51}N_8O_{15}$ [M + H + MeOH]$^+$ 799.3468, found 799.3455; **[α]$_D$**: –27.8 (*c* = 0.35, MeOH).

S2: m.p. >140 °C (decomp.); **^{1}H NMR** (600 MHz, CD_3OD): δ 8.10 (d, *J* = 8.5 Hz, 4H, Ar^c*H*), 7.98 (d, *J* = 8.4 Hz, 4H, Ar^d*H*), 5.47 (d, *J* = 3.6 Hz, 1H, C$^{1''}$*H*), 5.45 (d, *J* = 3.6 Hz, 1H, C$^{1''}$*H*), 5.28 (d, *J* = 1.9 Hz, 1H, C$^{1'}$*H*), 5.27 (d, *J* = 2.1 Hz, 1H, C$^{1'}$*H*), 4.52 (s, 1H, C$^{3'}$–C*H*O), 4.50 (s, 1H, C$^{3'}$–C*H*O), 4.48-4.36 (m, 4H, C$^{2'}$*H*, C$^{4'}$*H*), 4.17 (d, *J* = 2.5 Hz, 4H, CH_2C≡C), 4.08-4.04 (m, 2H, C$^{6''}$*H*), 3.90-3.81 (m, 4H, C$^{3''}$*H*, C$^{5''}$*H*), 3.75-3.68 (m, 4H, C^1*H*, C$^{6''}$*H*), 3.64-3.58 (br, 6H, C^2*H,* C^3*H,* C^4*H*), 3.56-3.50 (m, 4H, C^5*H,* C^6*H*), 3.35-3.31 (m, 2H, C$^{4''}$*H*), 3.26-3.21 (m, 2H, C$^{2''}$*H*), 2-85-2.82 (br, 6H, C$^{2''}$–NCH_3), 2.62 (t, *J* = 2.5 Hz, 2H, C≡C*H*), 1.26 (d, *J* = 6.3 Hz, 3H), 1.25 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (151 MHz, CD_3OD): δ 169.5 (*C*^{a}), 168.3 (*C*^{f}), 163.3 (q, *J* = 33.7 Hz, CF_3CO_2H), 159.8 (C^1–NH*C*(NH)NHR), 157.5 (C^3–NH*C*(NH)NH_2), 140.0 (*C*^{b}), 135.6 (*C*^{e}), 129.7 (*C*^{c}), 129.0 (*C*^{d}), 118.2 (q, *J* = 292.2 Hz, *C*F_3CO_2H), 108.3 (*C*$^{1''}$), 108.2 (*C*$^{1''}$), 98.6 (C$^{3'}$–*C*HO), 98.4 (C$^{3'}$–*C*HO), 97.1 (*C*$^{1'}$), 96.9 (*C*$^{1'}$), 88.4 (*C*$^{2'}$), 87.5 (*C*$^{2'}$), 83.2 (*C*$^{3'}$), 82.7 (*C*$^{3'}$), 81.2 (*C*^{4}), 80.4 (CH_2*C*≡C), 78.5 (*C*$^{4'}$), 78.3 (*C*$^{4'}$), 75.6 (*C*^{5}), 75.6 (*C*^{5}), 75.4 (*C*$^{5''}$), 72.9 (*C*^{6}), 72.9 (*C*^{2}), 72.3 (C≡*C*H), 72.1 (*C*$^{4''}$), 70.6 (*C*$^{3''}$), 63.3 (*C*$^{2''}$), 63.1 (*C*$^{2''}$), 62.8 (*C*$^{6''}$), 62.7 (*C*$^{6''}$), 60.7 (*C*^{1}), 59.9 (*C*^{3}), 59.8 (*C*^{3}), 33.1 (C$^{2''}$–NCH_3), 32.7 (C$^{2''}$–NCH_3), 30.1 (CH_2C≡C), 13.2 (*C*$^{5'}$), 12.9 (*C*$^{5'}$); **IR** (thin film): v 3308, 1673, 1203, 1138 cm^{-1}; **ESI-HRMS** calcd for $C_{33}H_{51}N_8O_{15}$ [M + H + MeOH]$^+$ 799.3468, found 799.3458; **[α]$_D$**: –37.2 (*c* = 0.48, MeOH).

Crude analytical HPLC (5-95% A/B, monitoring at λ = 254 nm for 17 min):



Crude MALDI-TOF:



We have performed a negative control experiment where we mixed streptomycin sesquisulfate (72.8 mg, 0.10 mmol, 1.0 equiv) and DCH (19.7 mg, 0.10 mmol, 1.0 equiv) in 2 mL of a 1:3 mixture of THF and aq. buffer pH 3, 25 mM (prepared as described in general procedure 1). The solution was stirred at rt for 8 h, quenched with aq. $NaHSO_3$ and lyophilized. The residue was dissolved in D_2O and the ^{1}H-NMR spectrum was recorded and compared with the ^{1}H-NMR of the starting material. We observed that several proton and carbon signals split to two after treatment with chlorinating agent (see below for a comparison between the spectra, zoomed at the aliphatic methyl peaks). This effect is more pronounced in the signals assigned to and close to the streptose ring, so we attribute this to a possible tautomerization of the aldehyde group at the streptose ring (middle, five-membered ring), to give the corresponding internal hemiaminal products.

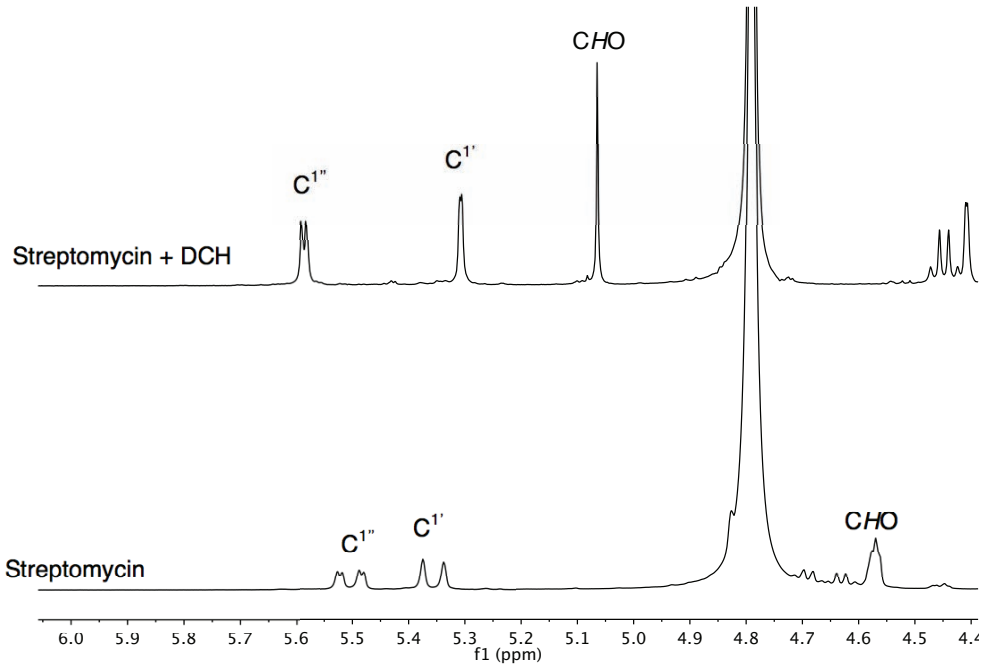
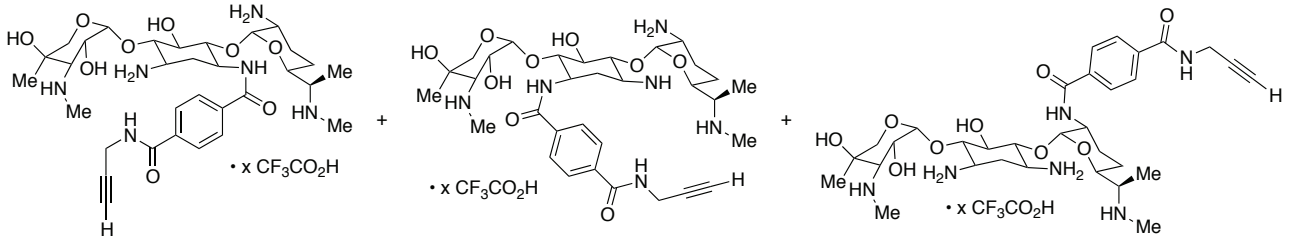


Figure S1. Comparison between 1H-NMR (4.5-6.0 ppm-zoomed region) of streptomycin before and after treatment with DCH.

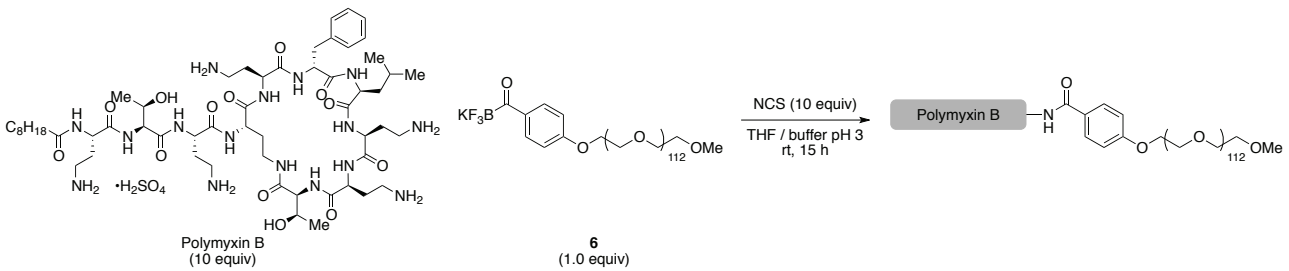
_N_-(4-(_N_-Propargylcarbamoyl)benzoyl)gentamicin C_1.



Prepared by following general procedure 3 using gentamicin C_1 free base (139 mg, 0.29 mmol, 3.0 equiv), NCS (40 mg, 0.29 mmol, 3.0 equiv) and KAT **1l** (28.4 mg, 0.10 mmol, 1.0 equiv) in 4 mL of a 1:3 mixture of THF and aq. buffer pH 3, 25 mM (prepared as described in general procedure 1) for 3 h. The solution was lyophilized and the residue purified by preparative reverse phase HPLC (YMC C18 column, A/B eluent gradient: 5-50% for 25 min, t_R = 18.2 min) to give the title compound as a white powder (20.2 mg, 25%). **m.p.** >140 °C (decomp); **^{1}H NMR** (600 MHz, CD_3OD): δ 7.94-7.89 (m, 4H), 6.00 (br s, 1H), 5.10 (d, *J* = 7.4 Hz, 1H), 4.31-4.22 (m, 2H), 4.16 (d, *J* = 2.6 Hz, 2H), 4.11-4.07 (m, 1H), 4.05 (d, *J* = 12.5 Hz, 1H), 4.00 (dd, *J* = 10.7, 3.4 Hz, 1H), 3.83-3.75 (m, 2H), 3.47-3.36 (m, 3H), 3.34-3.30 (m, 1H), 3.16 (d, *J* = 10.7 Hz, 1H), 2.90-2.85 (m, 1H), 2.75 (br s, 3H), 2.66 (br s, 3H), 2.61 (t, *J* = 2.5 Hz, 1H), 2.40-2.33 (m, 1H), 2.19-2.09 (m, 2H),2.07-1.93 (m, 2H), 1.87-1.81 (m, 1H), 1.68-1.56 (m, 2H), 1.31 (d, *J* = 6.6 Hz, 3H), 1.24 (s, 3H); **^{13}C NMR** (150 MHz, CD_3OD): δ 169.6, 168.9, 138.6, 138.2, 129.0, 128.7, 100.6, 96.6, 83.7, 80.7, 78.8, 76.9, 72.3, 70.8, 70.0, 69.1, 68.3, 66.1, 59.3, 50.9, 50.5, 50.2, 36.1, 32.3, 32.1, 30.2, 25.1, 22.3, 22.2, 10.6; **IR** (thin film): v 3293, 3041, 1675, 1201, 1134 cm^{-1}; **ESI-HRMS** calcd for $C_{32}H_{51}N_6O_9$ $[M + H]^+$ 663.3712, found 663.3706; **$[\alpha]_D$**: +57.9 (*c* = 0.14, MeOH).

Note: from our control experiments, we have not observed any substantial change in NMR spectra of gentamicin C1 after treatment with NCS.

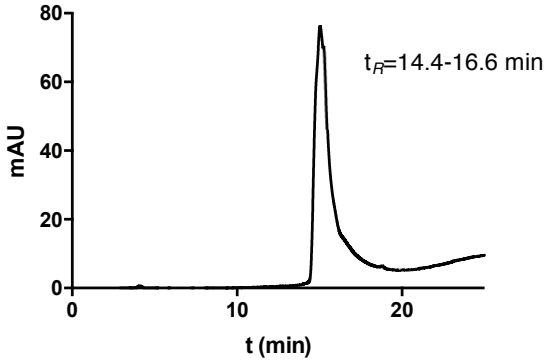
_N_-MonoPEGylated polymyxin B



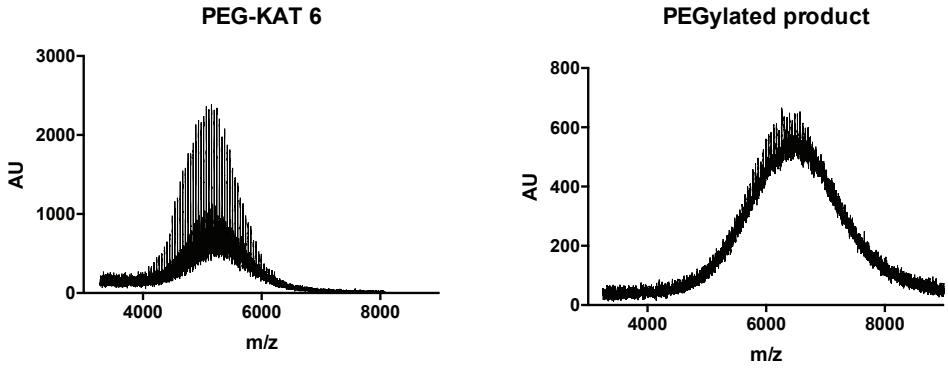
Prepared by following general procedure 3 using polymyxin sulfate (130.3 mg, 0.10 mmol, 10.0 equiv), NCS (13.3 mg, 0.10 mmol, 10.0 equiv) and PEG-KAT **6** (MW ~5,000 Da, 50.0 mg, 0.010 mmol, 1.0 equiv) in 1 mL of a 1:3 mixture of THF and aq. buffer pH 3, 25 mM (prepared as described in general procedure 1) for 15 h.

The solution was purified by spin filtration (MWCO = 3,000 Da, washing with MeCN / 0.1 M HCl (1:3, 4 x 10 mL)) and lyophilized to give the title compound as a white powder (46.5 mg, 74%).

Analytical HPLC (20-95% A/B, monitoring at λ = 354 nm, 17 min):

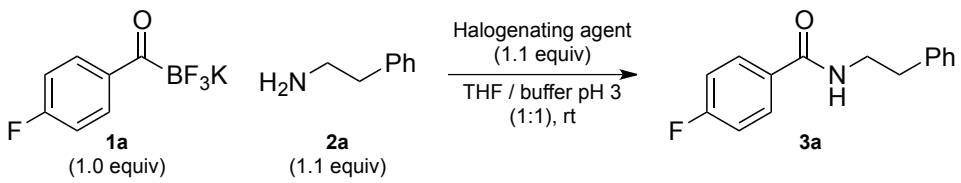


MALDI-TOF:



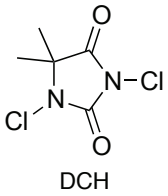
Optimization Studies

Screening of Halogenating Agents

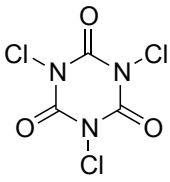


Entry	Halogenating agent	Time (min)	**3a** (%yield)*	Comments
1	NCS	30	88	-
2	NBS	90	18	Messy mixture
3	NIS	90	44	Messy mixture
4	Selectfluor®	60	42	-
5	NaOCl	90	22	Messy mixture
6	DCH	30	92	-
7	TCCA	30	22	Messy mixture
8	Chloramine-T	30	-	No reaction
9	Palau'Chlor	30	82	-
10	-	30	-	No reaction

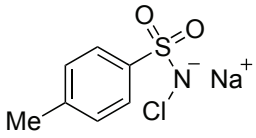
*NMR yield



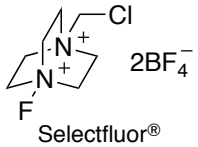
DCH



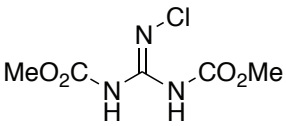
TCCA



Chloramine-T



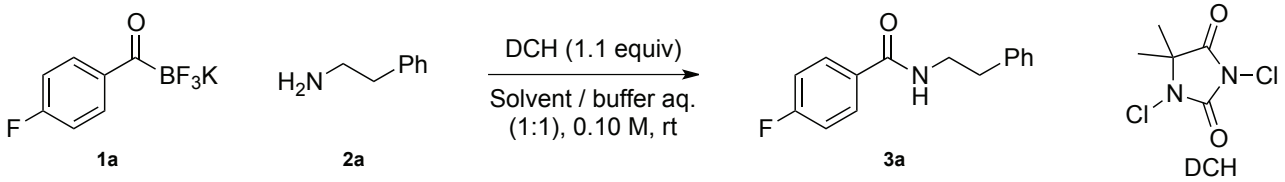
Selectfluor®



Palau'Chlor"

In a round bottom flask, **1a** (23.0 mg, 0.10 mmol, 1.0 equiv) was dissolved in 1 mL of a 1:1 mixture of THF and aq. buffer pH 3, 25 mM (prepared by dissolving citric acid monohydrate (4.48 g, 21.35 mmol) and trisodium citrate dihydrate (1.07 g, 3.64 mmol) in distilled water (1 L), final pH was adjusted using 0.1 M NaOH and HCl solutions). 2-Phenethylamine (13.6 µL, 0.11 mmol, 1.1 equiv) and halogenating agent (1.1 equiv) were added sequentially and the mixture allowed to stir at rt for 30 to 90 min. The solution was quenched with sat. $NaHSO_3$ (0.3 mL), poured into H_2O/brine and extracted with EtOAc (3 x 3 mL). The organic extracts were collected, dried over Na_2SO_4, filtered and evaporated in vacuo. The reaction yield was measured by NMR analysis of the crude, using nitromethane (5.4 µL, 0.10 mmol) as internal standard.

Screening of Solvents and pH.



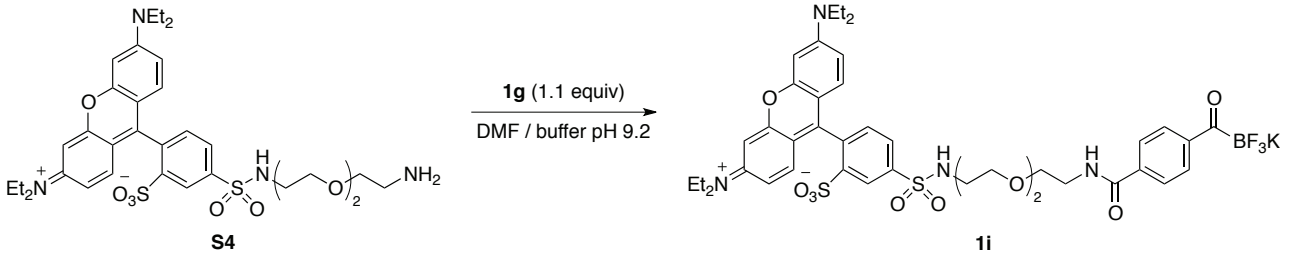
Entry	Solvent	pH	Time (min)	**3a** (%yield)*	Comments
1	tBuOH	3	30	85	With NCS
2	MeCN	3	30	85	With NCS
3	MeOH	3	30	71	With NCS
4	THF	3	30	92	-
5	THF	4	30	91	-
6	THF	5	30	84	-
7	THF	6	30	75	-
8	THF	7	30	25	-
9	THF	8	30	traces	-
10	THF	9	30	traces	-
11	THF	1.4	30	85	-
12	THF	0.5	30	52	-
13	THF	0.5	60	24	[**1a**] = 10 mM

*NMR yield

In a round bottom flask, **1a** (23.0 mg, 0.10 mmol, 1.0 equiv) was dissolved in 1 mL of a 1:1 mixture of an organic solvent and aq. buffer (pH values from 1.4 to 9). 2-Phenethylamine (13.6 µL, 0.11 mmol, 1.1 equiv) and DCH (21.7 mg, 0.11 mmol, 1.1 equiv) were added sequentially and the mixture allowed to stir at rt for 30 min. The solution was quenched with sat. $NaHSO_3$ (0.3 mL), poured into H_2O/brine and extracted with EtOAc (3 x 3 mL). The organic extracts were collected, dried over Na_2SO_4, filtered and evaporated in vacuo. The reaction yield was measured by NMR analysis of the crude, using nitromethane (5.4 µL, 0.10 mmol) as internal standard.

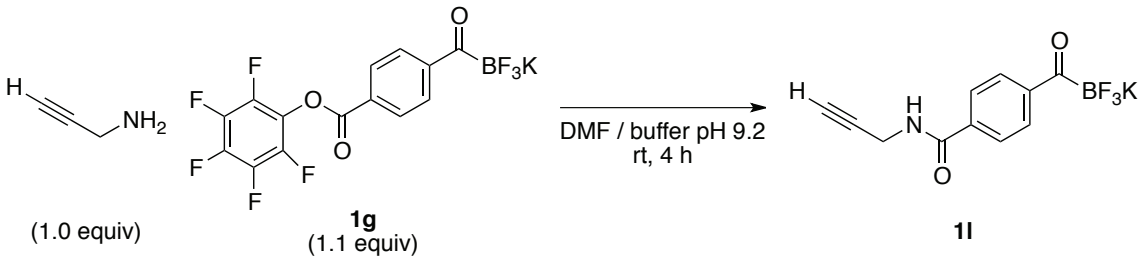
Preparation of Starting Materials

Preparation of 2-(6-(Diethylamino)-3-(diethyliminio)-3*H*-xanthen-9-yl)-5-(*N*-(2-(2-(2-(4-(*N*-(2-phenylethyl)carbamoyl)benzamido)ethoxy)ethoxy)ethyl)sulfamoyl)benzenesulfonate (3v).



A round-bottom flask was charged with KAT **1g** (130 mg, 0.30 mmol, 1.1 equiv) and 2-(6-(diethylamino)-3-(diethyliminio)-3*H*-xanthen-9-yl)-5-(*N*-(2-(2-(2-aminoethoxy)ethoxy)ethyl)sulfamoyl)benzenesulfonate (**S4**, 38.4 µL, 0.60 mmol, 1.2 equiv). DMF (1 mL) and aq. buffer pH 9.2 (1.5 mL, 0.1 M, prepared by dissolving potassium carbonate anhydrous (1.01 g, 7.31 mmol) and potassium bicarbonate anhydrous (9.27 g, 92.7 mmol) in distilled water (1 L), final pH was adjusted using 1 M NaOH and HCl solutions) were added and the solution stirred at rt for 6h. The solution was purified by preparative reverse phase HPLC (Shiseido C18 column 50 x 250 mm, flow = 40 mL/min, 20% A in 10 min, then 20-95% A/B in 40 min, monitoring at λ = 301 nm, t_R = 31.6 min). The fractions were pooled, neutralized with anhydrous KF (pH 5–6) and lyophilized. The residue was dissolved in MeOH, filtered and evaporated to give a magenta solid (161 mg, 62%) in >90% purity (by NMR). The structure was confirmed after conversion to amide **3v**, as described in general procedure 1.

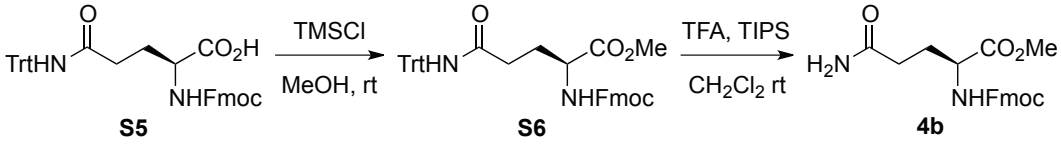
Preparation of potassium 4-(*N*-propargylcarbamoyl)benzoyltrifluoroborate 1l.



A round-bottom flask was charged with KAT **1g** (213.0 mg, 0.50 mmol, 1.2 equiv) and propargylamine (38.4 µL, 0.60 mmol, 1.2 equiv). DMF (1 mL) and aq. buffer pH 9.2 (2 mL, 0.1 M, prepared as described for the synthesis of **1i**) were added and the solution stirred at rt for 4h. The solution was evaporated until a yellowish oil remained in the flask. Addition of CH_2Cl_2 caused the product to precipitate. The suspension was filtered and the filter cake was redissolved in anhydrous acetone. The solution was filtered and evaporated to

give **1l** as a white solid (95.2 mg, 65%). **m.p.** >180 °C (decomp); **^{1}H NMR** (600 MHz, acetone-d_6): δ 8.37 (t, J = 5.3 Hz, 1H, NH), 8.10 (d, J = 8.0 Hz, 2H), 7.94 (d, J = 8.4 Hz, 2H), 4.21 (dd, J = 5.6, 2.5 Hz, 2H, CH_2), 2.67 (t, J = 2.5 Hz, 1H, CH); **^{13}C NMR** (151 MHz, acetone-d6): δ 235.0 (br), 167.1, 143.9, 137.2, 129.1, 127.8, 81.5, 71.9, 29.5; **^{19}F NMR** (470 MHz, acetone-d_6): δ −144.8; **^{11}B NMR** (160 MHz, acetone-d_6): δ −0.74; **IR** (thin film): v 3296, 1677, 1634, 1536, 1206, 1133 cm^{-1}; **ESI-HRMS** calcd for $C_{11}H_8BF_3NO_2$ $[M-K]^-$ 254.0606, found 254.0612.

Preparation of Fmoc-L-glutamine methyl ester 4b.[17]

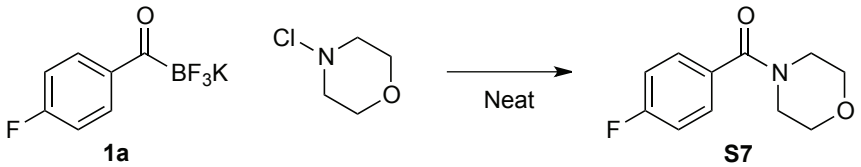


S5 **S6** **4b**

L-glutamine methyl ester derivative **S6** was prepared according to a reported procedure.[18] To a round-bottom flask charged with N^{α}-Fmoc-N^{ω}-Trt-L-glutamine (**S5**, 3.05 g, 5.0 mmol, 1.0 equiv), TMSCl (3.2 mL, 25 mmol, 5.0 equiv) and MeOH (10 mL) were added sequentially and the mixture was stirred at rt for 3 h. The suspended solid formed during the reaction was filtered off, dissolved in EtOAc and washed with $NaHCO_3$ to afford **S6** (2.98 g, 95%), which was pure enough to be used in the next step.

Amide **4b** was prepared by subjecting **S6** to standard trityl deprotection conditions[19]. To a round-bottom flask containing **S6** (2.98 g, 4.77 mmol, 1.0 equiv) were added CH_2Cl_2 (30 mL), TIPS (2 mL, 10 mmol, 2.1 equiv) and TFA (10 mL). The solution was stirred at rt for 30 min and evaporated in vacuo. The crude material was purified by column chromatography on silica gel (CH_2Cl_2/MeOH = 100:5, 1% AcOH) to give **4b** as a white solid (1.2 g, 66%). The spectral data was in accordance with the literature.

Preparation of *N*-(4-fluorobenzoyl)morpholine[20].

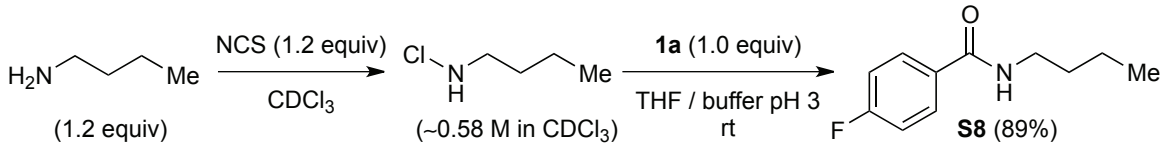


1a **S7**

In a round-bottom flask, potassium 4-fluorobenzoyltrifluoroborate (**1a**, 23 mg, 0.10 mmol, 1.0 equiv) and *N*-chloromorpholine (150.0 µL, 1.95 mmol, 19.5 equiv) were stirred neat for 30 min at rt. The reaction was quenched with sat. aq. $NaHSO_3$ (0.5 mL), poured in H_2O/brine and extracted with AcOEt (3 x 3 mL). The

organic extracts were collected, dried over Na_2SO_4, filtered and evaporated in vacuo. The residue was purified by column chromatography on silica gel (eluting with CH_2Cl_2/MeOH 100:2.5) to afford **S7** as a colorless oil (14.7 mg, 70%). The spectral data was in accordance with the literature. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 (dd, *J* = 8.5, 5.4 Hz, 2H, ArH), 7.10 (t, *J* = 8.6 Hz, 2H, ArH), 3.85-3.41 (br, 8H, CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 169.5, 163.5 (d, *J* = 250.2 Hz), 131.3 (d, *J* = 3.5 Hz), 129.4 (d, *J* = 8.5 Hz), 115.7 (d, *J* = 21.8 Hz), 66.8; **^{19}F NMR** (375 MHz, $CDCl_3$): δ −109.9.

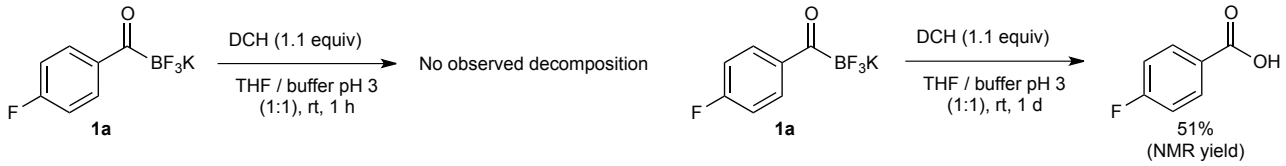
Preparation and acylation of *N*-chlorobutylamine.



In a Schlenk flask under N_2 atmosphere, $CDCl_3$ (2 mL), *n*-butylamine (198 µL, 2.0 mmol) and NCS (267 mg, 2.0 mmol, 1.0 equiv) were introduced, stirred at rt for 10 min, and filtered. The concentration of *N*-chlorobutylamine on the filtrate was calculated by NMR analysis (using nitromethane (5.4 µL, 0.10 mmol) as internal standard) and found to be ca. 0.58 M. The solution was used for the next step without further manipulation. The spectral data of *N*-chlorobutylamine was in accordance with the literature[21].

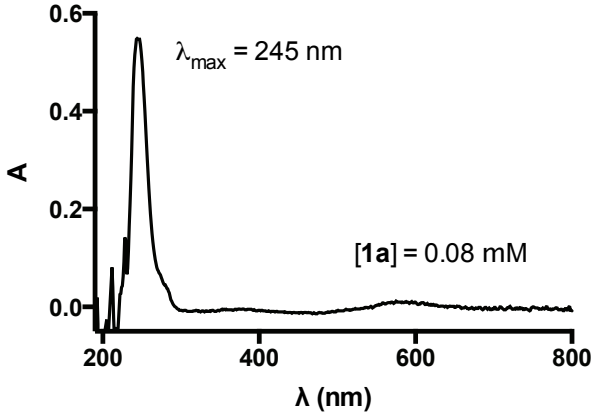
A round bottom flask was charged with potassium 4-fluorobenzoyltrifluoroborate **1a** (23.0 mg, 0.10 mmol, 1.0 equiv) and THF (0.5 mL). To this suspension, the freshly prepared solution of *N*-chlorobutylamine (206 µL, 0.12 mmol, 1.2 equiv, ca. 0.58 M in $CDCl_3$) and a pH3 buffer aq. (0.5 mL, citric acid and trisodium citrate, 25mM) were sequentially added. The mixture was stirred at rt for 45 min, quenched with sat. aq. $NaHSO_3$ (0.3 mL), poured in H_2O/brine and extracted with EtOAc (3 x 3 mL). The organic extracts were collected, dried over Na_2SO_4, filtered and evaporated in vacuo. The residue was purified by column chromatography on silica gel (eluting with EtOAc/hexanes 1:2) to afford *N*-butyl-4-fluorobenzamide **S8** as a white solid (17.4 mg, 89%). The spectral data was in accordance with the literature.[22] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.76 (dd, *J* = 8.8, 5.3 Hz, 2H, ArH), 7.09 (t, *J* = 8.6 Hz, 2H, ArH), 3.44 (td, *J* = 7.2, 5.7 Hz, 2H, CH_2), 1.59 (p, *J* = 7.8 Hz, 2H, CH_2), 1.40 (sx, *J* = 7.5 Hz, 2H, CH_2), 0.95 (t, *J* = 7.3 Hz, 2H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.5, 164.6 (d, *J* = 251.5 Hz), 131.0 (d, *J* = 3.2 Hz), 129.1 (d, *J* = 8.8 Hz), 115.5 (d, *J* = 21.9 Hz), 39.9, 31.7, 20.2, 13.8; **^{19}F NMR** (375 MHz, $CDCl_3$): δ −108.6.

Stability of KAT 1a towards chlorinating agents.

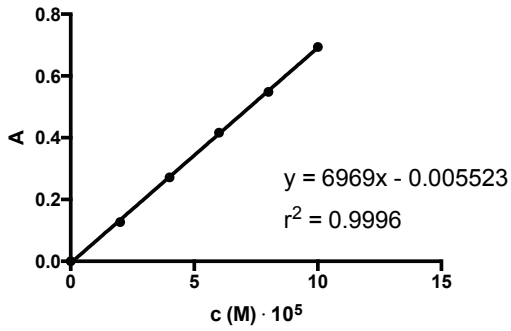


1a is essentially stable towards DCH for several hours. However, after stirring 15 h a solution of **1a** (23.0 mg, 0.10 mmol, 1.0 equiv) and DCH (21.7 mg, 0.11 mmol, 1.1 equiv) in a 1:1 mixture of THF and citrate buffer pH 3 (1 mL), partial decomposition of **1a** to 4-fluorobenzoic acid was observed by LC-MS analysis of the reaction mixture. The solution was quenched with sat. aq. $NaHSO_3$ (0.5 mL), poured into HCl 1 M and brine and extracted with EtOAc (3 x 3 mL). The organic extracts were collected, dried over Na_2SO_4, filtered and evaporated in vacuo. 4-Fluorobenzoic acid was formed in 51% yield as determined by NMR analysis of the residue using $MeNO_2$ (5.41 µL, 0.10 mmol) as internal standard.

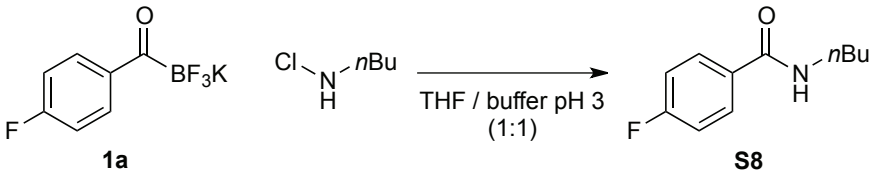
UV-Vis Spectrum and Determination of Molar Absorptivity of 1a



To determine the molar absorptivity of 4-fluorobenzoyltrifluoroborate **1a**, seriated solutions of **1a** (final concentrations 3-15 mM) were prepared in a 1:1 mixture of THF / buffer aq. pH 3 (prepared by dissolving citric acid monohydrate (4.48 g, 21.35 mmol) and trisodium citrate dihydrate (1.07 g, 3.64 mmol) in distilled water (1 L), final pH was adjusted using 0.10 M NaOH and HCl solutions). Absorbances at 245 nm are measured and plotted over molar concentration. The extinction coefficient of **1a** was found to be $6.97 \cdot 10^3$ M^{-1} cm^{-1}.



Kinetic Studies of the Acylation of *N*-chlorobutylamine Monitored by UV.



λ_{max} = 245 nm

ε = 6.97·10^3 M^{-1} cm^{-1} ε = 3.74·10^3 M^{-1} cm^{-1}

A solution of around 0.10 mM concentration of **1a** in a 1:1 mixture of THF and aq. buffer pH 3 was prepared. The concentration was measured by UV-Vis (measuring the absorbance at 245 nm, ε = 6.97·10^3 M^{-1} cm^{-1}) and found to be 0.12 mM. 2 mL (0.24 µmol, 1 equiv) were transferred to a quartz cuvette equipped with a stir bar. Freshly prepared *N*−chlorobutylamine (prepared as described above, 50.3 mM, 4.89 µL, 0.24 µmol, 1 equiv) was added and the absorbance at 245 nm was monitored at rt while stirring slowly. Concentrations of starting material were calculated from the molar absorptivities of both **1a** and **S8**, by the following equation:

$$C_{1a} = \frac{A_t - (\varepsilon_{S8} C_0)}{\varepsilon_{1a} - \varepsilon_{S8}}$$

Where A_t is total absorbance value measured, C_0 is the initial concentration value and ε_{1a} and ε_{S8} are the extinction coefficients of **1a** and **S8** respectively.

The reaction between **1a** and *N*−chlorobutylamine is a bimolecular process that follows a second-order kinetics. Reaction rates can be written as follows:

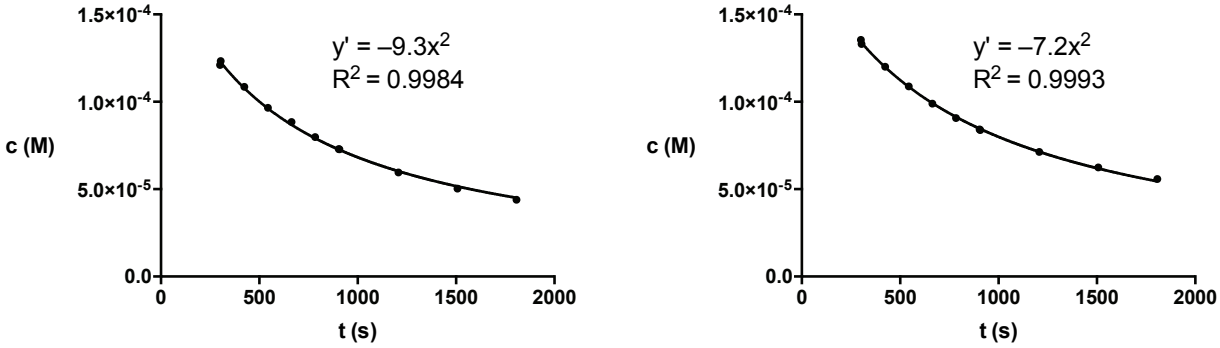
$$v = -\frac{d[A]}{dt} = k[A][B]$$

Since the reaction was carried out with stoichiometric amounts of both reagents, the equation above can be converted to the following equation:

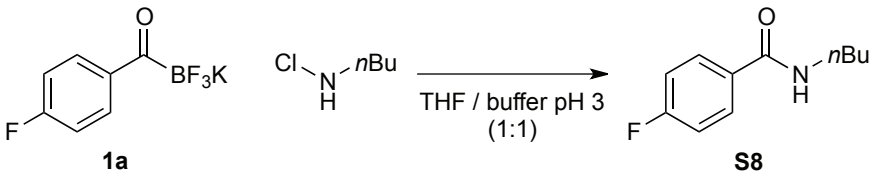
$$v = -\frac{d[A]}{dt} = k[A]^2$$

The differential equation above shows that second-order rate constants can be determined by plotting [A] against t. Non-linear fit of the data by using this equation gave the corresponding best-fit second-order rate constants with reasonable r^2 values.

From the plots below, a second-order kinetic constant of 8.3 ± 1.5 M^{-1} s^{-1} was obtained.



Kinetic Studies of the Acylation of *N*-chlorobutylamine Monitored by HPLC.

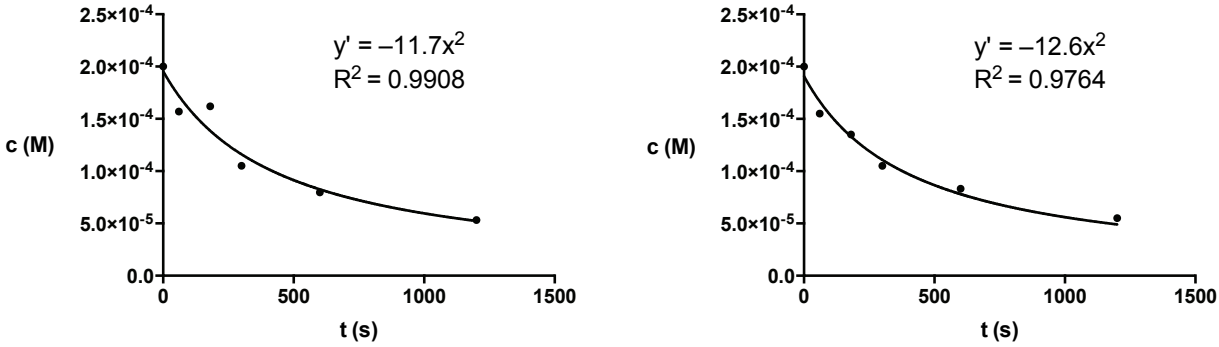


λ_{max} = 245 nm

$\varepsilon = 6.97 \cdot 10^3$ M^{-1} cm^{-1}

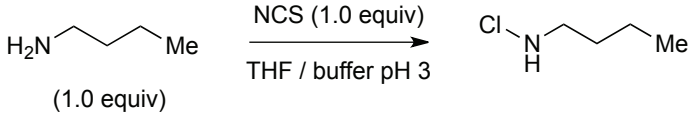
$\varepsilon = 3.74 \cdot 10^3$ M^{-1} cm^{-1}

A round-bottom flask was charged with a solution of **1a** in a 1:1 mixture of THF and aq. buffer pH 3 (1 mL, 0.2 mM, 0.20 µmol, 1.0 equiv). Freshly prepared *N*−chlorobutylamine (prepared and analyzed as described above, 0.21 µmol, 1.05 equiv) was added and the mixture stirred at rt. Aliquots (60 µL) of the solution were removed at periodic time intervals, mixed with 0.2 M aq. KOH (60 µL) to quench the reaction and analyzed by HPLC. The average second order rate constant was determined to be 12.1 ± 0.6 M^{-1} s^{-1}

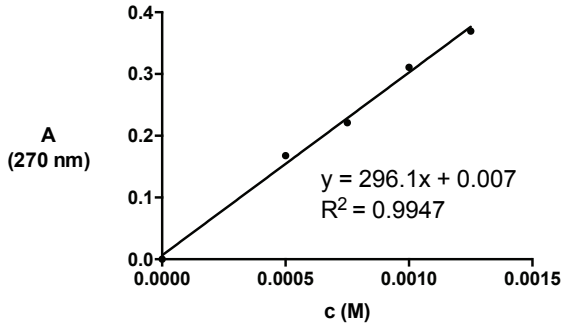


By combining the four values obtained from both UV and HPLC methods, the obtained value for the kinetic constant is k ~10 M^{-1} s^{-1}.

Determination of Molar Absorptivity and Rate Constant of Formation of *N*-chlorobutylamine.



N-chlorobutylamine was prepared and its concentration determined in a similar manner as described above, but using CD_3CN in replacement of $CDCl_3$. To determine the molar absorptivity of *N*-chlorobutylamine, seriated solutions (final concentrations 0.50-1.25 mM) were prepared in a 1:1 mixture of THF / buffer aq. pH 3 (prepared by dissolving citric acid monohydrate (4.48 g, 21.35 mmol) and trisodium citrate dihydrate (1.07 g, 3.64 mmol) in distilled water (1 L), final pH was adjusted using 0.10 M NaOH and HCl solutions). Absorbances at 270 nm are measured and plotted over molar concentration. The extinction coefficient of **1a** was found to be 296.1 ± 6.0 M^{-1} cm^{-1}.



A solution of *N*-butylamine in a 1:1 mixture of THF and aq. buffer pH 3 was prepared (2 mL, 2.5 mM). NCS (50 µL from 100 mM solution, final conc. 2.5 mM) was added. The absorbance at 270 nm was measured

while mildly stirring the solution. Concentrations of *N*−chlorobutylamine produced were calculated and plotted over time.

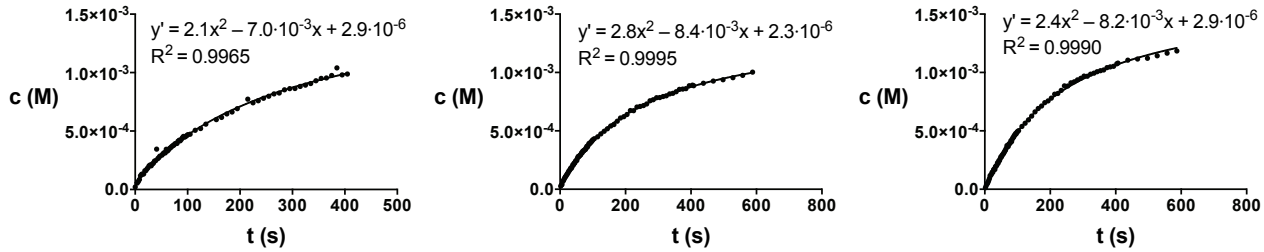
As we are plotting product concentration ([*P*]) over time (t), the starting material concentration at a time t ([*A*]) needs to be properly converted to product concentration, as follows:

$$[A] = [A_0] - [P]$$

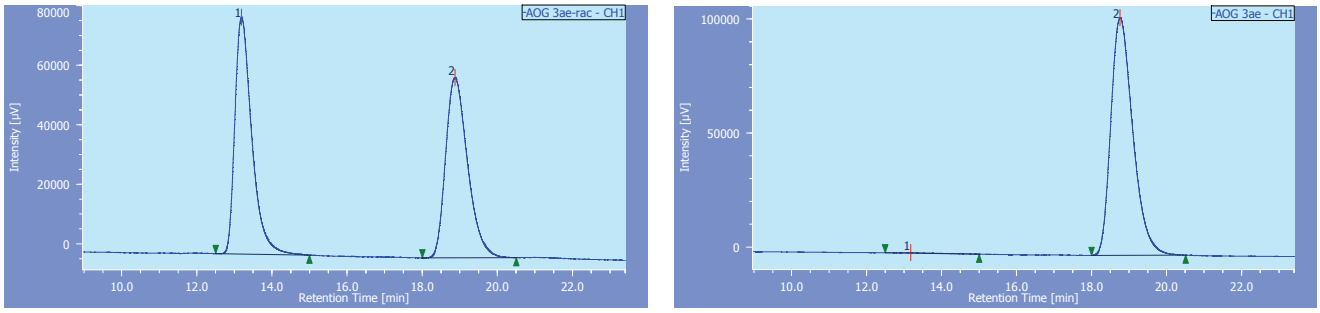
Where A_0 is the initial starting material concentration. This gives the following differential equation:

$$v = \frac{d[P]}{dt} = k[P]^2 + k[A_0]^2 - 2k[A_0][P]$$

By fitting the data with the differential equation above, the corresponding best-fit rate constants were obtained with excellent r^2 values. The average second order rate constant was found to be 2.4 ± 0.4 M^{-1} s^{-1}.



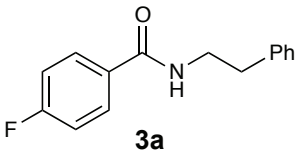
Epimerization Studies of Compound 3c.



HPLC: Daicel Chiralcel (4.6 ×250 mm); *i*PrOH/hexane (1:4), flow 0.5 mL/min. Retention times: 13,2 min (minor), 18.9 min (major). ee = 99.5%.

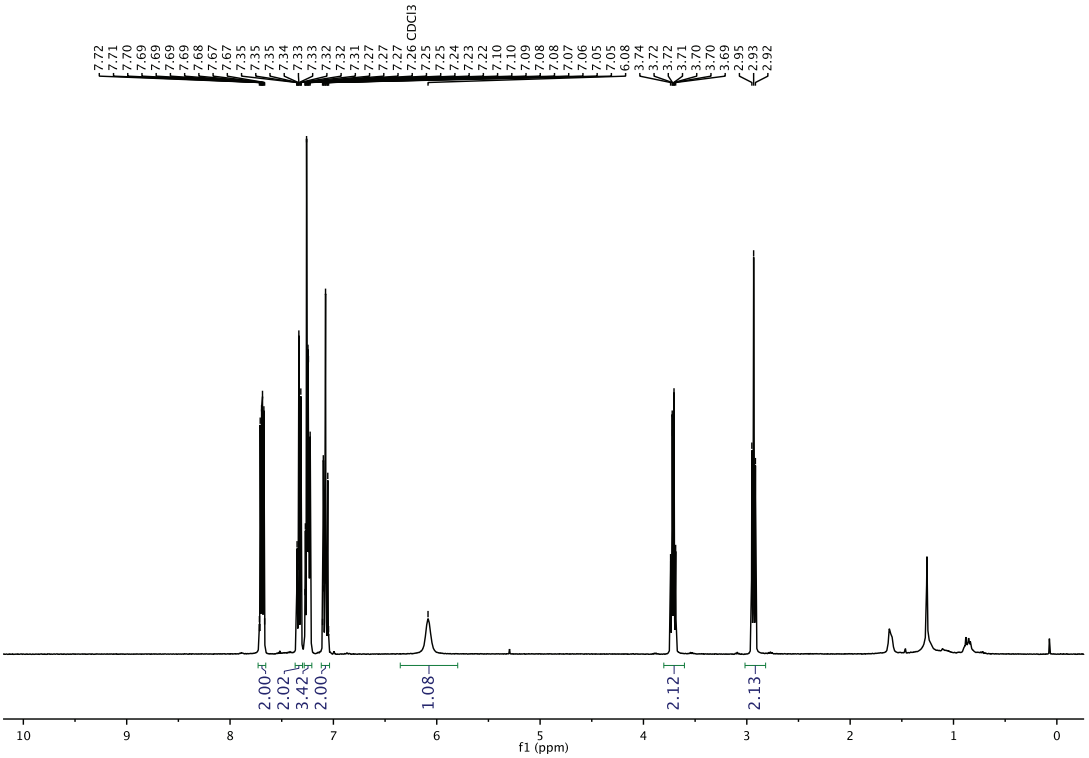
Spectroscopic Data

***N*-(2-Phenylethyl)-4-fluorobenzamide (3a).**

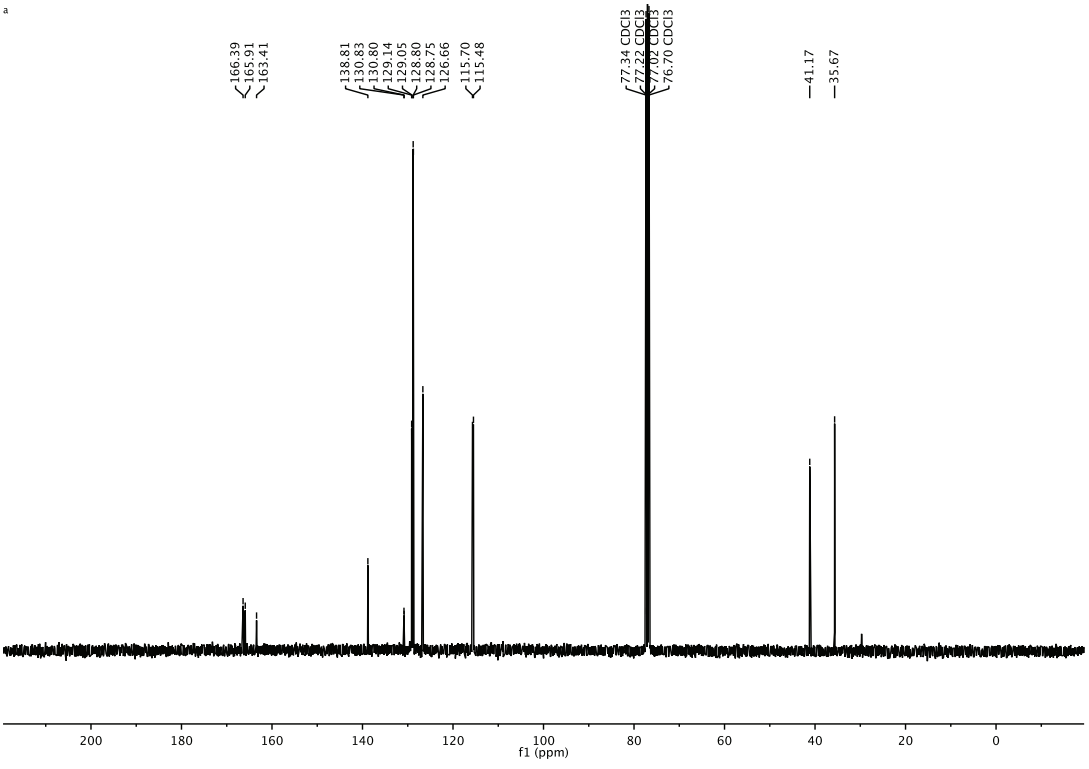


3a

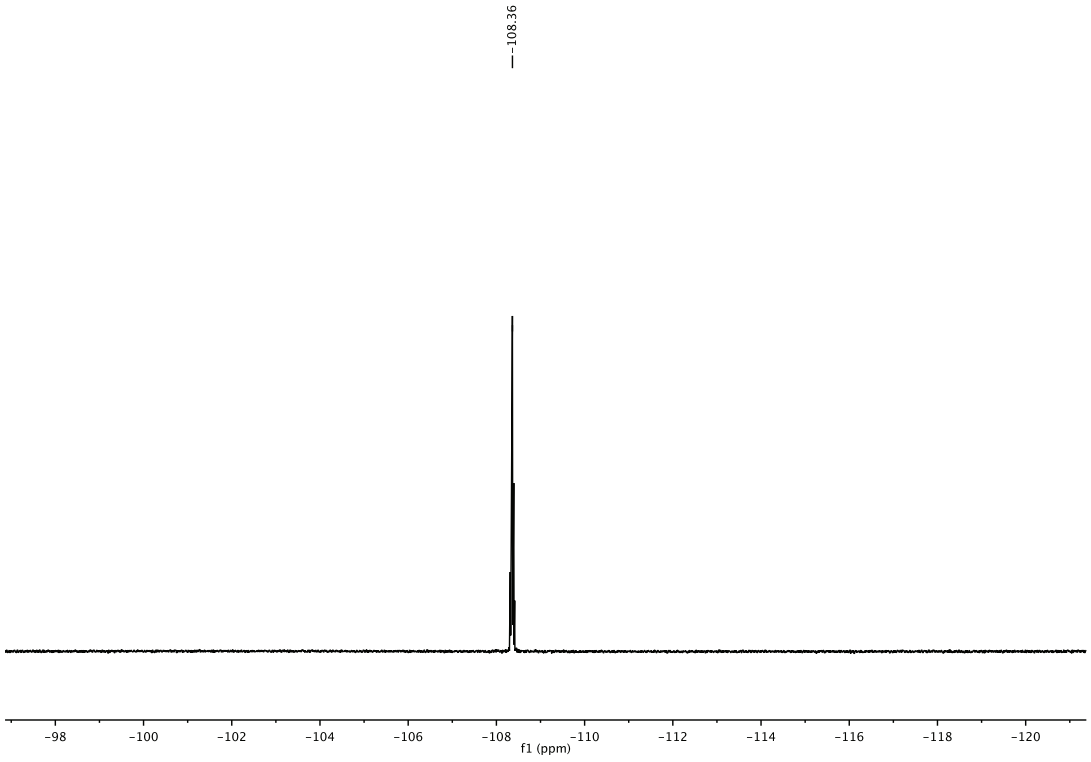
^{1}H NMR (400 MHz, $CDCl_3$)



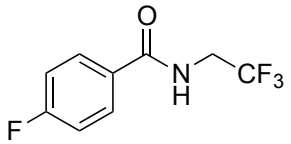
^{13}C NMR (100 MHz, $CDCl_3$)



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

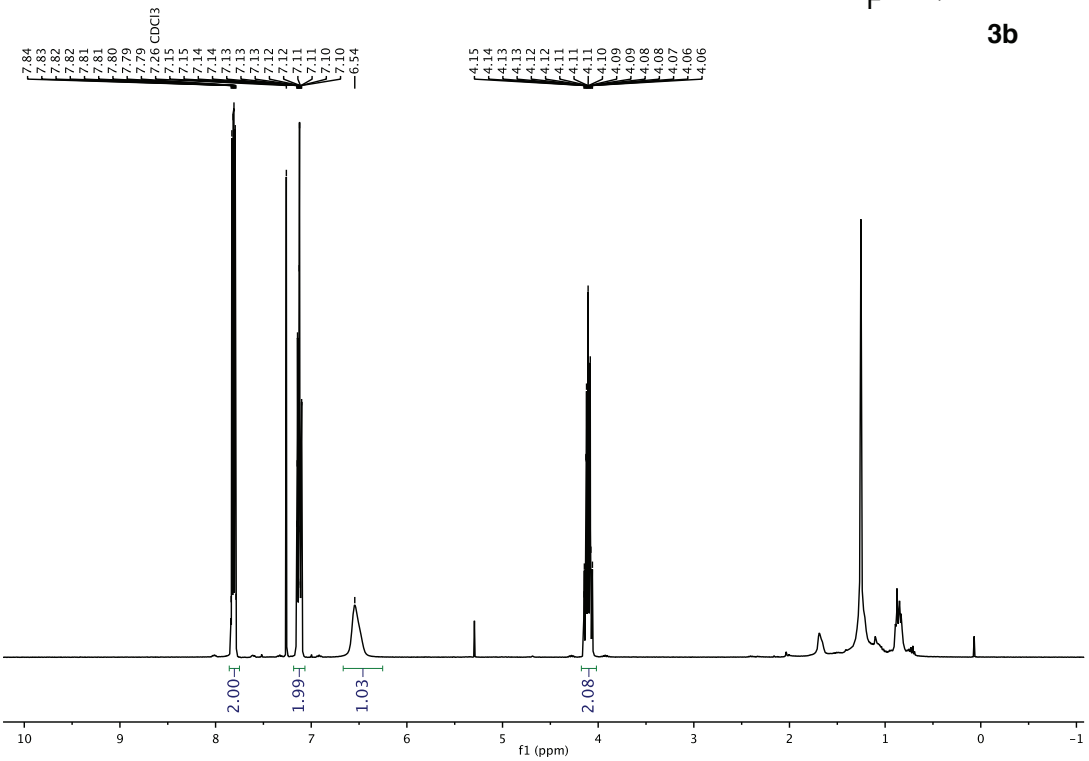


***N*-(2,2,2-Trifluoroethyl)-4-fluorobenzamide (3b).**

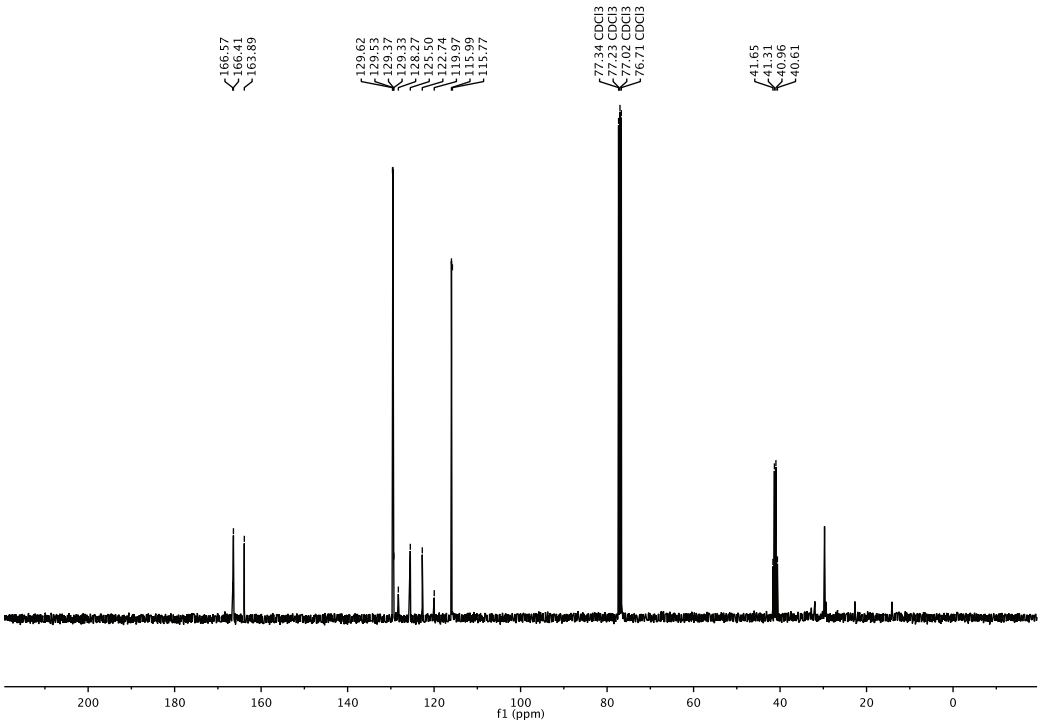


3b

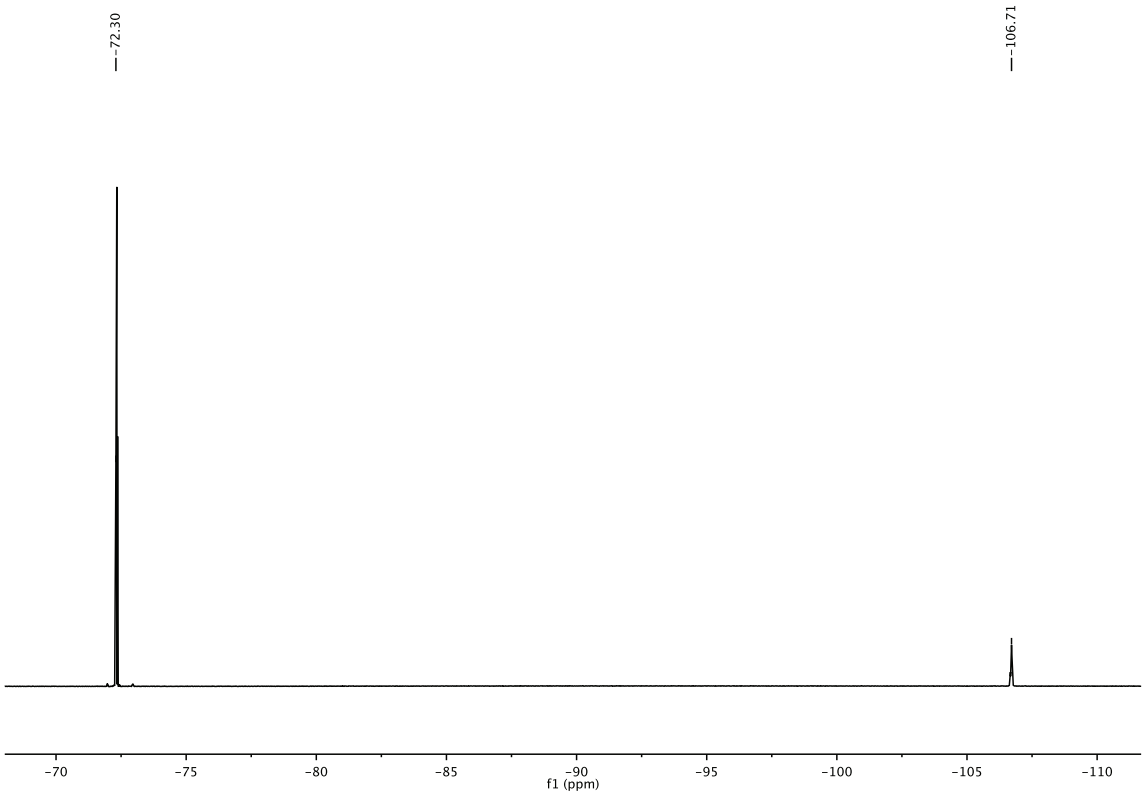
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)

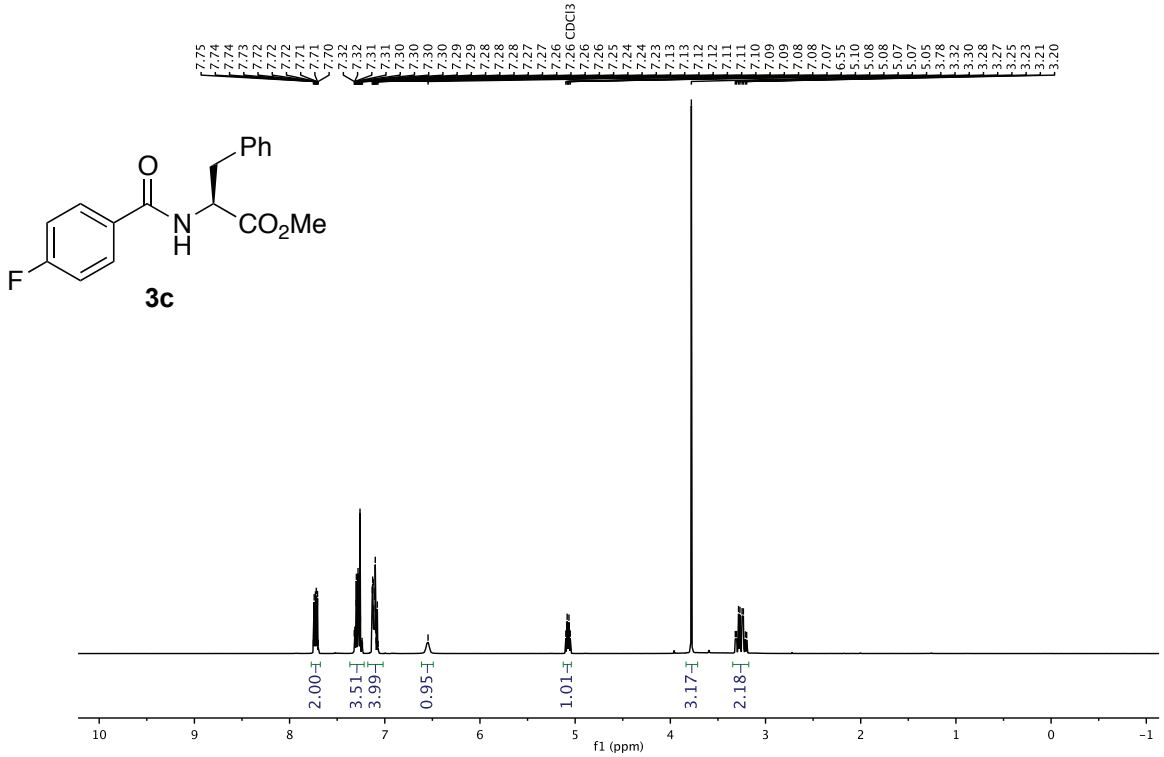


^{19}F NMR (377 MHz, $CDCl_3$)

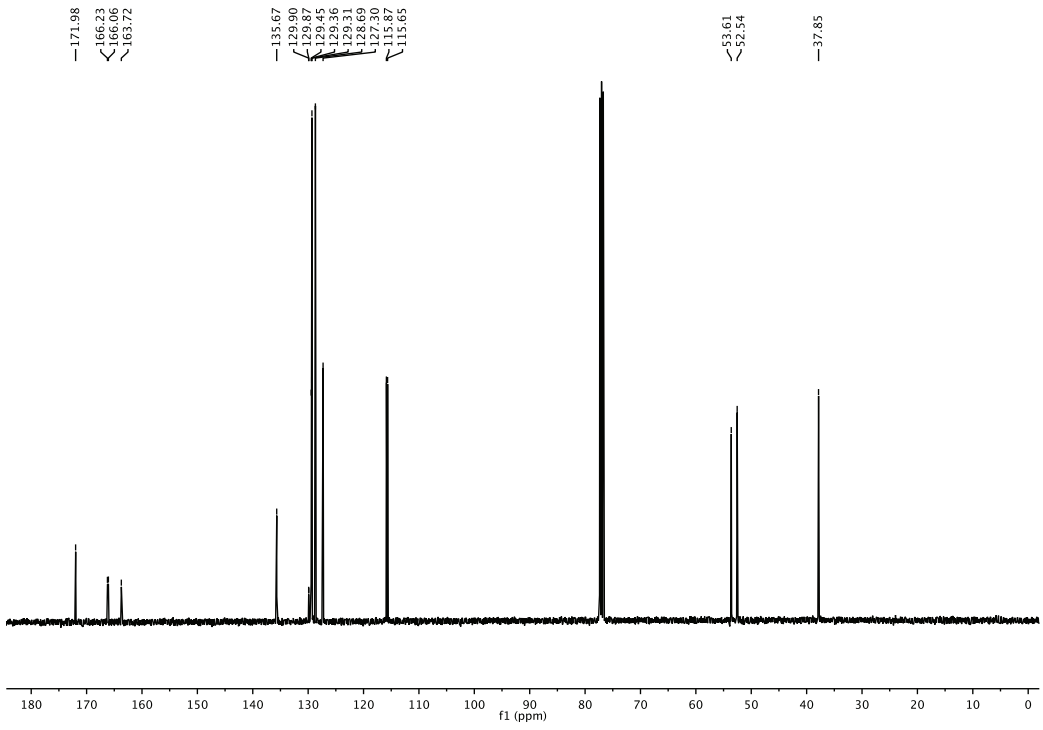


(*S*)-*N*-(4-Fluorobenzoyl)phenylalanine methyl ester (3c).

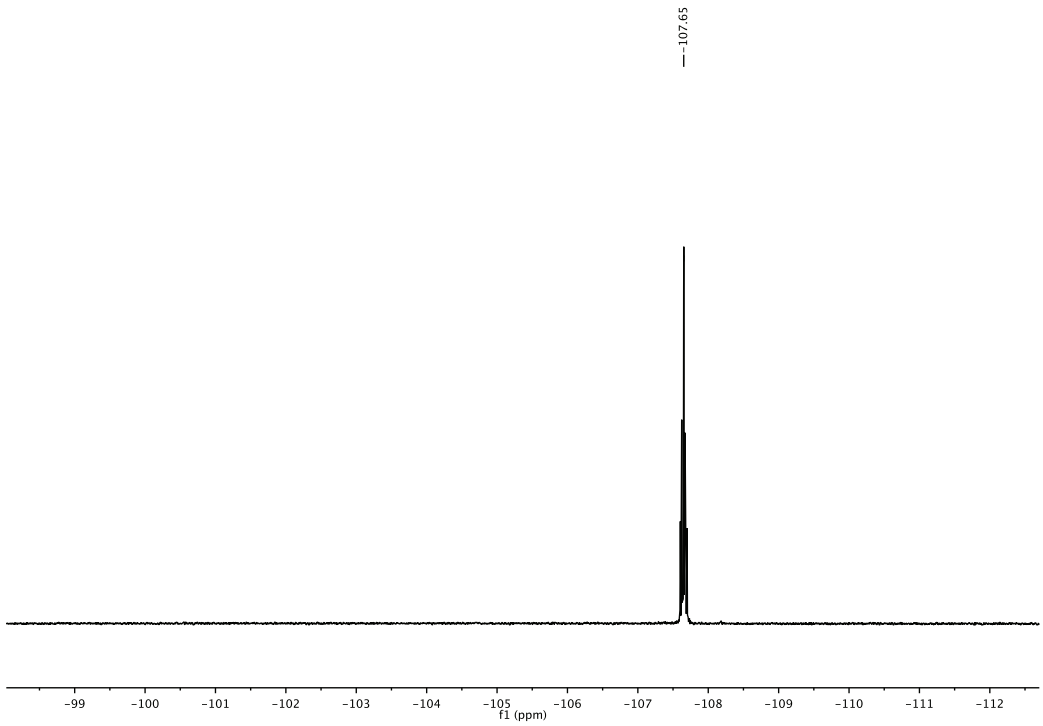
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)

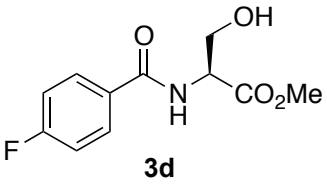


^{19}F NMR (377 MHz, $CDCl_3$)

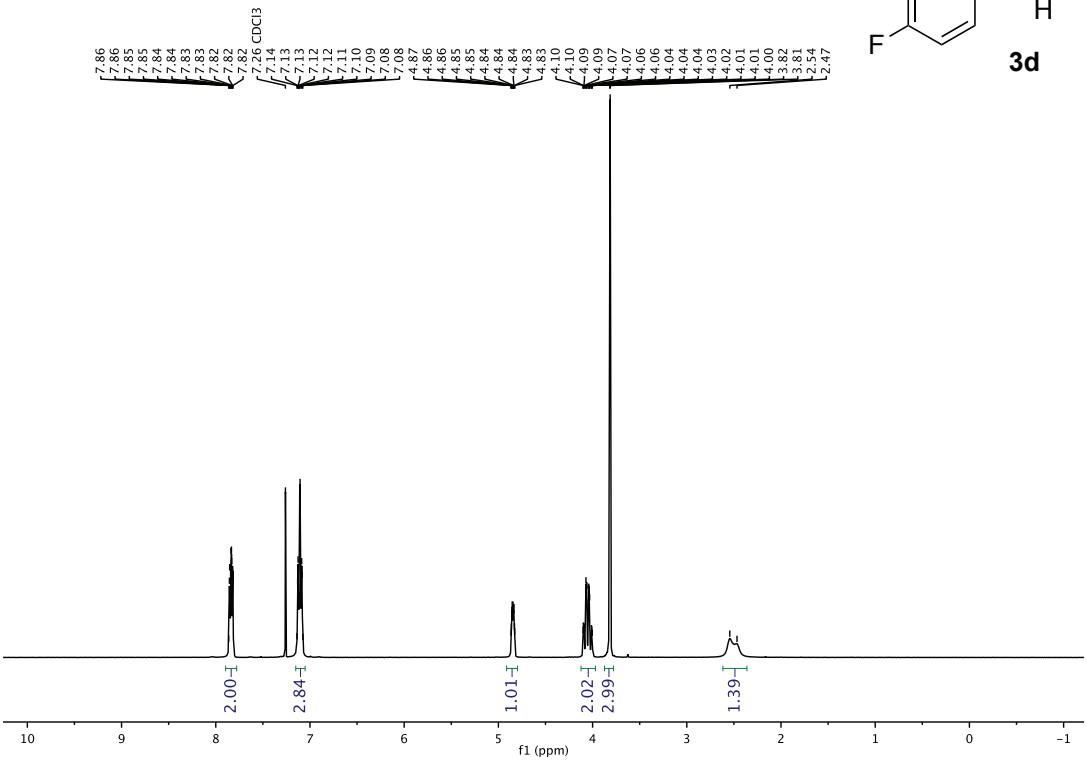


(*S*)-*N*-(4-Fluorobenzoyl)serine methyl ester (3d).

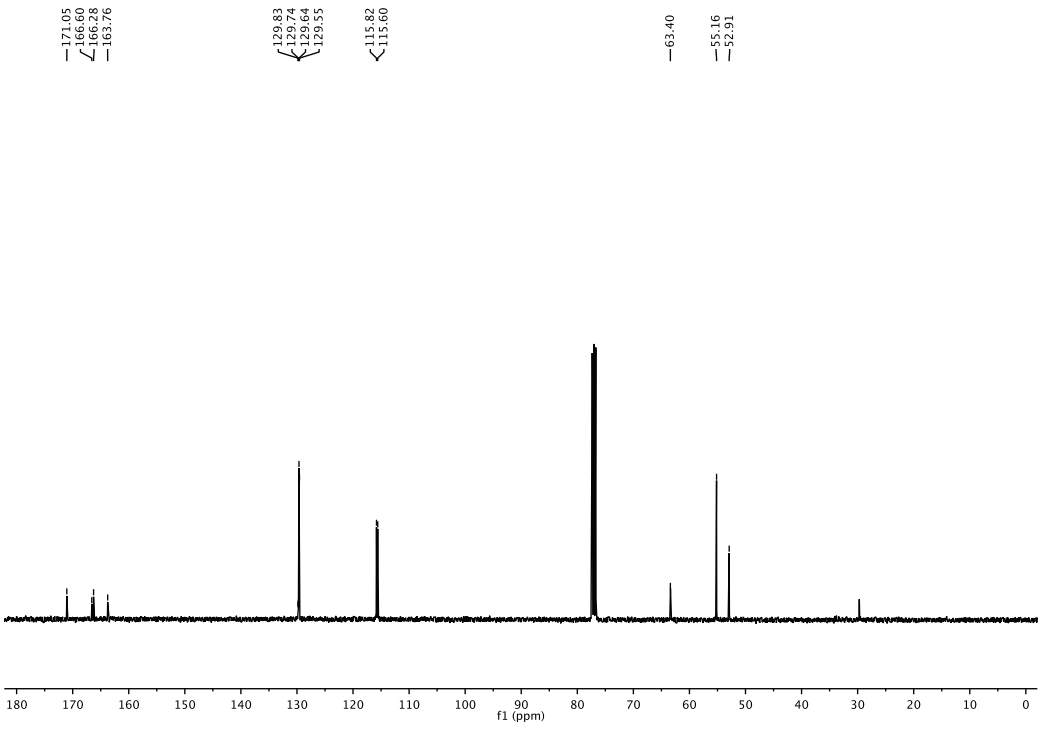
^{1}H NMR (400 MHz, $CDCl_3$)



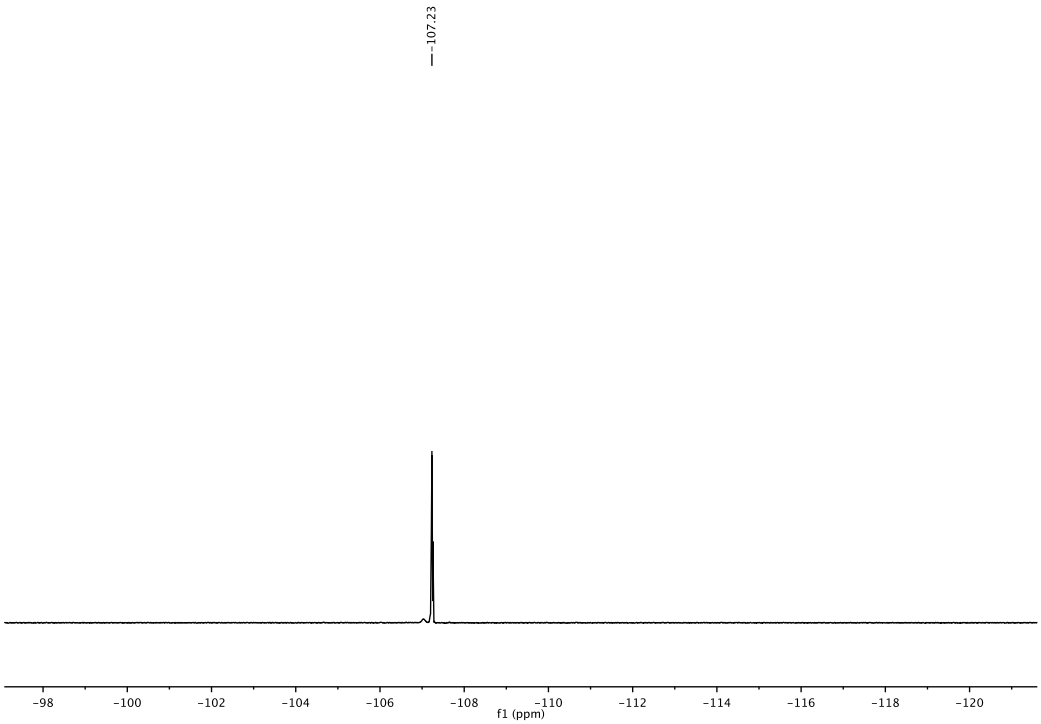
3d



^{13}C NMR (100 MHz, $CDCl_3$)

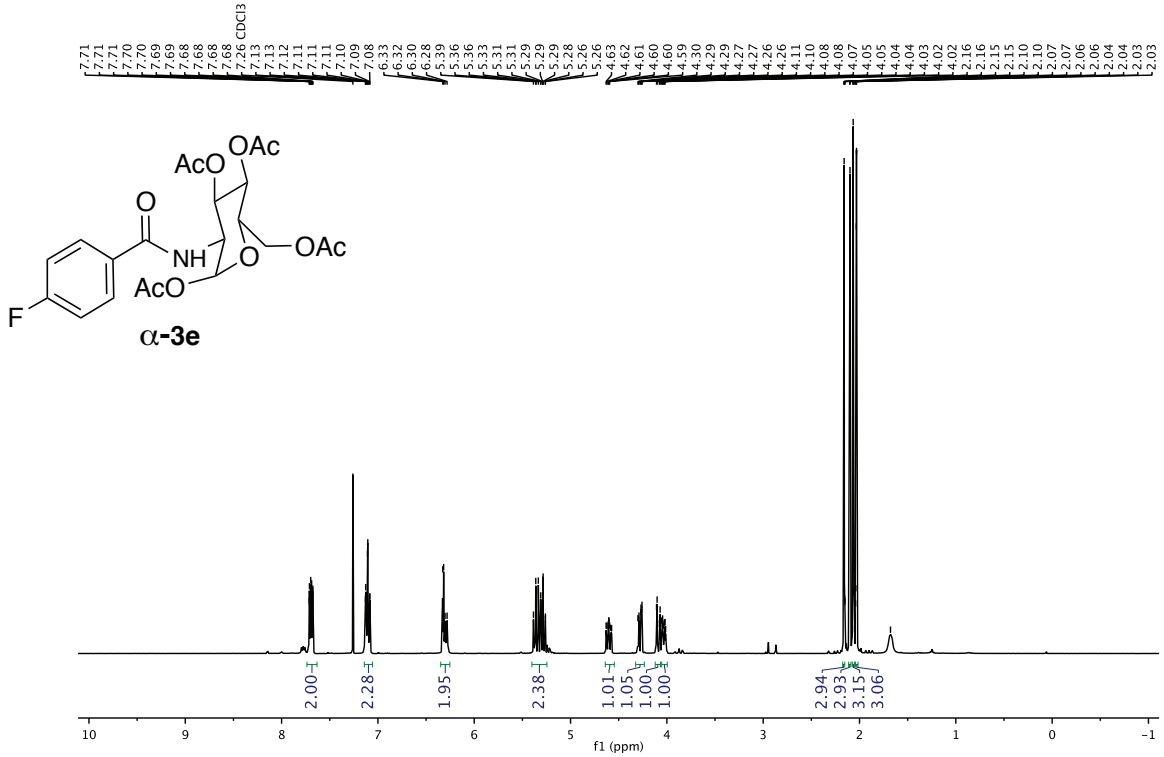


^{19}F NMR (377 MHz, $CDCl_3$)

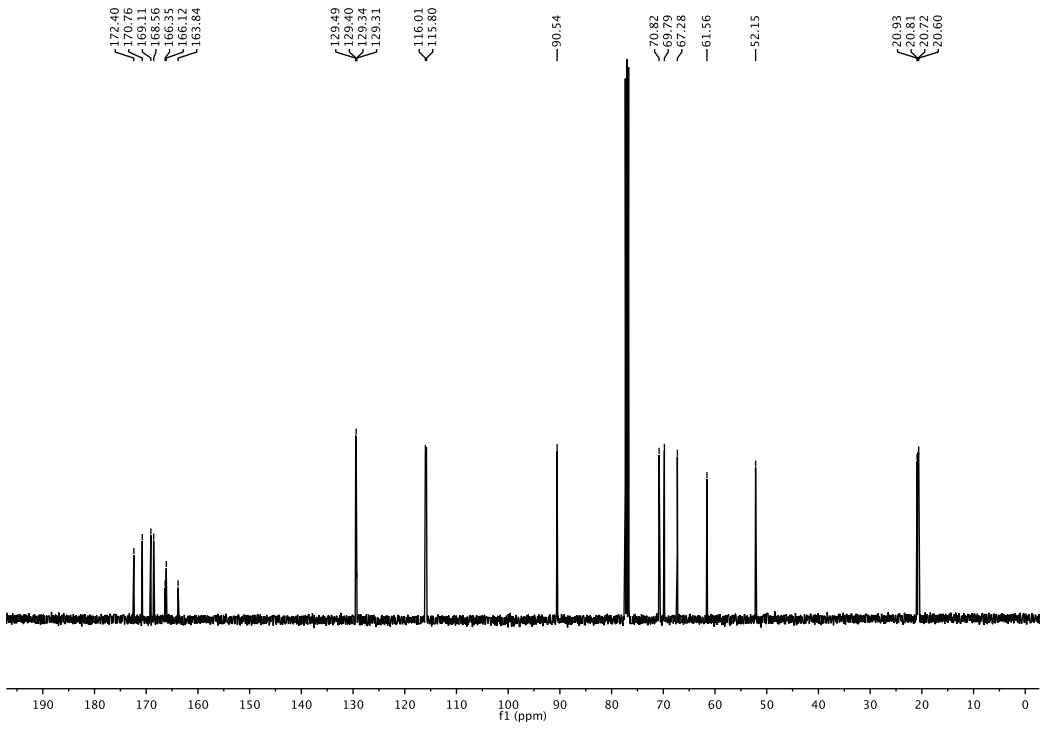


2-(4-Fluorobenzamido)-2-deoxy-1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose (α -3e).

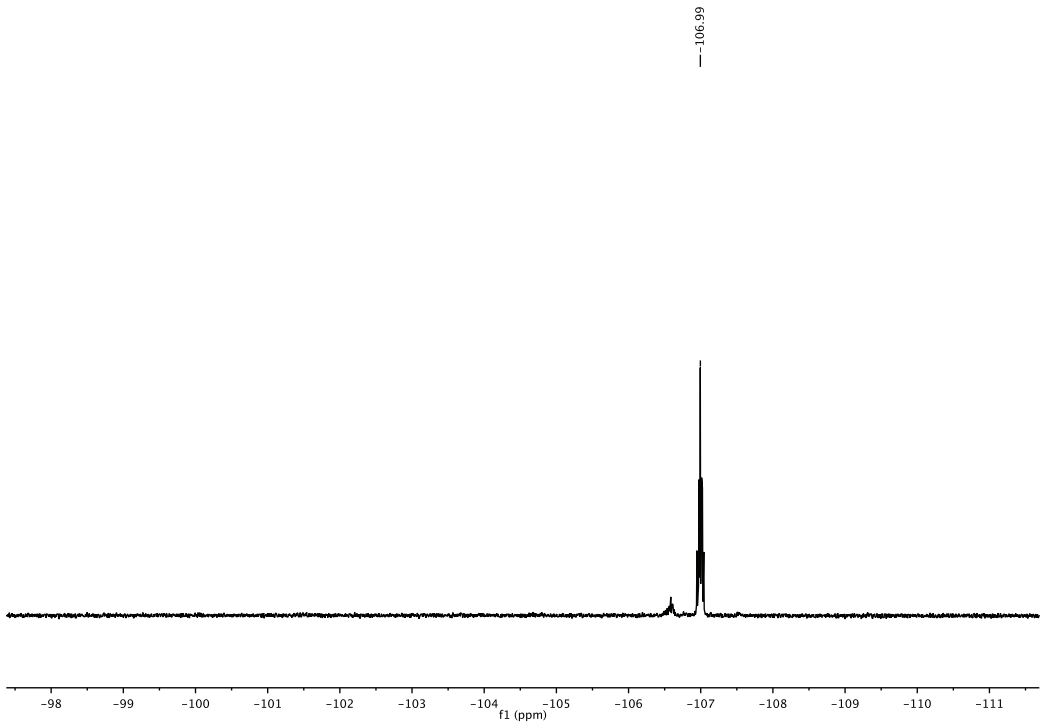
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)

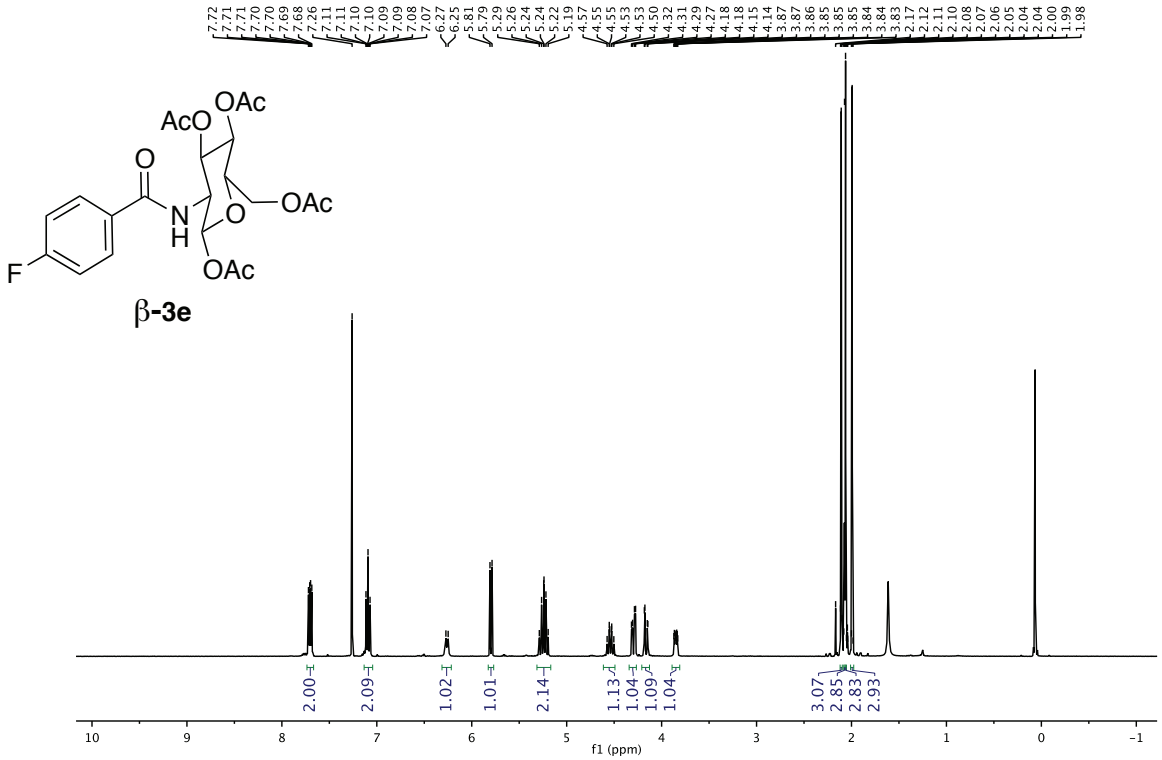


^{19}F NMR (377 MHz, $CDCl_3$)

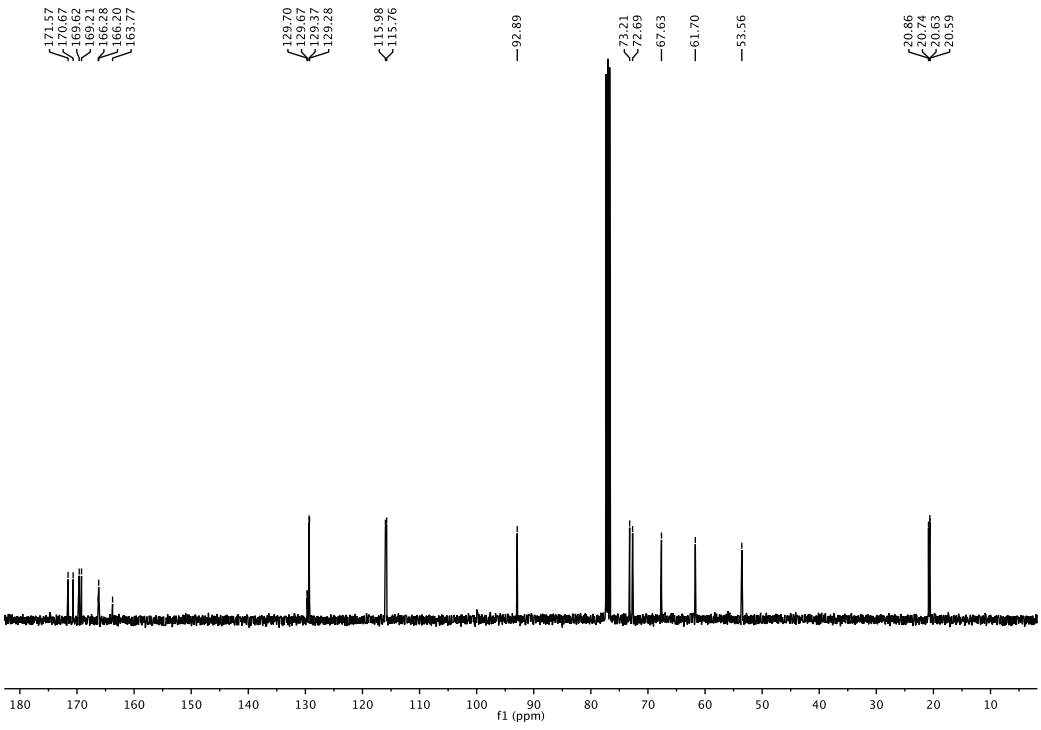


2-(4-Fluorobenzamido)-2-deoxy-1,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (β -3e).

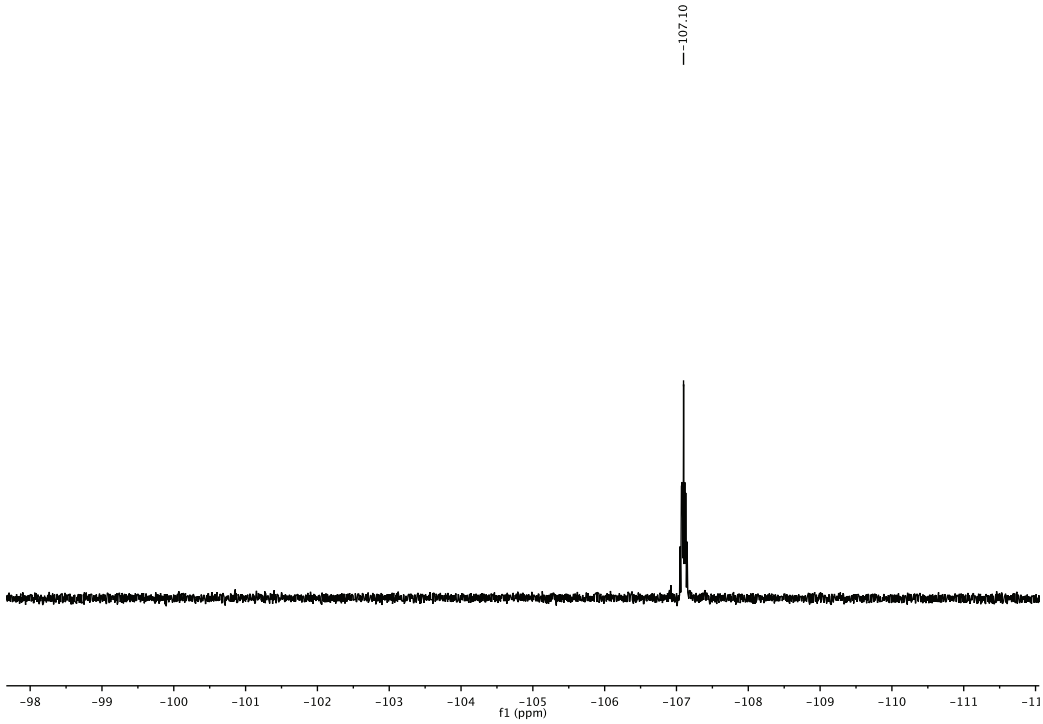
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)

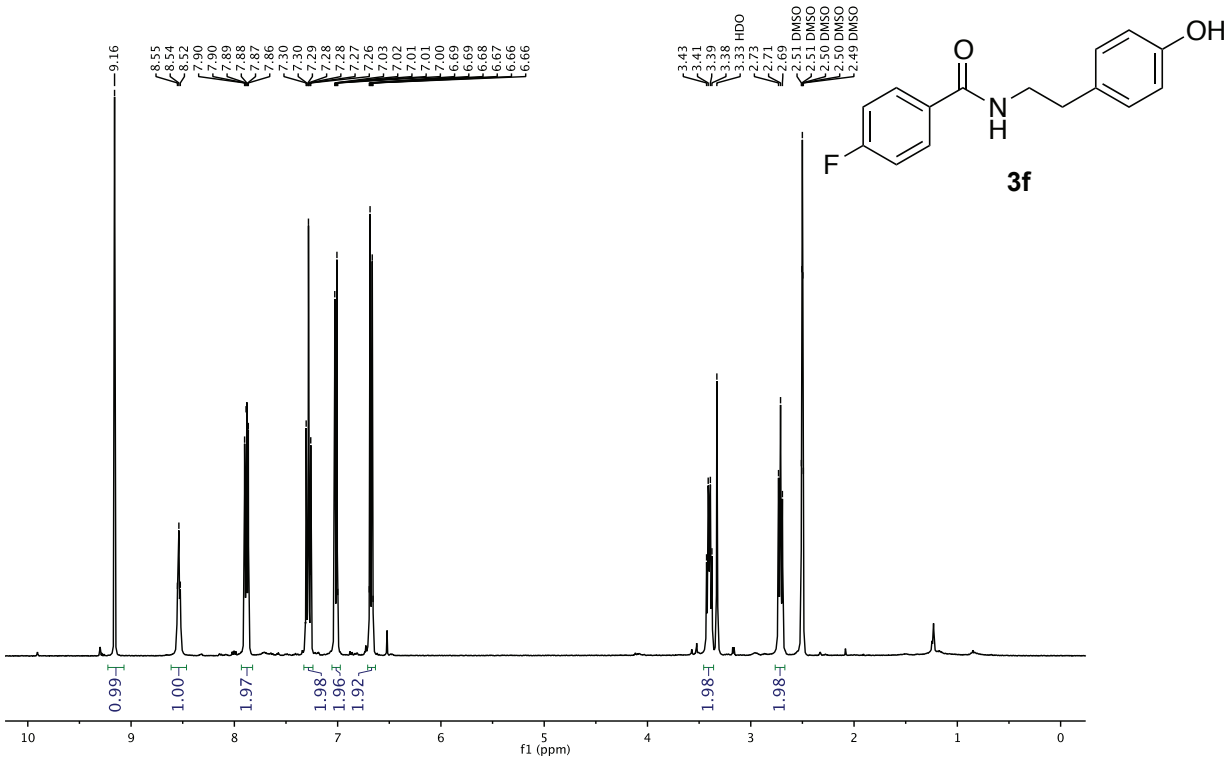


^{19}F NMR (377 MHz, $CDCl_3$)

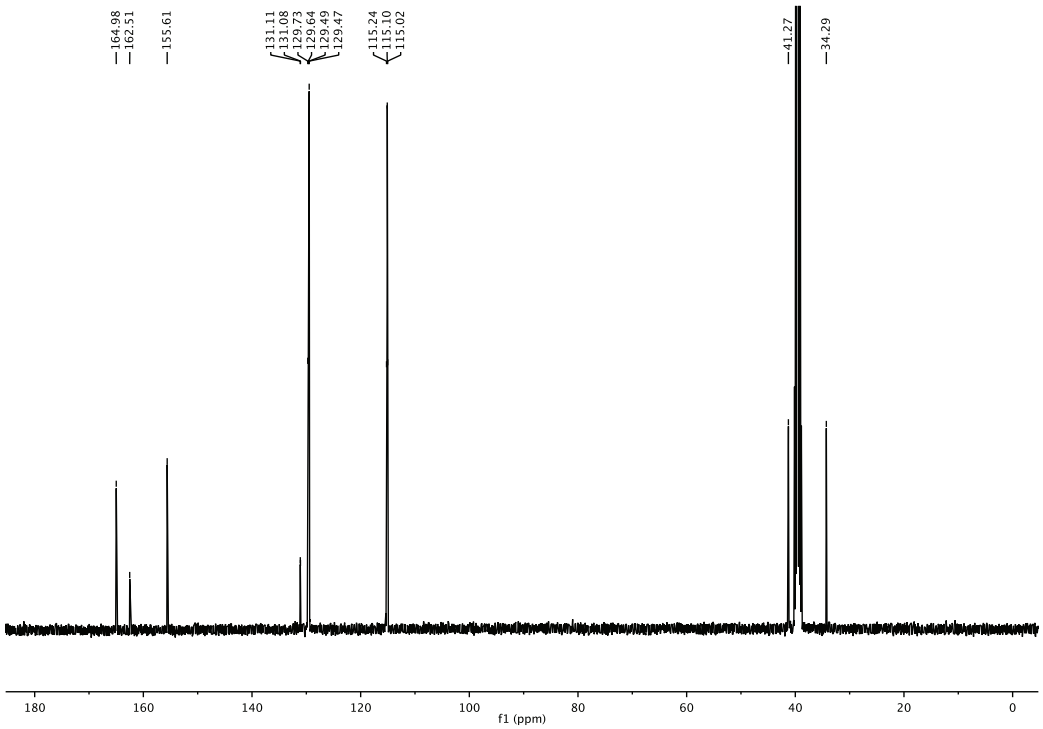


***N*-(2-(4-Hydroxyphenyl)ethyl)-4-fluorobenzamide (3f).**

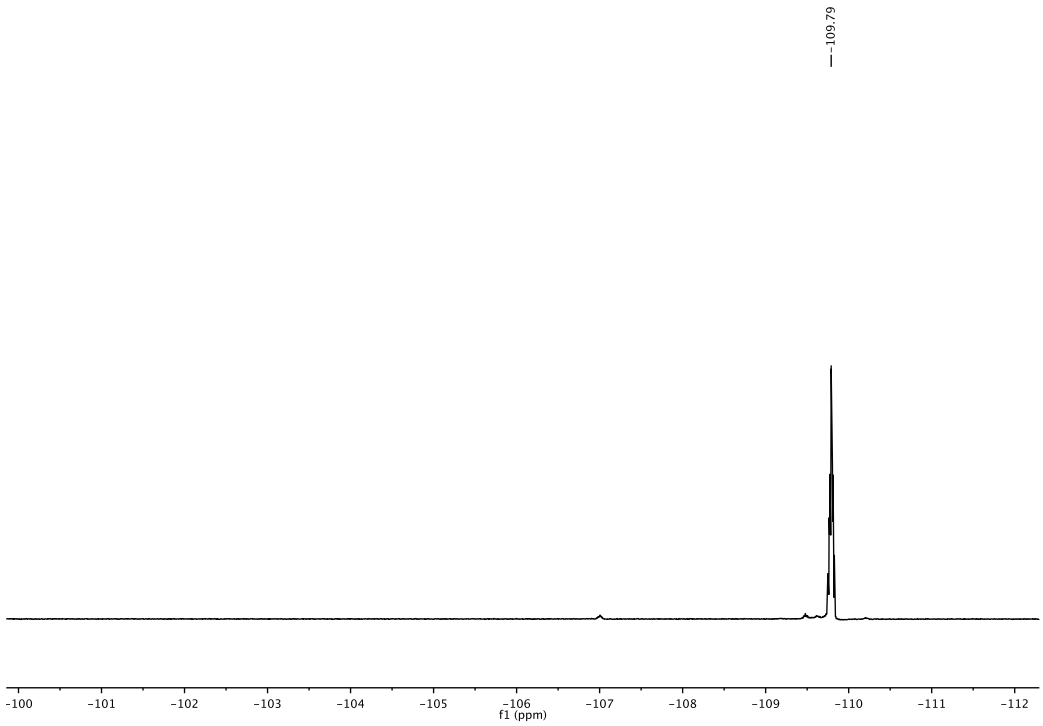
^{1}H NMR (400 MHz, DMSO-*d*6)



^{13}C NMR (100 MHz, DMSO-*d*6)

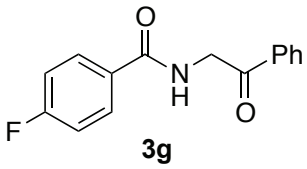


^{19}F NMR (377 MHz, DMSO-*d*6)

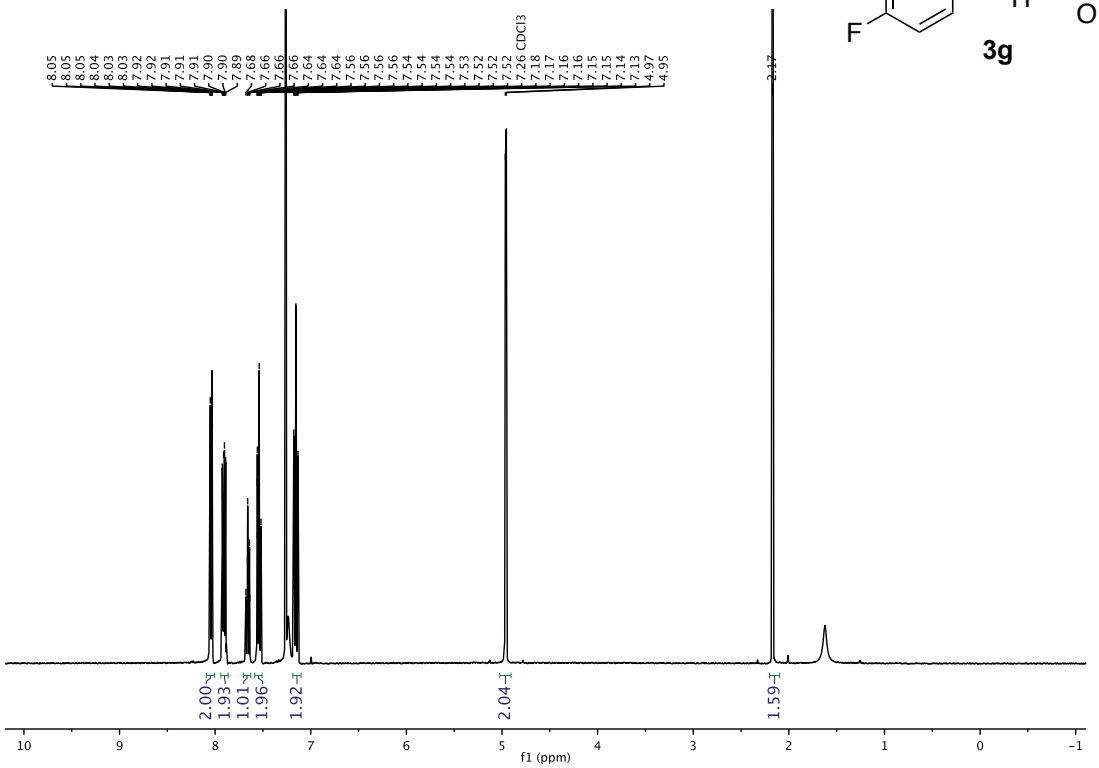


***N*-(2-Oxo-2-phenylethyl)-4-fluorobenzamide (3g).**

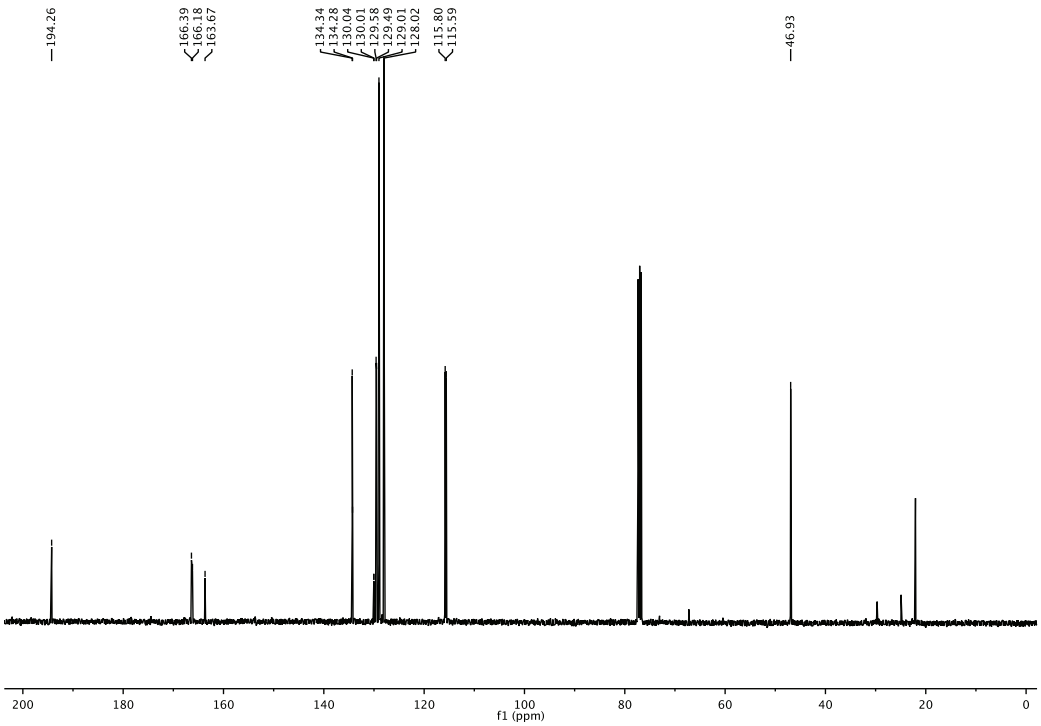
^{1}H NMR (400 MHz, $CDCl_3$)



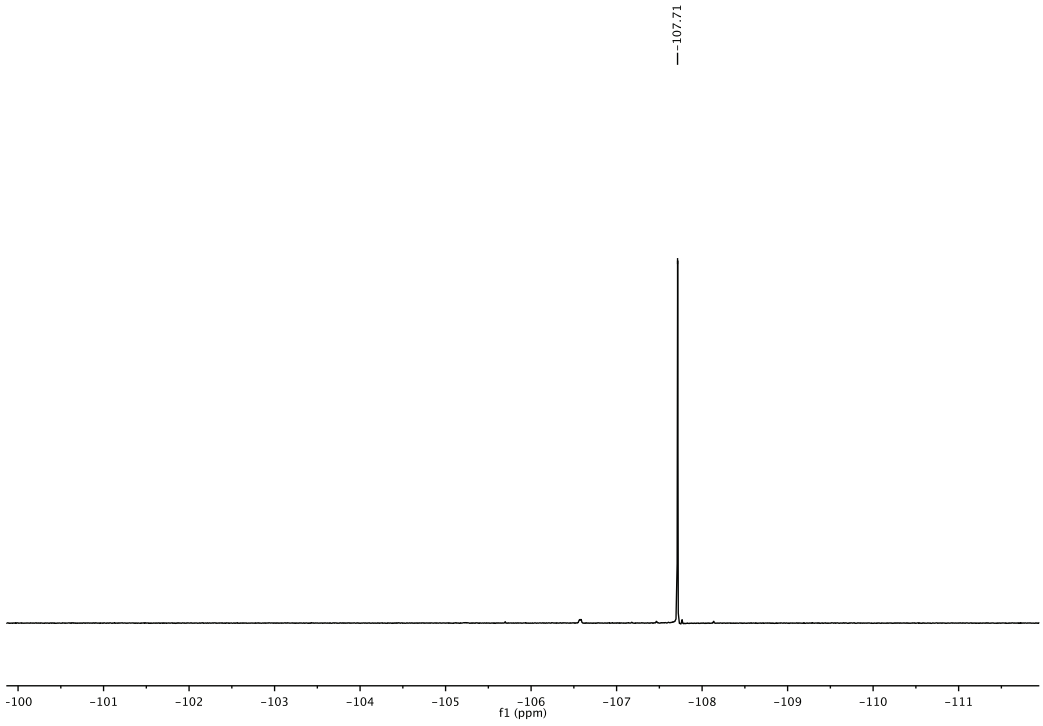
3g



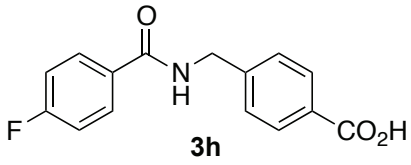
^{13}C NMR (100 MHz, $CDCl_3$)



^{19}F NMR (400 MHz, $CDCl_3$)

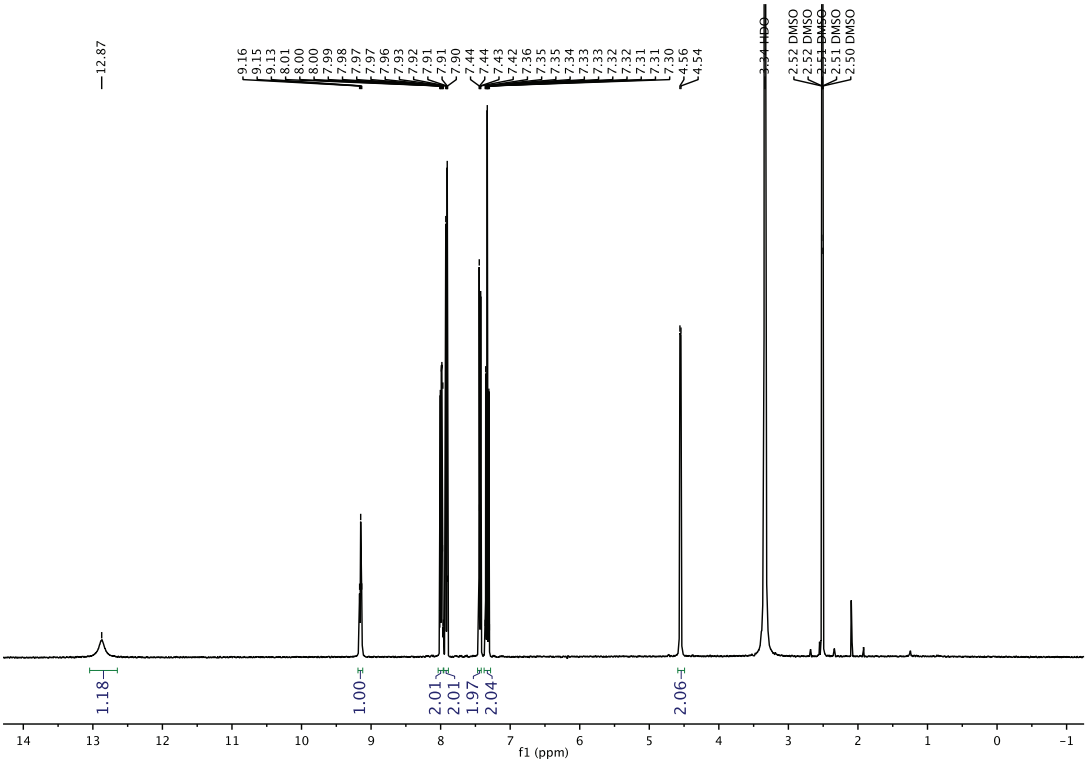


4-(4-Fluorobenzamido)methylbenzoic acid (3h).

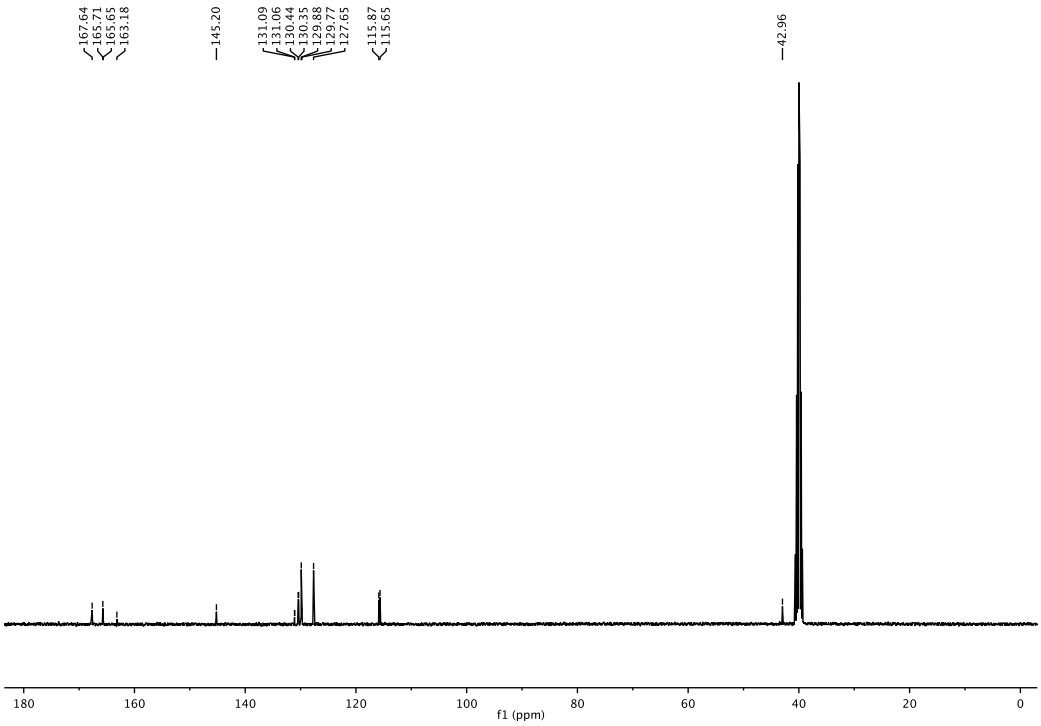


3h

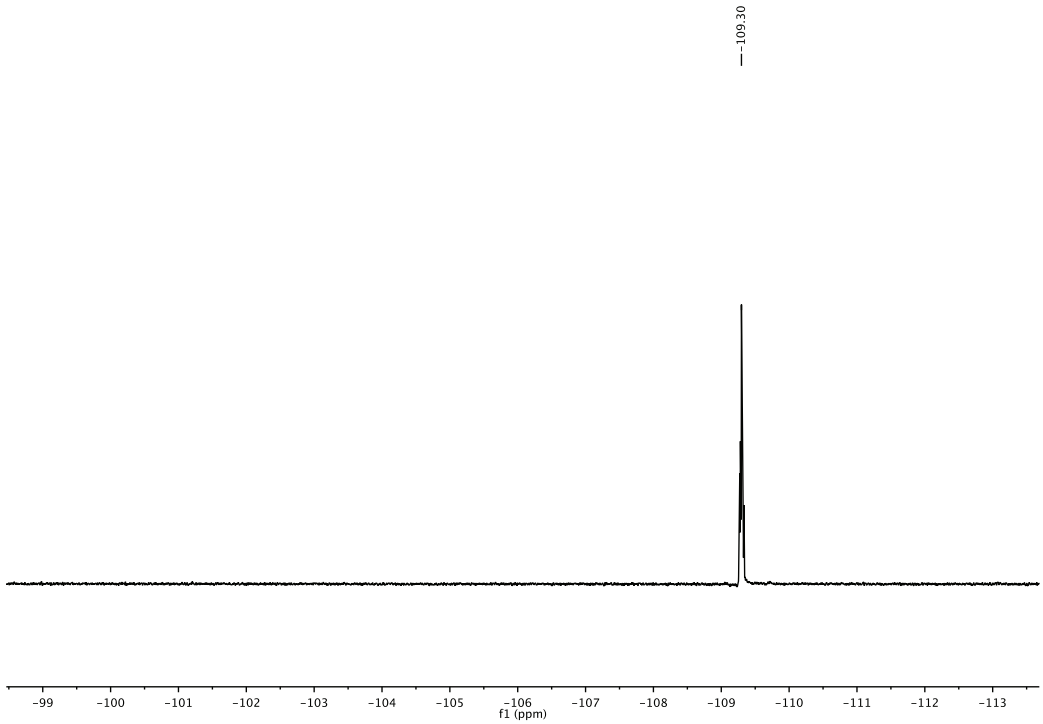
^{1}H NMR (400 MHz, DMSO-d_6)



^{13}C NMR (400 MHz, DMSO-d_6)

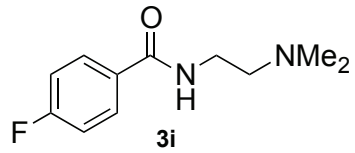


^{19}F NMR (377 MHz, DMSO-d_6)

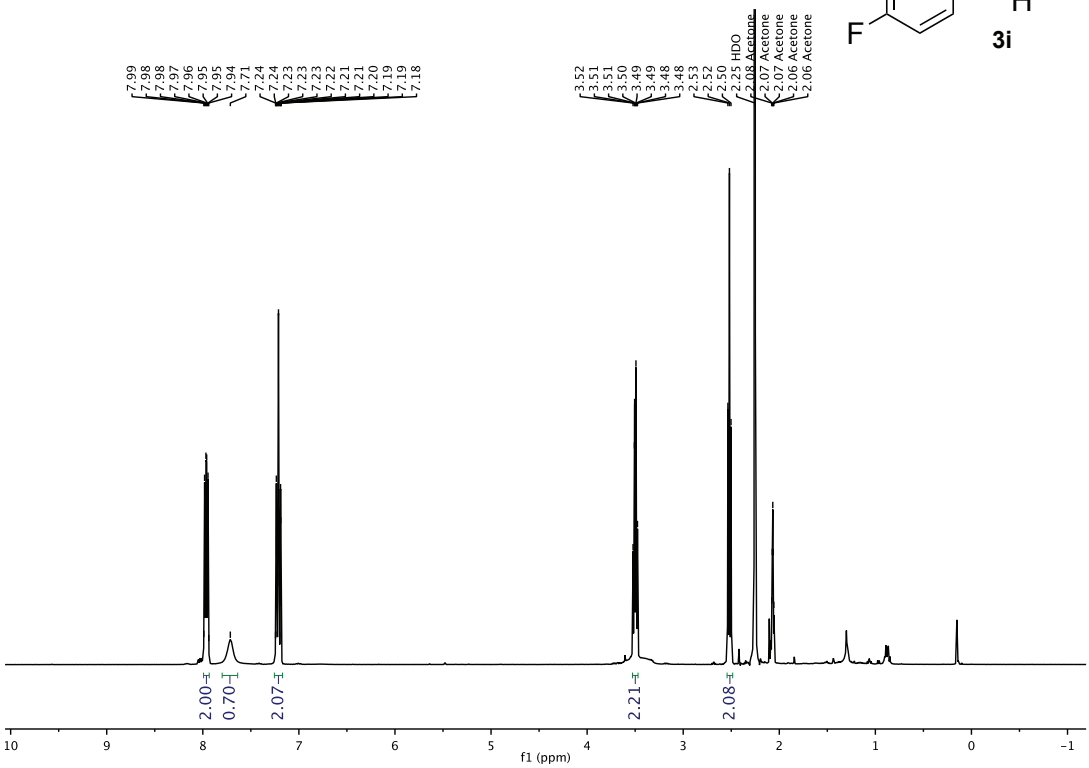


***N*-(2-Dimethylaminoethyl)-4-fluorobenzamide (3i).**

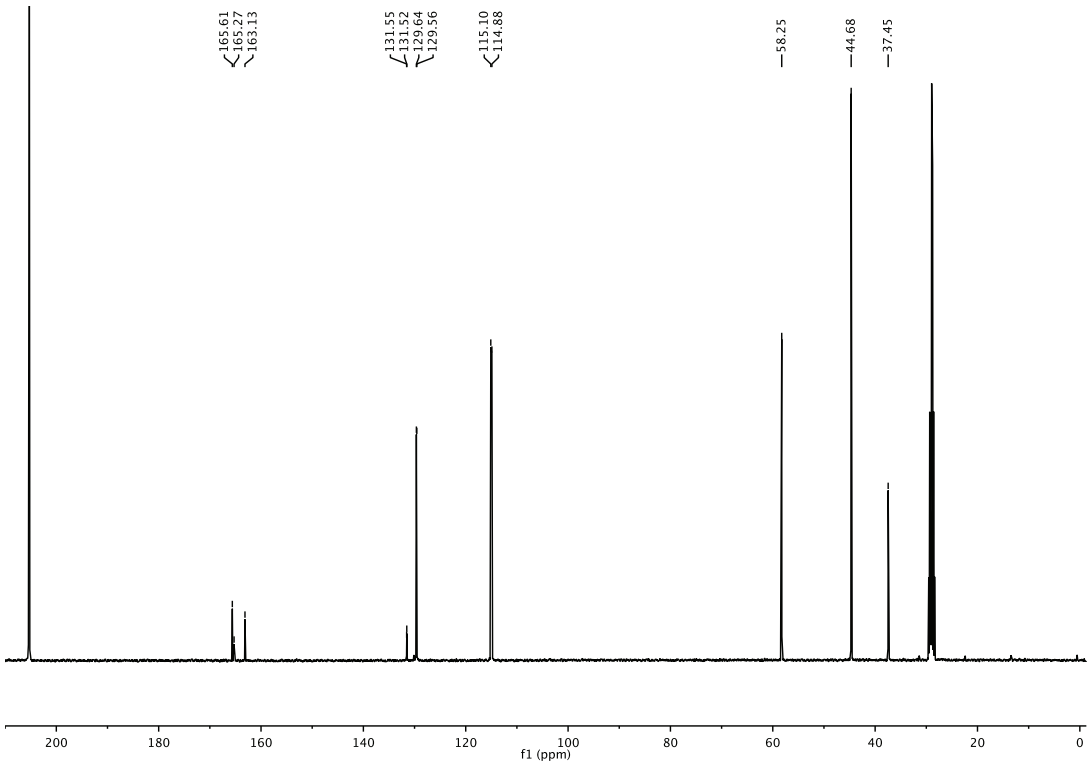
^{1}H NMR (400 MHz, $(CD_3)_2CO$)



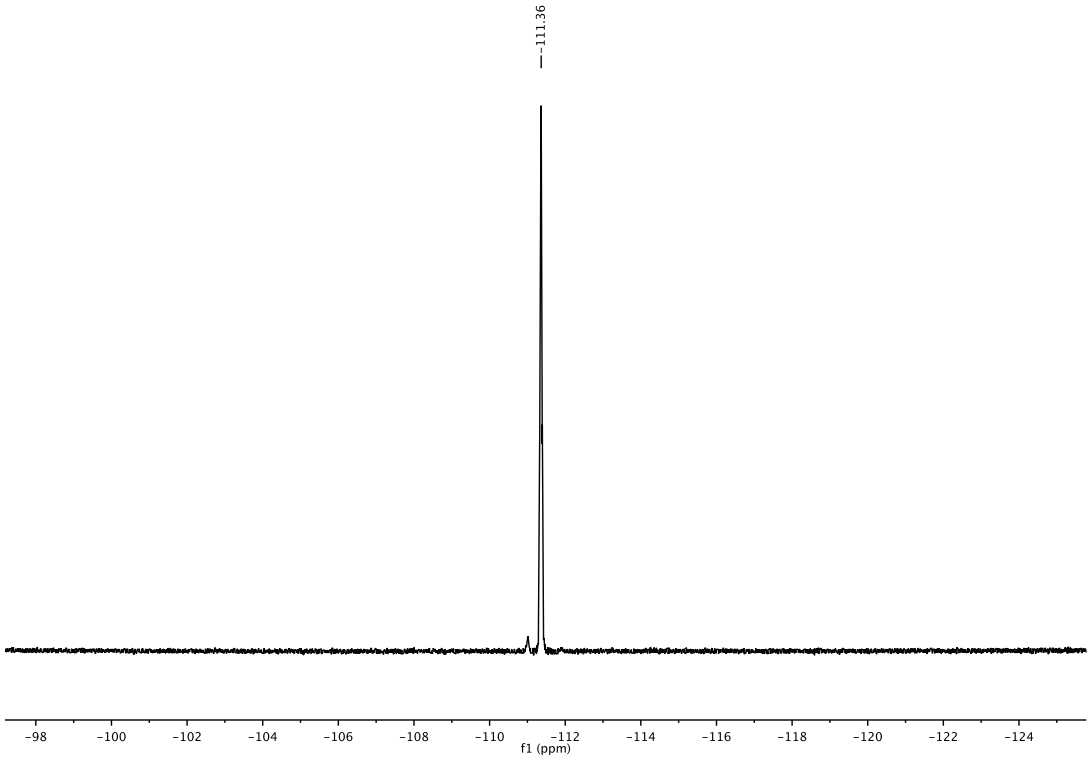
3i



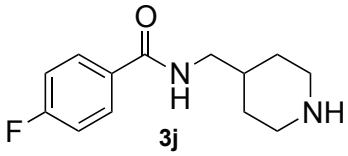
^{13}C NMR (100 MHz, $(CD_3)_2CO$)



^{19}F NMR (377 MHz, $(CD_3)_2CO$)

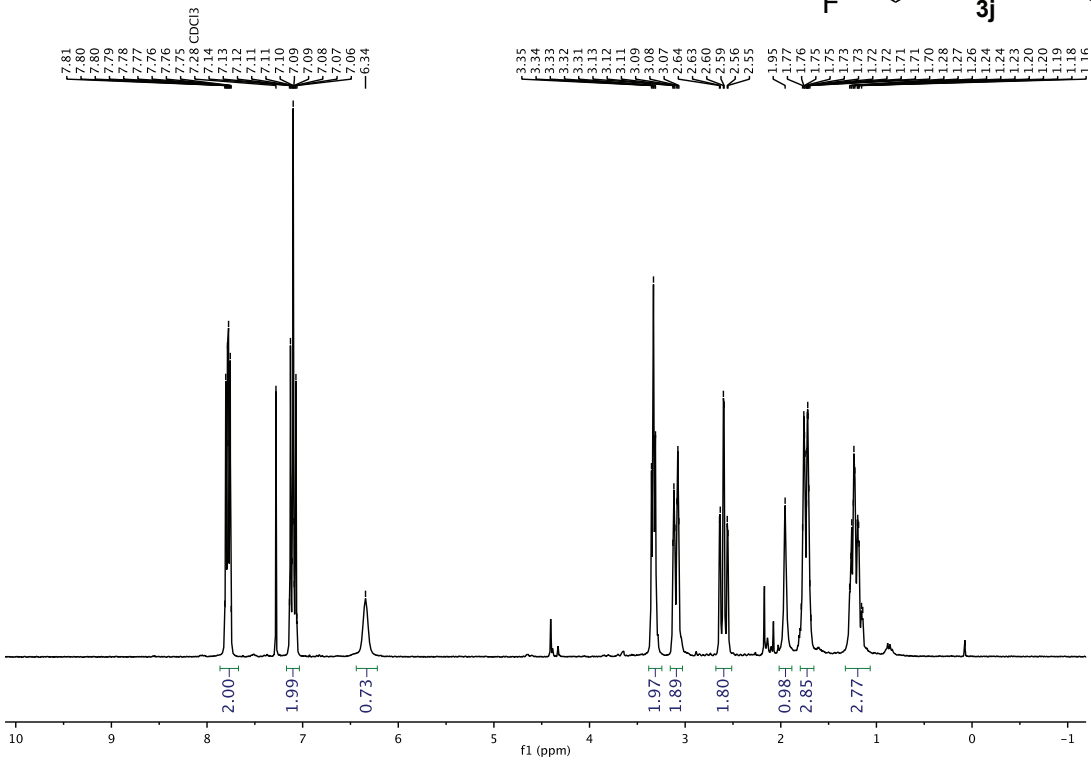


***N*-(Piperidin-4-ylmethyl)-4-fluorobenzamide (3j).**

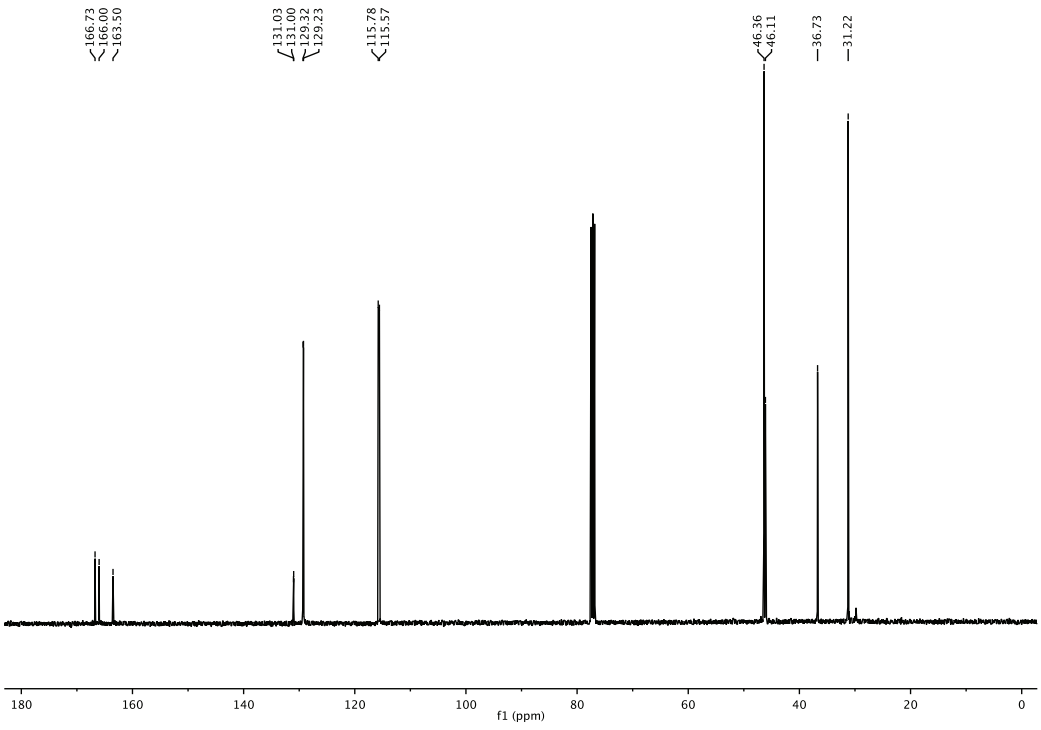


3j

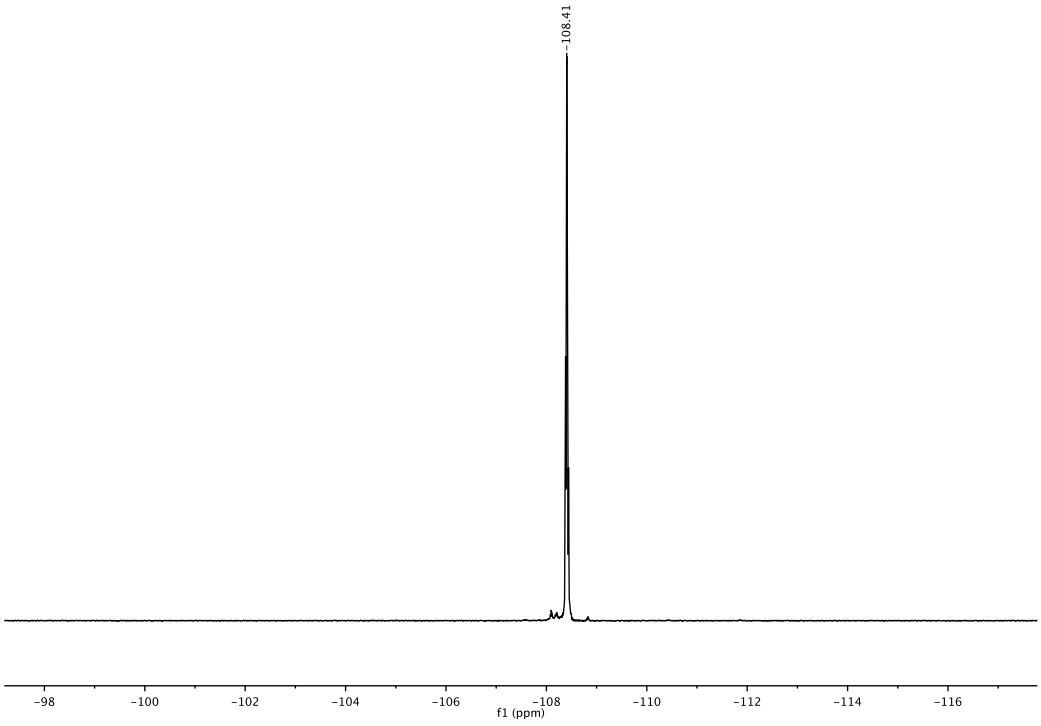
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)

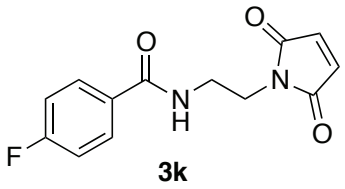


^{19}F NMR (377 MHz, $CDCl_3$)

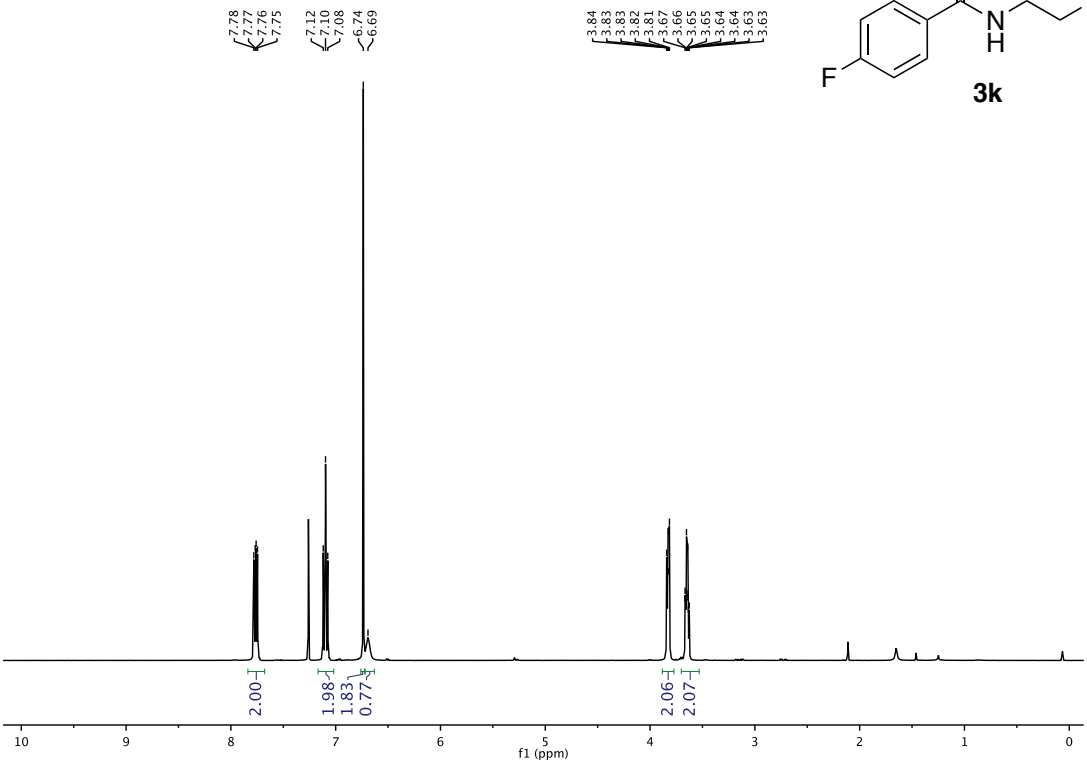


***N*-(2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethyl)-4-fluorobenzamide (3k).**

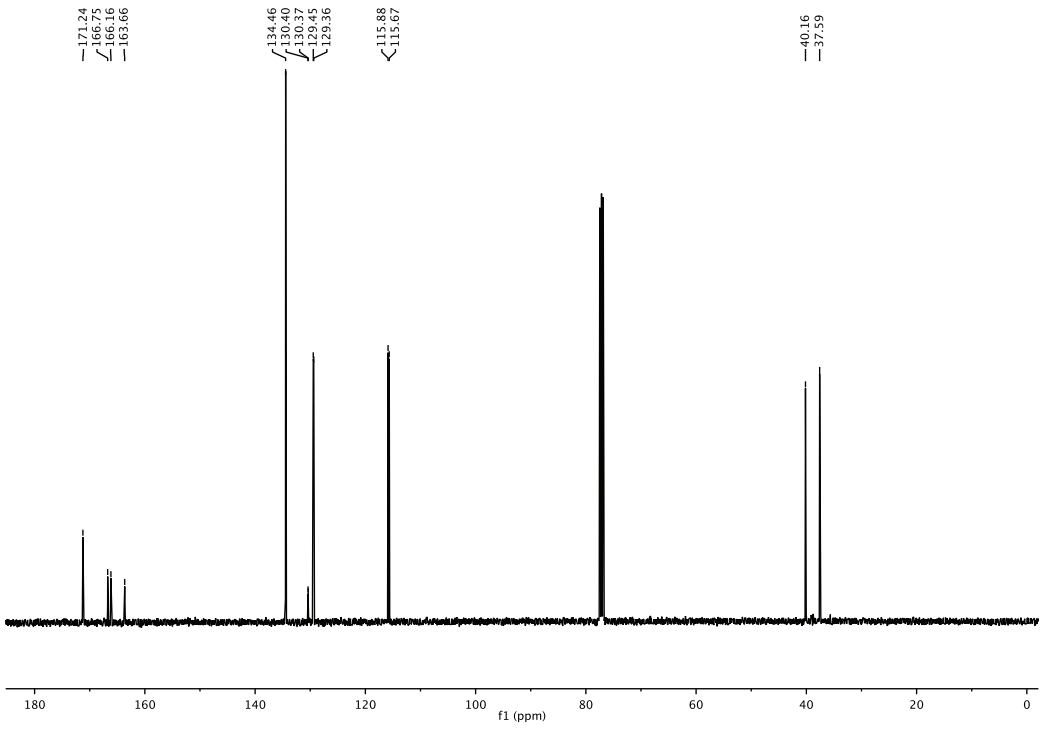
^{1}H NMR (400 MHz, $CDCl_3$)



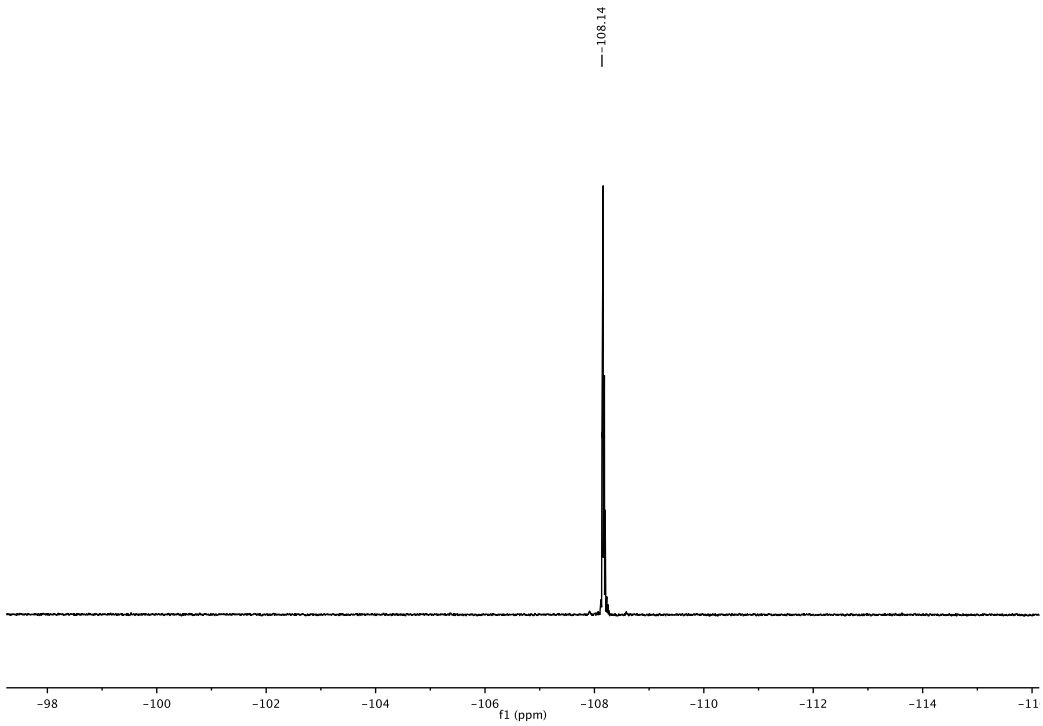
3k



^{13}C NMR (100 MHz, $CDCl_3$)

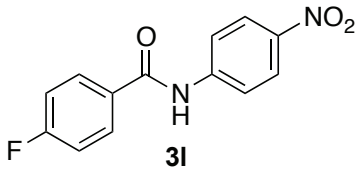


^{19}F NMR (377 MHz, $CDCl_3$)

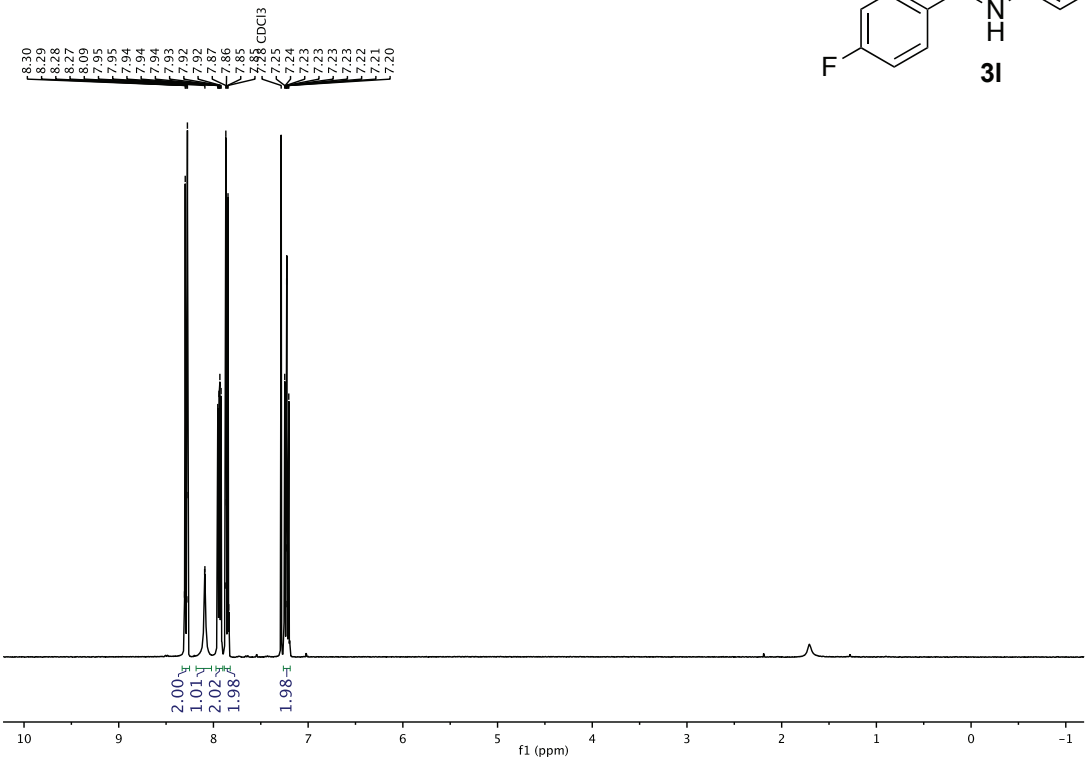


***N*-(4-Nitrophenyl)-4-fluorobenzamide (3l).**

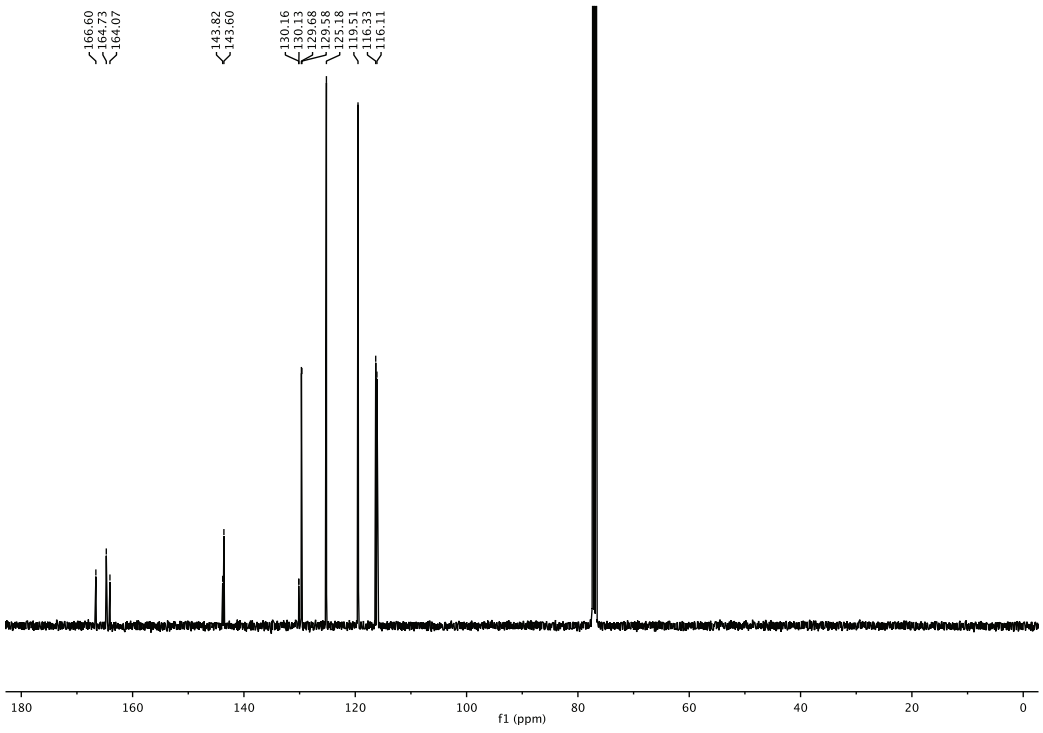
^{1}H NMR (400 MHz, $CDCl_3$)



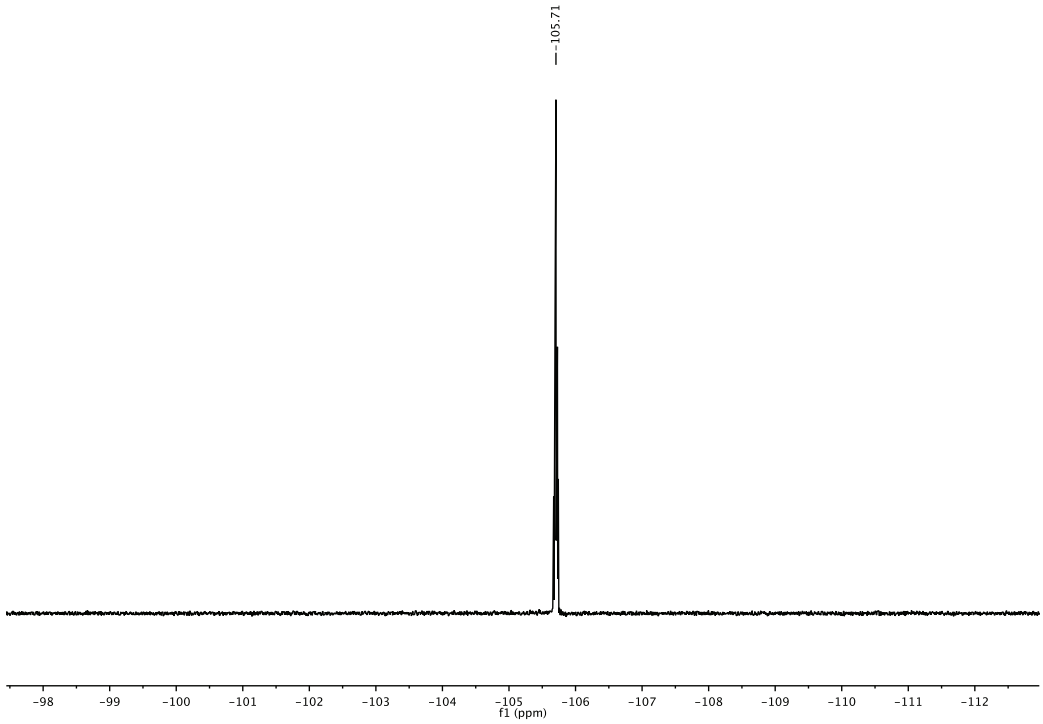
3l



^{13}C NMR (100 MHz, $CDCl_3$)

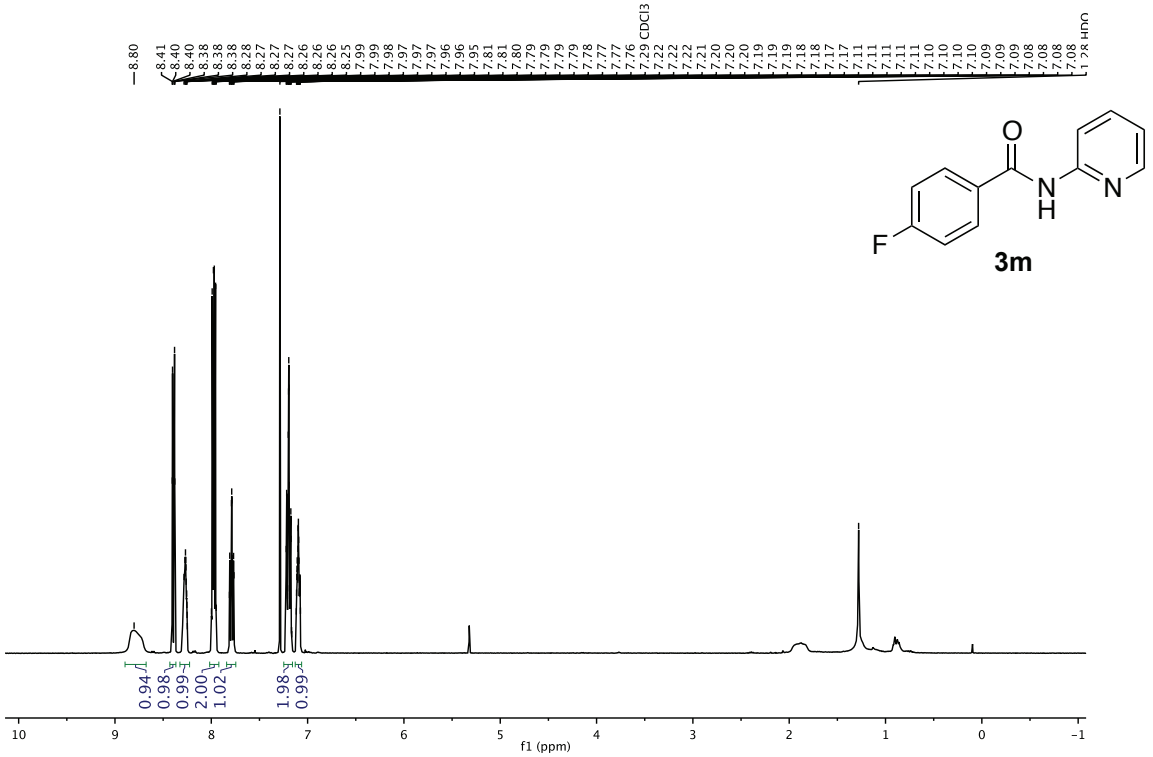


^{19}F NMR (377 MHz, $CDCl_3$)

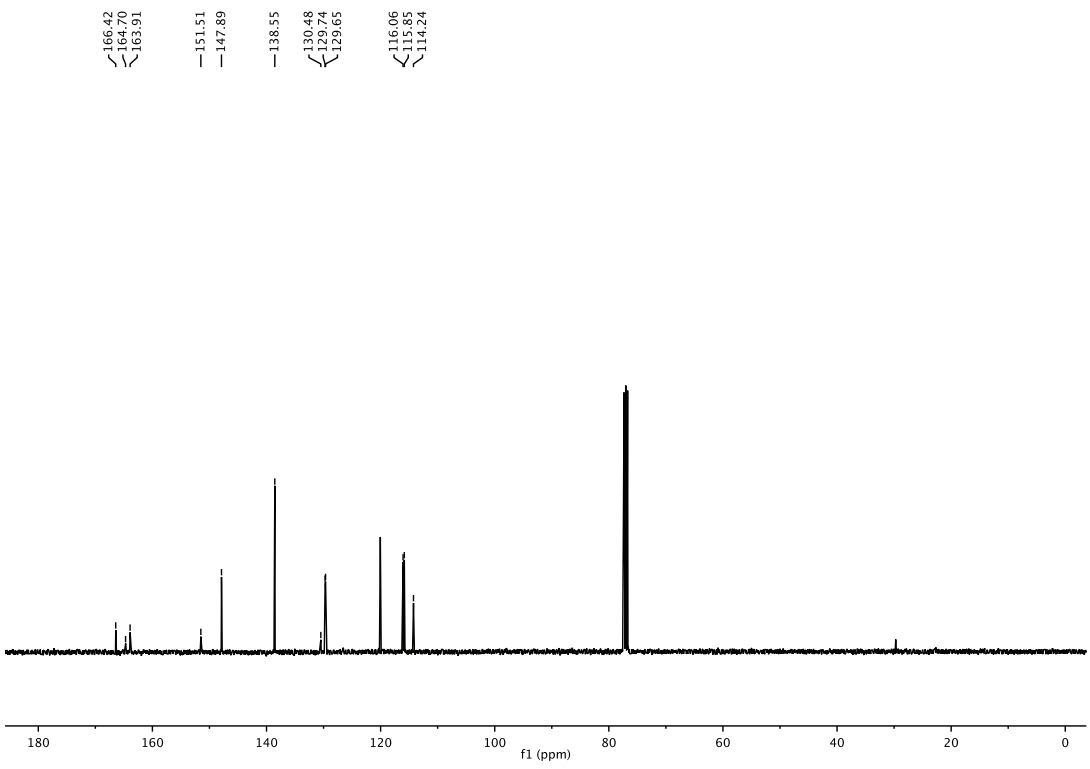


***N*-(2-Pyridyl)-4-fluorobenzamide (3m).**

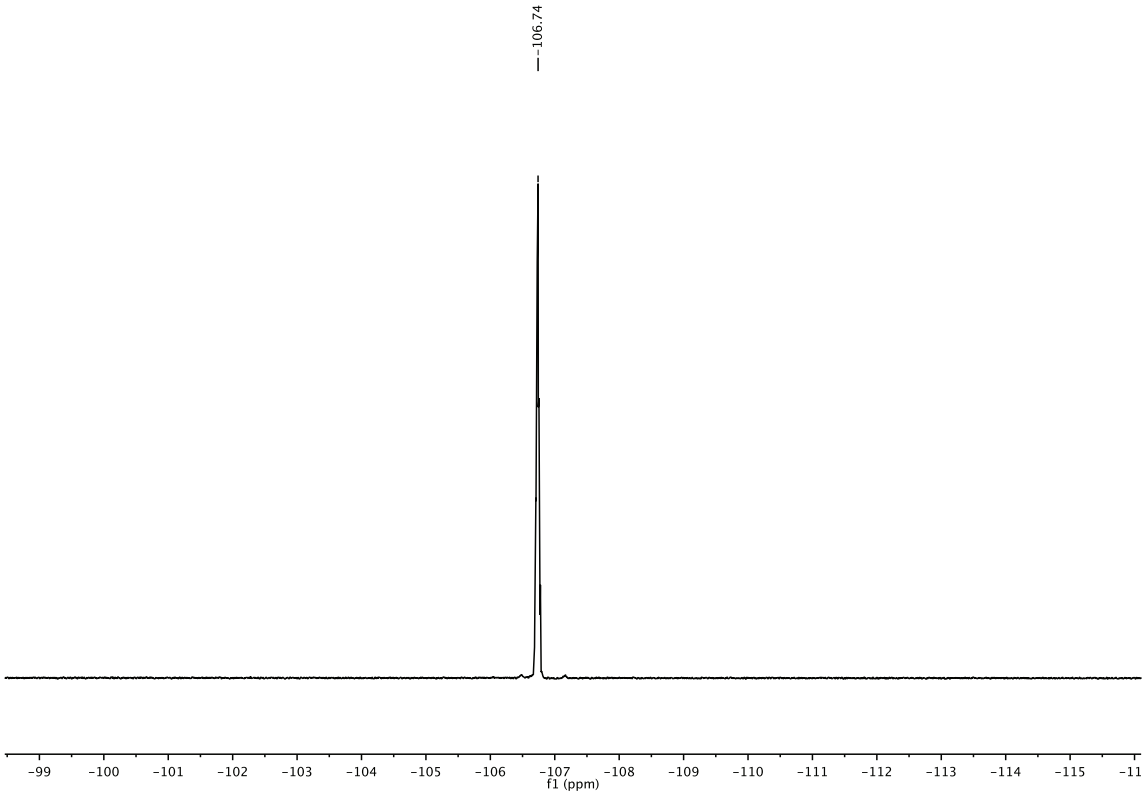
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)

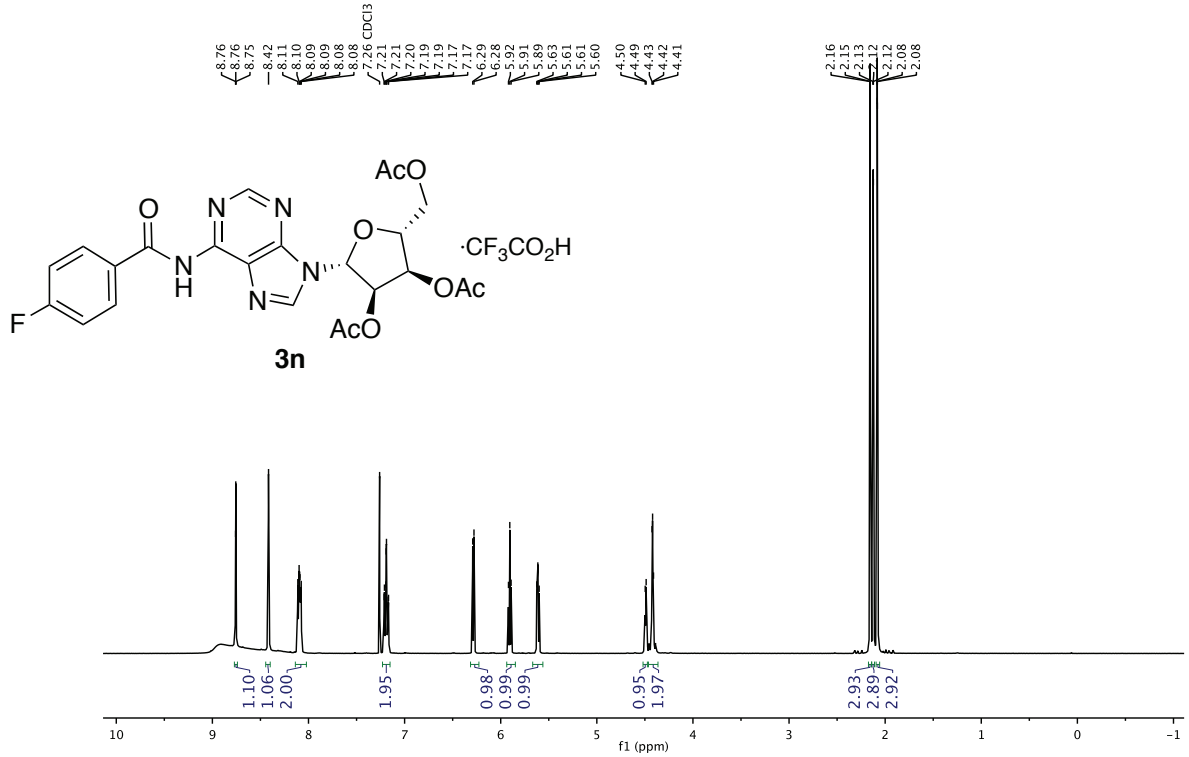


^{19}F NMR (377 MHz, $CDCl_3$)

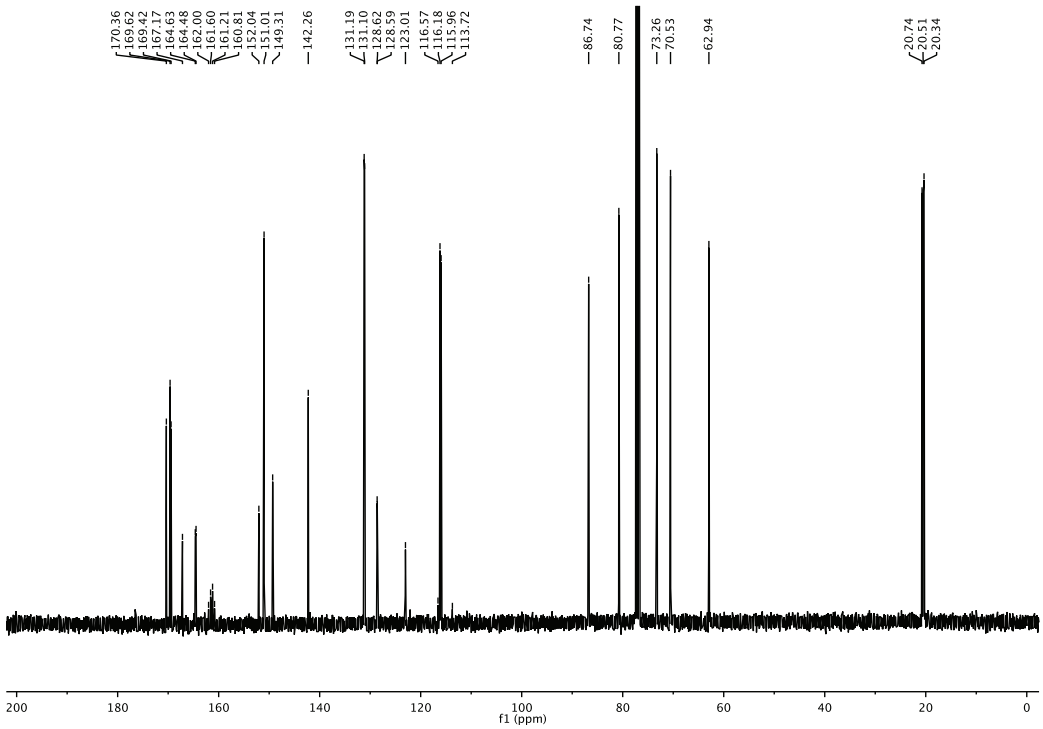


1-(6-(4-Fluorobenzamido)-9*H*-purin-9-yl)-1-deoxy-2,3,5-tri-*O*-acetyladenosine trifluoroacetate salt (3n).

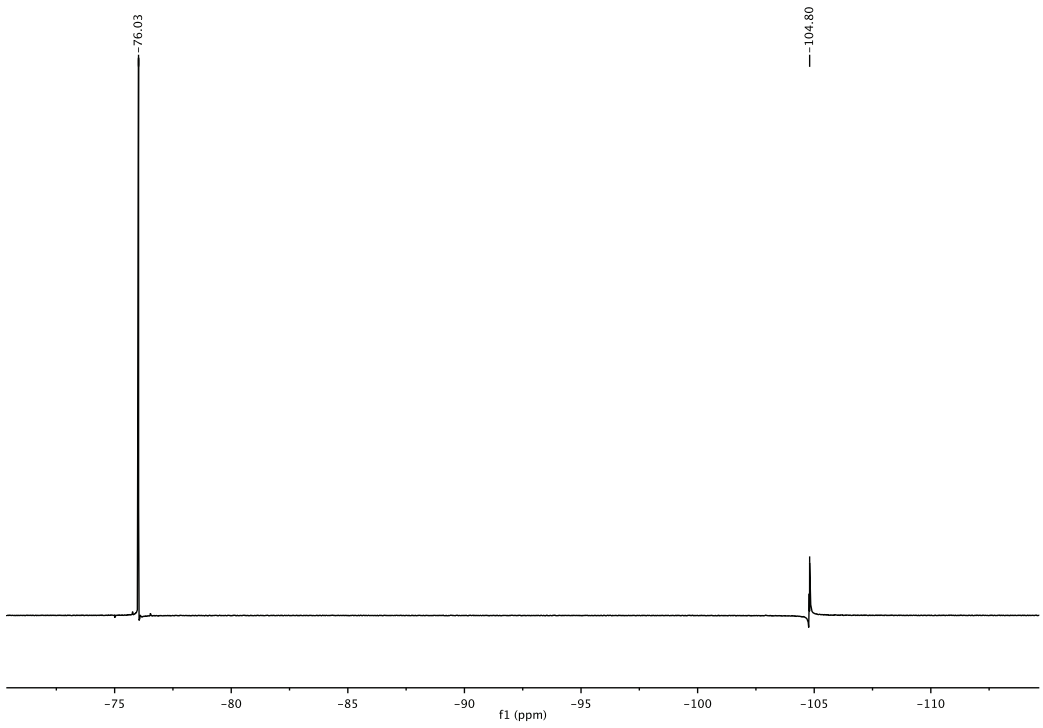
^{1}H NMR (400 MHz, $CDCl_3$)



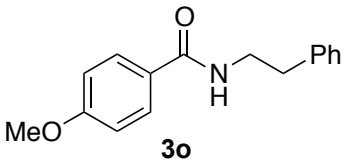
^{13}C NMR (100 MHz, $CDCl_3$)



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

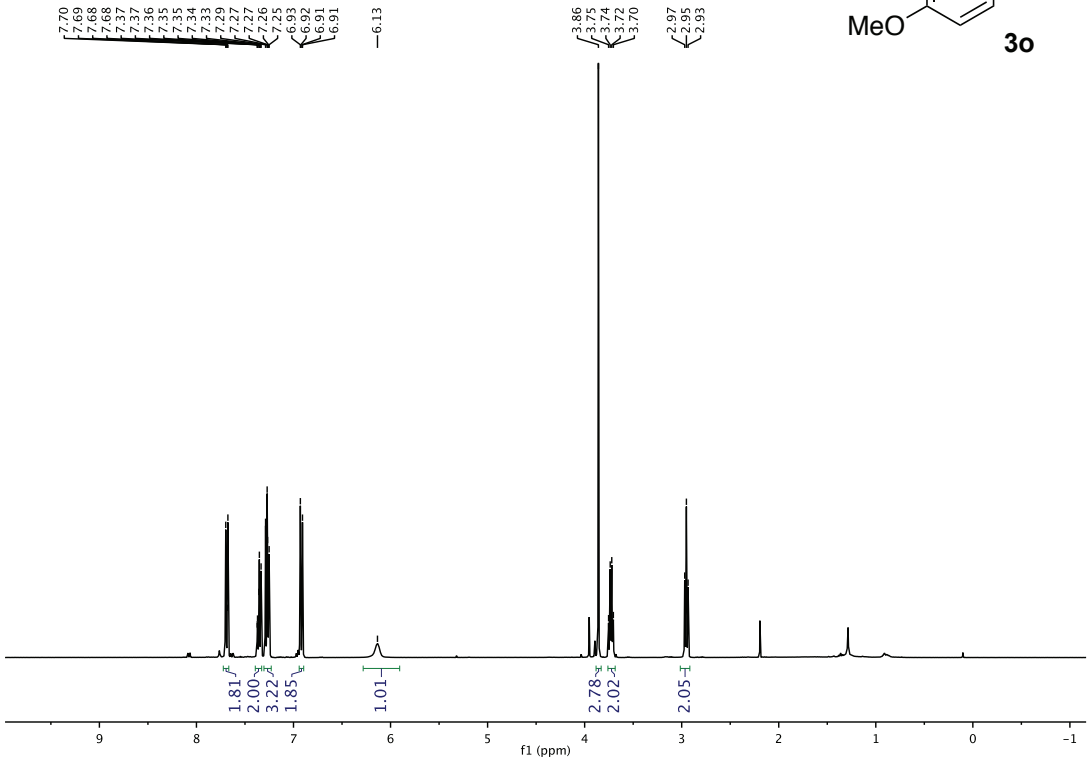


_N_-(2-Phenylethyl)-4-methoxybenzamide (3o)

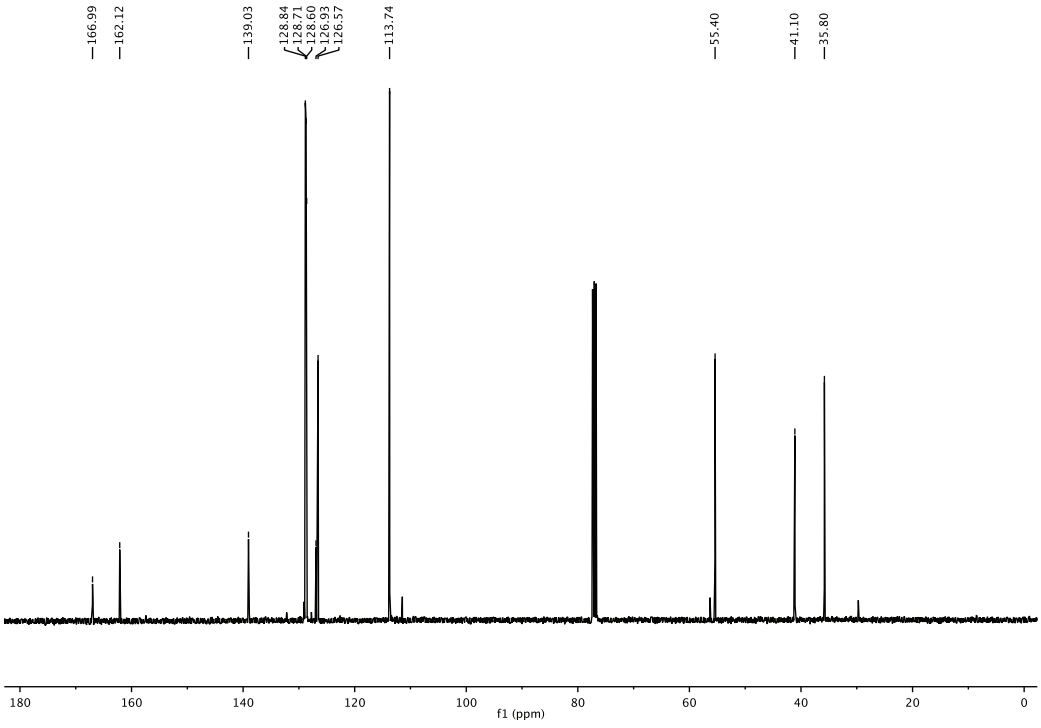


3o

^{1}H NMR (400 MHz, $CDCl_3$)

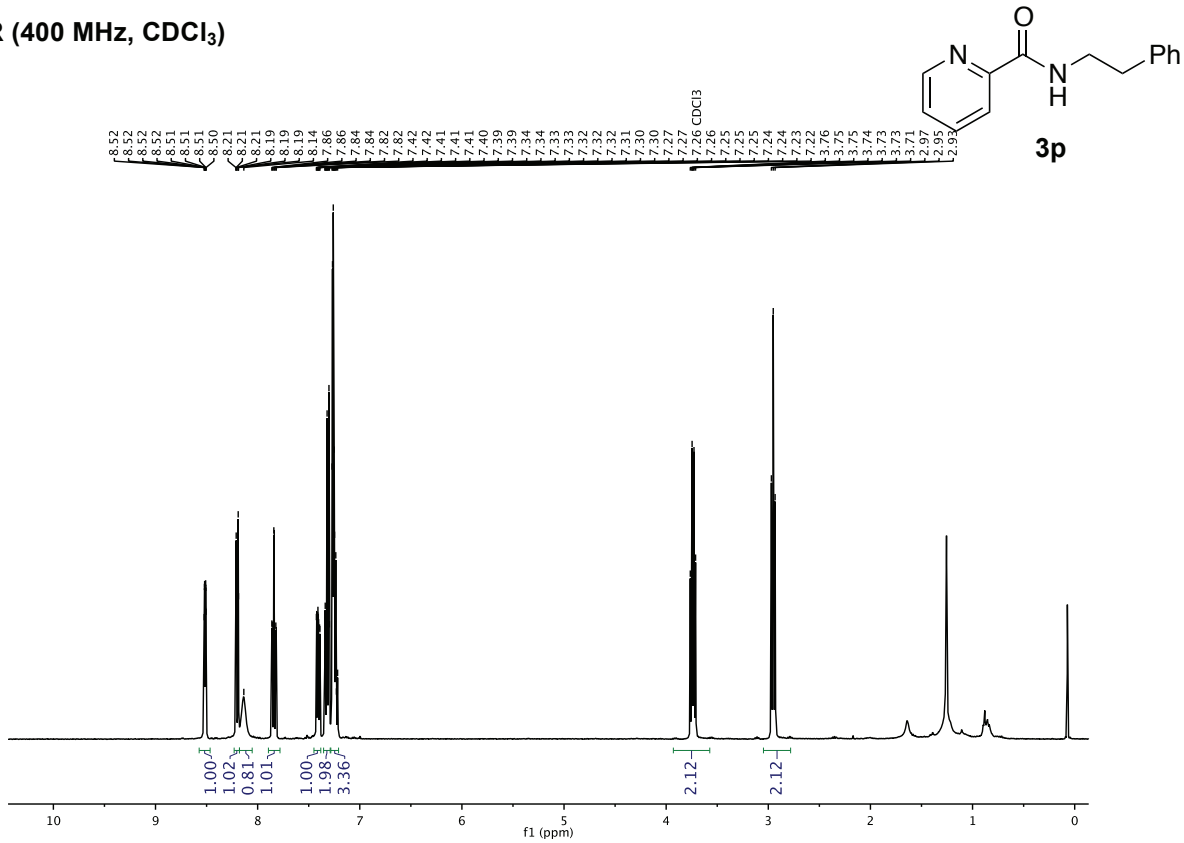


^{13}C NMR (100 MHz, $CDCl_3$)

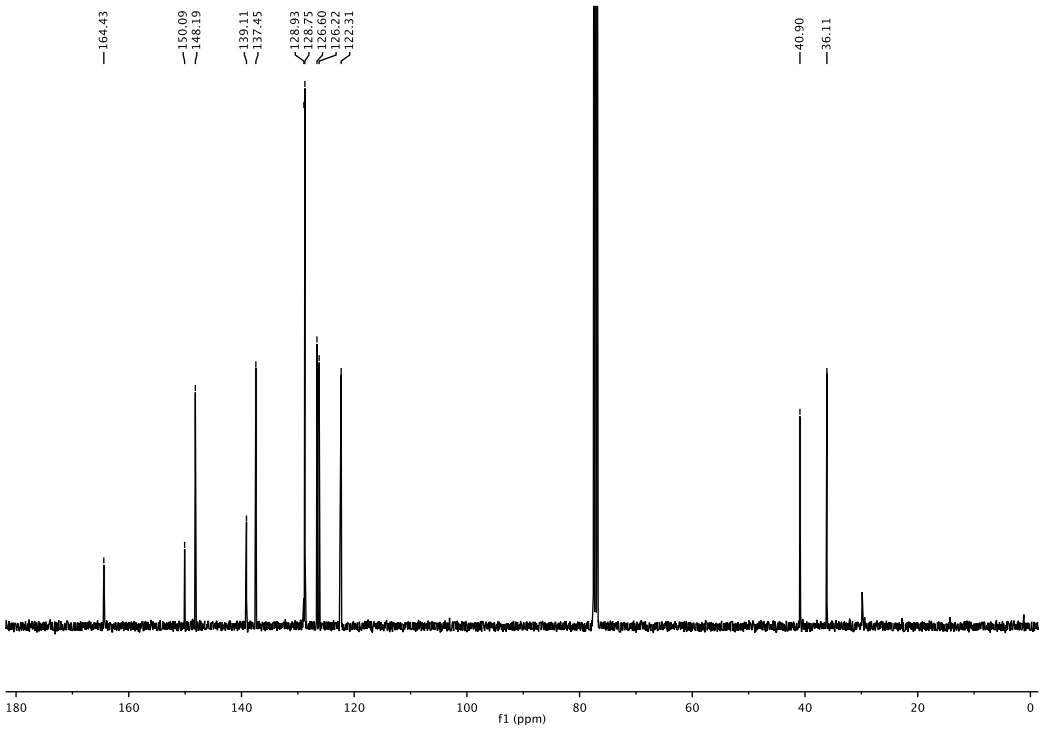


***N*-(2-Phenylethyl)-2-picolinamide (3p)**

^{1}H NMR (400 MHz, $CDCl_3$)

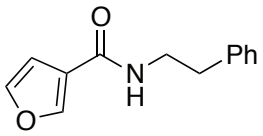


^{13}C NMR (100 MHz, $CDCl_3$)

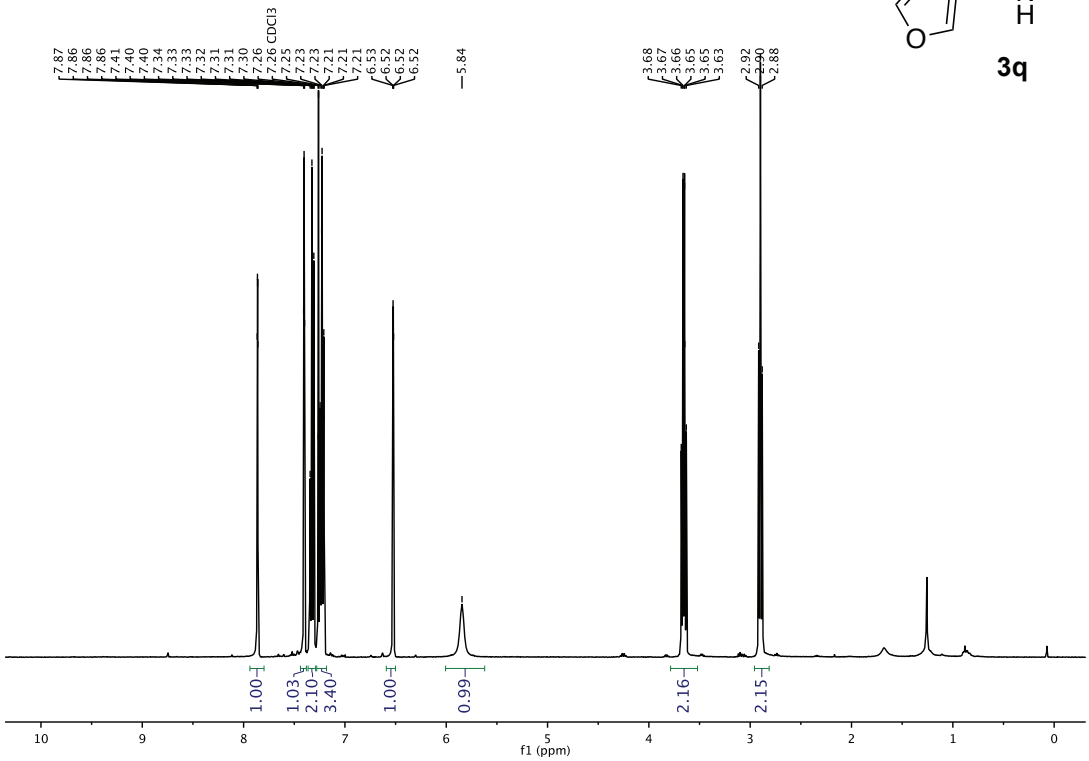


***N*-(2-Phenylethyl)-3-furamide (3q).**

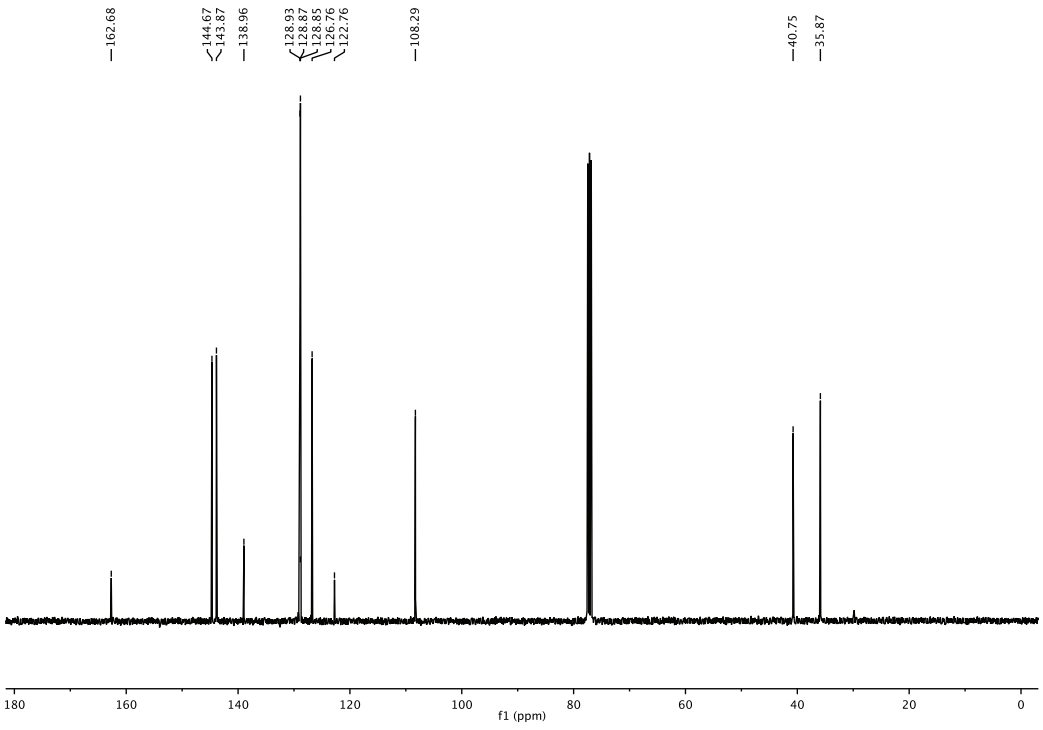
^{1}H NMR (400 MHz, $CDCl_3$)



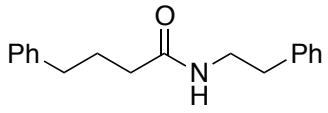
3q



^{13}C NMR (100 MHz, $CDCl_3$)

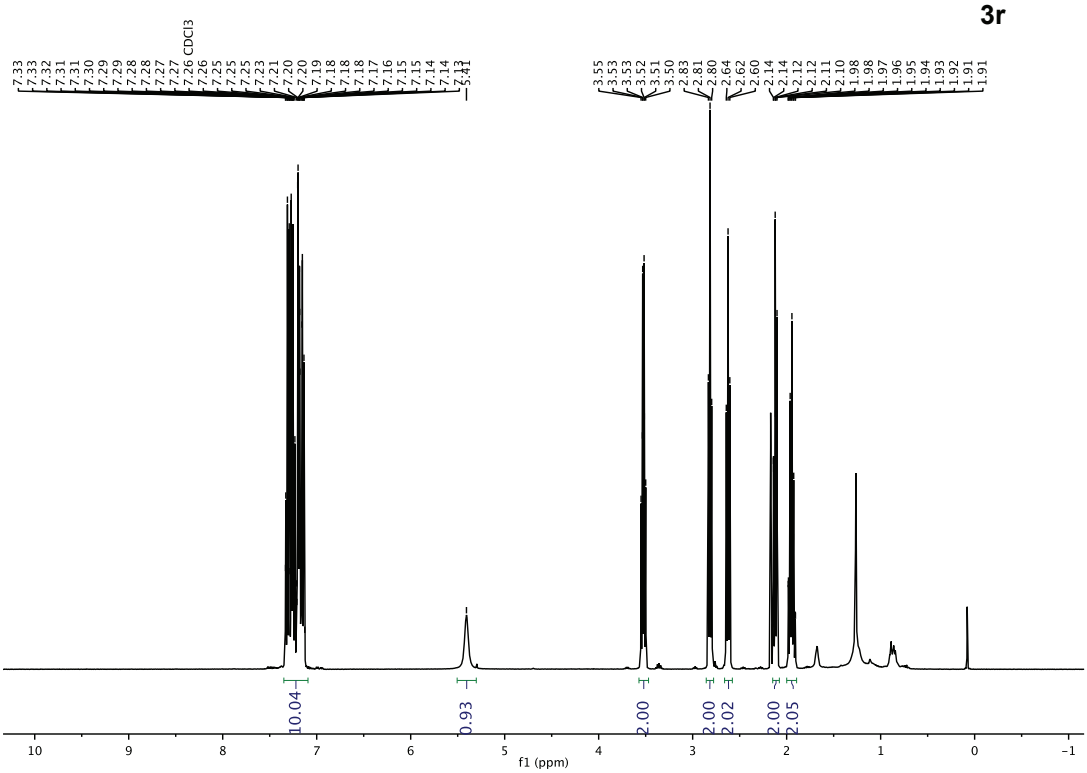


***N*-(2-Phenylethyl)-4-phenylbutanamide (3r).**

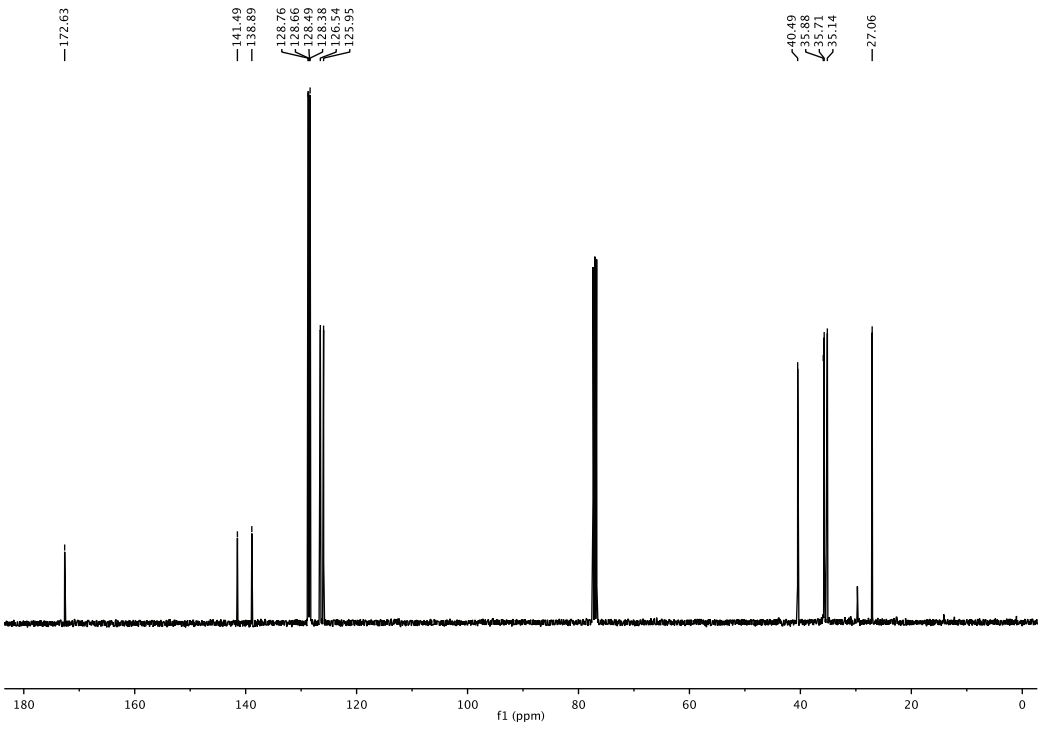


3r

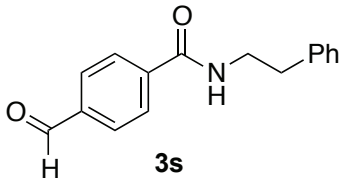
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)

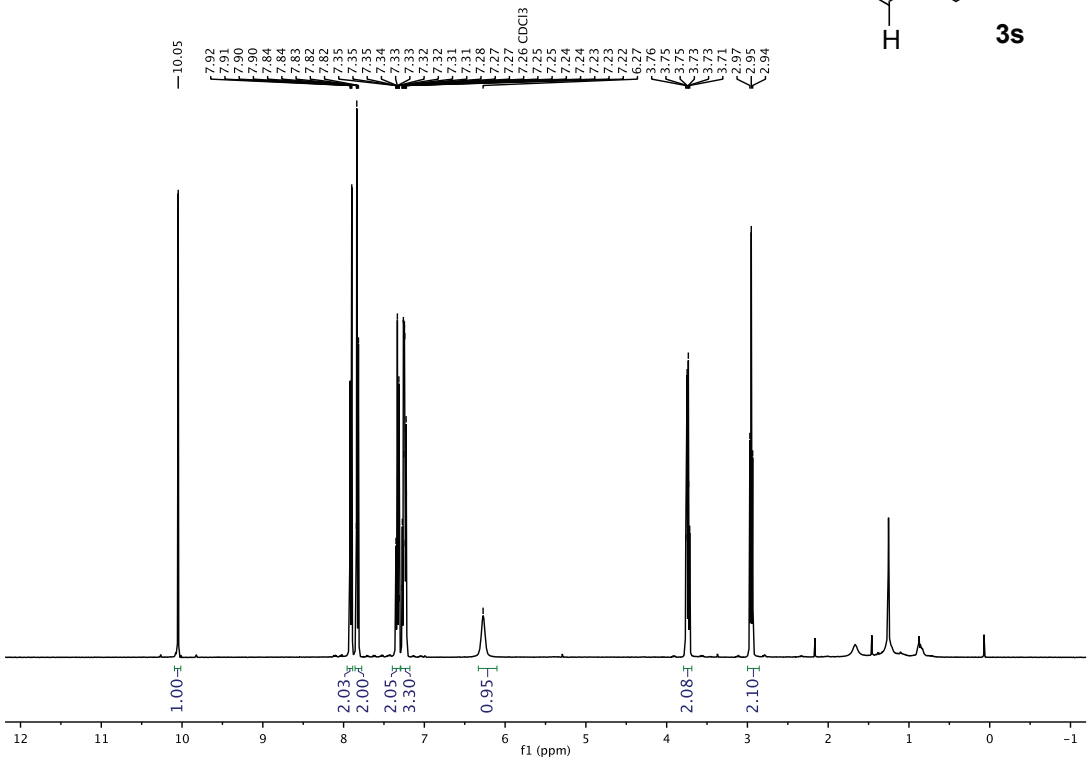


***N*-(2-Phenylethyl)-4-formylbenzamide (3s).**

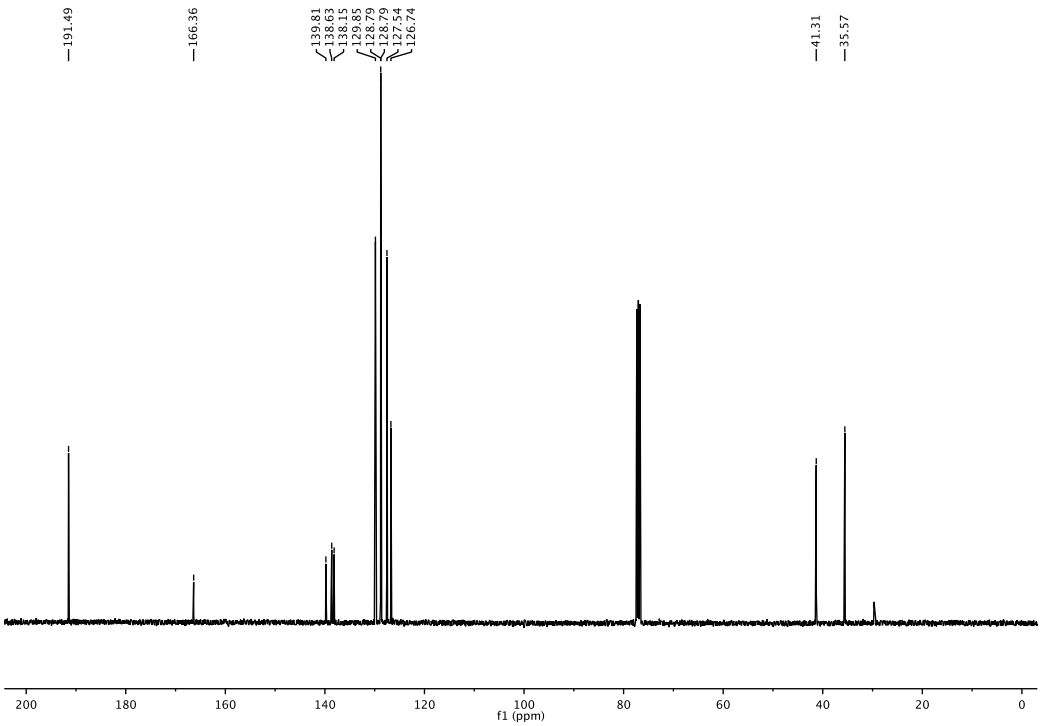


3s

^{1}H NMR (400 MHz, $CDCl_3$)

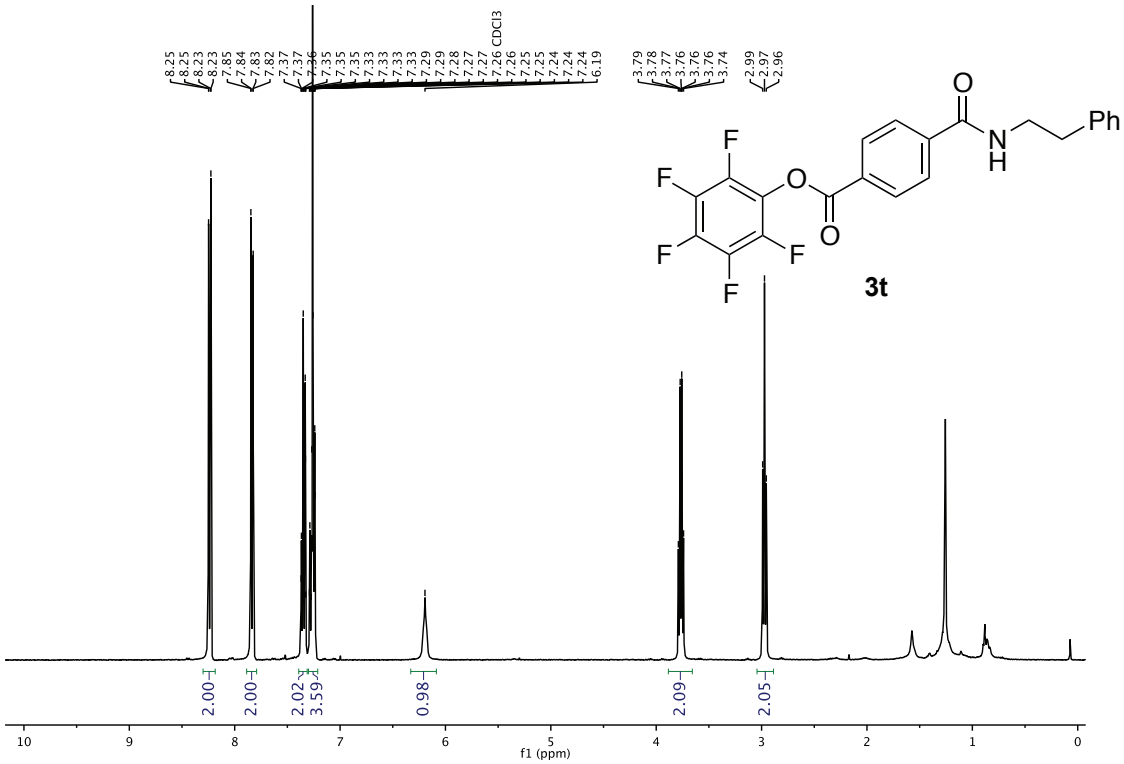


^{13}C NMR (100 MHz, $CDCl_3$)

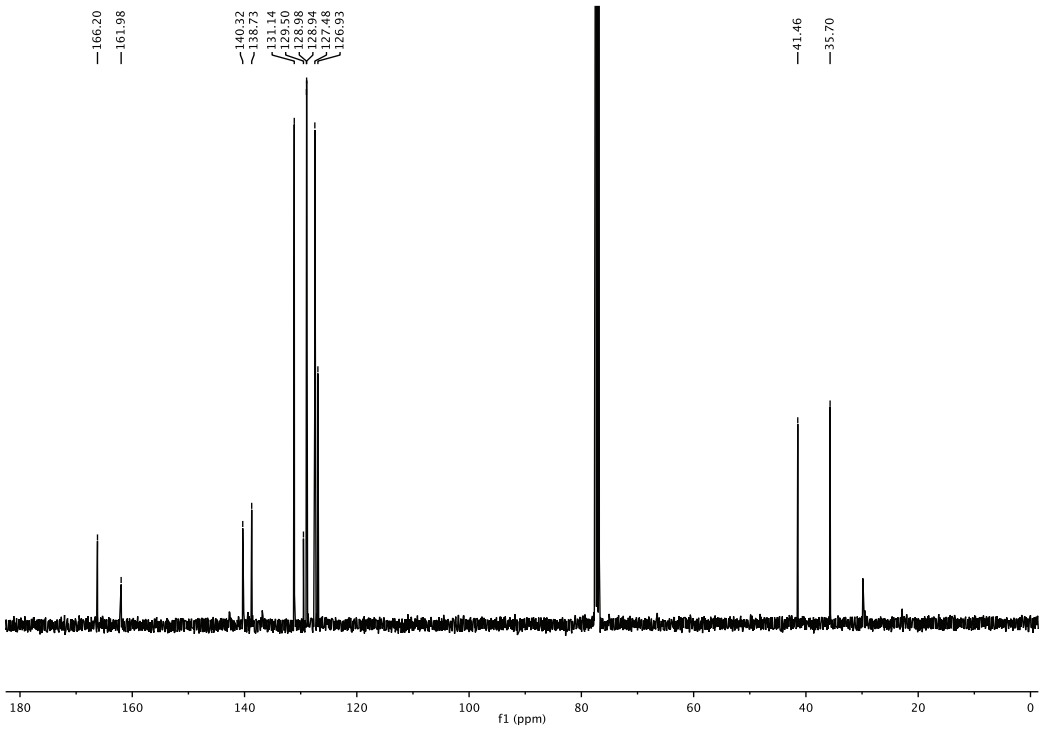


Pentafluorophenyl 4-(*N*-(2-phenylethyl)carbamoyl)benzoate (3t).

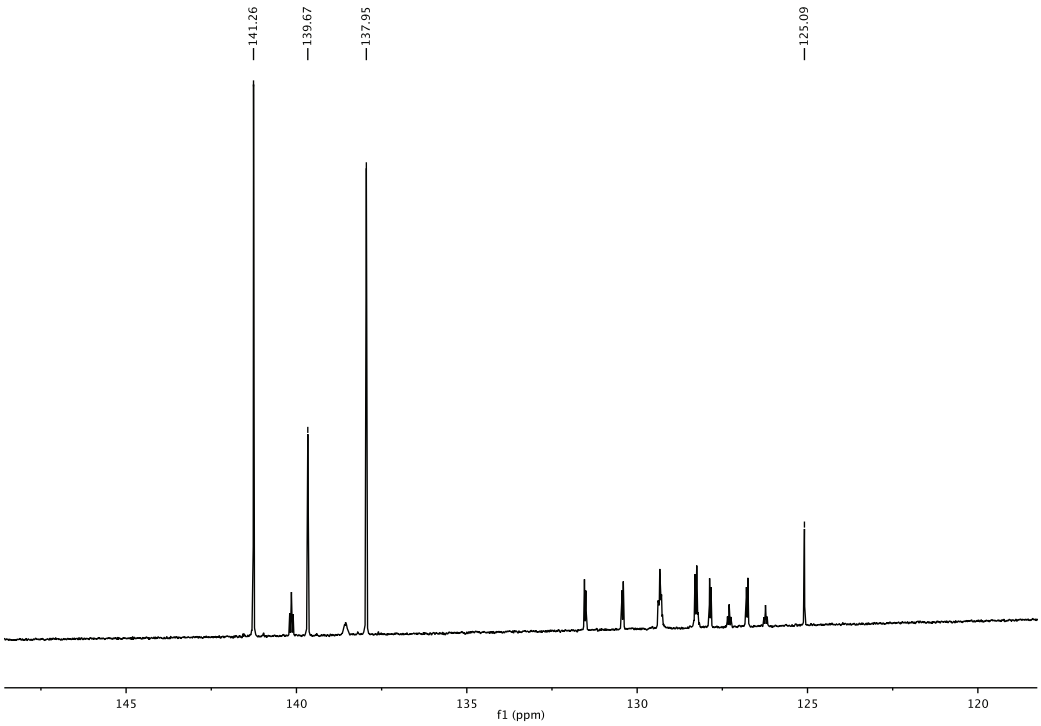
^{1}H NMR (600 MHz, $CDCl_3$)



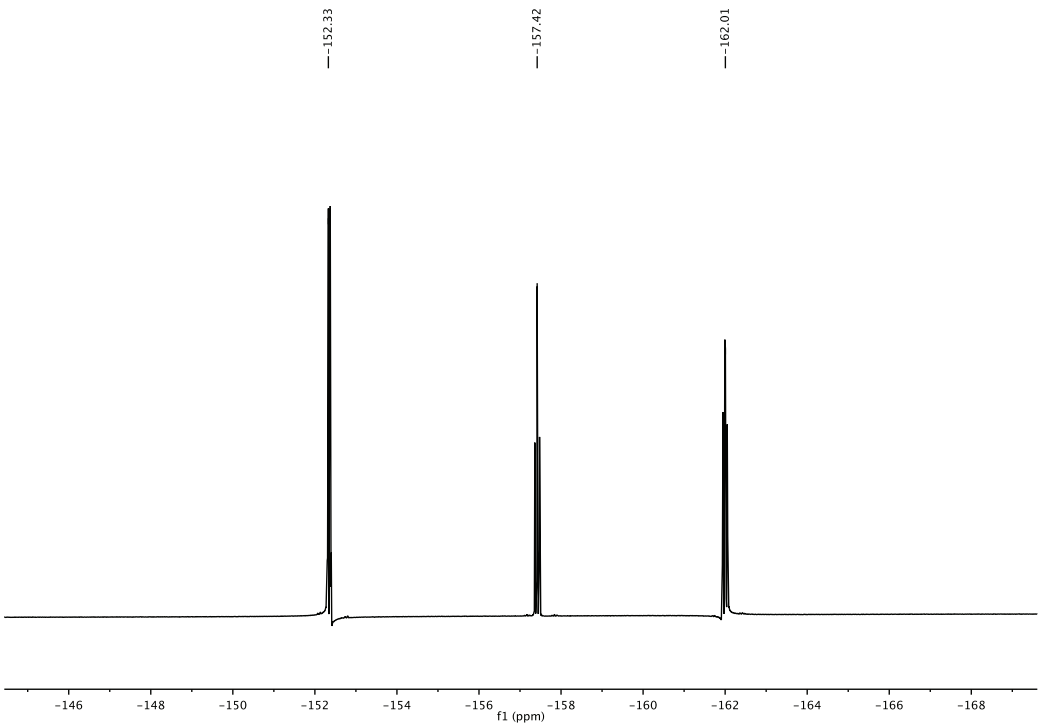
^{13}C NMR (150 MHz, $CDCl_3$)



^{13}C {^{19}F} NMR (500 MHz, $CDCl_3$)

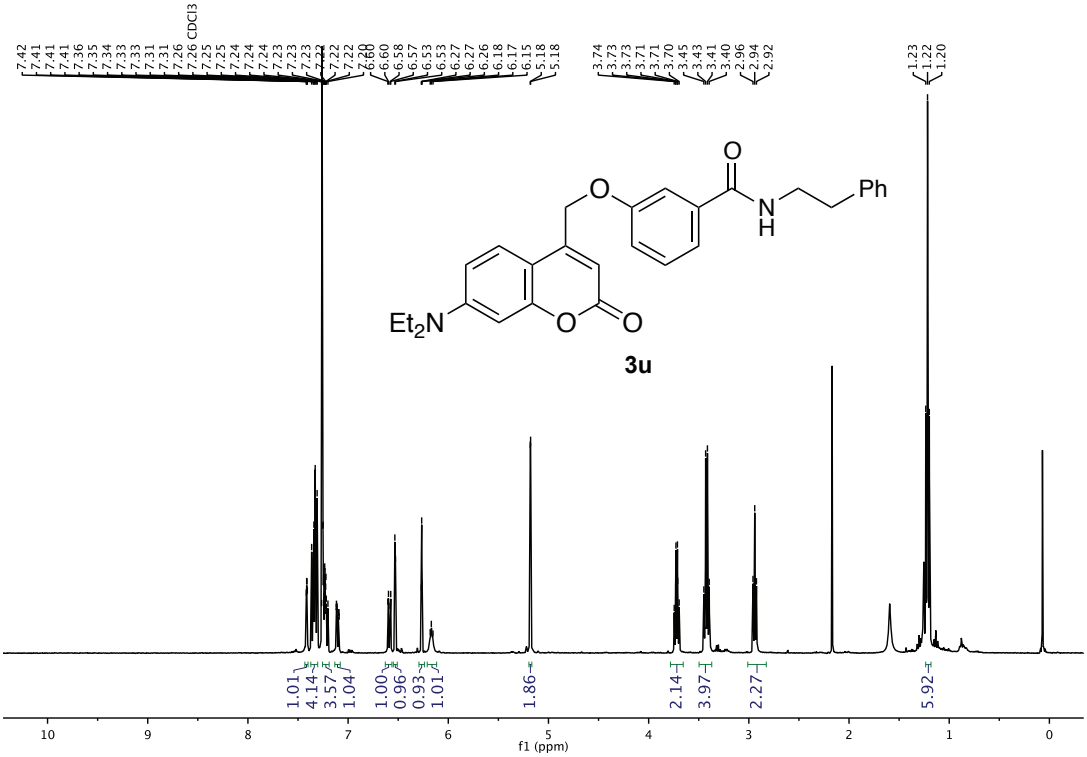


^{19}F NMR (377 MHz, $CDCl_3$)

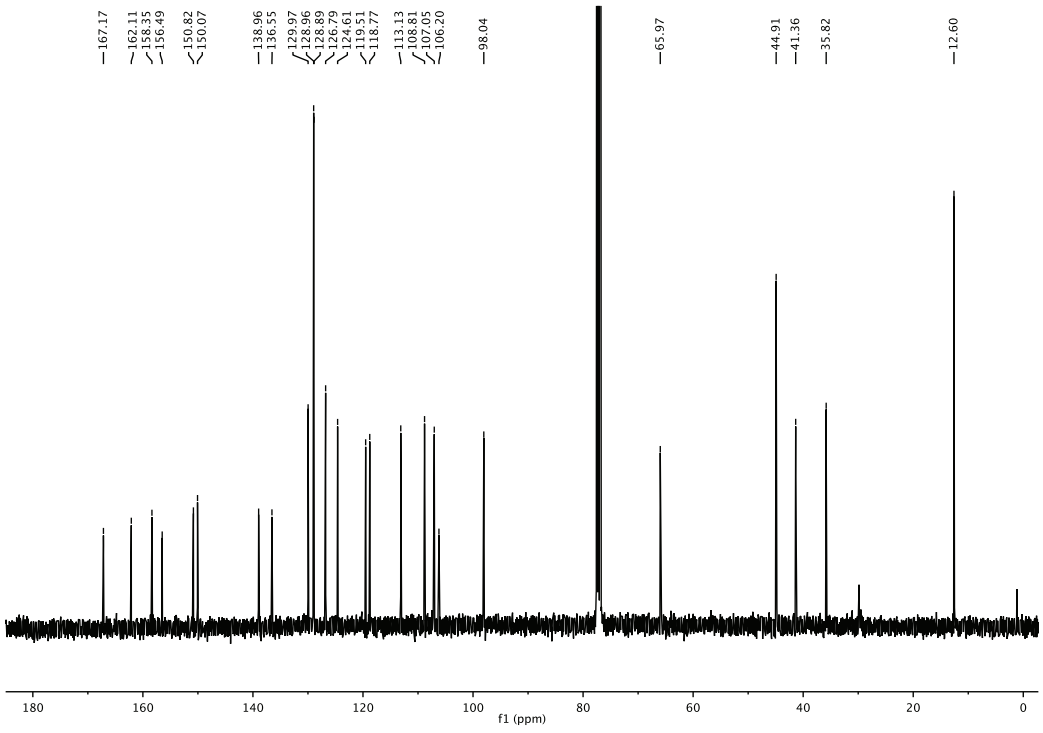


3-((7-(Diethylamino)-2-oxo-2*H*-chromen-4-yl)methoxy)-*N*-(2-phenylethyl)benzamide (3u).

^{1}H NMR (400 MHz, $CDCl_3$)

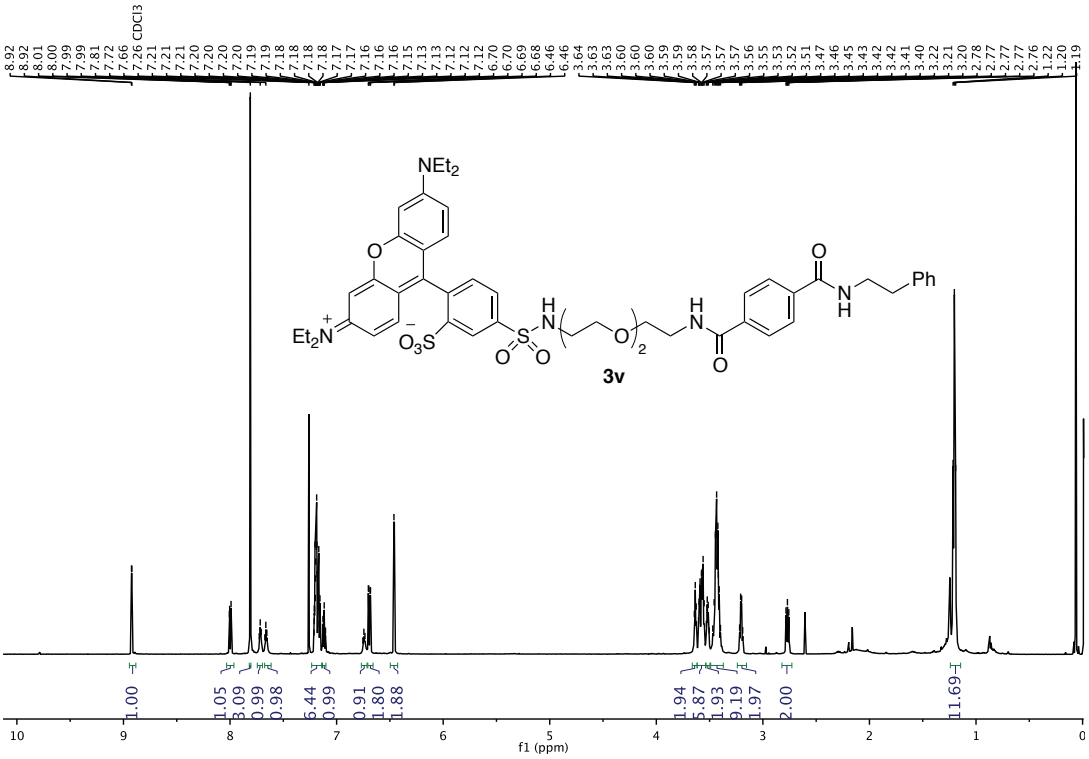


^{13}C NMR (100 MHz, $CDCl_3$)

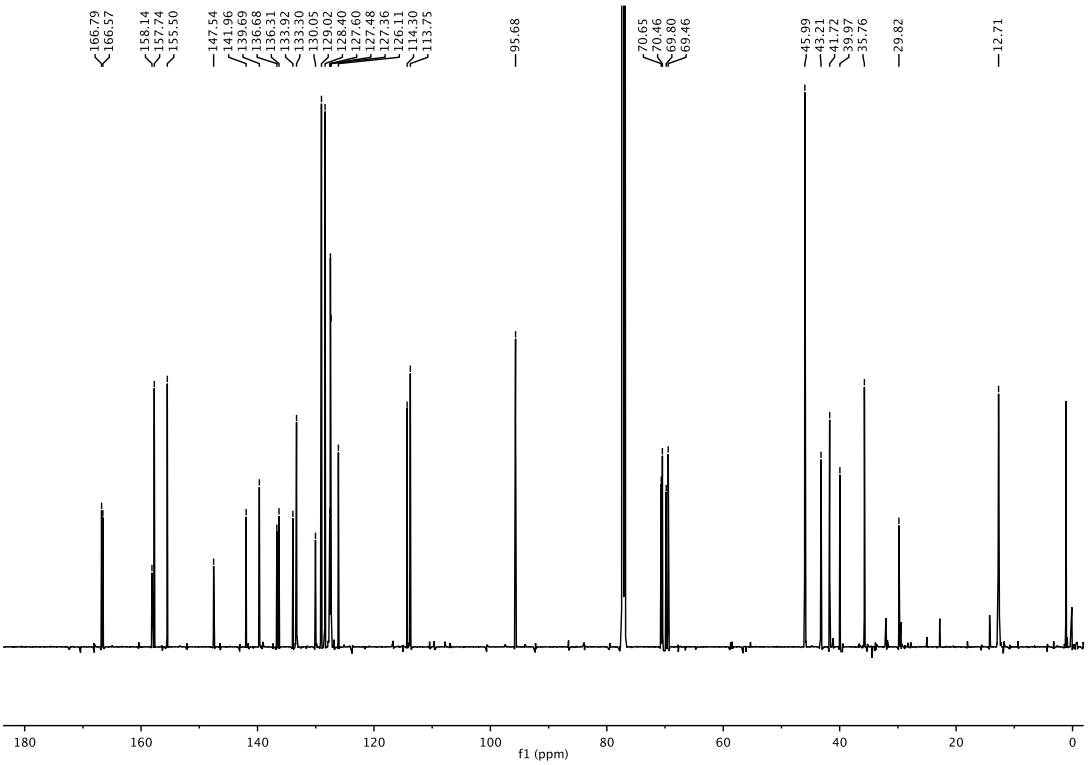


2-(6-(Diethylamino)-3-(diethyliminio)-3*H*-xanthen-9-yl)-5-(*N*-(2-(2-(2-(4-(*N*-(2-phenylethyl)carbamoyl)benzamido)ethoxy)ethoxy)ethyl)sulfamoyl)benzenesulfonate (3v).

^{1}H NMR (400 MHz, $CDCl_3$)

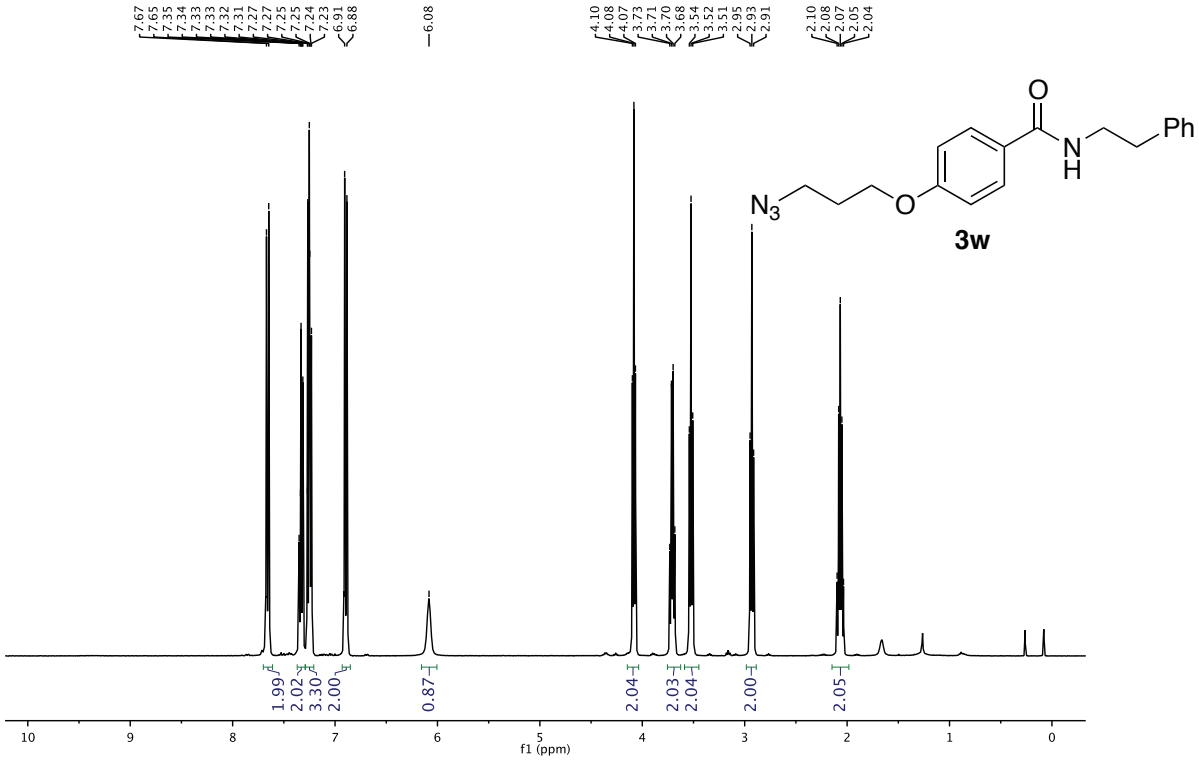


^{13}C NMR (100 MHz, $CDCl_3$)

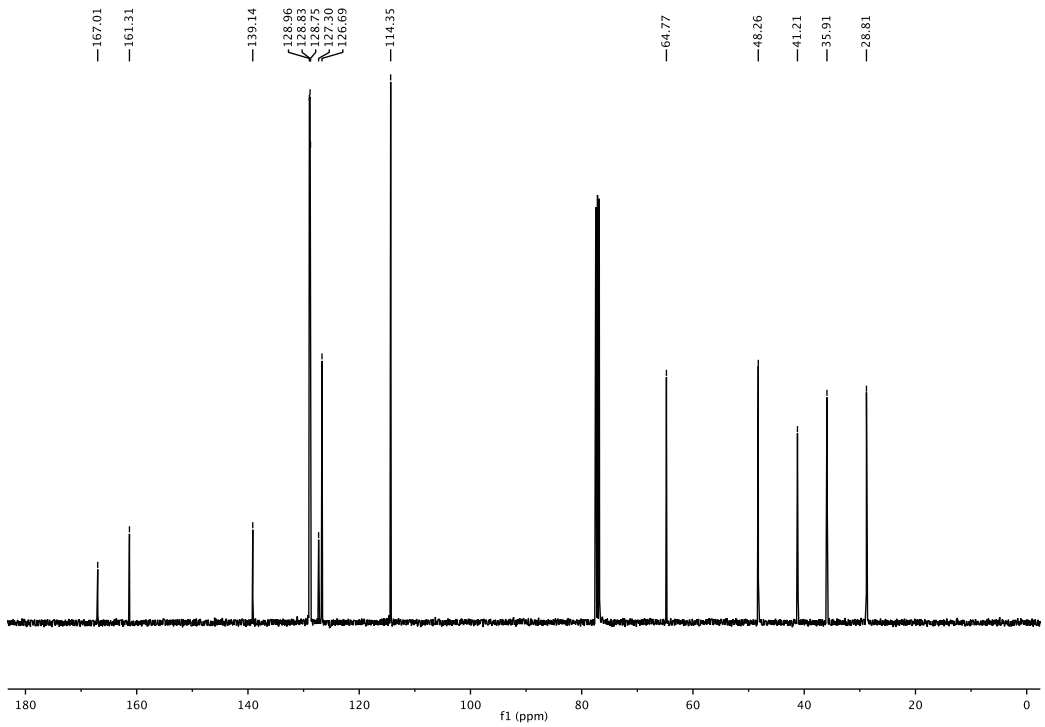


4-(3-Azidopropoxy)-*N*-(2-phenylethyl)benzamide (3w).

^{1}H NMR (400 MHz, $CDCl_3$)

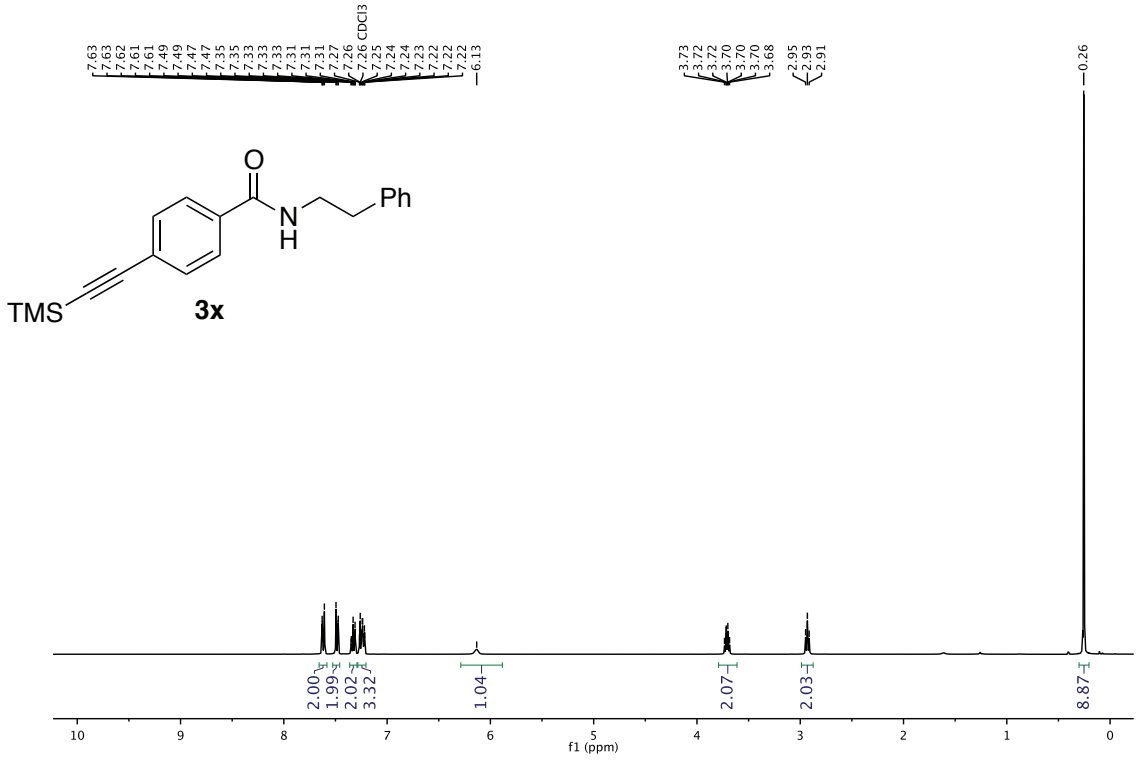


^{13}C NMR (100 MHz, $CDCl_3$)

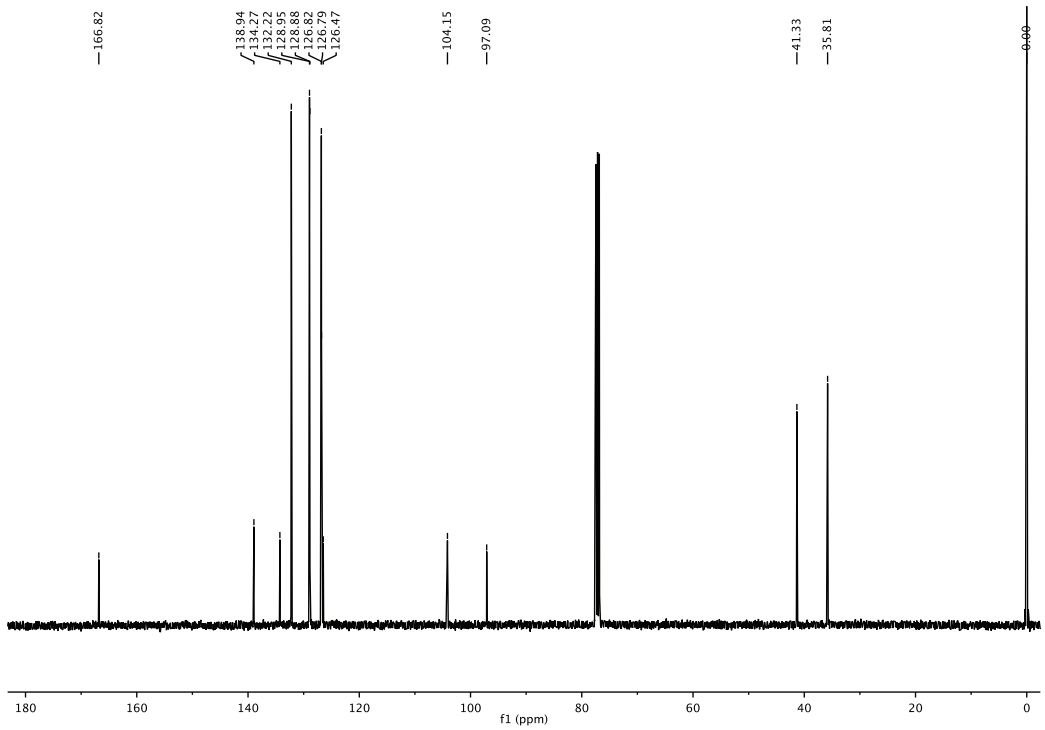


***N*-(2-phenylethyl)-4-(2-trimethylsilylethynyl)benzamide (3x).**

^{1}H NMR (400 MHz, $CDCl_3$)

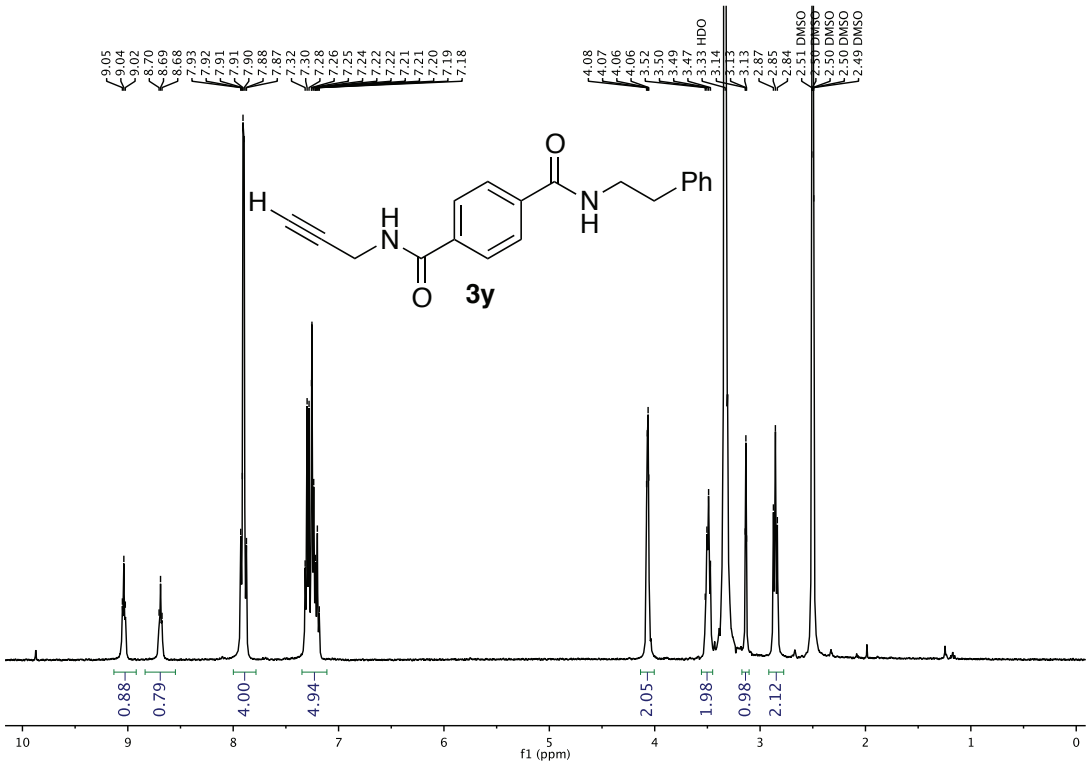


^{13}C NMR (100 MHz, $CDCl_3$)

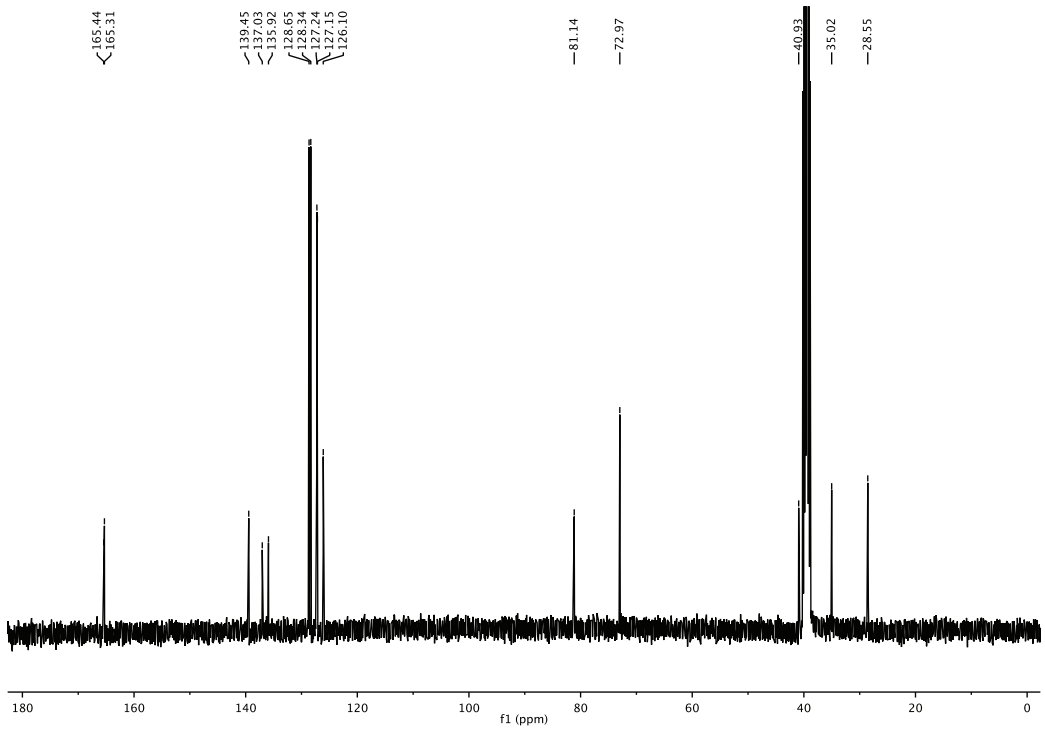


***N*-(2-Phenylethyl)-*N'*-propargylterephthalimide (3y).**

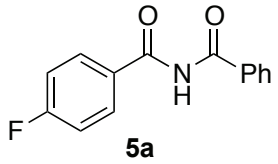
^{1}H NMR (400 MHz, DMSO-d_6)



^{13}C NMR (100 MHz, DMSO-d_6)

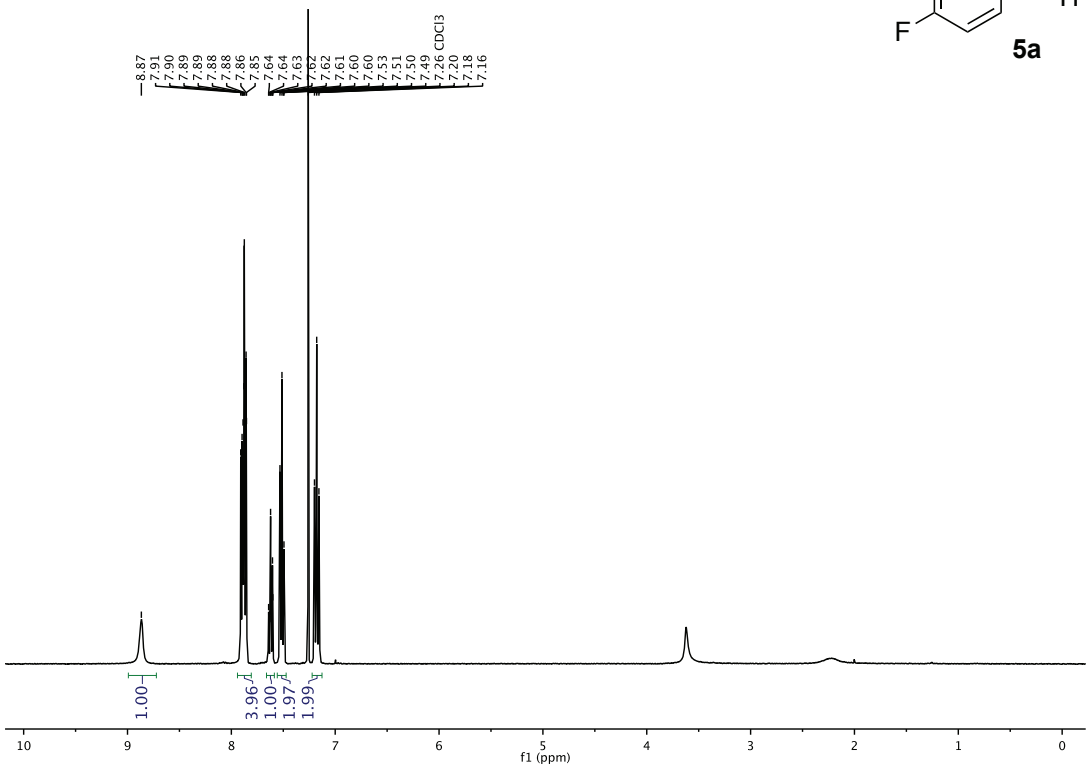


***N*-Benzoyl-4-fluorobenzamide (5a).**

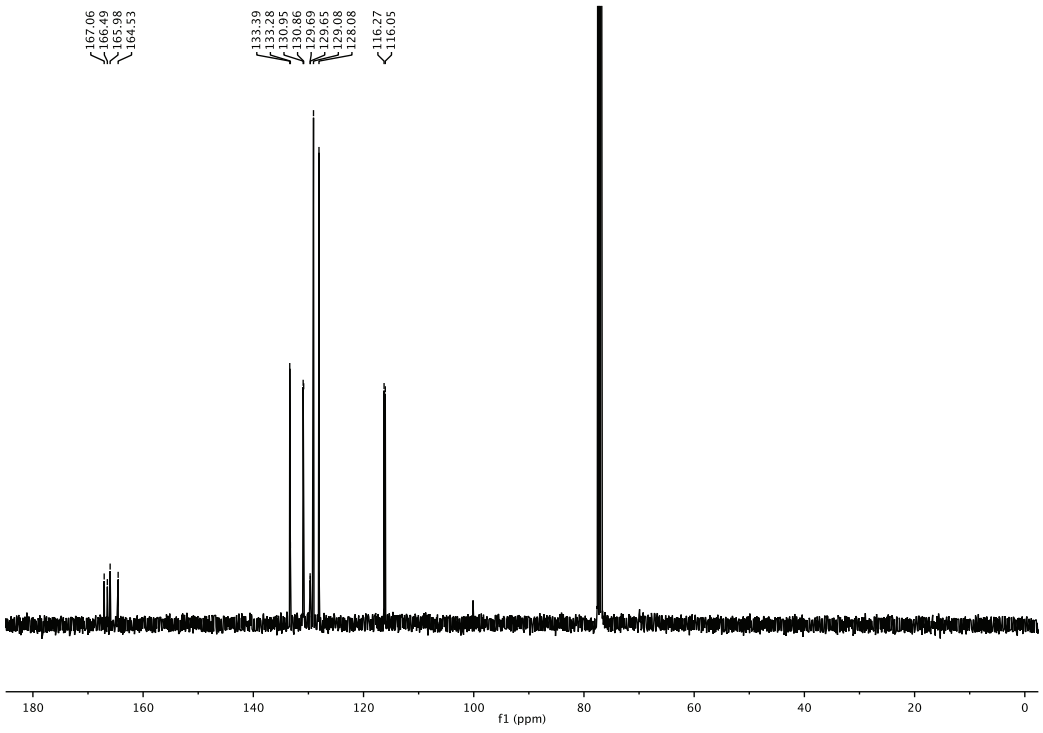


5a

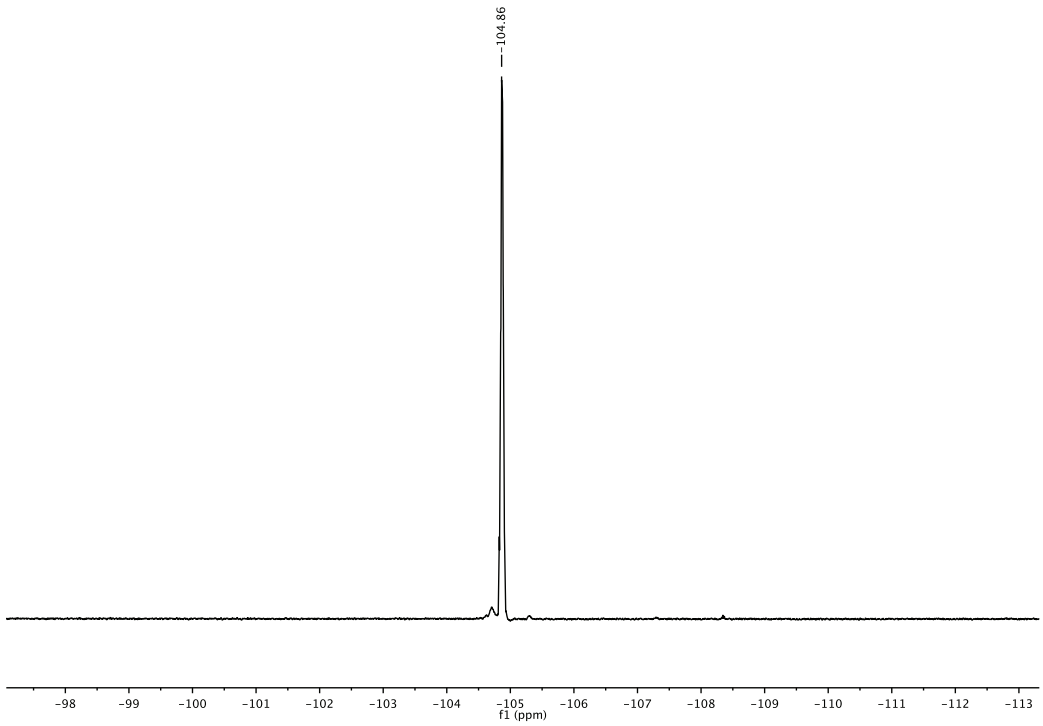
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)

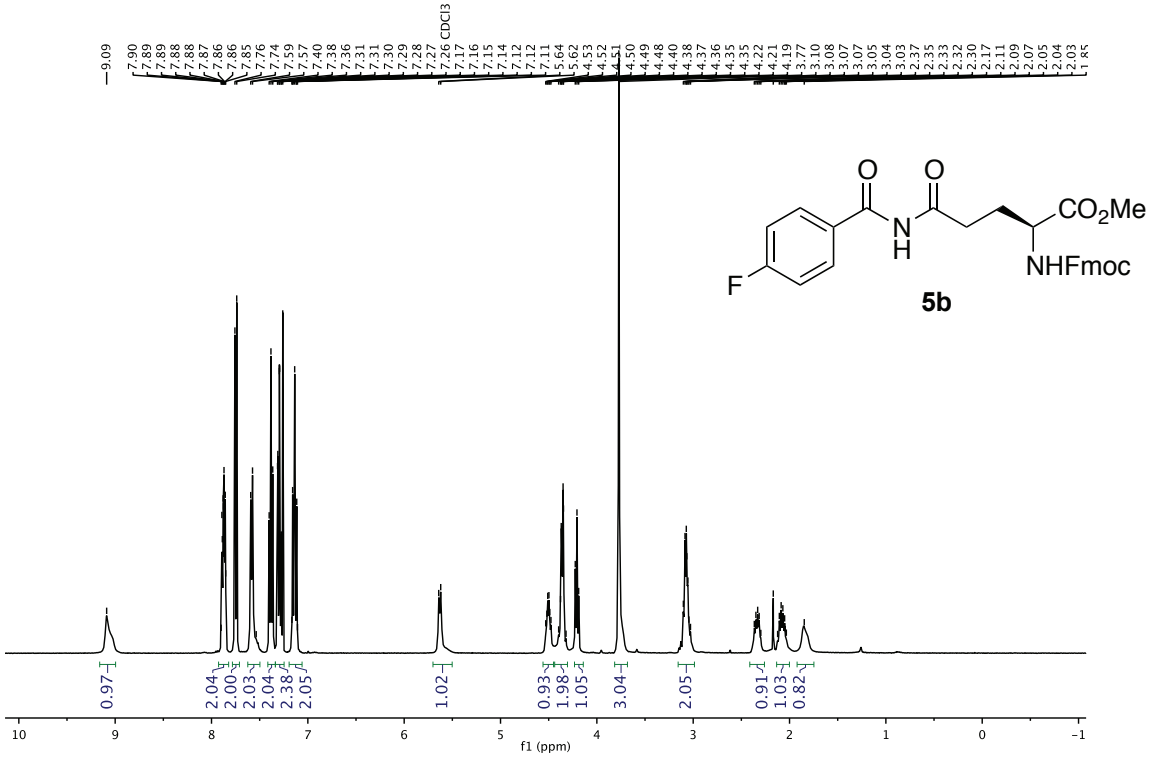


^{19}F NMR (377 MHz, $CDCl_3$)

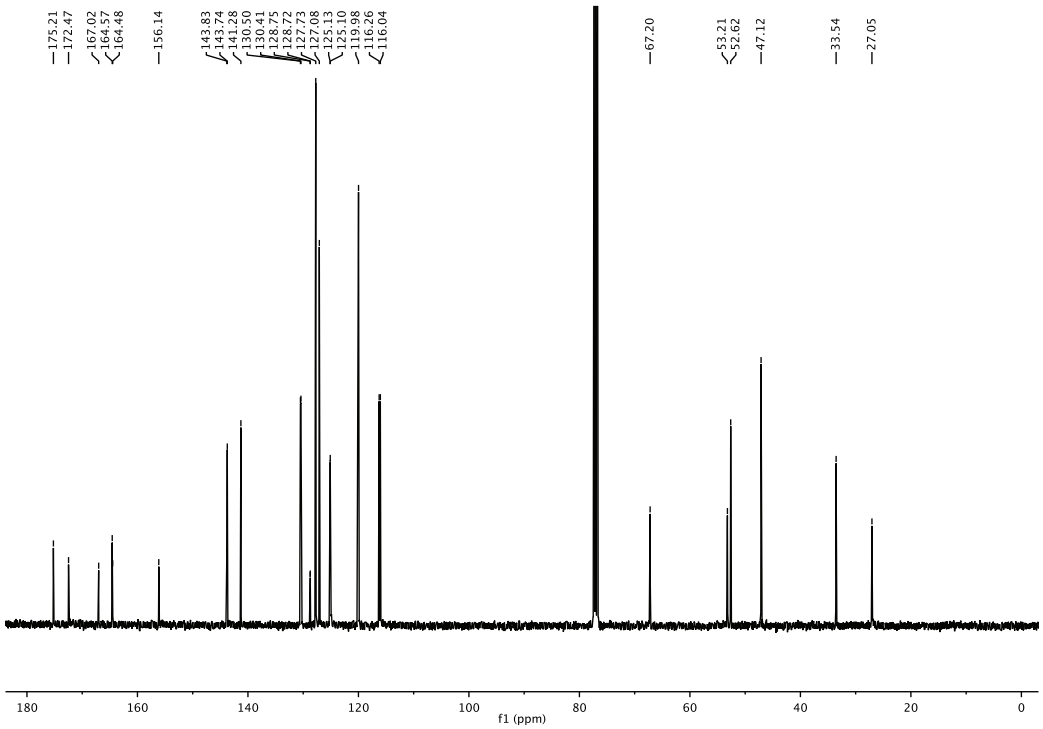


(*S*)-Methyl 2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-5-(4-fluorobenzamido)-5-oxopentanoate (5b).

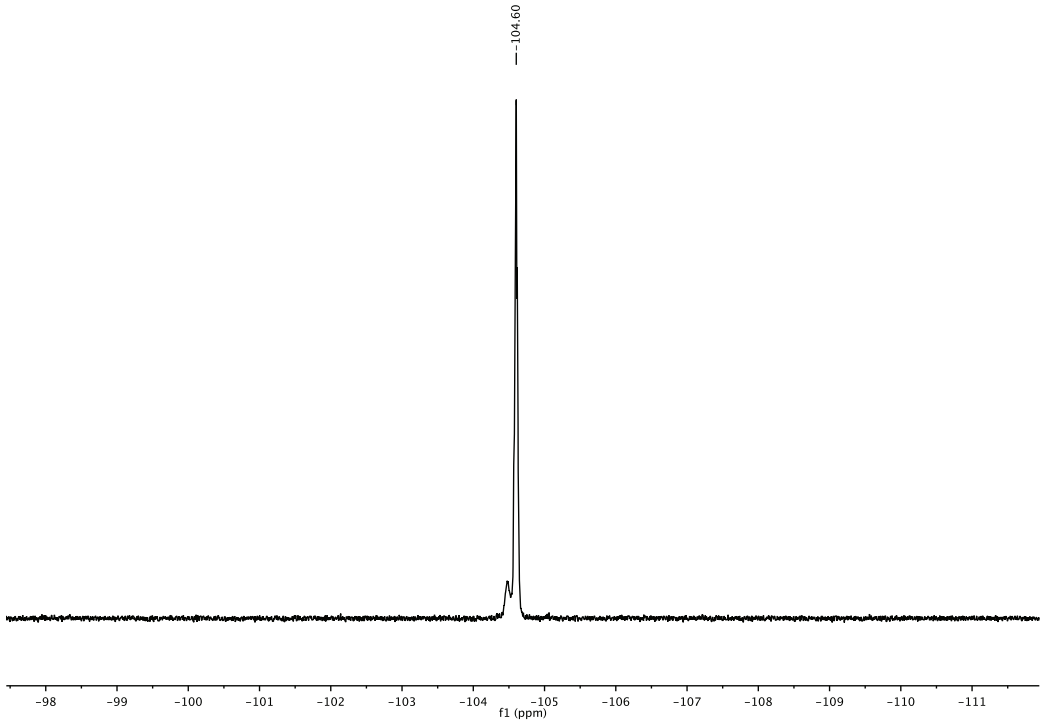
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)

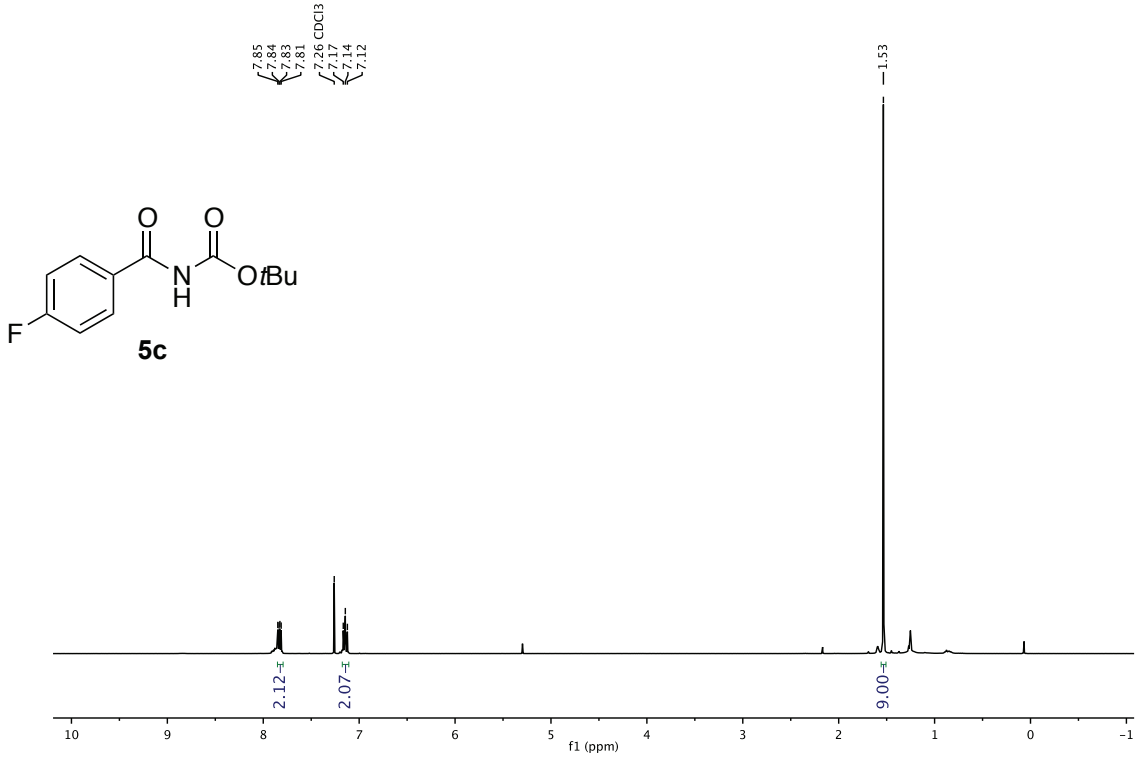


^{19}F NMR (377 MHz, $CDCl_3$)

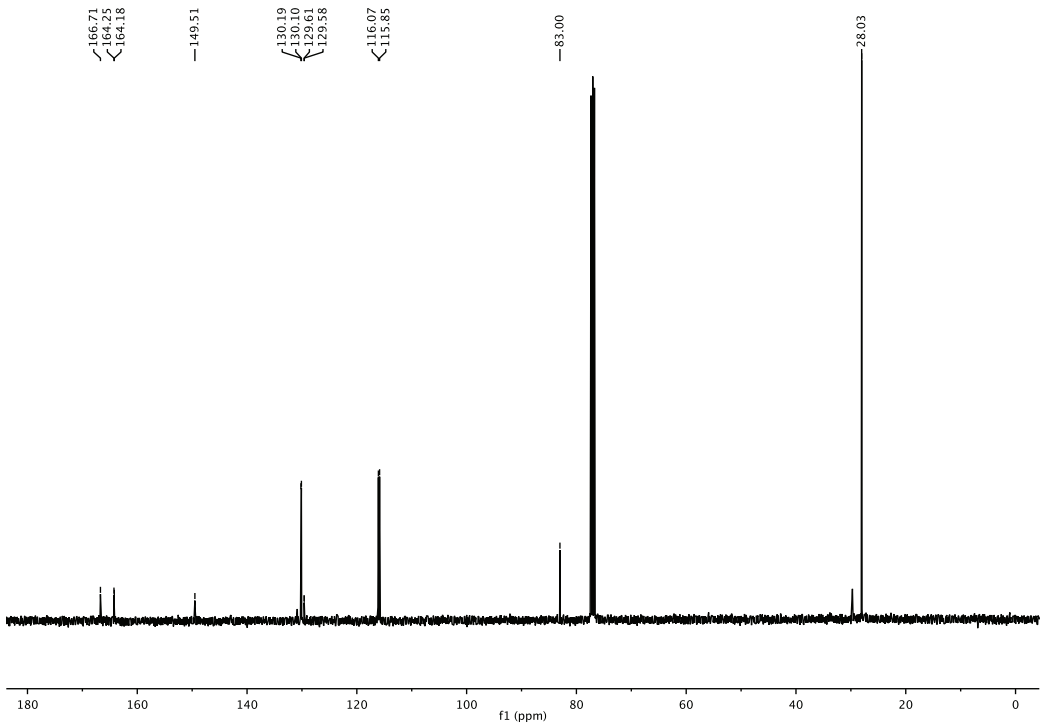


***tert*-Butyl *N*-4-fluorobenzoylcarbamate (5c).**

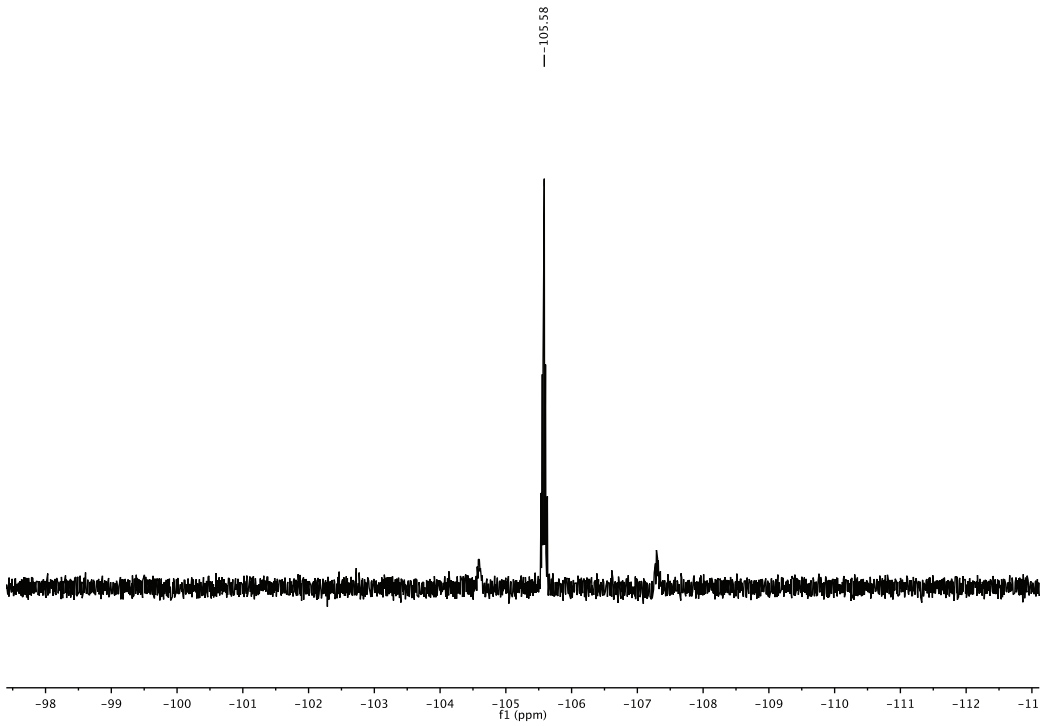
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)

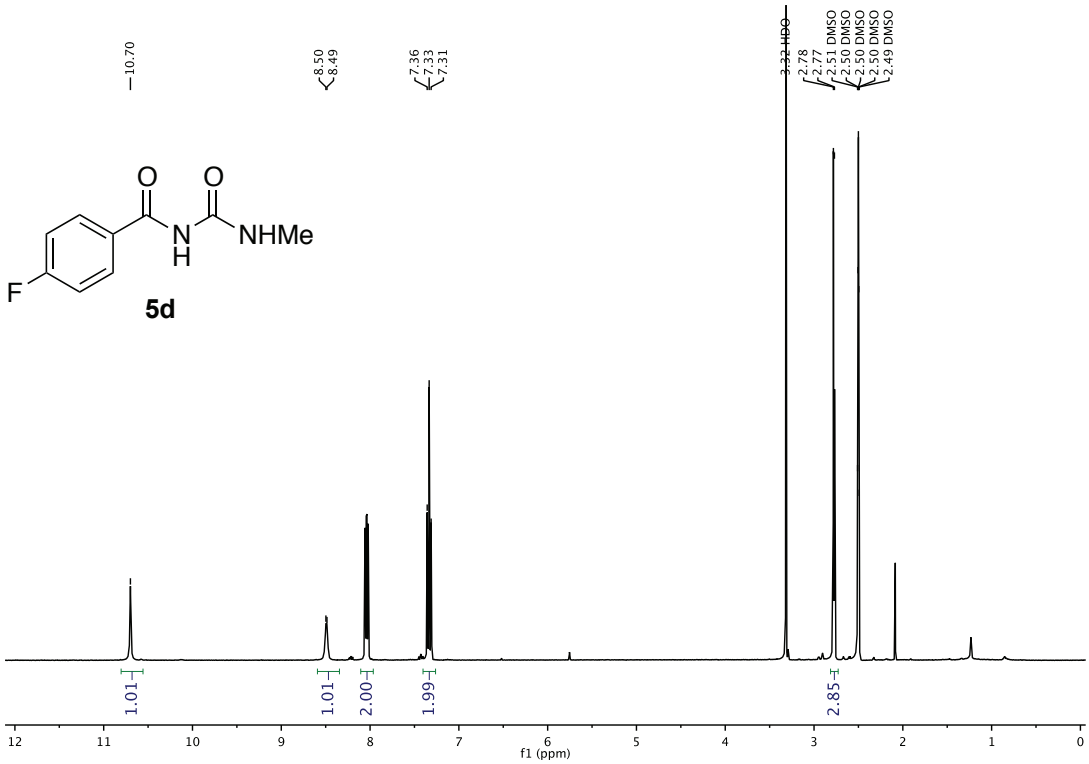


^{19}F NMR (282 MHz, $CDCl_3$)

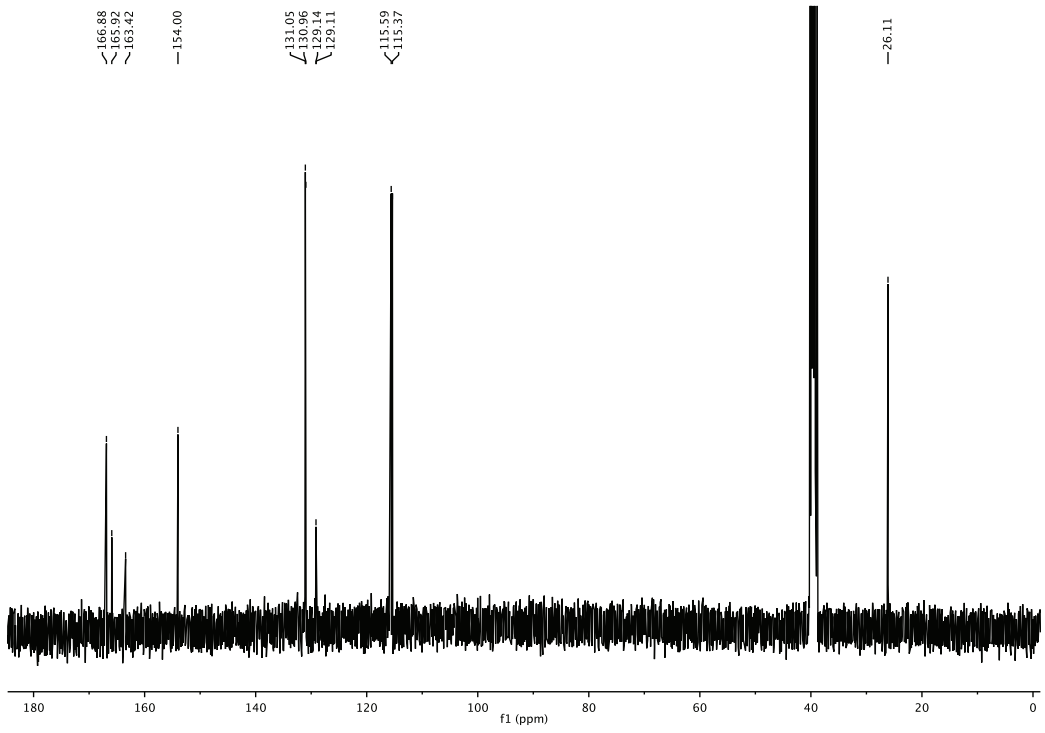


***N*-(4-Fluorobenzoyl)-*N*'-methylurea (5d).**

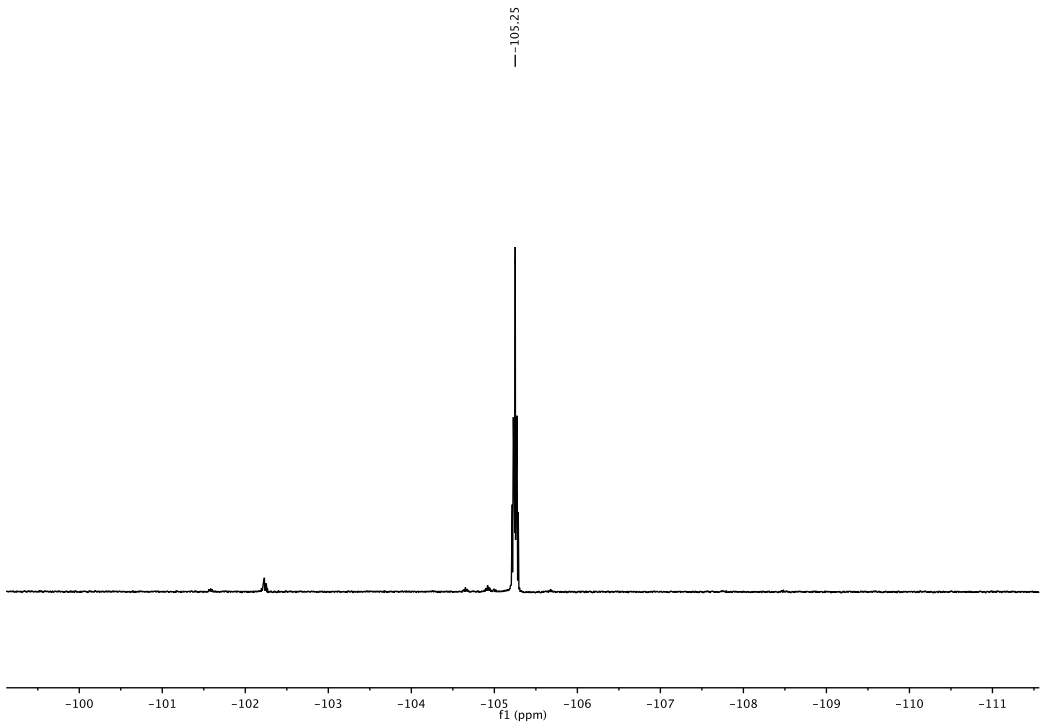
^{1}H NMR (400 MHz, DMSO-d_6)



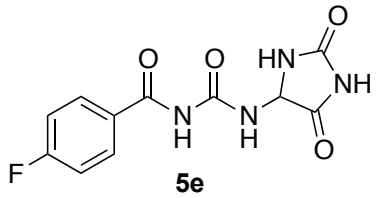
^{13}C NMR (100 MHz, DMSO-d_6)



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

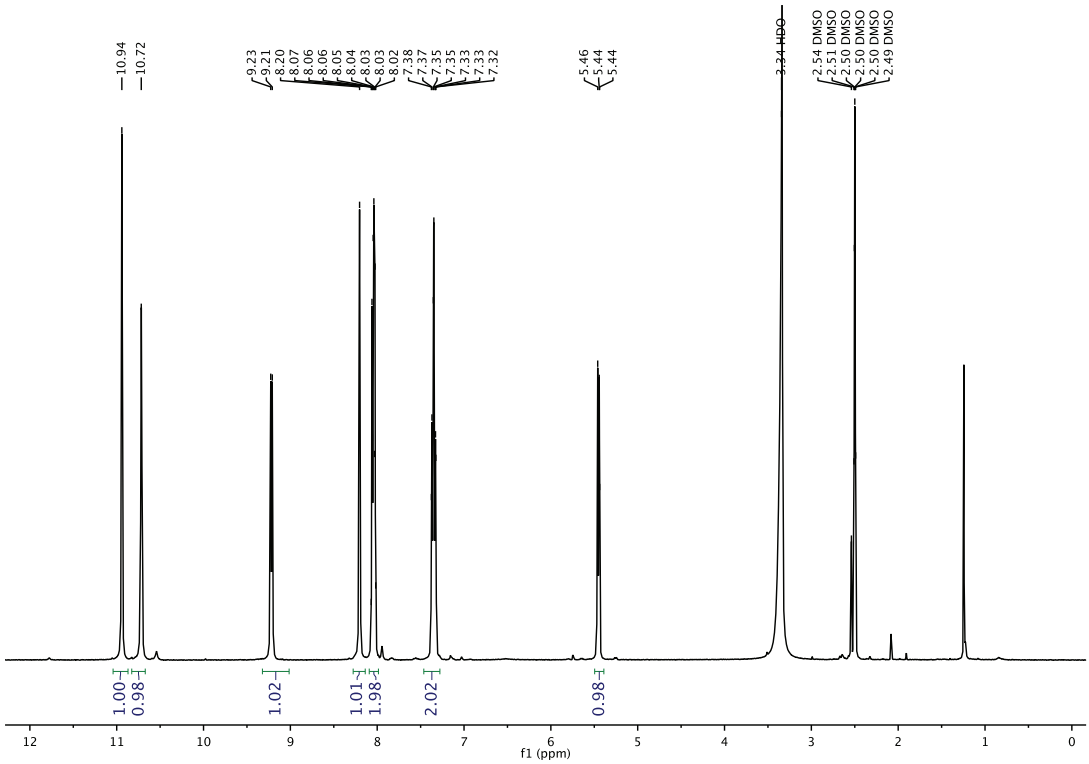


***N*-((2,5-Dioxoimidazolidin-4-yl)carbamoyl)-4-fluorobenzamide (5e).**

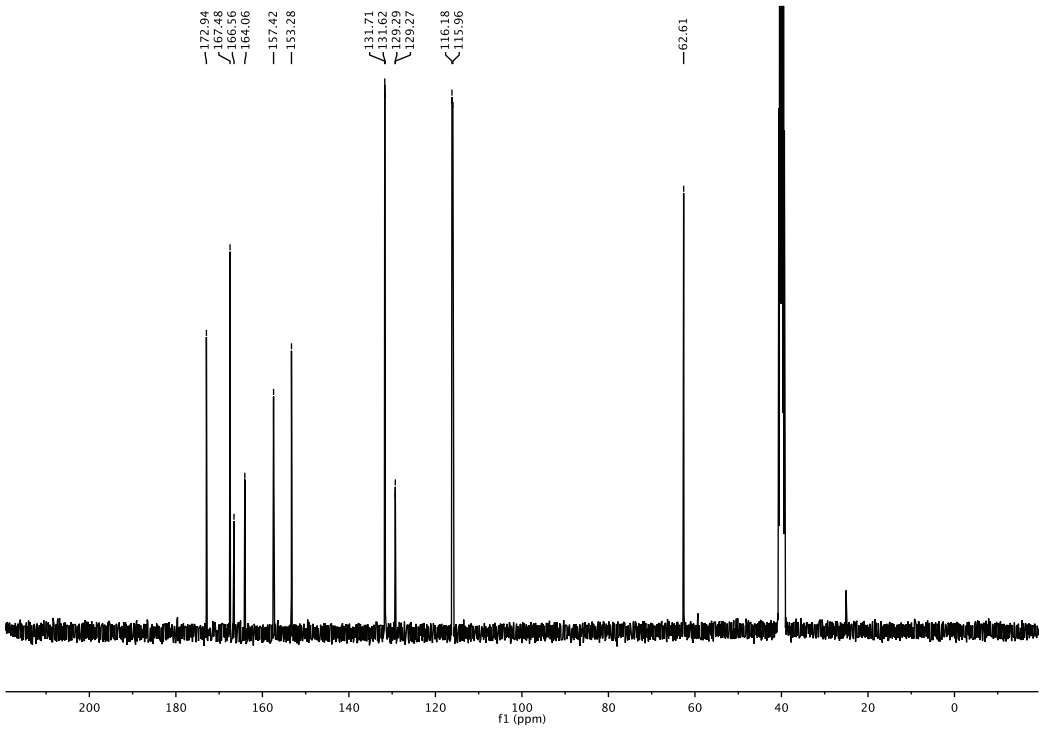


5e

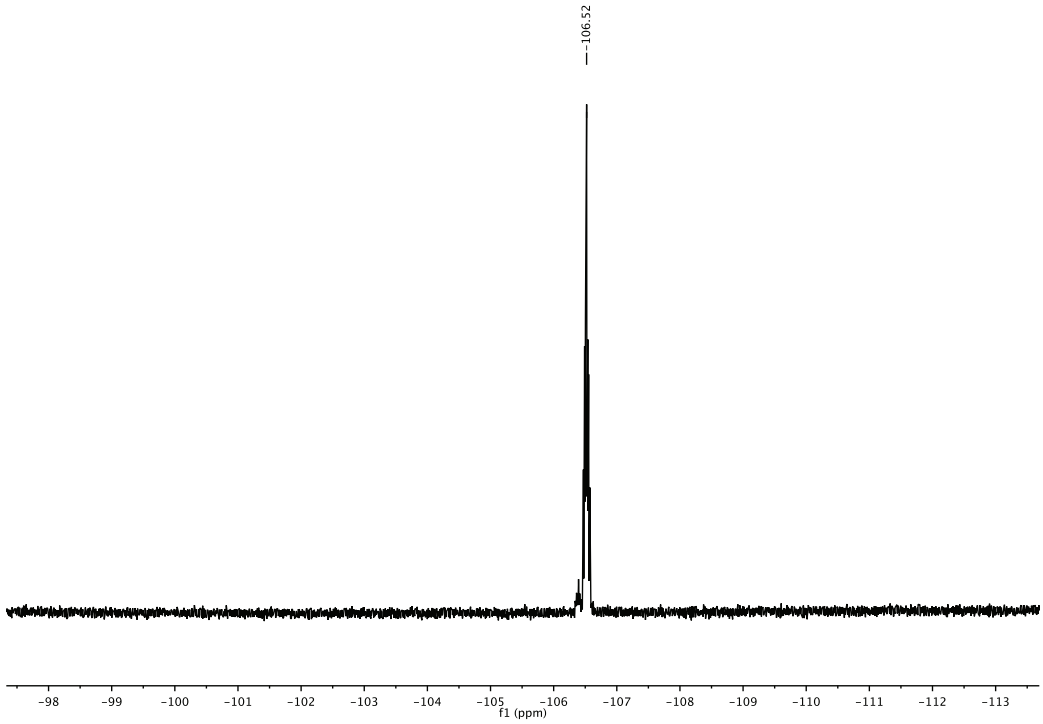
^{1}H NMR (400 MHz, DMSO-d_6)



^{13}C NMR (100 MHz, DMSO-d_6)

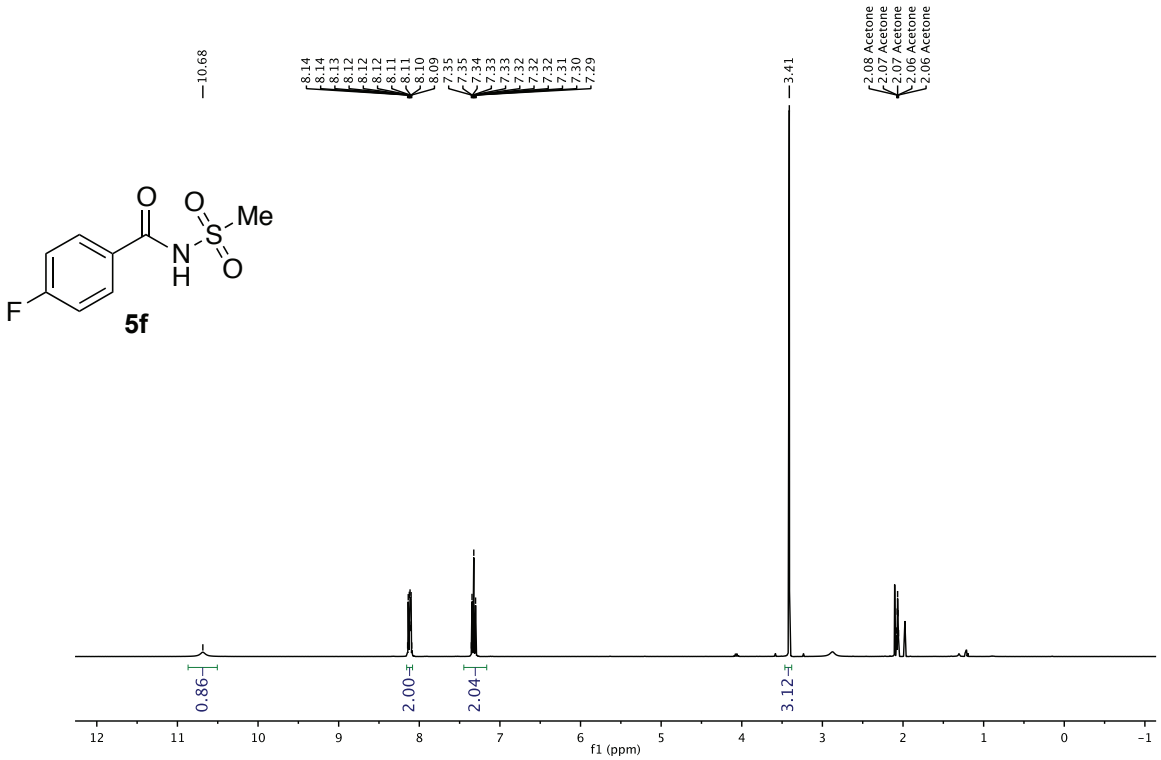


^{19}F NMR (282 MHz, DMSO-d_6)

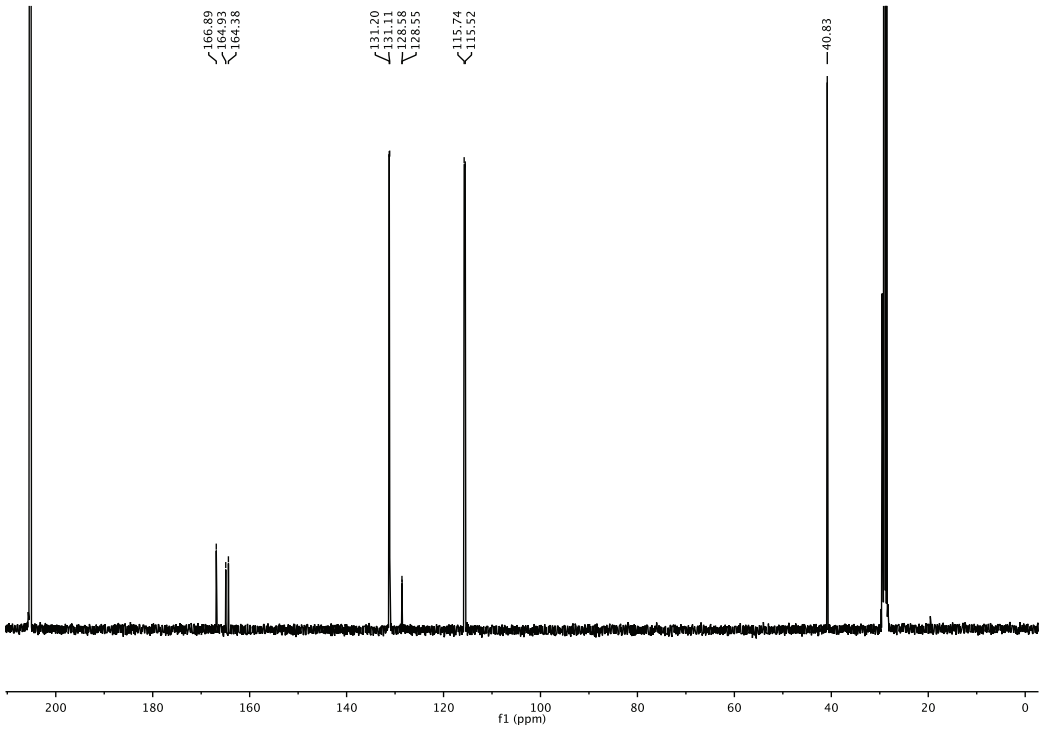


***N*-Methanesulfonyl-4-fluorobenzamide (5f).**

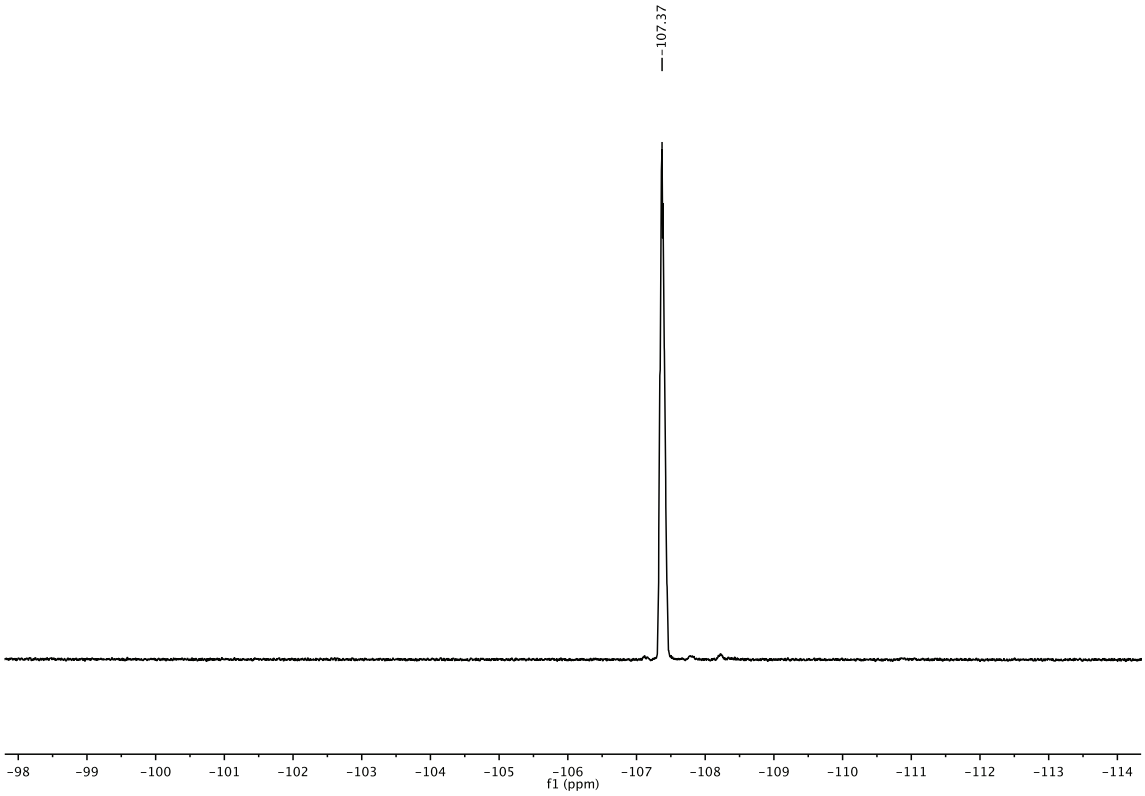
^{1}H NMR (400 MHz, $(CD_3)_2CO$)



^{13}C NMR (100 MHz, $(CD_3)_2CO$)

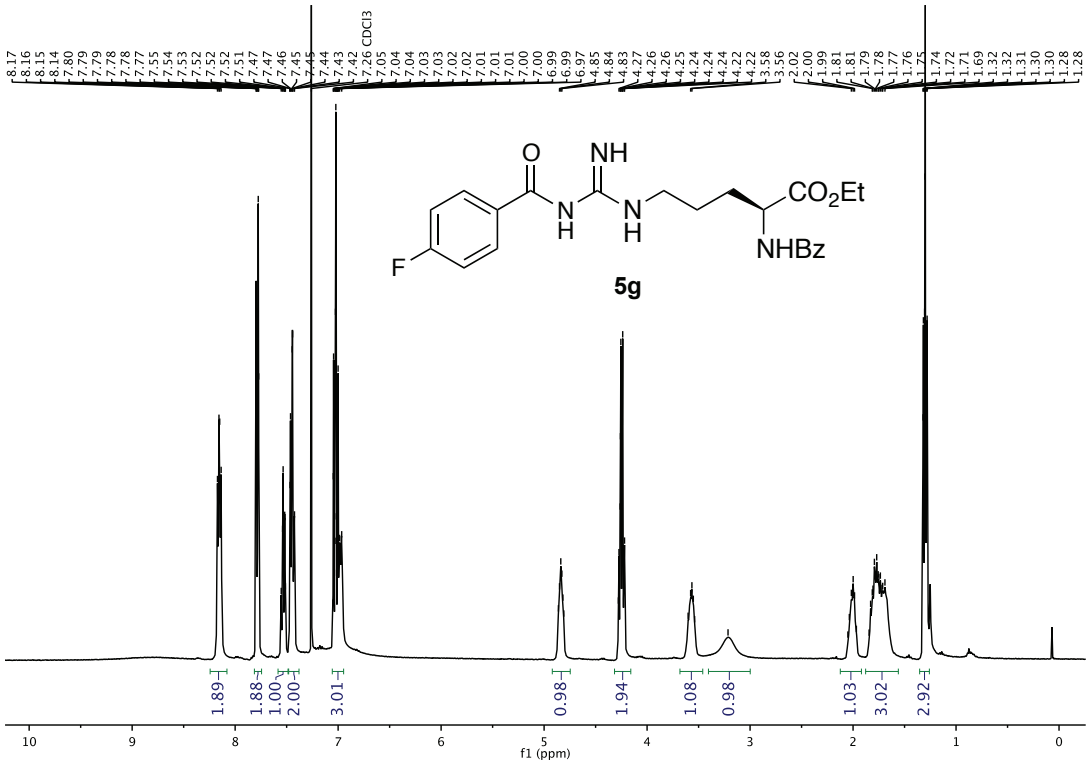


^{19}F NMR (377 MHz, $(CD_3)_2CO$)

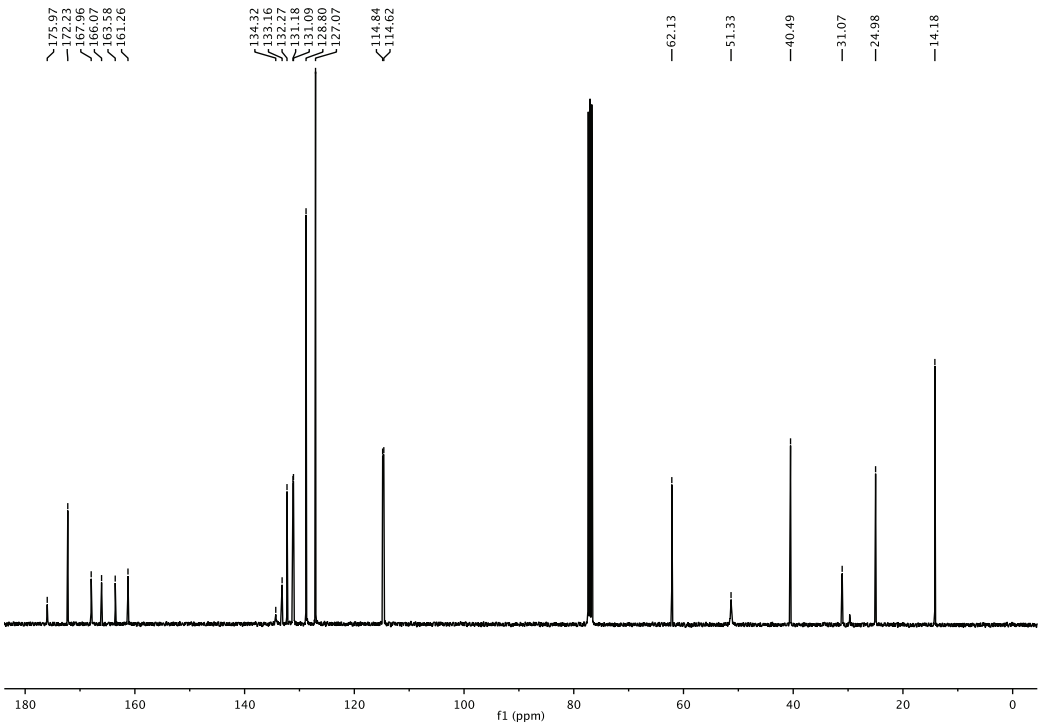


N^{α}-Benzoyl-N^{ω}-(4-fluorobenzoyl)-L-arginine ethyl ester 5g.

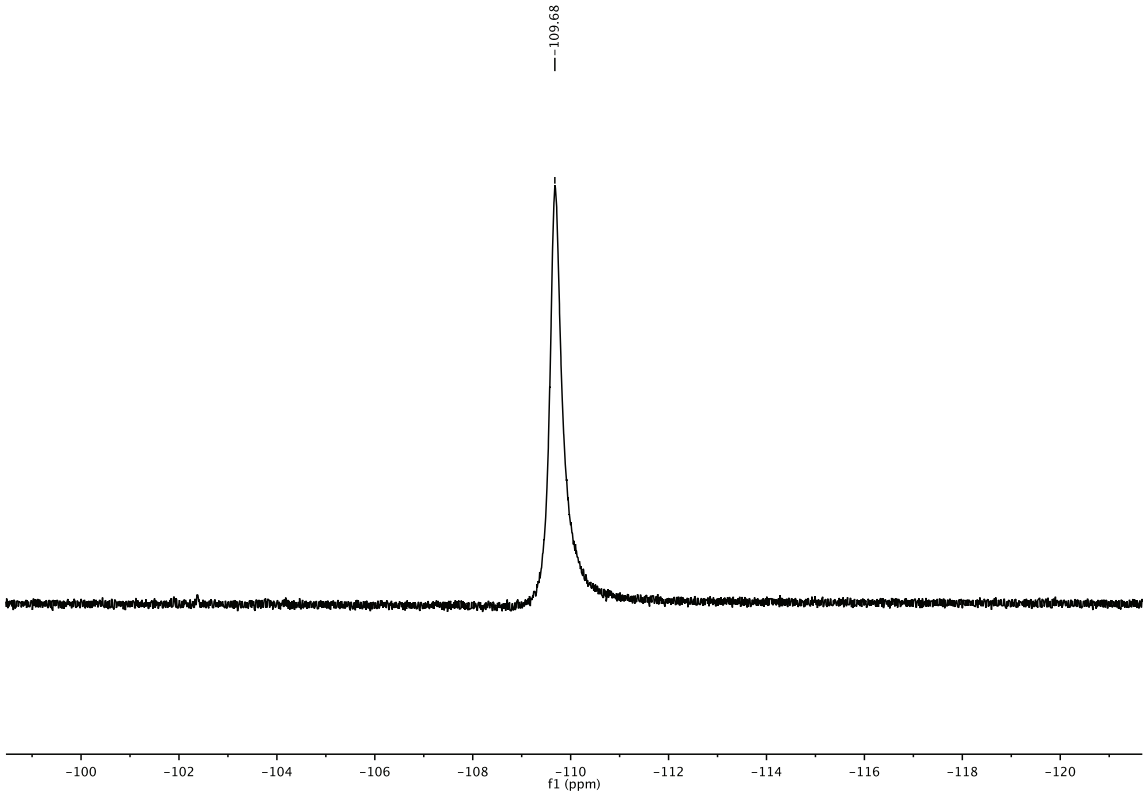
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)

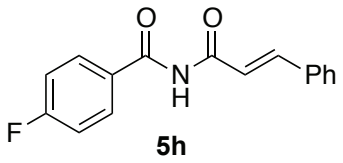


^{19}F NMR (377 MHz, $CDCl_3$)

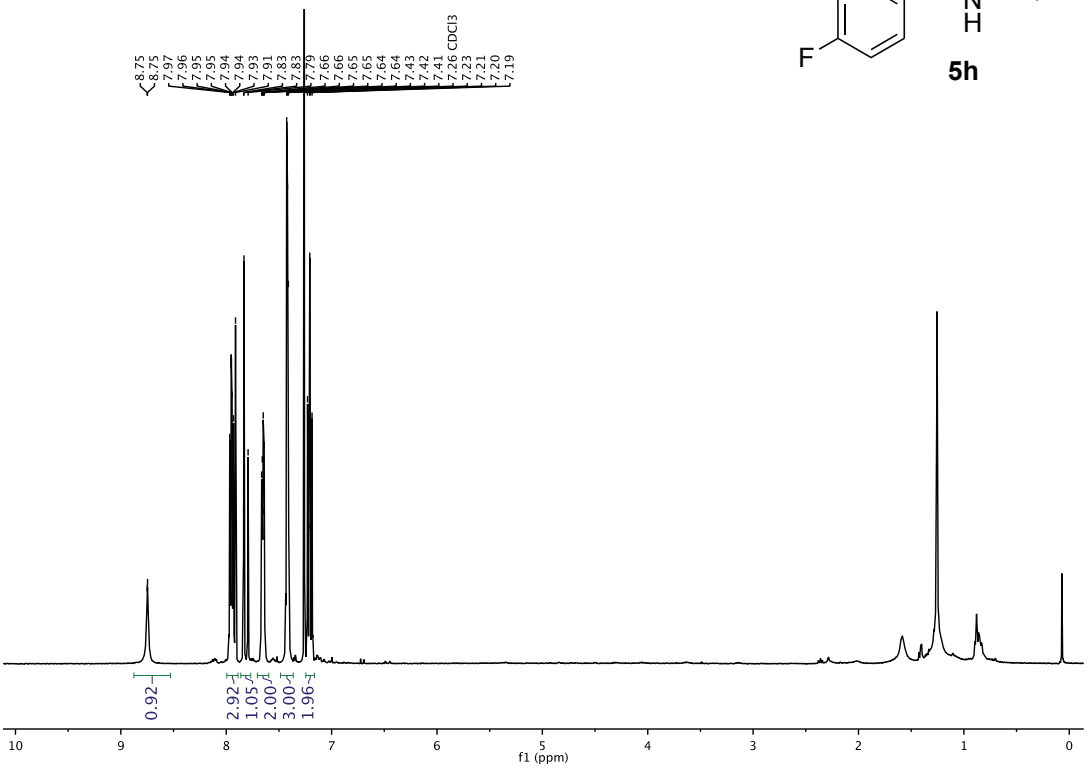


***N*-(*E*)-Cinnamoyl-4-fluorobenzamide (5h).**

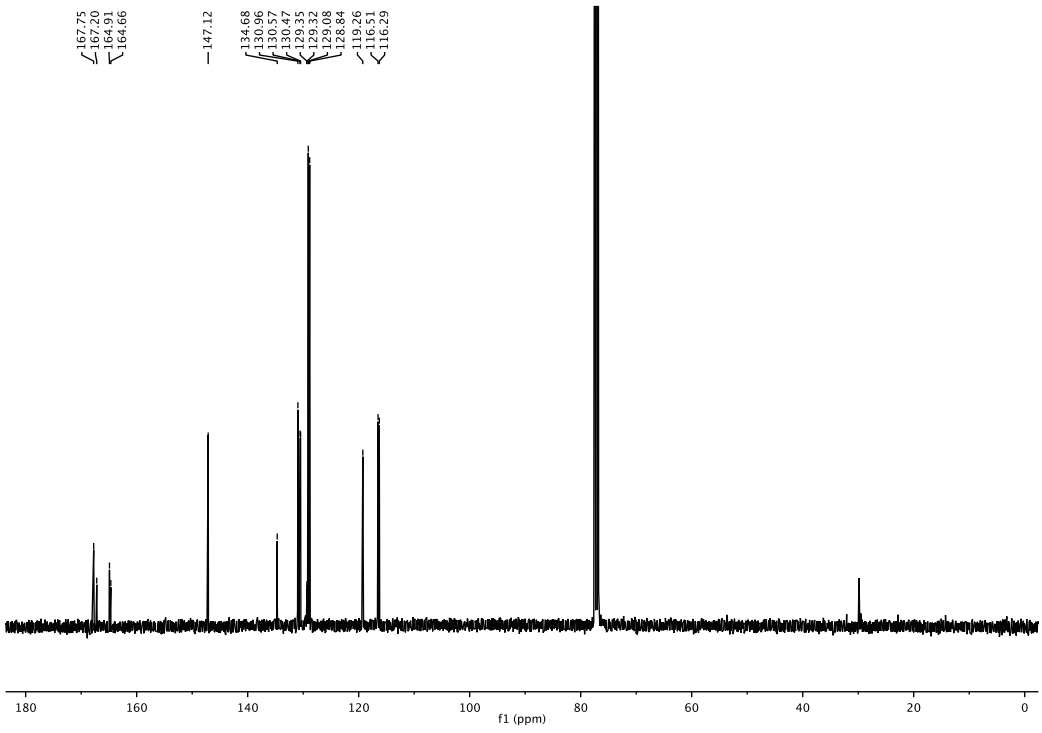
^{1}H NMR (400 MHz, $CDCl_3$)



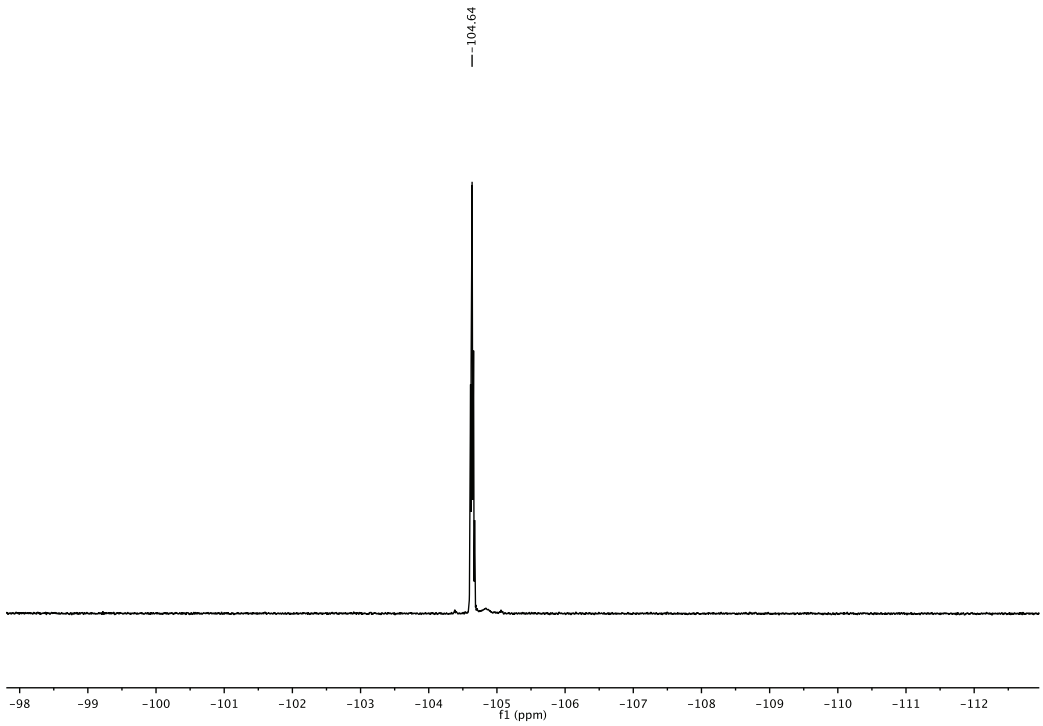
5h



^{13}C NMR (100 MHz, $CDCl_3$)

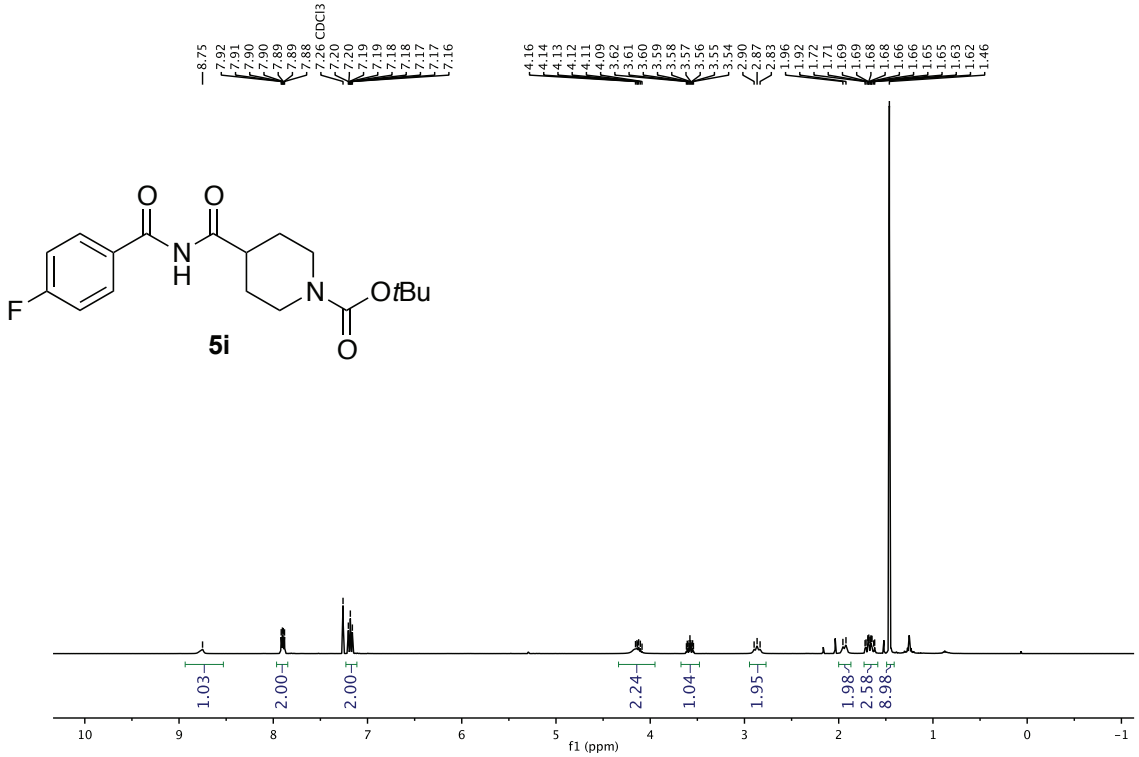


^{19}F NMR (377 MHz, $CDCl_3$)

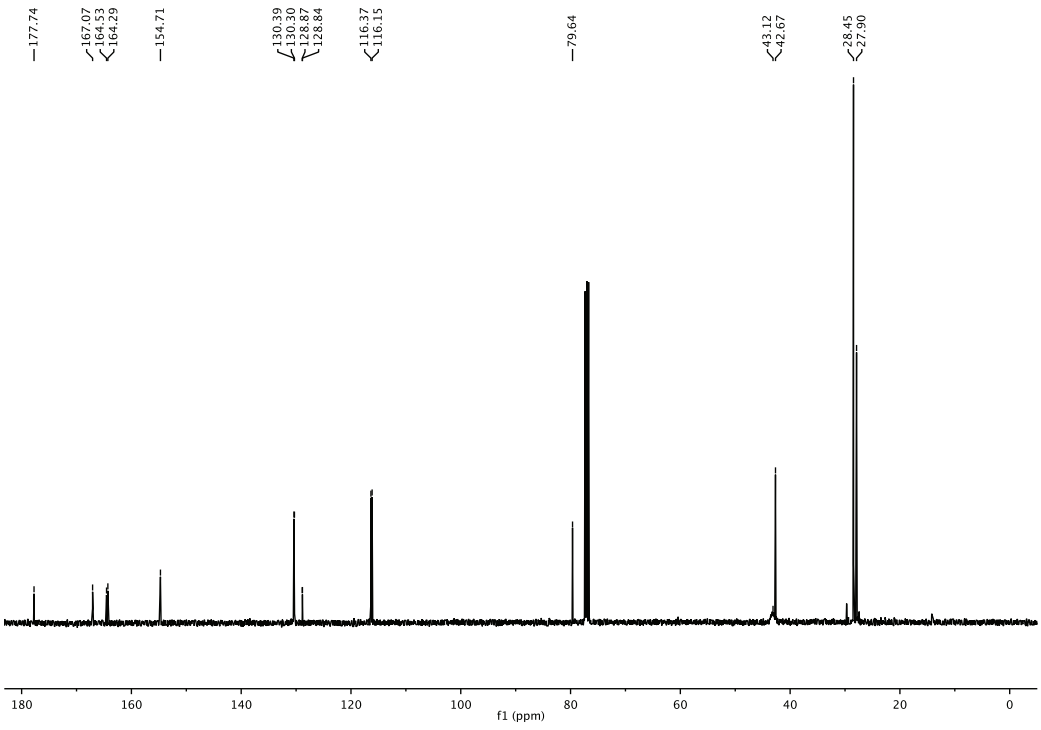


***tert*-Butyl 4-((4-fluorobenzoyl)carbamoyl)piperidine-1-carboxylate (5i).**

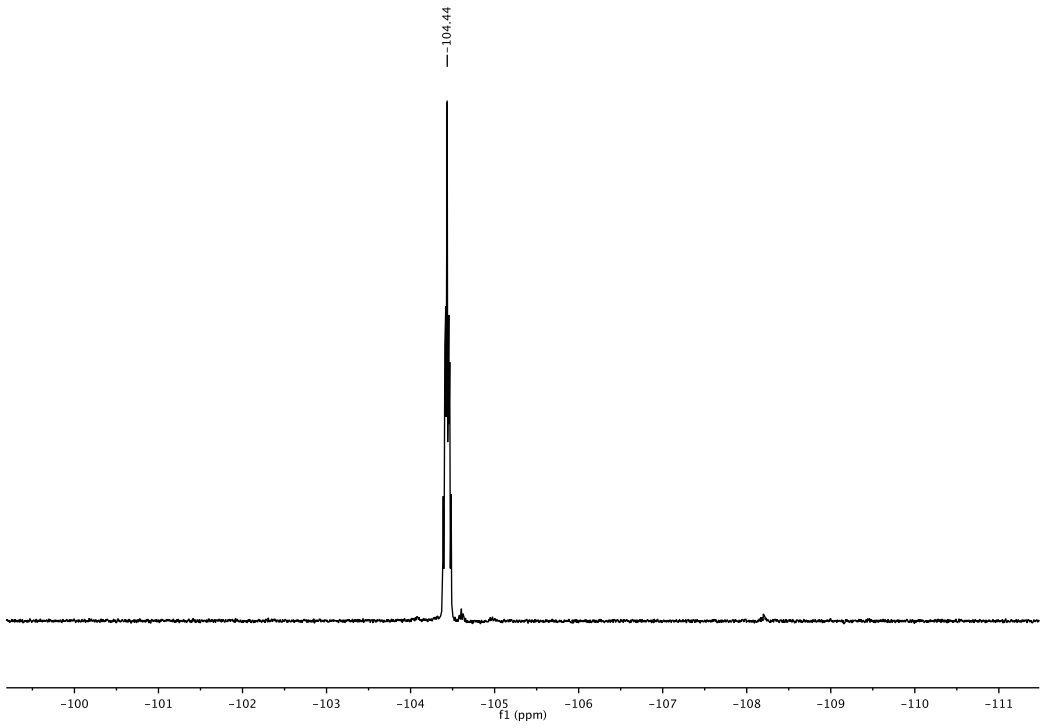
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)

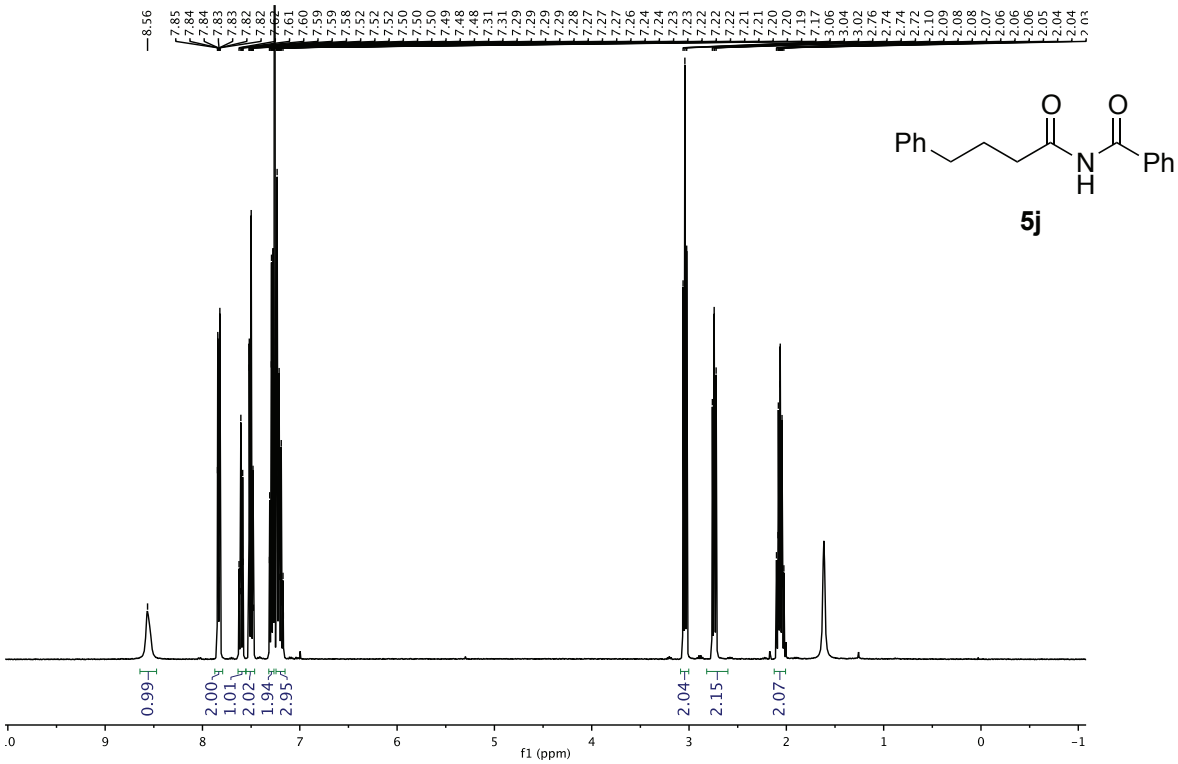


^{19}F NMR (377 MHz, $CDCl_3$)



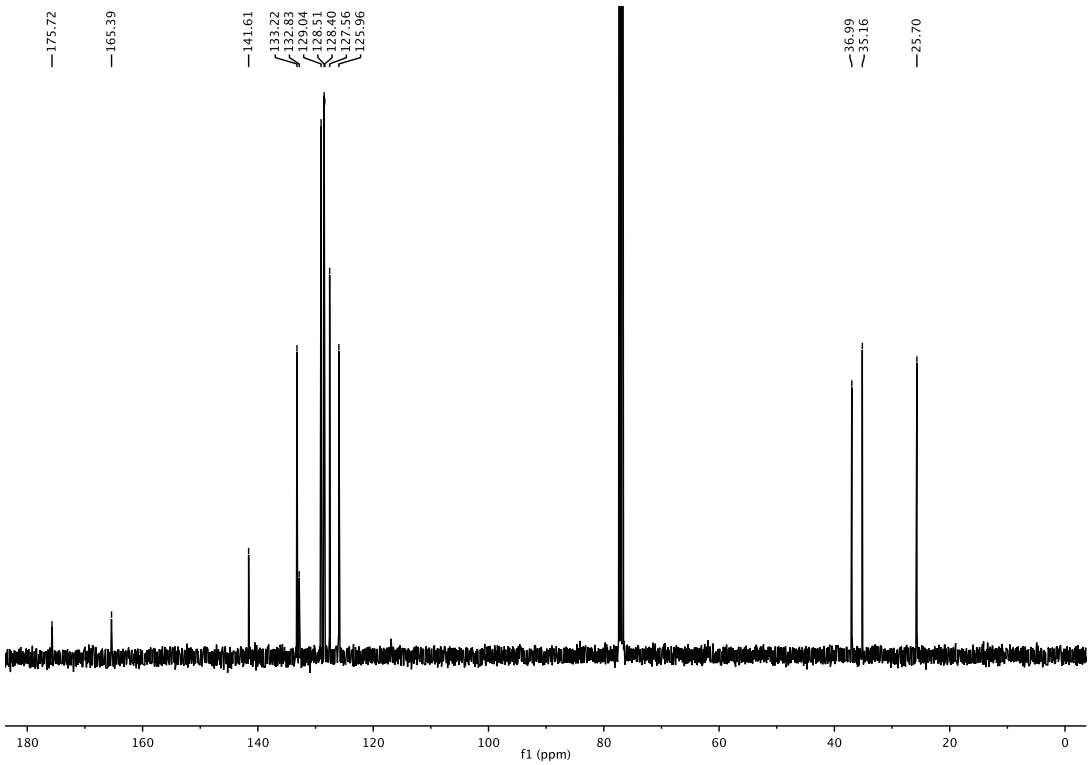
_N_-Benzoyl-4-phenylbutanamide (5j)

^{1}H NMR (400 MHz, $CDCl_3$)



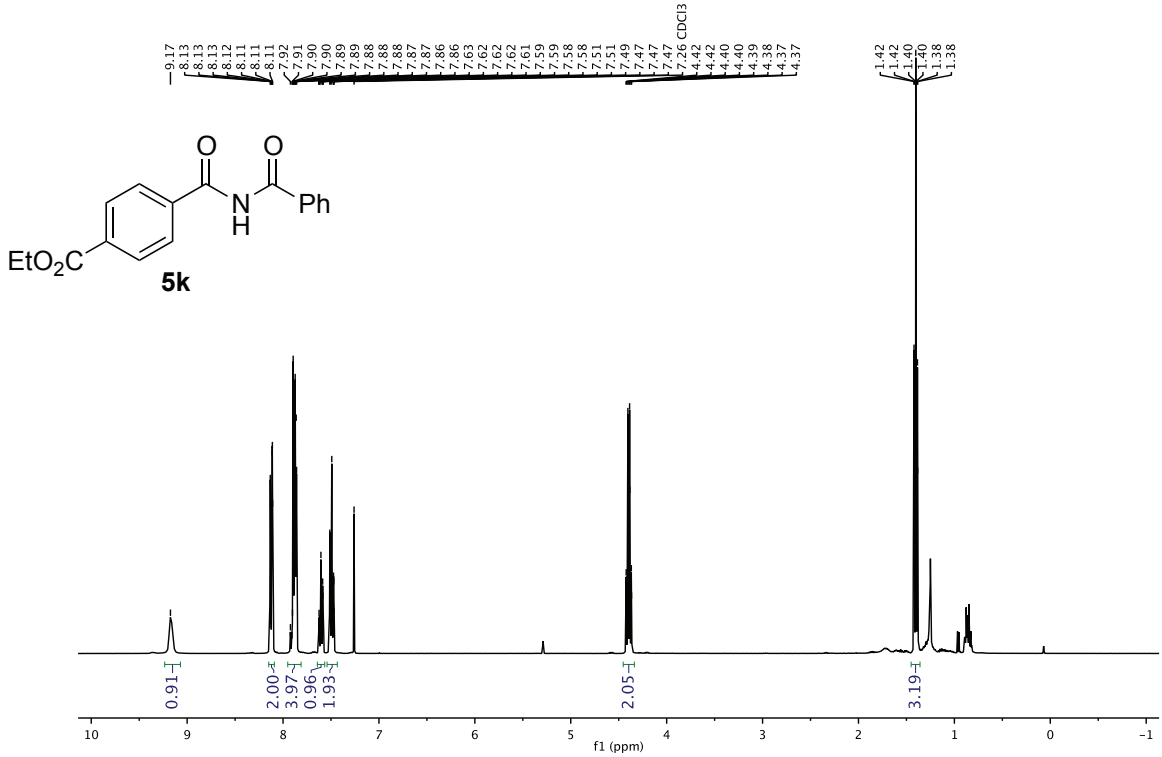
5j

^{13}C NMR (100 MHz, $CDCl_3$)

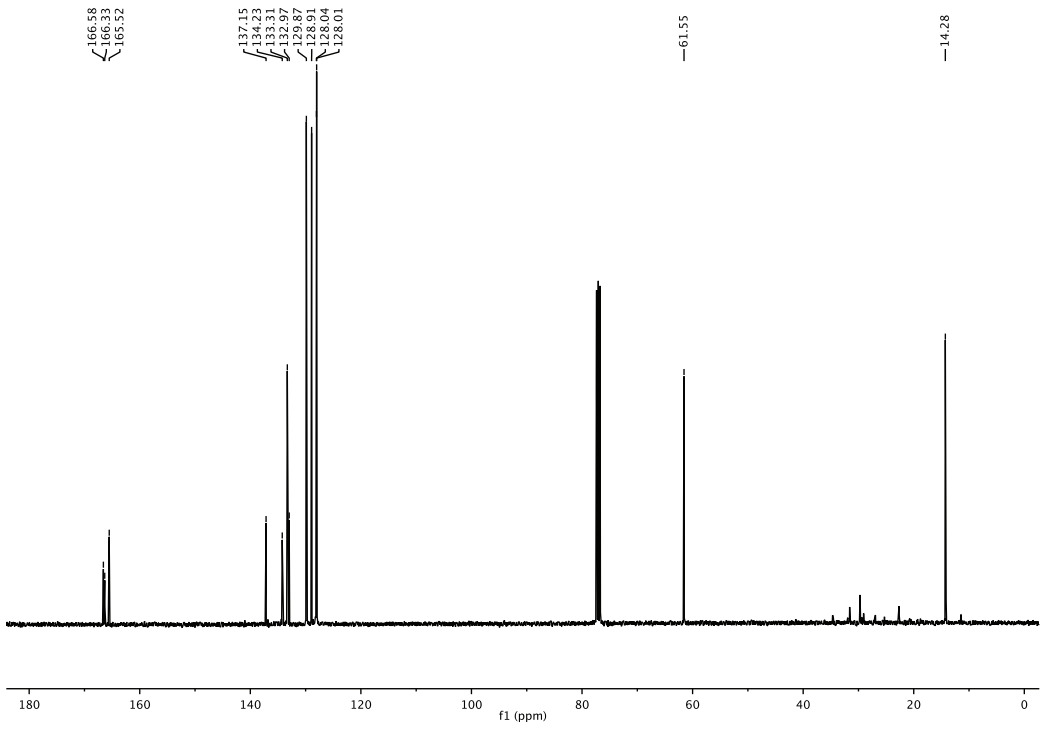


Ethyl 4-(benzoylcarbamoyl)benzoate (5k)

^{1}H NMR (400 MHz, $CDCl_3$)

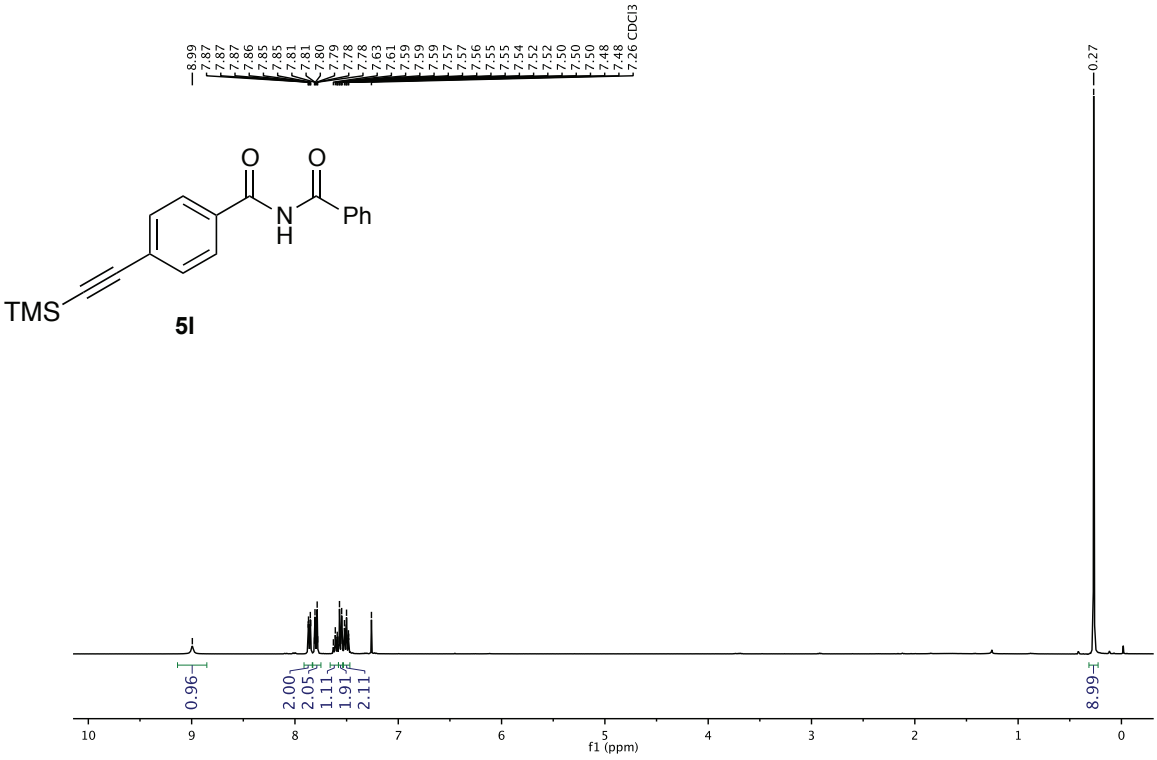


^{13}C NMR (100 MHz, $CDCl_3$)

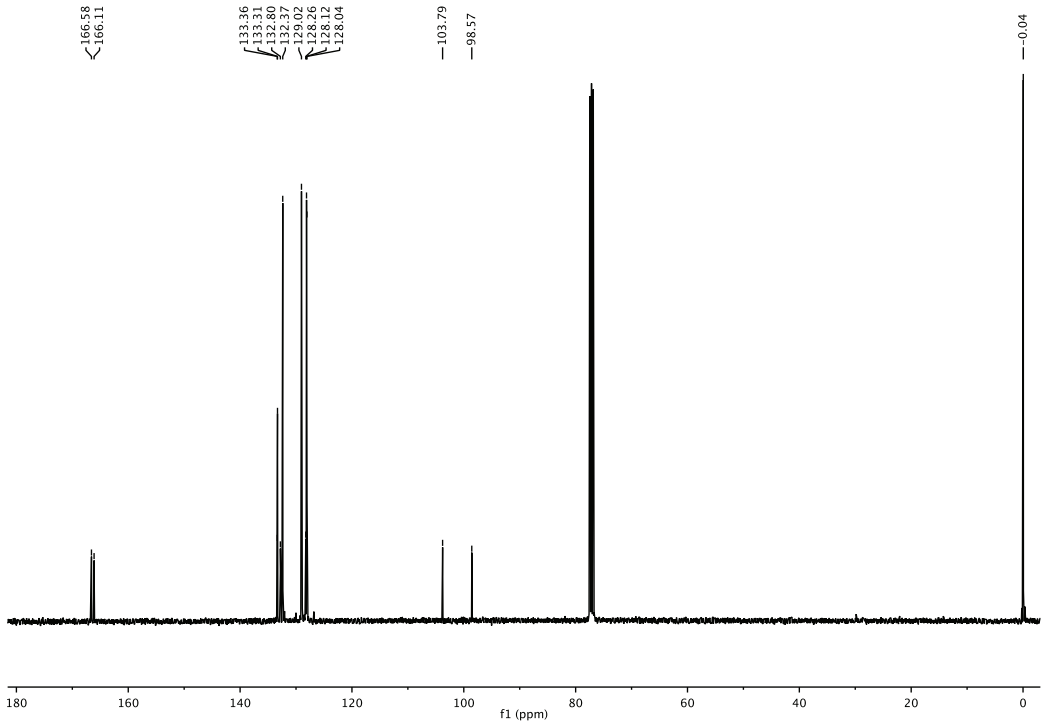


***N*-Benzoyl-4-(2-trimethylsilylethynyl)benzamide (5l).**

^{1}H NMR (400 MHz, $CDCl_3$)

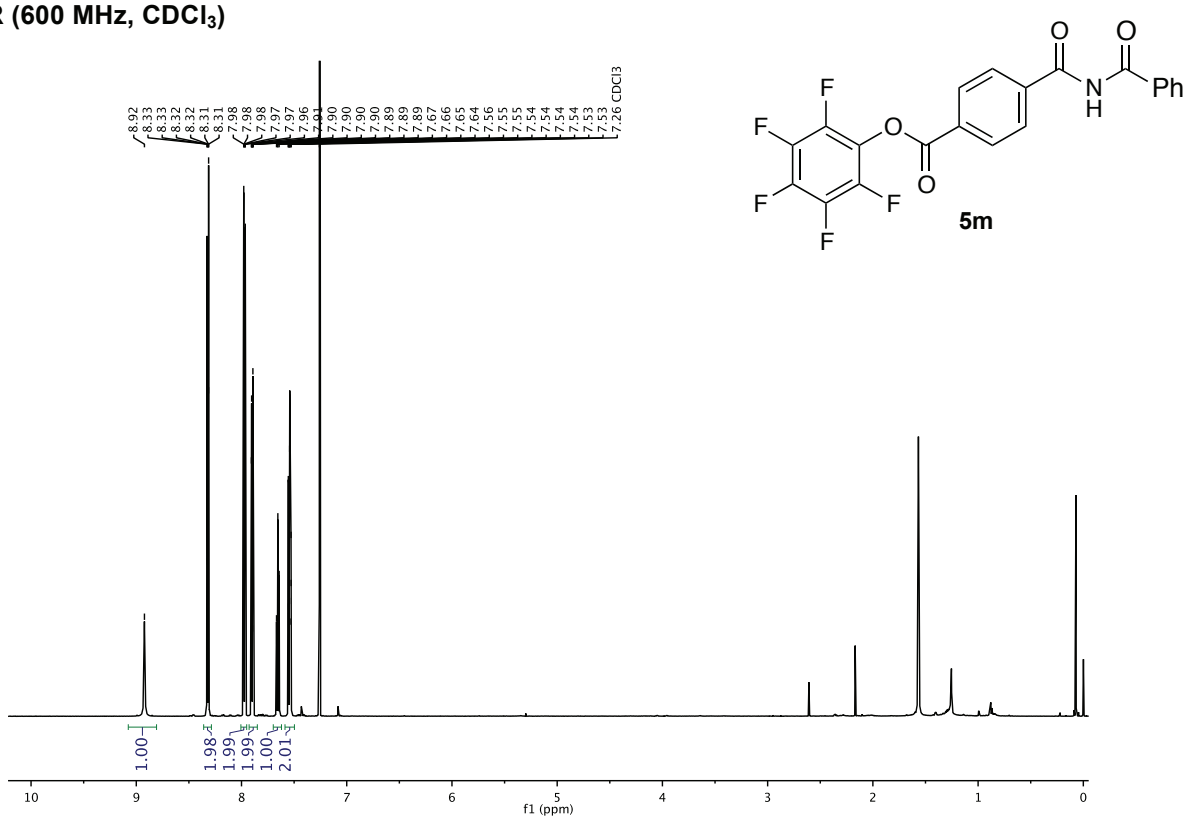


^{13}C NMR (100 MHz, $CDCl_3$)



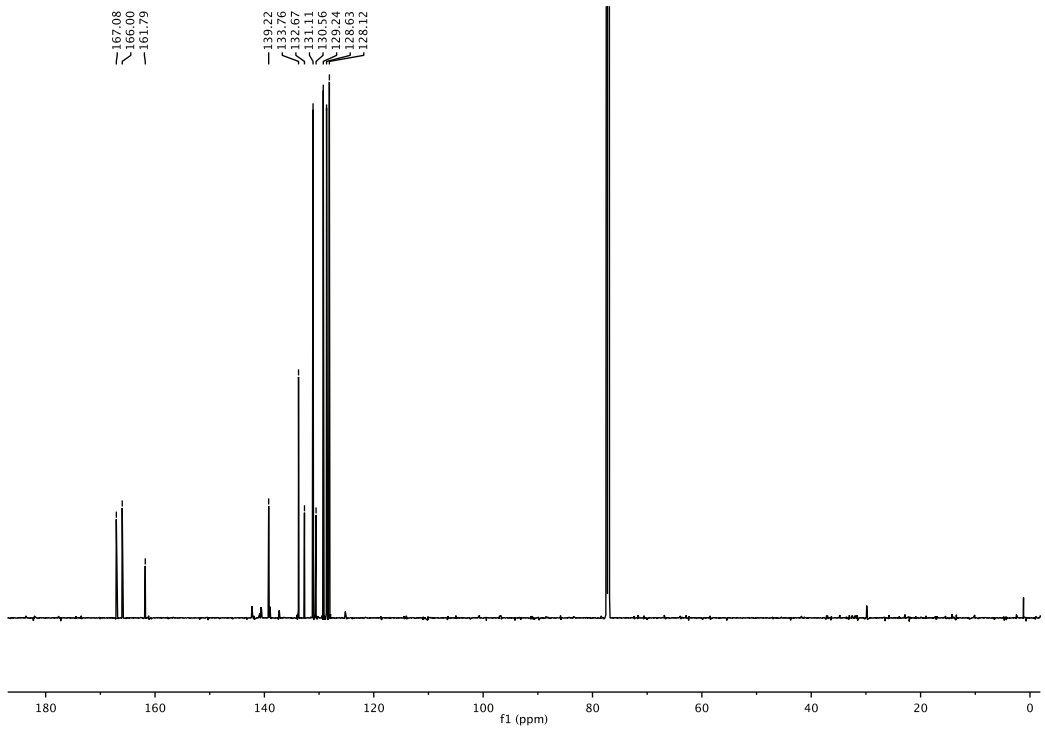
Pentafluorophenyl 4-(*N*-benzoylcarbamoyl)benzoate (5m).

^{1}H NMR (600 MHz, $CDCl_3$)

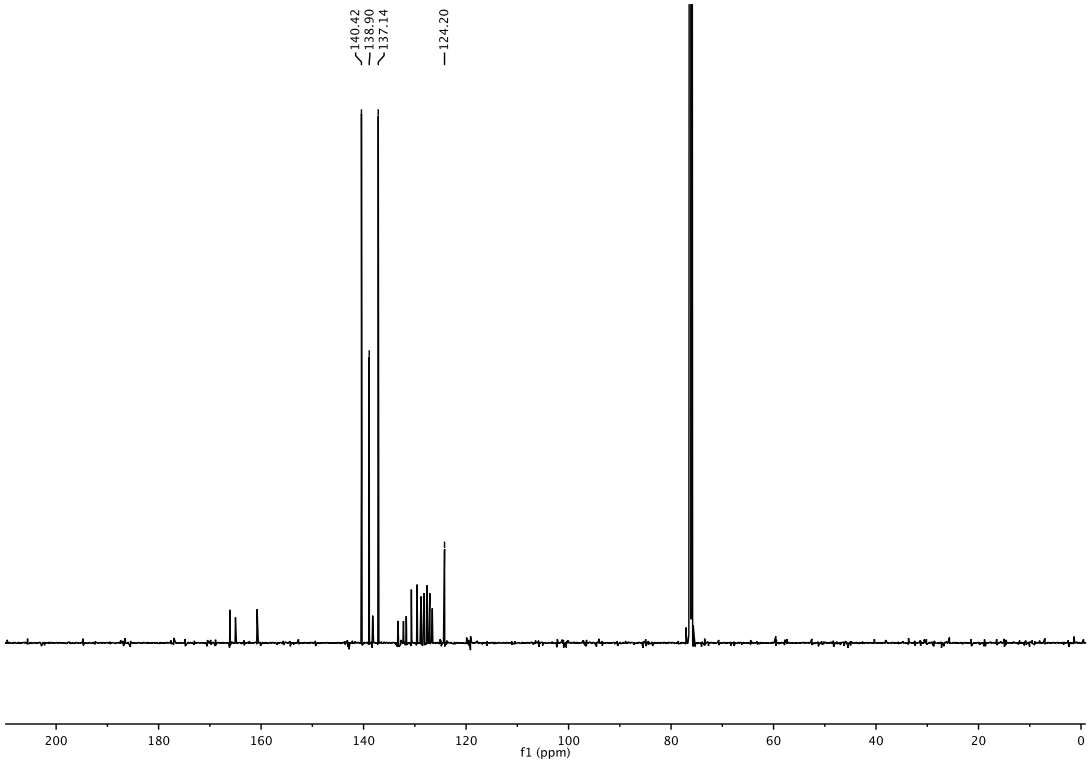


5m

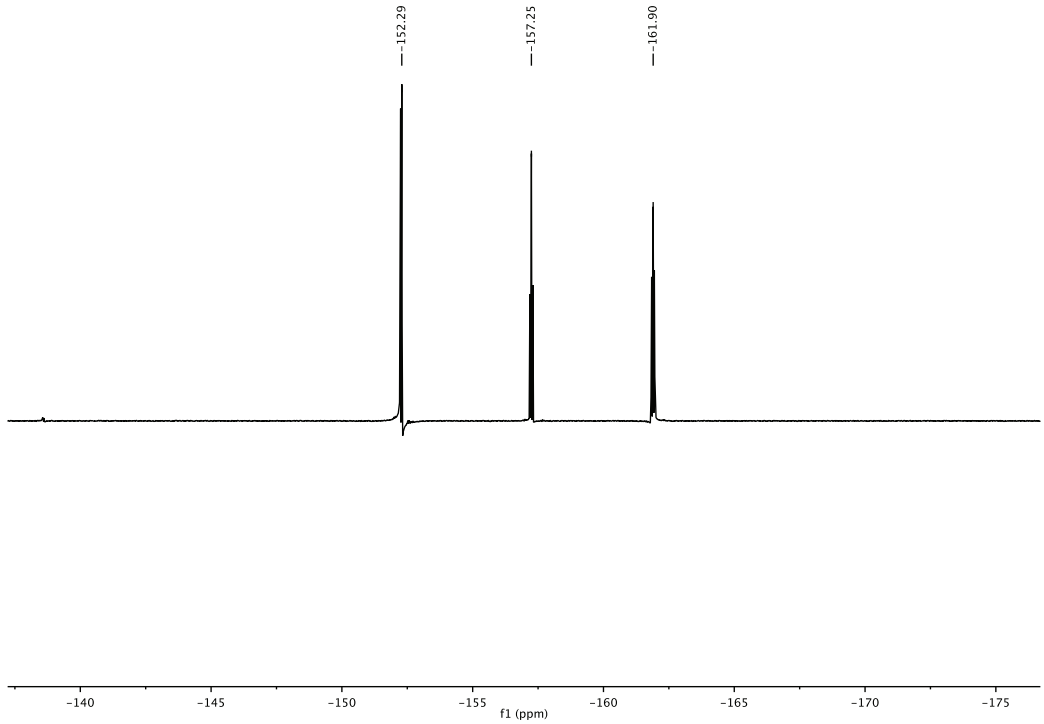
^{13}C NMR (150 MHz, $CDCl_3$)



^{13}C {^{19}F} NMR (150 MHz, $CDCl_3$)

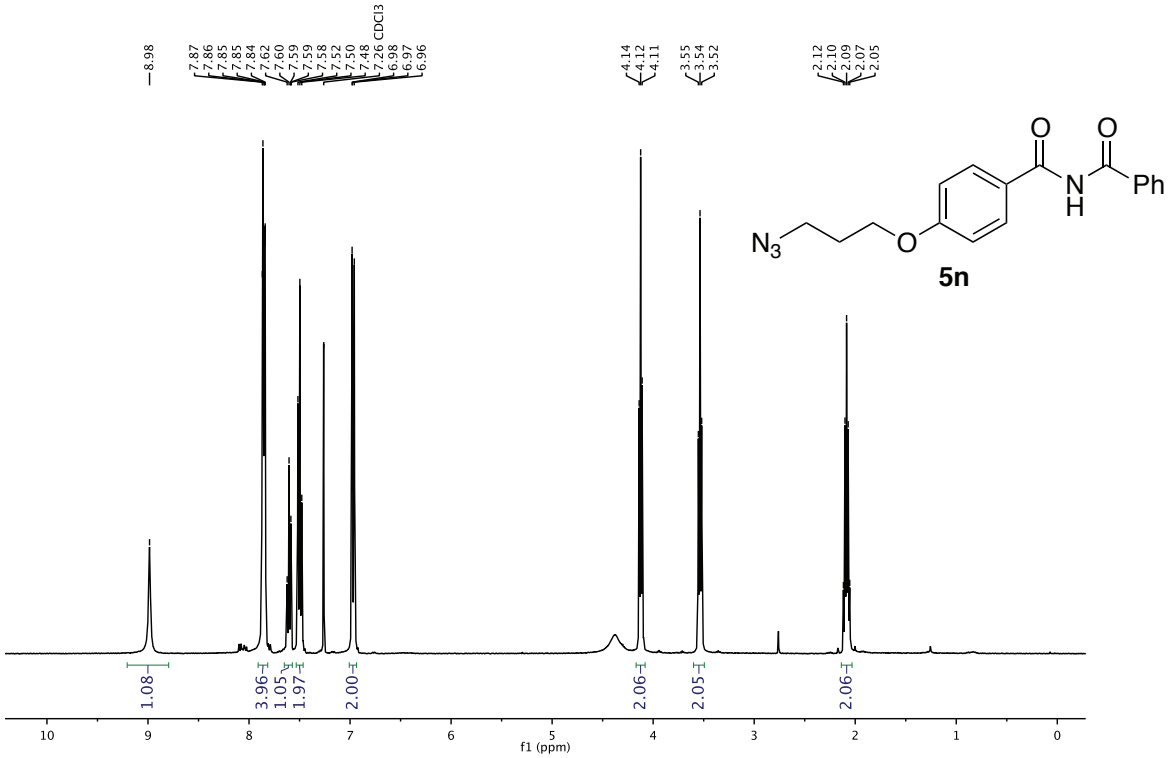


^{19}F NMR (377 MHz, $CDCl_3$)

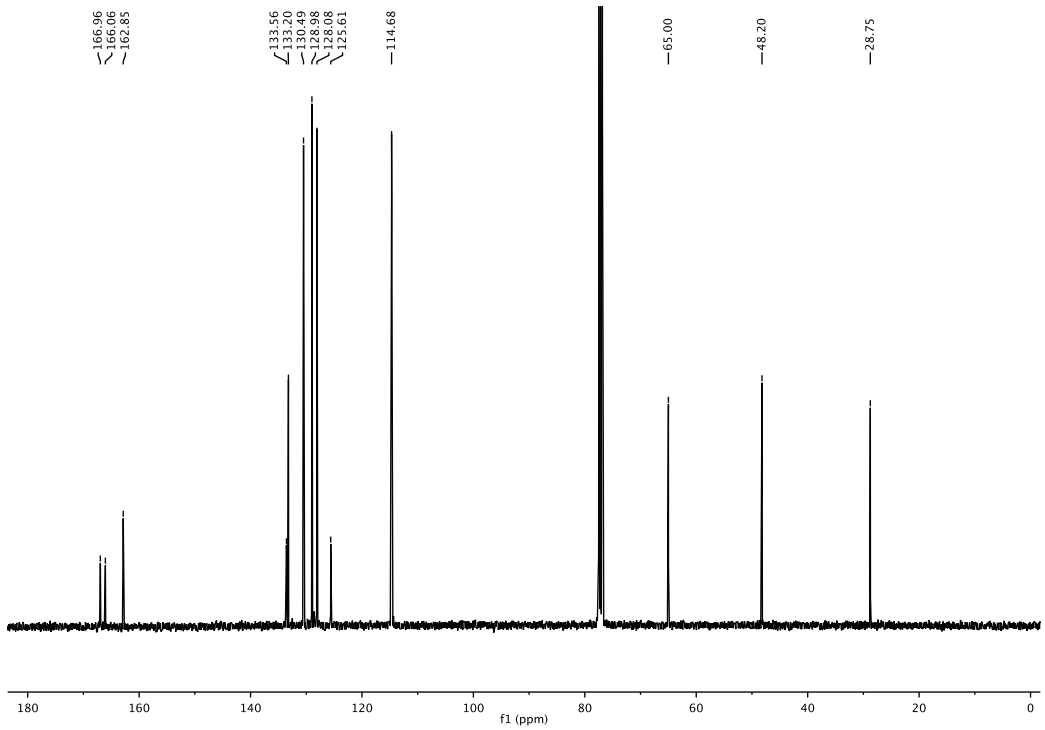


4-(3-Azidopropoxy)-*N*-benzoylbenzamide (5n).

^{1}H NMR (400 MHz, $CDCl_3$)

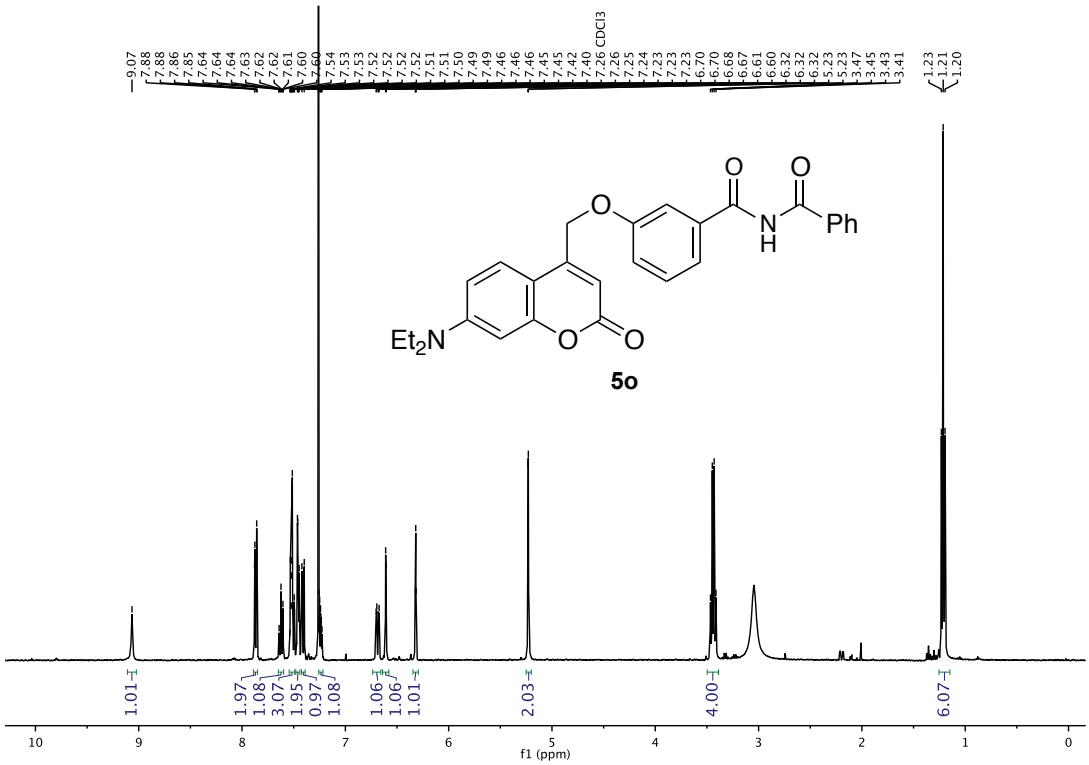


^{13}C NMR (100 MHz, $CDCl_3$)

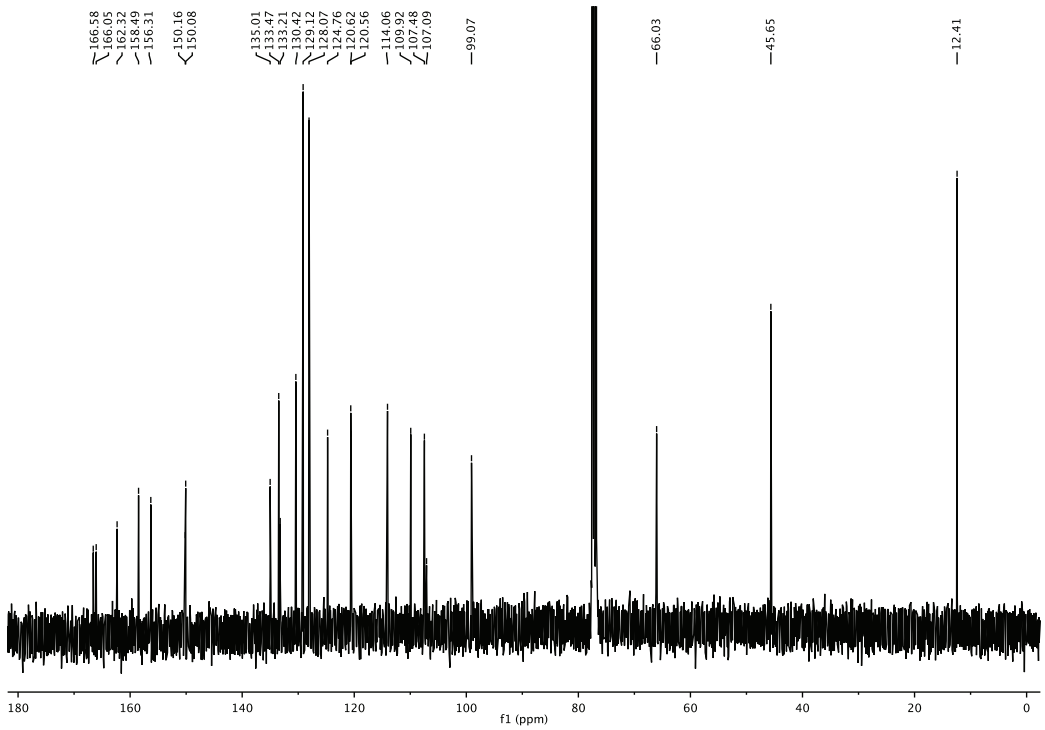


3-((7-(Diethylamino)-2-oxo-2*H*-chromen-4-yl)methoxy)-*N*-benzoylbenzamide (5o).

^{1}H NMR (400 MHz, $CDCl_3$)

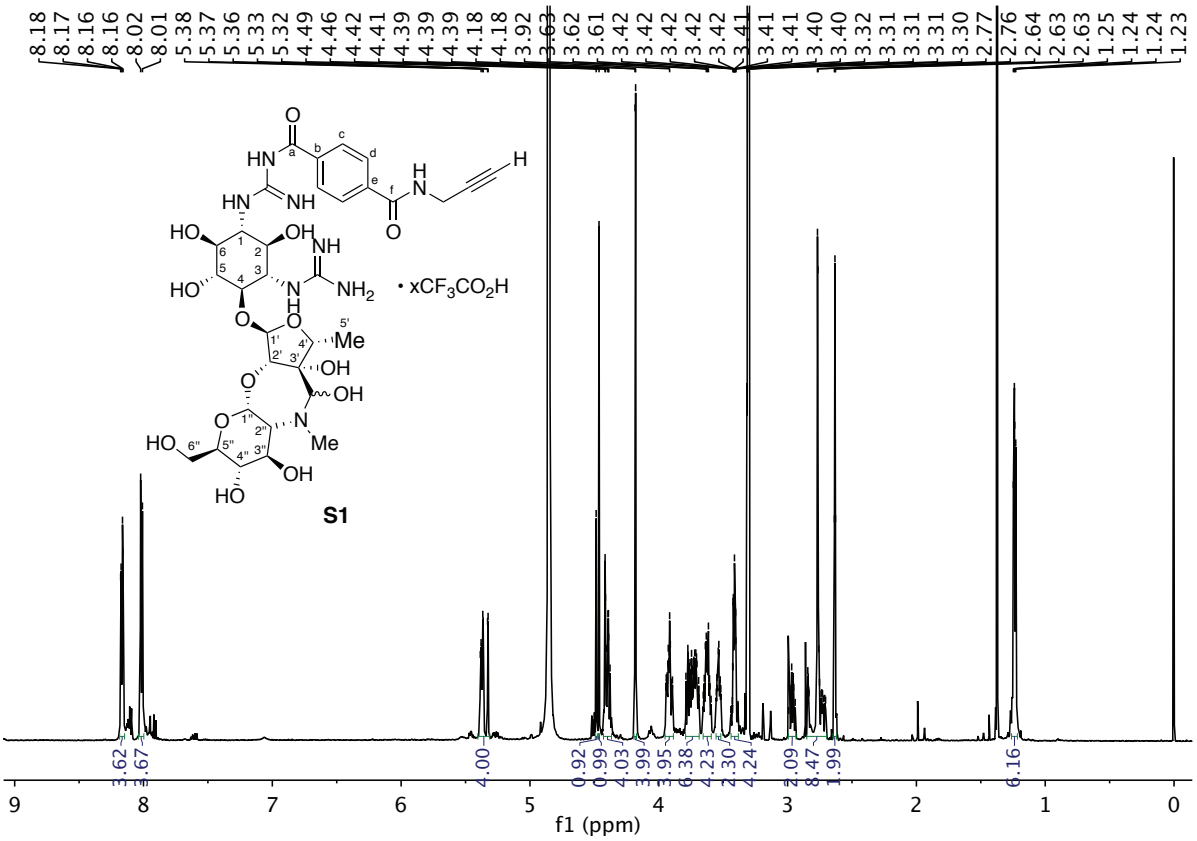


^{13}C NMR (100 MHz, $CDCl_3$)

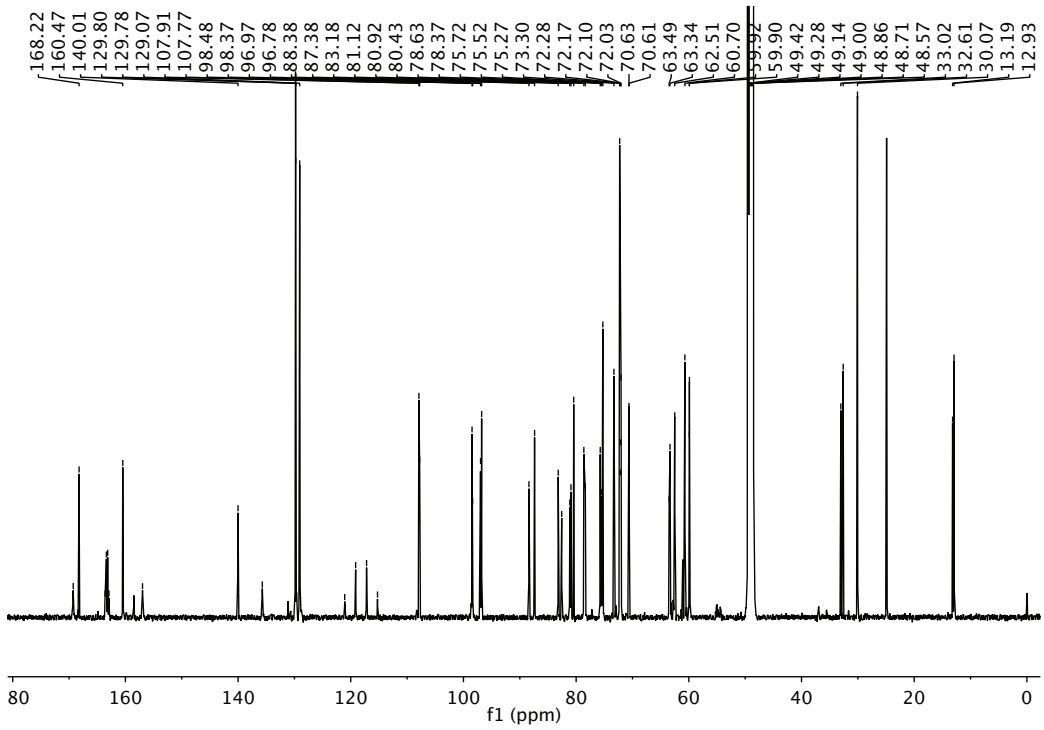


$N^G(C^1)$-(4-(N-propargylcarbamoyl)benzoyl)streptomycin sesquisulfate S1.

1H NMR (600 MHz, CD3OD)

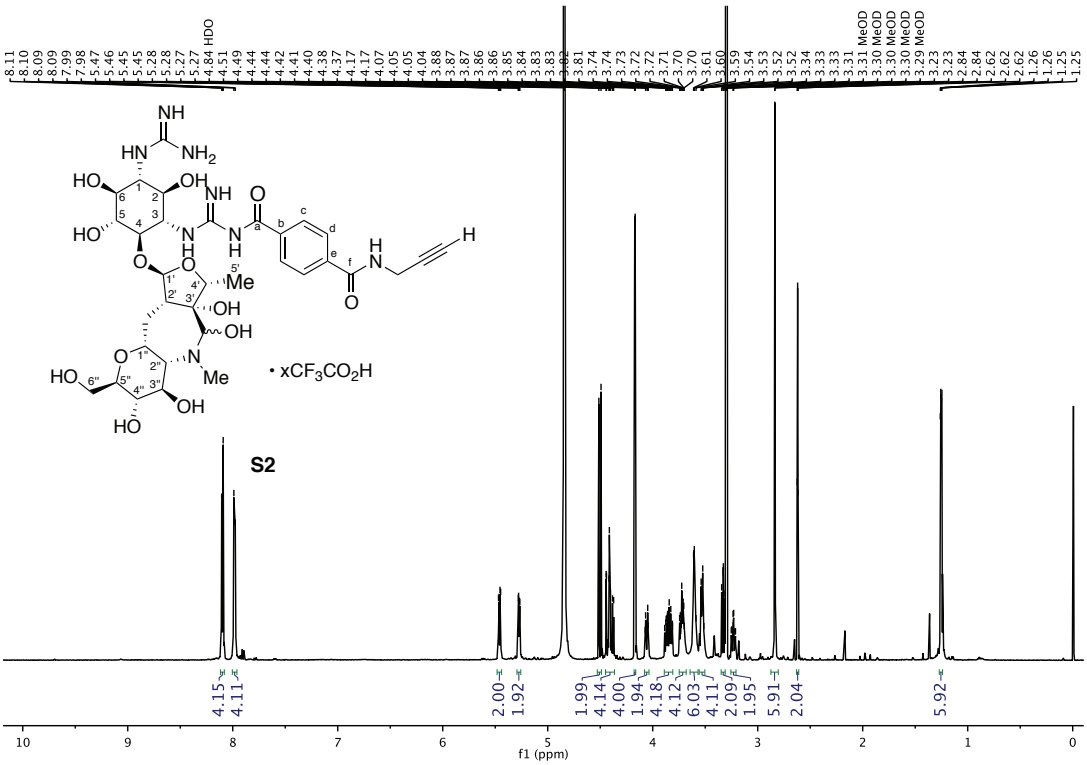


^{13}C NMR (150 MHz, CD_3OD)

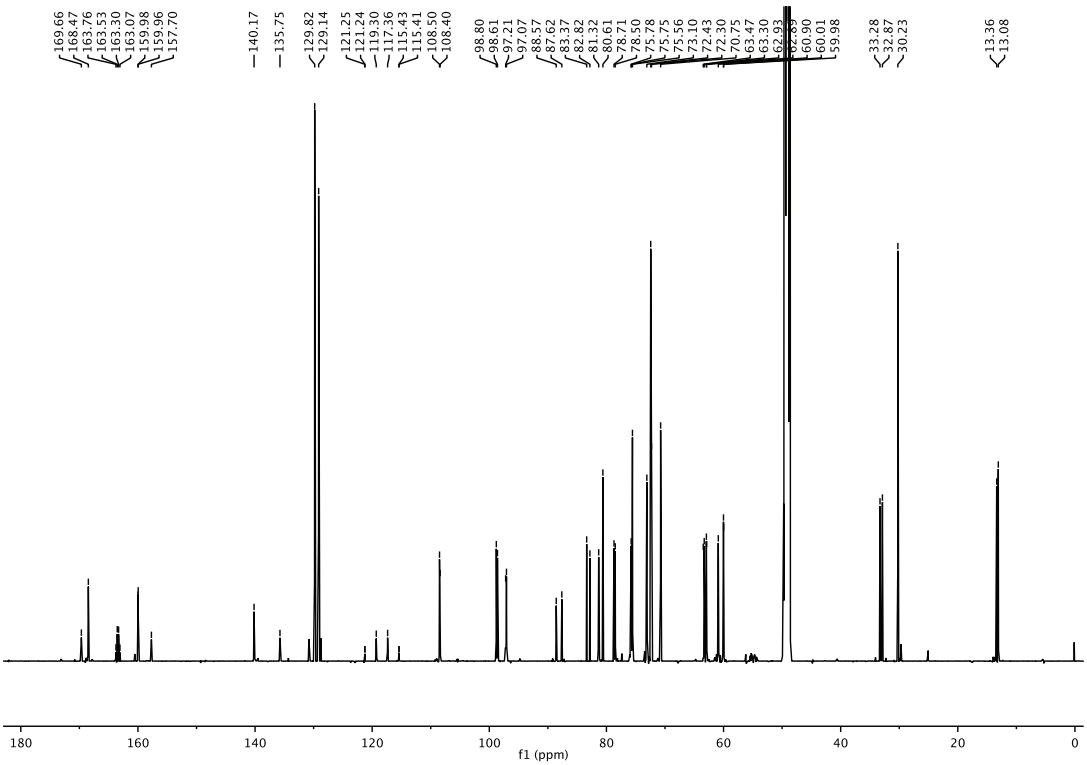


$N^G(C^3)$-(4-(*N*-propargylcarbamoyl)benzoyl)streptomycin sesquisulfate S2.

^{1}H NMR (600 MHz, CD_3OD)

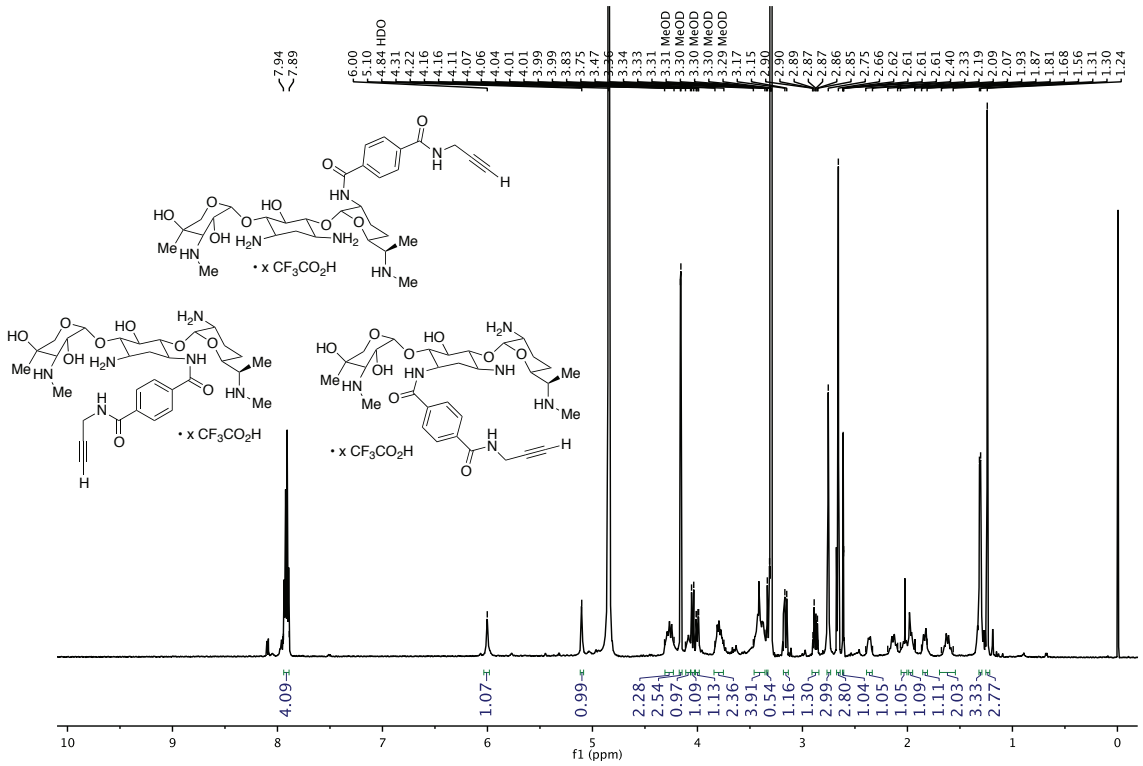


^{13}C NMR (150 MHz, CD_3OD)

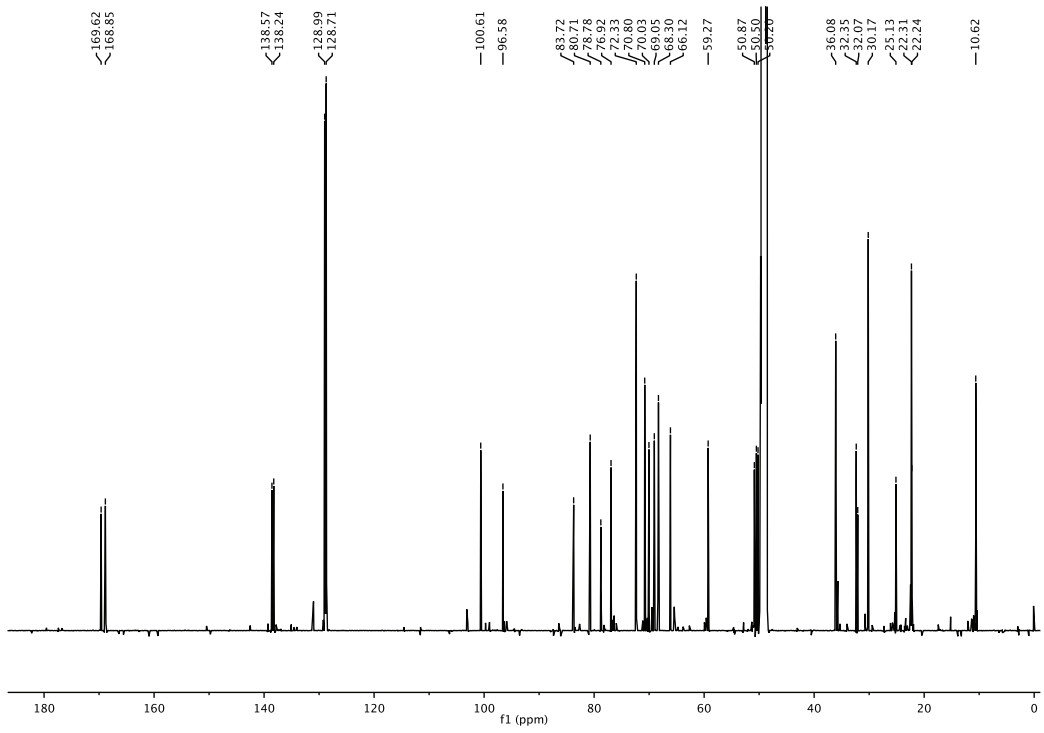


_N_-(4-(_N_-Propargylcarbamoyl)benzoyl)gentamicin C_1.

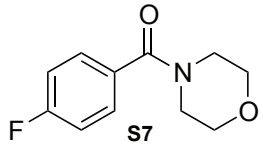
^{1}H NMR (600 MHz, CD_3OD)



^{13}C NMR (150 MHz, CD_3OD)

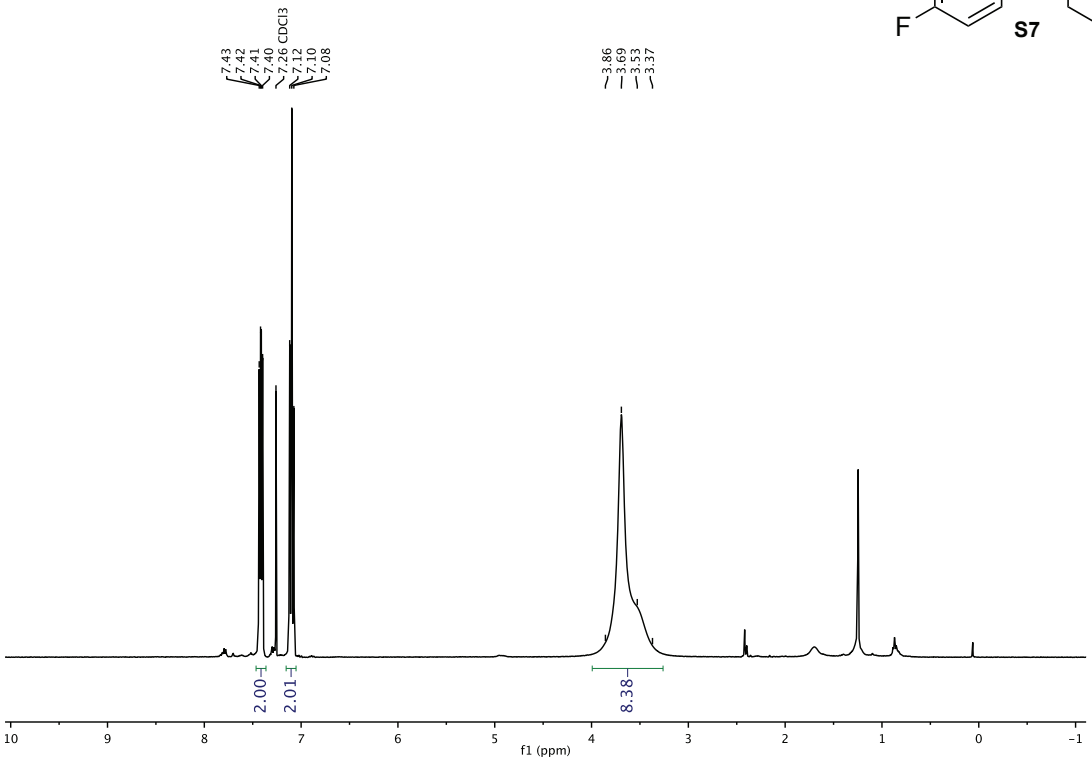


***N*-(4-Fluorobenzoyl)morpholine (S7).**

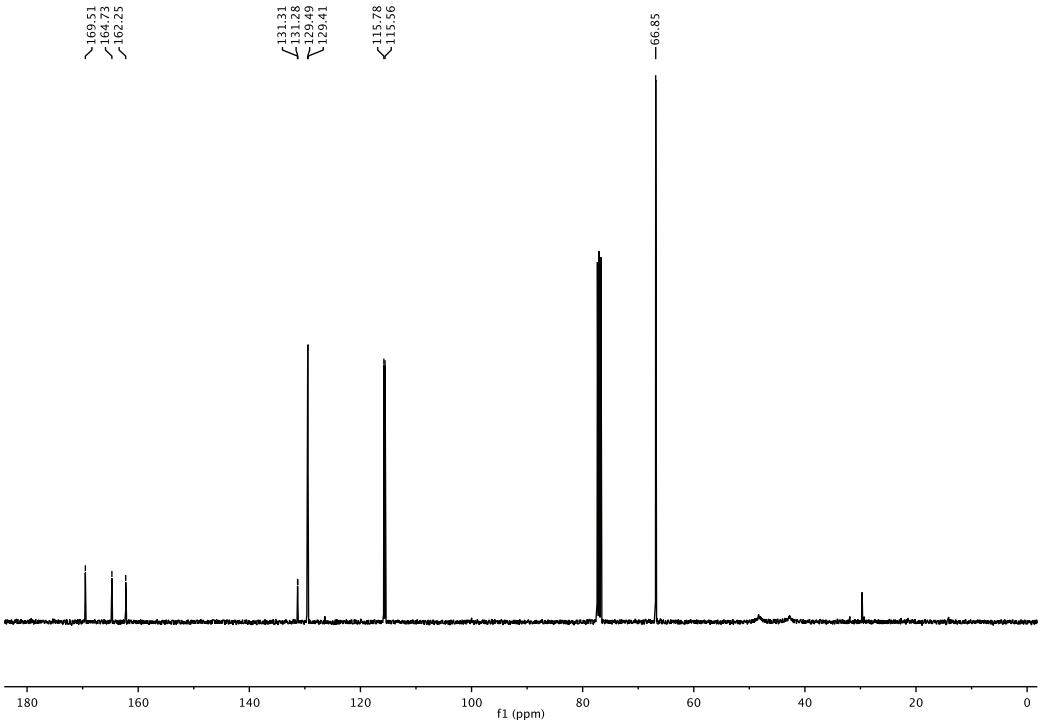


S7

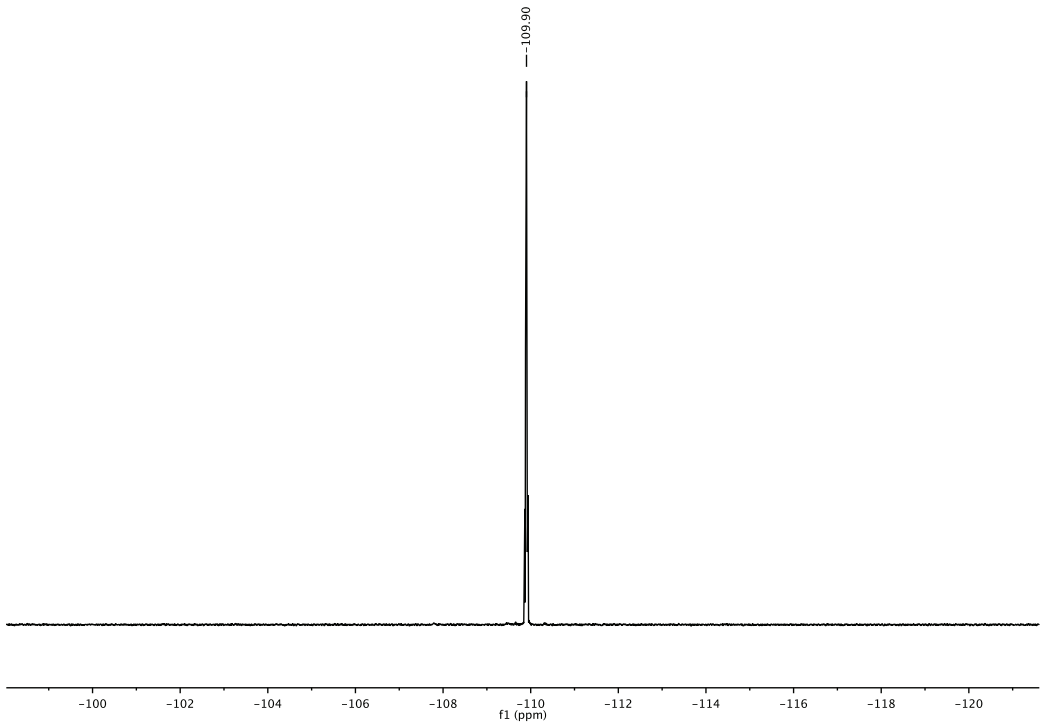
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)

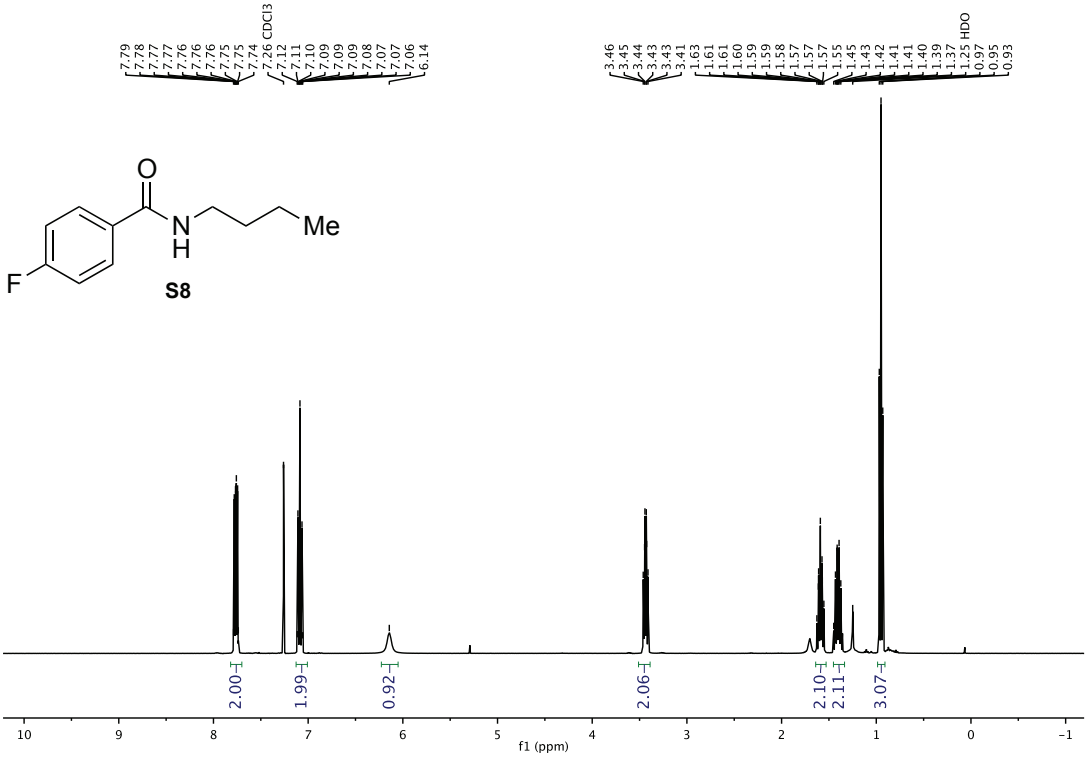


^{19}F NMR (377 MHz, $CDCl_3$)

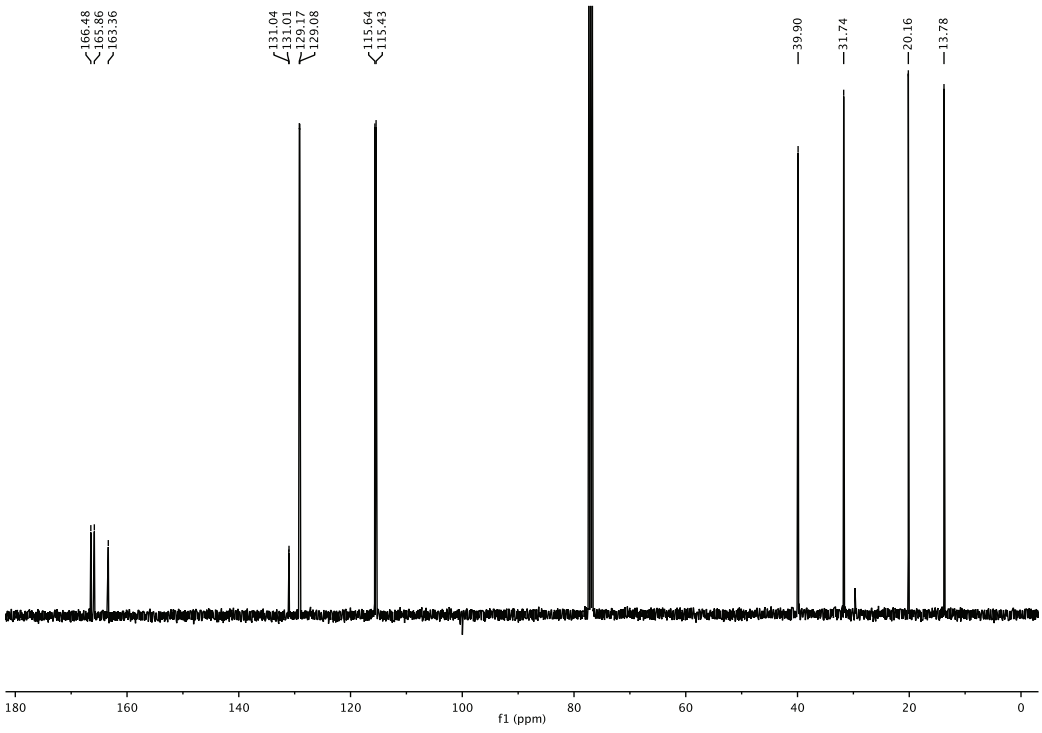


_N_-Butyl-4-fluorobenzamide (S8)

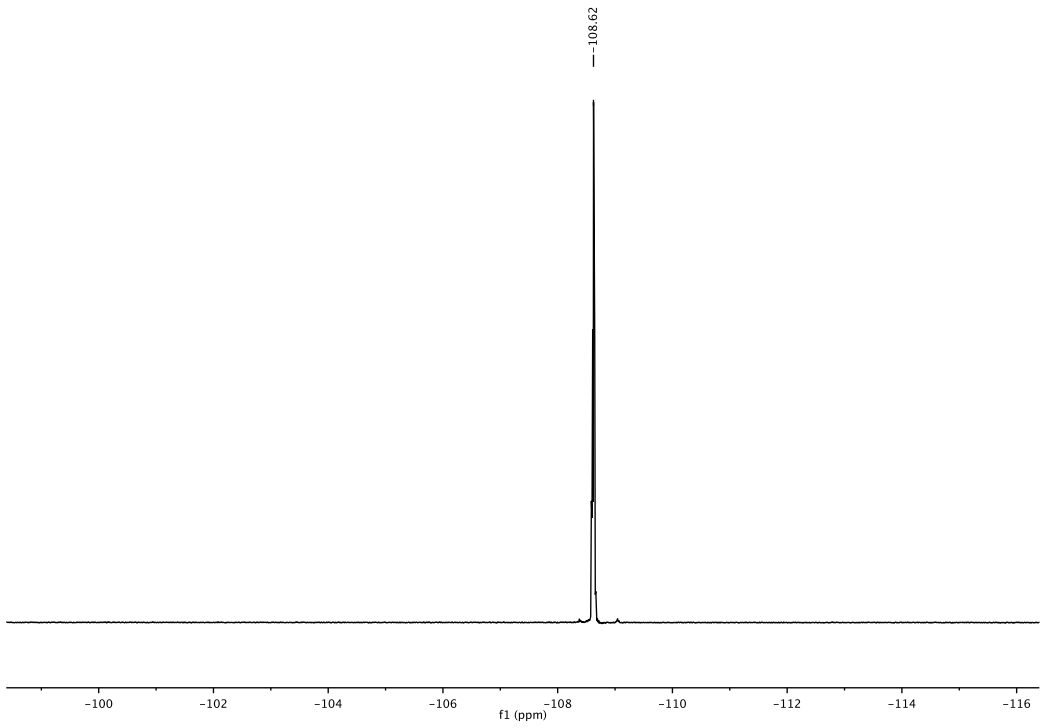
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)



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



References

(1) Paquette, L.; Crich, D.; Fuchs, P.; Molander, G. A., Eds. *Encyclopedia of reagents for organic synthesis*, 2nd Ed.; Wiley, Chichester, 2009.

(2) Goswami, L. N.; Houston, Z. H.; Sarma, S. J.; Jalisatgi, S. S.; Hawthorne, M. F. *Org. Biomol. Chem.* **2013**, *11*, 1116.

(3) Antczak, C.; Bauvois, B.; Monneret, C.; Florent, J. C. *Bioorg. Med. Chem.* **2001**, *9*, 2843.

(4) Sunbul, M.; Jäschke, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 13401.

(5) Noda, H.; Erős, G.; Bode, J. W. *J Am Chem Soc* **2014**, *135*, 5611.

(6) Erős, G.; Kushida, Y.; Bode, J. W. *Angew. Chemie Int. Ed.* **2014**, *53*, 7604.

(7) Liu, S. M.; Mazunin, D.; Pattabiraman, V. R.; Bode, J. W. *Org. Lett.* **2016**, *18*, 5336–5339.

(8) Dumas, A. M.; Bode, J. W. *Org. Lett.* **2012**, *14,* 2138–2141.

(9) Singh, P.; Pirio, M.; Leung, K. D.; Tsay, Y.-G. *Can. J. Chem* **1984**, *62*, 2471-2477.

(10) Grohmann, C.; Wang, H.; Glorius, F. *Org. Lett.* **2012**, *14*, 656.

(11) Ji, Y.-F.; Yan, H.; Jiang, Q.-B. *Eur. J. Org. Chem.* **2015**, 2051.

(12) Gualtierotti, J. B.; Schumacher, X.; Fontaine, P.; Masson, G.; Wang, Q.; Zhu, J. *Chem. Eur. J.* **2012**, *18*, 14812.

(13) Morimoto, H.; Fujiwara, R.; Shimizu, Y.; Morisaki, K.; Ohshima, T. *Org. Lett.* **2014**, *16*, 2018.

(14) Dumas, A. M.; Molander, G. A.; Bode, J. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 5683.

(15) Wang, F.; Liu, H.; Fu, H.; Jiang, Y.; Zhao, Y. *Adv. Synth. Catal.* **2009**, *351*, 246.

(16) Ran, L.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Chem. Asian J.* **2014**, *9*, 577.

(17) Srinivas, M.; Hudwekar, A. D.; Venkateswarlu, V.; Reddy, G. L.; Kumar, K. A A.; Vishwakarma, R. A; Sawant, S. D. *Tetrahedron Lett.* **2015**, *56*, 4775.

(18) Li, J.; Sha, Y. *Molecules* **2008**, *13*, 1111.

(19) Friede, M. et al. *Pept. Res.* **1992**, *5*, 145.

(20) Melomedov, J.; Wünsche von Leupoldt, A.; Meister, M.; Laquai, F.; Heinze, K. *Dalton Trans.* **2013**, *42*, 9727.

(21) Guillemin, J. C.; Denis, J. M. *Synthesis* **1985**, *12*, 1131.

(22) Zhu, C.; Wei, W.; Du, P.; Wan, X. *Tetrahedron* **2014**, *70*, 9615.