Electronic Supplementary Material (ESI) for Green Chemistry.

Supporting Information

Exploiting Intramolecular Hydrogen Bond for Highly (Z)-Selective & Metal Free Synthesis of Amide Substituted β-aminoenones

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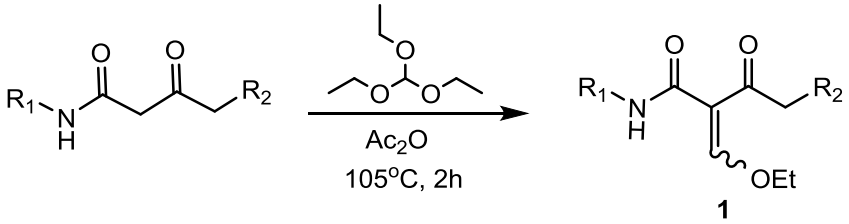
1. General Information:

All reagents and solvents were used from Sigma-Aldrich and used without treatment, unless otherwise indicated. All NMR spectra were recorded on Bruker AV400. Proton and carbon-13 NMR spectra are reported as chemical shifts (δ) in parts per million (ppm) relative to residual undeuterated solvent peak using the Bruker internal referencing procedure (edlock). Coupling constants (J) are reported in units of hertz (Hz) and are rounded to the nearest 0.5. The following abbreviations are used to describe multiplets: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet) and br (broad). 2D techniques (NOESY) were also used to assist on structural confirmation. Infrared spectra were recorded as neat compound using a Perkin-Elmer FT-IR spectrometer and absorptions are reported in wavenumbers (cm^{-1}). Melting points of solids were measured on a Buchi melting point M-565 apparatus and are uncorrected. Specific rotations ($[\alpha]_D$) were determined at 20°C on a Anton Paar MCP 200 Polarimeter. HPLC purity and chiral HPLC were recorded using an Agilent 6300 Series system. HPLC was carried out with Discovery® C18, 5 µm column (15 cm x 4.6 mm) using gradients between 0.1% TFA in water (Solvent A) and CH_3CN. Chiral HPLC was carried out with Daicel Chiralcel® OD-H column using gradients n-Hexane/Isopropanol in the ratio 85:15. High resolution mass spectra were recorded on a 6530 Q-TOF (Agilent Technologies). The single crystal X-ray diffraction studies of **2b** were performed using Bruker AXS Kappa APEX II CCD Diffractometer.

2. General scheme and procedure for preparation[1] of EMD of β-keto amides 1:



1

Mixture of E & Z

The required β-keto amide (1 eq), acetic anhydride (3 eq) and triethylorthoformate (1.2 eq) were stirred at 105°C until reaction completion. The reaction completions were monitored by TLC (Hexanes/EtOAc: 70/30). After reaction completion, Compound **1a, 1b** and **1c** were isolated as solids by cooling to -15 ^oC and filtered to isolate as solids and used as such for the next step. Compound **1d, 1e** and **1f** the reaction mixtures were concentrated to dryness and the mixtures were dissolved in dichloromethane, washed with cold brine solution and the organic layer was dried over sodium sulfate. The sodium sulfate were filtered and concentrated the organic layer to dryness to afford product (**1d, 1e** and **1f**) and used as such for the next step.

3. General procedure for preparation of 2 & 3:

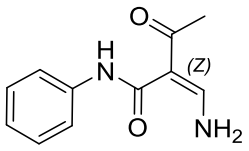
Typical procedure for 2: To a solution of ethoxymethylidine-β-keto amide **1** (1 eq) in methanol (10.0 mL) and ammonium hydroxide solution (2 eq) were added. The reaction mixture was heated at 60 ^oC until completion. Reaction completion was monitored by TLC (Hexanes/EtOAc: 70/30). Upon cooling to room temperature, the reaction mixture was poured to 20 ml of ice cold water. The precipitated white solids were collected by filtration and dried in vacuum to afford **2**.

Typical procedure for 3: To a solution of ethoxymethylidine-β-keto amide **1** (1eq) in methanol (10.0 mL) and substituted primary amine (1.01 eq) were added. The reaction mixture was heated at 60 ^oC until completion. Reaction completion was monitored by TLC (Hexanes/EtOAc: 70/30). Upon cooling to room temperature, the reaction mixture was further cooled to 0^oC. The precipitated solids were collected by filtration and dried in vacuum to afford pure compound **3**.

Note: In case of aryl/heteroaryl amines the product was thrown out of solvent during the course of reaction; after the reaction completion the reaction mixture was cooled to RT and the precipitated solids were collected by filtration and dried in vacuum to afford the pure product. For compound (**3b, 3c, 3e, 3l, 3m,**

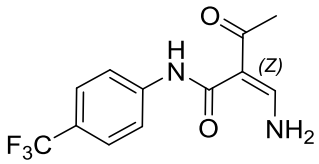
3n, 3o, 3p, 3q, 3r and 3s) the solid product started thrown out immediately after completion of reaction. So after cooling to room temperature the solids were filtered and dried to afford pure product.

(Z)-2-(Aminomethylene)-3-oxo-N-phenylbutanamide (2a):



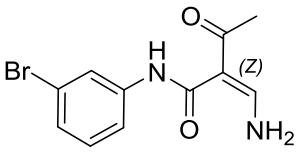
White solid: mp. 121-123 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 2.23 (s, 3H), 5.94 (br, 1H), 7.00 (t, *J*=7.6 Hz, 1H), 7.22-7.26 (m, 2H), 7.50-7.51 (d, *J*=8.4 Hz, 2H), 7.84-7.90 (m, 1H), 10.15 (br, 1H), 11.60 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 26.1, 103.8, 120.8, 123.7, 128.8, 138.8, 159.2, 167.4, 196.2; **IR** (Neat, cm^{-1}): 3313, 3185, 2167, 2000, 1626, 1583, 1526, 1441, 1376, 1327, 1300, 1240, 1199, 1178, 1156, 1125, 1045, 1009, 950, 904, 796, 757, 692; **HPLC** Purity: 99.61%; Anal. Calculated for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72, found: C, 64.95; H, 5.56; N, 13.25, Isolated Yield: 416 mg, 95.0%.

(Z)-2-(aminomethylene)-3-oxo-N-(4-(trifluoromethyl)phenyl)butanamide (2b):



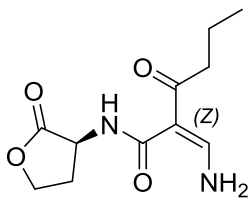
White solid: mp. 218.3 - 221.1 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 2.29 (s, 3H), 7.62 (d, J= 8.8 Hz, 2H), 7.78 (d, J= 8.4 Hz, 2H), 8.17 (dd, J= 15.2 Hz, 8 Hz, 1H), 8.82 (br, 1H), 9.83 (br, 1H), 12.26 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 26.1, 101.0, 119.3, 122.7 (q, *J*=32 Hz), 124.4 (q, *J*=269 Hz), 126.0, 142.4, 161.6, 167.3, 196.1; **^{19}F NMR** (376 MHz, DMSO-d_6) δ = -60.92; **IR** (Neat, cm^{-1}): 3312, 3092, 1660, 1544, 1414, 1384, 1343, 1318, 1257, 1198, 1180, 1157, 1136, 1100, 1061, 1013, 951, 850, 824, 776, 757, 710, 654; **HPLC** Purity: 99.89%; Anal. Calculated for $C_{12}H_{11}F_3N_2O_2$: C, 52.95; H, 4.07; N, 10.29, found: C, 53.43; H, 3.67; N, 10.44; Isolated Yield: 1.78 g, 98.5%.

(Z)-2-(aminomethylene)-N-(3-bromophenyl)-3-oxobutanamide (2c):



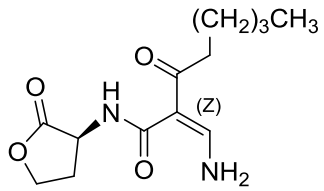
Off white solid: mp. 209.5-210.0°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 2.28 (s, 3H), 7.19-7.27 (m, 2H), 7.32-7.35 (m, 1H), 8.09 (s, 1H), 8.14 (dd, *J*=15.6 Hz, 8.8 Hz, 1H), 8.77 (br, 1H), 9.80 (br, 1H), 12.07 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 26.1, 100.9, 118.2, 121.6, 121.7, 125.3, 130.7, 140.4, 161.5, 167.1, 196.1; **IR** (Neat, cm^{-1}): 3349, 3227, 3061, 2158, 1654, 1565, 1523, 1474, 1422, 1376, 1328, 1303, 1246, 1191,1132, 1066, 1042, 1006, 991, 953, 878, 776, 675; **HPLC** Purity: 99.35%; Anal. Calculated for $C_{11}H_{11}BrN_2O_2$: C, 46.67; H, 3.92; N, 9.89, found: C, 46.90; H, 3.56; Br, 28.22; N, 9.97; Isolated Yield: 893.5 mg, 96.0%.

(S,Z)-2-(aminomethylene)-3-oxo-N-(2-oxotetrahydrofuran-3-yl)hexanamide (2d):



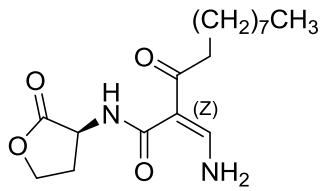
Faint yellow solid: mp. 128.6-129.7°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 0.88 (t, *J*=7.2 Hz, 3H), 1.47-1.54(m, 2H), 2.22-2.30 (m, 1H), 2.39-2.45 (m, 1H), 2.49-2.53 (m, 2H), 4.18-4.24 (m, 1H), 4.32-4.37 (m, 1H), 4.53-4.60 (m, 1H), 8.07 (dd, *J*=15.2 Hz, 8.8 Hz, 1H), 8.41 (br, 1H), 9.73 (br, 1H), 9.98 (d, *J*=7.6 Hz, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 13.8, 18.7, 28.5, 38.5, 47.6, 65.3, 100.5, 159.9, 168.8, 175.6, 197.4; **IR** (Neat, cm^{-1}): 3289, 3167, 2952, 2870, 2216, 2169, 2033, 1773, 1759, 1618, 1562, 1518, 1459, 1386, 1334, 1310, 1286, 1246, 1223, 1177, 1089, 1022, 995, 968, 953, 875, 794; **HPLC** Purity: 99.5%; **$[\alpha]_D^{20}$** : +11.02 (c=1, CH_3OH); Anal. Calculated for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66, found: C, 55.24; H, 6.13; N, 11.58; Isolated Yield: 841 mg, 94.3%.

(S,Z)-2-(aminomethylene)-3-oxo-N-(2-oxotetrahydrofuran-3-yl)octanamide (2e):



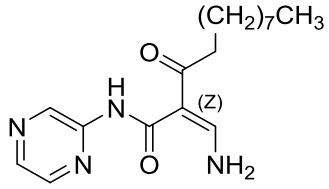
Faint yellow solid: mp. 119.7-120.9°C; **^{1}H NMR** (400 MHz, $CDCl_3$)δ =0.89 (t, *J*=7.2 Hz), 1.22-1.37(m, 4H), 1.57-1.64 (m, 2H-merged with H_2O peak), 2.34-2.44 (m, 1H), 2.51 (t, *J*=7.6 Hz, 2H), 2.57-2.64 (m, 1H), 4.24-4.31 (m, 1 H), 4.47-4.57 (m, 2H), 5.98 (br, 1H), 7.95 (dd, *J*=14 Hz, 8.4 Hz, 1H), 9.98 (br, 1H), 10.19 (d, *J*=7.2 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 13.9, 22.5, 25.4, 29.3, 31.6, 37.5, 48.1, 65.8, 102.5, 158.3, 169.6, 175.6, 198.7; **IR** (Neat, cm^{-1}): 3286, 2955, 2869, 2164, 1770, 1622, 1565, 1522, 1383, 1336, 1317, 1280, 1217, 1157, 1093, 1018, 957, 848, 793, 707; **HPLC** Purity: 98.94%; **$[\alpha]_D^{20}$** : -14.44 (c=1, $CHCl_3$); Anal. Calculated for $C_{13}H_{20}N_2O_4$: C, 58.19; H, 7.51; N, 10.44; found: C, 58.40; H, 7.24; N, 9.90; Isolated Yield: 420 mg, 93.1%.

(S,Z)-2-(aminomethylene)-3-oxo-N-(2-oxotetrahydrofuran-3-yl)dodecanamide (2f):



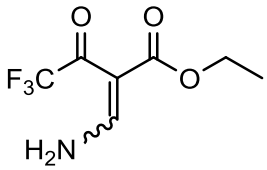
Faint yellow solid: mp. 120.1-120.9 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ =0.87 (t, *J*=6.8 Hz, 3H), 1.25-1.29 (m, 12H), 1.56-1.61 (m, 2H-merged with H_2O peak), 2.34-2.44 (m, 1H), 2.50 (t, *J*=7.2 Hz, 2H), 2.56-2.64 (m, 1H), 4.24-4.31 (m, 1H), 4.47-4.57 (m, 1H), 6.01 (br, 1H), 7.95 (dd, *J*=14.4 Hz, 8.4 Hz, 1H), 9.96 (br, 1H), 10.19 (d, *J*=7.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 14.1, 22.7, 25.8, 29.2, 29.3, 29.4, 29.5, 31.8, 37.6, 48.1, 65.8, 102.4, 158.3, 169.6, 175.6, 198.8; **IR** (Neat, cm^{-1}): 3298, 3172, 2923, 2853, 2164, 1781, 1768, 1619, 1565, 1519, 1467, 1383, 1355, 1337, 1314, 1283, 1254, 1216, 1171, 1096, 1023, 1001, 950, 883, 799, 699; **HPLC** Purity: 98.68%; **$[\alpha]_D^{20}$** : -7.48 (c=1, $CHCl_3$); **HRMS (EI)** m/z: calculated for $C_{17}H_{28}N_2O_4$ $[M+Na]^+$: 347.1947, found: 347.1950; Isolated Yield: 430 mg 93.7%.

(Z)-2-((ethylamino)methylene)-3-oxo-N-(4-(trifluoromethyl)phenyl)butanamide (2g):



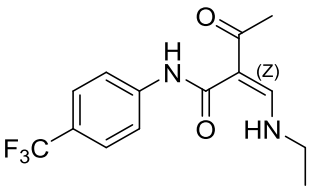
Pale green solid: mp. 99.7 -100.7 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ =0.85 (t, *J*=6.8 Hz, 3H), 1.25 (br, 12H), 1.53 (br, 2H), 2.64 (t, *J*=7.6 Hz, 2H), 8.25 (dd, *J*=15.6 Hz, 8.8 Hz, 1H), 8.30-8.36 (m, 2H), 8.86 (br, 1H), 9.43 (s, 1H), 9.82 (br, 1H), 12.54 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 13.9, 22.1, 25.4, 28.7, 28.8, 28.9, 31.2, 36.9, 100.0, 136.2, 139.1, 142.8, 148.7, 161.2, 167.1, 198.6; **IR** (Neat, cm^{-1}) 3383, 3218, 2921, 2852, 1659, 1513, 1411, 1383, 1340, 1292, 1267, 1190, 1165, 1145, 1099, 1054, 1009, 963, 866, 846, 720, 667; **HPLC** Purity: 98.08%; Anal. Calculated for $C_{17}H_{26}N_4O_2$: C, 64.12; H, 8.23; N, 17.60, found: C, 63.90; H, 7.83; N, 16.90; Isolated Yield: 168 mg, 91.7%.

EZ-2-(aminomethylene)-4,4,4-trifluoro-3-oxo-ethylester-butanoic acid (2h):



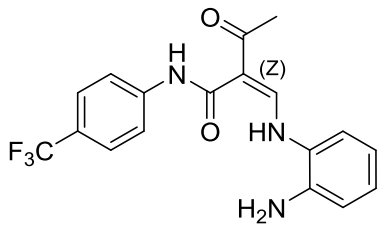
Light yellow solid: mp. 78.2-79.9 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ =1.29 (m, 3H), 4.25 (m, 2H), 6.77-6.95 (br, 1H), 8.11 & 8.27 (dd, *J*=16 Hz, 8.8 Hz, 1H), 9.87 & 9.18 (br, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 13.9 & 14.0, 60.6 & 60.8, 98.1 & 98.7, 116.8 & 117.2 (q, *J*=286 & 289 Hz), 160.3 & 162.0, 165.4 & 167.3, 180.0 & 178.3 (q, J=36 & 34 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$) δ =-73.19, -71.75; **IR** (Neat, cm^{-1}) 3439, 3212, 1720, 1677, 1651, 1639, 1618, 1562, 1478, 1417, 1384, 1362, 1319, 1221, 1199, 1187, 1161, 1132, 1018, 917, 777, 739, 708; Anal. Calculated for $C_7H_8F_3NO_3$: C, 39.82; H, 3.82; N, 6.63, found: C, 39.62; H, 3.63; N, 6.72; Isolated Yield: 410 mg, 93.3%.

(Z)-2-((ethylamino)methylene)-3-oxo-N-(4-(trifluoromethyl)phenyl)butanamide (3a)



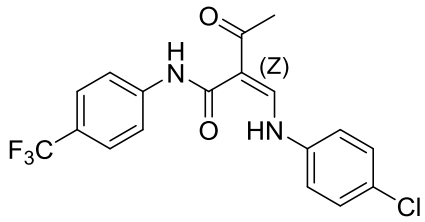
White powder: mp. 125.7-127.4 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 1.22 (t, *J*=7.2 Hz, 3H), 2.29 (s, 3H), 3.45-3.52 (m, 2H), 7.63 (d, J= 8.4 Hz, 2H), 7.78 (d, J= 8.4 Hz ,2H), 8.24 (d, J= 14 Hz, 1H), 10.50 (m, 1H), 12.35 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 15.9, 26.1, 44.3, 99.9, 119.2, 122.6 (q, *J*=32 Hz), 124.4(q, *J*=269 Hz), 126.0, 142.4, 162.0, 167.3, 195.4; **^{19}F NMR** (376 MHz) δ = -60.24; **IR** (Neat, cm^{-1}): 3224.8, 2976.6, 1650.7, 1582.9, 1532, 1452.9, 1406.9, 1379.2, 1322.6, 1257.4, 1181.7, 1150.6, 1093.6, 1061.8, 1012.8, 989.2, 954.2, 837.1, 819.7, 800.9, 774.6, 678.8; **HPLC** Purity: 98.29%; **HRMS (EI)** m/z: calculated for $C_{14}H_{15}F_3N_2O_2$ $[M+H]^+$: 301.1164, found: 301.1184; Isolated Yield: 917 mg, 92.0%.

(Z)-2-((2-aminophenylamino)methylene)-3-oxo-N-(4-(trifluoromethyl)phenyl) butanamide (3b):



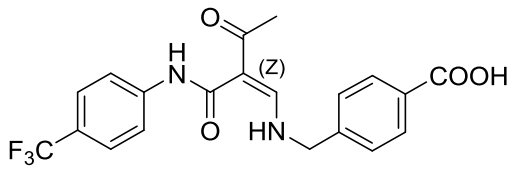
Yellow solid: mp. 202.4-203.5 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 2.42(s, 3H), 3.80 (s, 2H), 6.83-6.89 (m, 2H), 7.09-7.13 (m, 2H), 7.56 (d, *J*=8.4 Hz, 2H), 7.75 (d, *J*=8.4 Hz, 2H), 8.25 (d, *J*=12.8 Hz, 1H), 12.08 (s, 1H), 12.46 (d, *J*=12 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 26.3, 104.5, 117.5, 119.7, 119.9, 120.2, 124.3 (q, *J*=270 Hz), 125.0 (q, *J*=32 Hz), 126.1, 127.2, 127.5, 138.7, 141.5, 156.1, 167.8, 196.2; **^{19}F NMR** (376 MHz, $CDCl_3$) δ= -61.96; **IR** (Neat, cm^{-1}): 3428, 3356, 3141, 3046, 2196, 2160, 2024, 2005, 1646, 1535, 1503, 1463, 1413, 1374, 1315, 1281, 1265, 1186, 1158, 1147, 1104, 1066, 1016, 982, 956, 929, 906, 841, 788, 744, 680, 637, 622, 606; **HPLC** Purity: 98.29%; **HRMS (EI)** m/z: calculated for $C_{18}H_{16}F_3N_3O_2$ $[M+H]^+$: 364.1273, found: 364.1272; Isolated Yield: 1.10 g, 91.2%.

(Z)-2-((4-chlorophenylamino)methylene)-3-oxo-N-(4-(trifluoromethyl)phenyl) butanamide (3c):



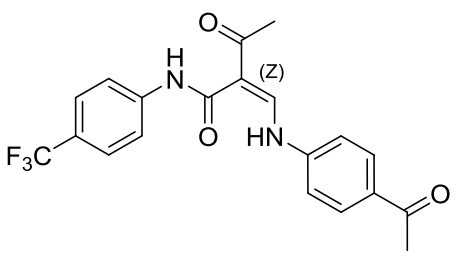
White solid: mp. 228.4-230.6°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 2.50 (s, 3H), 7.49 (d, *J*=8.8 Hz, 2H), 7.61 (d, *J*=8.8 Hz, 2H), 7.69 (d, *J*=8.8 Hz, 2H), 7.85 (d, *J*=8.4 Hz, 2H), 8.60 (d, *J*=12.8 Hz, 1H), 12.18 (s, 1H), 12.34 (d, *J*=13.2 Hz, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 26.7, 103.0, 119.8, 120.1, 123.0 (q, *J*=32 Hz), 124.3 (q, *J*=270 Hz), 126.1, 129.2, 129.3, 138.0, 141.8, 155.2, 166.9, 197.5; **^{19}F NMR** (376 MHz, DMSO-d_6) δ = -60.32; **IR** (Neat, cm^{-1}): 3018, 2013, 1660, 1586, 1541, 1495, 1414, 1382, 1315, 1256, 1186, 1151, 1103, 1067, 1011, 954, 845, 815, 778, 705, 690; **HPLC** Purity: 99.95%; **HRMS (EI)** m/z: calculated for $C_{18}H_{14}ClF_3N_2O_2$ $[M+H]^+$: 383.0774, found: 383.0775; Isolated Yield: 1.23 g, 96.8%.

(Z)-4-((3-oxo-2-(4-(trifluoromethyl)phenylcarbamoyl)but-1-enylamino)methyl)benzoic acid (3d):



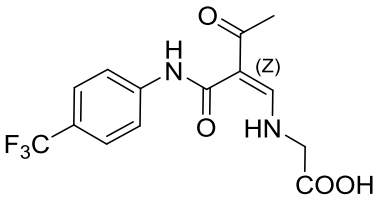
White spongy solid: mp. 203.4-207.7°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 2.33 (s, 3H), 4.77 (d, *J*=6 Hz, 2H), 7.49 (d, *J*=8 Hz, 2H), 7.63 (d, *J*=8.8 Hz, 2H), 7.78 (d, *J*=8.4 Hz, 2H), 7.97 (d, *J*=8 Hz, 2H), 8.44 (d, *J*=13.6 Hz, 1H), 10.81-10.75 (m, 1H), 12.30 (s, 1H), 12.67 (br, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 26.3, 52.3, 100.7, 119.4, 123.0 (q, *J*=32 Hz), 124.4 (q, *J*=269 Hz), 126.1, 129.7, 130.3, 142.3, 142.8, 162.8, 167.1, 167.2, 195.9; **^{19}F NMR** (376 MHz, DMSO-d_6) δ = -60.26; **IR** (Neat, cm^{-1}) 3750, 2987, 2618, 2047, 1715, 1615, 1589, 1530, 1448, 1424, 1402, 1381, 1351, 1315, 1278, 1248, 1184, 1157, 1108, 1065, 1035, 1023, 1014, 993, 957, 837, 795, 760, 744, 694, 679; **HPLC** Purity: 99.87%; **HRMS (EI)** m/z: calculated for $C_{20}H_{17}F_3N_2O_4$ $[M+H]^+$: 407.1219, found: 407.1219; Isolated Yield: 1.22 g, 90.5%.

(Z)-2-((4-acetylphenylamino)methylene)-3-oxo-N-(4-(trifluoromethyl)phenyl)butanamide (3e):



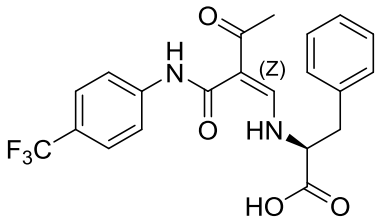
Off-white solid: mp. 194.1-195.0°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 2.49 (s, 3H), 2.60 (s, 3H), 7.25 (d, *J*=8.4 Hz, 2H), 7.58 (d, *J*=8.4 Hz, 2H), 7.74 (d, *J*=8 Hz, 2H), 8.03 (d, *J*=8.4 Hz, 2H), 8.41 (d, *J*=12.4 Hz, 1H), 11.96 (s, 1H), 12.81 (d, *J*=11.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 26.4, 26.5, 105.3, 116.9, 120.4, 123.0 (q, *J*=32 Hz), 124.3 (q, *J*=270 Hz), 126.1, 130.6, 134.1, 141.2, 142.6, 152.1, 167.2, 196.3, 196.7; **^{19}F NMR** (376 MHz, $CDCl_3$) δ = -62.01; **IR** (Neat, cm^{-1}): 3047, 2168, 1918, 1674, 1658, 1634, 1576, 1534, 1414, 1389, 1355, 1300, 1253, 1211, 1178, 1147, 1100, 1065, 1011, 951, 908, 842, 827, 772, 678; **HPLC** Purity: 99.91%; Anal. Calculated for $C_{20}H_{17}F_3N_2O$: C, 50.92; H, 3.97; N, 8.48, found: C, 50.75; H, 3.21; N, 8.20; Isolated Yield: 1.18 g, 91.1%.

(Z)-2-(3-oxo-2-(4-(trifluoromethyl)phenylcarbamoyl)but-1-enylamino)acetic acid (3f):



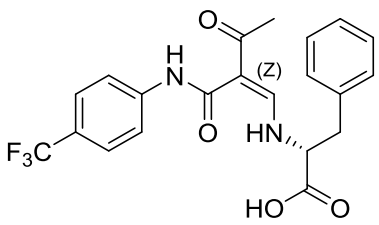
White powder: mp. 200- 204.7 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 2.29 (s, 3H), 4.30 (d, *J*=6 Hz, 2H), 7.65 (d, *J*= 8.8 Hz, 2H), 7.80 (d, *J*= 8.4 Hz ,2H), 8.27 (d, *J*= 13.6 Hz, 1H), 10.48-10.54 (m, 1H), 12.27 (s, 1H), 13.09 (br, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 25.1, 48.9, 99.9, 101.2, 119.3, 122.8(q, *J*=30 Hz), 124.4(q, *J*=269 Hz), 126.0,128.4, 141.3, 162.3, 166.1, 169.7, 194.9; **^{19}F NMR** (376 MHz, DMSO-d_6) δ = -60.32; **IR** (Neat, cm^{-1}) 3312, 3092, 1660, 1618, 1544, 1414, 1384, 1343, 1318, 1257, 1198, 1180, 1157, 1136, 1100, 1061, 1013, 951, 850, 824, 776, 757, 710, 654; **HPLC** Purity: 98.92%; Anal. Calculated for $C_{14}H_{13}F_3N_2O_4$: C, 50.92; H, 3.97; N, 8.48, found: C, 50.75; H, 3.21; N, 8.20; Isolated Yield: 1.00 g 91.2%.

(S,Z)-2-(3-oxo-2-(4-(trifluoromethyl)phenylcarbamoyl)but-1-enylamino)-3-phenylpropanoic acid (3g):



White solid: mp. 160.1-163.4 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 2.06 (s, 3H), 3.10 (dd, J=14 Hz, 8.8 Hz, 1H), 3.30 (dd, J=14 Hz, 4.8 Hz, 1H-H_2O peak merged), 4.67-4.72 (m, 1H), 7.22-7.28 (m, 3H), 7.31-7.34 (m, 2H), 7.64 (d, *J*=8.8 Hz, 2H), 7.77 (d, *J*=8.4 Hz, 2H), 7.88 (d, *J*=13.6 Hz, 1H), 10.65 (dd, *J*=13.2 Hz, 8.8 Hz, 1H), 12.17 (s, 1H), 13.55 (br, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 25.9, 39.0, 62.0, 100.4, 119.4, 122.8 (q, *J*=32 Hz), 124.4(q, *J*=269 Hz), 126.1, 128.4, 126.9, 129.6, 136.0, 142.1, 161.6, 167.0, 171.5, 195.7; **^{19}F NMR** (376 MHz, DMSO-d_6) δ = -60.26; **IR** (Neat, cm^{-1}): 2923, 2349, 2180, 1960, 1715, 1650, 1628, 1601, 1537, 1449, 1413, 1384, 1357, 1322, 1276, 1244, 1223, 1202, 1184, 1167, 1110, 1067, 1014, 995, 963, 885, 872, 845, 829, 801, 769, 744, 704, 684; **HPLC** Purity: 99.07%; **Enantiomeric ratio (er)**: 100:0; **$[\alpha]_D^{20}$** : -229.83 (c=1, CH_3OH); **HRMS (EI)** m/z: calculated for $C_{21}H_{19}F_3N_2O_4$ $[M+Na]^+$: 443.1195, found: 443.1208; Isolated Yield: 1.25 g, 89.6%.

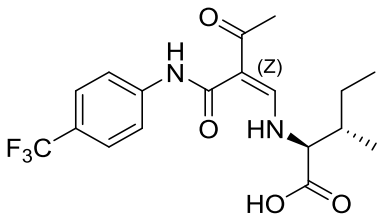
(R,Z)-2-(3-oxo-2-(4-(trifluoromethyl)phenylcarbamoyl)but-1-enylamino)-3-phenylpropanoic acid (3h):



White solid: mp. 163.1-168.7°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 2.07 (s, 3H), 3.10 (dd, J=13.6 Hz, 8.4 Hz, 1H), 3.30 (dd, J=13.6 Hz, 4.4 Hz, 1H, H_2O peak merged), 4.69-4.74 (m, 1H), 7.22-7.27 (m, 3H), 7.31-7.35 (m, 2H), 7.65 (d, *J*=8.8 Hz, 2H), 7.77 (d, *J*=8.4 Hz, 2H), 7.90 (d, *J*=13.6 Hz, 1H), 10.65 (dd, *J*=13.2 Hz, 8.8 Hz, 1H), 12.17 (s, 1H), 13.55 (br, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 25.9, 39.1 (merged with solvent residual peak), 61.9, 100.5, 119.5, 122.8 (q, *J*=32 Hz), 124.4(q, *J*=269 Hz), 126.1,

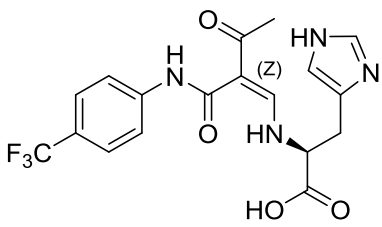
128.4, 126.9, 129.6, 136.0, 142.1, 161.7, 167.1, 171.5, 195.8; **^{19}F NMR** (376 MHz, DMSO-d_6) δ = -60.26; **IR** (Neat, cm^{-1}): 3028, 2348, 2196, 2170, 1976, 1742, 1653, 1529, 1381, 1322, 1273, 1177, 1098, 1064, 1014, 981, 962, 835, 735, 698; **HPLC** Purity: 98.77%; **Enantiomeric ratio (er)**: 99.2:0.8; **$[\alpha]_D^{20}$** : +233.44 (c=1, CH_3OH); **HRMS (EI)** m/z: calculated for $C_{21}H_{19}F_3N_2O_4$ $[M+H]^+$: 421.1375, found: 421.1381; Isolated Yield: 1.29 g, 93.1%.

(2S,3S)-3-methyl-2-((Z)-3-oxo-2-(4-(trifluoromethyl)phenylcarbamoyl)but-1-enylamino)pentanoic acid(3i):



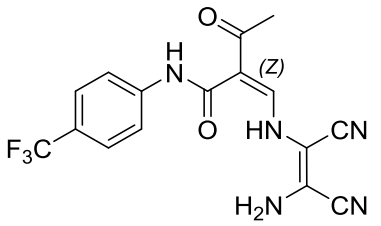
White solid: mp. 194.2-196.0 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 0.91 (m, 6H), 1.16 (m, 1H), 1.45 (m, 1H), 1.99 (m, 1H), 2.30 (s, 3H), 4.37 (dd, *J*=9.6 Hz, 4.4 Hz, 1H), 7.65 (d, *J*=8.8 Hz, 2H), 7.78 (d, *J*=8.4 Hz, 2H), 8.31 (d, *J*=13.2 Hz, 1H), 10.85 (q, *J*=13.2 Hz, 9.6 Hz, 1H), 12.30 (s, 1H), 13.44 (br, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 11.4, 15.2, 24.2, 26.2, 38.0, 65.8, 100.7, 119.6, 122.9 (q, *J*=32 Hz), 124.4 (q, *J*=270 Hz), 126.1, 142.1, 162.2, 167.5, 171.7, 196; **^{19}F NMR** (376 MHz, DMSO-d_6) δ = -60.29; **IR** (Neat, cm^{-1}): 2965, 1727, 1661, 1618, 1596, 1516, 1382, 1318, 1258, 1240, 1203, 1179, 1153, 1135, 1110, 1064, 1012, 990, 960, 898, 846, 827, 808, 748, 659; **CHIRAL HPLC** Purity: 99.82%; **$[\alpha]_D^{20}$**: -24.012 (c=1, CH_3OH); **HRMS (EI)** m/z: calculated for $C_{18}H_{21}F_3N_2O_4$ $[M+H]^+$:, found: ; Isolated Yield: 1.15 g, 89.7%.

(S,Z)-3-(1H-imidazol-5-yl)-2-(3-oxo-2-(4-(trifluoromethyl)phenylcarbamoyl)but-1-enylamino)propanoic acid (3j):



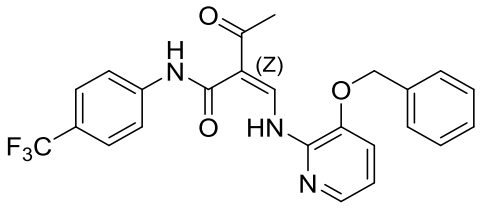
White solid: mp. 204-205.3°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 2.14 (s, 3H), 3.03-3.09 (m, 1H), 3.19-3.23 (m, 1H), 4.58-4.63 (m, 1H), 6.97 (s, 1H), 7.63 (d, *J*=8.4 Hz, 2H), 7.77 (d, *J*=8.4 Hz, 2H), 7.83 (s, 1H), 7.94 (d, *J*=13.6 Hz, 1H), 10.70 (dd, *J*=13.2 Hz, *J*= 8.4 Hz, 1H), 11.45 (br, 2H), 12.21 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 26.0, 31.07, 61.1, 100.3, 116.6, 119.3, 122.7 (q, *J*=32 Hz), 124.4 (q, *J*=270 Hz), 126.1, 132.7, 135.1, 142.3, 161.6, 167.0, 171.7, 195.7; **^{19}F NMR** (376 MHz, DMSO-d_6) δ = -60.24; **IR** (Neat, cm^{-1}): 3129, 2032, 1567, 1529, 1376, 1316, 1254, 1187, 1154, 1109, 1066, 1010, 987, 953, 837, 701, 666; **HPLC** Purity: 98.60%; **$[\alpha]_D^{20}$** : -44.85 (c=1, $(CH_3)_2SO$); **HRMS (EI)** m/z: calculated for $C_{18}H_{17}F_3N_4O_4$ $[M+Na]^+$: 433.1100, found: 433.1108 ; Isolated Yield: 1.19 g, 87.4%.

(Z)-2-(((Z)-2-amino-1,2-dicyanovinylamino)methylene)-3-oxo-N-(4-(trifluoromethyl)phenyl)butanamide (3k):



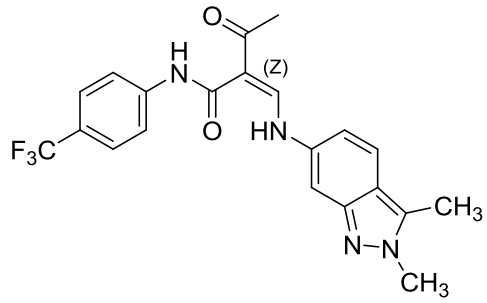
Brown solid: mp. 192.5°C (decomposition); **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 2.36(s, 3H), 7.64-7.74 (m, 4H), 7.84 (d, *J*=8.8 Hz, 2H), 8.21 (d, *J*=12.4 Hz, 1H), 11.19 (d, *J*=12.4 Hz, 1H), 11.98 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 26.4, 93.8, 104.4, 113.8, 116.2, 119.8, 123.7 (q, *J*=32 Hz), 124.3 (q, *J*=269 Hz), 126.1, 146.7, 159.4, 166.3, 197.2; **^{19}F NMR** (376 MHz, DMSO-d_6) δ = -60.34; **IR** (Neat, cm^{-1}): 3427, 3349, 3029, 2220, 2166, 2021, 1983, 1648, 1586, 1531, 1398, 1377, 1320, 1299, 1252, 1187, 1158, 1107, 1066, 1014, 950, 895, 855, 834, 764, 732, 674; **HPLC** Purity: 98.60%; **HRMS (EI)** m/z: calculated for $C_{16}H_{12}F_3N_5O_2$ $[M+H]^+$: 364.1021, found: 364.1019; Isolated Yield: 1.09 g, 90.4%.

(Z)-2-((3-(benzyloxy)pyridin-2-ylamino)methylene)-3-oxo-N-(4-(trifluoromethyl)phenyl)butanamide (3l):



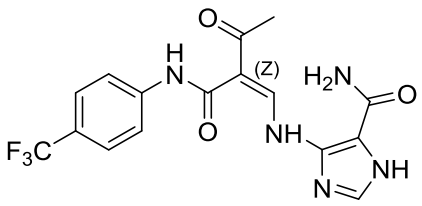
White spongy powder: mp. 214.0-214.9°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 2.54 (s, 3H), 5.27(s, 2H), 7.03 (dd, *J*=8.4 Hz, 5.2Hz, 1H), 7.24 (d, *J*=1.2 Hz, 1H), 7.38-7.47 (m, 3H), 7.57-7.60 (m, 4H), 7.82 (d, J= 8.8 Hz, 2H), 7.96 (d, *J*=4.8 Hz, 1H), 9.25 (d, 12 Hz, 1H), 12.00 (s, 1H), 13.24 (d, *J*=12.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 25.6, 69.5, 104.6, 118.6, 119.0, 119.1, 124.1 (q, *J*=32 Hz), 124.7 (q, *J*=270 Hz), 125.0, 125.8, 127.3, 127.7, 134.5, 138.5, 140.3, 140.7, 142.4, 149.5, 166.1, 196.8; **^{19}F NMR** (376 MHz, $CDCl_3$) δ = -61.86; **IR** (Neat, cm^{-1}): 3068, 1650, 1628, 1590, 1562, 1529, 1471, 1460, 1449, 1413, 1393, 1372, 1315, 1271, 1252, 1216, 1180, 1154, 1106, 1065, 1036, 1024, 1012, 974, 950, 840,825, 783, 752, 728, 690; **HPLC** Purity: 98.18%; **HRMS (EI)** m/z: calculated for $C_{24}H_{20}F_3N_3O_3$ $[M+H]^+$: 456.1535, found: 456.1548; Isolated Yield: 1.40 g, 92.6%.

(Z)-2-((2,3-dimethyl-2H-indazol-6-ylamino)methylene)-3-oxo-N-(4-(trifluoromethyl)phenyl)butanamide (3m):



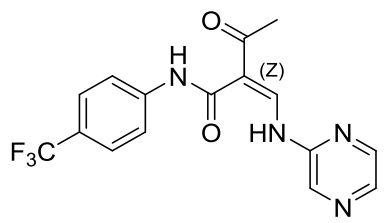
Off-white powder: mp. 219.0-220.8 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 2.48 (s, 3H), 2.64 (s, 3H), 4.15 (s, 3H), 6.95 (d, *J*=8.4 Hz, 2H), 7.42 (s, 1H), 7.57-7.64 (m, 3H), 7.76 (d, *J*= 8.4 Hz, 2 H), 8.46 (d, *J*=12.8 Hz, 2H), 12.06 (s, 1H), 12.70 (d, *J*= 12 Hz, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 9.4, 26.8, 37.1, 102.1, 102.8, 114.0, 118.6, 119.8, 124.1 (q, *J*=32 Hz), 124.7 (q, *J*=270 Hz), 125.7, 126.1, 134.5, 137.9, 141.8, 145.0, 155.0, 167.1, 197.5; **^{19}F NMR** (376 MHz, CDCl3) δ = -61.95; **IR** (Neat, cm^{-1}) 3013, 2156, 1631, 1583, 1534, 1403, 1368, 1318, 1267, 1200, 1179, 1159, 1108, 1062, 1008, 953, 903, 855, 840, 785, 766, 741, 693, 668; **HPLC** Purity: 99.98%; **HRMS (EI)** m/z: calculated for $C_{21}H_{19}F_3N_4O_2$ $[M+Na]^+$: 439.1358, found: 439.1381; Isolated Yield: 1.27 g, 91.9%.

(Z)-5-(3-oxo-2-(4-(trifluoromethyl)phenylcarbamoyl)but-1-enylamino)-1H-imidazole-4-carboxamide (3n):



Off-white powder: mp. 227.5-228.8 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 2.30 (s, 3H), 7.41 (s, 2H), 7.69 (d, J= 8.4 Hz, 2H),7.82 (s, 1H), 7.85 (d, J= 8.4 Hz ,2H), 8.92 (d, J= 12.8 Hz, 1H), 12.06 (s, 1H), 12.52 (s, 1H), 12.85 (d, J= 13.2 Hz); **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 26.4, 103.1, 108.7, 119.6, 123.6 (q, *J*=32 Hz), 124.7 (q, *J*=269 Hz), 126.1, 142.0, 142.6, 151.8, 161.1, 166.1, 197.0; **^{19}F NMR** (376 MHz, DMSO-d_6) δ = -60.27; **IR** (Neat, cm^{-1}) 3123, 1656, 1611, 1567, 1525, 1451, 1414, 1377, 1304, 1274, 1252, 1186, 1157, 1107, 1062, 1012, 992, 953, 848, 828, 793, 768, 696, 676; **HPLC** Purity: 99.54%; **HRMS (EI)** m/z: calculated for $C_{16}H_{14}F_3N_5O_3$ $[M+H]^+$: 382.1127, found: 382.1127; Isolated Yield: 1.18 g 93.2%.

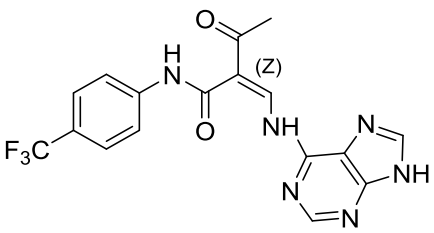
(Z)-3-oxo-2-((pyrazin-2-ylamino)methylene)-N-(4-(trifluoromethyl)phenyl)butanamide (3o):



White spongy solid: mp. 207.6-208.6°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 2.50 (s, 3H-merged with residual solvent peak), 7.70 (d, *J*=8.4 Hz, 2H), 7.88 (d, *J*=8.4 Hz, 2H), 7.45 (m, 2H), 8.91 (s, 1H), 9.08 (d, *J*=12.4 Hz, 1H), 11.89 (s, 1H), 12.32 (d, *J*=12 Hz, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 26.6, 105.8, 119.9, 123.6 (q, *J*=32 Hz), 124.7 (q, *J*=269 Hz), 126.1, 136.5, 140.6, 141.6, 142.3, 147.0, 151.4, 166.0, 198.0; **^{19}F NMR** (376 MHz, DMSO-d_6) δ = -60.36; **IR** (Neat, cm^{-1}) 3016, 1664, 1632, 1594,

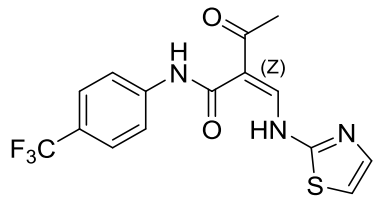
1546, 1525, 1476, 1442, 1415, 1380, 1317, 1289, 1257, 1189, 1157, 1141, 1104, 1062, 1009, 977, 953, 912, 849, 836, 777, 732, 703; **HPLC** Purity: 99.82%; **HRMS (EI)** m/z: calculated for $C_{16}H_{13}F_3N_4O_2$ $[M+H]^+$: 351.1069, found: 351.1087; Isolated Yield: 1.05 g, 90.3%.

(Z)-2-((9H-purin-6-ylamino)methylene)-3-oxo-N-(4-(trifluoromethyl)phenyl)butanamide (3p):



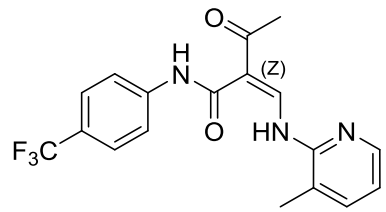
Off-white solid: mp. 294.0°C-295.6°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 2.56 (s, 3H), 7.73 (d, *J*=8.8 Hz, 2H), 7.91 (d, *J*=8.4 Hz, 2H), 8.60 (s, 1H), 8.71 (s, 1H), 9.60 (d, *J*=12 Hz, 1H), 11.89 (s, 1H), 12.85 (d, *J*=12 Hz, 1 H), 13.76 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6+CD_2Cl_2) δ= 26.7, 106.5, 120.2, 121.0, 123.8, 126.2, 141.3, 144.1, 146.8, 151.9, 152.0, 153.2, 166.4, 198.3 (Solubility of the sample is very poor in all deuterated NMR solvents so the peaks in the 13C spectra is not as good as other samples); ^{19}F NMR (376 MHz, DMSO-d_6) δ = -60.40; **IR** (Neat, cm^{-1}) 3098, 2991, 2839, 1781, 1665, 1619, 1573, 1533, 1468, 1434, 1410, 1372, 1318, 1305, 1272, 1254, 1179, 1166, 1148, 1104, 1075, 1060, 1010, 957, 940, 925, 889, 847, 818, 796, 722, 686, 673; **HPLC** Purity: 99.41%; **HRMS (EI)** m/z: calculated for $C_{17}H_{13}F_3N_6O_2$ $[M+Na]^+$: 413.0950, found: 413.0954; Isolated Yield: 1.20 g, 92.6%.

(Z)-3-oxo-2-((thiazol-2-ylamino)methylene)-N-(4-(trifluoromethyl)phenyl)butanamide (3q):



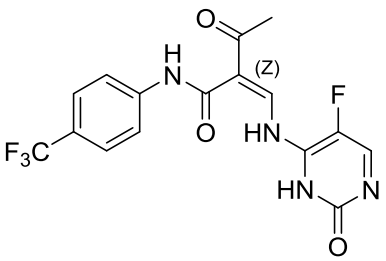
Peach solid: mp. 162.9-164.5°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 2.46 (s, 3H), 7.38 (d, *J*=3.6 Hz, 1H), 7.52 (d, *J*=3.2 Hz, 1H), 7.68 (d, *J*=8.8 Hz, 2H), 7.85 (d, *J*=8.4 Hz, 2H), 8.83 (d, *J*=12 Hz, 1H), 11.77 (s, 1H), 12.54 (d, *J*=12 Hz, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 26.5, 105.6, 116.0, 119.8, 123.5 (q, *J*=32 Hz), 124.3 (q, *J*=270 Hz), 126.1, 139.2, 141.7, 151.6, 161.0, 165.5, 197.7; **^{19}F NMR** (376 MHz, DMSO-d_6) δ = -60.39; **IR** (Neat, cm^{-1}): 3029, 2098, 2041, 2013, 1972, 1658, 1583, 1546, 1512, 1460, 1395, 1317, 1292, 1254, 1195, 1159, 1101, 1065, 1014, 971, 950, 883, 867, 839, 776, 695, 666; **HPLC** Purity: 99.79%; **HRMS (EI)** m/z: calculated for $C_{15}H_{12}F_3N_3O_2S$ $[M+H]^+$: 356.0681, found: 356.0681; Isolated Yield: 1.09 g, 92.4%.

(Z)-2-((3-methylpyridin-2-ylamino)methylene)-3-oxo-N-(4-(trifluoromethyl)phenyl) butanamide (3r):



White solid: mp. 224.9-225.5°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 2.42 (s, 3H), 2.54 (s, 3H), 7.02-7.05 (m, 1H), 7.53-7.59 (m, 3H), 7.78 (d, *J*=8.8 Hz, 2H), 8.23 (d, *J*=4.4 Hz, 1H), 9.35 (d, *J*=12 Hz, 1H), 12.06 (s, 1H), 12.96 (d, *J*=10.8 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 16.5, 26.7, 105.2, 120.2, 120.3, 121.2, 125.4 (q, *J*=32 Hz), 126.1, 126.9 (q, *J*=270 Hz), 139.6, 141.4, 146.0, 148.8, 151.9, 167.6, 197.9; **^{19}F NMR** (376 MHz, $CDCl_3$) δ = -61.98; **IR** (Neat, cm^{-1}): 3028, 2012, 1660, 1597, 1579, 1541, 1470, 1455, 1435, 1410, 1379, 1314, 1268, 1253, 1194, 1169, 1155, 1101, 1063, 1011, 986, 954, 910, 847, 811, 777, 756, 731, 679; **HPLC** Purity: 99.74%; **HRMS (EI)** m/z: calculated for $C_{18}H_{16}F_3N_3O_2$ $[M+H]^+$: 364.1273, found: 364.1278; Isolated Yield: 1.12 g, 92.9%.

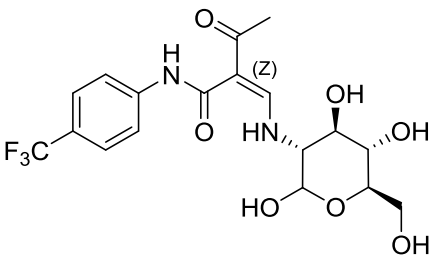
(Z)-2-((5-fluoro-2-oxo-2,3-dihydropyrimidin-4-ylamino)methylene)-3-oxo-N-(4-(trifluoromethyl)phenyl) butanamide (3s):



White solid: mp. 269.8-271.0°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 2.53 (s, 3H), 7.73 (d, *J*=8.4 Hz, 2H), 7.87 (d, *J*=7.6 Hz, 2H), 8.28 (d, *J*=4 Hz, 1H), 8.90 (d, *J*=11.2 Hz, 1H), 11.61 (br, 1H), 11.72 (s, 1H), 12.51 (d,

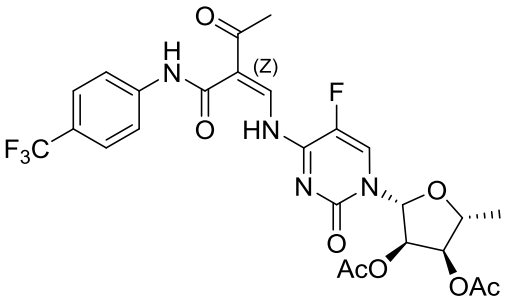
J=11.6 Hz, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 26.8, 108.6, 119.6, 120.4, 122.8, 124.4, 126.2, 141.0, 148.6, 166.0, 198.7 (Solubility of the sample is very poor in all deuterated NMR solvents so the peaks in the ^{13}C spectra is not as good as other samples); **^{19}F NMR** (376 MHz, DMSO-d_6) δ = -60.30, -60.45; **IR** (Neat, cm^{-1}) 3048, 2749, 1659, 1590, 1542, 1481, 1444, 1416, 1389, 1321, 1268, 1188, 1154, 1111, 1068, 1057, 1035, 1018, 960, 888, 844, 834, 793, 772, 733, 721, 683; **HPLC** Purity: 98.18%; **HRMS (EI)** m/z: calculated for $C_{16}H_{12}F_4N_4O_3$ $[M+H]^+$: 385.0924, found: 385.0946; Isolated Yield: 1.18 g, 92.5%.

(Z)-3-oxo-N-(4-(trifluoromethyl)phenyl)-2-(((3R,4R,5S,6R)-2,4,5-trihydroxy-6-(hydroxymethyl) tetrahydro-2H-pyran-3-ylamino)methylene)butanamide (3t):



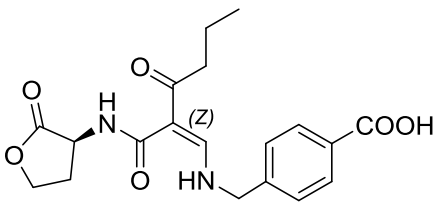
White solid: mp. 139.5-140.4°C; **^{1}H NMR** (400 MHz DMSO-d_6) δ = 2.28 (s, 3H), 3.15-3.18 (m, 1H), 3.38-3.42 (m, 1H), 3.38-3.42 (m, 1H), 3.47-3.53 (m, 2H), 3.64-3.67 (m, 2H), 4.51 (t, *J*=6 Hz, 1H), 5.09 (d, *J*=6 Hz, 1H), 5.16 (t, *J*=3.6 Hz, 1H), 5.32 (d, *J*=5.6 Hz, 1H), 7.04 (d, *J*=4 Hz, 1H), 7.64 (d, *J*=8.8 Hz, 2H), 7.79 (d, *J*=8.8 Hz, 2H), 8.23 (d, *J*=13.6 Hz), 10.47 (dd, *J*=13.2 Hz, 9.2 Hz, 1H), 12.33 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ =26.1, 60.8, 64.1, 70.3, 71.4, 72.4, 90.5, 100.2, 119.4, 122.8 (q, *J*=32 Hz), 124.4 (q, *J*=269 Hz), 126.1, 142.3, 162.7, 167.5, 195.6; **^{19}F NMR** (376 MHz, DMSO-d_6) δ = -60.25; **IR** (Neat, cm-^{1}) 3370, 1659, 1592, 1533, 1410, 1380, 1320, 1254, 1170, 1114, 1067, 1015, 960, 919, 839, 793; **HPLC** Purity: 98.18%; **$[\alpha]_D^{20}$** : +121.30 (c=1, CH_3OH); **HRMS (EI)** m/z: calculated for $C_{18}H_{21}F_3N_2O_7$ $[M+H]^+$: 435.1379, found: 435.1389; Isolated Yield: 1.26 g, 87.4%.

(2R,3R,4R,5R)-2-(5-fluoro-2-oxo-4-((Z)-3-oxo-2-(4-(trifluoromethyl)phenylcarbamoyl)but-1-enylamino) pyrimidin-1(2H)-yl)-5-methyltetrahydrofuran-3,4-diyl diacetate (3u):



White solid: mp. 205.8-206.9 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 1.54 (d, *J*=6.4 Hz, 3H), 2.15 (d, *J*=6 Hz, 6H), 2.58 (s, 3H), 4.36 (quint, 1H), 5.04 (t, *J*=6 Hz, 1H), 5.39 (t, *J*=5.6 Hz, 1H), 6.06 (d, *J*=4 Hz 1H), 7.63 (d, *J*=8.8 Hz, 2H), 7.77-7.80 (m, 3H), 9.05 (d, *J*=11.2 Hz, 1H), 11.75 (s, 1H), 13.16 (d, *J*=10.8 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 18.6, 20.49, 20.51, 27.2, 73.9, 74.0, 78.3, 89.4, 110.5, 120.6, 124.1(q, *J*=270 Hz), 126.0 (q, *J*=32 Hz), 126.2 (q, *J*=3.8 Hz), 128.2 (d, *J*= 35 Hz), 137.0 (d, *J*= 246 Hz), 140.5, 147.9, 152.2 (d, *J*=12 Hz), 152.7, 165.9, 169.6, 169.7, 199.1; **^{19}F NMR** (376 MHz, $CDCl_3$) δ = -62.13, -167.19; **IR** (Neat, cm^{-1}): 3105, 1754, 1687, 1664, 1649, 1592, 1537, 1474, 1408, 1371, 1318, 1272, 1239, 1208, 1159, 1108, 1092, 1063, 1011, 954, 896, 840, 817, 775, 718; **HPLC** Purity: 99.74%; **$[\alpha]_D^{20}$** : +55.29 (c=1, $CHCl_3$); **HRMS (EI)** m/z: calculated for $C_{25}H_{24}F_4N_4O_8$ $[M+Na]^+$: 607.1428, found: 607.1441 ; Isolated Yield: 435 mg, 89.7%.

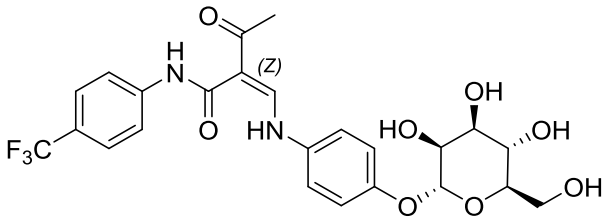
(S,Z)-4-((3-oxo-2-(2-oxotetrahydrofuran-3-ylcarbamoyl)hex-1-enylamino)methyl)benzoic acid (3v):



Faint yellow solid: mp. 178.2-180.4°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 0.89 (t, *J*=7.6 Hz, 3H), 1.49-1.58 (m, 2H), 2.21-2.31 (m, 1H), 2.38-2.45 (m, 1H), 2.58 (t, *J*=7.2 Hz, 2H), 4.17-4.23 (m, 1H), 4.34 (t, *J*=8.4 Hz, 1H), 4.53-4.60 (m, 1H), 4.70 (d, *J*=6.4 Hz, 2H), 7.45 (d, *J*=8 Hz, 2H), 7.95 (d, *J*=8 Hz, 2H), 8.33 (d, *J*=13.2 Hz, 1H), 10.05 (d, *J*=7.2 Hz, 1H), 10.68-10.75 (m, 1H), 12.96 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 13.8, 18.7, 28.4, 38.5, 47.8, 51.8, 65.3, 100.2, 127.5, 129.6, 129.9, 143.2, 161.4, 167.0, 168.7, 175.5, 197.2; **IR** (Neat, cm^{-1}): 3848, 3750, 3650, 2965,

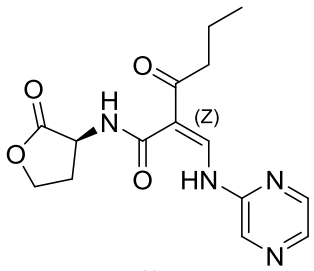
2296, 2164, 1976, 1758, 1696, 1638, 1611, 1575, 1525, 1428, 1400, 1370, 1320, 1286, 1207, 1164, 1114, 1055, 1019, 1010, 985, 945, 854, 817, 783, 750, 694; **HPLC** Purity: 98.88%; **$[\alpha]_D^{20}$** : +8.796 (c=1, CH_3OH); Anal. Calculated for $C_{19}H_{22}N_2O_6$: C, 60.95; H, 5.92; N, 7.48, found: C, 60.69; H, 5.71; N, 7.42; Isolated Yield: 256 mg 92.1%.

(Z)-3-oxo-N-(4-(trifluoromethyl)phenyl)-2-((4-((2R,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl) tetrahydro-2H-pyran-2-yloxy)phenylamino)methylene)butanamide (3w):



Off-white solid: mp. 250.1-250.6°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 2.49 (s, 3H), 3.39-3.53 (m, 3H), 3.61 (d, *J*=11.2 Hz, 1H), 3.68 (dd, *J*=9.2 Hz, 3.2 Hz, 1H), 3.84 (s, 1H), 4.47 (br, 1H), 4.78-4.84 (br, 2H), 5.03 (br, 1H), 5.37 (s, 1H), 7.16 (d, *J*=8.8 Hz, 2H), 7.50 (d, *J*=8.8 Hz, 2H), 7.69 (d, *J*=8.8 Hz, 2H), 7.85 (d, *J*=8.8 Hz, 2H), 8.55 (d, *J*=13.2 Hz, 1H), 12.28 (s, 1H), 12.35 (d, *J*=13.2 Hz, 1H) ; **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 26.6, 61.0, 66.7, 70.0, 70.6, 75.0, 99.2, 102.1, 117.8, 119.7, 123.1 (q, *J*=33 Hz), 124.4(q, *J*=269 Hz), 126.1, 133.5, 141.9, 154.2, 155.4, 167.2, 197.1; **^{19}F NMR** (376 MHz, DMSO-d_6) δ = -60.27; **IR** (Neat, cm^{-1}): 3488, 3327, 2935, 2165, 2026, 1654, 1583, 1532, 1508, 1439, 1413, 1383, 1318, 1270, 1255, 1238, 1183, 1152, 1110, 1088, 1065, 1045, 1002, 964, 888, 847, 815, 780, 669; **HPLC** Purity: 99.57%; **$[\alpha]_D^{20}$** : +89.95 (C=0.52, $(CH_3)_2SO$); Anal. Calculated for $C_{24}H_{25}F_3N_2O_8$: C, 54.75; H, 4.79; N, 5.32, found: C, 54.70; H, 4.40; N, 5.08; Isolated Yield: 410 mg, 93.9%.

(S,Z)-3-oxo-N-(2-oxotetrahydrofuran-3-yl)-2-((pyrazin-2-ylamino)methylene)hexanamide (3x):



Faint yellow solid: mp. 184.5-186.4°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 1.00 (t, *J*=7.6 Hz, 3H), 1.67-1.76 (m, 2H), 2.36-2.44 (m, 1H), 2.66-2.71 (m, 1H), 2.74 (t, *J*=7.2 Hz, 2H), 4.28-4.34 (m, 1H), 4.51-4.61 (m, 2H), 8.29-8.34 (m, 3H), 9.10 (d, *J*=11.2 Hz, 1H), 10.20 (d, *J*=6.8 Hz, 1H), 12.77 (d, *J*=11.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 13.9, 18.7, 29.4, 39.8, 48.5, 65.8, 106.0, 135.8, 140.2, 142.4, 147.1, 149.3, 169.2, 174.8, 199.8; **IR** (Neat, cm^{-1}): 3240, 2965, 1774, 1627, 1594, 1524, 1481, 1438, 1383, 1342, 1312, 1285, 1207, 1169, 1142, 1063, 1024, 1012, 981, 948, 897, 878, 842, 797, 754, 680; **HPLC** Purity: 99.79%; **$[\alpha]_D^{20}$** : +15.24 (c=1, $CHCl_3$); Anal. Calculated for $C_{15}H_{18}N_4O_4$: C, 56.60; H, 5.70; N, 17.60, found: C, 56.92; H, 5.74; N, 16.79; Isolated Yield: 220 mg 93.1%.

Reference:

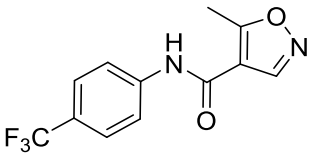
1. (a) A. Riahi, M. Shkoor, O. Fatunsin, R. A. Khera, C. Fischer, P. Langer, Org. Biomol. Chem. 2009, 7, 4248–4251. (b) A. X. Wang, O. Xie, B. Lane, K. W. Mollison, G. C. Hsieh, K. Marsh, M. P. Sheets, J. R. Luly, M. J. Coghlan, Bioorg. Med. Chem. Lett. 1998, 8, 2787-2792. (c) A. E. Bouakher, R. L. Goff, J. Tasserie, J. Lhoste, A. Martel, S. Comesse, Org. Lett. 2016, 18, 2383−2386.

4. Synthesis[1] of Leflunomide (4a) & Teriflunomide (4b):

Typical procedure for 4a (Leflunomide): To a solution of 2-ethoxymethyleneacetoacetyl-(4-trifluoromethyl)aniline **1b** (0.5 g, 1.66 mmol) in ethanol (3 ml) was slowly added to an ice cooled solution of hydroxylamine hydrochloride (0.12 g, 1.72 mmol) in 2 M NaOH (0.91 ml). The mixture was heated to reflux for 1 hour, cooled to room temperature and evaporated to dryness. The residue was dissolved in ethyl acetate (50 ml) and water (10 ml). The organic layer was separated, extracted with water to remove inorganics, dried with sodium sulfate and the ethyl acetate layer was evaporated. The residue was crystallised in toluene to yield of **4a**.

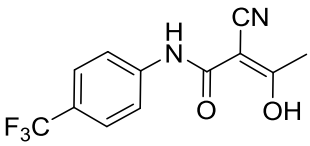
Typical procedure for 4b (Teriflunomide): To a solution of 5-Methylisoxazole-4-(4-trifluoromethyl)carboxanilide **4a** in (0.20 g, 0.74 mmol) methanol (5 ml), pH was adjusted to 1 with concentrated hydrochloric acid and the suspension was stirred during 24 hours. The suspension was then filtered and dried under vacuum to obtain a white solid. The solid was then crystallised with acetone (5 ml) to afford compound **4b**.

5-Methylisoxazole-4-(4-trifluoromethyl)carboxanilide (4a):



Off-white solid; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 2.69 (s, 3H), 7.72 (d, J= 8.4 Hz, 2H), 7.93 (d, J= 8.4 Hz, 2H), 9.10 (s, 1H), 10.35 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 12.1, 111.7, 119.9, 122.8 (q, *J*=32 Hz, 124.5 (q, *J*=269 Hz), 125.9, 142.2, 149.0, 159.5, 173.3; Isolated Yield: 0.358 g, 80%.

2-Cyano-3-hydroxy-N-[4-(trifluoromethyl)phenyl]-2-butenamide (4b):



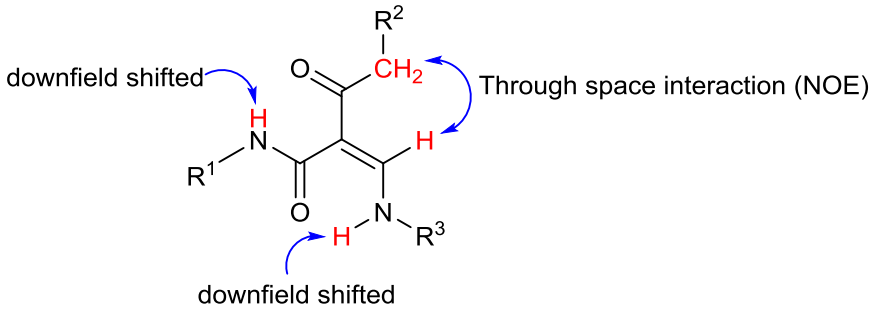
White solid; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 2.26 (s, 3H), 7.67 (d, J= 8.4 Hz, 2H), 7.78 (d, J= 8.4 Hz, 2H), 10.81 (br, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ = 23.4, 80.5, 119.9, 122.7 (q, *J*=32 Hz, 124.4 (q, *J*=269 Hz), 125.7, 141.8, 166.4, 187.1; Isolated Yield: 0.168 g, 84%.

Reference:

1. (a) K. P. Hirth, E. Mann, L. K. Shawyer, A.Ullrich, I.Szekely, T.Bajor, J.Haimichael, L.Orfi, A.Levitzki, A.Gazit, P. C. Tang, R.Lammers, US Pat., 6,331,555 B1, 2001. (b) T-X. Metro, J. Bonnamour, T. Reidon, A. Duprez, J. Sarpoulet, J. Martinez, F. Lamaty, Chem. Commun., 2012, 48, 11781.

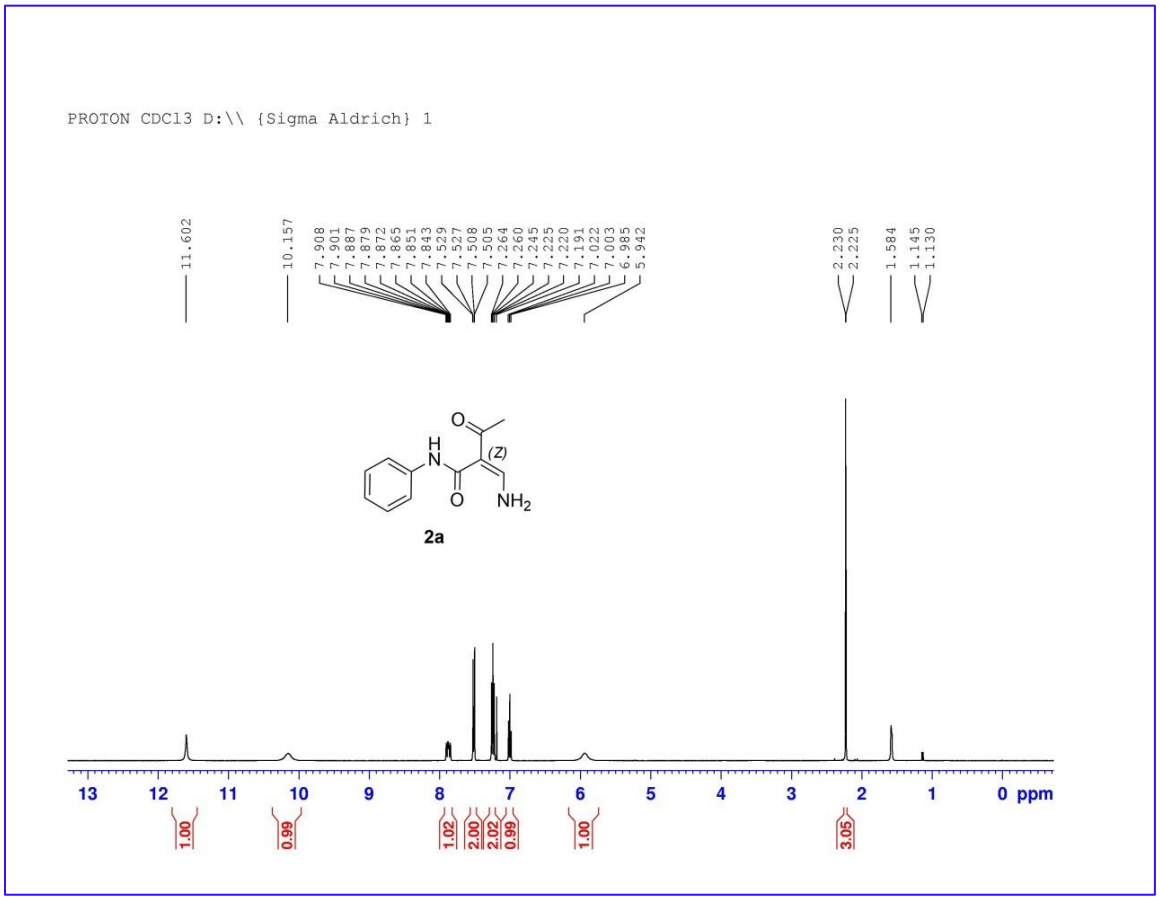
5. Chemical Shift (δ) data of NH in ppm:

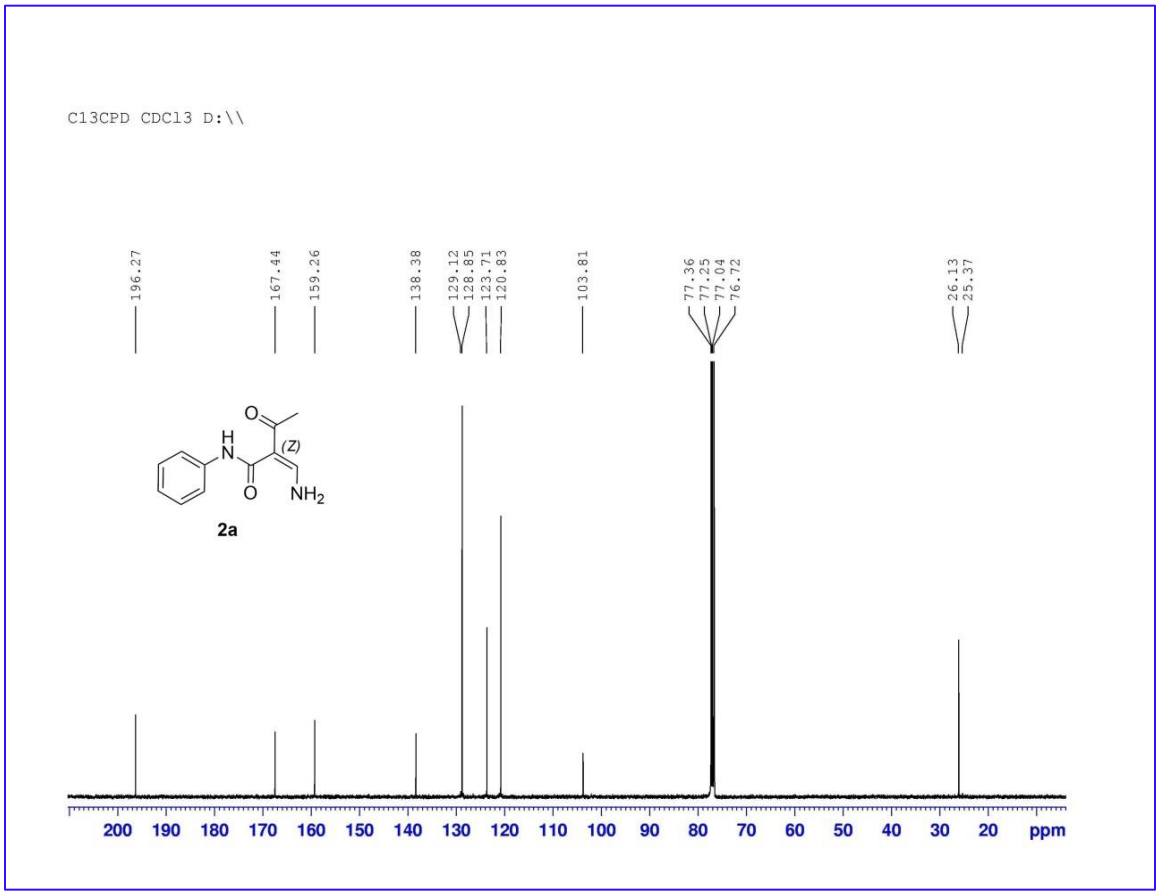
Code	$\delta NH_{(1)}$	$\delta NH_{(2)}$	$\delta NH_{(3)}$ If R^3=H	Solvent
2a	11.60	10.15	5.94	$CDCl_3$
2b	12.26	9.83	8.82	DMSO-d_6
2c	12.07	9.80	8.77	DMSO-d_6
2d	9.98	9.73	8.41	DMSO-d_6
2e	10.19	9.98	5.98	$CDCl_3$
2f	10.19	9.96	6.01	$CDCl_3$
2g	12.28	10.08	5.92	$CDCl_3$
3a	12.36	10.50	-	DMSO-d_6
3b	12.08	12.46	-	$CDCl_3$
3c	12.18	12.34	-	DMSO-d_6
3d	12.30	10.78	-	DMSO-d_6
3e	11.96	12.81	-	$CDCl_3$
3f	12.27	10.51	-	DMSO-d_6
3g	12.17	10.65	-	DMSO-d_6
3h	12.17	10.65	-	DMSO-d_6
3i	12.30	10.85	-	DMSO-d_6
3j	12.21	10.70	-	DMSO-d_6
3k	11.98	11.19	-	DMSO-d_6
3l	12.00	13.24	-	$CDCl_3$
3m	12.06	12.70	-	$CDCl_3$
3n	12.06	12.85	-	DMSO-d_6
3o	11.89	12.32	-	DMSO-d_6
3p	11.89	12.85	-	DMSO-d_6
3q	11.77	12.54	-	DMSO-d_6
3r	12.06	12.96	-	$CDCl_3$
3s	11.72	12.51	-	DMSO-d_6
3t	12.33	10.47	-	DMSO-d_6
3u	11.75	13.16	-	$CDCl_3$
3v	12.96	10.71	-	DMSO-d_6
3w	12.28	12.35	-	DMSO-d_6
3x	10.20	12.77	-	$CDCl_3$

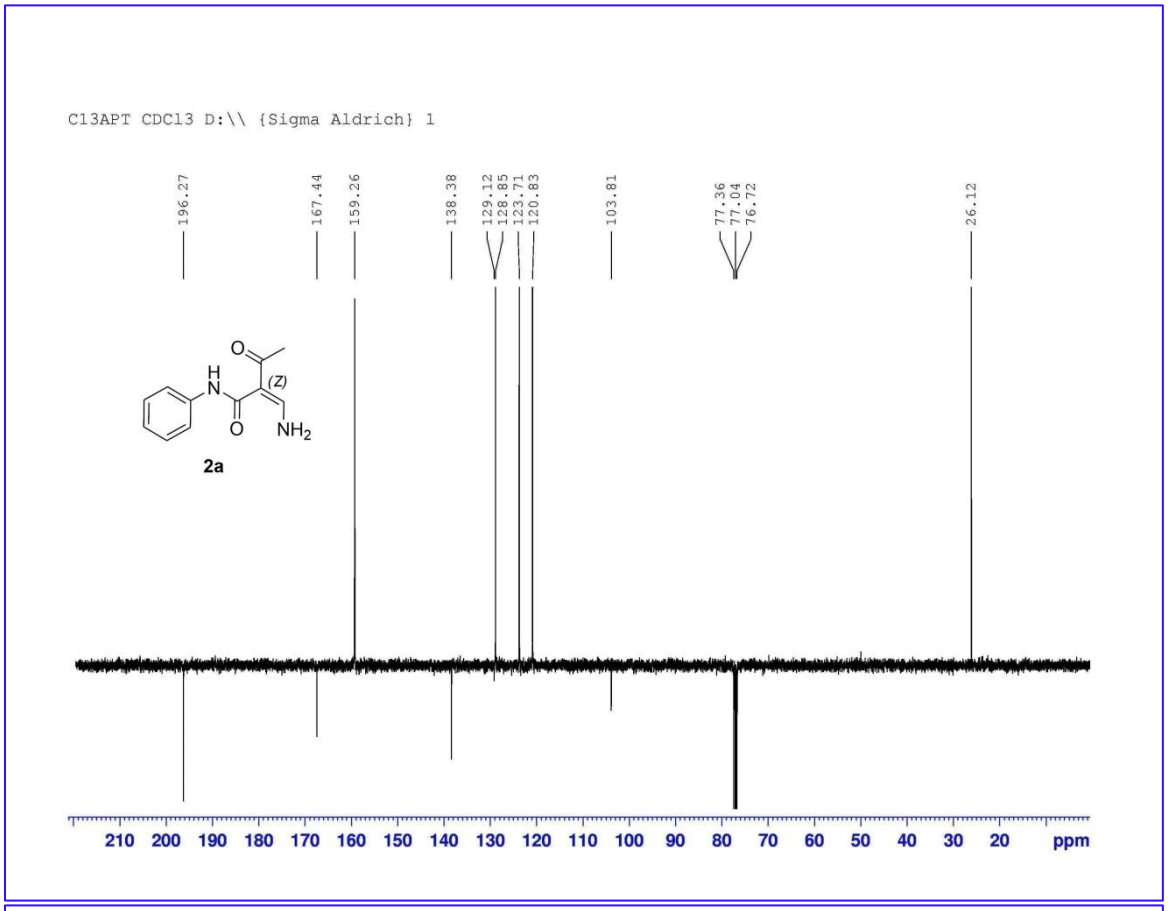


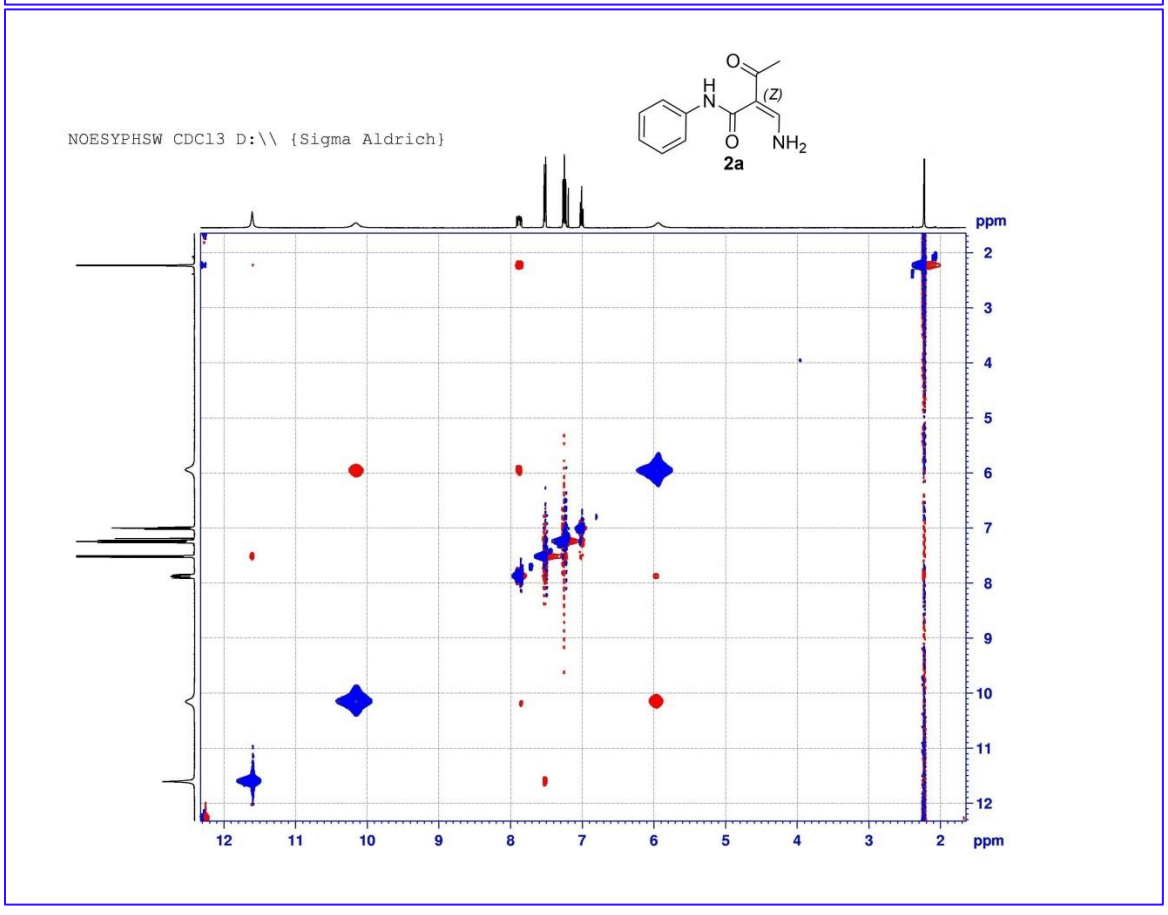
^{1}H NMR of **2** & **3** confirms intramolecular hydrogen bonding's between Carbonyl and NH groups. Isomer configuration was assigned by NOE interaction.

6. Copies of 1H, 13C, 19F NMR and NOE spectra.

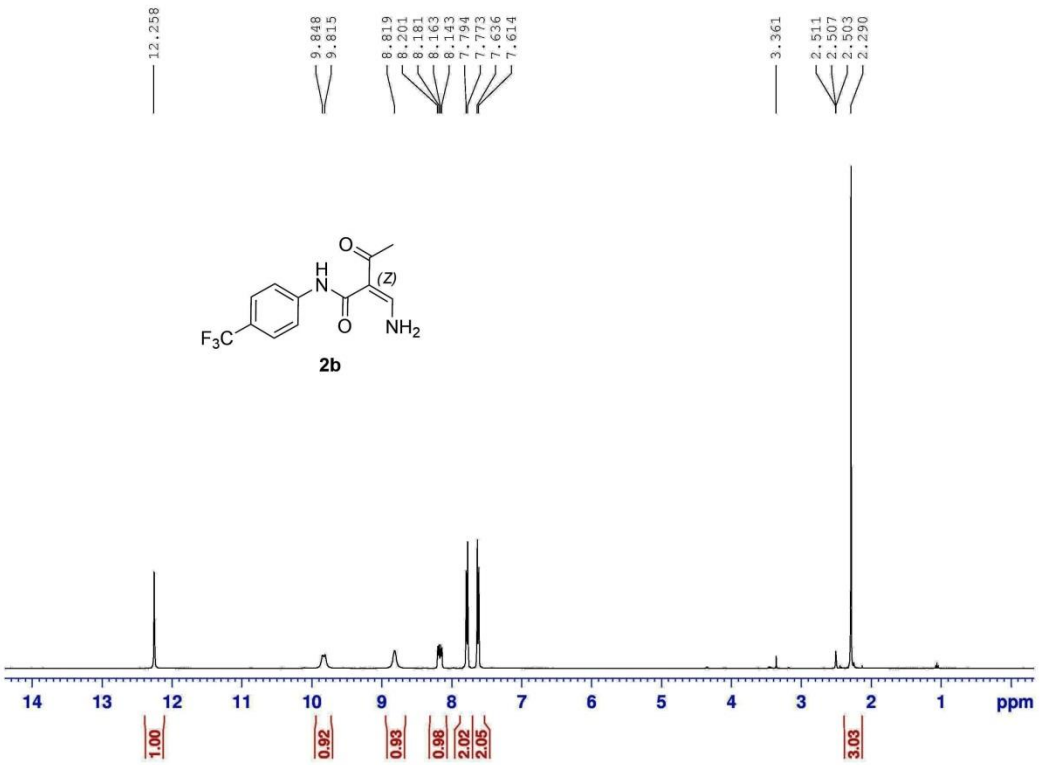




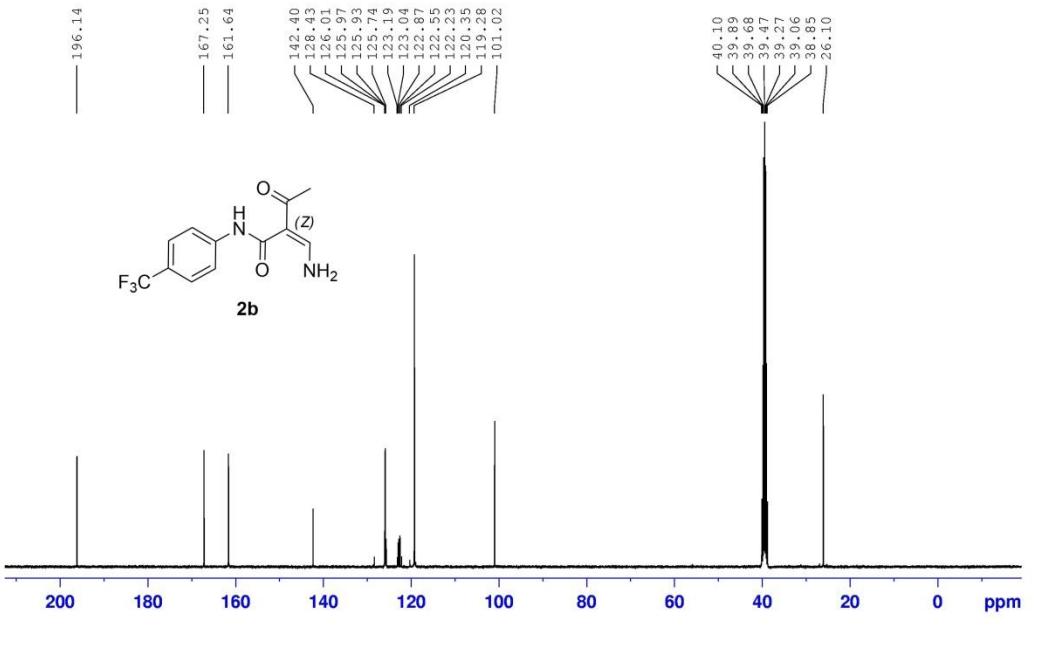

C13APT CDCl3 D:\\ {Sigma Aldrich} 1
196.27
167.44
159.26
138.38
129.12
128.85
123.71
120.83
103.81
77.36
77.04
76.72
26.12
O
H
N
(Z)
O
NH2
2a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


NOESYPHSW CDCl3 D:\\ {Sigma Aldrich}
O
H
N
(Z)
O
NH2
2a
ppm
2
3
4
5
6
7
8
9
10
11
12
12 11 10 9 8 7 6 5 4 3 2 ppm

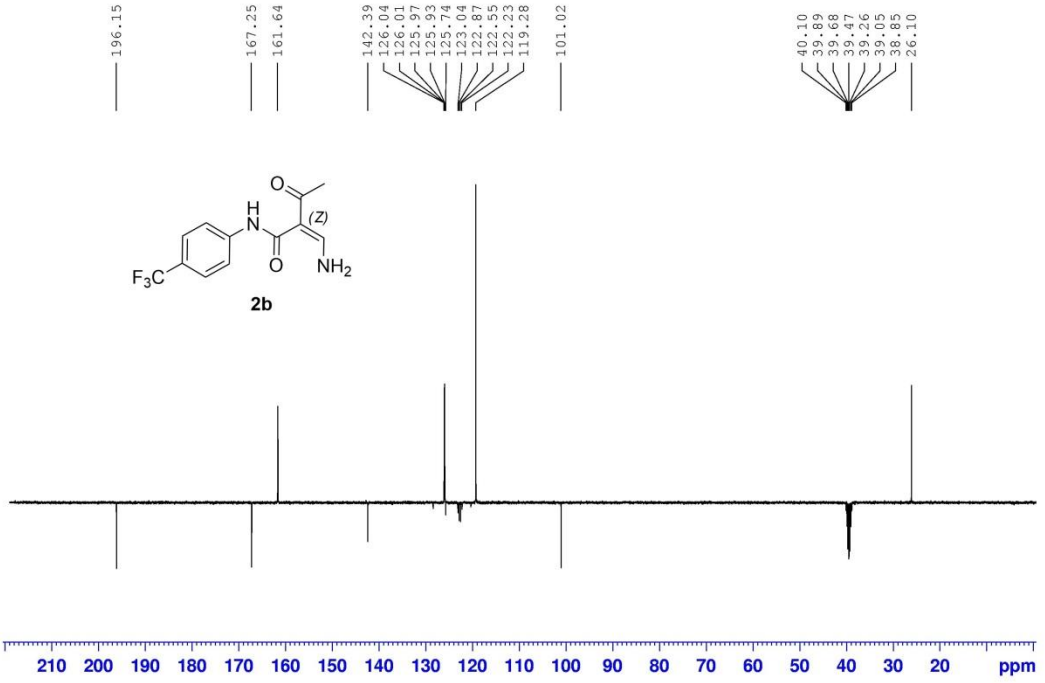
PROTON DMSO D:\\ {Sigma Aldrich} 1



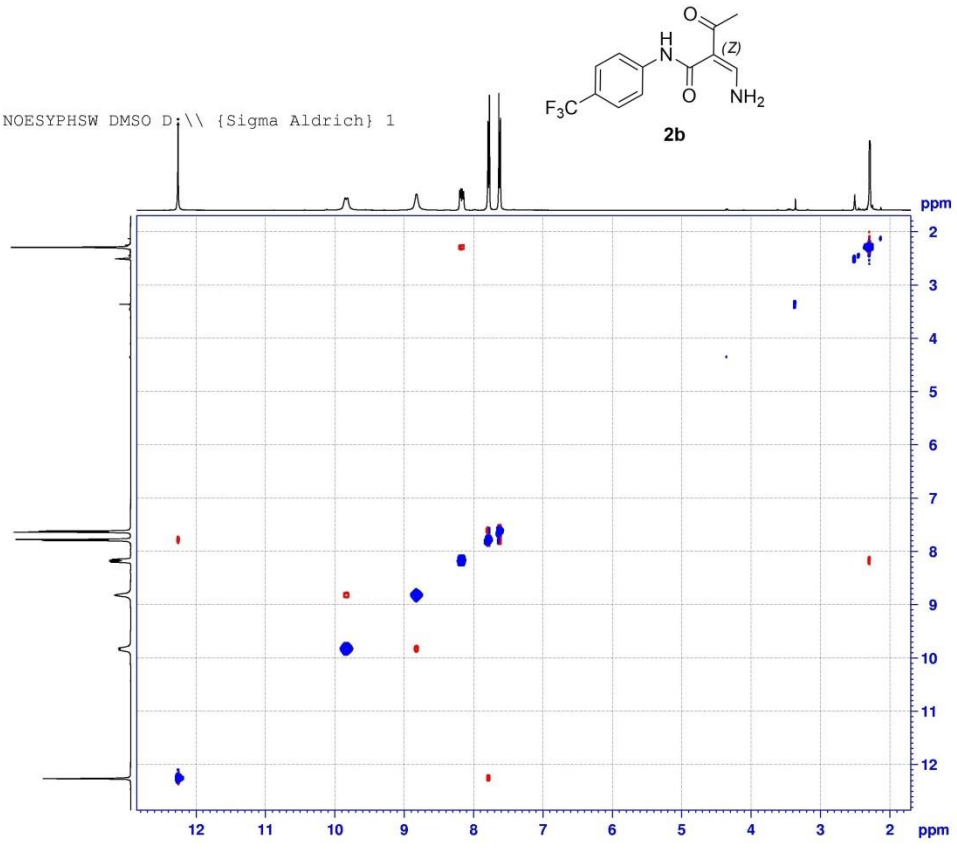
C13CPD DMSO D:\\ {Sigma Aldrich} 1



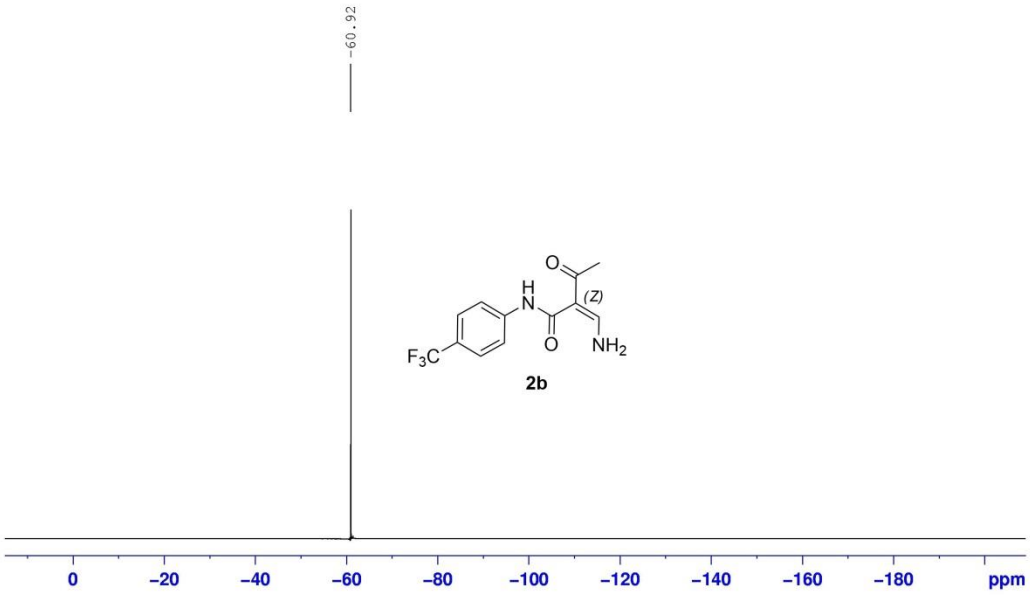
C13APT DMSO D:\\ {Sigma Aldrich} 1



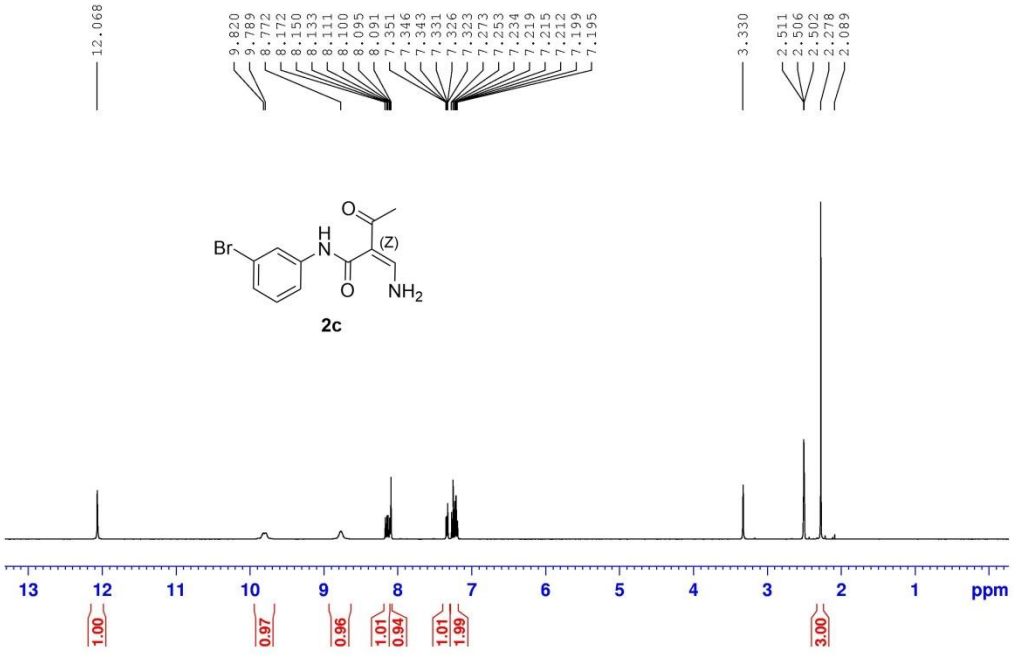
NOESYPHSW DMSO D:\\ {Sigma Aldrich} 1



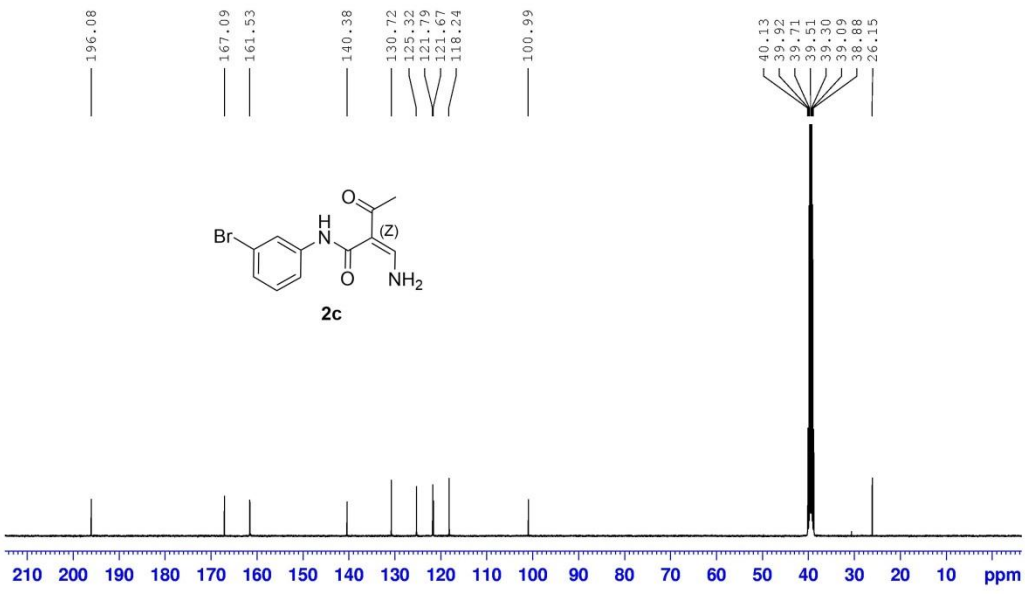
F19 DMSO D:\\ {Sigma Aldrich} 1



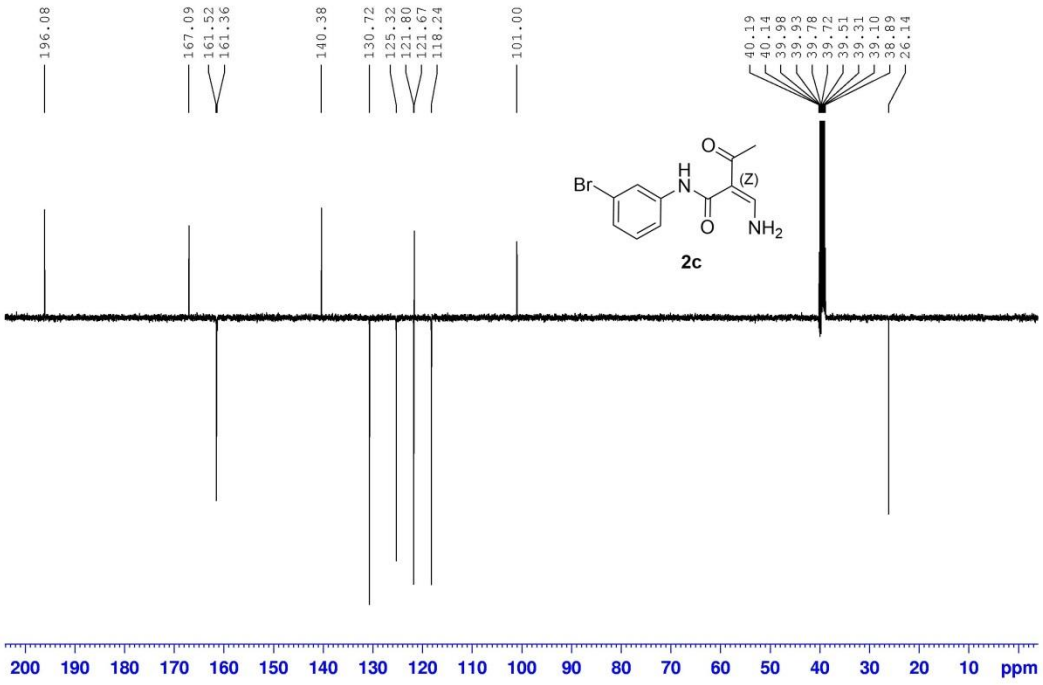
PROTON DMSO D:\\ {Sigma Aldrich} 1

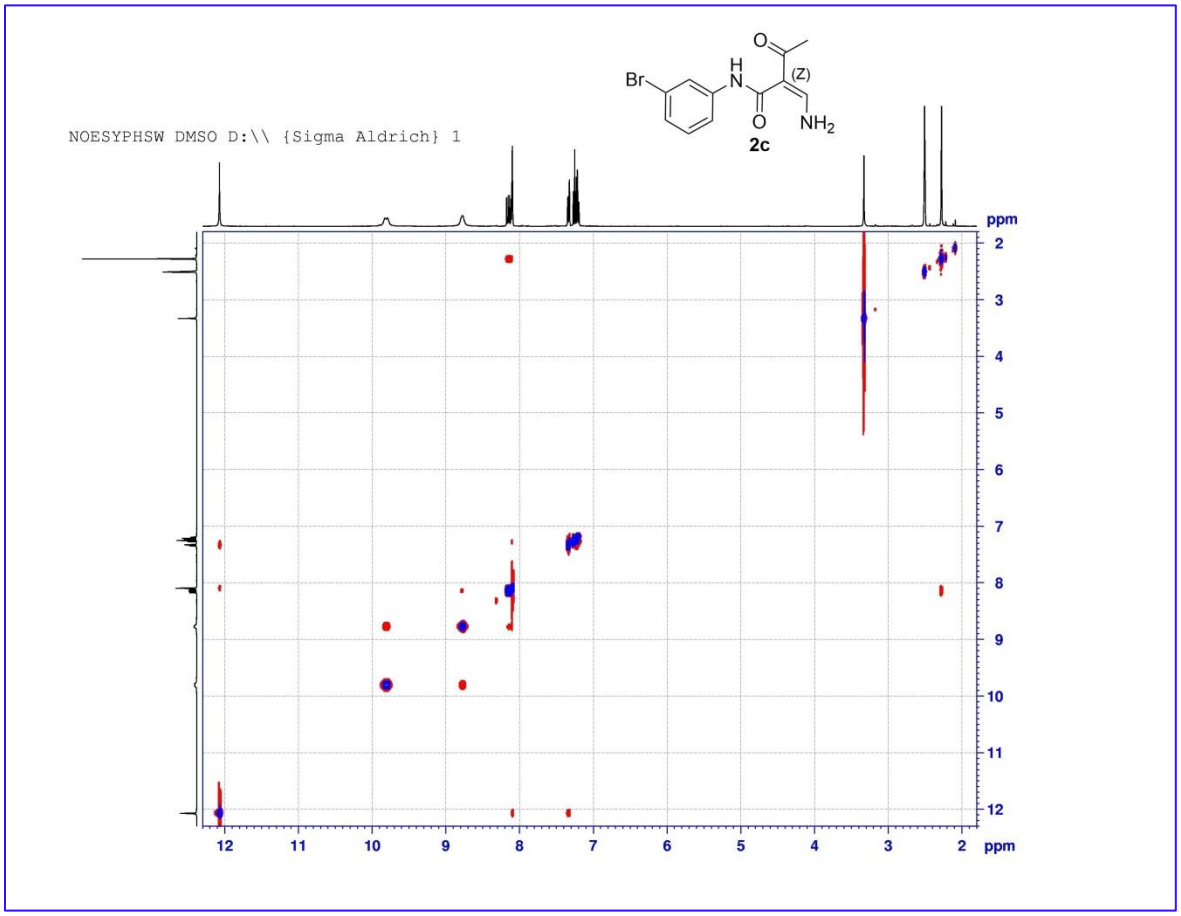


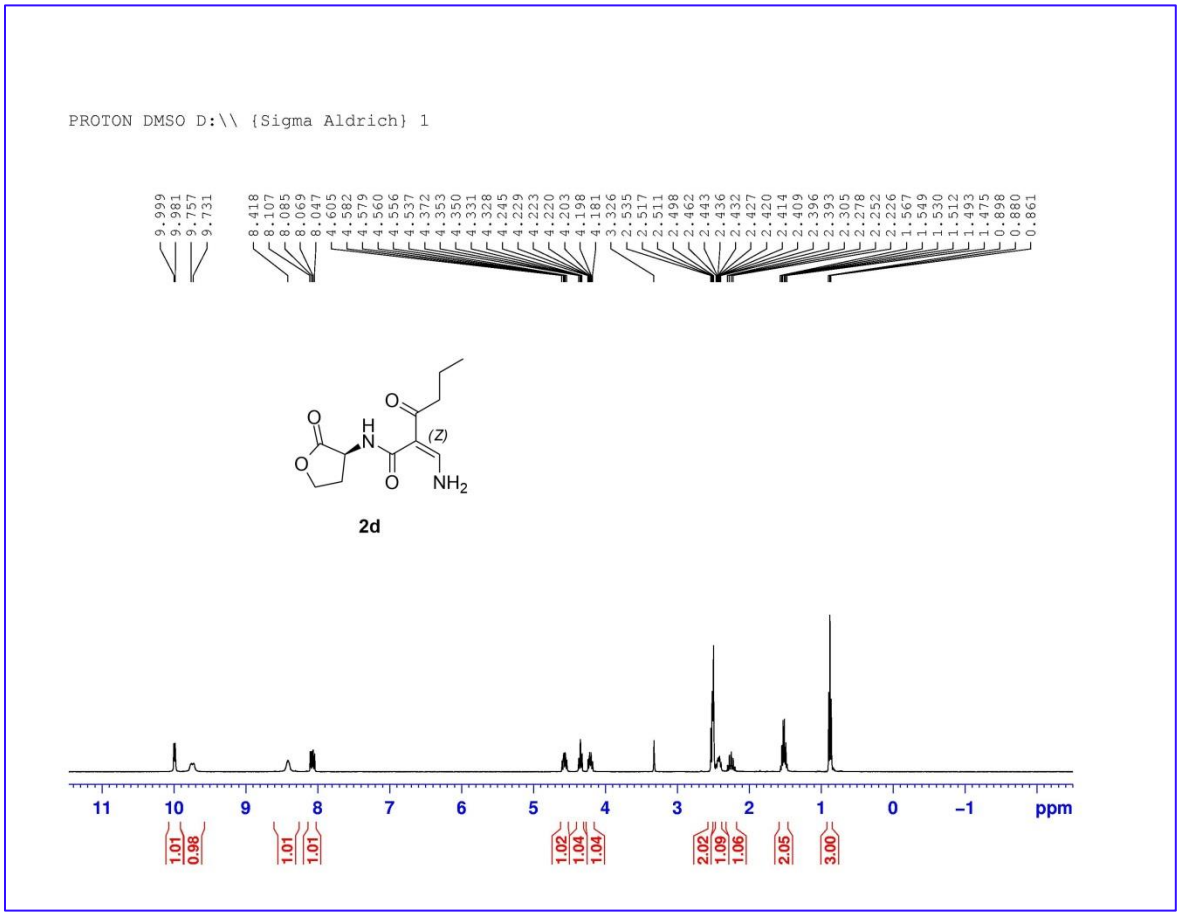
C13CPD DMSO D:\\ {Sigma Aldrich} 1



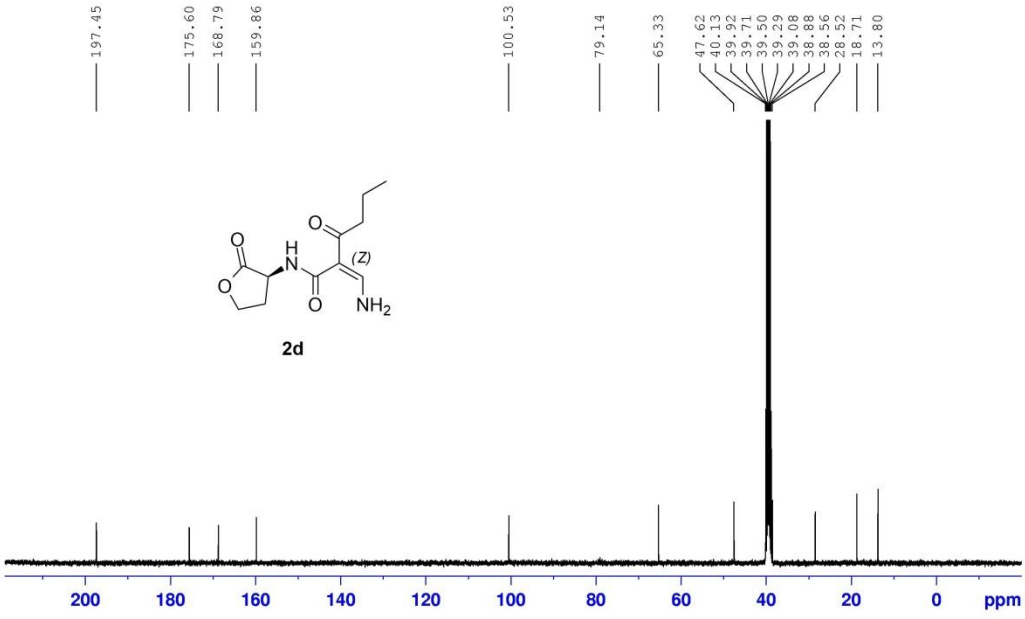
C13APT DMSO D:\\ {Sigma Aldrich} 1




NOESYPHSW DMSO D:\\ {Sigma Aldrich} 1
Br
H
N
O
(Z)
NH2
2c
ppm
12
11
10
9
8
7
6
5
4
3
2

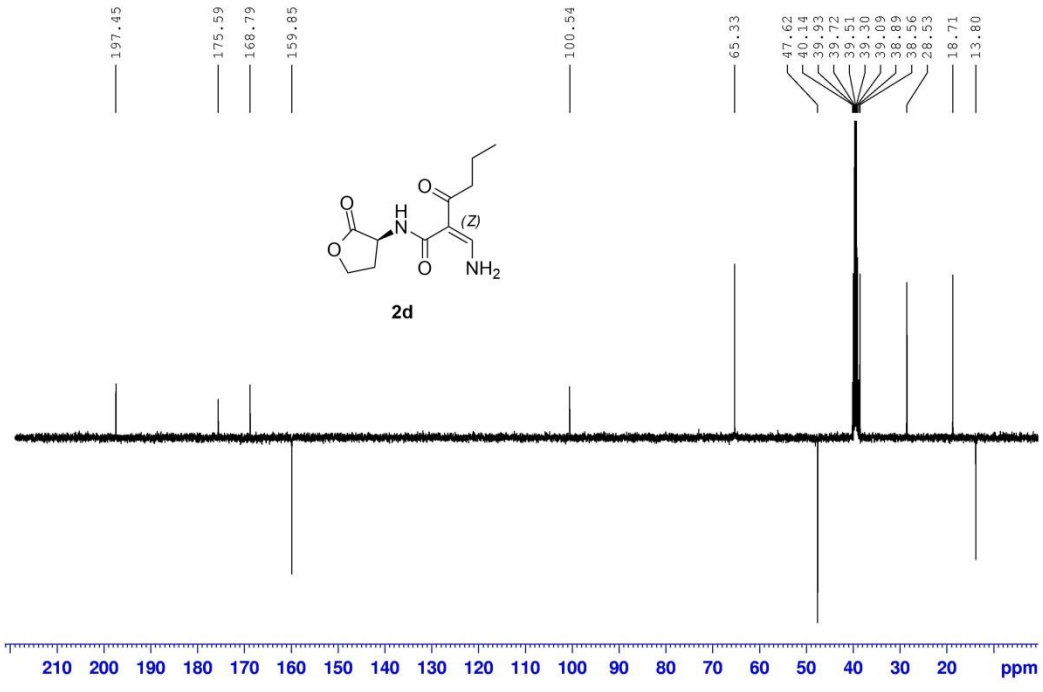

PROTON DMSO D:\\ {Sigma Aldrich} 1
9.999
9.981
9.757
9.731
8.418
8.107
8.085
8.069
8.047
4.605
4.582
4.579
4.560
4.556
4.537
4.372
4.353
4.350
4.331
4.328
4.245
4.229
4.223
4.220
4.203
4.198
4.181
3.326
2.535
2.517
2.511
2.498
2.462
2.443
2.436
2.432
2.427
2.420
2.414
2.409
2.396
2.393
2.305
2.278
2.252
2.226
1.567
1.549
1.530
1.512
1.493
1.475
0.898
0.880
0.861
O
H
N
O
(Z)
O
O
NH2
2d
11
10
9
8
7
6
5
4
3
2
1
0
−1
ppm
1.01
0.98
1.01
1.01
1.02
1.04
1.04
2.02
1.09
1.06
2.05
3.00

C13CPD DMSO D:\\ {Sigma Aldrich} 1

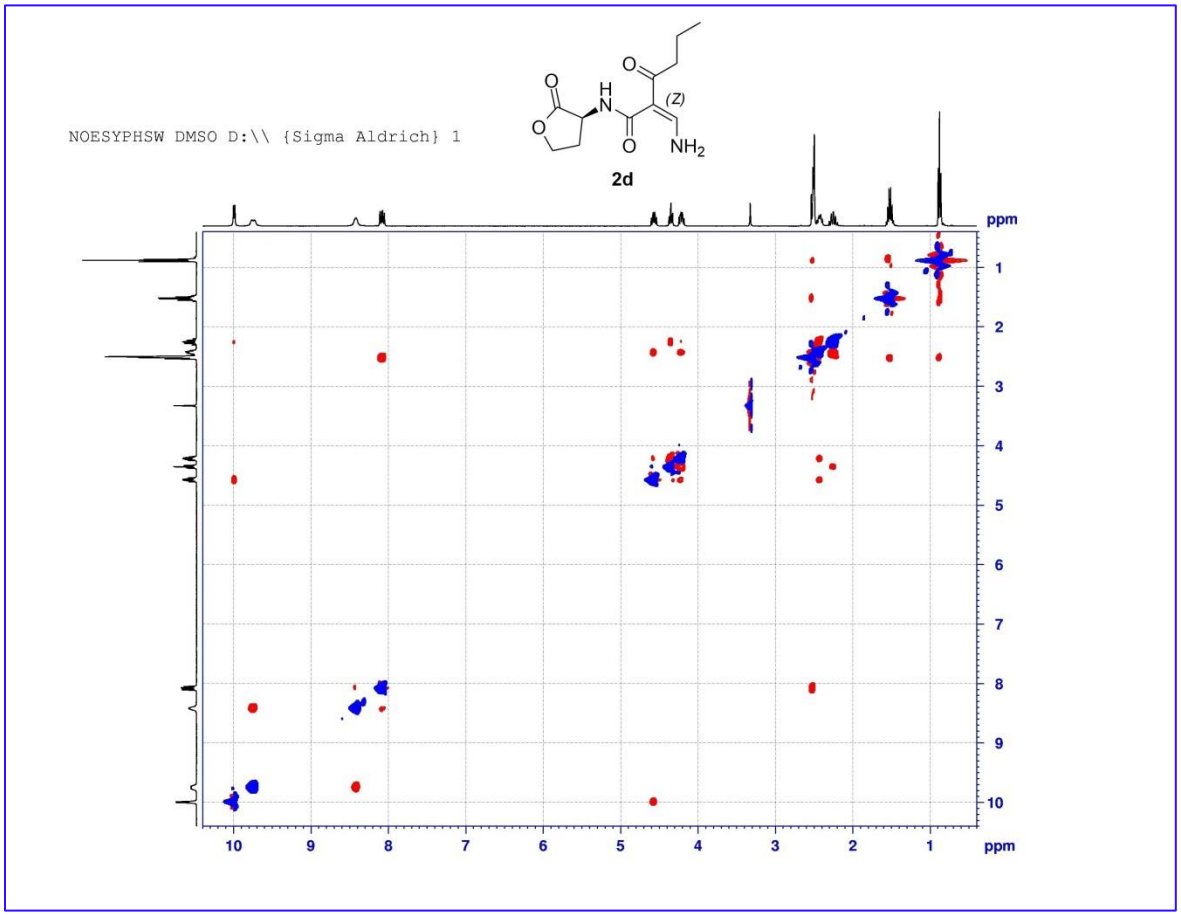


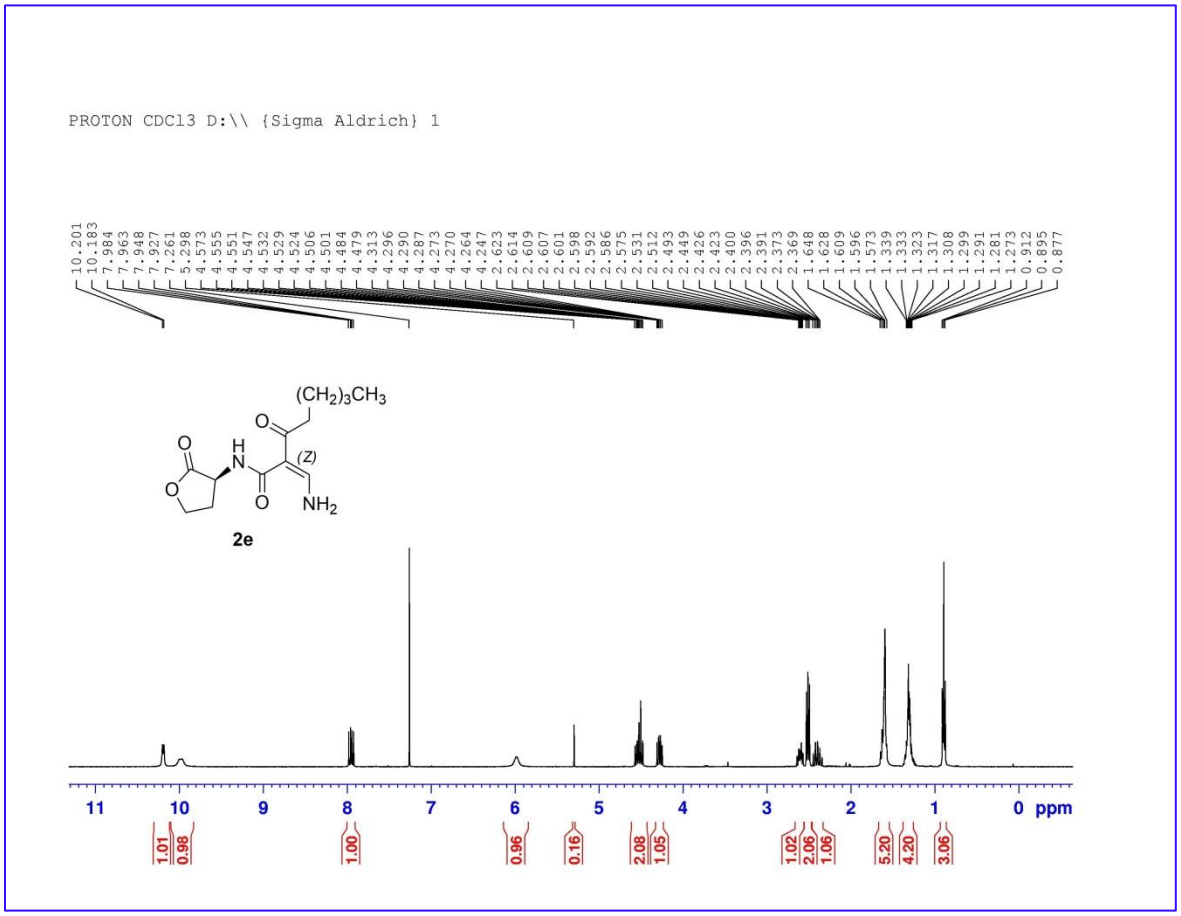
2d

C13APT DMSO D:\\ {Sigma Aldrich} 1

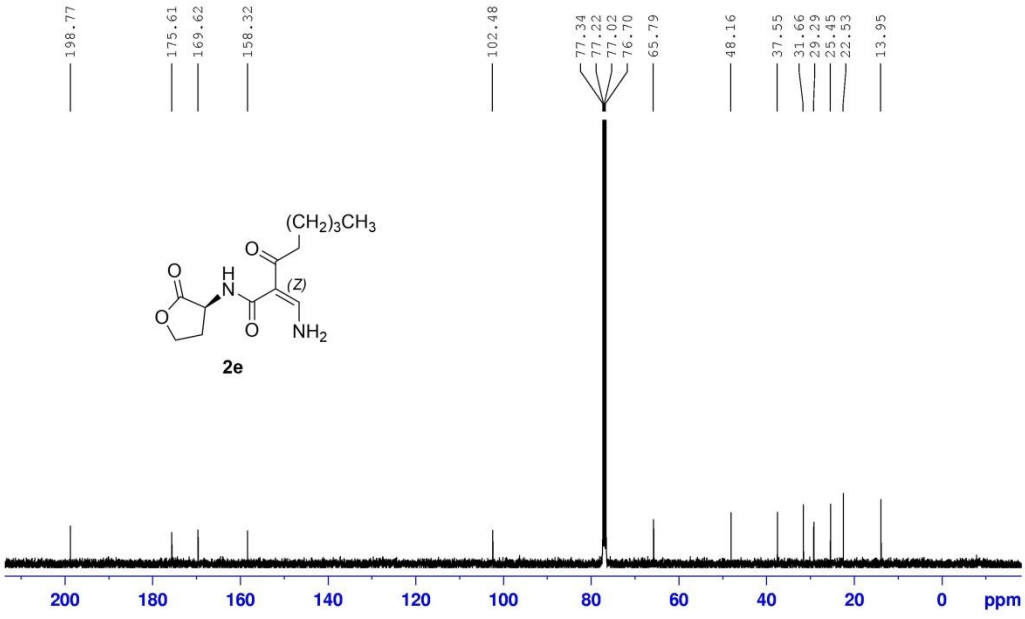


2d

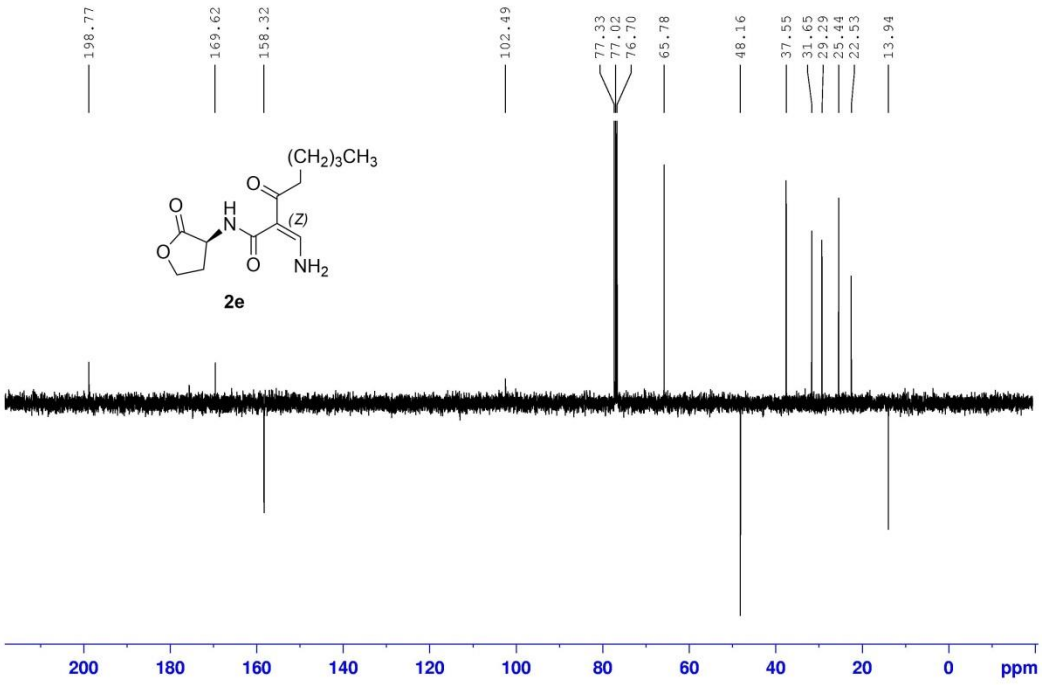

NOESYPHSW DMSO D:\\ {Sigma Aldrich} 1
2d
ppm
ppm

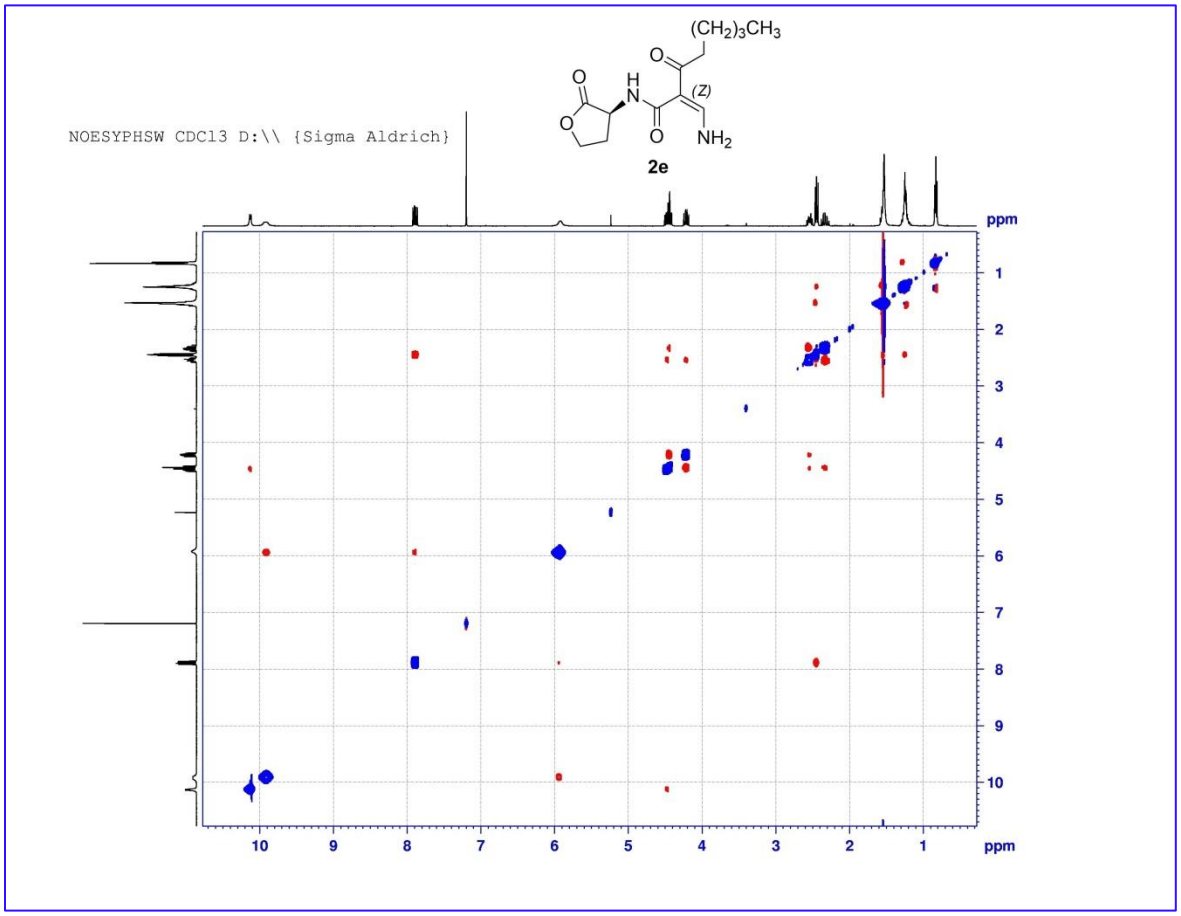

PROTON CDCl3 D:\\ {Sigma Aldrich} 1
10.201
10.183
7.984
7.963
7.948
7.927
7.261
5.298
4.573
4.555
4.551
4.547
4.532
4.529
4.524
4.506
4.501
4.484
4.479
4.313
4.296
4.290
4.287
4.273
4.270
4.264
4.247
2.623
2.614
2.609
2.607
2.601
2.598
2.592
2.586
2.575
2.531
2.512
2.493
2.449
2.426
2.423
2.400
2.396
2.391
2.373
2.369
1.648
1.628
1.609
1.596
1.573
1.339
1.333
1.323
1.317
1.308
1.299
1.291
1.281
1.273
0.912
0.895
0.877
2e
ppm
1.01
0.98
1.00
0.96
0.16
2.08
1.05
1.02
2.06
1.06
5.20
4.20
3.06

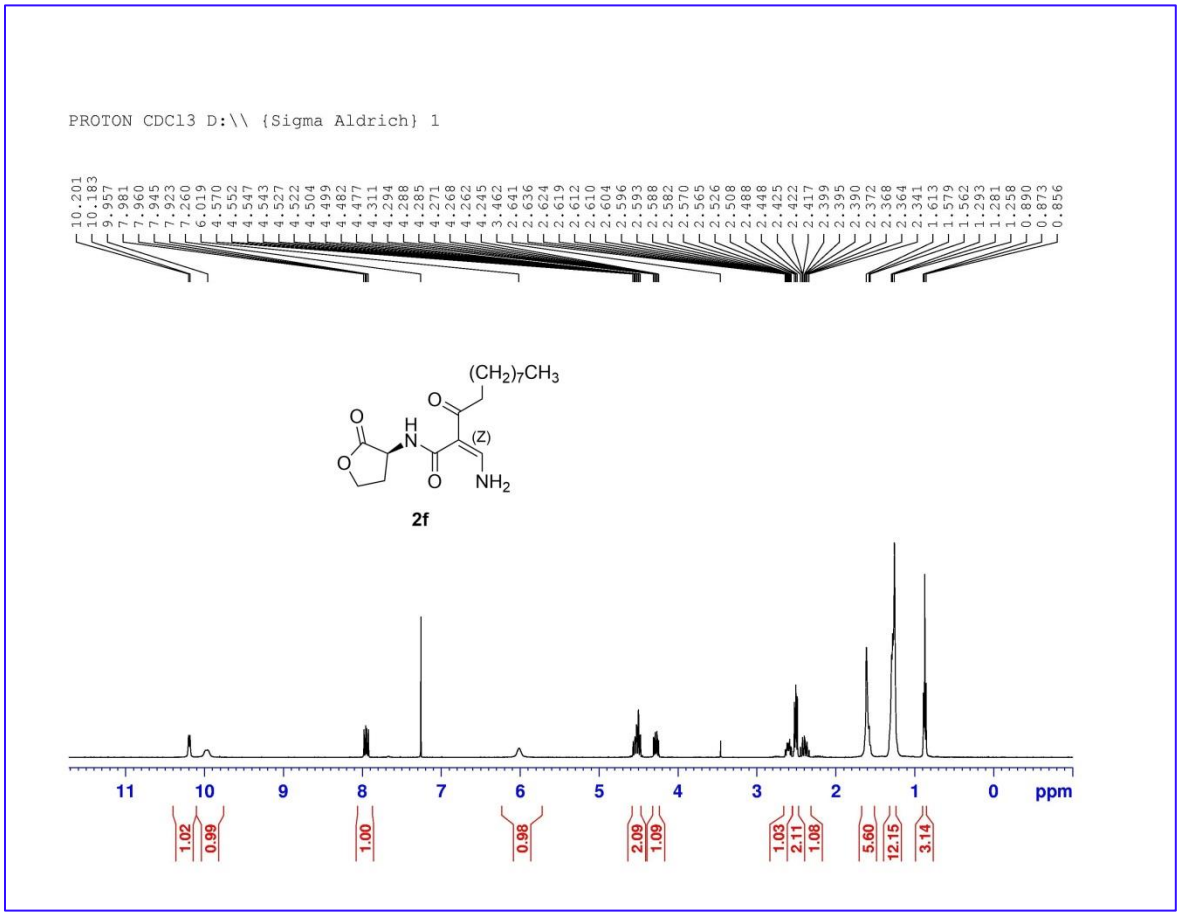
C13CPD CDCl3 D:\\ {Sigma Aldrich} 1



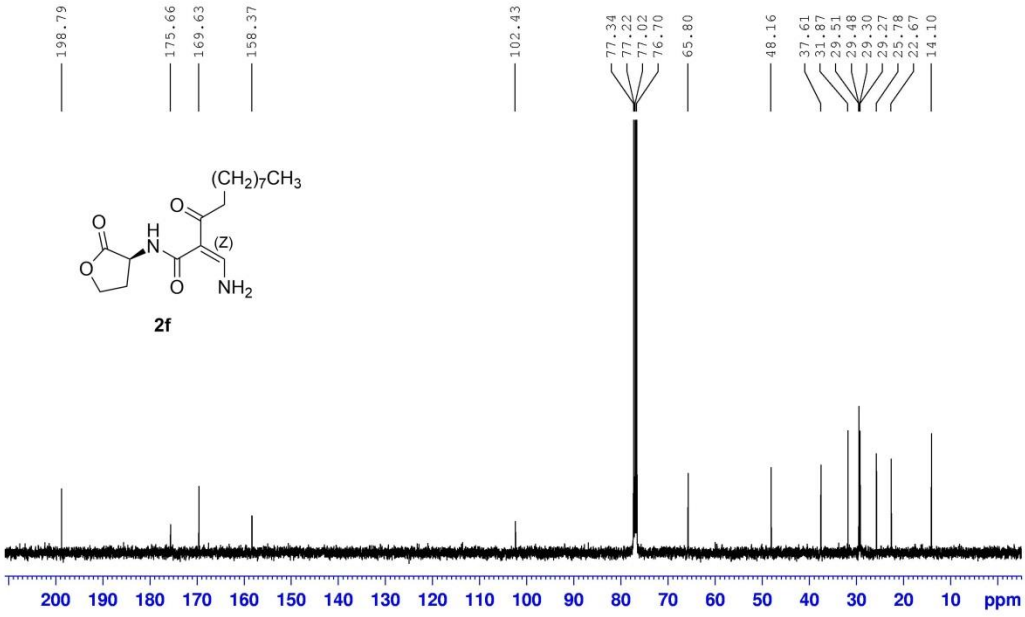
C13APT CDCl3 D:\\ {Sigma Aldrich} 1



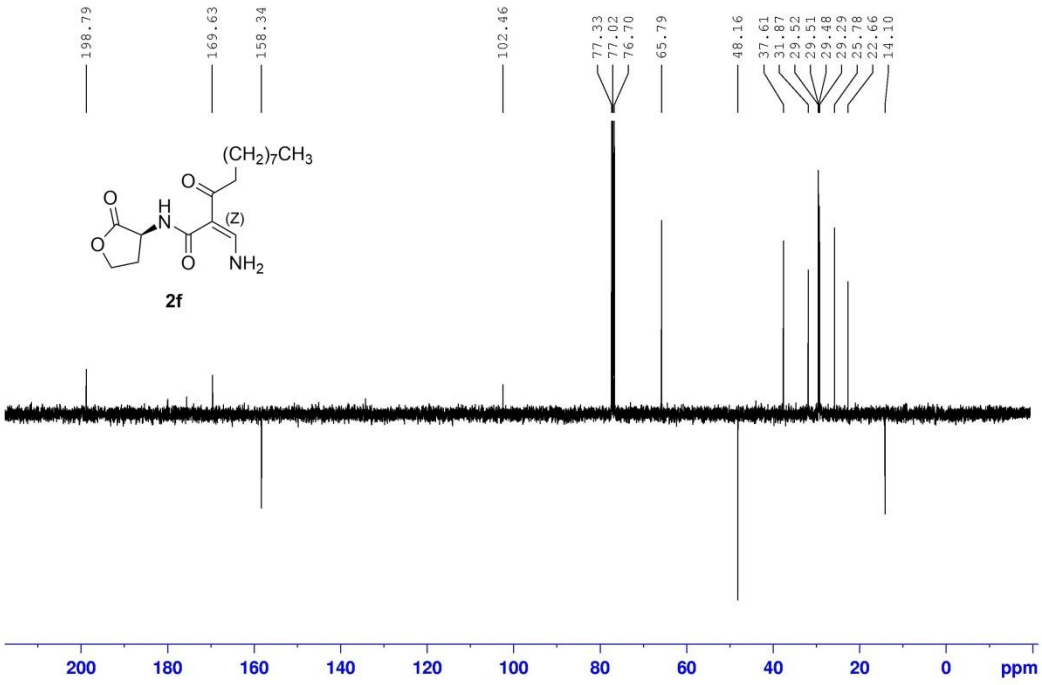

NOESYPHSW CDCl3 D:\\ {Sigma Aldrich}
(CH2)3CH3
O
O
H
N
O
(Z)
O
NH2
2e
ppm
1
2
3
4
5
6
7
8
9
10
10
9
8
7
6
5
4
3
2
1
ppm

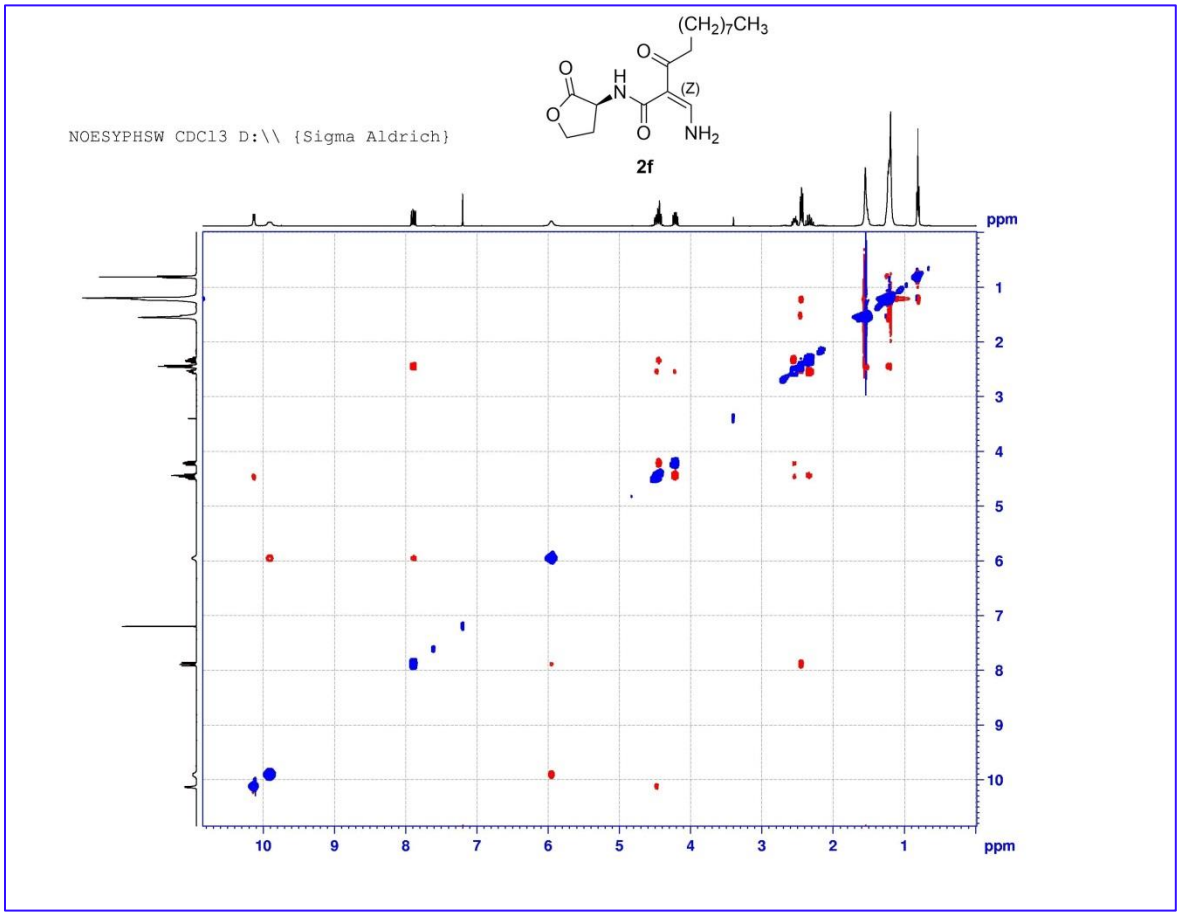

PROTON CDCl3 D:\\ {Sigma Aldrich} 1
10.201
10.183
9.957
7.981
7.960
7.945
7.923
7.260
6.019
4.570
4.552
4.547
4.543
4.527
4.522
4.504
4.499
4.482
4.477
4.311
4.294
4.288
4.285
4.271
4.268
4.262
4.245
3.462
2.641
2.636
2.624
2.619
2.612
2.610
2.604
2.596
2.593
2.588
2.582
2.570
2.565
2.526
2.508
2.488
2.448
2.425
2.422
2.417
2.399
2.395
2.390
2.372
2.368
2.364
2.341
1.613
1.579
1.562
1.293
1.281
1.258
0.890
0.873
0.856
(CH2)7CH3
O
O
H
N
O
(Z)
O
NH2
2f
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.02
0.99
1.00
0.98
2.09
1.09
1.03
2.11
1.08
5.60
12.15
3.14

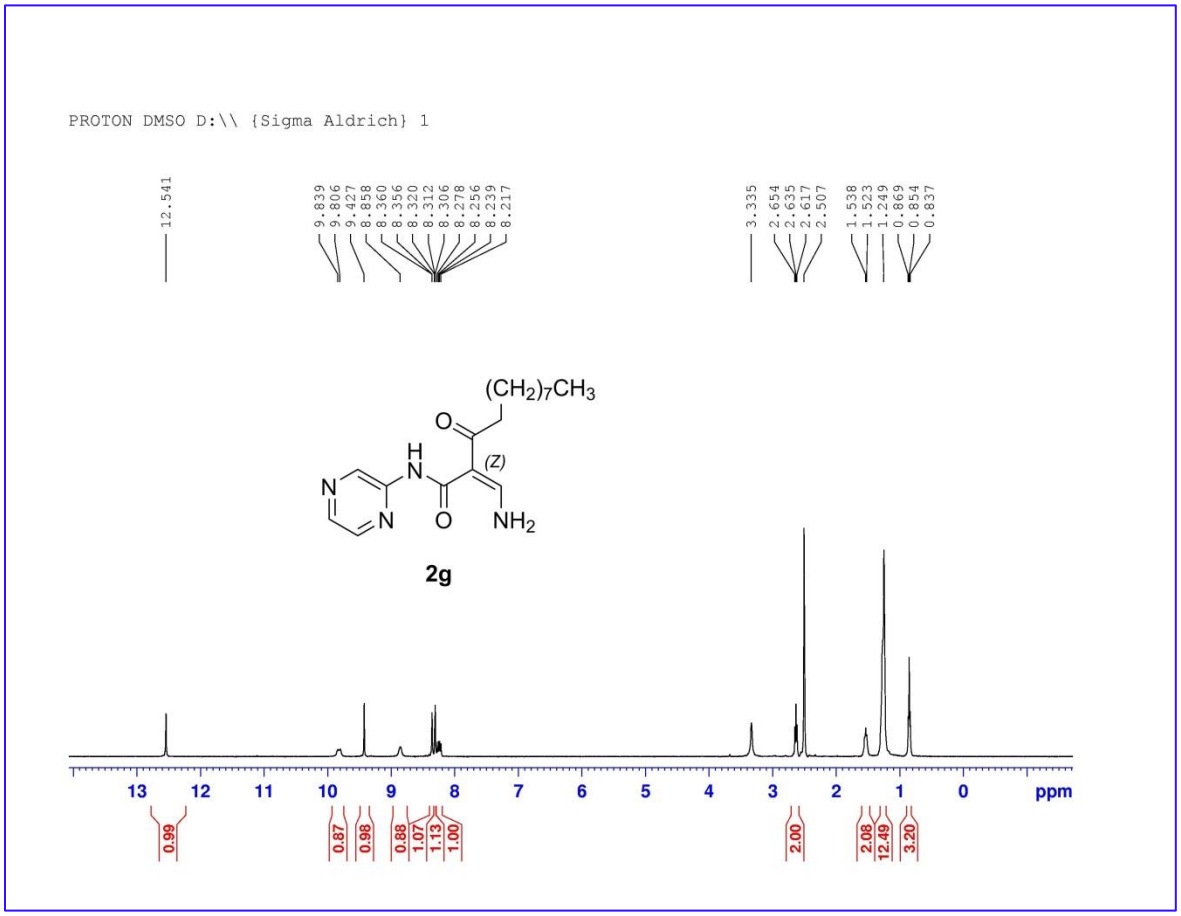
C13CPD CDCl3 D:\\ {Sigma Aldrich} 1



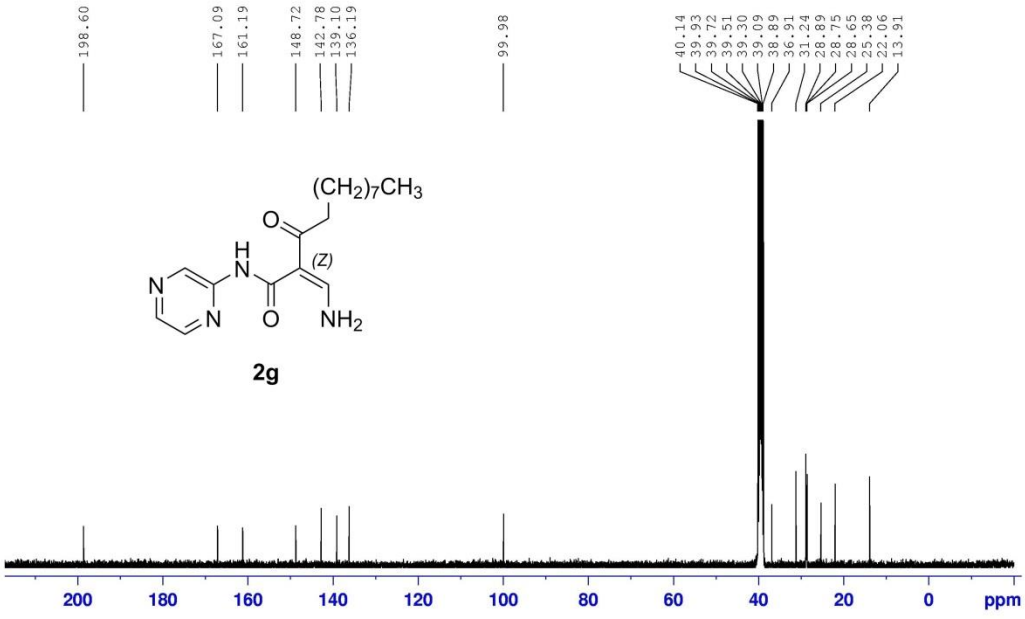
C13APT CDCl3 D:\\ {Sigma Aldrich} 1




NOESYPHSW CDCl3 D:\\ {Sigma Aldrich}
2f
ppm

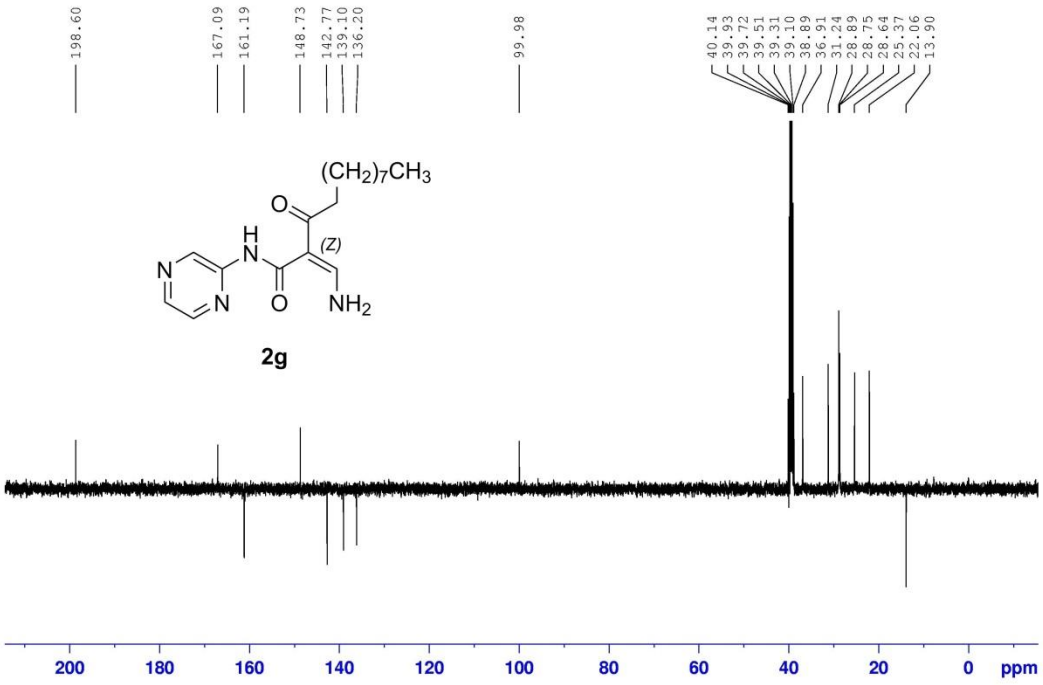

PROTON DMSO D:\\ {Sigma Aldrich} 1
12.541
9.839
9.806
9.427
8.858
8.360
8.356
8.320
8.312
8.306
8.278
8.256
8.239
8.217
3.335
2.654
2.635
2.617
2.507
1.538
1.523
1.249
0.869
0.854
0.837
2g
ppm
0.99
0.87
0.98
0.88
1.07
1.13
1.00
2.00
2.08
12.49
3.20

C13CPD DMSO D:\\ {Sigma Aldrich} 1

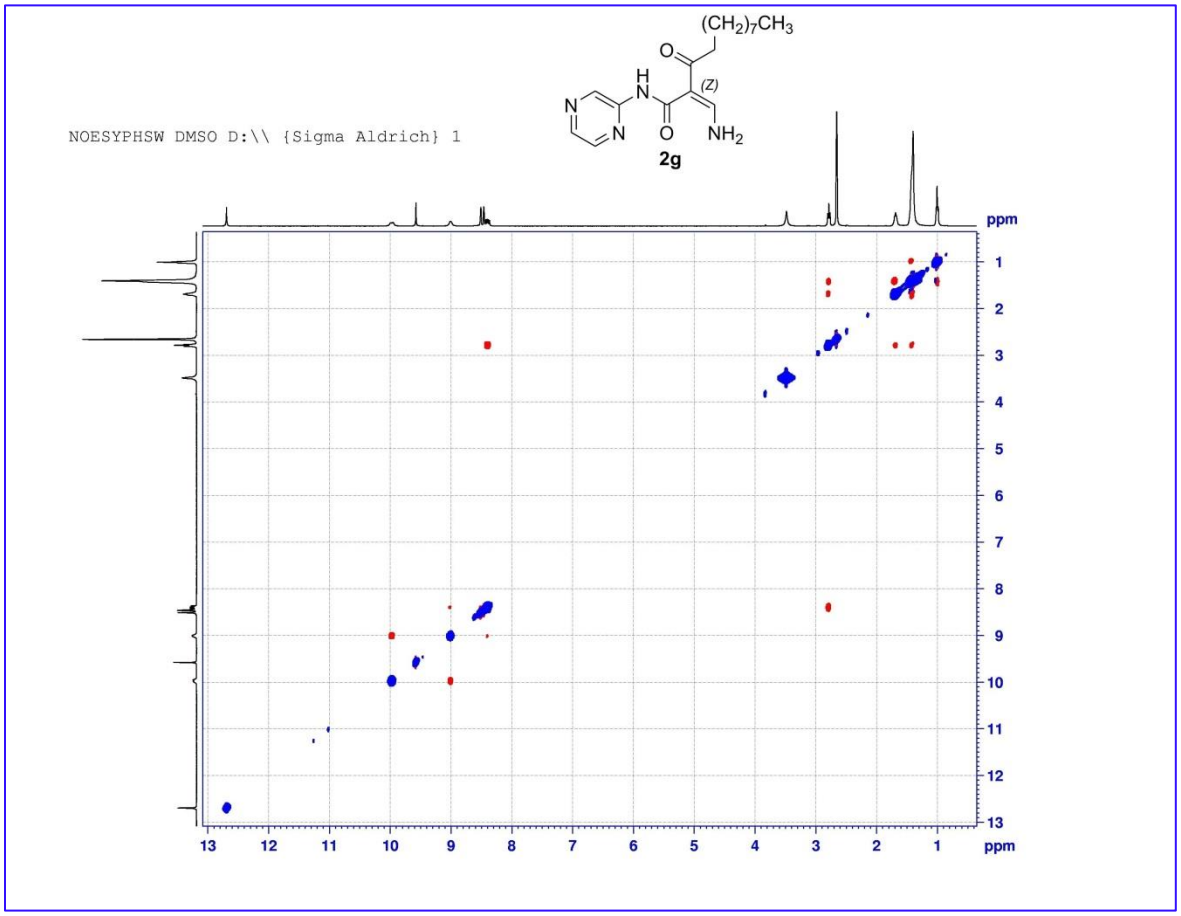


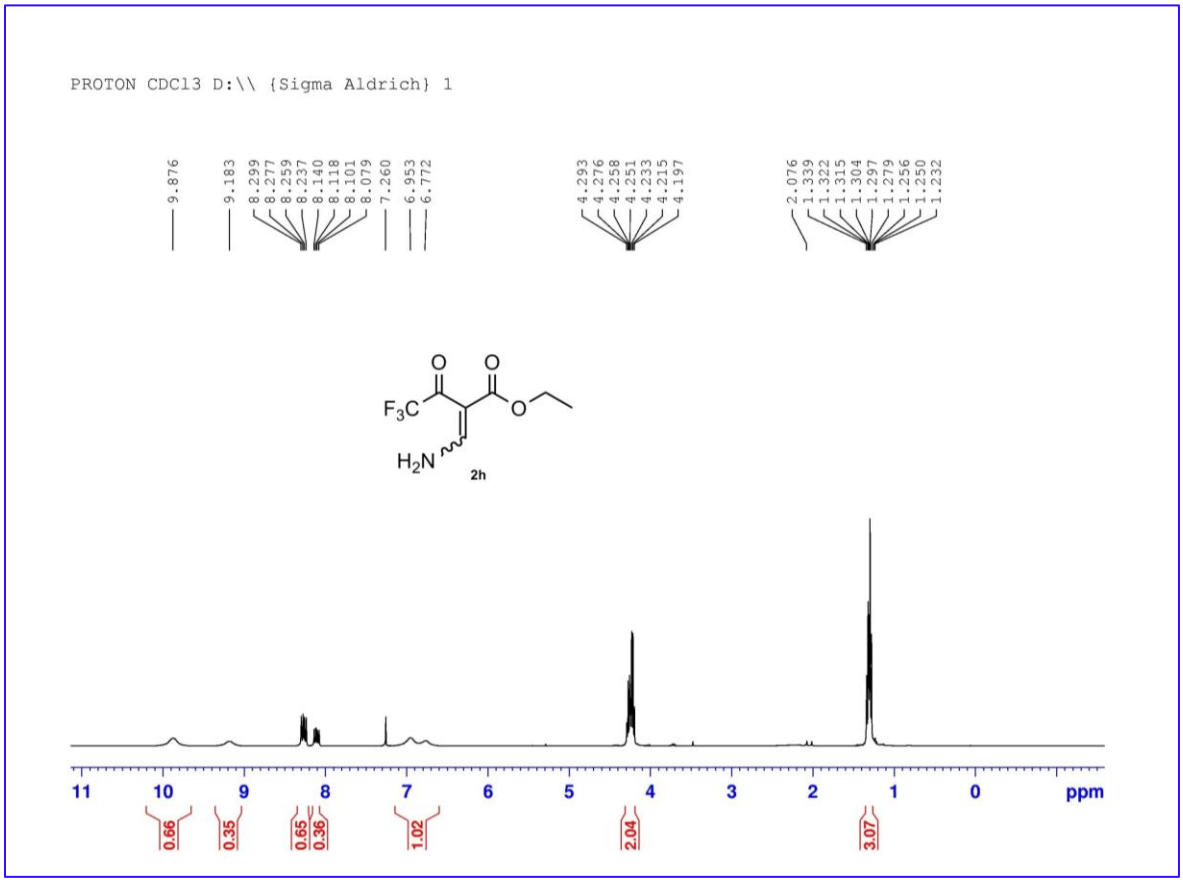
2g

C13APT DMSO D:\\ {Sigma Aldrich} 1

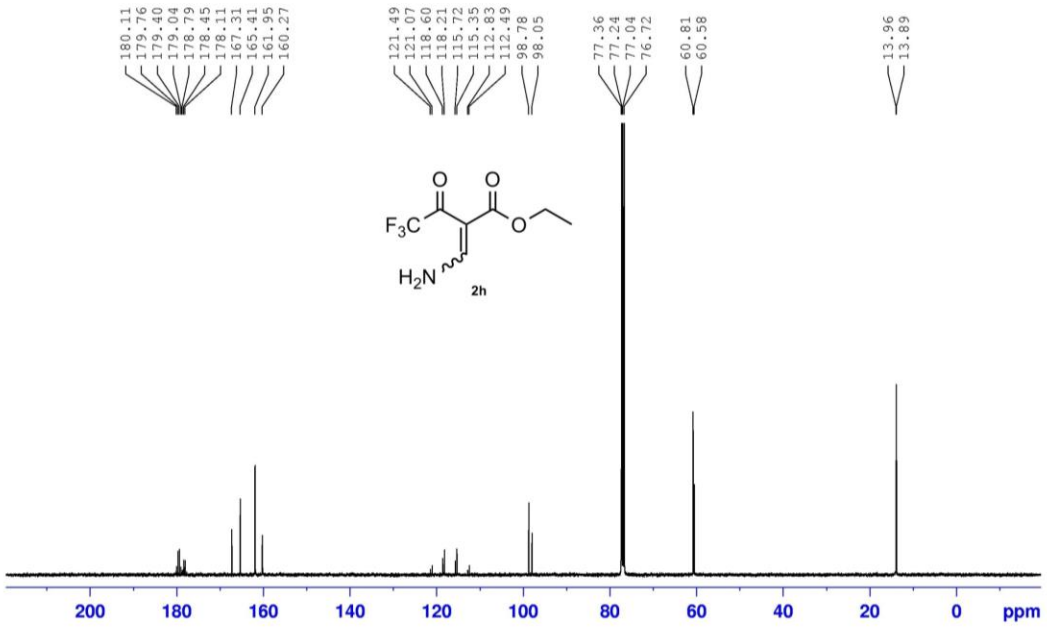


2g

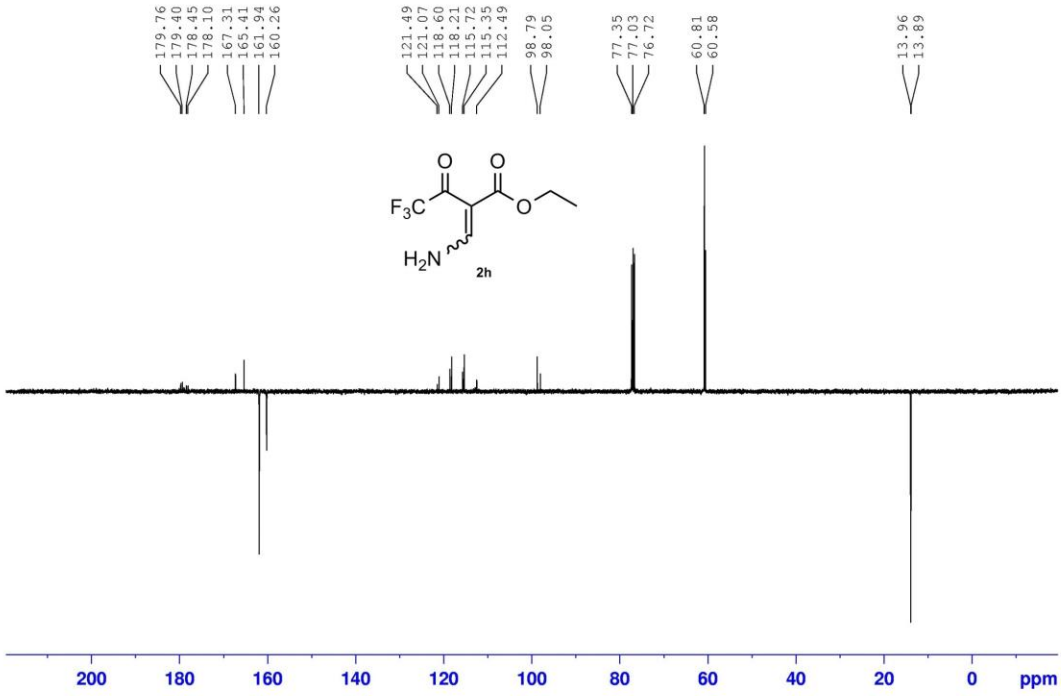

NOESYPHSW DMSO D:\\ {Sigma Aldrich} 1
(CH2)7CH3
O
H
N
(Z)
N
N
O
NH2
2g
ppm
1
2
3
4
5
6
7
8
9
10
11
12
13
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm


PROTON CDCl3 D:\\ {Sigma Aldrich} 1
9.876
9.183
8.299
8.277
8.259
8.237
8.140
8.118
8.101
8.079
7.260
6.953
6.772
4.293
4.276
4.258
4.251
4.233
4.215
4.197
2.076
1.339
1.322
1.315
1.304
1.297
1.279
1.256
1.250
1.232
O
O
F3C
O
H2N
2h
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.66
0.35
0.65
0.36
1.02
2.04
3.07

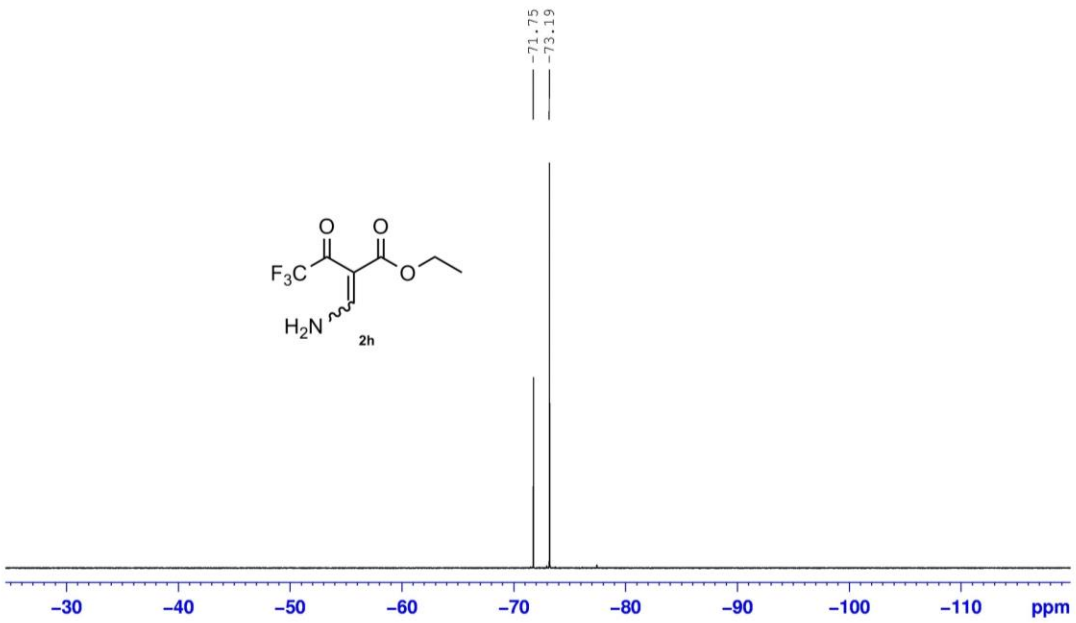
C13CPD CDCl3 D:\\ {Sigma Aldrich} 1



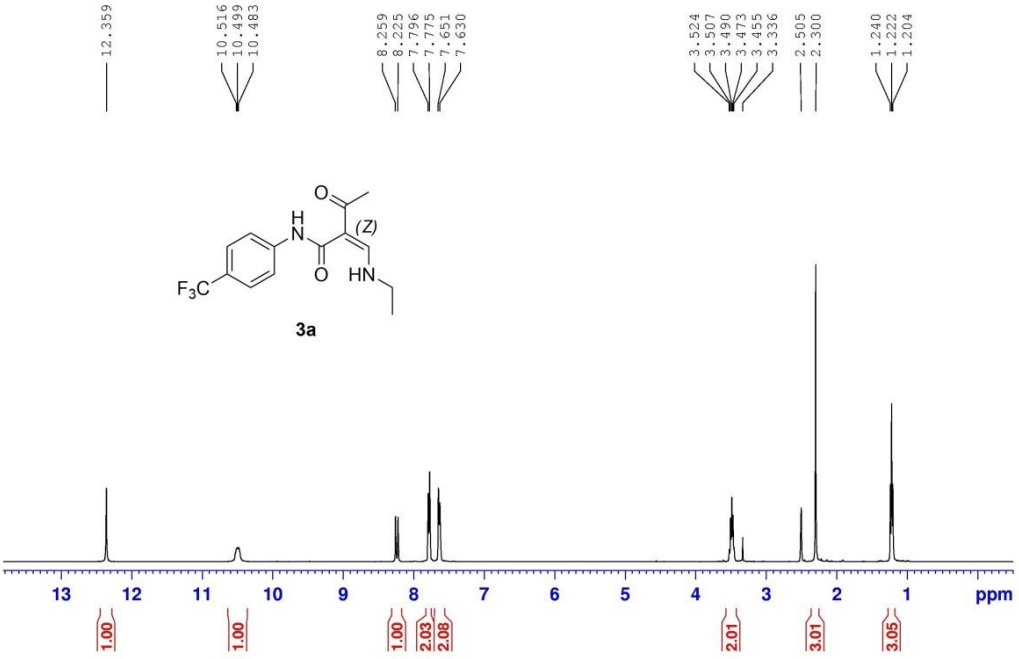
C13APT CDCl3 D:\\ {Sigma Aldrich} 1



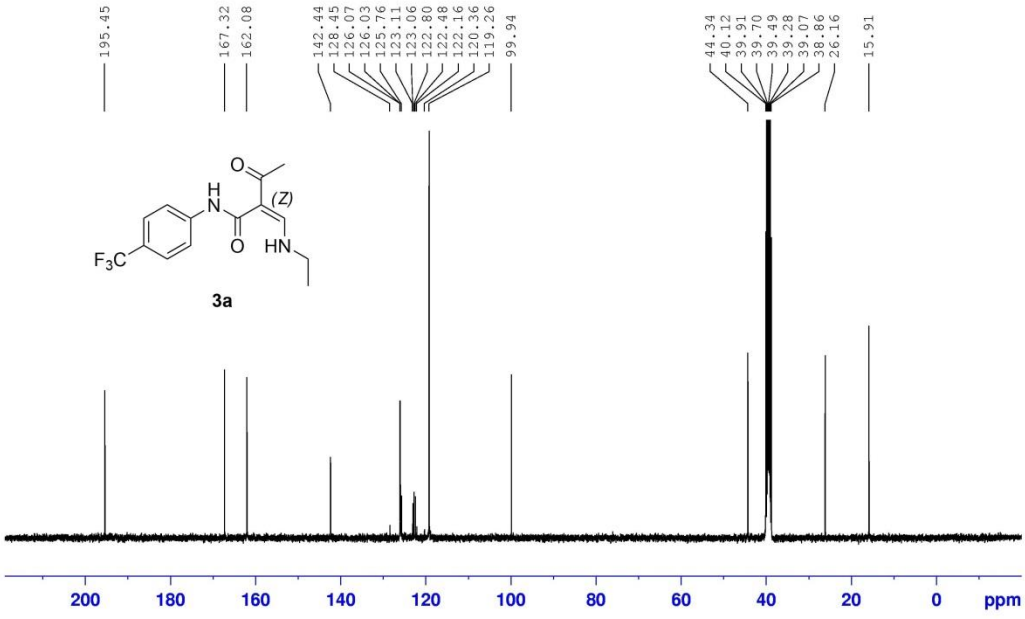
F19 CDCl3 D:\\ {Sigma Aldrich} 1



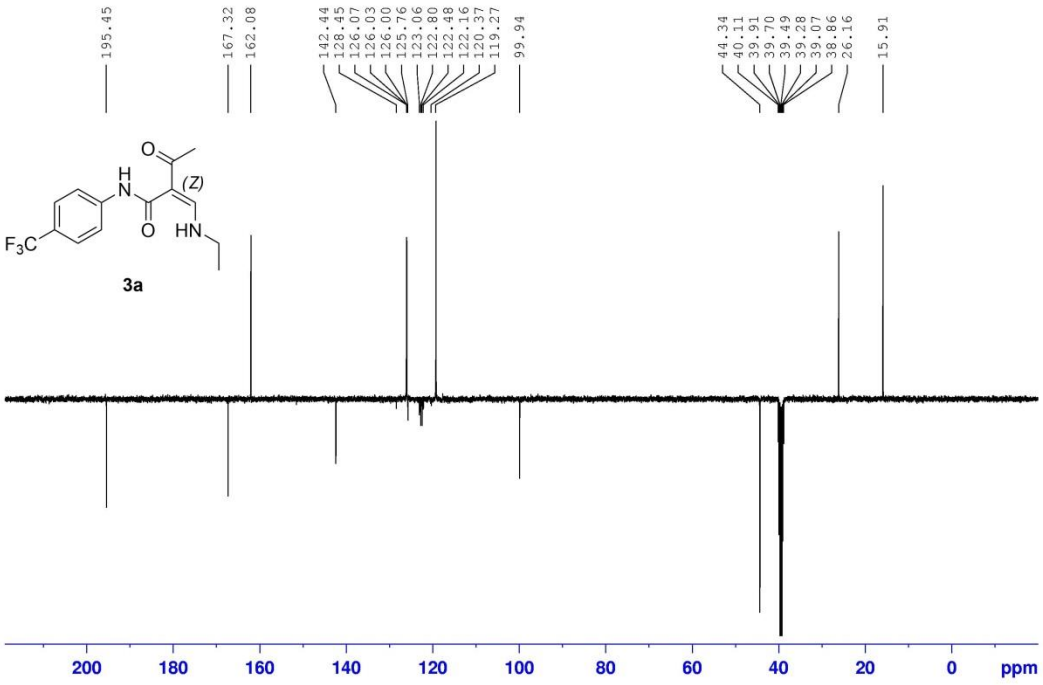
PROTON DMSO D:\\ {Sigma Aldrich} 1

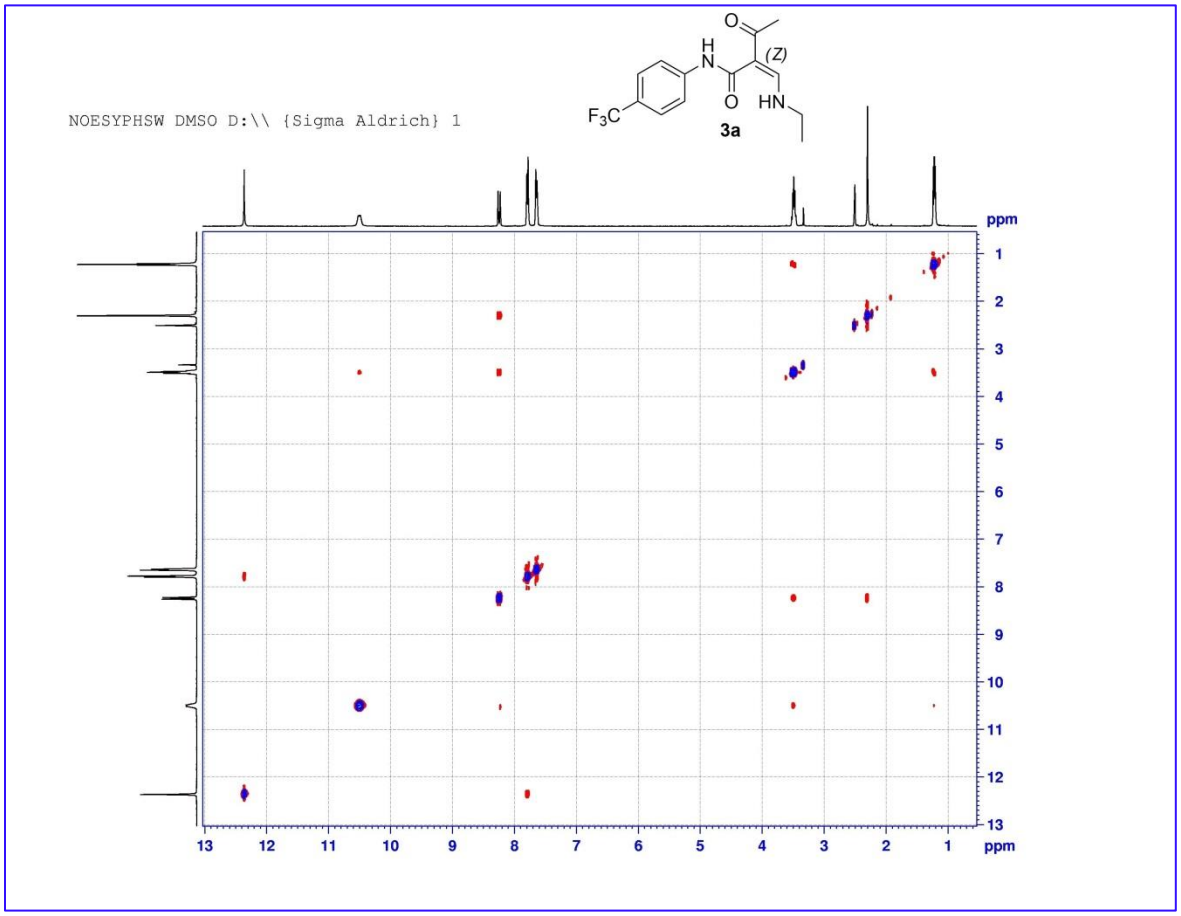


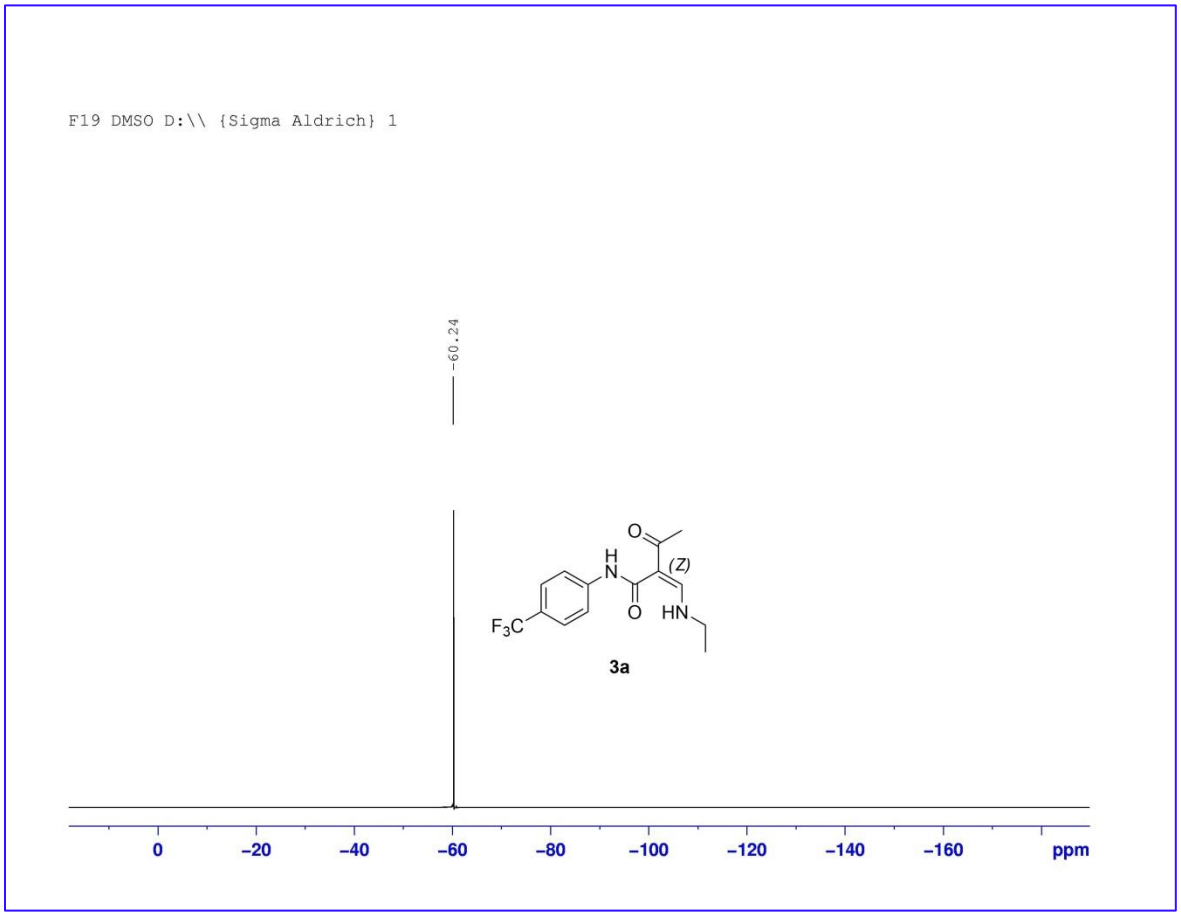
C13CPD DMSO D:\\ {Sigma Aldrich} 1



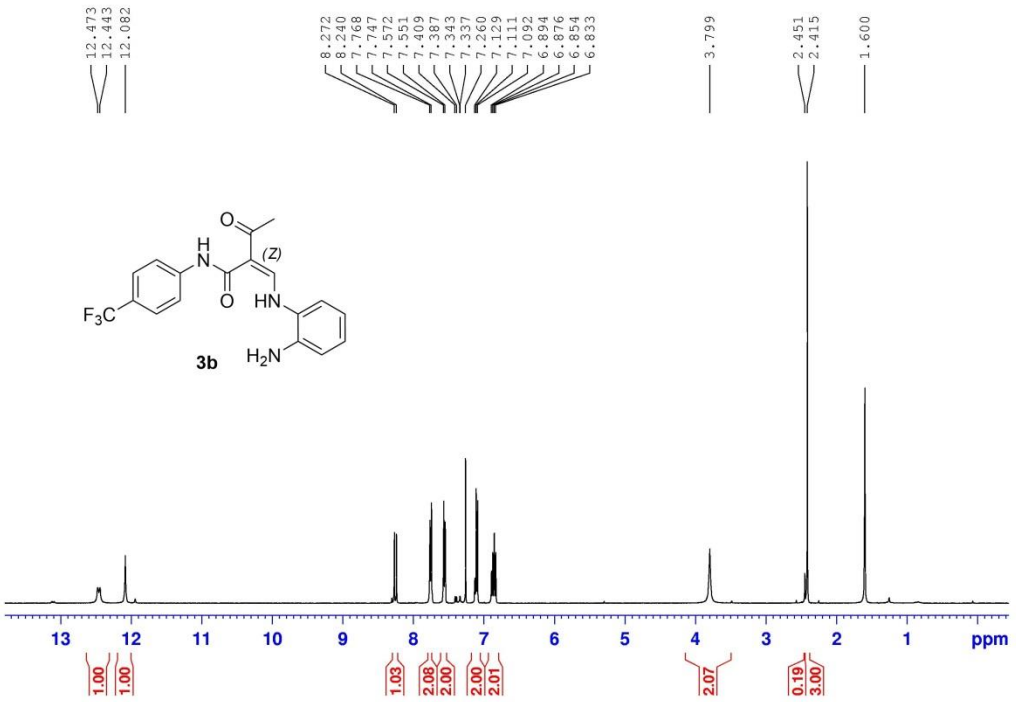
C13APT DMSO D:\\ {Sigma Aldrich} 1



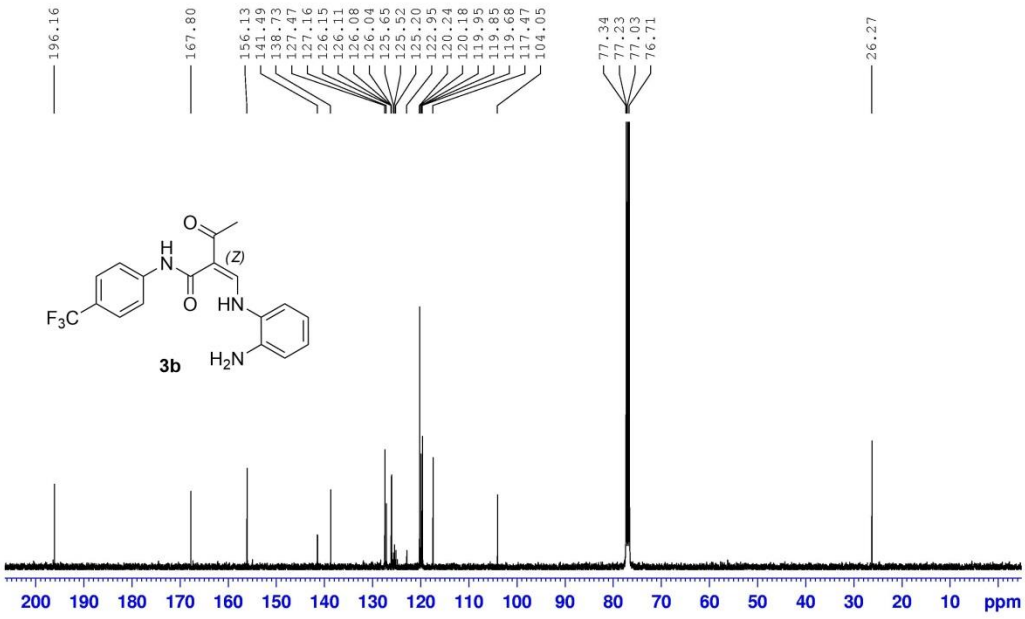

NOESYPHSW DMSO D:\\ {Sigma Aldrich} 1
3a
ppm
13 12 11 10 9 8 7 6 5 4 3 2 1 ppm

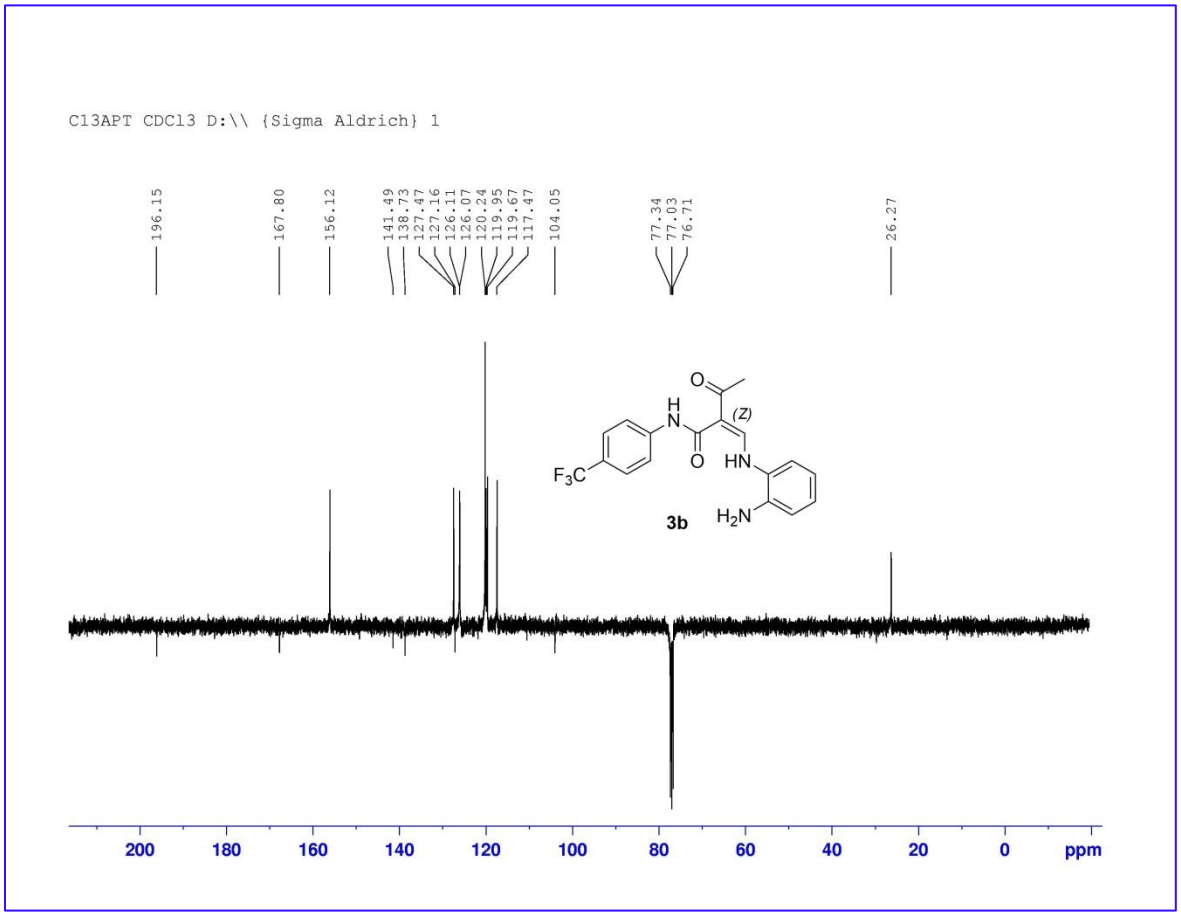

F19 DMSO D:\\ {Sigma Aldrich} 1
-60.24
3a
0 -20 -40 -60 -80 -100 -120 -140 -160 ppm

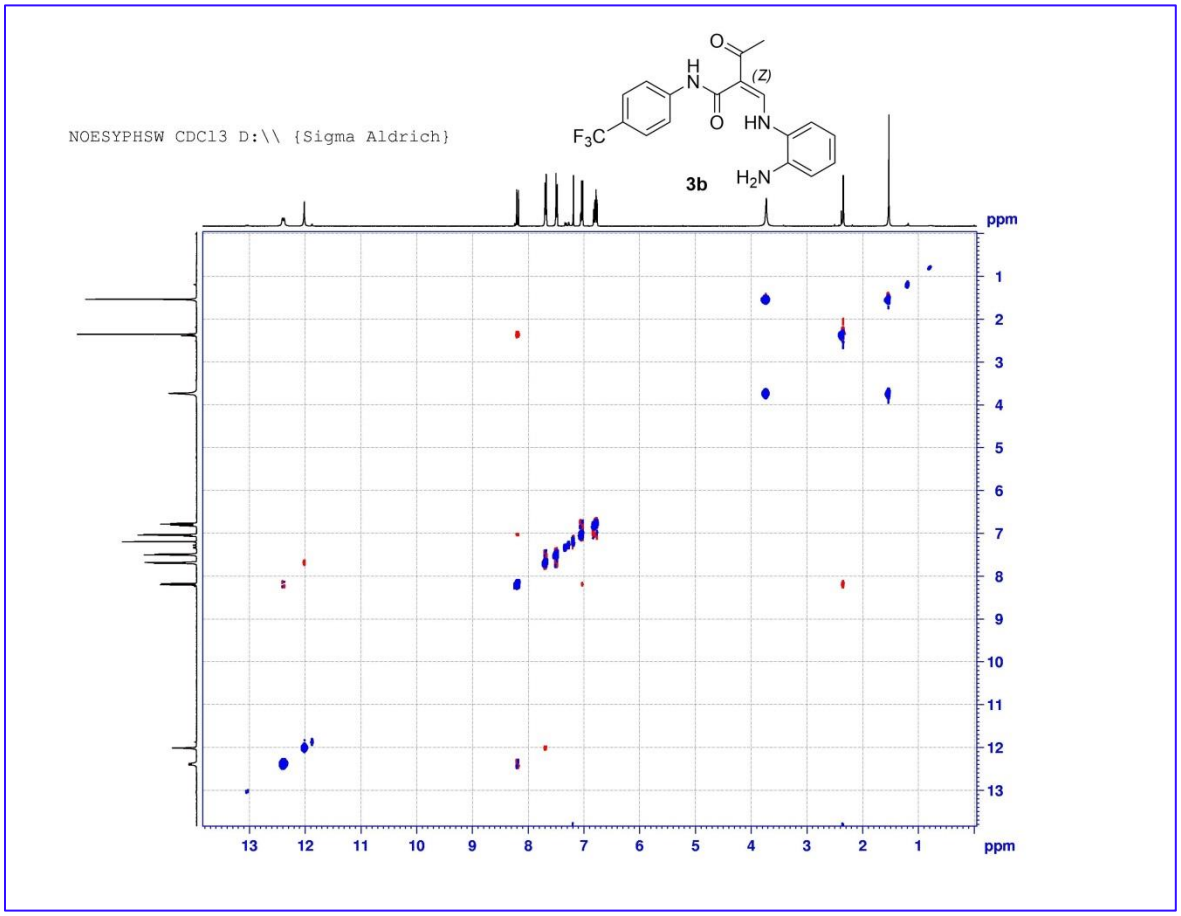
PROTON CDCl3 D:\\ {Sigma Aldrich} 1



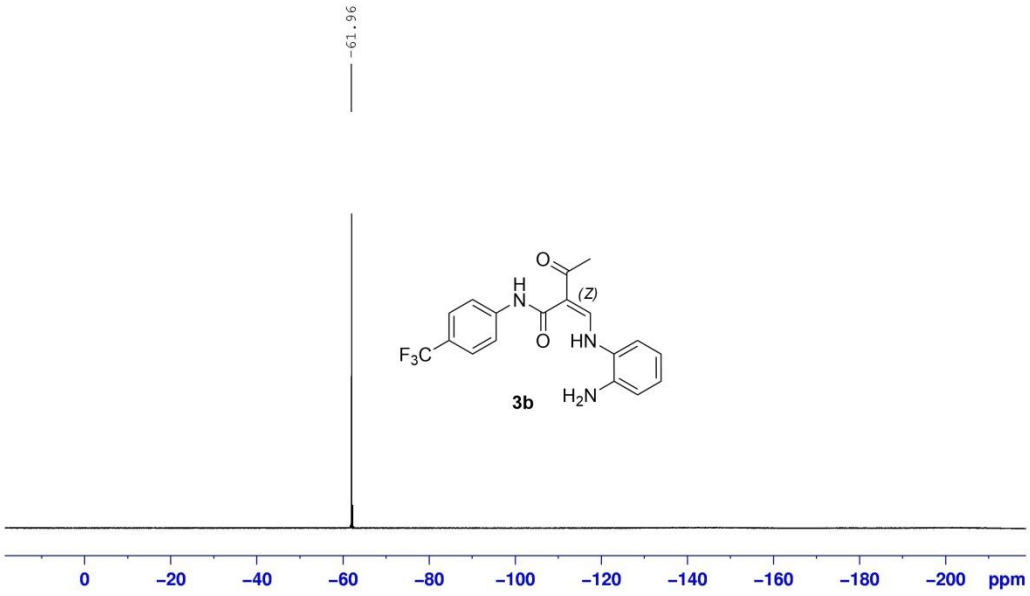
C13CPD CDCl3 D:\\ {Sigma Aldrich} 1



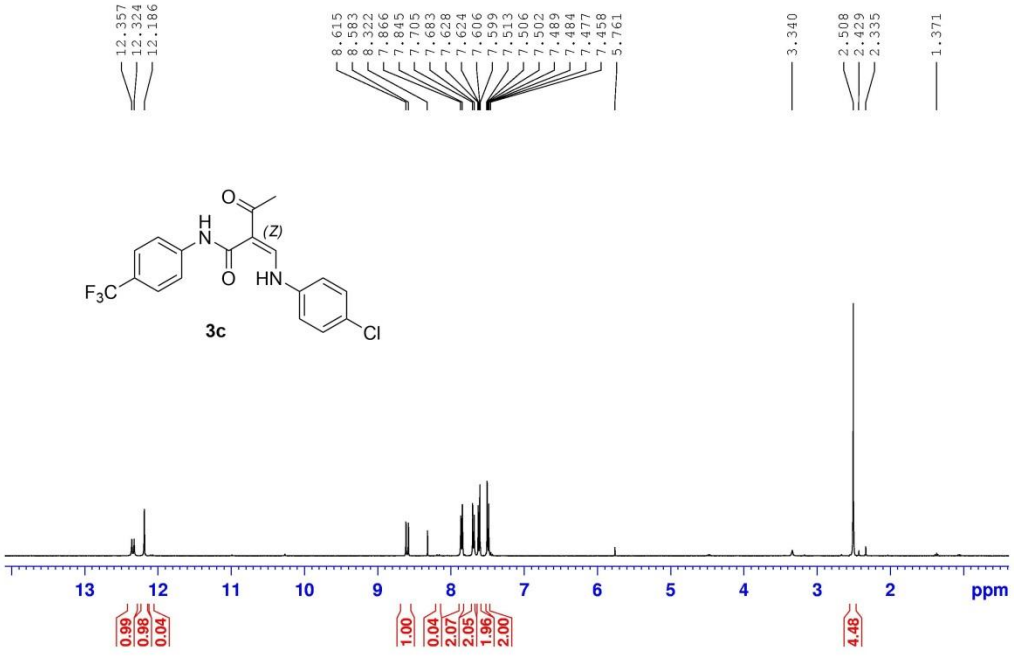

C13APT CDCl3 D:\\ {Sigma Aldrich} 1
196.15
167.80
156.12
141.49
138.73
127.47
127.16
126.11
126.07
120.24
119.95
119.67
117.47
104.05
77.34
77.03
76.71
26.27
3b
200
180
160
140
120
100
80
60
40
20
0
ppm


NOESYPHSW CDCl3 D:\\ {Sigma Aldrich}
3b
ppm
13
12
11
10
9
8
7
6
5
4
3
2
1

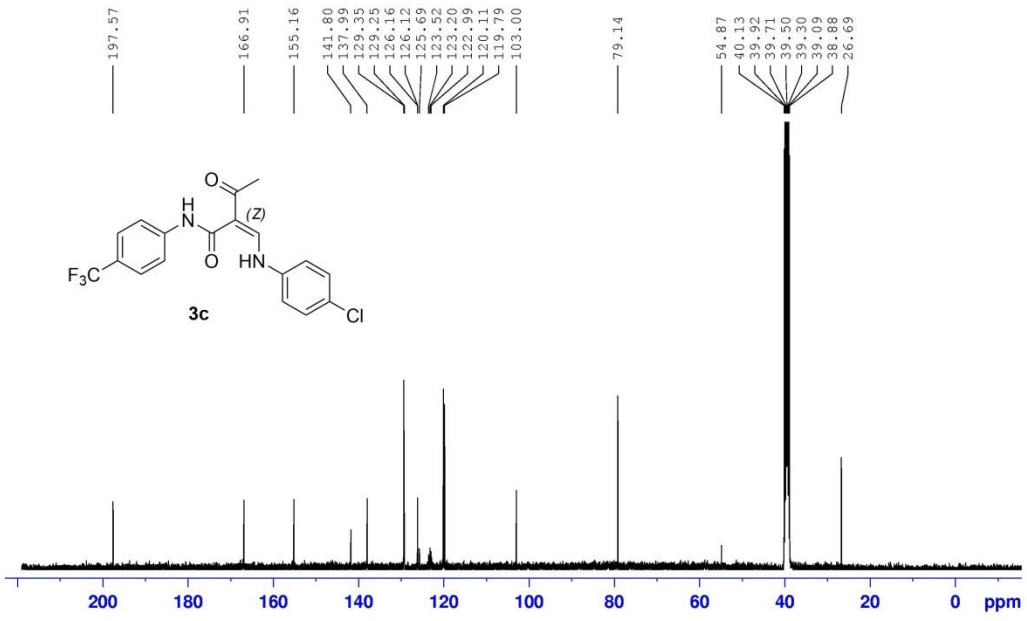
F19 CDCl3 D:\\ {Sigma Aldrich} 1



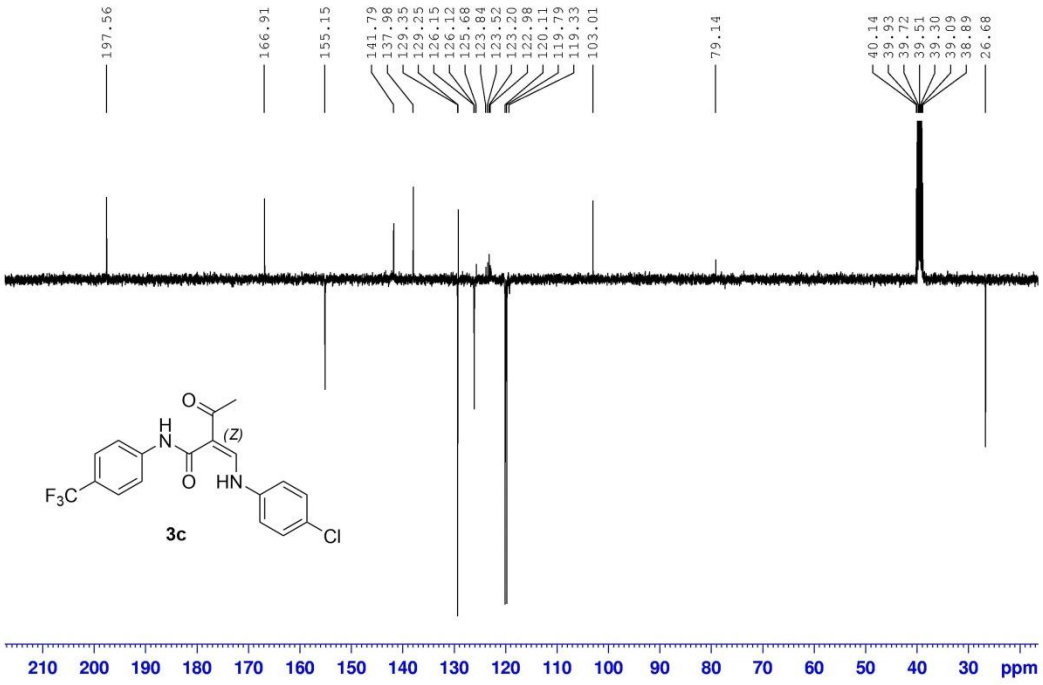
PROTON DMSO D:\\ {Sigma Aldrich} 1



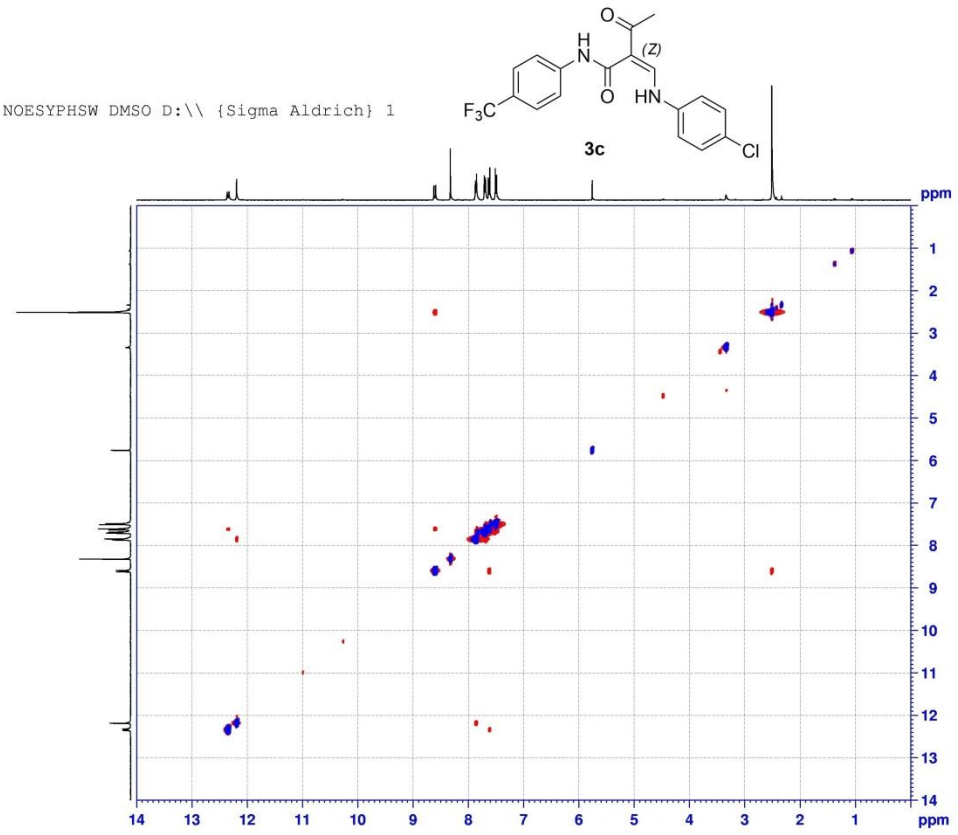
C13CPD DMSO D:\\ {Sigma Aldrich} 1



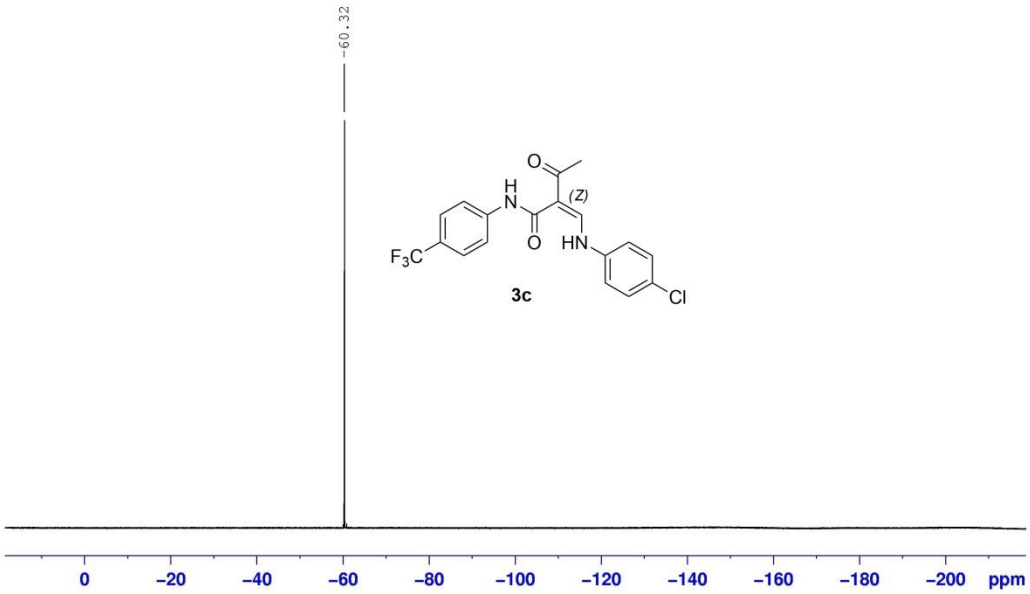
C13APT DMSO D:\\ {Sigma Aldrich} 1



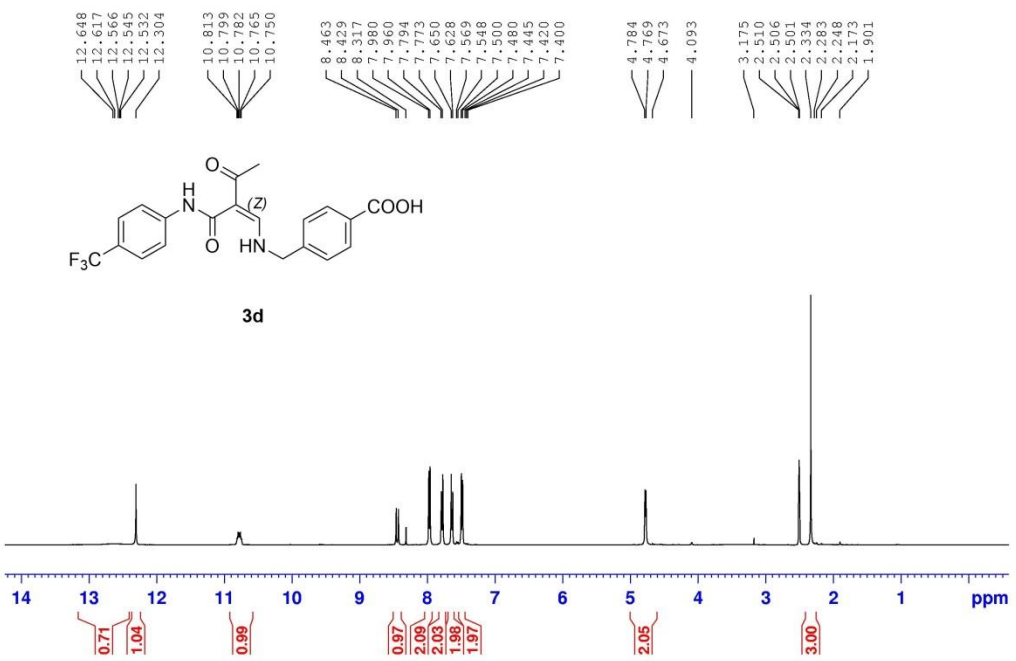
NOESYPHSW DMSO D:\\ {Sigma Aldrich} 1



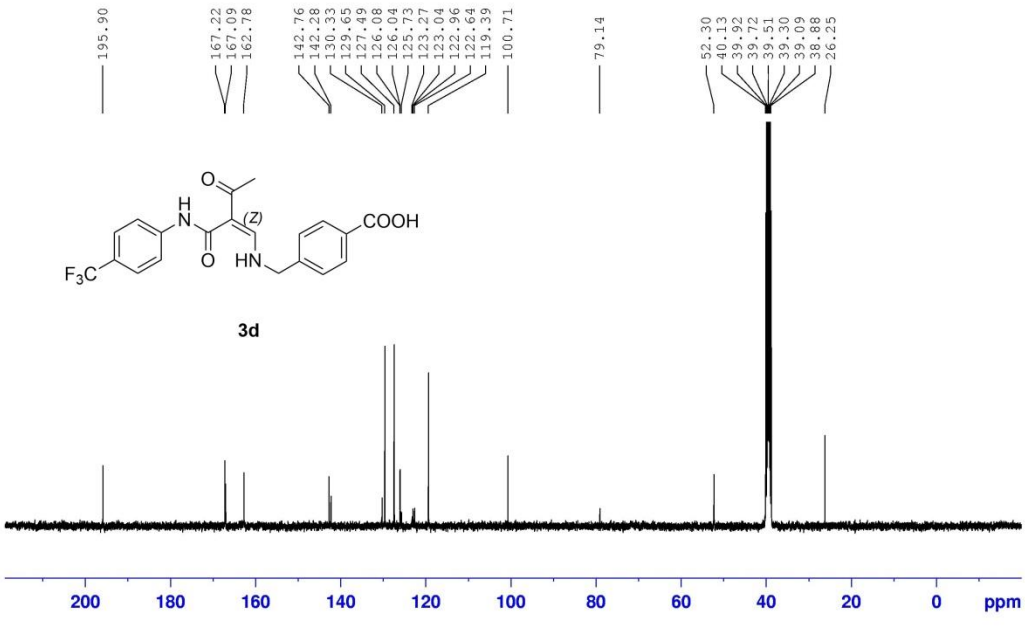
F19 DMSO D:\\ {Sigma Aldrich} 1

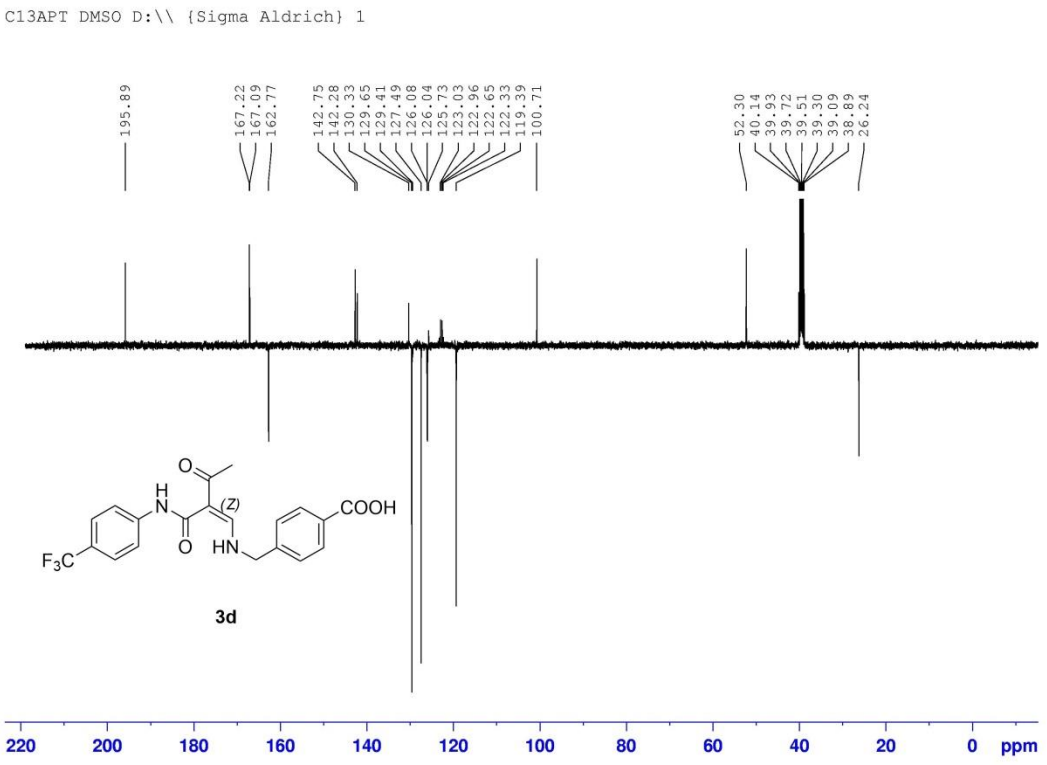


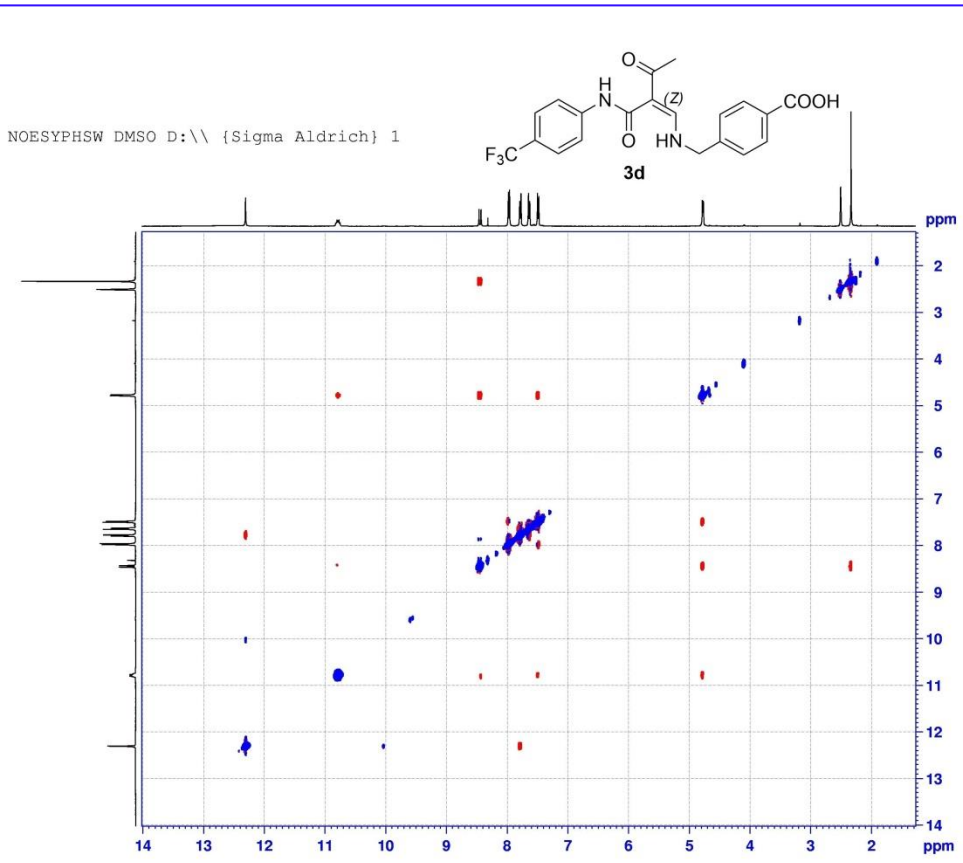
PROTON DMSO D:\\ {Sigma Aldrich} 1



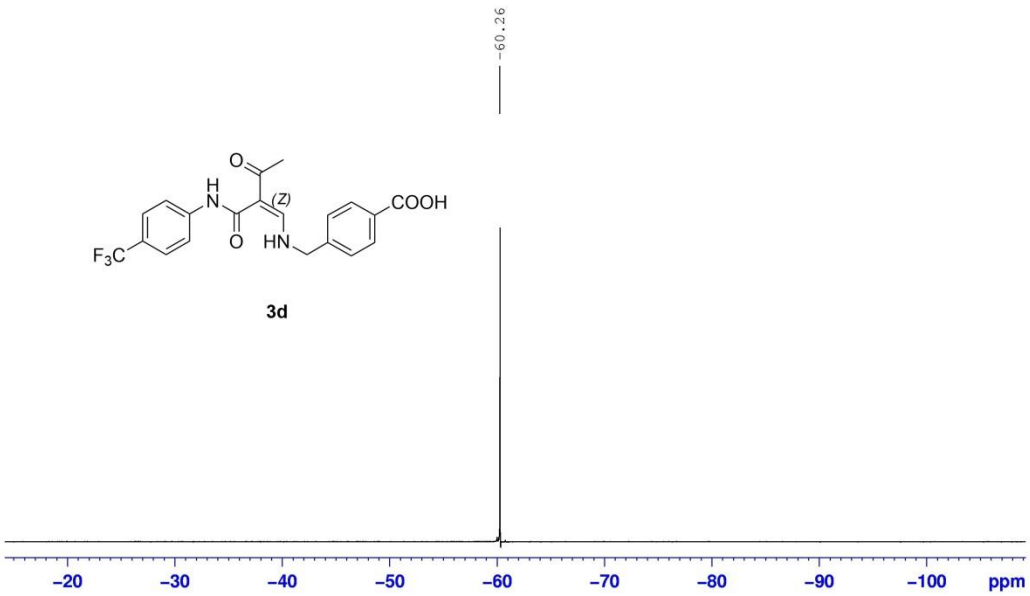
C13CPD DMSO D:\\ {Sigma Aldrich} 1



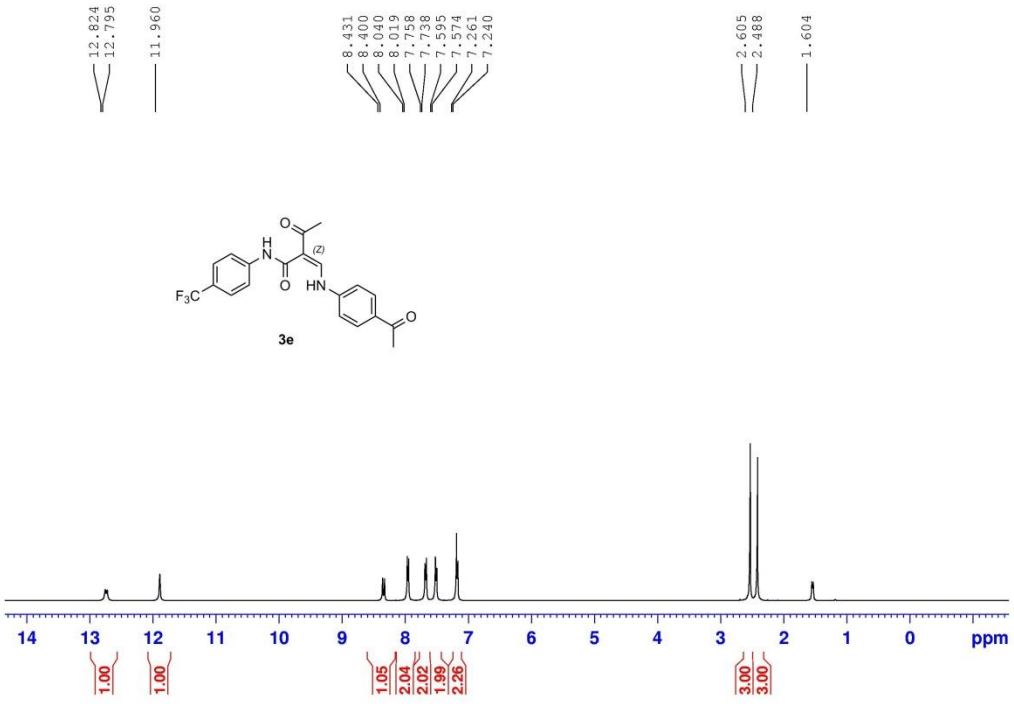

C13APT DMSO D:\\ {Sigma Aldrich} 1
195.89
167.22
167.09
162.77
142.75
142.28
130.33
129.65
129.41
127.49
126.08
126.04
125.73
123.03
122.96
122.65
122.33
119.39
100.71
52.30
40.14
39.93
39.72
39.51
39.30
39.09
38.89
26.24
3d
220
200
180
160
140
120
100
80
60
40
20
0
ppm


NOESYPHSW DMSO D:\\ {Sigma Aldrich} 1
3d
ppm
2
3
4
5
6
7
8
9
10
11
12
13
14
ppm

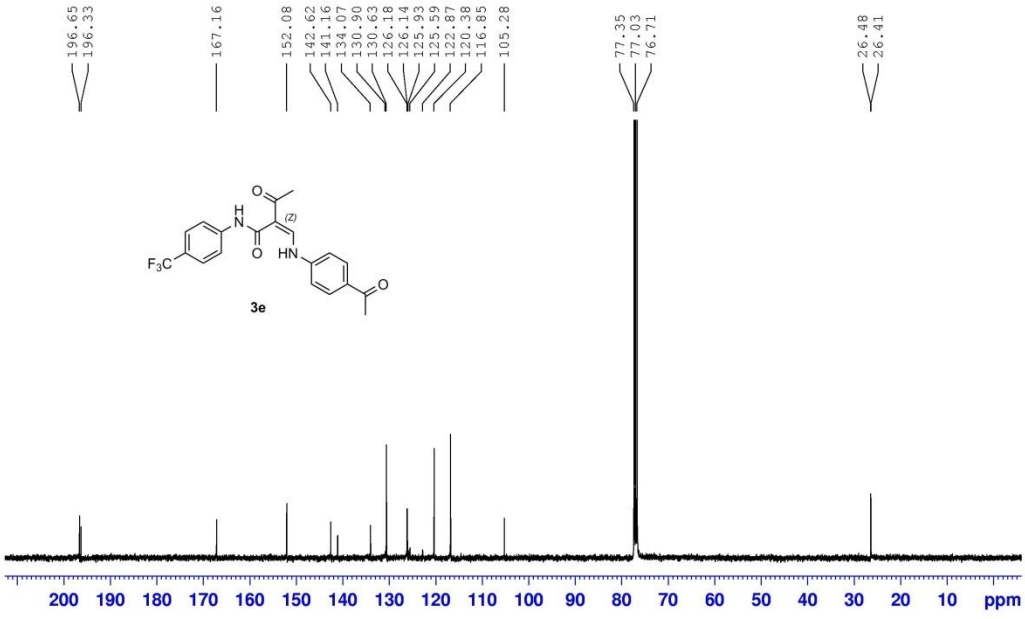
F19 DMSO D:\\ {Sigma Aldrich} 1



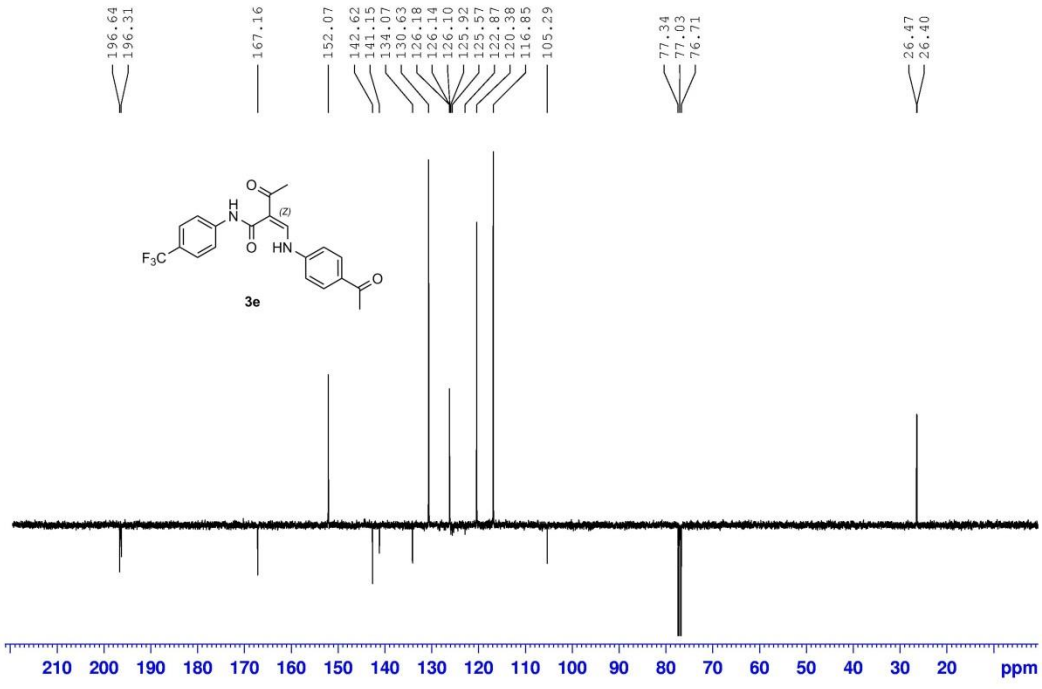
PROTON CDCl3 D:\\ {Sigma Aldrich} 1



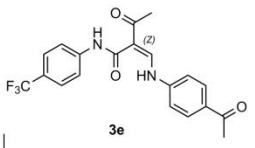
C13CPD CDCl3 D:\\ {Sigma Aldrich} 1



C13APT CDCl3 D:\\ {Sigma Aldrich} 1

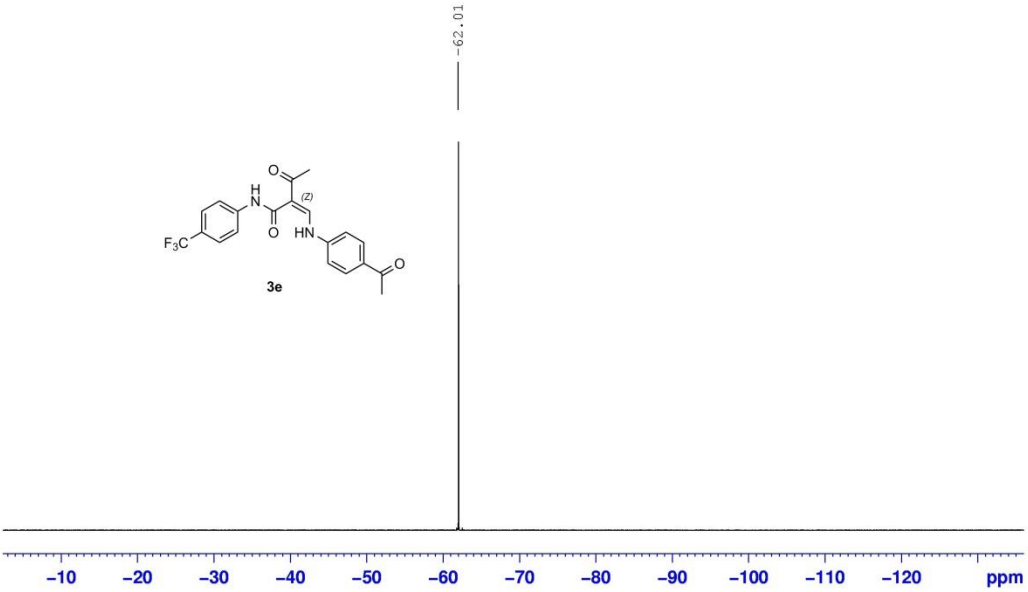


NOESYPHSW CDCl3 D:\\ {Sigma Aldrich}



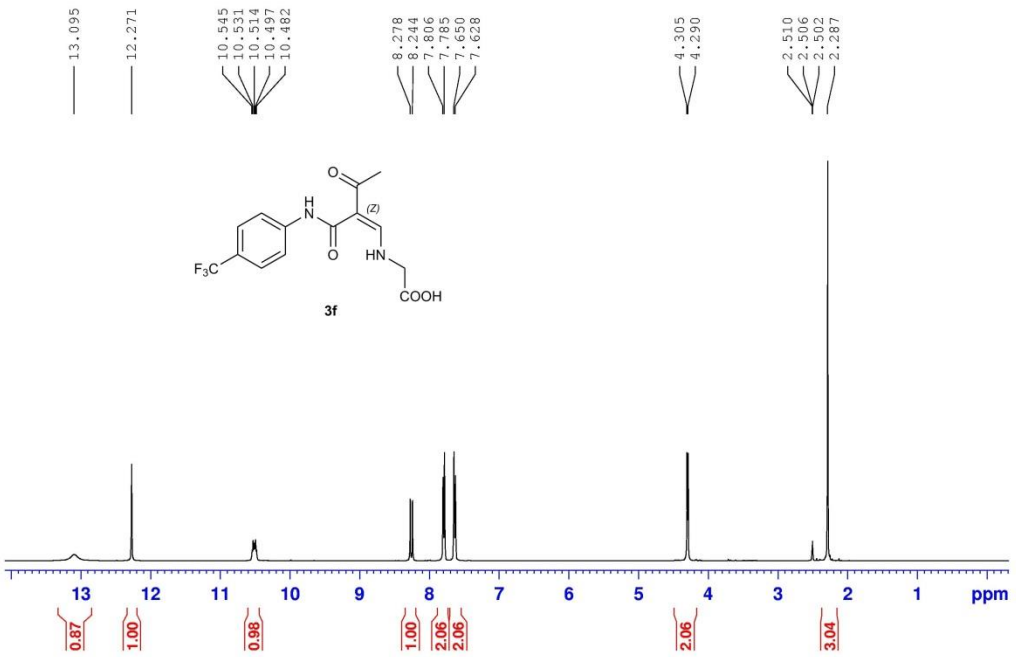
3e

F19 CDCl3 D:\\ {Sigma Aldrich} 1

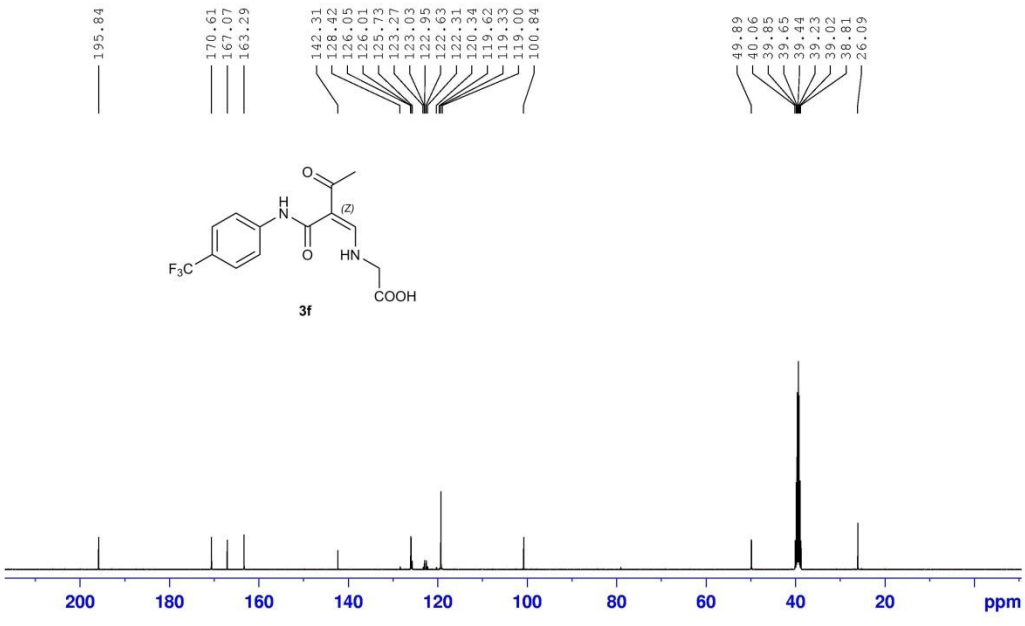


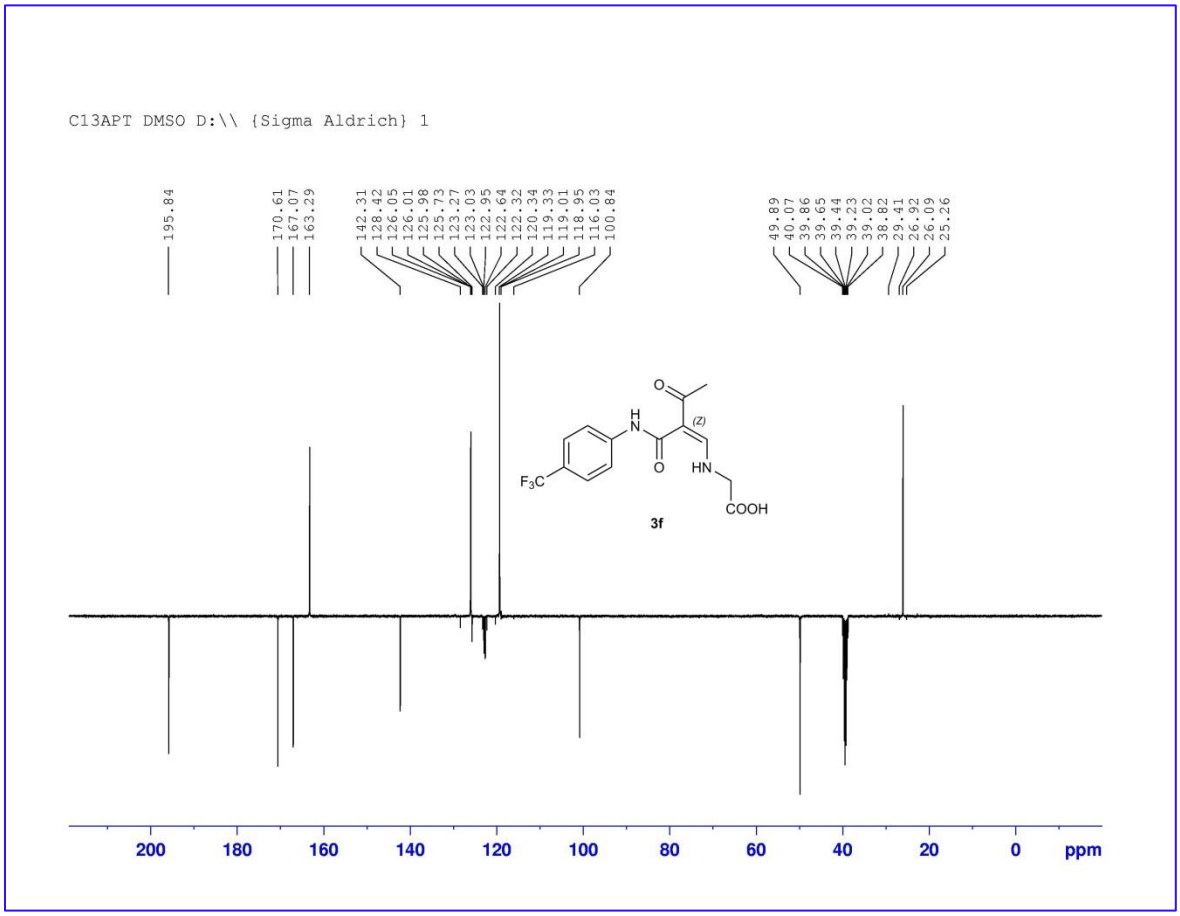
3e

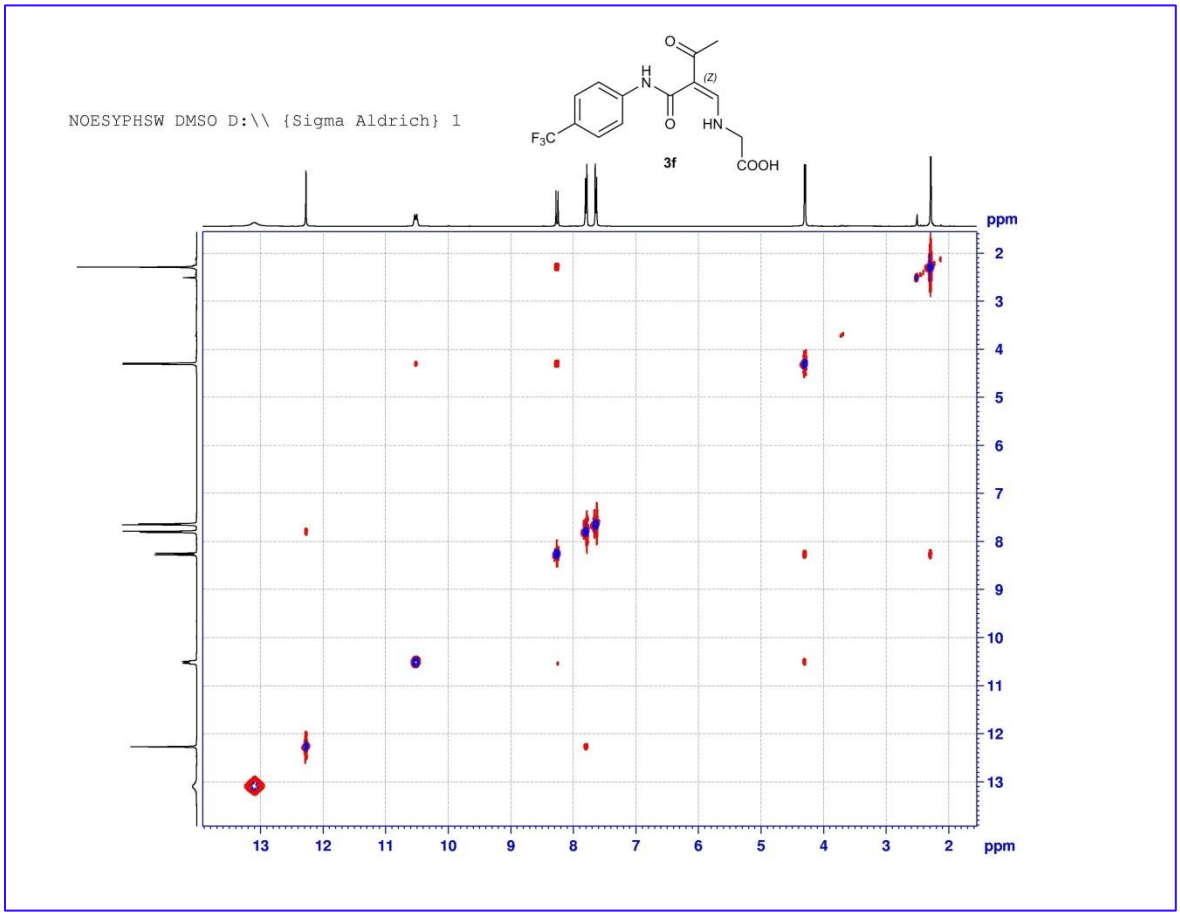
PROTON DMSO D:\\ {Sigma Aldrich} 1



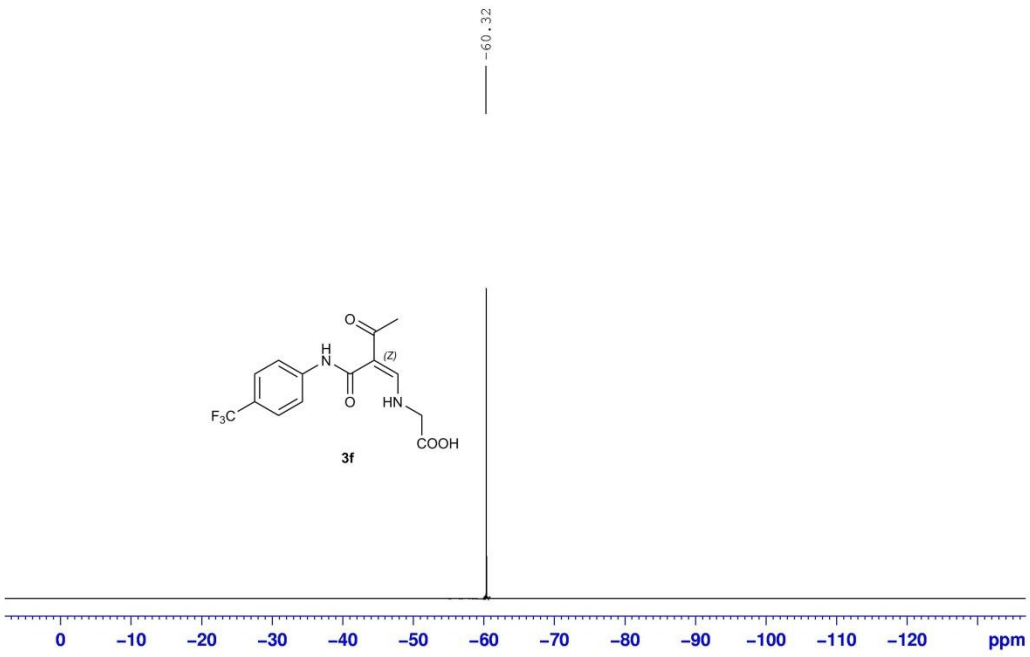
C13CPD DMSO D:\\ {Sigma Aldrich} 1



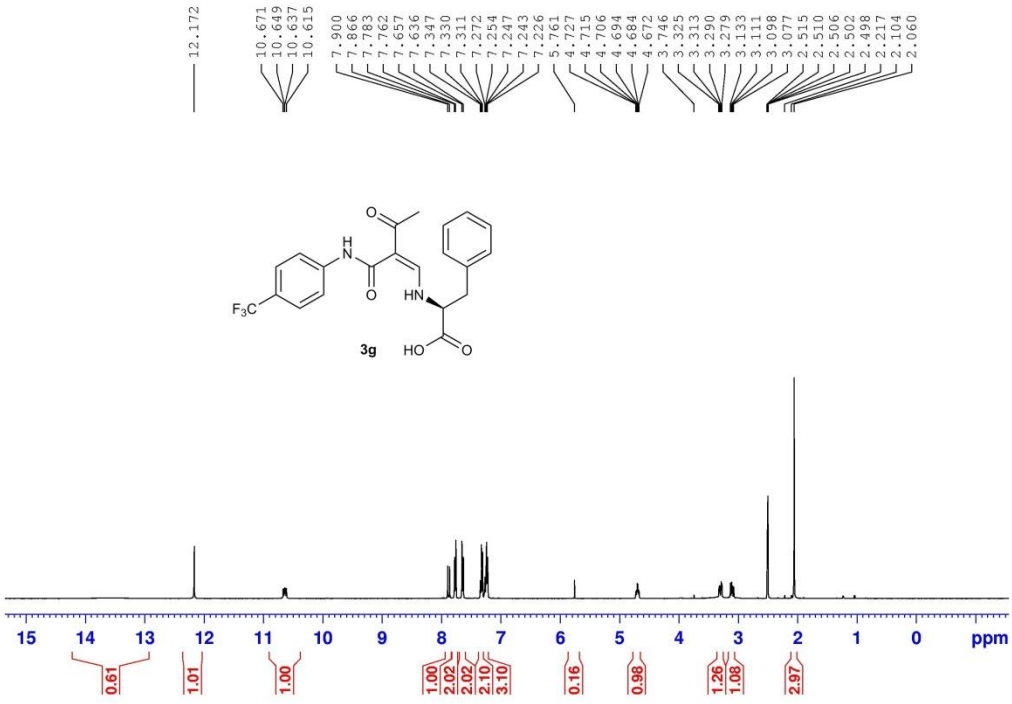

C13APT DMSO D:\\ {Sigma Aldrich} 1
195.84
170.61
167.07
163.29
142.31
128.42
126.05
126.01
125.98
125.73
123.27
123.03
122.95
122.64
122.32
120.34
119.33
119.01
118.95
116.03
100.84
49.89
40.07
39.86
39.65
39.44
39.23
39.02
38.82
29.41
26.92
26.09
25.26
3f
200
180
160
140
120
100
80
60
40
20
0
ppm


NOESYPHSW DMSO D:\\ {Sigma Aldrich} 1
3f
ppm
2
3
4
5
6
7
8
9
10
11
12
13
ppm

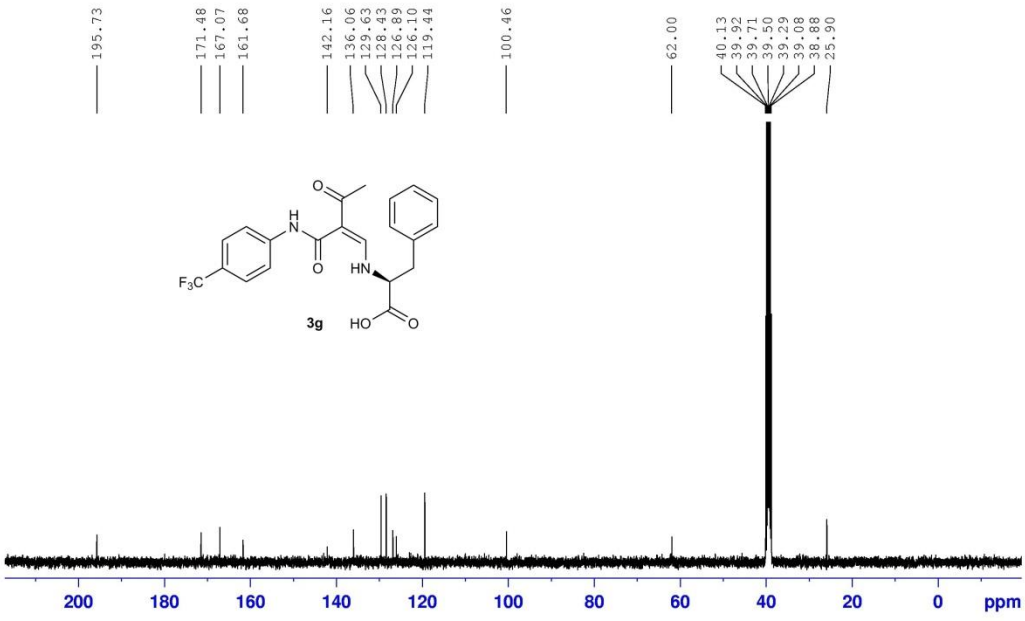
F19 DMSO D:\\ {Sigma Aldrich} 1



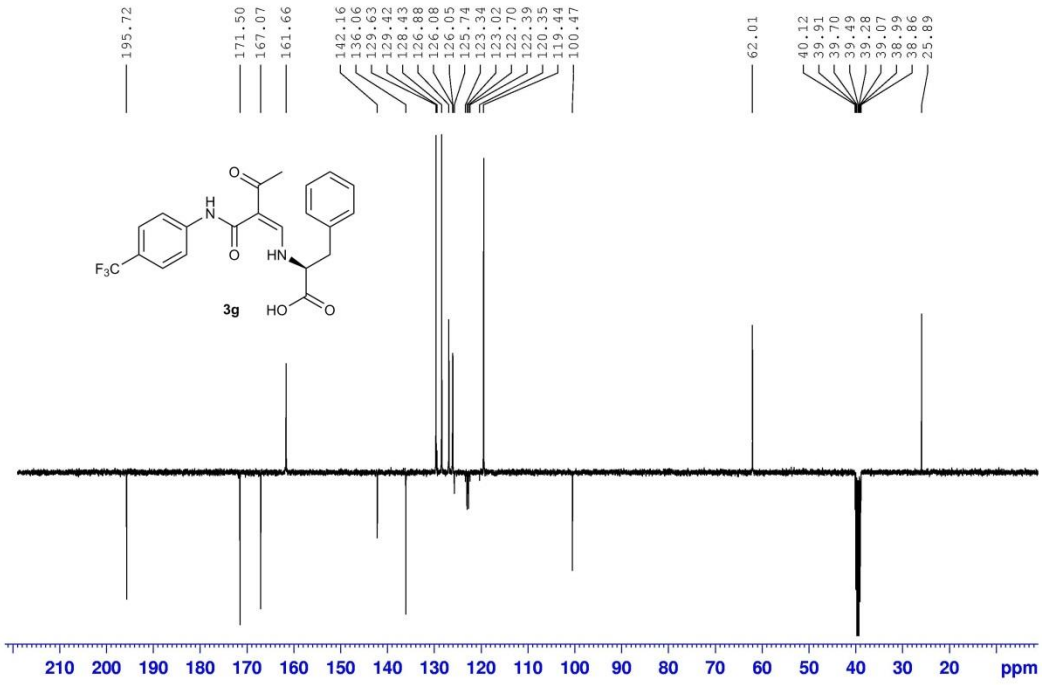
PROTON DMSO D:\\ {Sigma Aldrich} 1

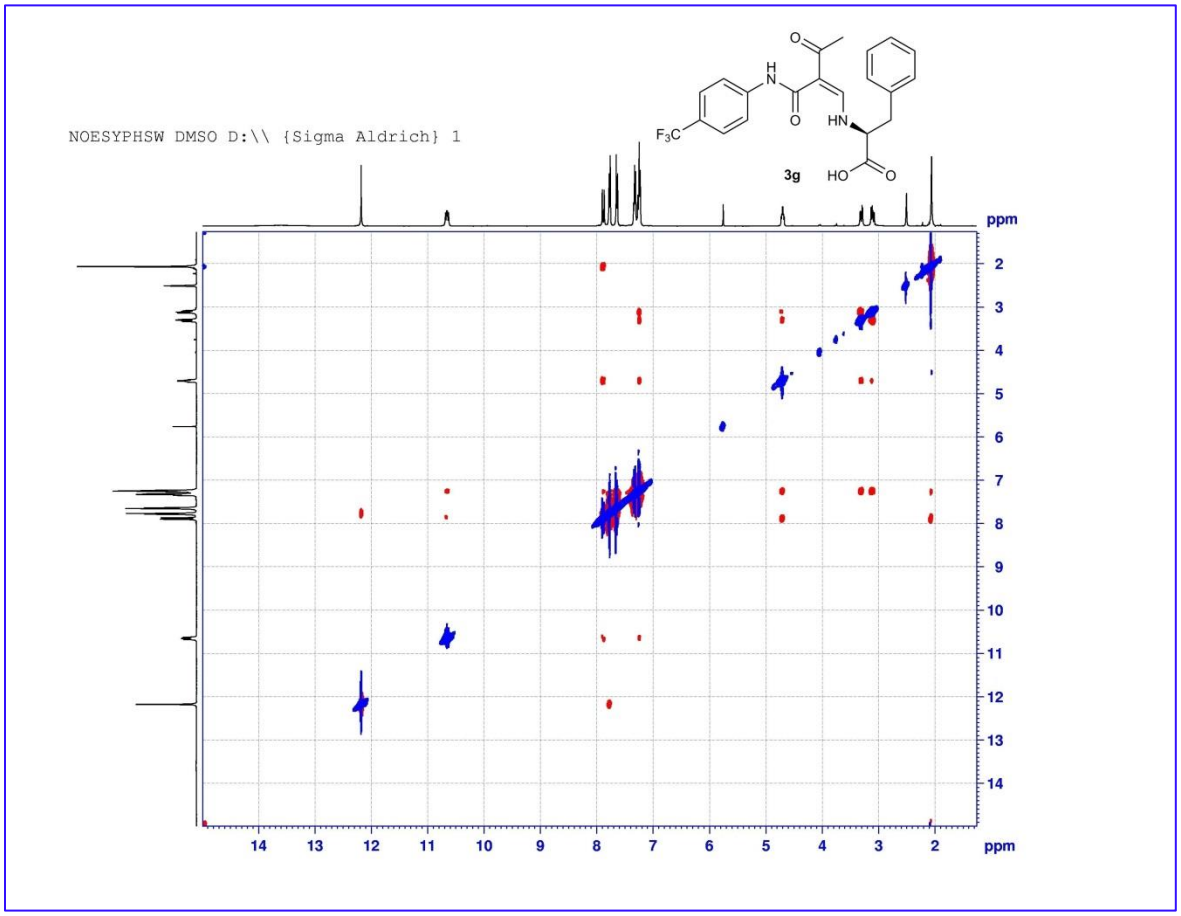


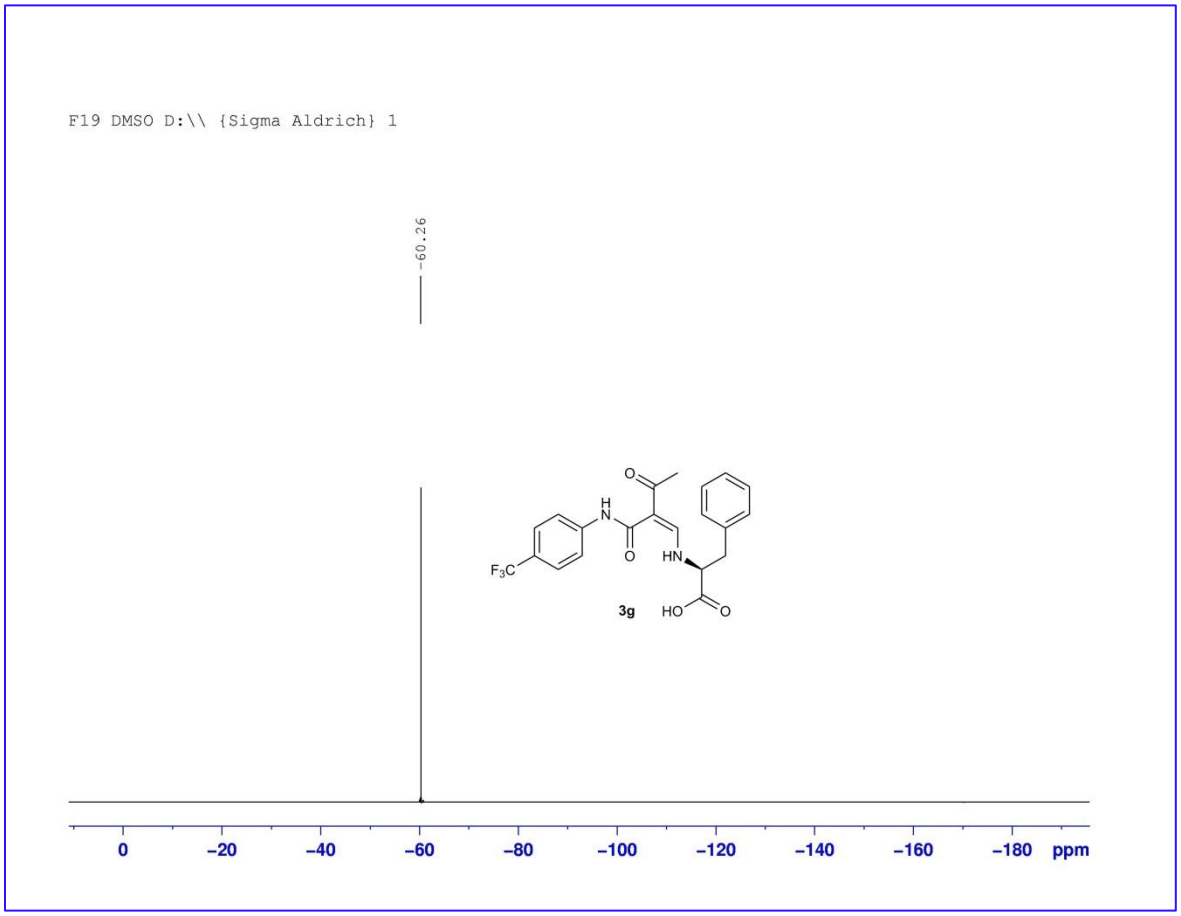
C13CPD DMSO D:\\ {Sigma Aldrich} 1



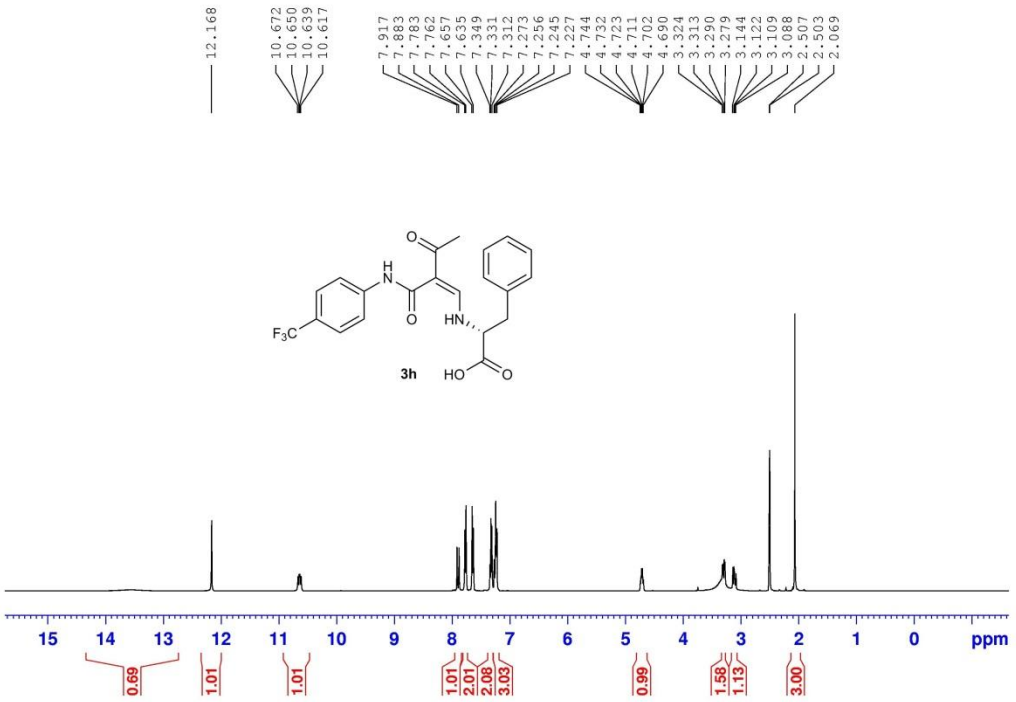
C13APT DMSO D:\\ {Sigma Aldrich} 1



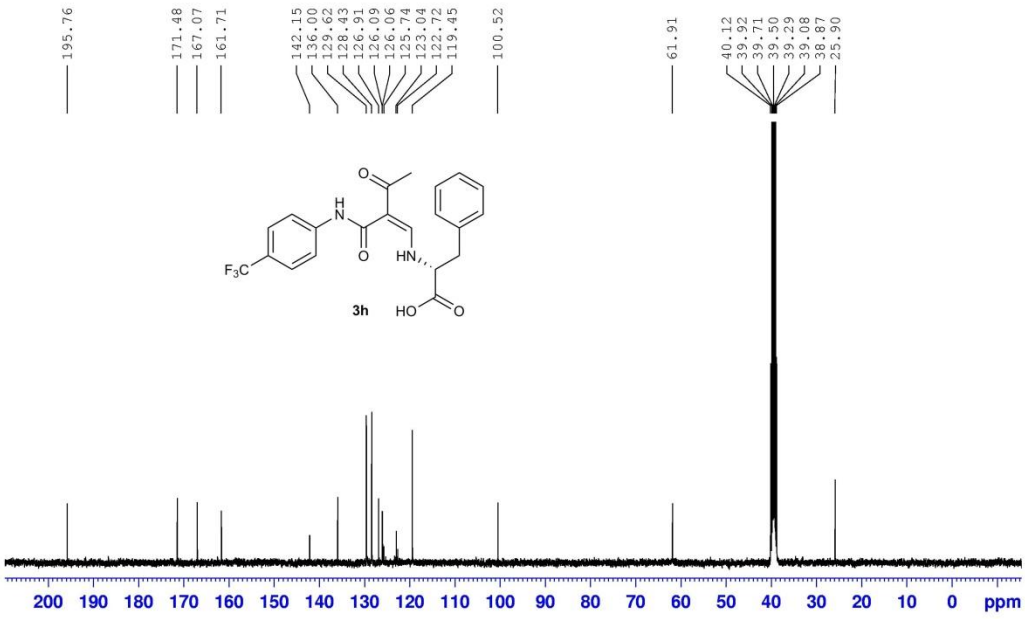

NOESYPHSW DMSO D:\\ {Sigma Aldrich} 1
3g
ppm
14 13 12 11 10 9 8 7 6 5 4 3 2 ppm

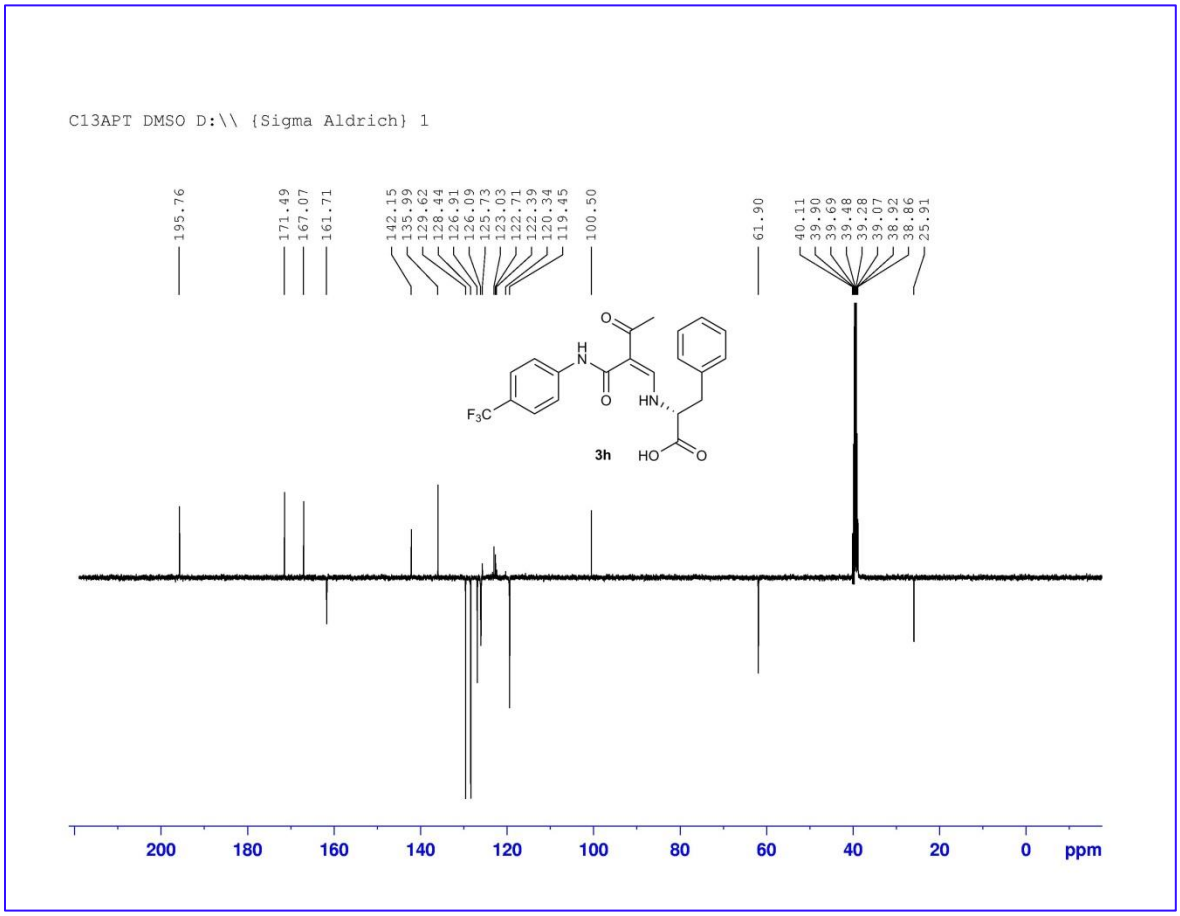

F19 DMSO D:\\ {Sigma Aldrich} 1
-60.26
3g
0 -20 -40 -60 -80 -100 -120 -140 -160 -180 ppm

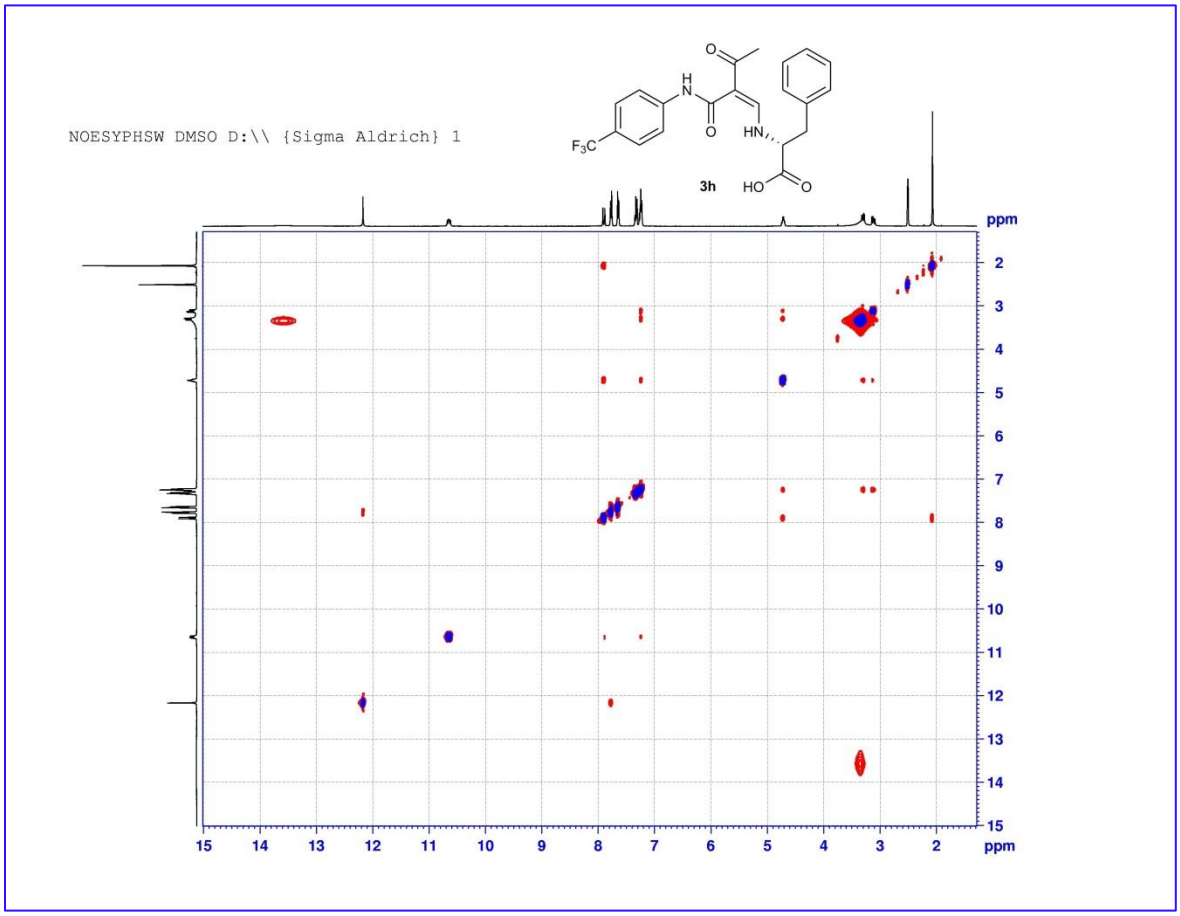
PROTON DMSO D:\\ {Sigma Aldrich} 1



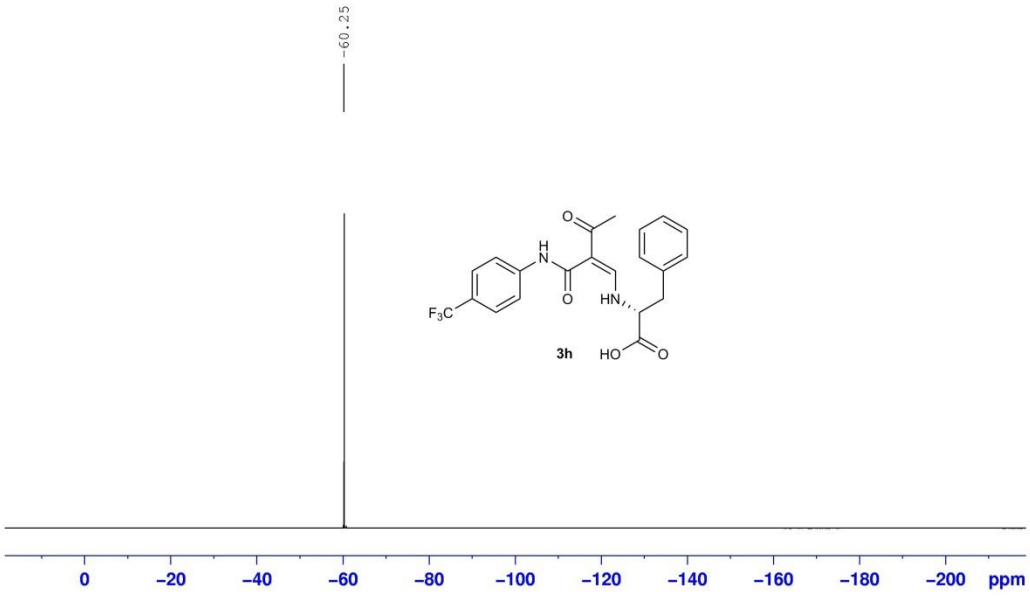
C13CPD DMSO D:\\ {Sigma Aldrich} 1



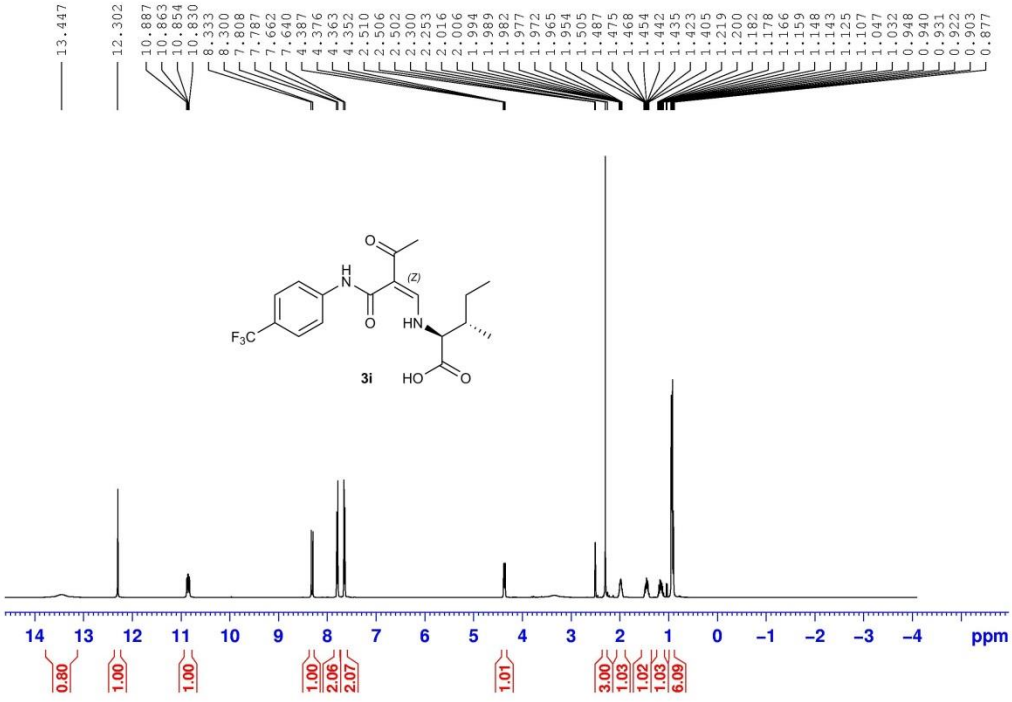

C13APT DMSO D:\\ {Sigma Aldrich} 1
195.76
171.49
167.07
161.71
142.15
135.99
129.62
128.44
126.91
126.09
125.73
123.03
122.71
122.39
120.34
119.45
100.50
61.90
40.11
39.90
39.69
39.48
39.28
39.07
38.92
38.86
25.91
3h
200
180
160
140
120
100
80
60
40
20
0
ppm


NOESYPHSW DMSO D:\\ {Sigma Aldrich} 1
3h
ppm
15
14
13
12
11
10
9
8
7
6
5
4
3
2

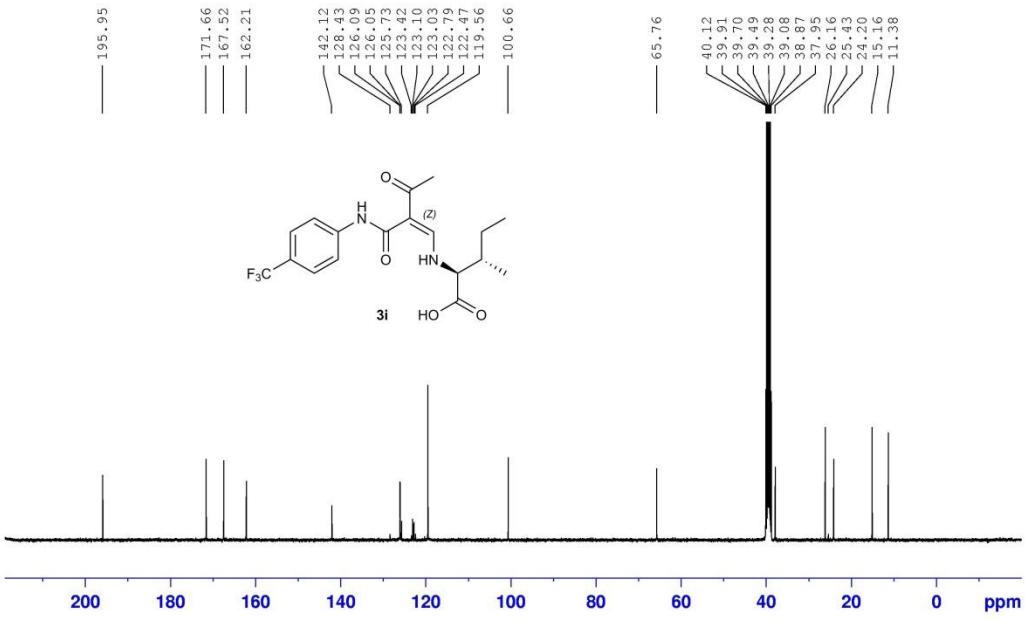
F19 DMSO D:\\ {Sigma Aldrich} 1



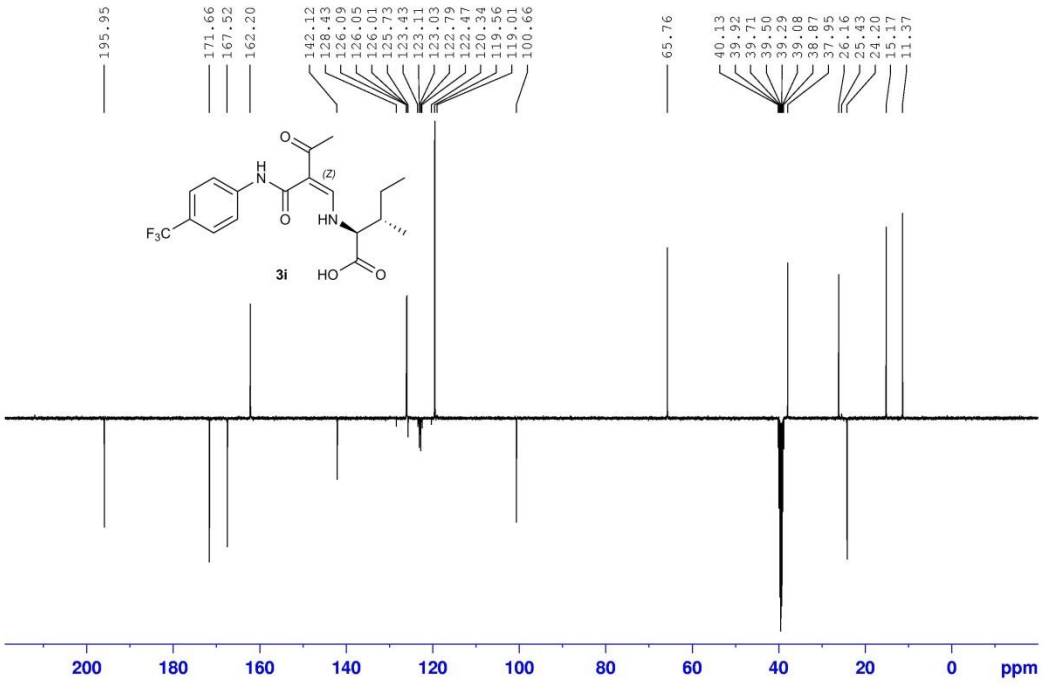
PROTON DMSO D:\\ {Sigma Aldrich} 1

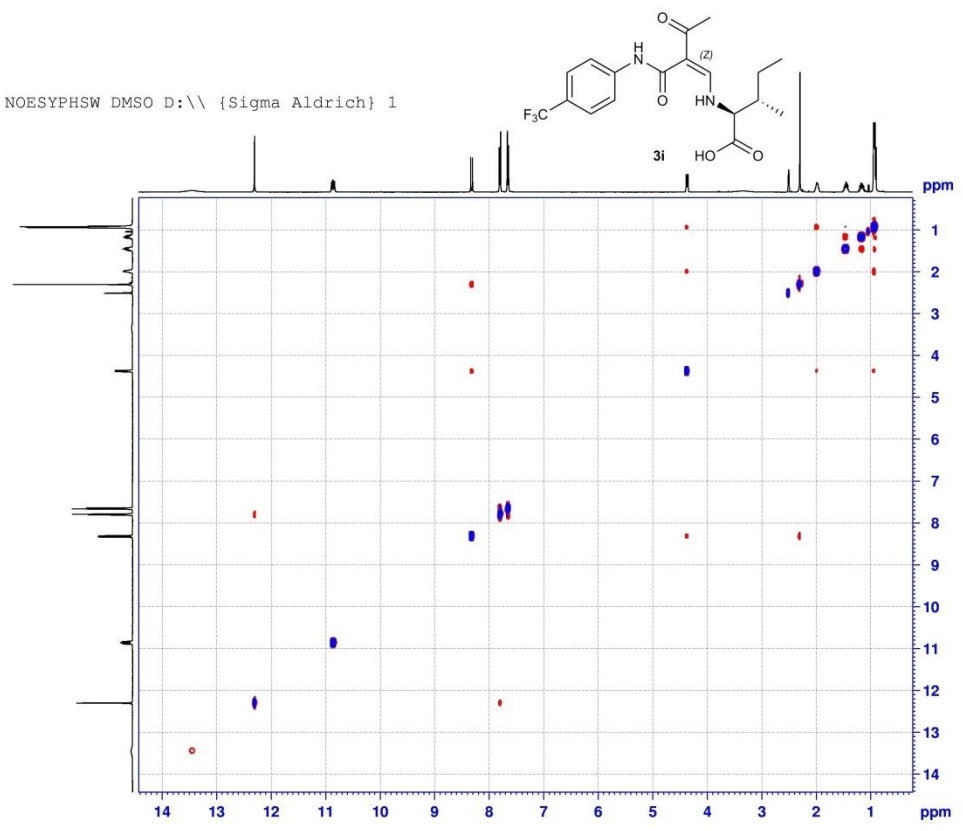


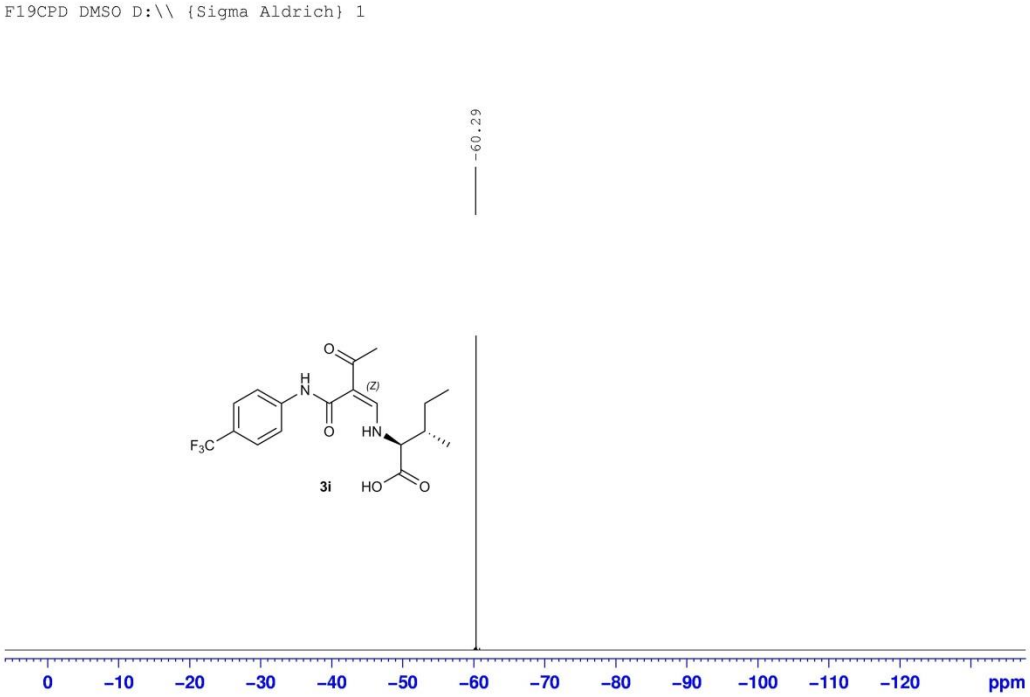
C13CPD DMSO D:\\ {Sigma Aldrich} 1



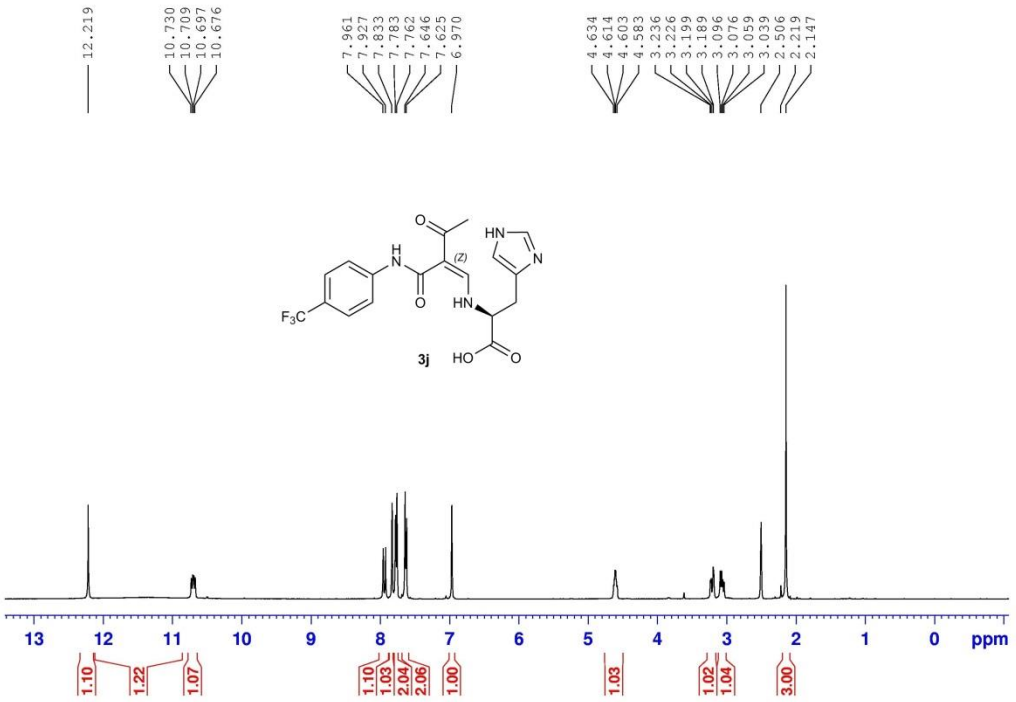
C13APT DMSO D:\\ {Sigma Aldrich} 1



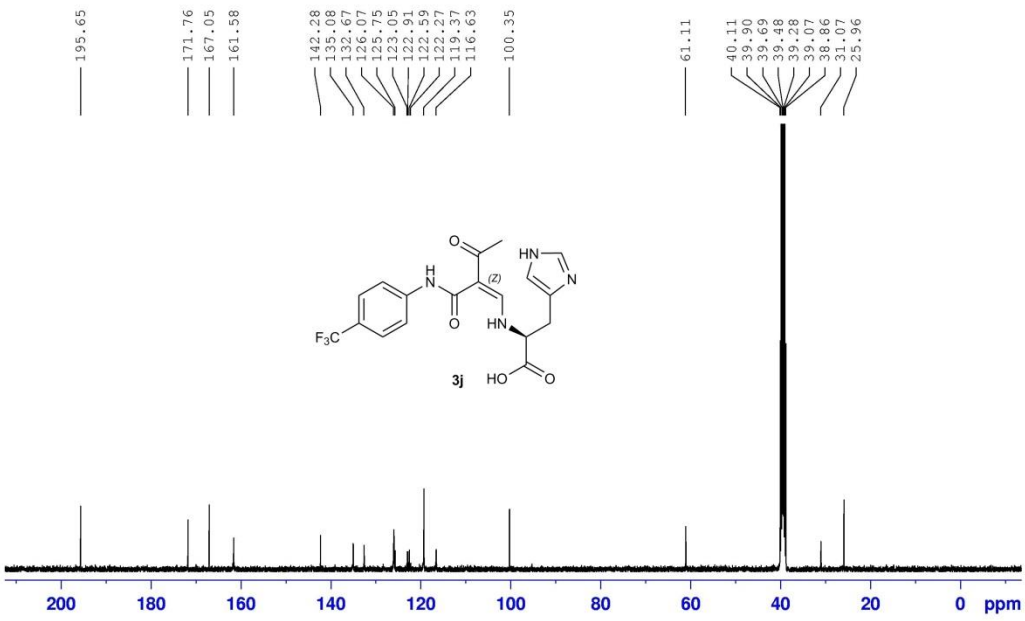

NOESYPHSW DMSO D:\\ {Sigma Aldrich} 1
3i
ppm
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm

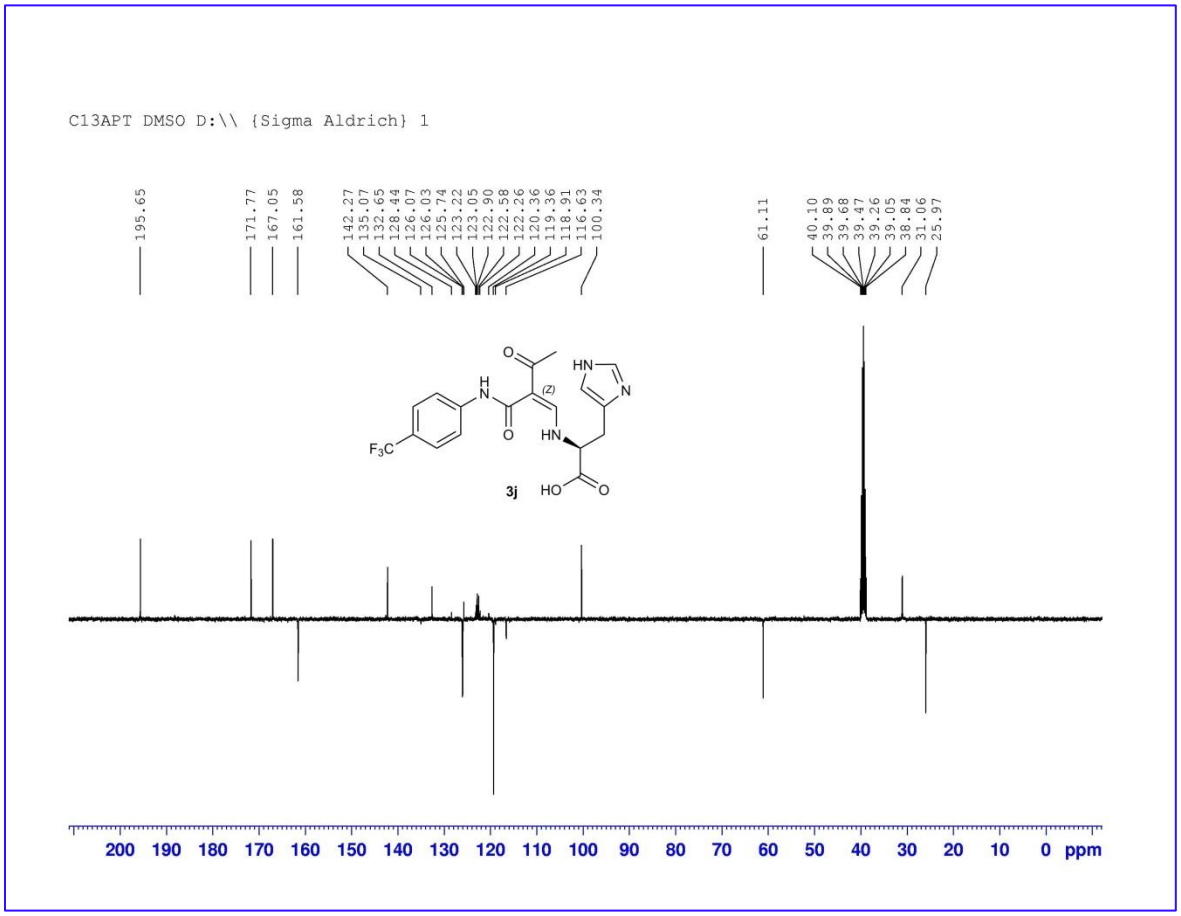

F19CPD DMSO D:\\ {Sigma Aldrich} 1
-60.29
3i
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 ppm

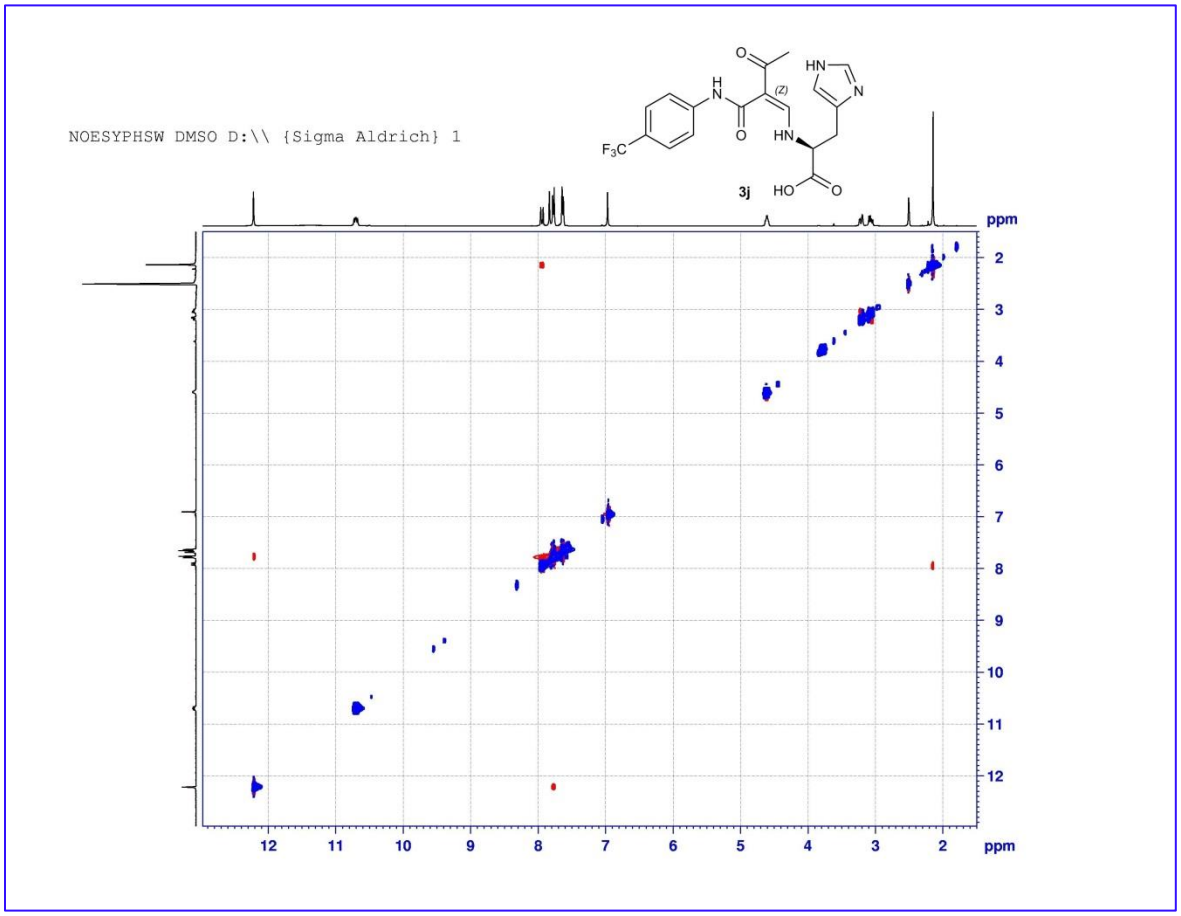
PROTON DMSO D:\\ {Sigma Aldrich} 1



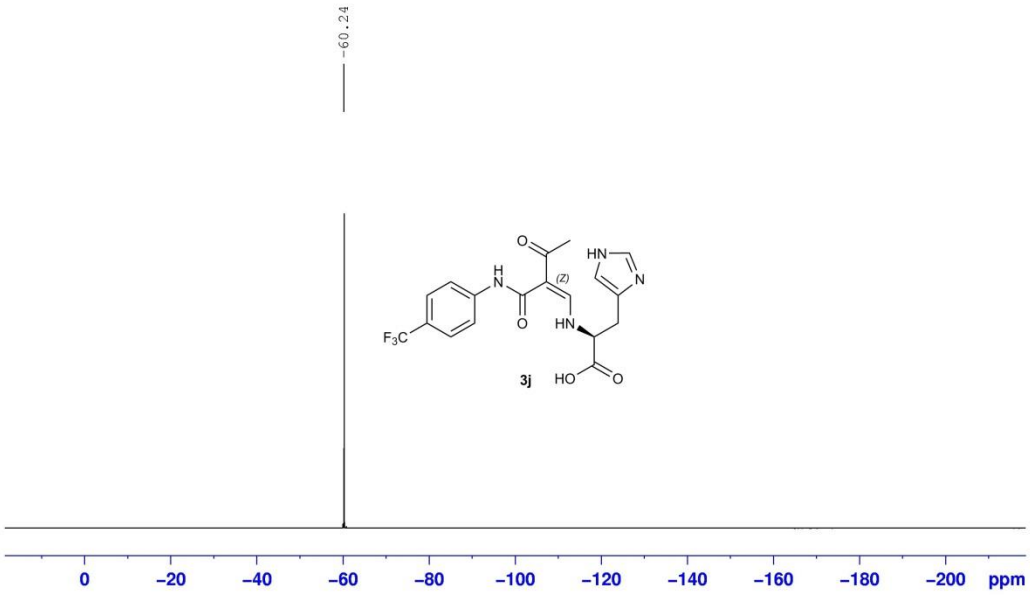
C13CPD DMSO D:\\ {Sigma Aldrich} 1



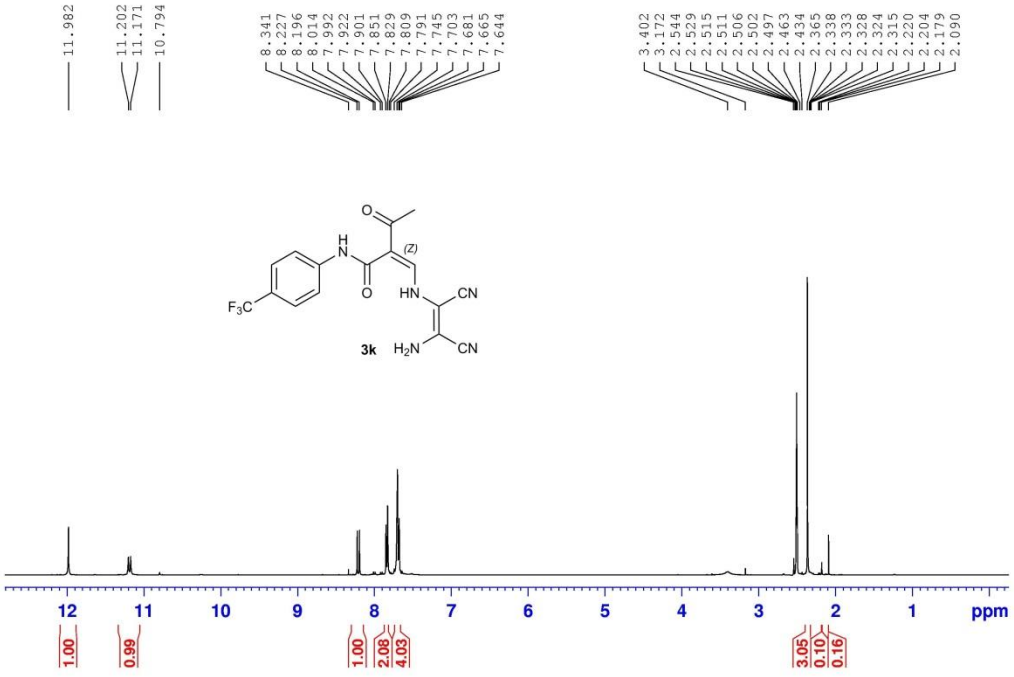

C13APT DMSO D:\\ {Sigma Aldrich} 1
195.65
171.77
167.05
161.58
142.27
135.07
132.65
128.44
126.07
126.03
125.74
123.22
123.05
122.90
122.58
122.26
120.36
119.36
118.91
116.63
100.34
61.11
40.10
39.89
39.68
39.47
39.26
39.05
38.84
31.06
25.97
3j
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


NOESYPHSW DMSO D:\\ {Sigma Aldrich} 1
3j
ppm
2 3 4 5 6 7 8 9 10 11 12
12 11 10 9 8 7 6 5 4 3 2 ppm

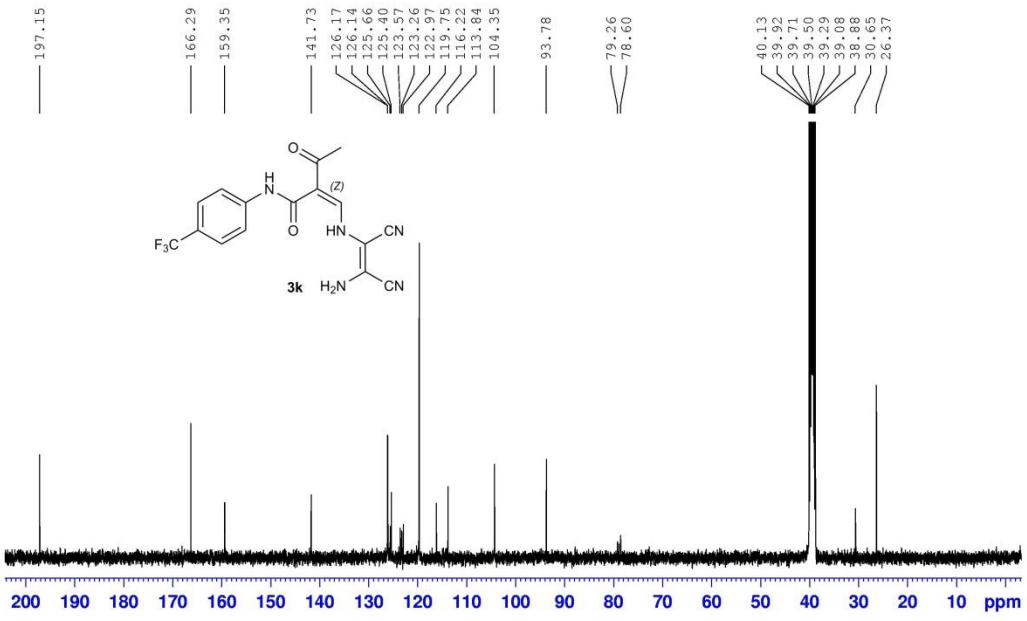
F19 DMSO D:\\ {Sigma Aldrich} 1



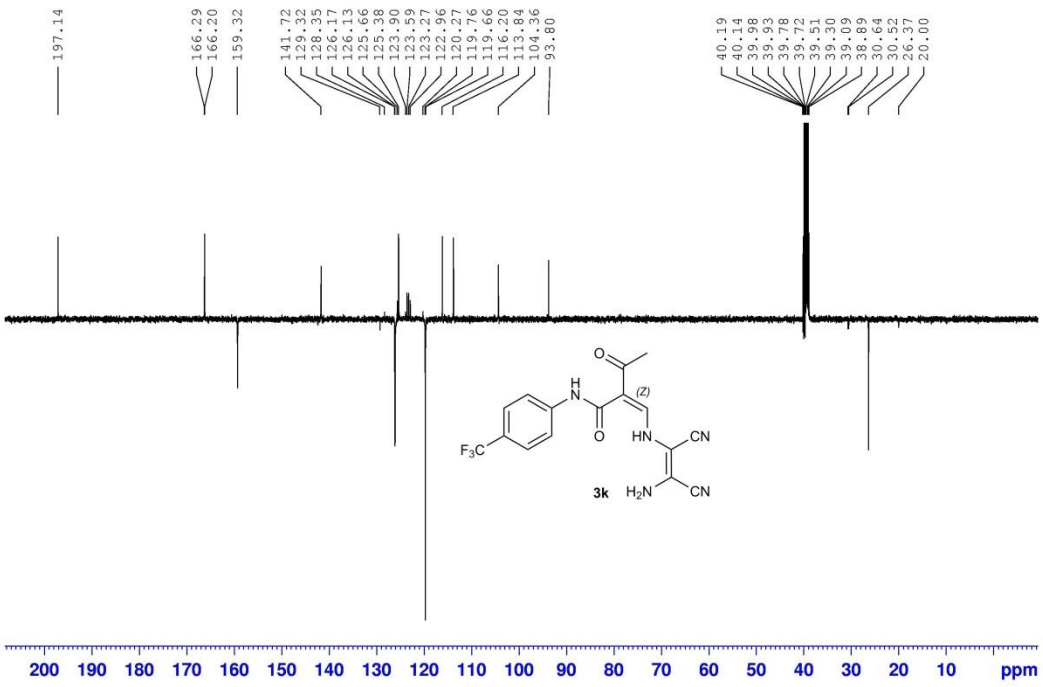
PROTON DMSO D:\\ {Sigma Aldrich} 1

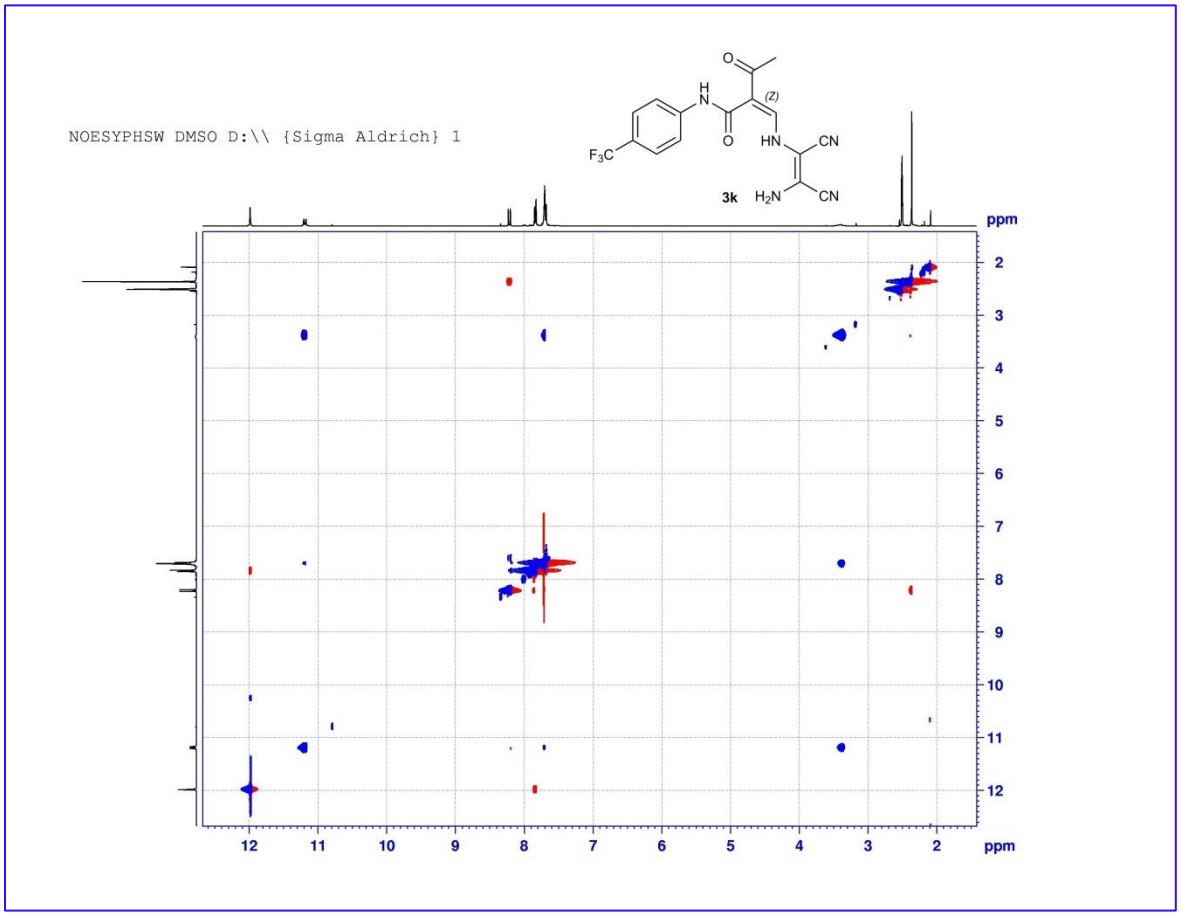


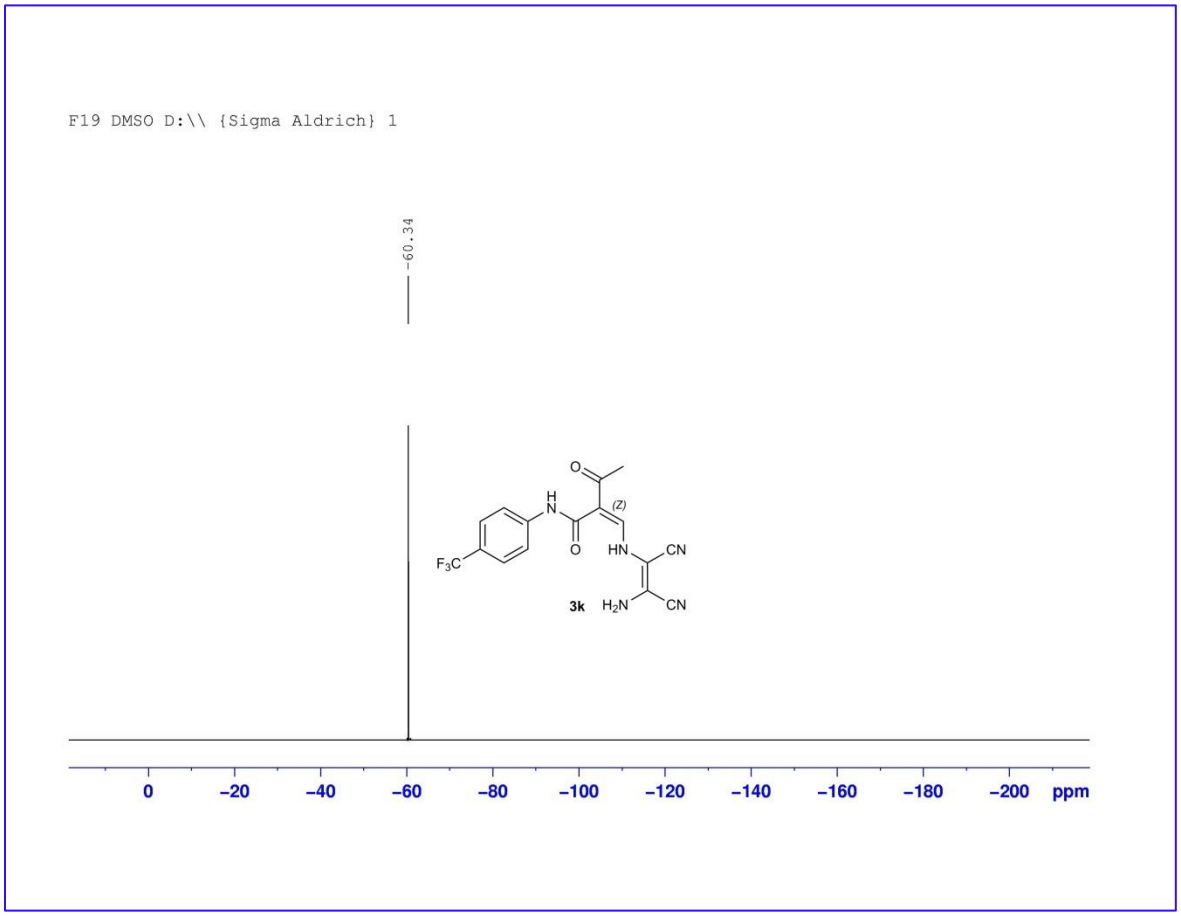
C13CPD DMSO D:\\ {Sigma Aldrich} 1



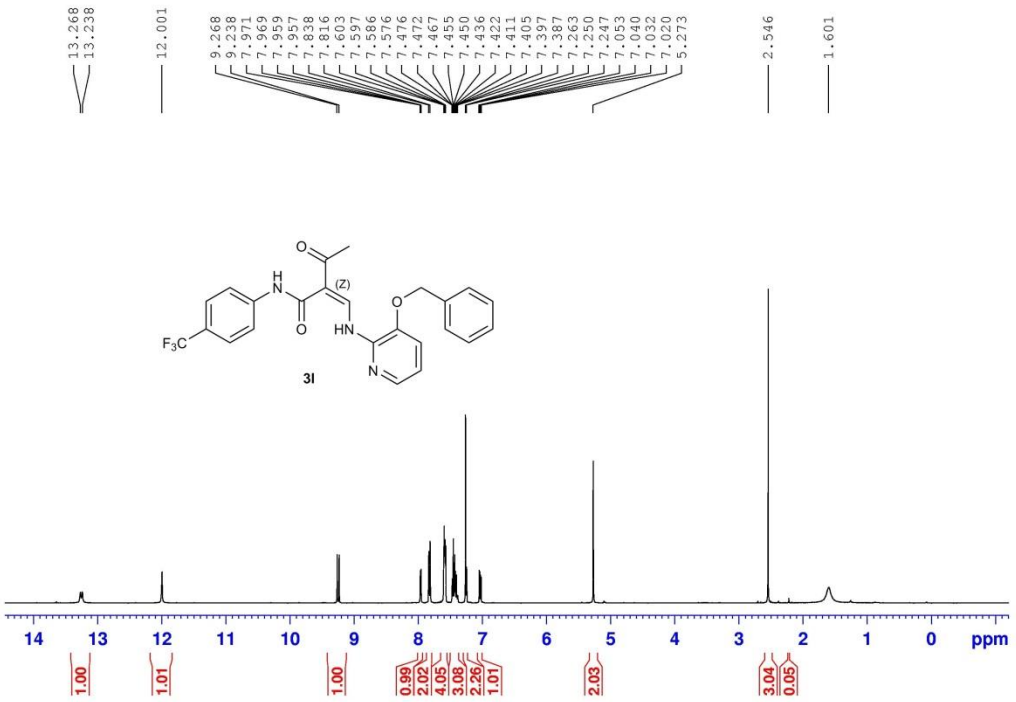
C13APT DMSO D:\\ {Sigma Aldrich} 1



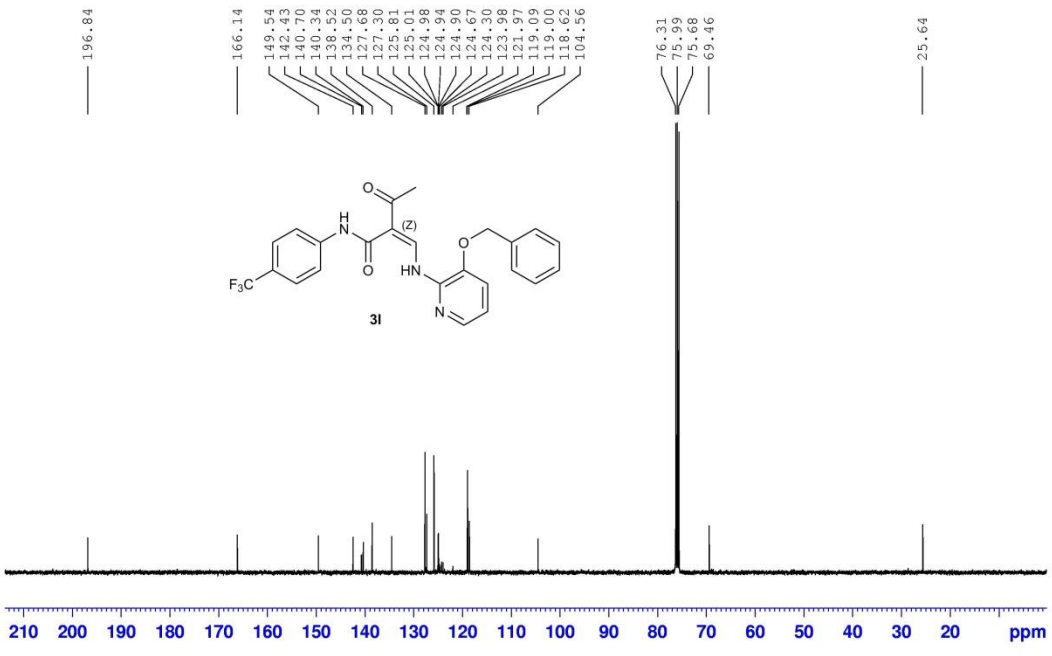

NOESYPHSW DMSO D:\\ {Sigma Aldrich} 1
3k
ppm
12 11 10 9 8 7 6 5 4 3 2 ppm

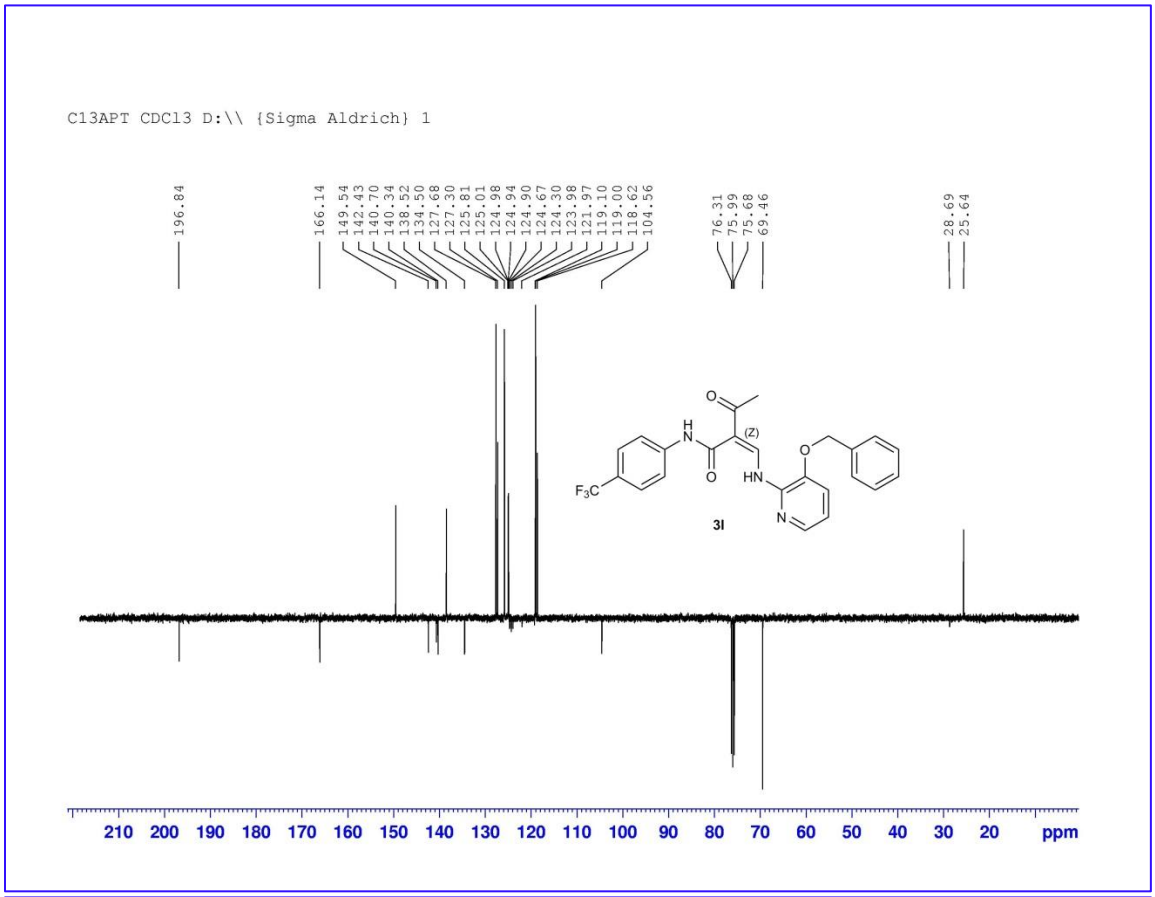

F19 DMSO D:\\ {Sigma Aldrich} 1
-60.34
3k
0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 ppm

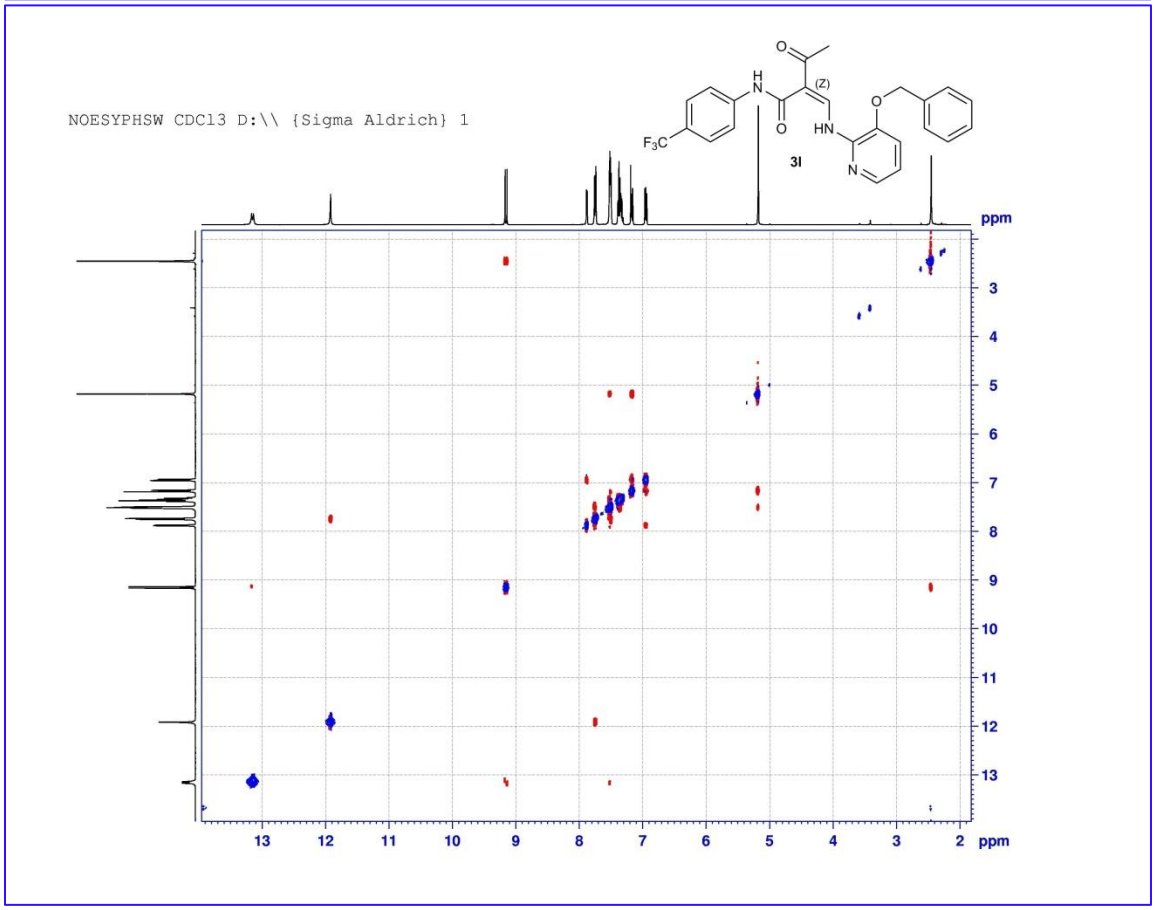
PROTON CDCl3 D:\\ {Sigma Aldrich} 1



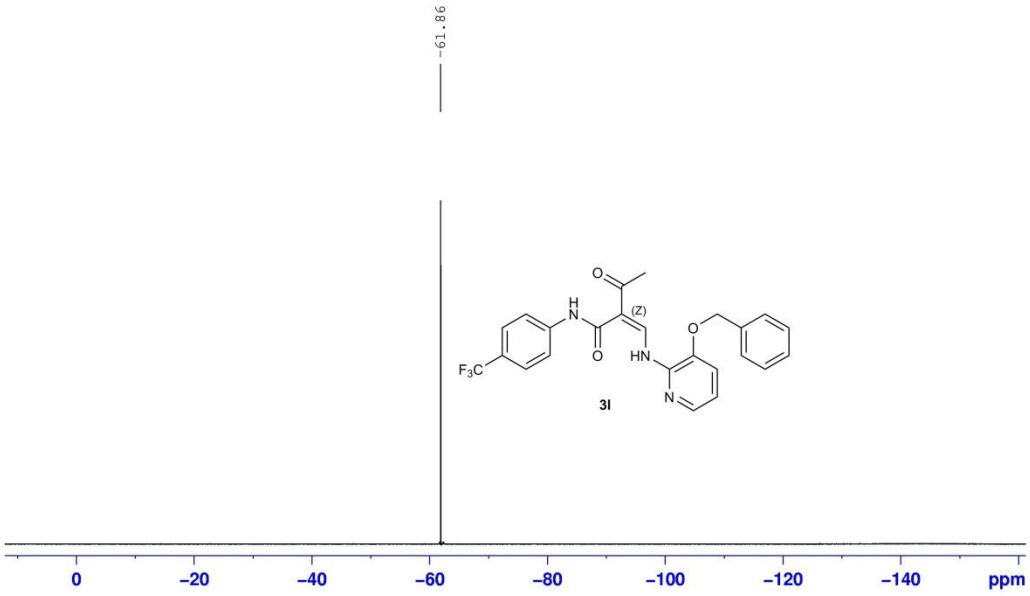
C13CPD CDCl3 D:\\ {Sigma Aldrich} 1



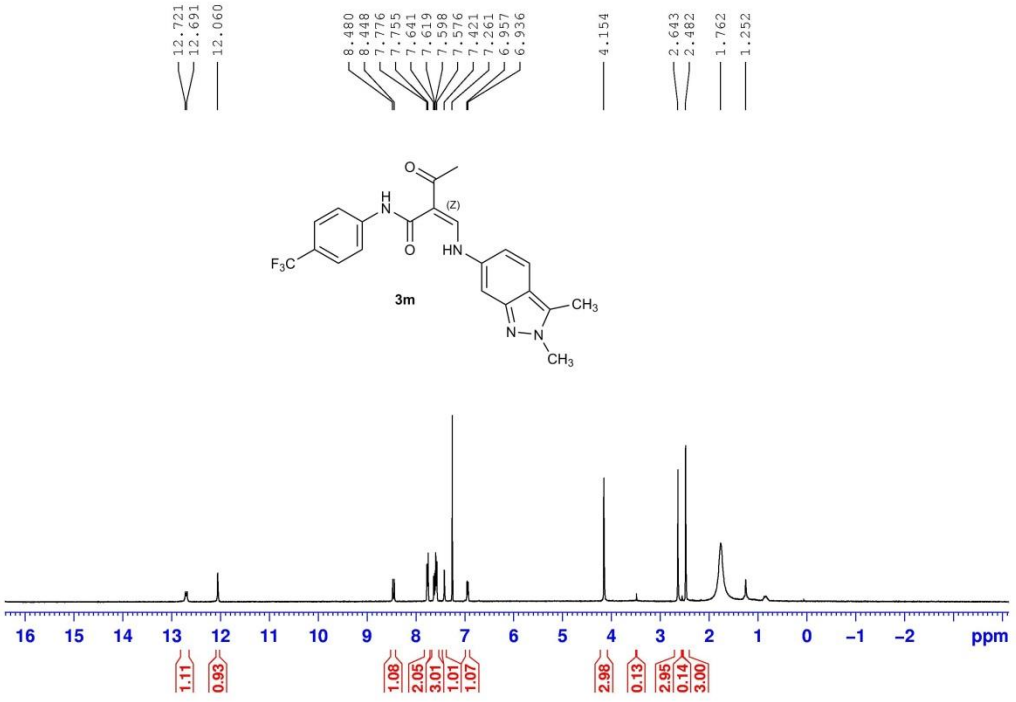

C13APT CDCl3 D:\\ {Sigma Aldrich} 1
196.84
166.14
149.54
142.43
140.70
140.34
138.52
134.50
127.68
127.30
125.81
125.01
124.98
124.94
124.90
124.67
124.30
123.98
121.97
119.10
119.00
118.62
104.56
76.31
75.99
75.68
69.46
28.69
25.64
3l
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


NOESYPHSW CDCl3 D:\\ {Sigma Aldrich} 1
3l
ppm
13 12 11 10 9 8 7 6 5 4 3 2 ppm

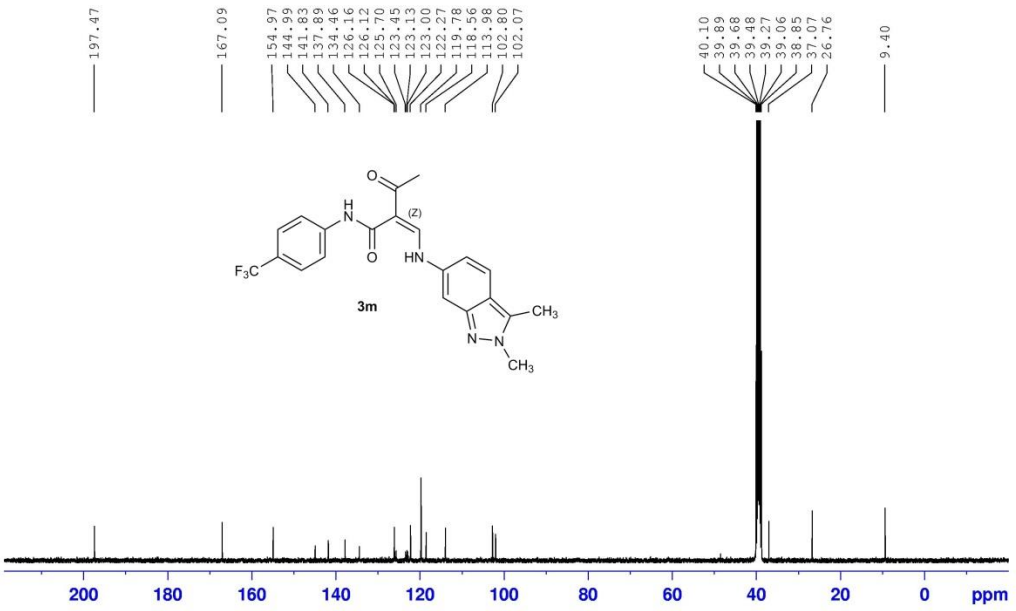
F19 CDCl3 D:\\ {Sigma Aldrich} 1



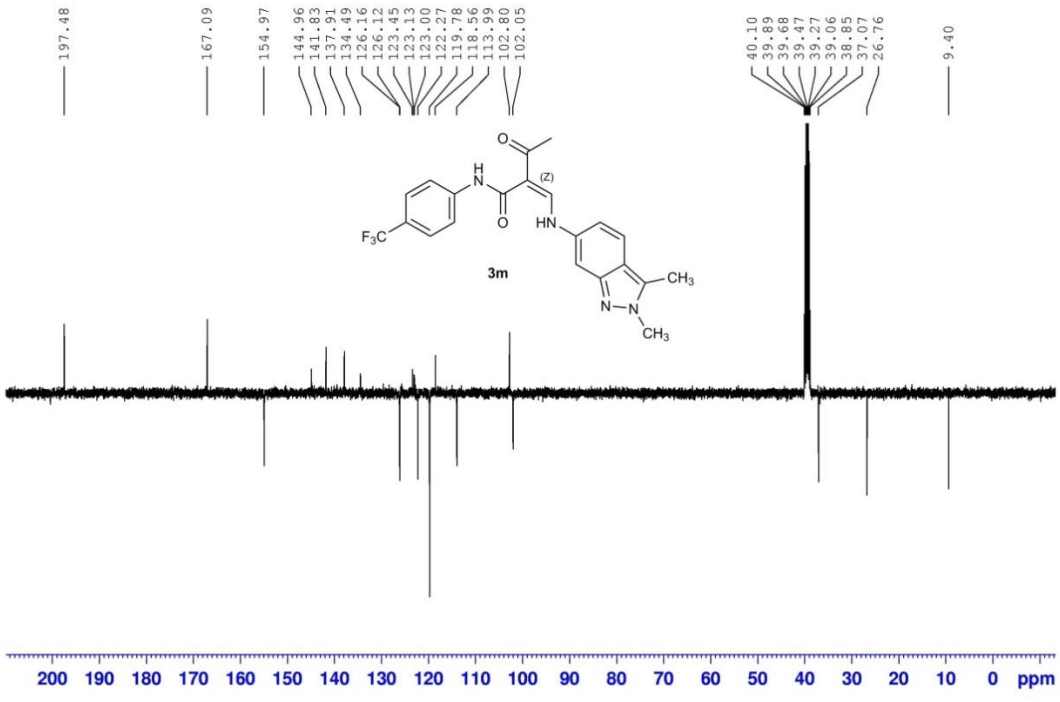
PROTON CDCl3 D:\\ {Sigma Aldrich} 1

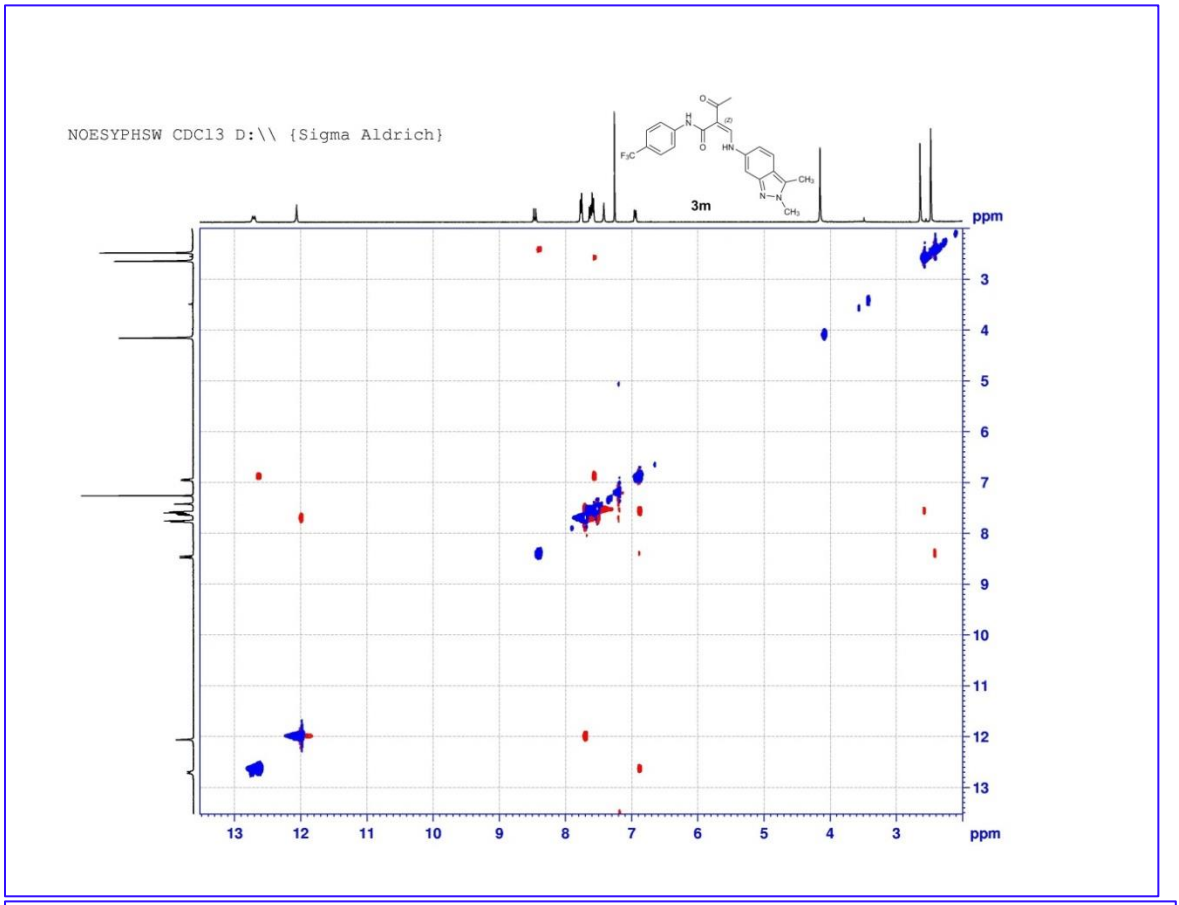


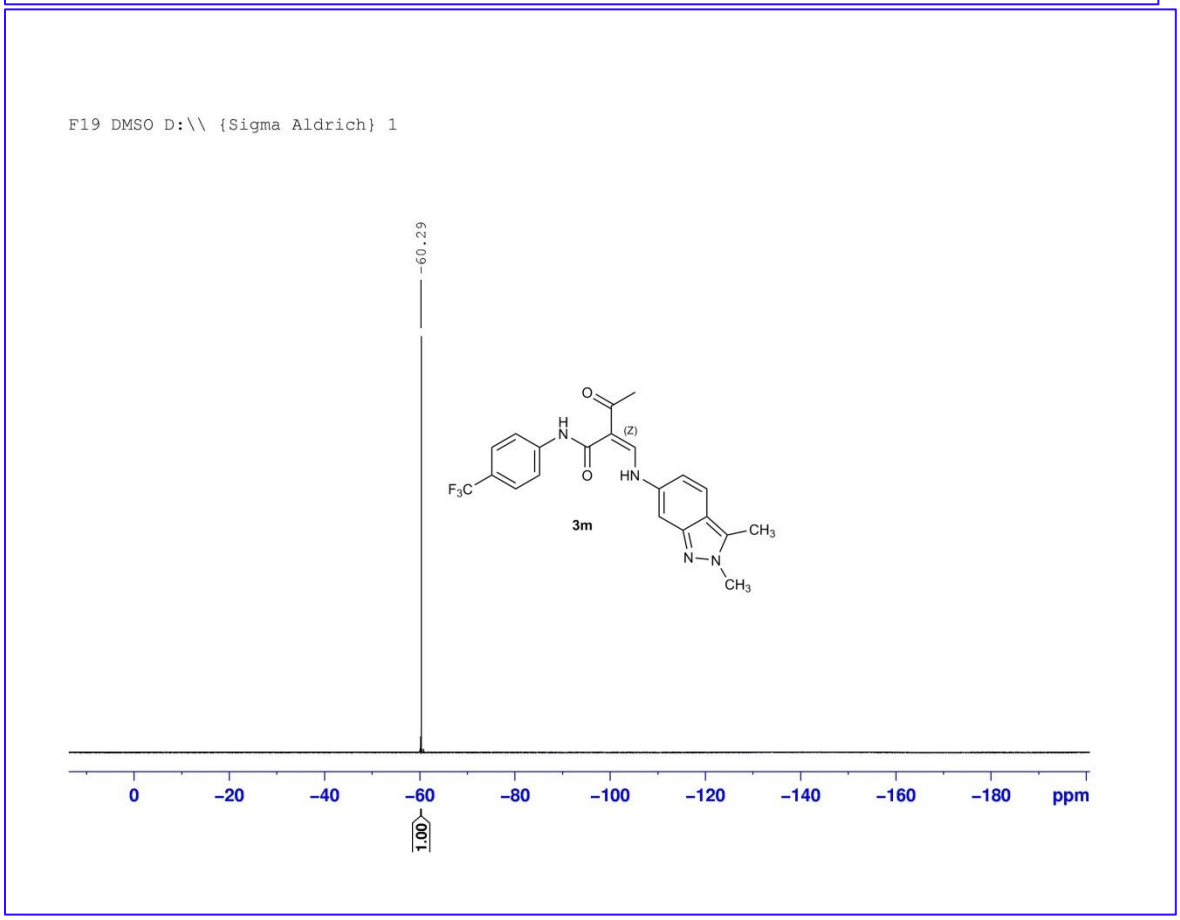
C13CPD DMSO D:\\ {Sigma Aldrich} 1



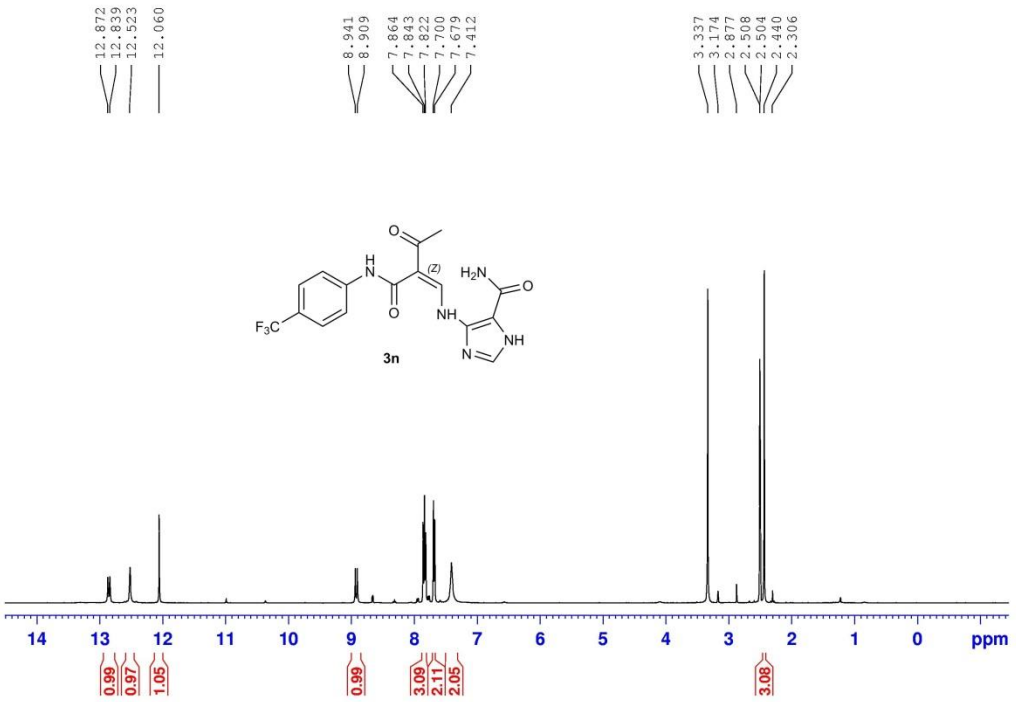
C13APT DMSO D:\\ {Sigma Aldrich} 1



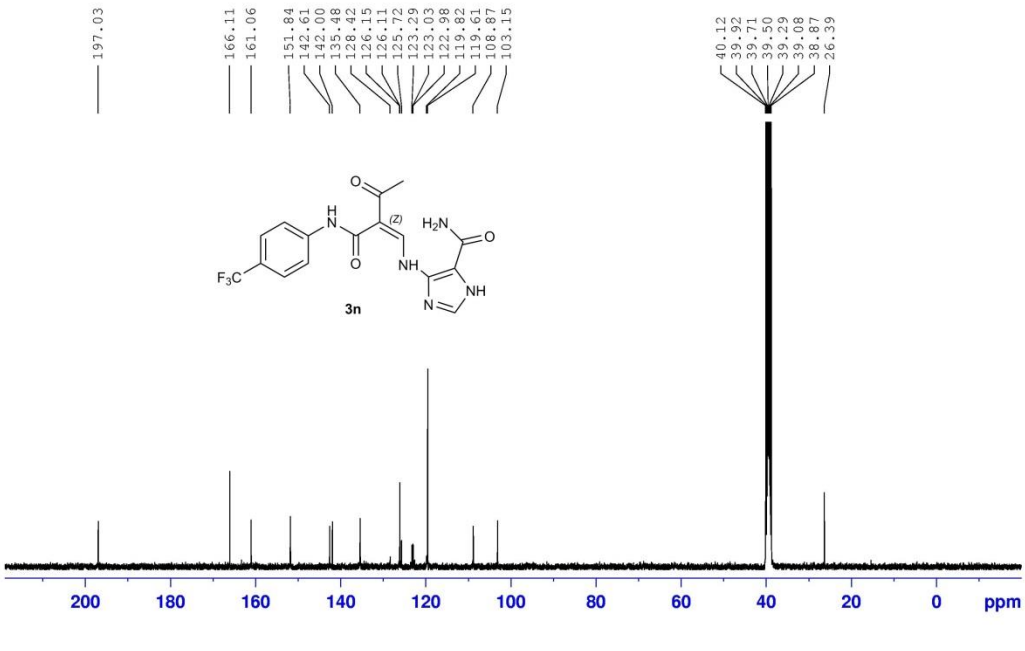

NOESYPHSW CDCl3 D:\\ {Sigma Aldrich}
3m
ppm
13
12
11
10
9
8
7
6
5
4
3

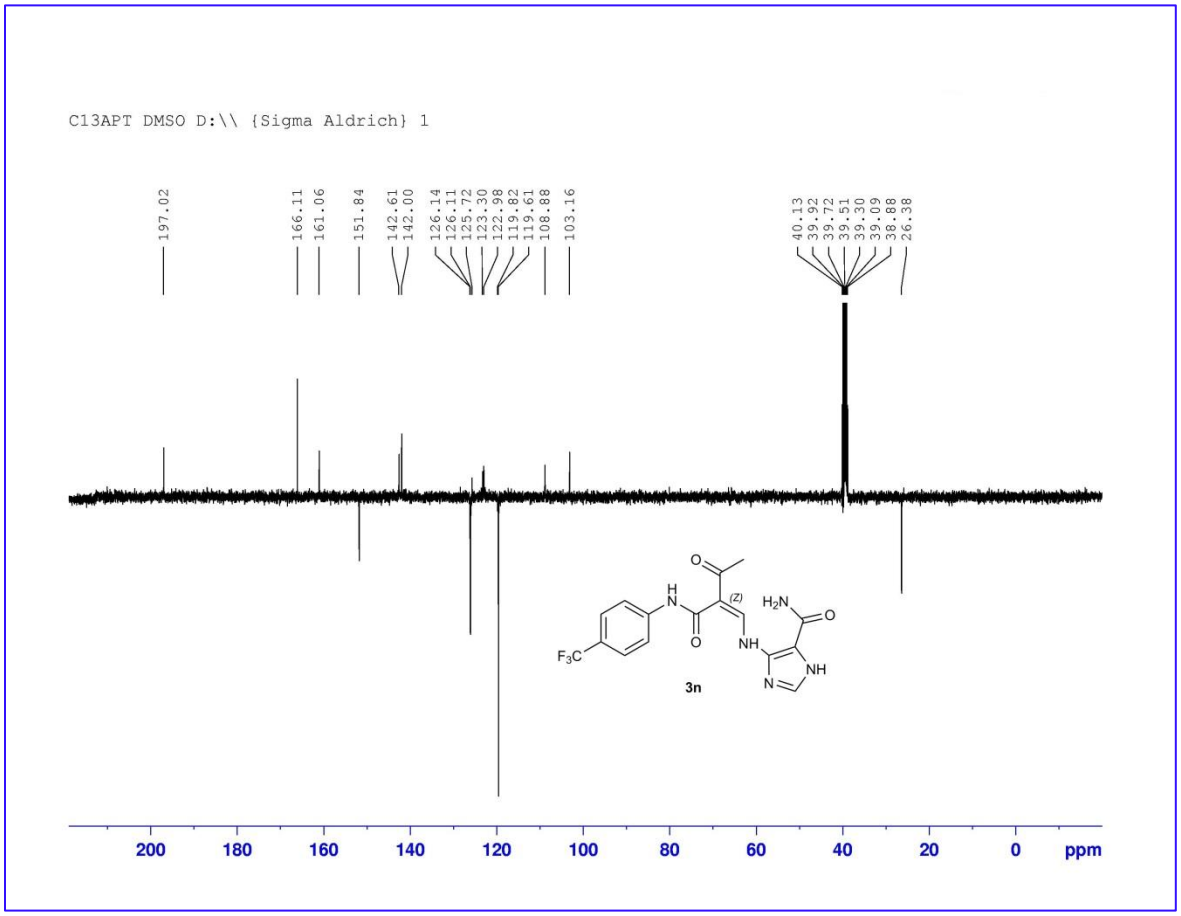

F19 DMSO D:\\ {Sigma Aldrich} 1
-60.29
3m
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
ppm
1.00

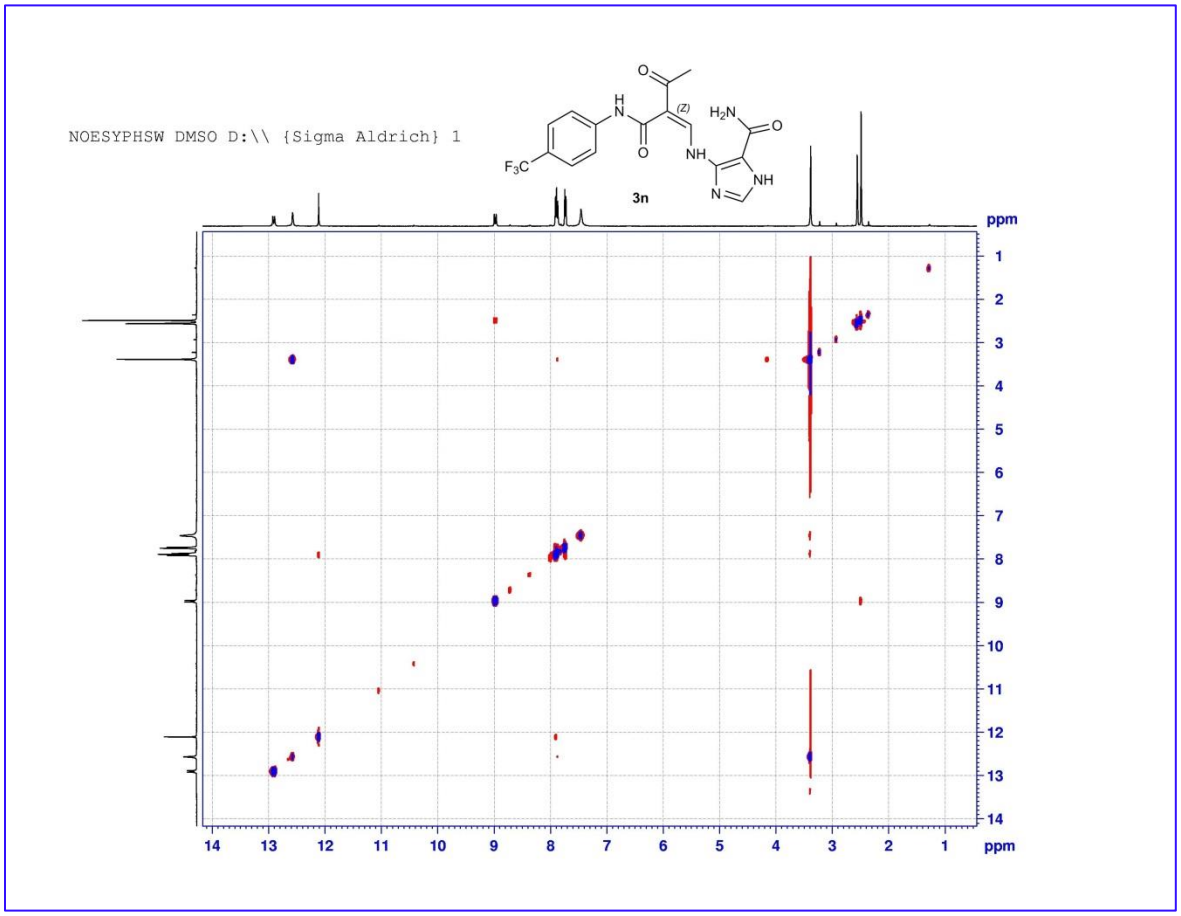
PROTON DMSO D:\\ {Sigma Aldrich} 1



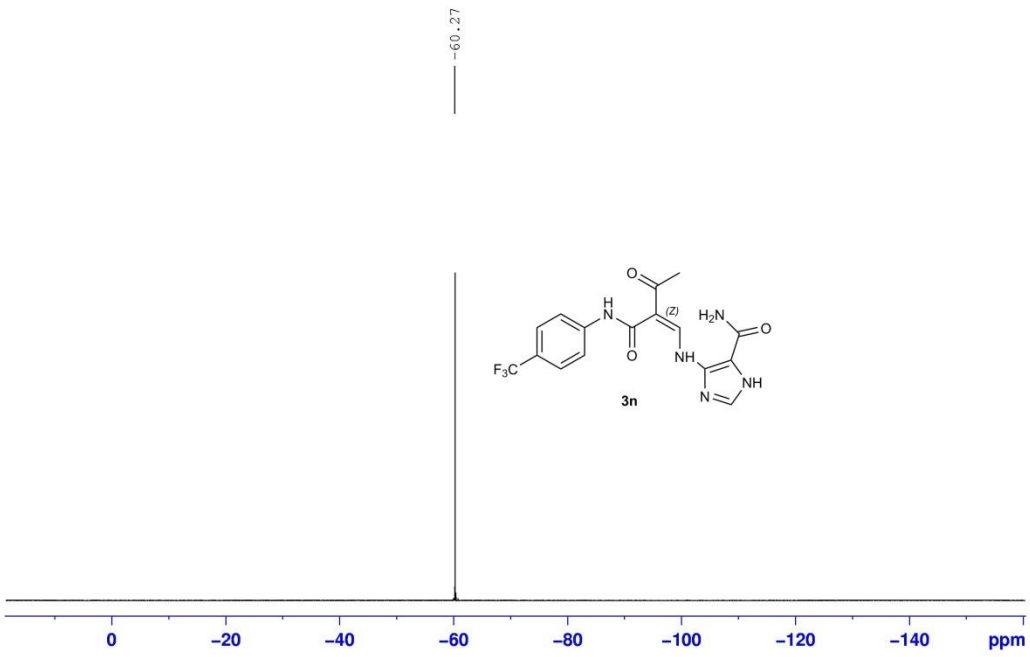
C13CPD DMSO D:\\ {Sigma Aldrich} 1



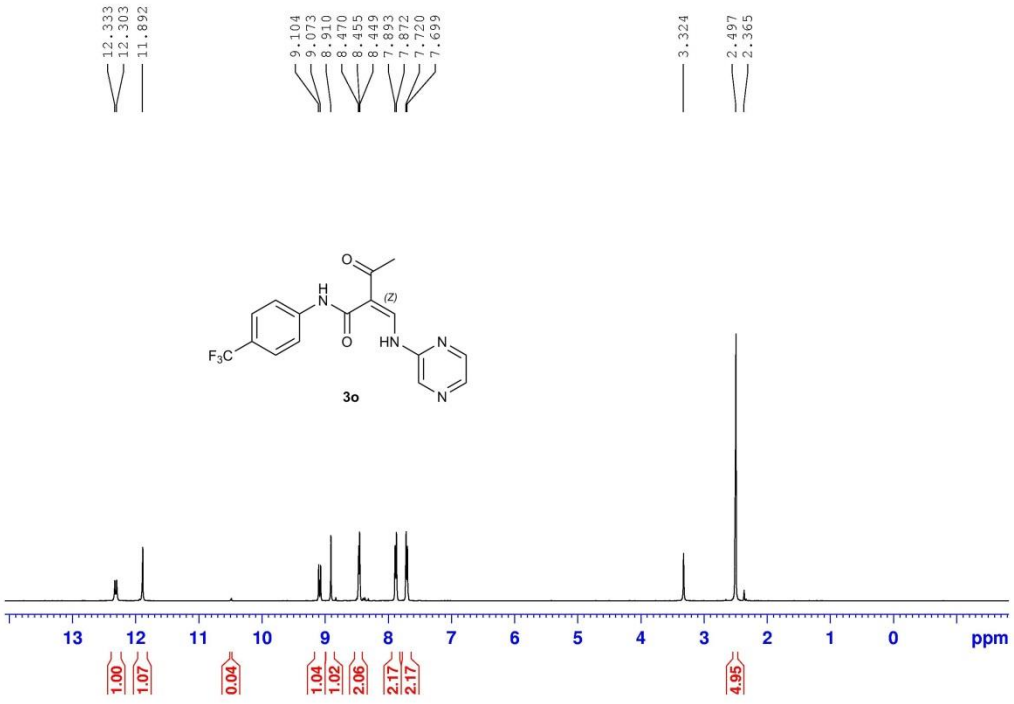

C13APT DMSO D:\\ {Sigma Aldrich} 1
197.02
166.11
161.06
151.84
142.61
142.00
126.14
126.11
125.72
123.30
122.98
119.82
119.61
108.88
103.16
40.13
39.92
39.72
39.51
39.30
39.09
38.88
26.38
3n
200
180
160
140
120
100
80
60
40
20
0
ppm


NOESYPHSW DMSO D:\\ {Sigma Aldrich} 1
3n
ppm
1
2
3
4
5
6
7
8
9
10
11
12
13
14
ppm

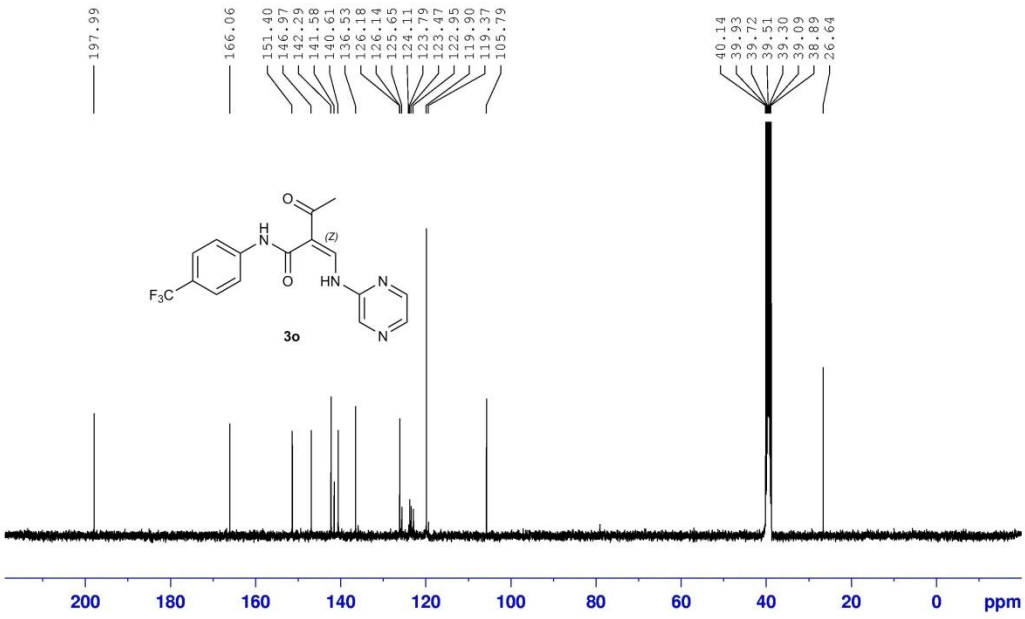
F19 DMSO D:\\ {Sigma Aldrich} 1



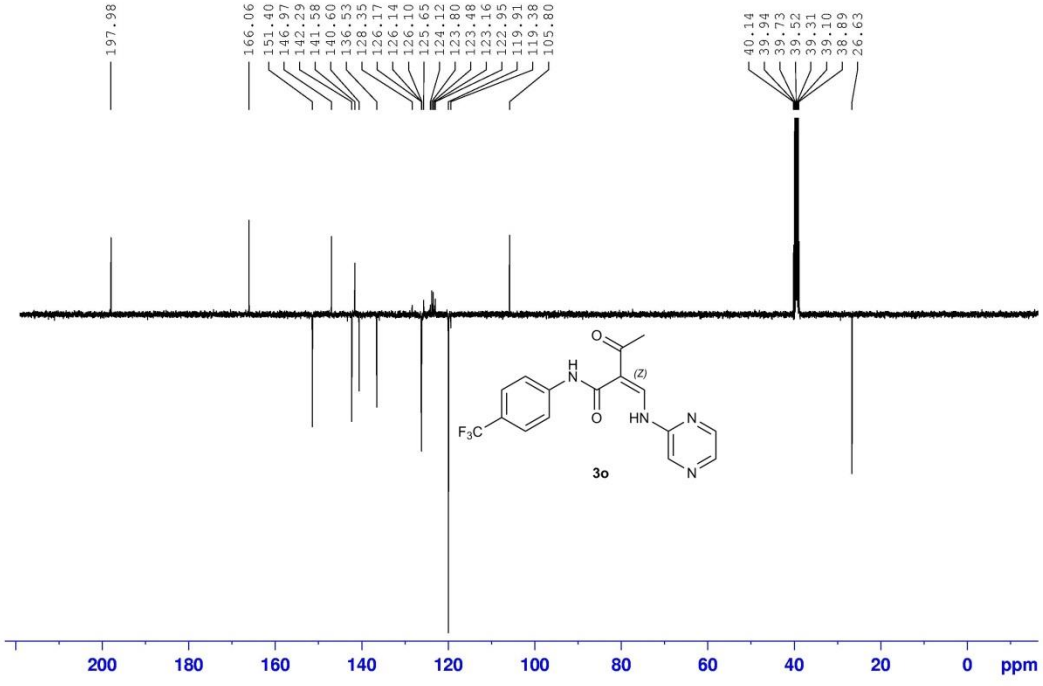
PROTON DMSO D:\\ {Sigma Aldrich} 1



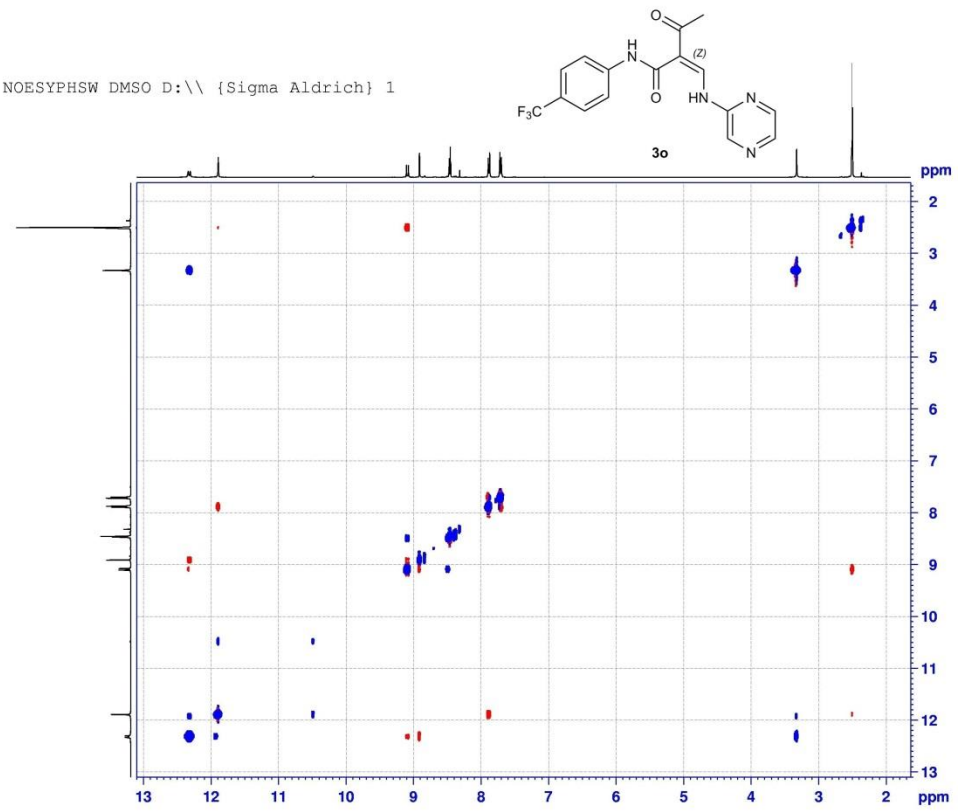
C13CPD DMSO D:\\ {Sigma Aldrich} 1



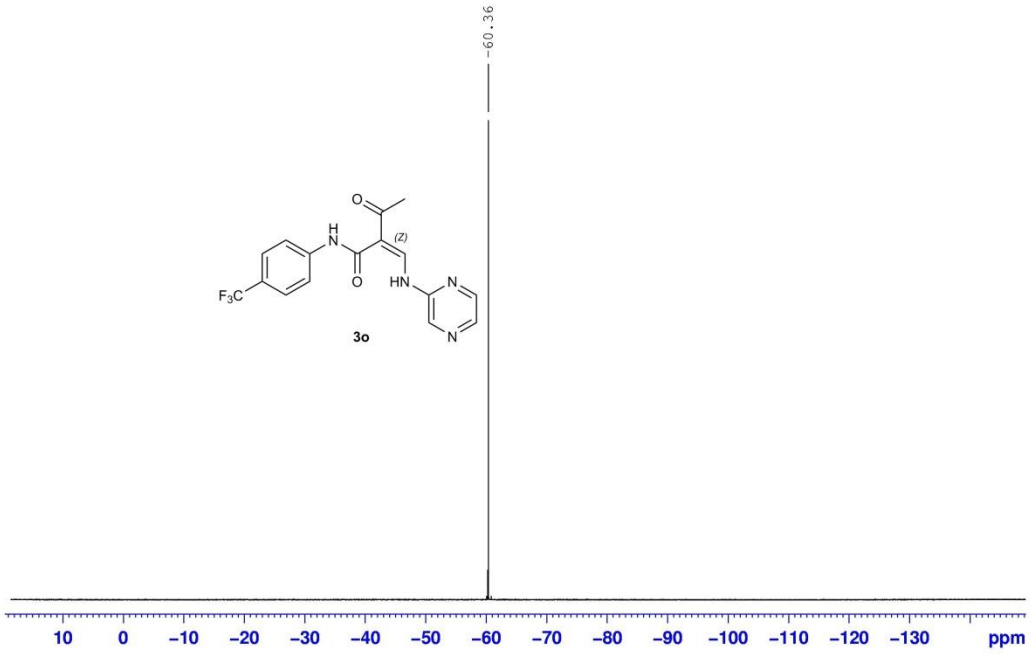
C13APT DMSO D:\\ {Sigma Aldrich} 1

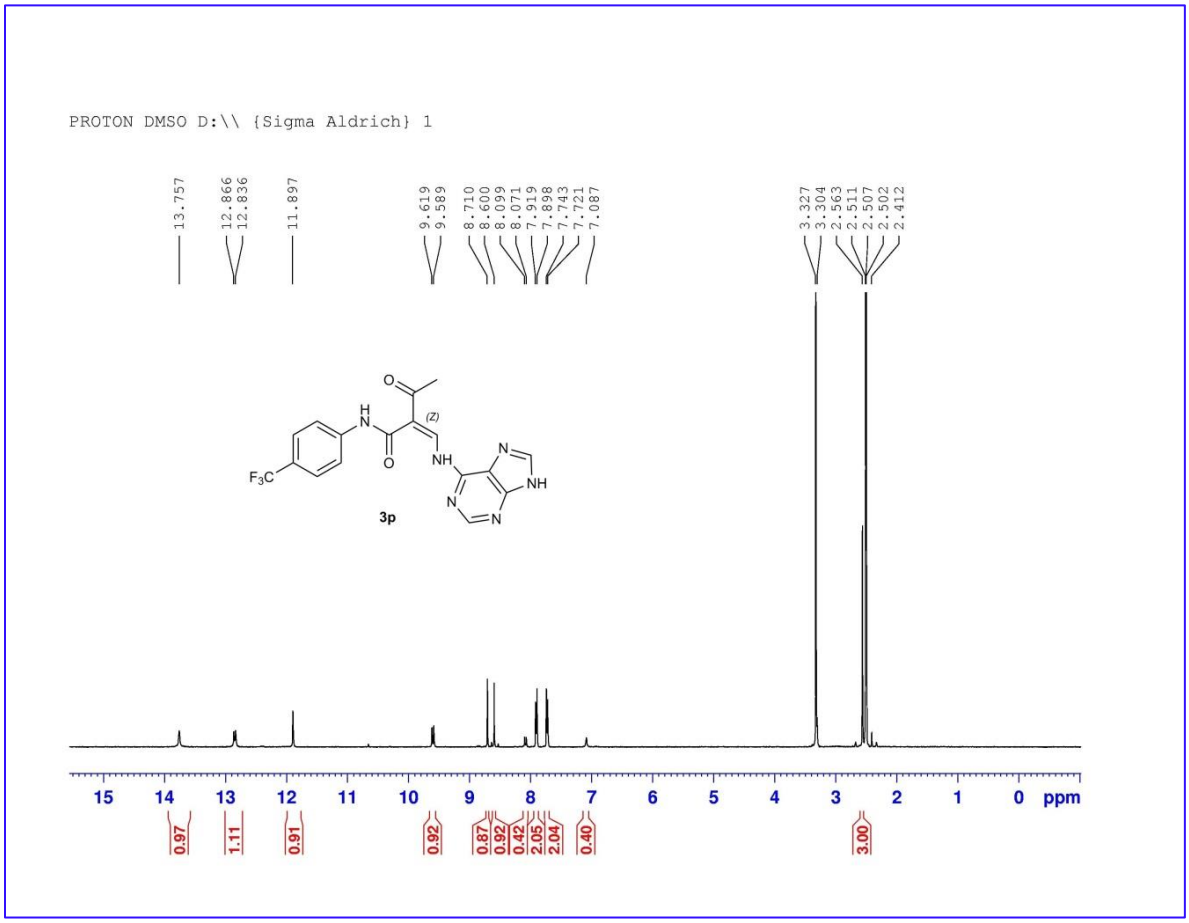


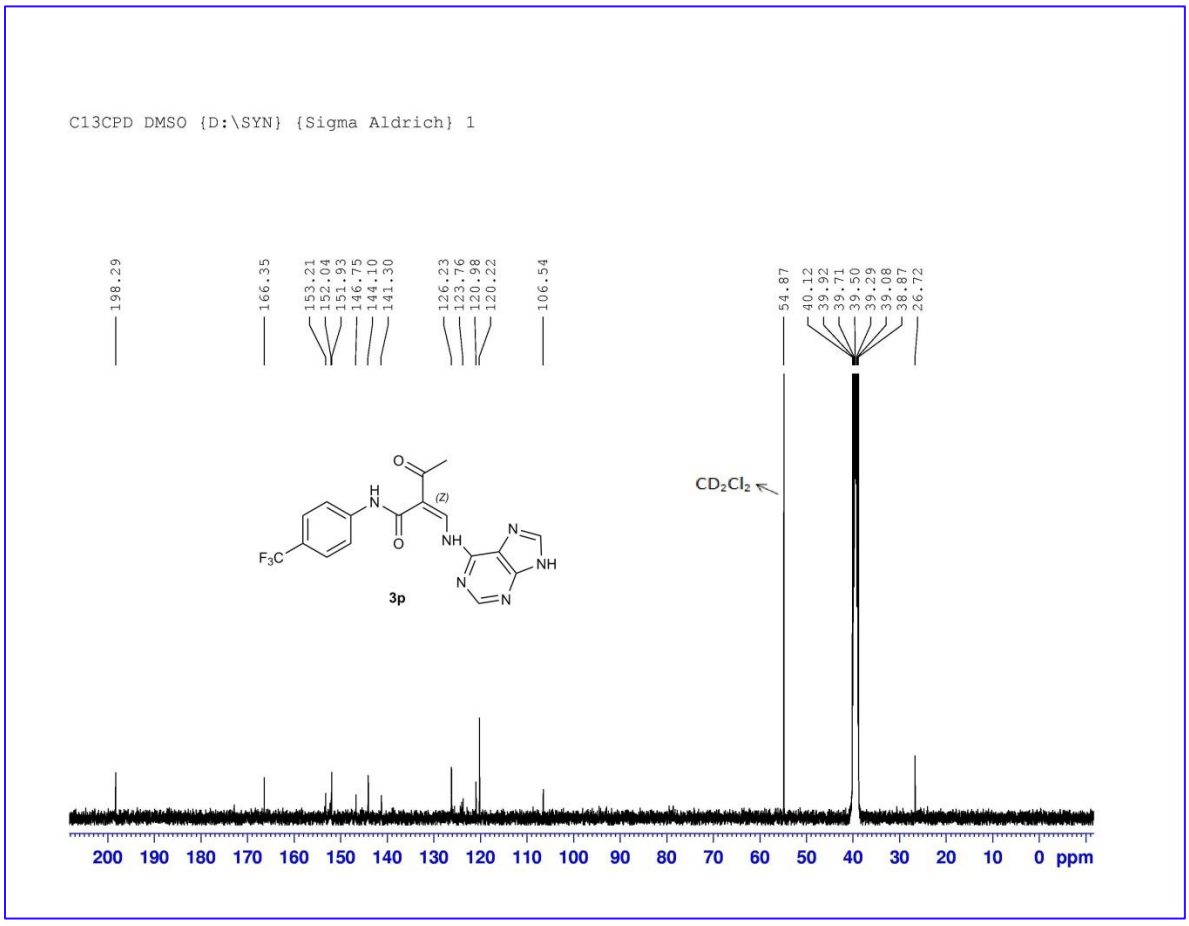
NOESYPHSW DMSO D:\\ {Sigma Aldrich} 1



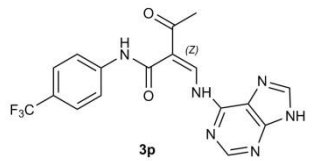
F19 DMSO D:\\ {Sigma Aldrich} 1



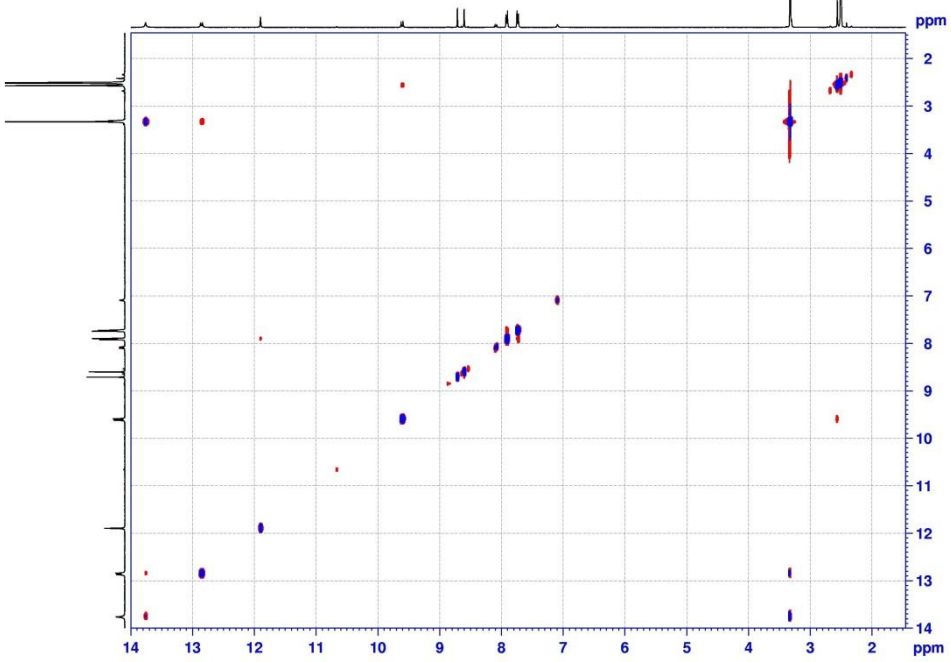

PROTON DMSO D:\\ {Sigma Aldrich} 1
13.757
12.866
12.836
11.897
9.619
9.589
8.710
8.600
8.099
8.071
7.919
7.898
7.743
7.721
7.087
3.327
3.304
2.563
2.511
2.507
2.502
2.412
3p
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.97
1.11
0.91
0.92
0.87
0.92
0.42
2.05
2.04
0.40
3.00


C13CPD DMSO {D:\SYN} {Sigma Aldrich} 1
198.29
166.35
153.21
152.04
151.93
146.75
144.10
141.30
126.23
123.76
120.98
120.22
106.54
54.87
40.12
39.92
39.71
39.50
39.29
39.08
38.87
26.72
CD2Cl2
3p
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

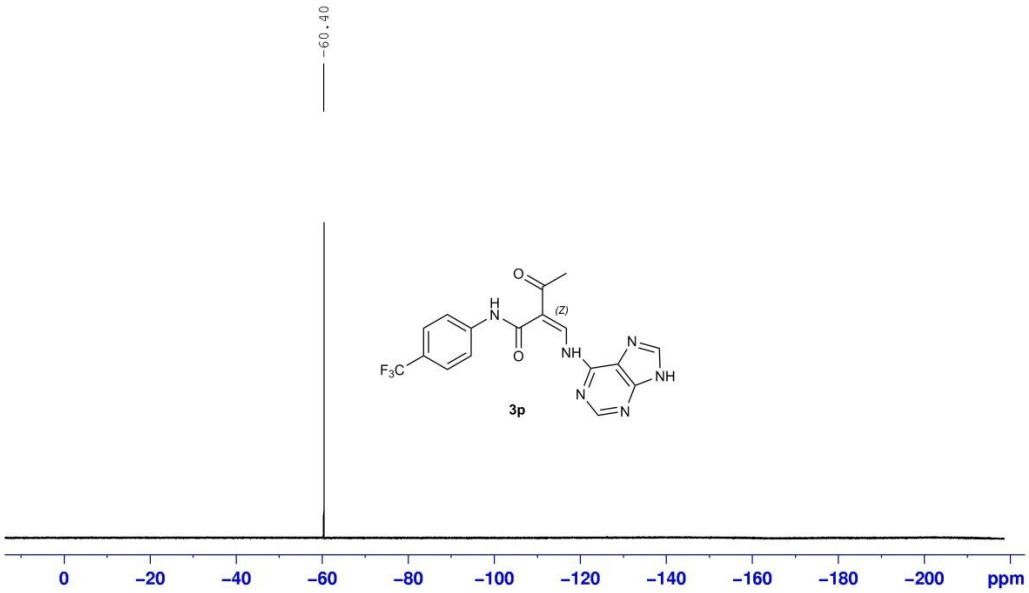
NOESYPHSW DMSO D:\\ {Sigma Aldrich} 1



3p

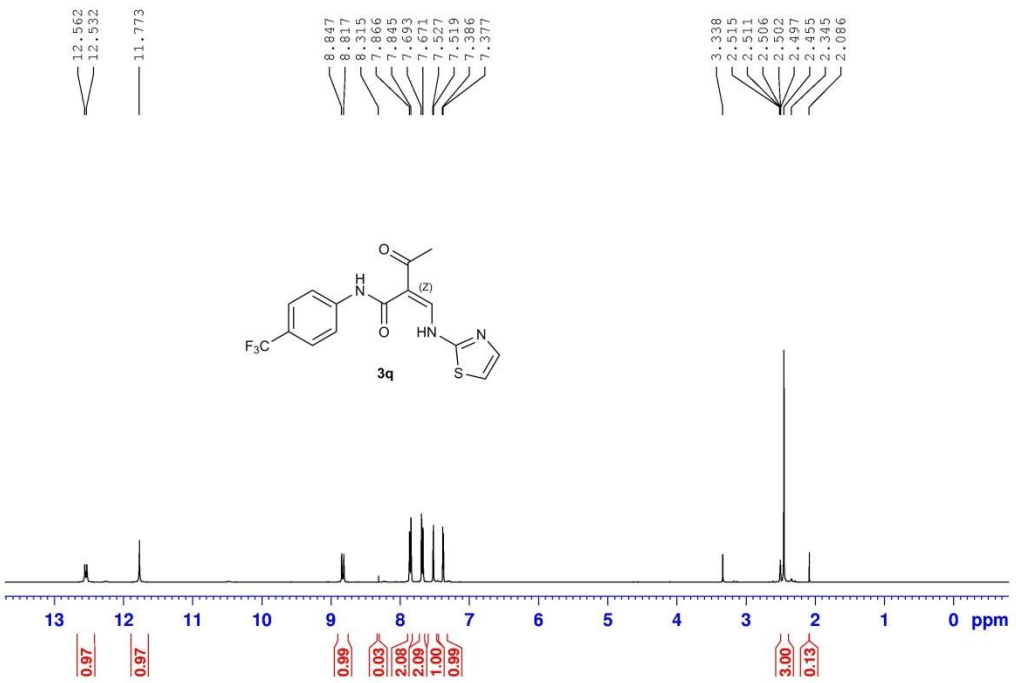


F19 DMSO D:\\ {Sigma Aldrich} 1

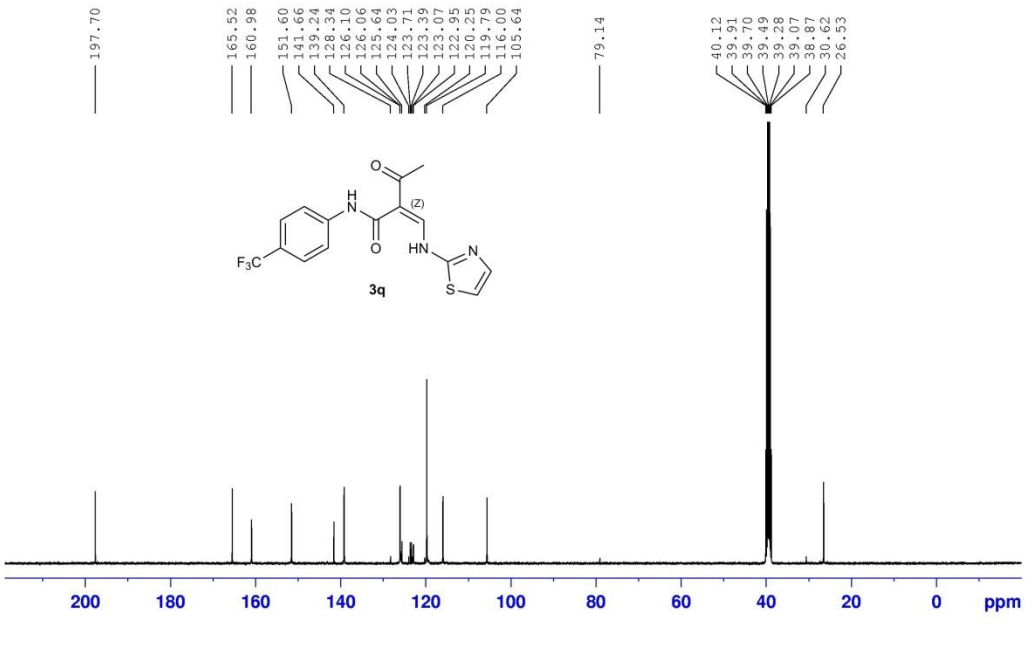


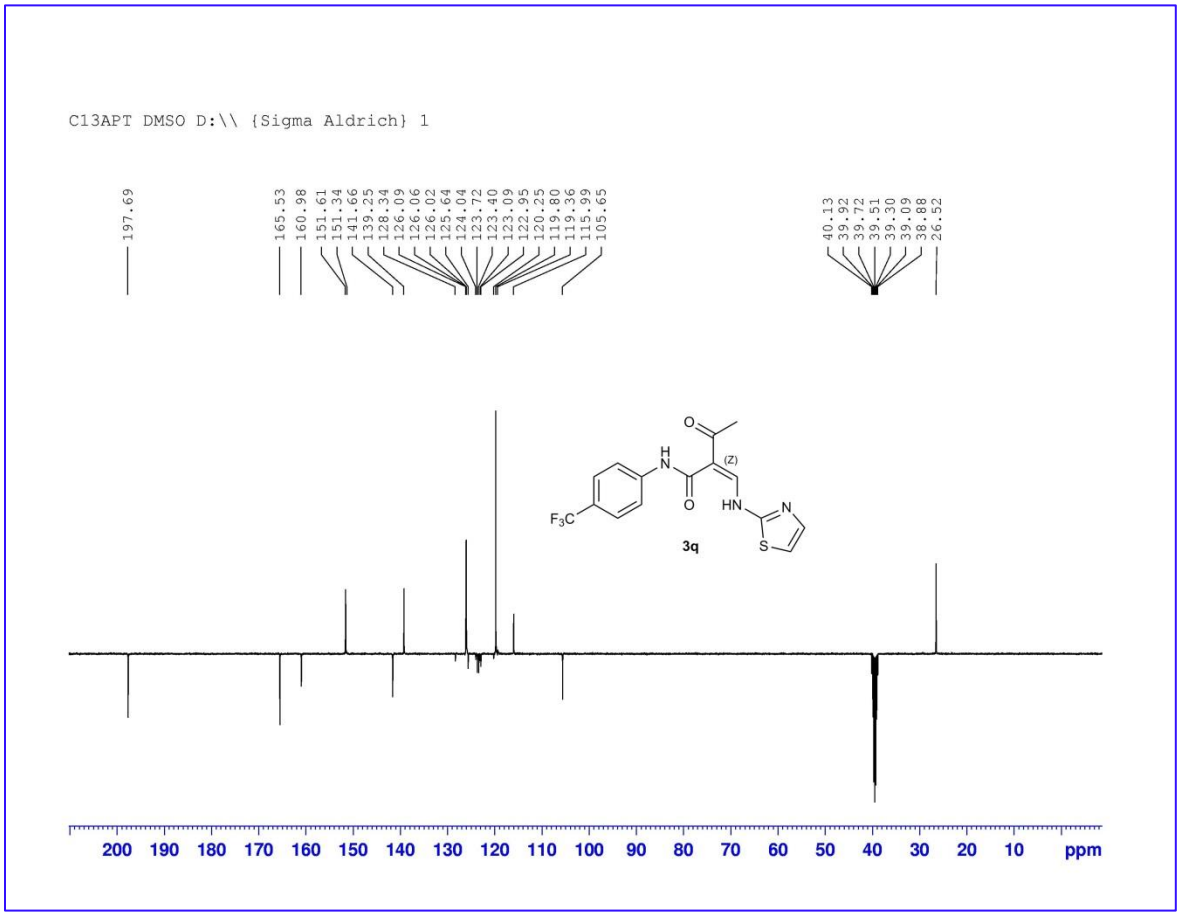
3p

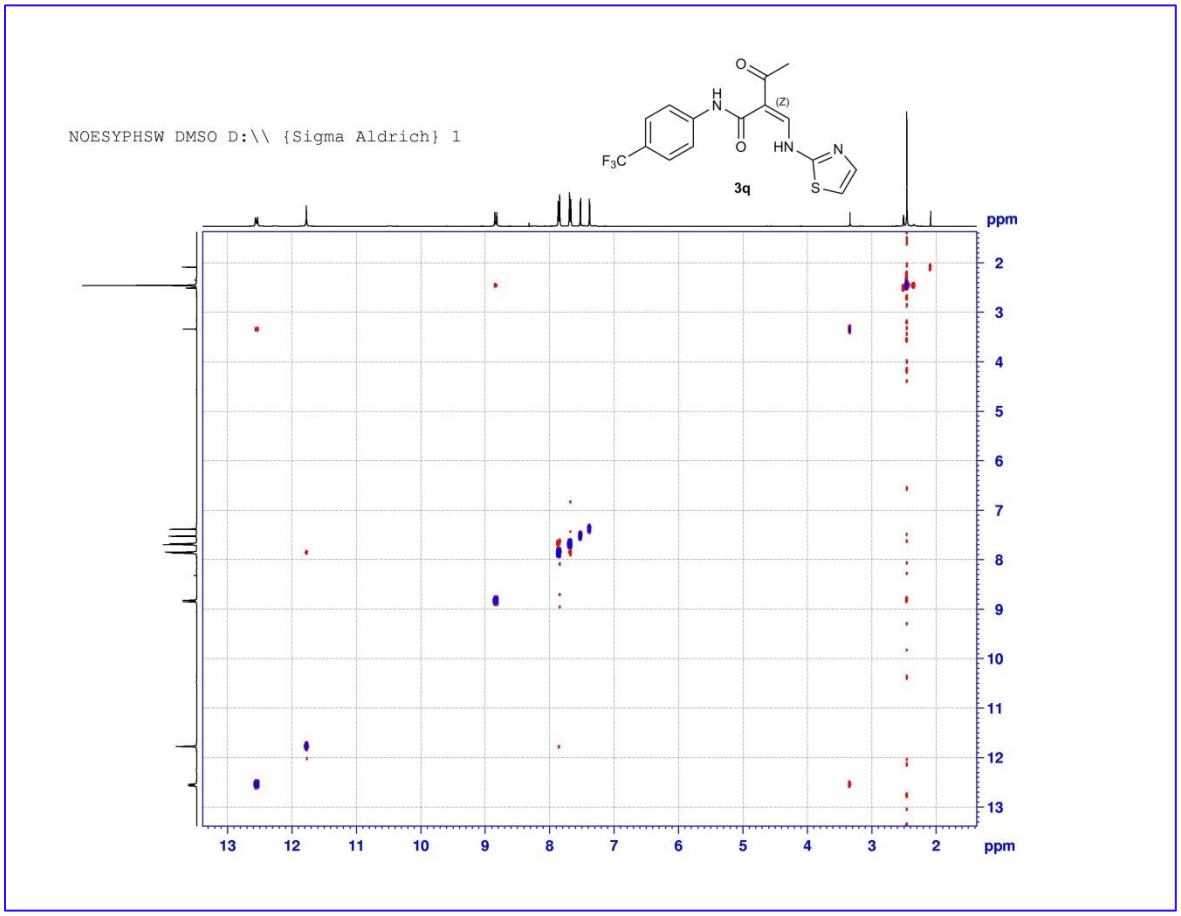
PROTON DMSO D:\\ {Sigma Aldrich} 1



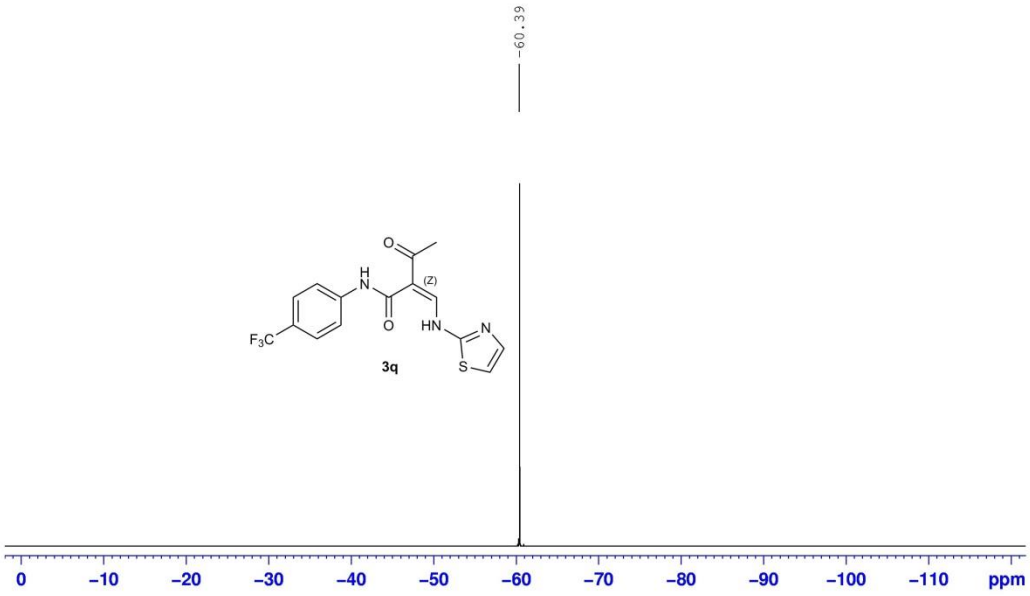
C13CPD DMSO D:\\ {Sigma Aldrich} 1



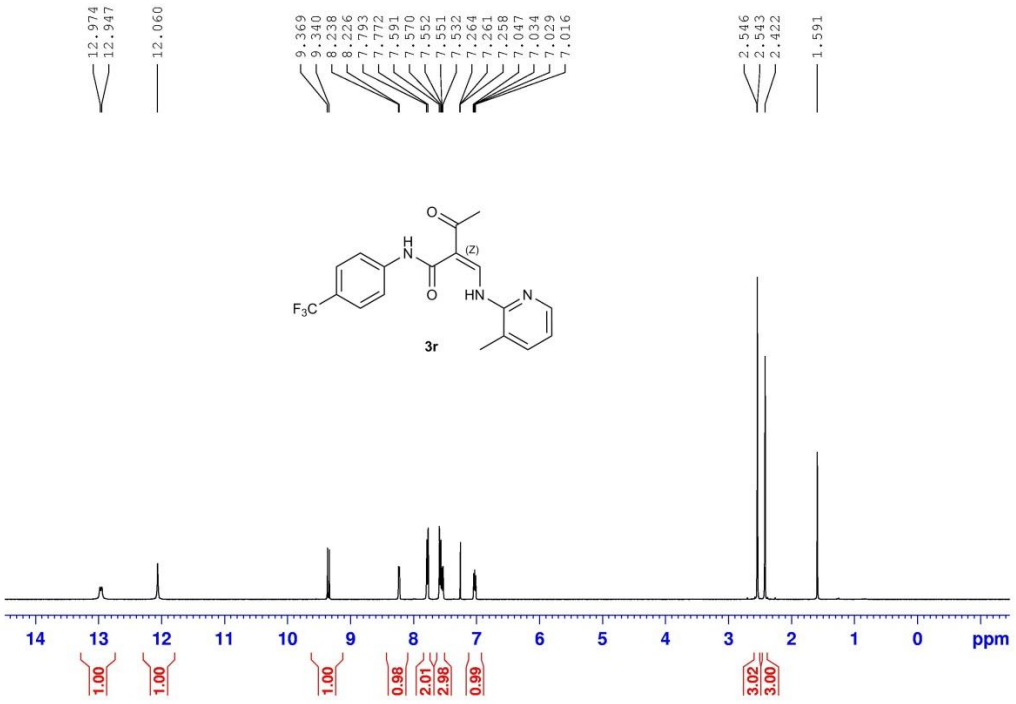

C13APT DMSO D:\\ {Sigma Aldrich} 1
197.69
165.53
160.98
151.61
151.34
141.66
139.25
128.34
126.09
126.06
126.02
125.64
124.04
123.72
123.40
123.09
122.95
120.25
119.80
119.36
115.99
105.65
40.13
39.92
39.72
39.51
39.30
39.09
38.88
26.52
3q
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


NOESYPHSW DMSO D:\\ {Sigma Aldrich} 1
3q
ppm
2
3
4
5
6
7
8
9
10
11
12
13
13 12 11 10 9 8 7 6 5 4 3 2 ppm

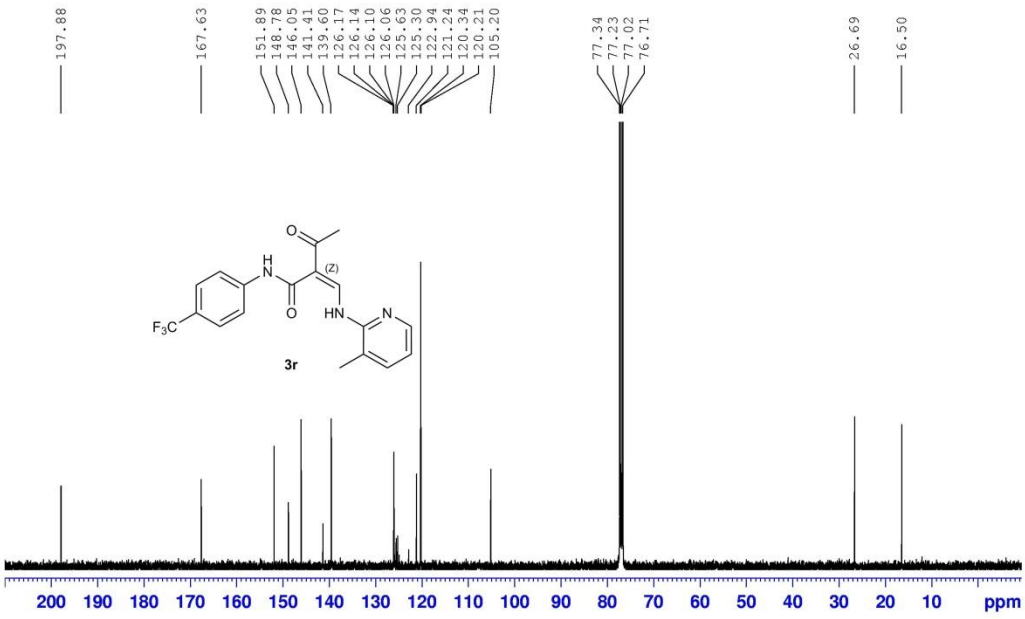
F19 DMSO D:\\ {Sigma Aldrich} 1



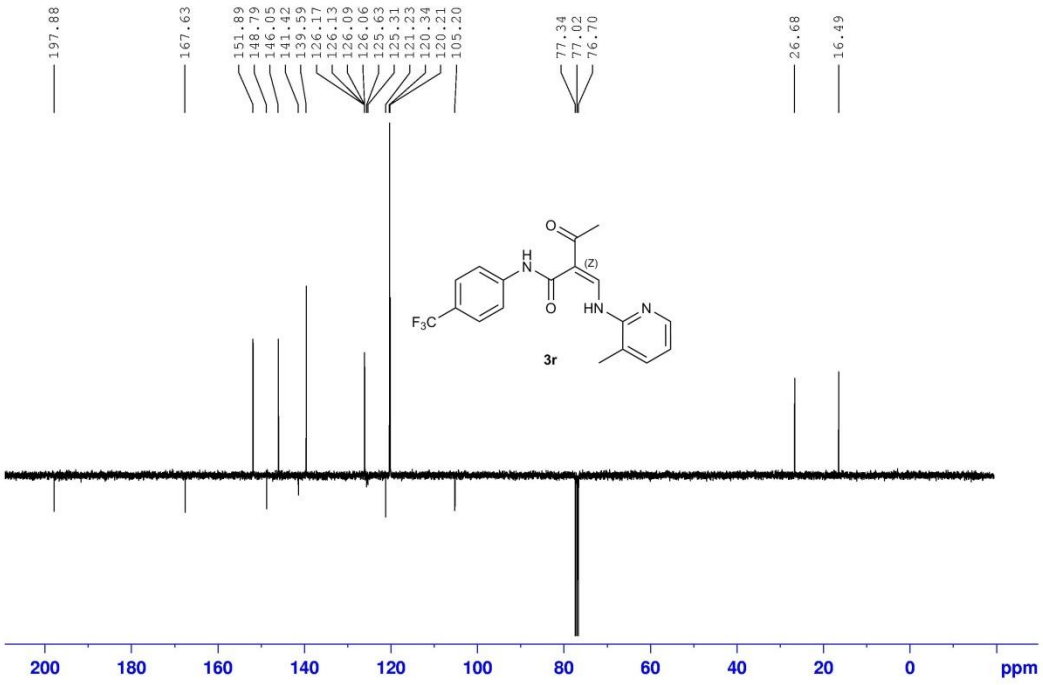
PROTON CDCl3 D:\\ {Sigma Aldrich} 1



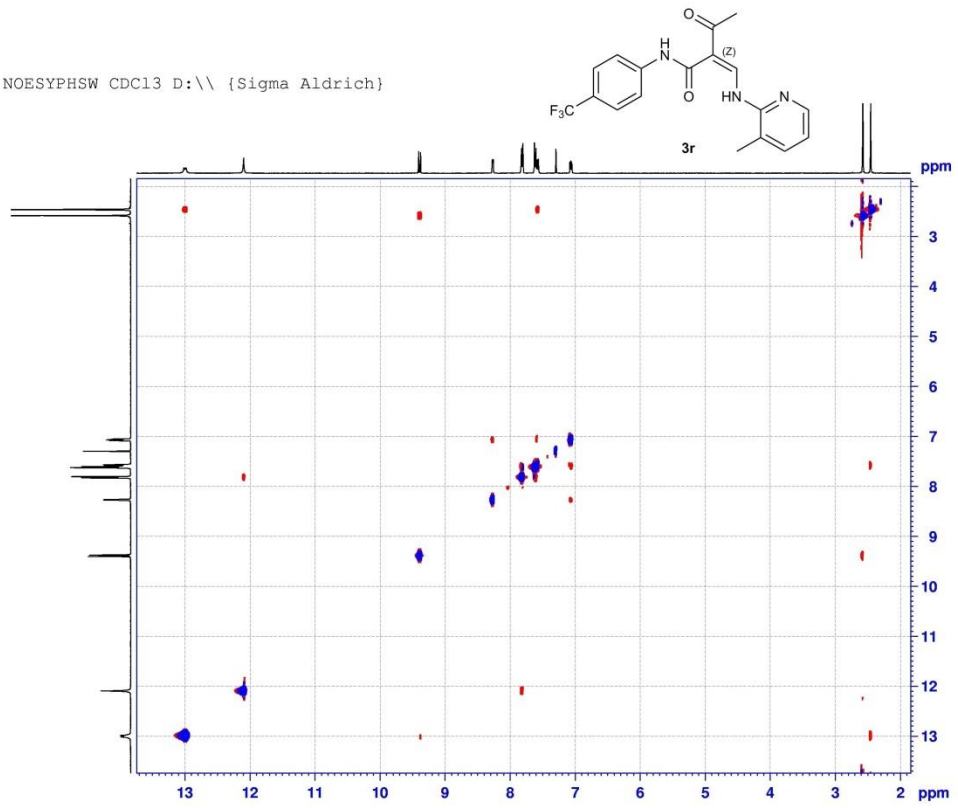
C13CPD CDCl3 D:\\ {Sigma Aldrich} 1



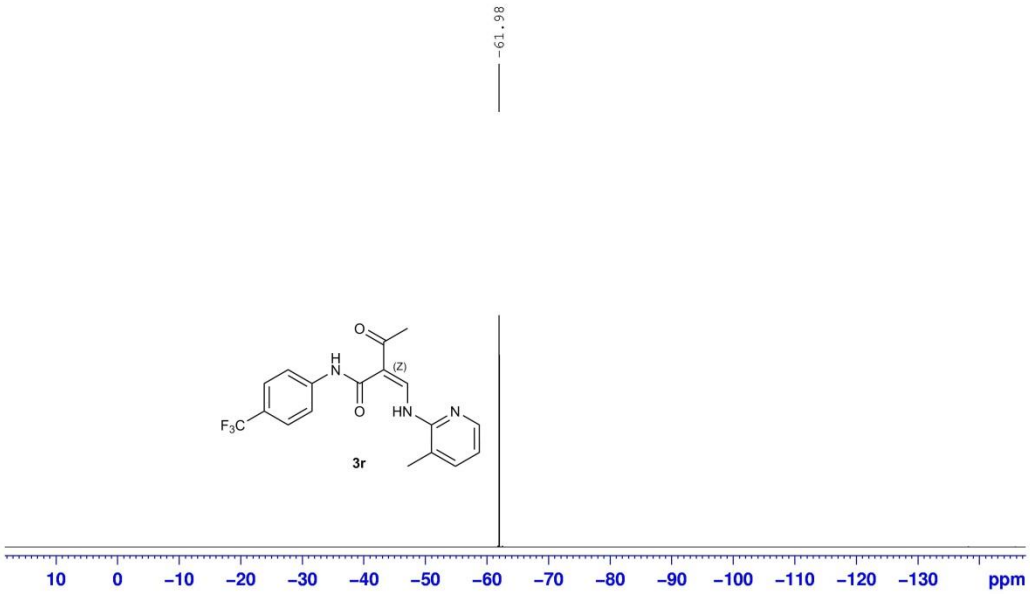
C13APT CDCl3 D:\\ {Sigma Aldrich} 1



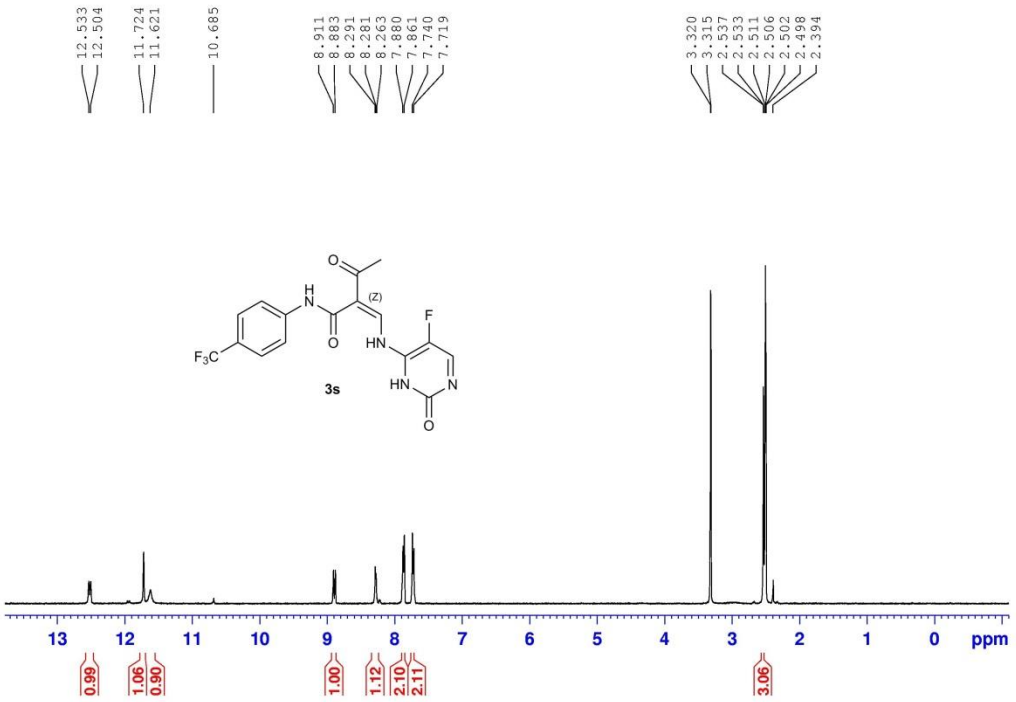
NOESYPHSW CDCl3 D:\\ {Sigma Aldrich}



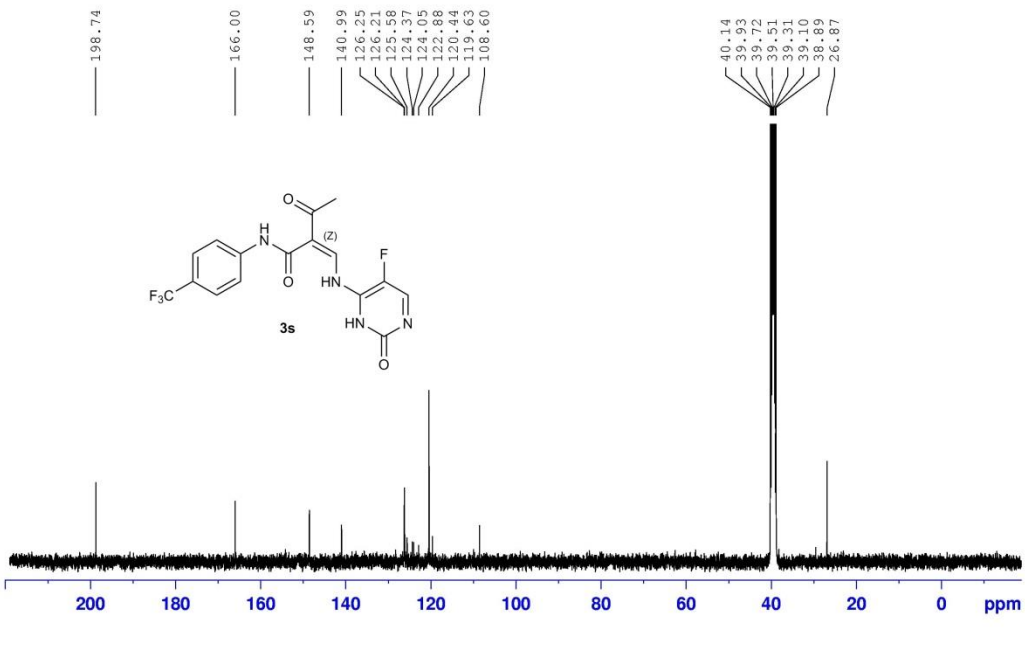
F19 CDCl3 D:\\ {Sigma Aldrich} 1

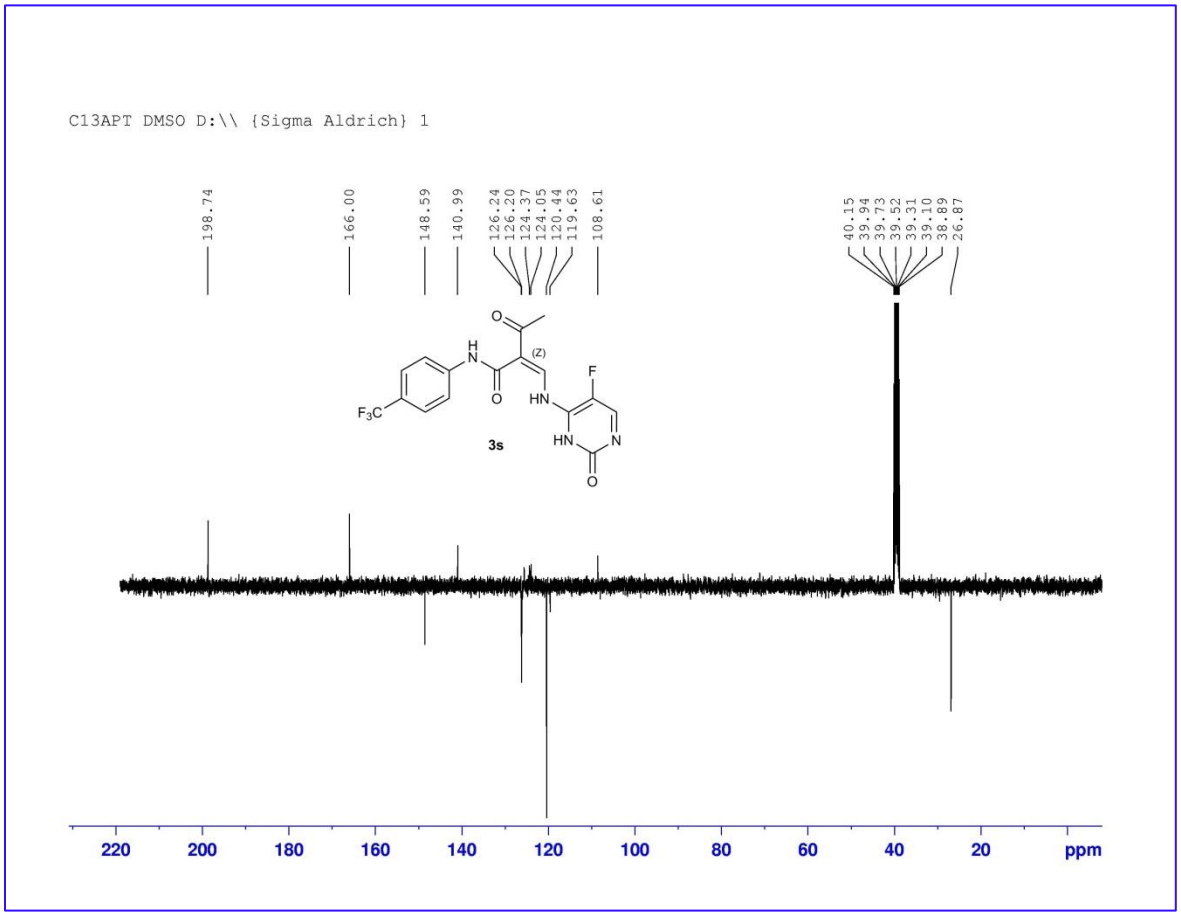


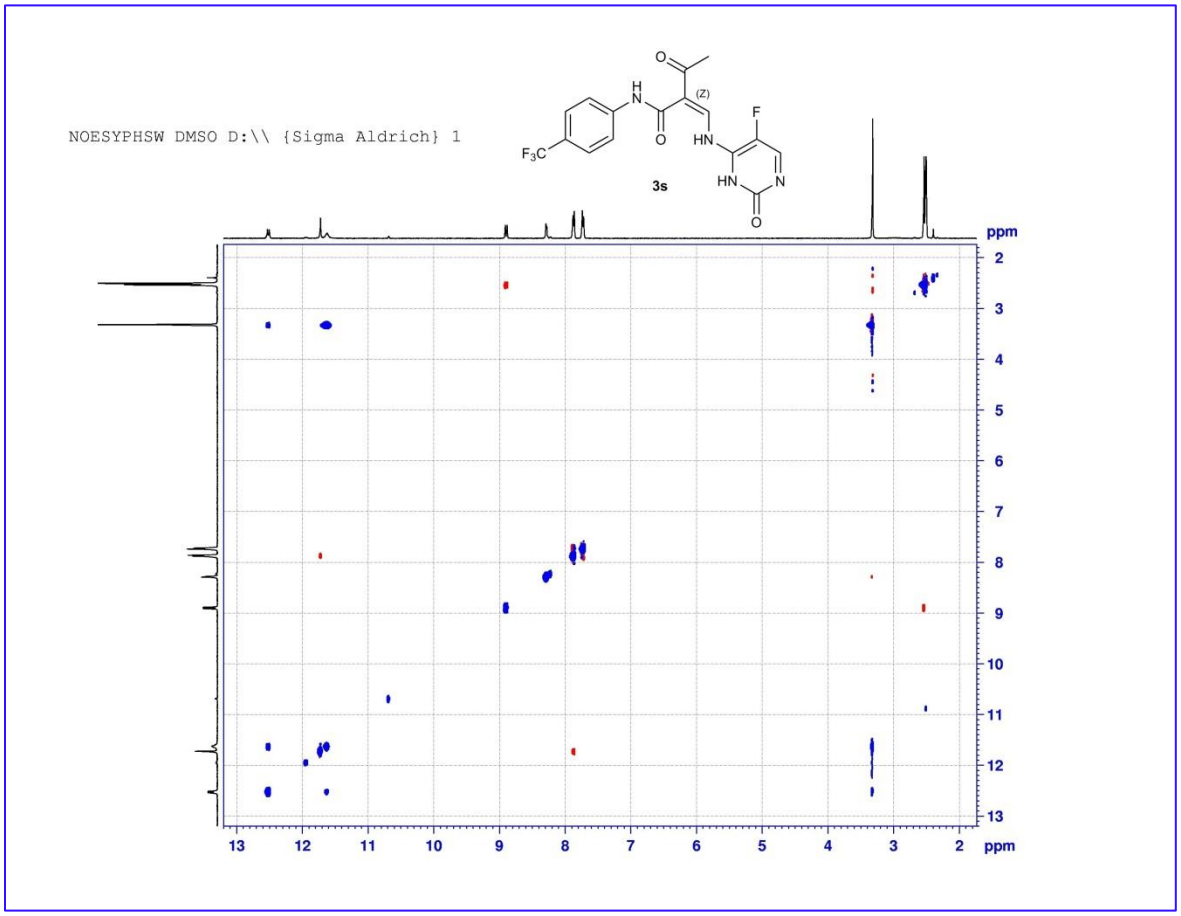
PROTON DMSO D:\\ {Sigma Aldrich} 1



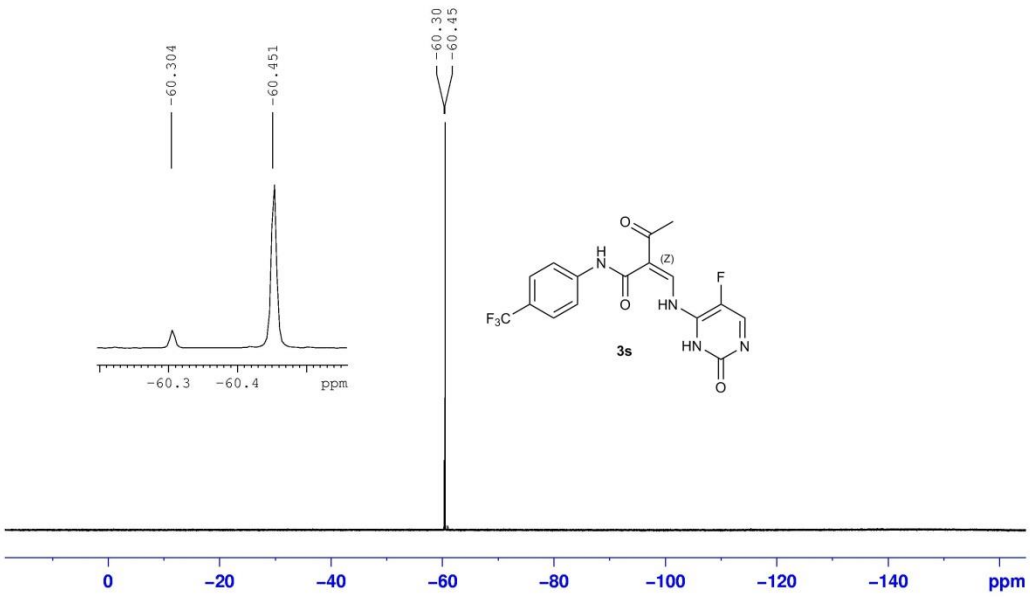
C13CPD DMSO D:\\ {Sigma Aldrich} 1



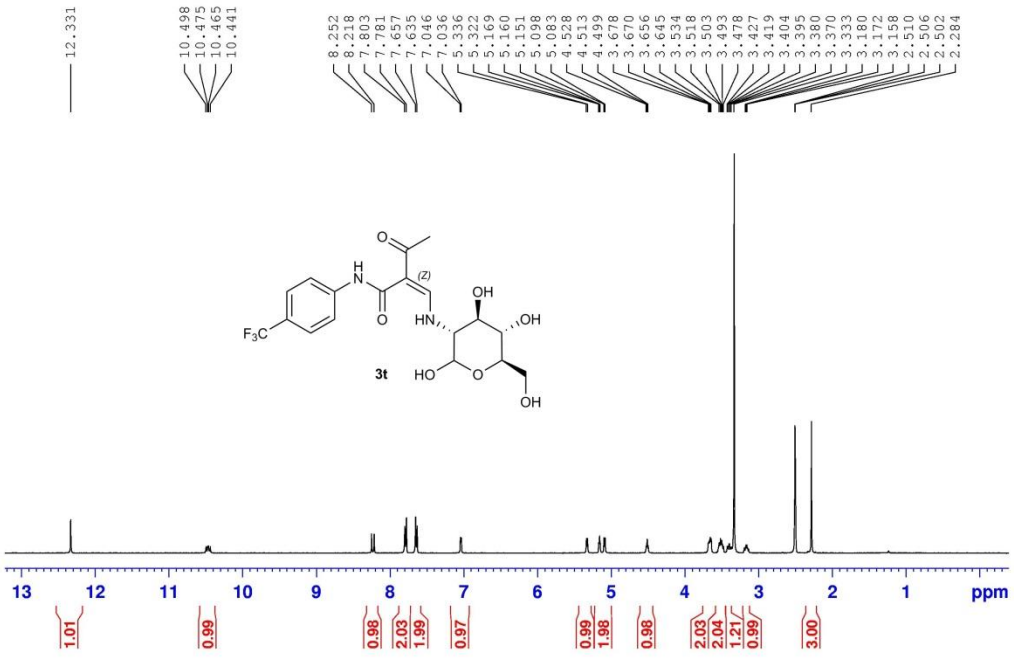

C13APT DMSO D:\\ {Sigma Aldrich} 1
198.74
166.00
148.59
140.99
126.24
126.20
124.37
124.05
120.44
119.63
108.61
40.15
39.94
39.73
39.52
39.31
39.10
38.89
26.87
3s
220
200
180
160
140
120
100
80
60
40
20
ppm


NOESYPHSW DMSO D:\\ {Sigma Aldrich} 1
3s
ppm
2
3
4
5
6
7
8
9
10
11
12
13
ppm

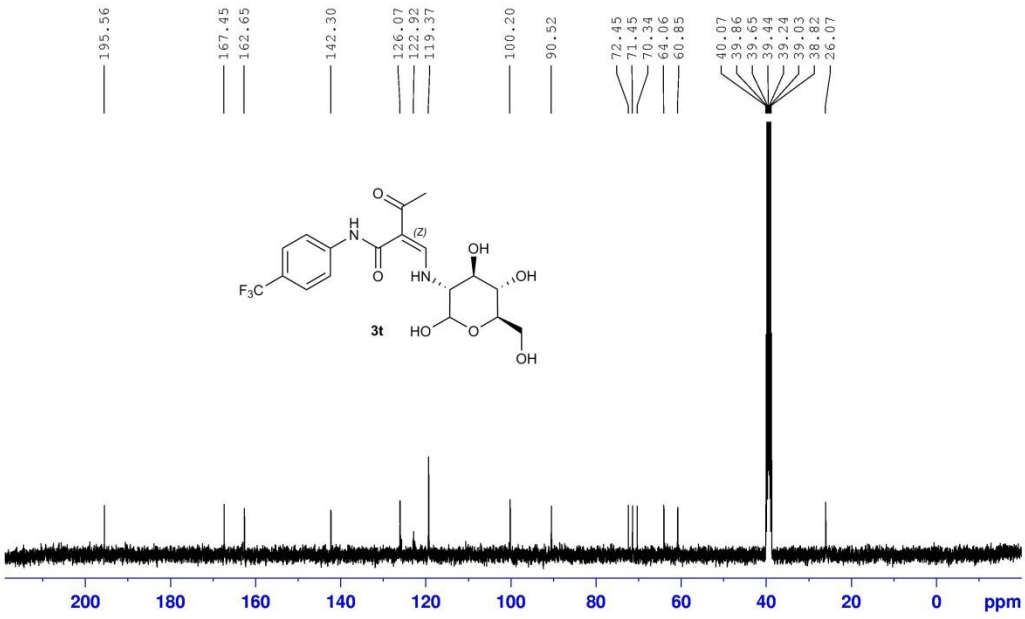
F19 DMSO D:\\ {Sigma Aldrich} 1



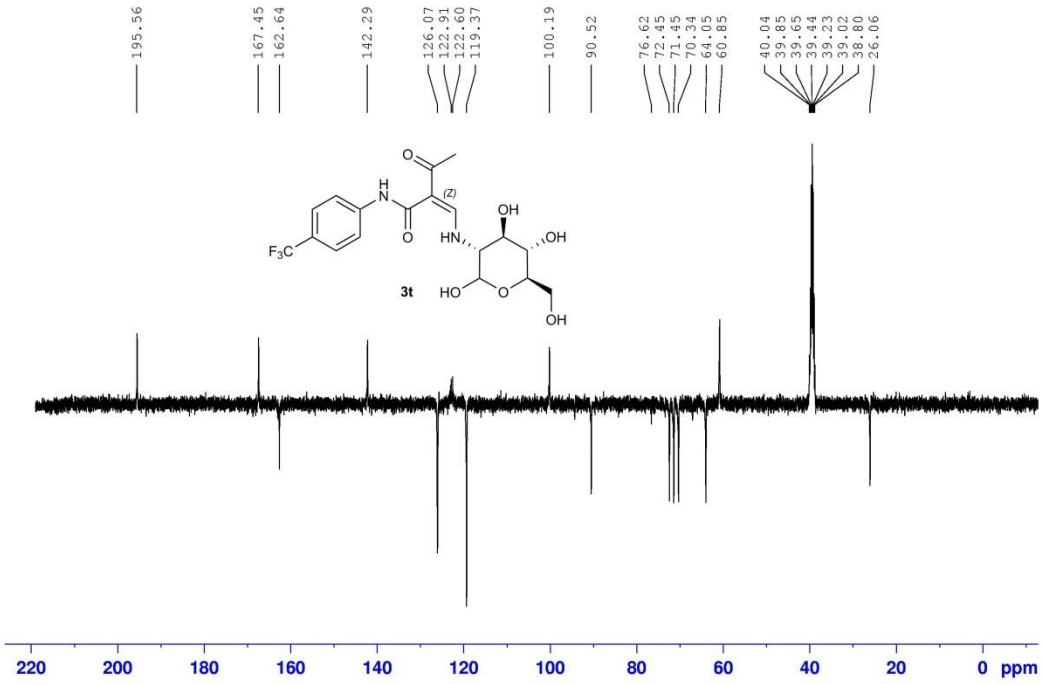
PROTON DMSO D:\\ {Sigma Aldrich} 1



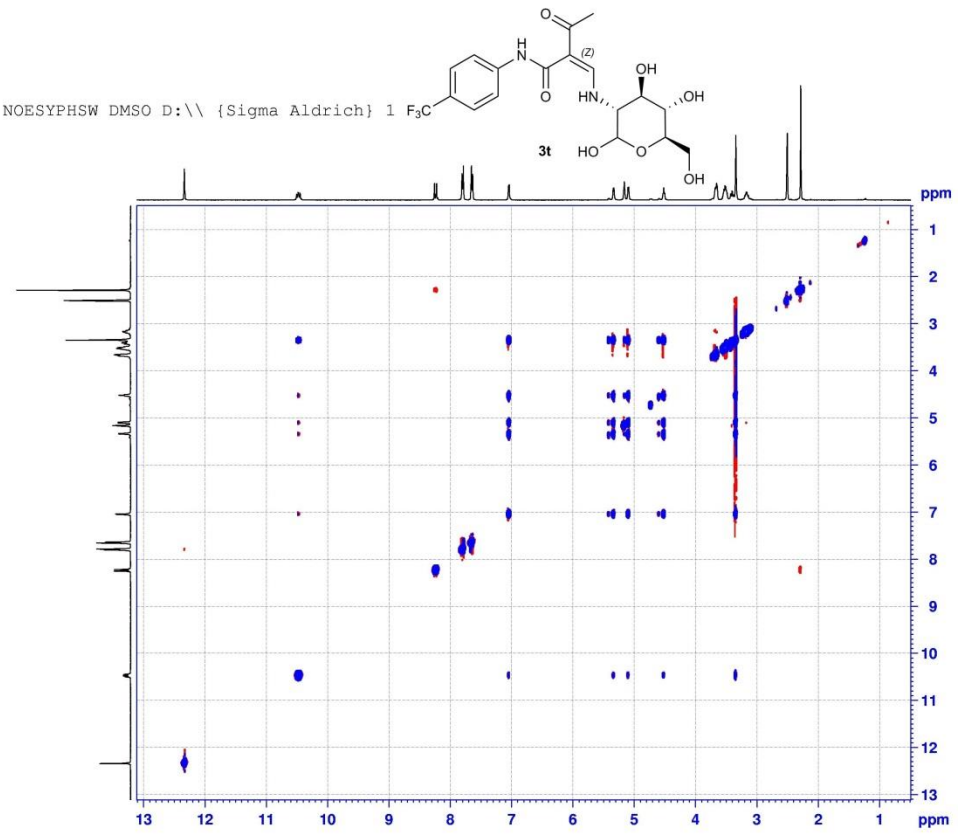
C13CPD DMSO D:\\ {Sigma Aldrich} 1



C13APT DMSO D:\\ {Sigma Aldrich} 1

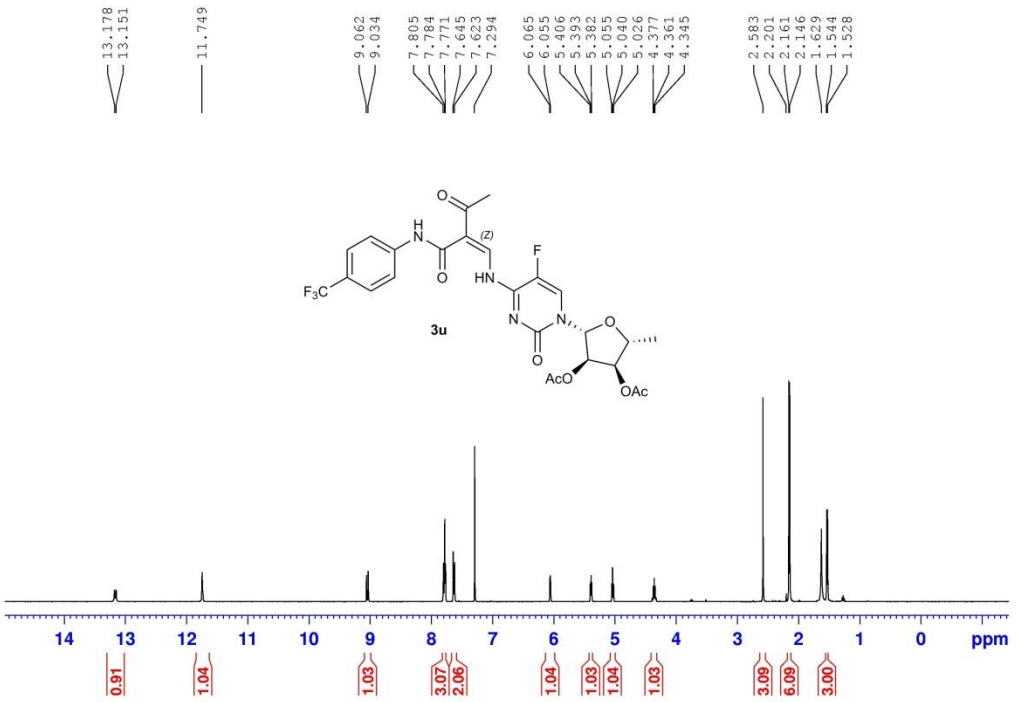


NOESYPHSW DMSO D:\\ {Sigma Aldrich} 1

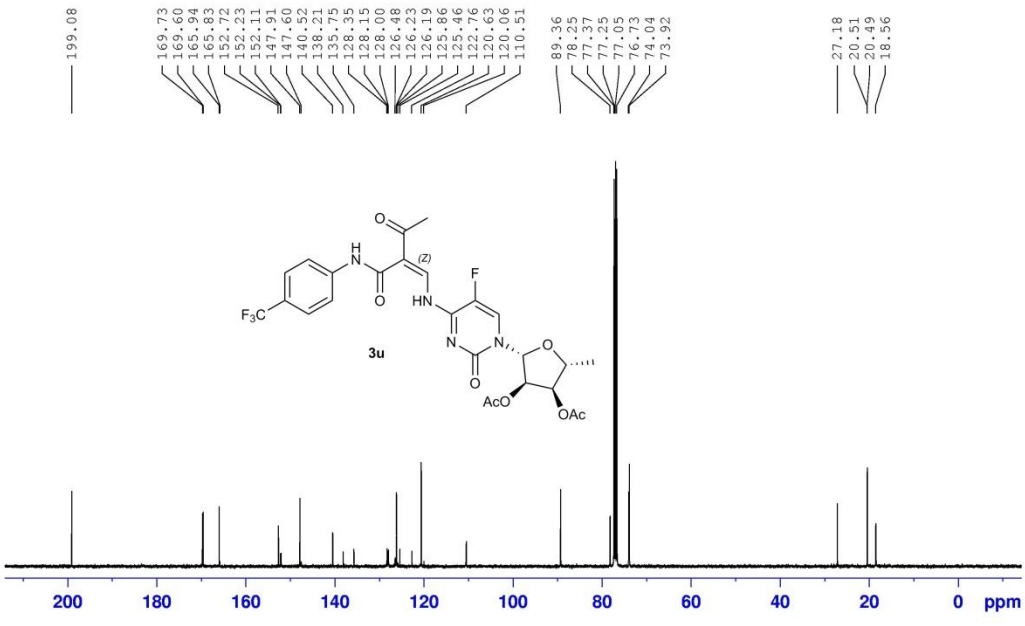


F19 DMSO D:\\ {Sigma Aldrich} 1

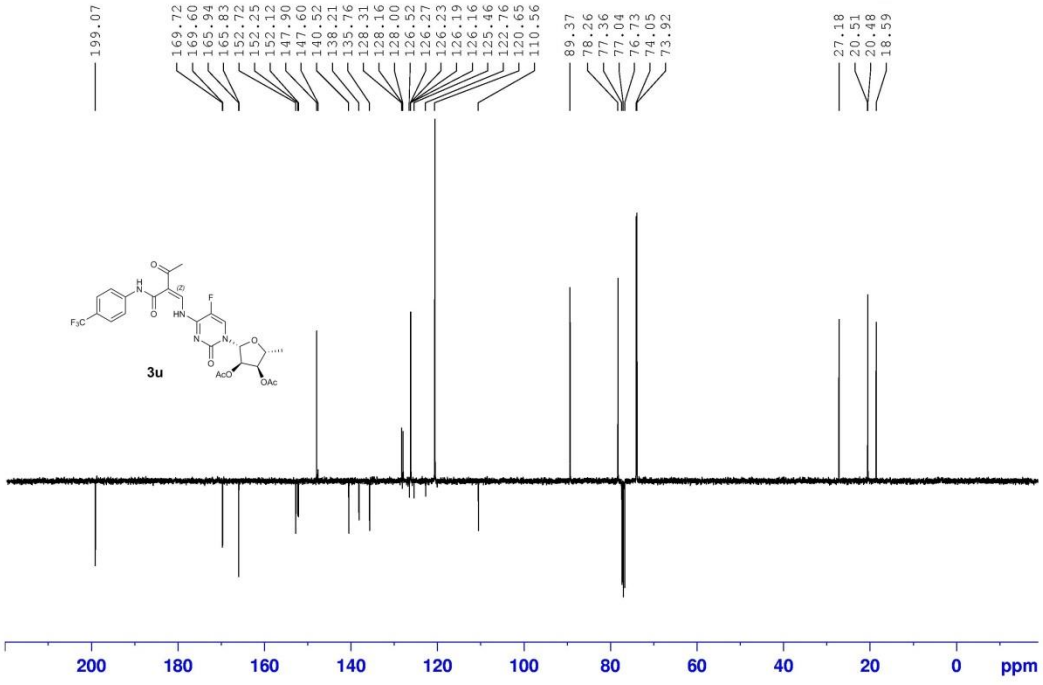
PROTON CDCl3 D:\\ {Sigma Aldrich} 1



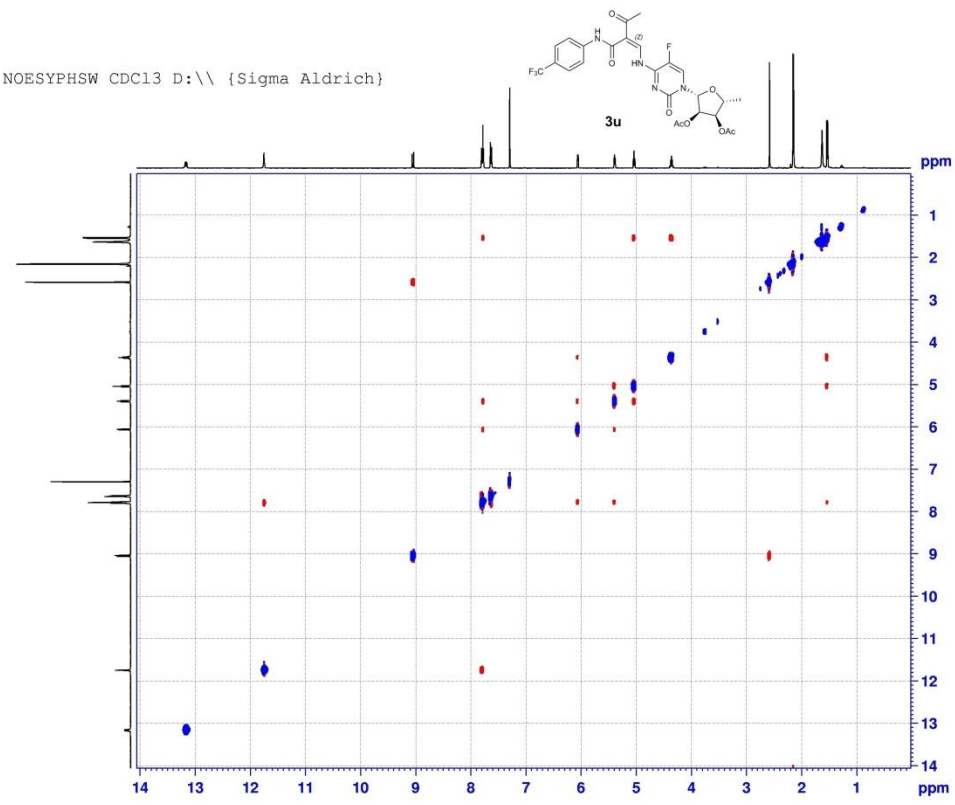
C13CPD CDCl3 D:\\ {Sigma Aldrich} 1



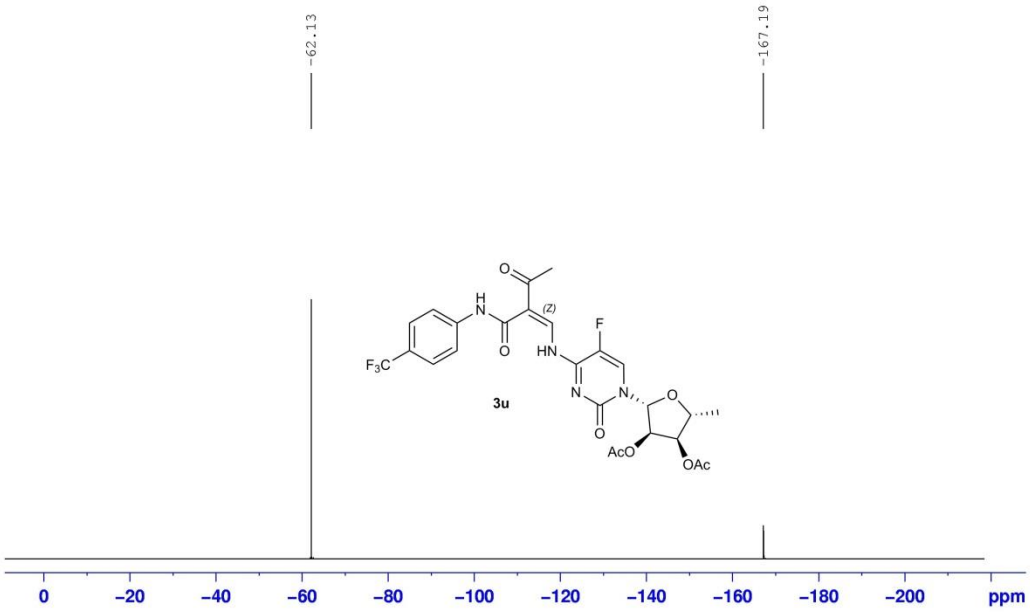
C13APT CDCl3 D:\\ {Sigma Aldrich} 1



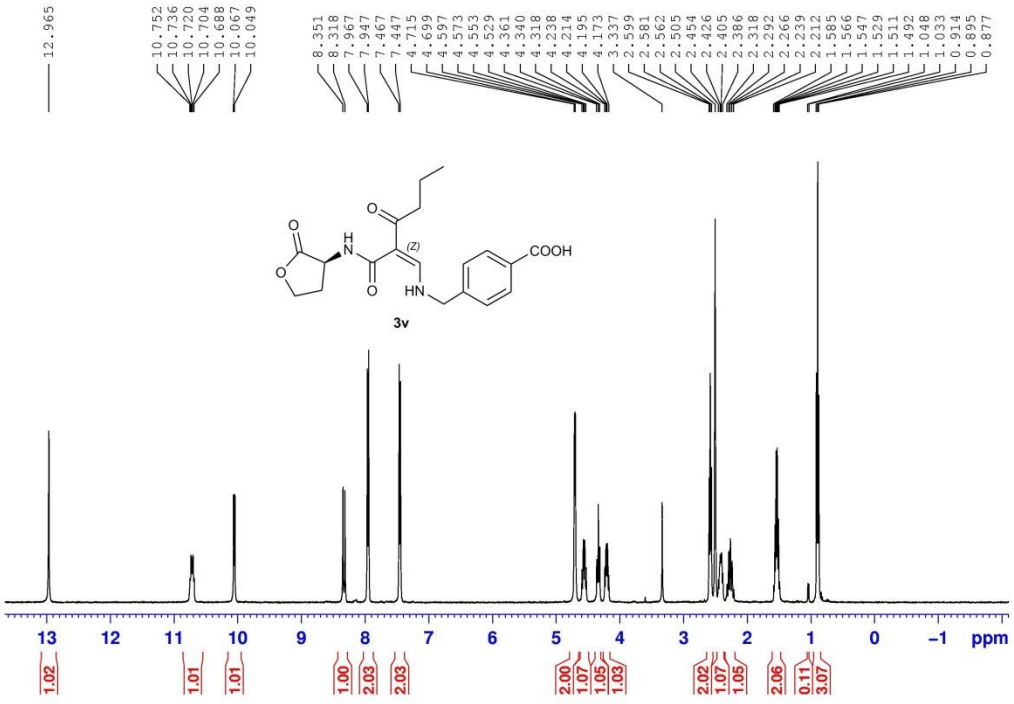
NOESYPHSW CDCl3 D:\\ {Sigma Aldrich}



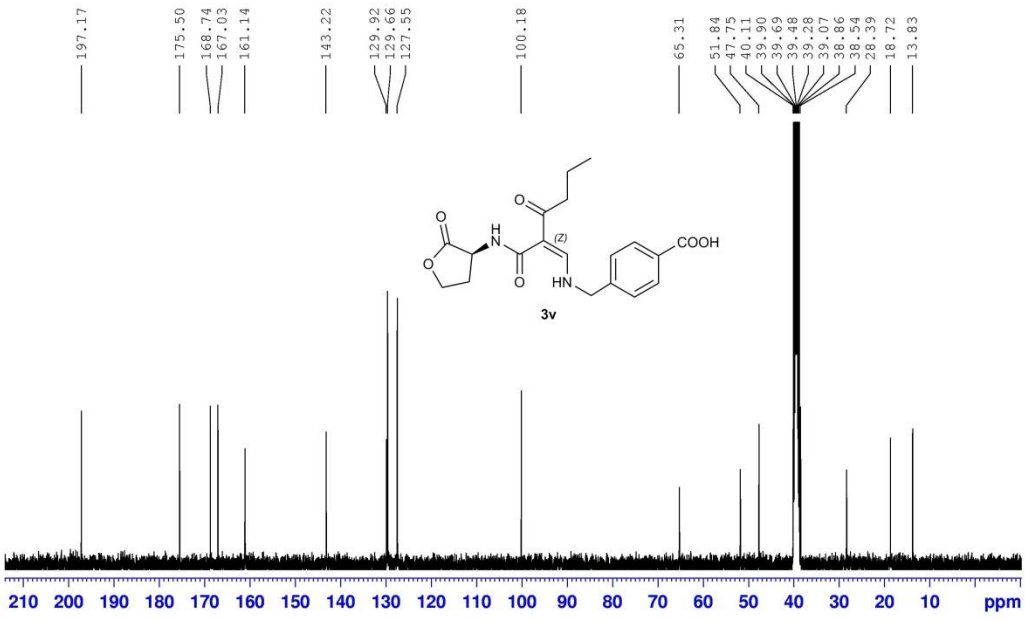
F19 CDCl3 D:\\ {Sigma Aldrich} 1



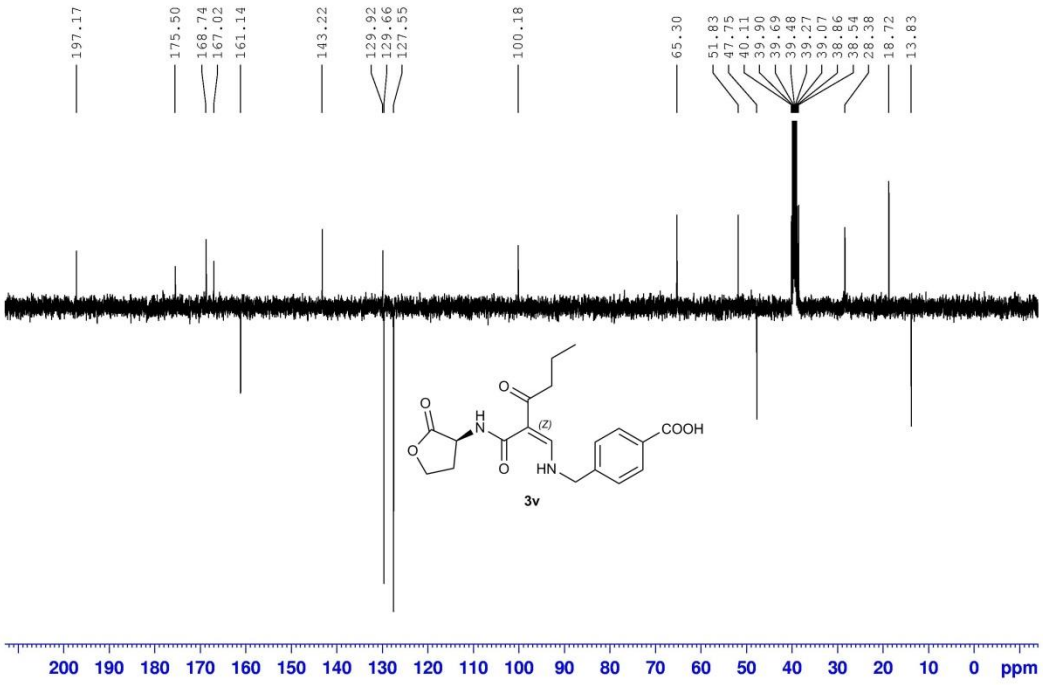
PROTON DMSO D:\\ {Sigma Aldrich} 1

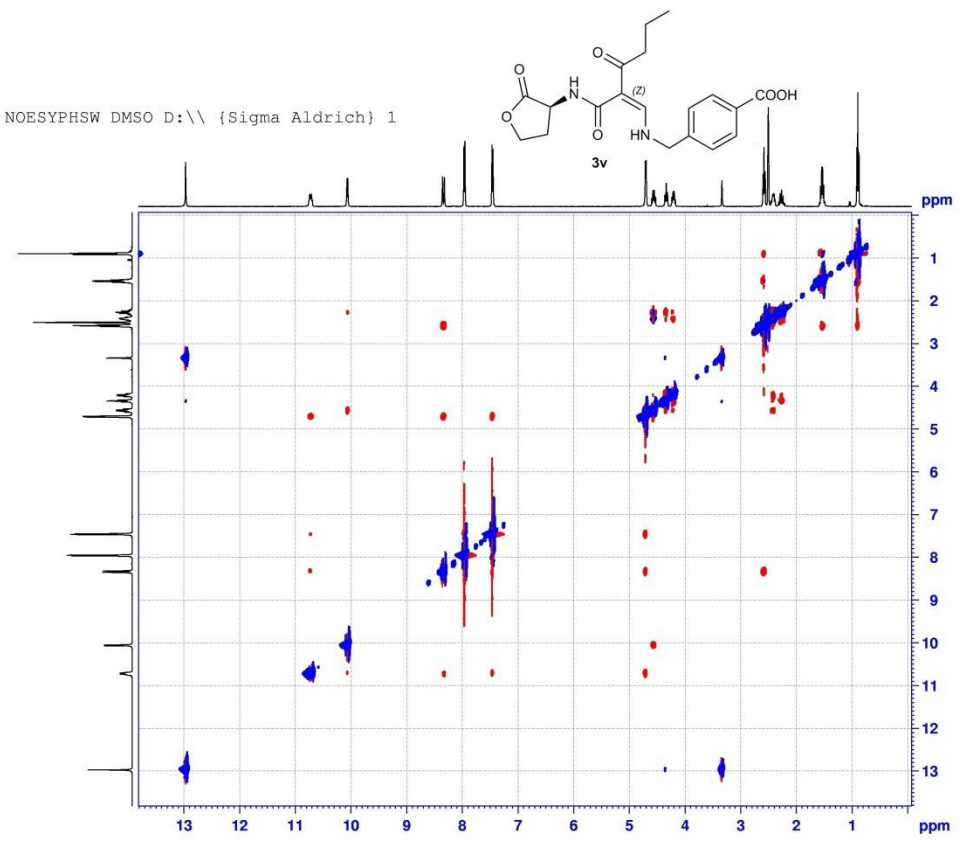


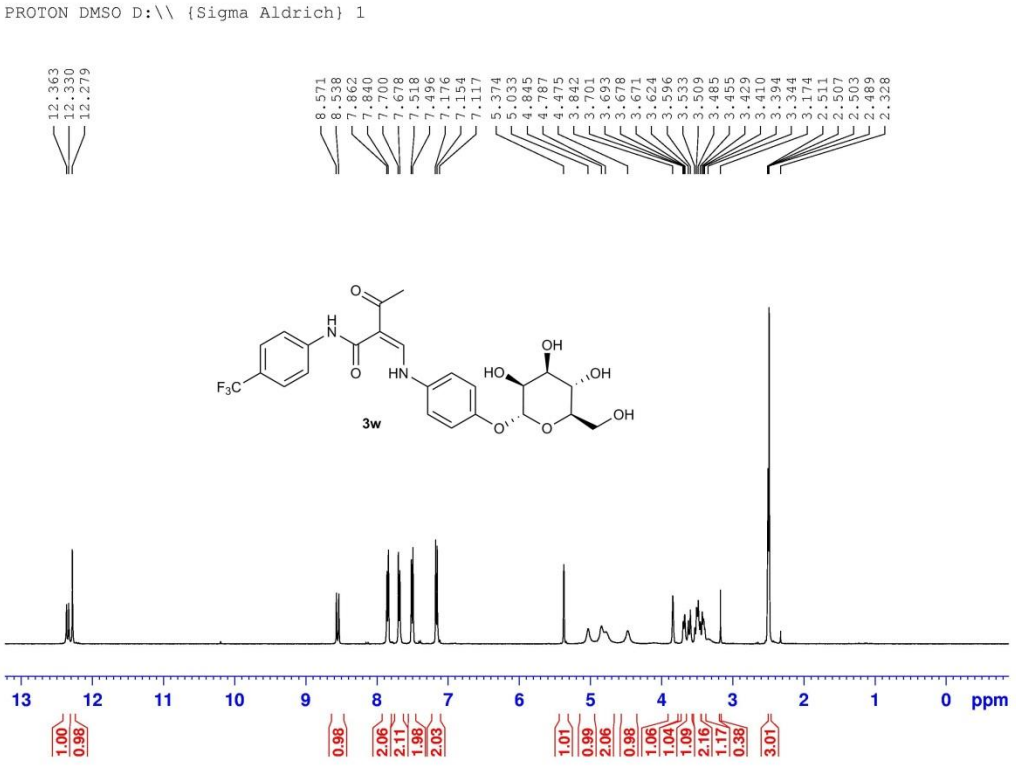
C13CPD DMSO D:\\ {Sigma Aldrich} 1



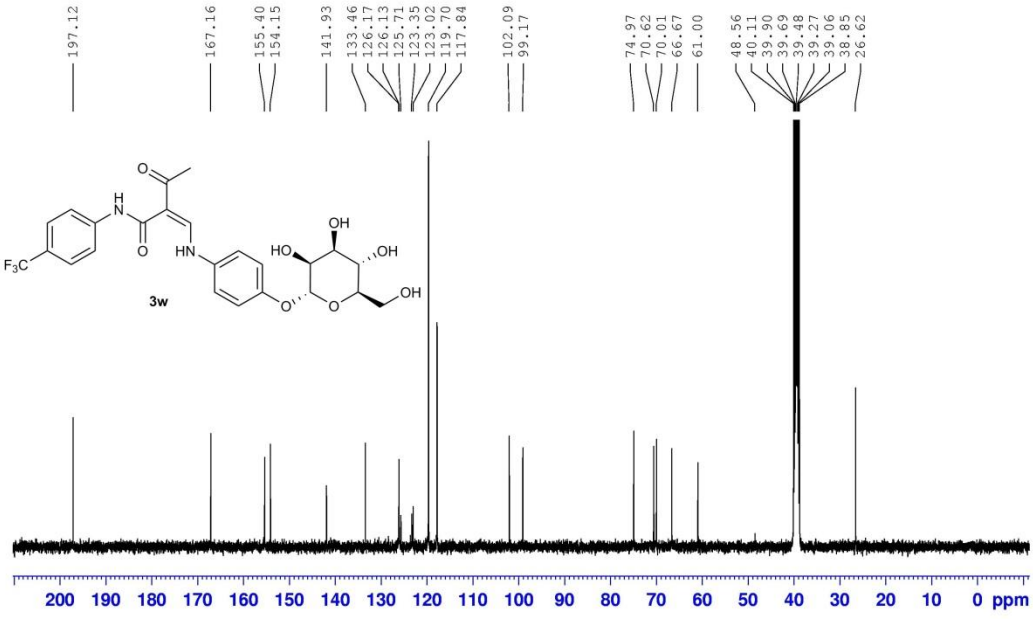
C13APT DMSO D:\\ {Sigma Aldrich} 1



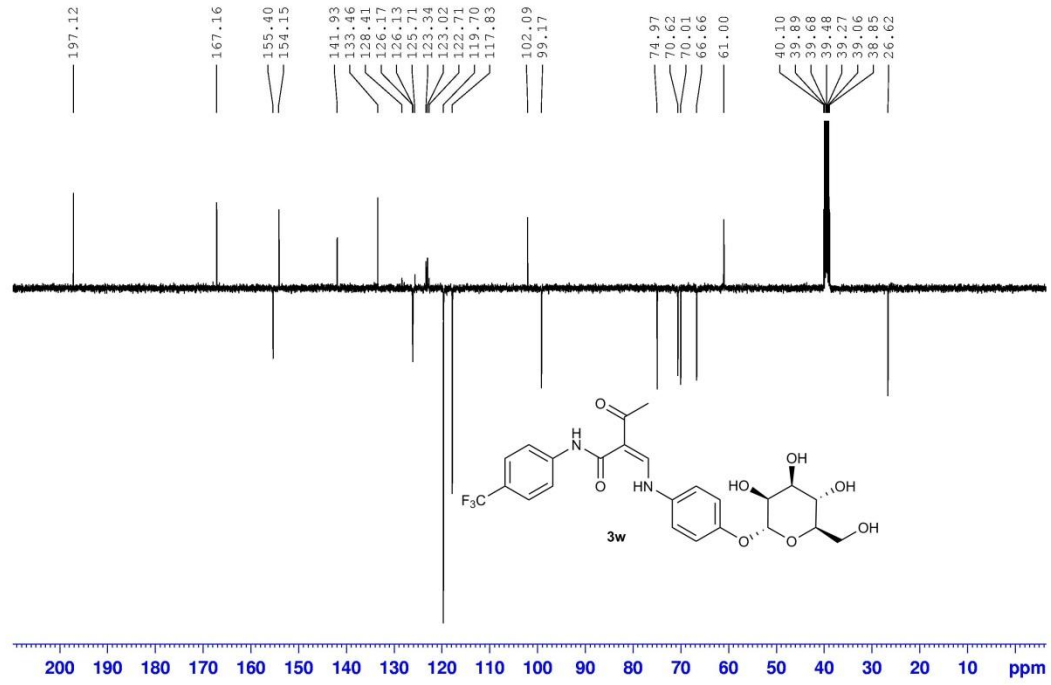

NOESYPHSW DMSO D:\\ {Sigma Aldrich} 1
3v
COOH
HN
ppm
13 12 11 10 9 8 7 6 5 4 3 2 1 ppm

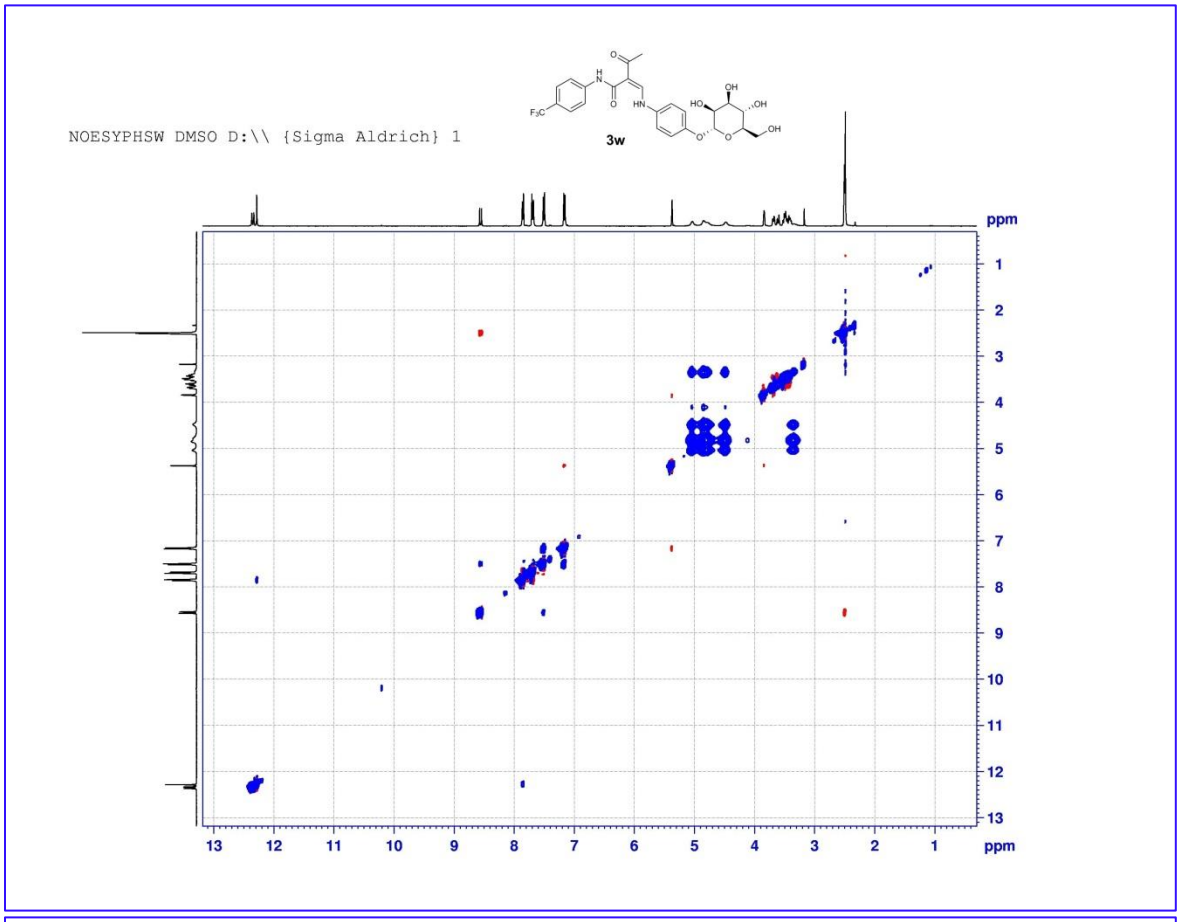

PROTON DMSO D:\\ {Sigma Aldrich} 1
12.363
12.330
12.279
8.571
8.538
7.862
7.840
7.700
7.678
7.518
7.496
7.176
7.154
7.117
5.374
5.033
4.845
4.787
4.475
3.842
3.701
3.693
3.678
3.671
3.624
3.596
3.533
3.509
3.485
3.455
3.429
3.410
3.394
3.344
3.174
2.511
2.507
2.503
2.489
2.328
3w
F3C
HN
OH
HO
OH
OH
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.00
0.98
0.98
2.06
2.11
1.98
2.03
1.01
0.99
2.06
0.98
1.06
1.04
1.09
2.16
1.17
0.38
3.01

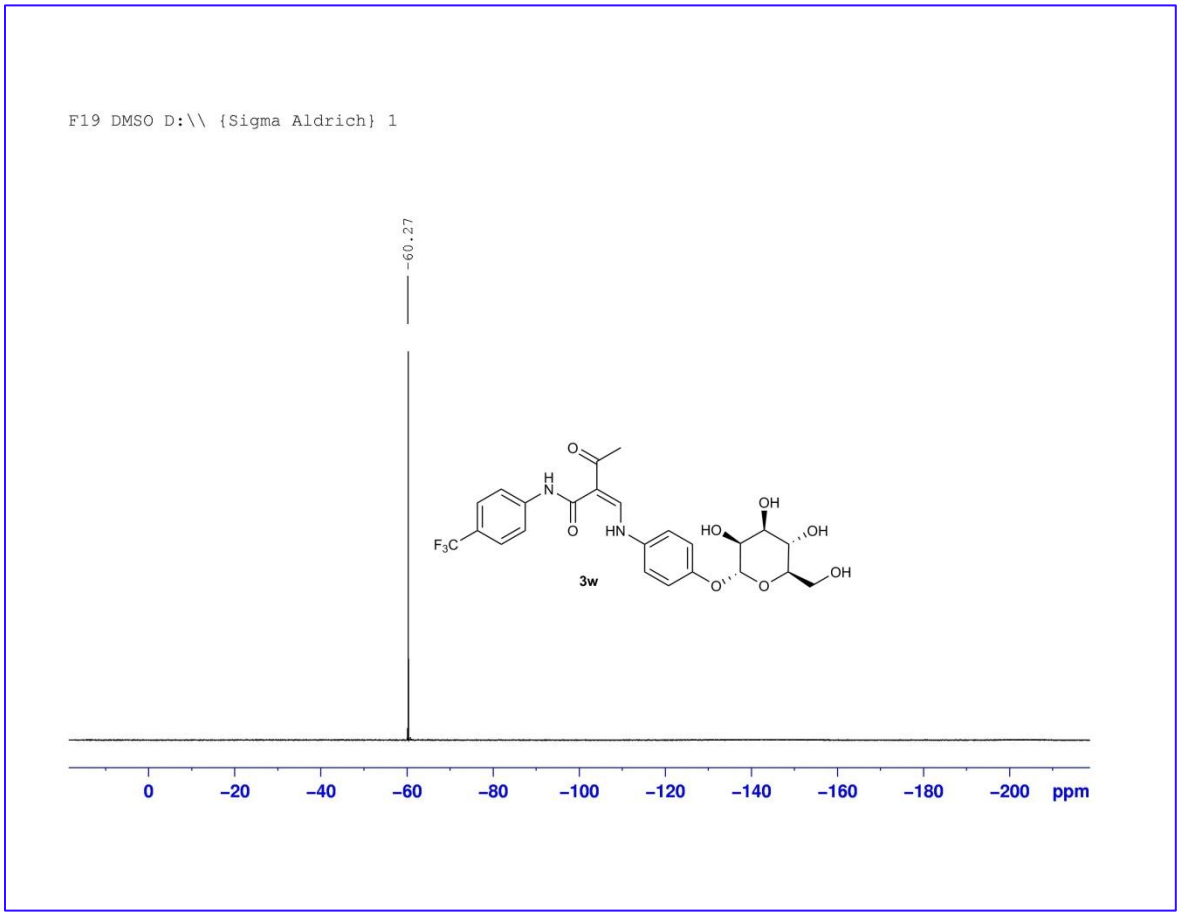
C13CPD DMSO D:\\ {Sigma Aldrich} 1



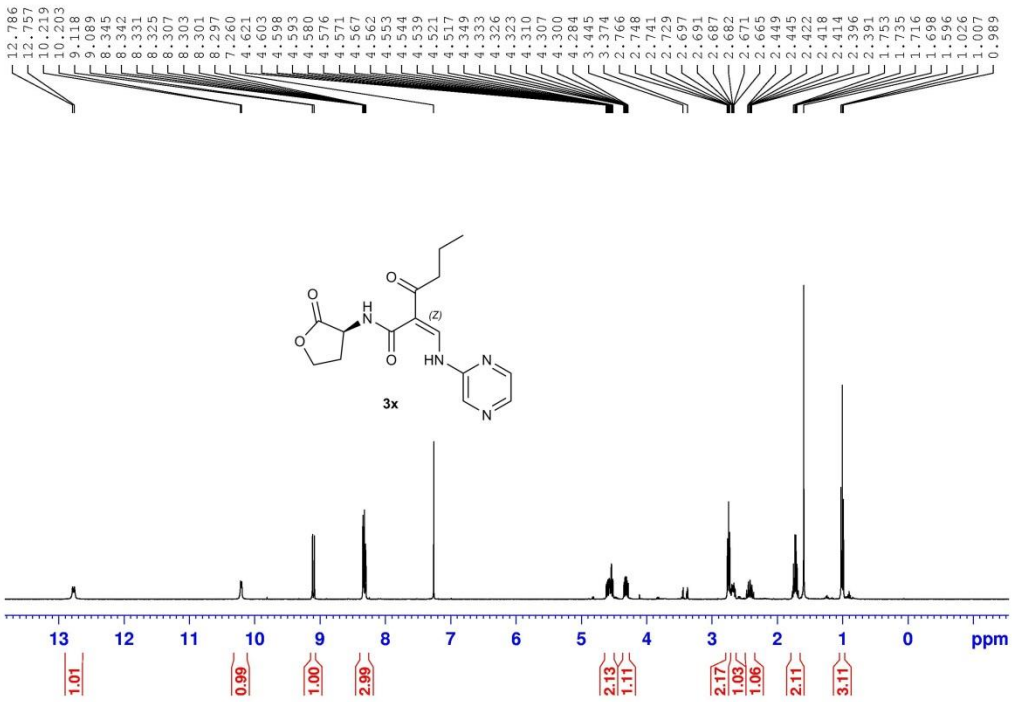
C13APT DMSO D:\\ {Sigma Aldrich} 1



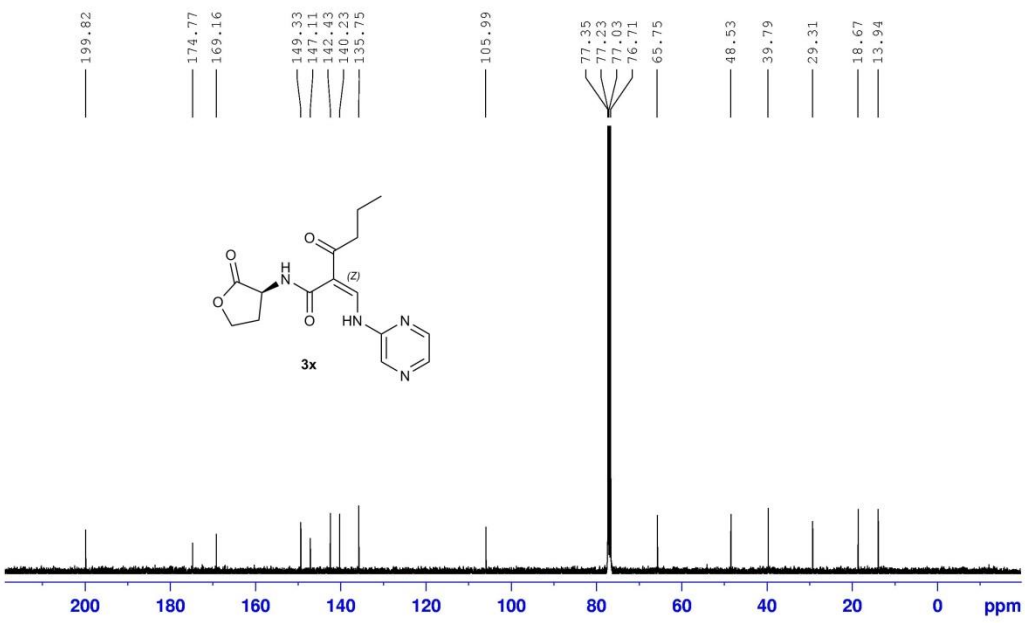

NOESYPHSW DMSO D:\\ {Sigma Aldrich} 1
3w
ppm
13 12 11 10 9 8 7 6 5 4 3 2 1 ppm

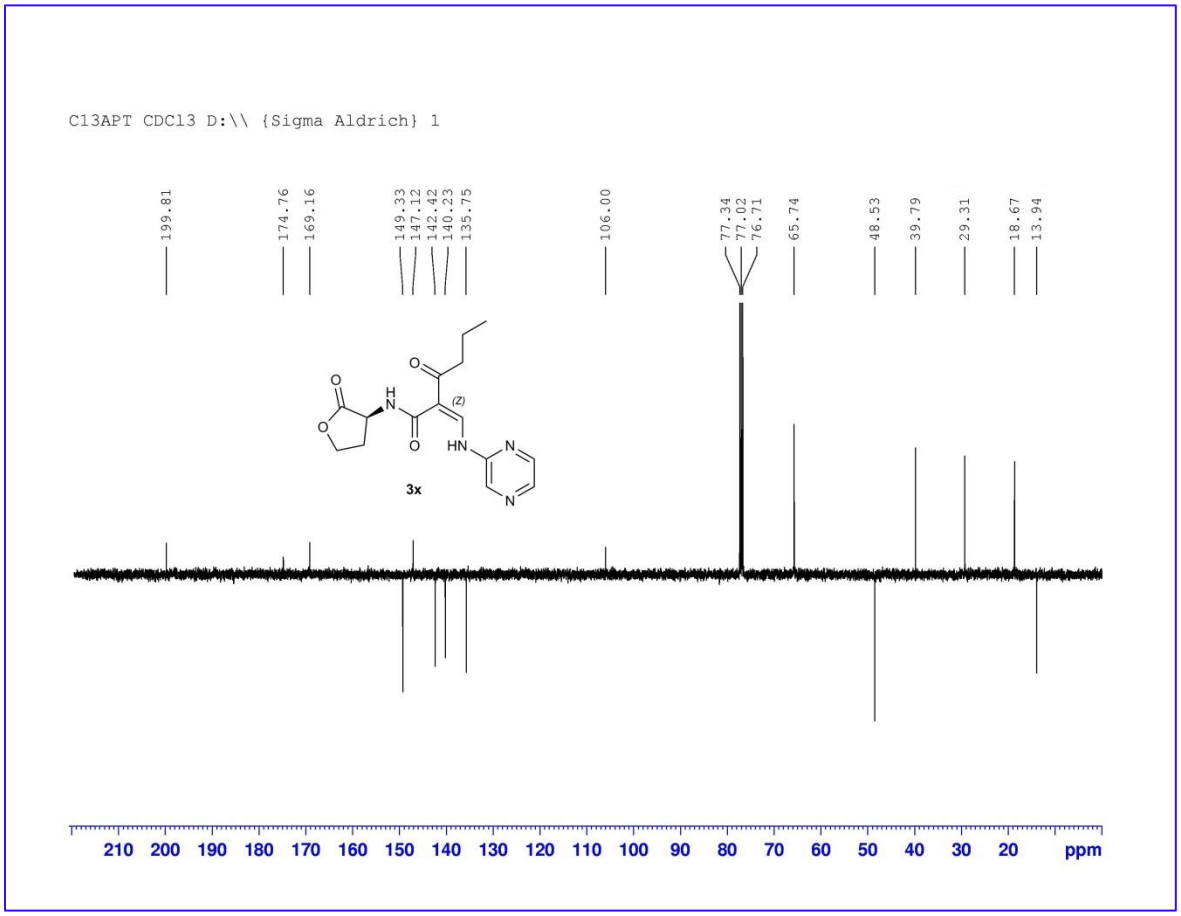

F19 DMSO D:\\ {Sigma Aldrich} 1
-60.27
3w
0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 ppm

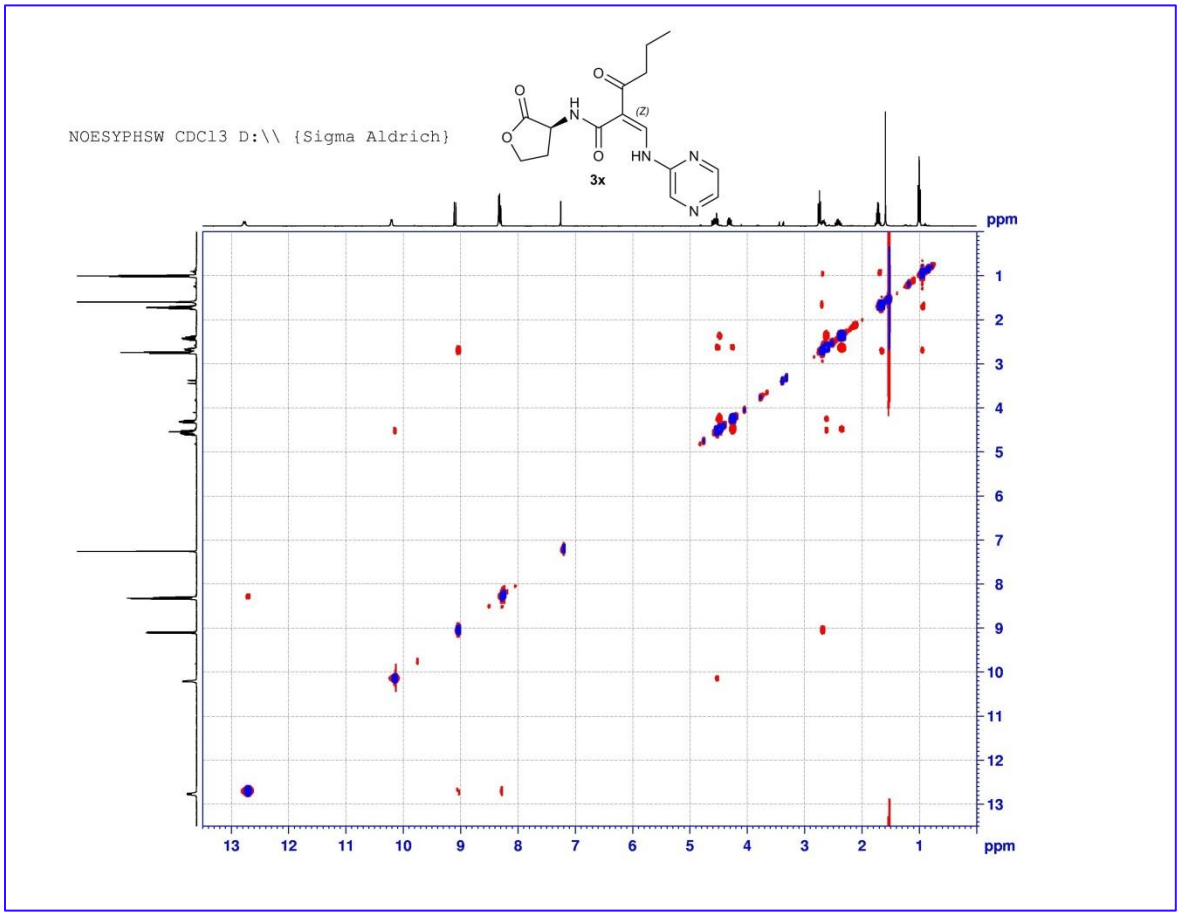
PROTON CDCl3 D:\\ {Sigma Aldrich} 1



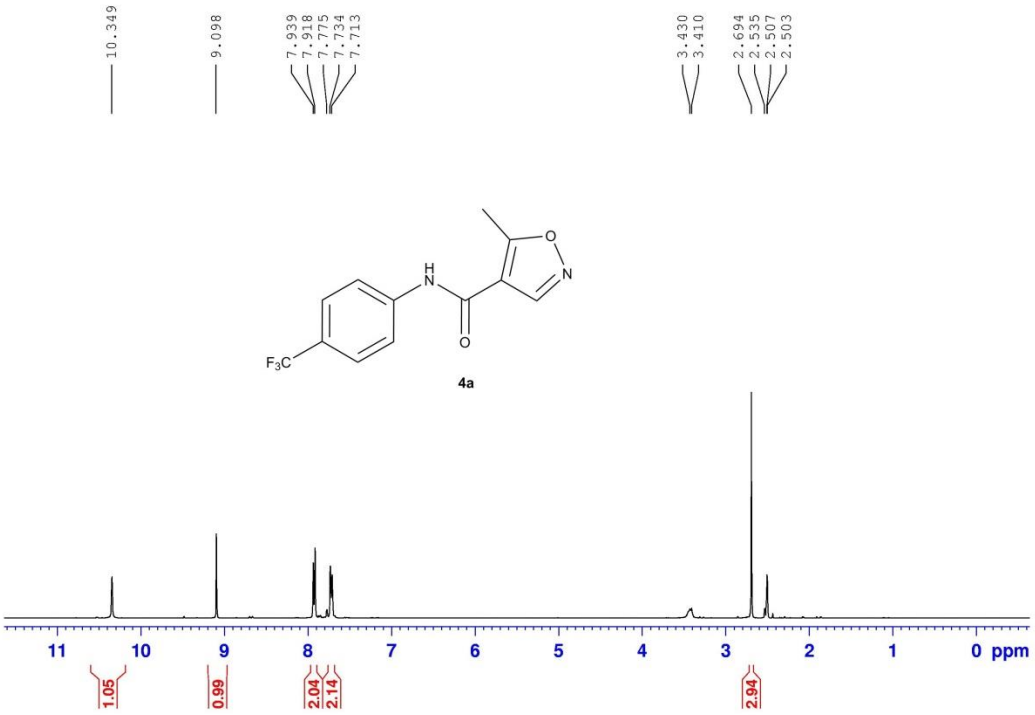
C13CPD CDCl3 D:\\ {Sigma Aldrich} 1



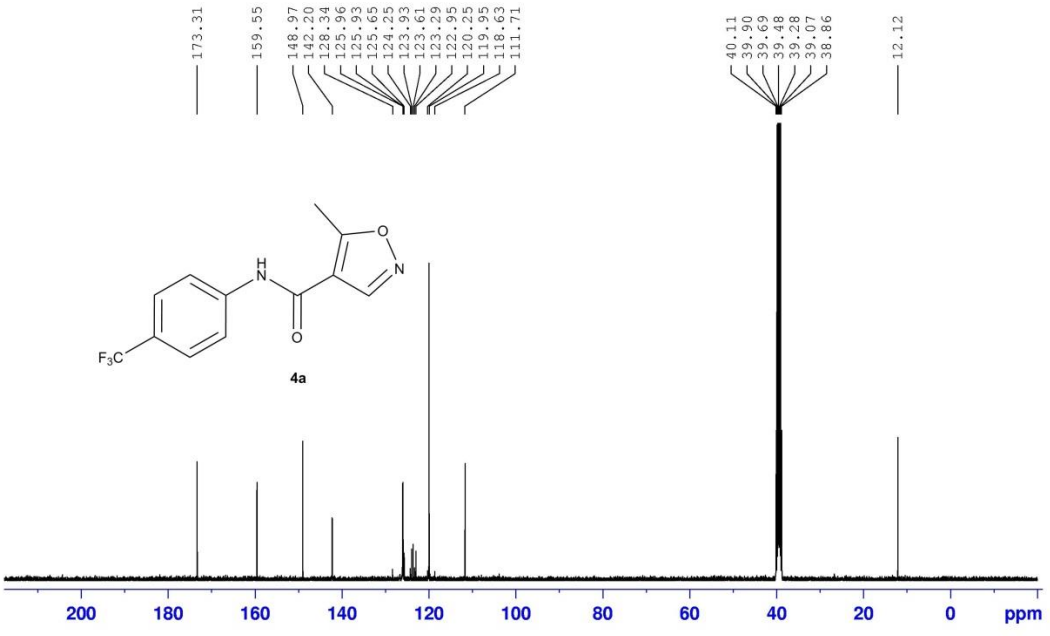

C13APT CDCl3 D:\\ {Sigma Aldrich} 1
199.81
174.76
169.16
149.33
147.12
142.42
140.23
135.75
106.00
77.34
77.02
76.71
65.74
48.53
39.79
29.31
18.67
13.94
3x
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


NOESYPHSW CDCl3 D:\\ {Sigma Aldrich}
3x
ppm
1 2 3 4 5 6 7 8 9 10 11 12 13
13 12 11 10 9 8 7 6 5 4 3 2 1 ppm

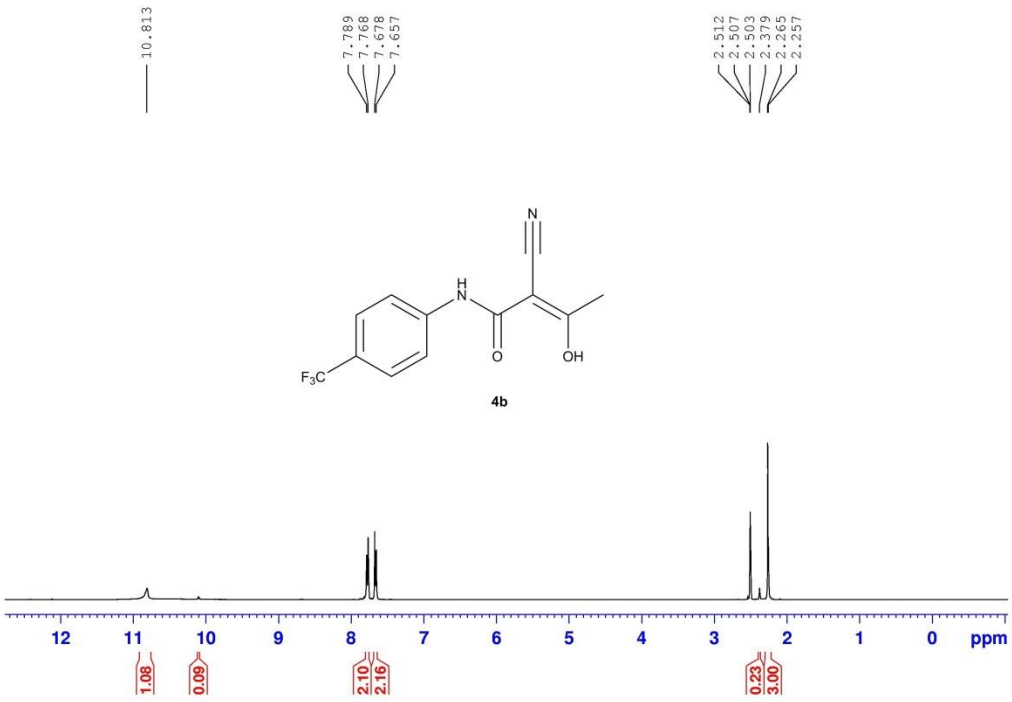
PROTON DMSO D:\\ {Sigma Aldrich} 1



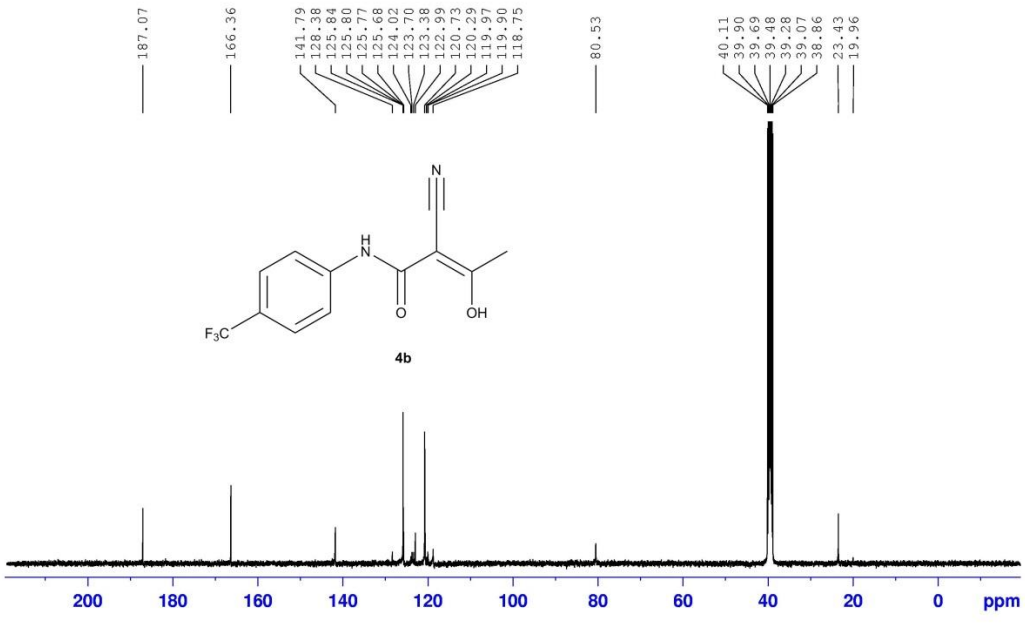
C13CPD DMSO D:\\ {Sigma Aldrich} 1



PROTON DMSO D:\\ {Sigma Aldrich} 1

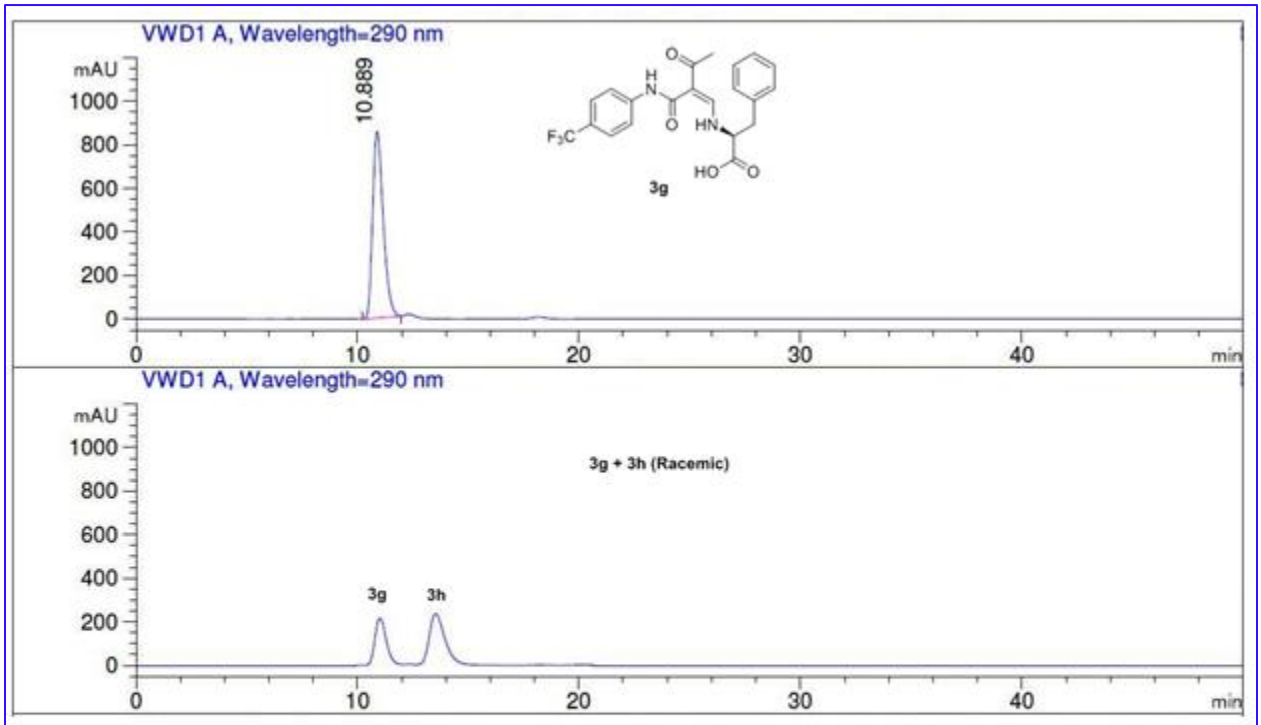


C13CPD DMSO D:\\ {Sigma Aldrich} 1



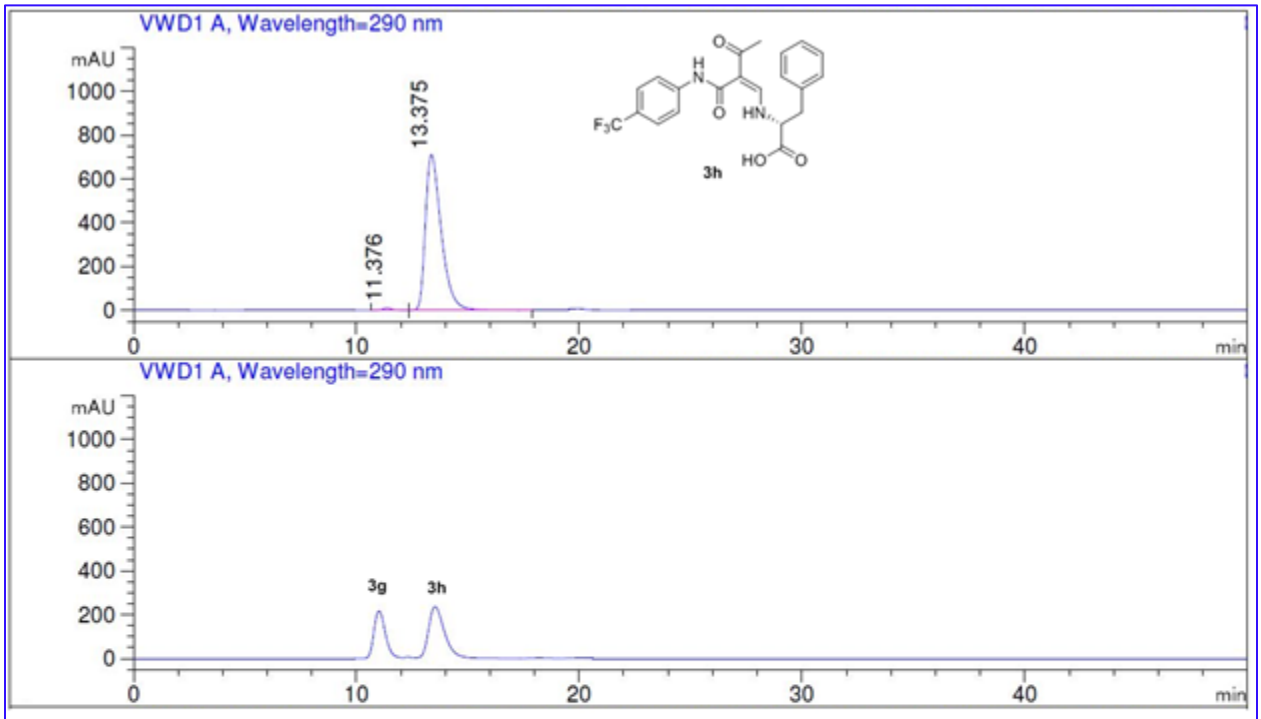
6. Chiral HPLC analysis of 3g & 3h:

The enantiomeric ratio was determined by HPLC with a Daicel Chiralcel® OD-H column using (85:15:0.1) n-Hexane/Isopropanol/Trifluro acetic acid. The stereochemistry of the product **3g** and **3h** was determined in comparison to its racemic material. Racemic material was prepared by mixing both **3g** and **3h.**



Signal VWD1 A, Wavelength=290 nm

Peak #	RT [min]	Type	Width [min]	Area	Area %
1	10.889	BB	0.511	28433.857	100.000



Signal VWD1 A, Wavelength=290 nm

Peak #	RT [min]	Type	Width [min]	Area	Area %
1	11.376	BB	0.420	287.535	0.812
2	13.375	BB	0.752	35124.754	99.188

7. X-ray Crystallographic data for 2b

Table 1. Crystal data and structure refinement for **2b**.

Identification code	shelx
Empirical formula	C12 H11 F3 N2 O2
Formula weight	272.23
Temperature	296(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P 21/n
Unit cell dimensions	a = 7.1752(11) A alpha = 90 deg. b = 13.714(2) A beta = 91.918(5) deg. c = 12.346(2) A gamma = 90 deg.
Volume	1214.1(3) A^3
Z, Calculated density	4, 1.489 Mg/m^3
Absorption coefficient	0.133 mm^-1
F(000)	560
Crystal size	0.250 x 0.200 x 0.200 mm
Theta range for data collection	2.220 to 25.997 deg.
Limiting indices	-8<=h<=8, -16<=k<=16, -14<=l<=15
Reflections collected / unique	13410 / 2383 [R(int) = 0.0492]
Completeness to theta = 25.242	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.962 and 0.9021
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2383 / 1 / 176
Goodness-of-fit on F^2	1.031
Final R indices [I>2sigma(I)]	R1 = 0.0693, wR2 = 0.1557
R indices (all data)	R1 = 0.1254, wR2 = 0.1866
Extinction coefficient	n/a
Largest diff. peak and hole	0.430 and -0.276 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **2b.**
U(eq)is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	6419(6)	6750(3)	-444(4)	53(1)
C(2)	4900(5)	7319(2)	30(3)	37(1)
C(3)	3453(5)	6862(3)	531(3)	46(1)
C(4)	2074(5)	7401(3)	977(3)	44(1)
C(5)	2092(5)	8415(2)	934(3)	36(1)
C(6)	3555(5)	8866(3)	435(3)	46(1)
C(7)	4947(5)	8318(3)	-8(3)	47(1)
C(8)	328(5)	9870(2)	1534(3)	40(1)
C(9)	-1379(5)	10153(2)	2080(3)	38(1)
C(10)	-1737(5)	11144(2)	2190(3)	41(1)
C(11)	-2677(5)	9465(3)	2501(3)	43(1)
C(12)	-4417(6)	9803(3)	3046(4)	68(1)
N(1)	619(4)	8899(2)	1405(3)	41(1)
N(2)	-732(4)	11865(2)	1882(3)	52(1)
O(1)	1459(4)	10476(2)	1222(3)	65(1)
O(2)	-2437(4)	8566(2)	2453(3)	59(1)
F(1)	6035(4)	5830(2)	-608(3)	107(1)
F(2)	7984(4)	6778(3)	157(3)	114(1)
F(3)	6942(4)	7085(2)	-1387(2)	86(1)

Table 3. Bond lengths [A] and angles [deg] for **2b**.

C(1)-F(1)	1.306(4)
C(1)-F(3)	1.318(5)
C(1)-F(2)	1.326(5)
C(1)-C(2)	1.477(5)
C(2)-C(7)	1.372(5)
C(2)-C(3)	1.377(5)
C(3)-C(4)	1.366(5)
C(3)-H(3)	0.9300
C(4)-C(5)	1.392(5)
C(4)-H(4)	0.9300
C(5)-C(6)	1.380(5)
C(5)-N(1)	1.392(4)
C(6)-C(7)	1.377(5)
C(6)-H(6)	0.9300
C(7)-H(7)	0.9300
C(8)-O(1)	1.232(4)
C(8)-N(1)	1.357(4)
C(8)-C(9)	1.470(5)
C(9)-C(10)	1.392(5)
C(9)-C(11)	1.435(5)
C(10)-N(2)	1.288(4)
C(10)-H(10)	0.9300
C(11)-O(2)	1.247(4)
C(11)-C(12)	1.510(5)
C(12)-H(12A)	0.9600

C(12)-H(12B)	0.9600
C(12)-H(12C)	0.9600
N(1)-H(1)	0.898(10)
N(2)-H(2A)	0.8600
N(2)-H(2B)	0.8600
F(1)-C(1)-F(3)	105.3(4)
F(1)-C(1)-F(2)	106.5(4)
F(3)-C(1)-F(2)	102.9(3)
F(1)-C(1)-C(2)	114.6(3)
F(3)-C(1)-C(2)	113.7(3)
F(2)-C(1)-C(2)	112.7(4)
C(7)-C(2)-C(3)	119.3(3)
C(7)-C(2)-C(1)	119.6(3)
C(3)-C(2)-C(1)	121.1(3)
C(4)-C(3)-C(2)	120.2(3)
C(4)-C(3)-H(3)	119.9
C(2)-C(3)-H(3)	119.9
C(3)-C(4)-C(5)	121.2(3)
C(3)-C(4)-H(4)	119.4
C(5)-C(4)-H(4)	119.4
C(6)-C(5)-C(4)	118.2(3)
C(6)-C(5)-N(1)	124.9(3)
C(4)-C(5)-N(1)	116.9(3)
C(7)-C(6)-C(5)	120.3(3)
C(7)-C(6)-H(6)	119.8
C(5)-C(6)-H(6)	119.8
C(2)-C(7)-C(6)	120.9(3)
C(2)-C(7)-H(7)	119.6
C(6)-C(7)-H(7)	119.6
O(1)-C(8)-N(1)	121.3(3)
O(1)-C(8)-C(9)	122.2(3)
N(1)-C(8)-C(9)	116.5(3)
C(10)-C(9)-C(11)	118.9(3)
C(10)-C(9)-C(8)	117.5(3)
C(11)-C(9)-C(8)	123.6(3)
N(2)-C(10)-C(9)	127.9(3)
N(2)-C(10)-H(10)	116.0
C(9)-C(10)-H(10)	116.0
O(2)-C(11)-C(9)	122.7(3)
O(2)-C(11)-C(12)	116.2(3)
C(9)-C(11)-C(12)	121.1(3)
C(11)-C(12)-H(12A)	109.5
C(11)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
C(11)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
C(8)-N(1)-C(5)	129.7(3)
C(8)-N(1)-H(1)	111(2)
C(5)-N(1)-H(1)	119(2)
C(10)-N(2)-H(2A)	120.0
C(10)-N(2)-H(2B)	120.0
H(2A)-N(2)-H(2B)	120.0

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for **2b**.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
C(1)	43(2)	46(2)	70(3)	-2(2)	17(2)	2(2)
C(2)	36(2)	33(2)	42(2)	-4(2)	4(2)	0(2)
C(3)	43(2)	27(2)	69(3)	-2(2)	13(2)	-2(2)
C(4)	39(2)	33(2)	62(3)	3(2)	17(2)	-5(2)
C(5)	36(2)	32(2)	40(2)	1(2)	8(2)	2(2)
C(6)	51(2)	27(2)	62(3)	2(2)	22(2)	0(2)
C(7)	43(2)	37(2)	61(3)	2(2)	19(2)	-7(2)
C(8)	40(2)	29(2)	51(2)	6(2)	8(2)	4(2)
C(9)	34(2)	33(2)	47(2)	0(2)	7(2)	1(2)
C(10)	36(2)	38(2)	49(2)	2(2)	10(2)	3(2)
C(11)	37(2)	41(2)	53(3)	1(2)	11(2)	-3(2)
C(12)	54(3)	54(3)	100(4)	-8(3)	36(3)	-8(2)
N(1)	38(2)	29(2)	58(2)	4(1)	21(2)	2(1)
N(2)	51(2)	28(2)	79(3)	-1(2)	20(2)	4(1)
O(1)	54(2)	30(1)	113(3)	4(2)	45(2)	-1(1)
O(2)	52(2)	34(1)	94(2)	4(2)	28(2)	-6(1)
F(1)	95(2)	40(1)	191(4)	-19(2)	69(2)	6(1)
F(2)	55(2)	170(3)	116(3)	-42(2)	-13(2)	49(2)
F(3)	98(2)	80(2)	83(2)	-2(2)	48(2)	15(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters(A^2 x 10^3) for **2b**.

x	y	z	U(eq)
H(3)	3414	6185	566	55
H(4)	1106	7085	1317	53
H(6)	3601	9543	399	56
H(7)	5930	8630	-337	56
H(10)	-2834	11307	2527	49
H(12A)	-4466	10502	3040	102
H(12B)	-5495	9546	2663	102
H(12C)	-4395	9574	3781	102
H(2A)	297	11757	1566	63
H(2B)	-1092	12454	1993	63
H(1)	-300(40)	8550(20)	1690(30)	53(12)

Table 6. Torsion angles [deg] for **2b**.

F(1)-C(1)-C(2)-C(7)	-164.0(4)
F(3)-C(1)-C(2)-C(7)	-42.7(6)
F(2)-C(1)-C(2)-C(7)	74.0(5)
F(1)-C(1)-C(2)-C(3)	17.5(6)
F(3)-C(1)-C(2)-C(3)	138.7(4)
F(2)-C(1)-C(2)-C(3)	-104.6(5)
C(7)-C(2)-C(3)-C(4)	0.5(6)

C(1)-C(2)-C(3)-C(4)	179.1(4)
C(2)-C(3)-C(4)-C(5)	0.3(7)
C(3)-C(4)-C(5)-C(6)	-0.7(6)
C(3)-C(4)-C(5)-N(1)	179.6(4)
C(4)-C(5)-C(6)-C(7)	0.3(6)
N(1)-C(5)-C(6)-C(7)	-180.0(4)
C(3)-C(2)-C(7)-C(6)	-0.9(6)
C(1)-C(2)-C(7)-C(6)	-179.5(4)
C(5)-C(6)-C(7)-C(2)	0.5(7)
O(1)-C(8)-C(9)-C(10)	3.1(6)
N(1)-C(8)-C(9)-C(10)	-178.0(4)
O(1)-C(8)-C(9)-C(11)	-176.7(4)
N(1)-C(8)-C(9)-C(11)	2.2(6)
C(11)-C(9)-C(10)-N(2)	178.8(4)
C(8)-C(9)-C(10)-N(2)	-1.0(6)
C(10)-C(9)-C(11)-O(2)	-178.6(4)
C(8)-C(9)-C(11)-O(2)	1.2(6)
C(10)-C(9)-C(11)-C(12)	0.7(6)
C(8)-C(9)-C(11)-C(12)	-179.5(4)
O(1)-C(8)-N(1)-C(5)	-0.6(7)
C(9)-C(8)-N(1)-C(5)	-179.5(4)
C(6)-C(5)-N(1)-C(8)	-3.7(7)
C(4)-C(5)-N(1)-C(8)	176.0(4)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for **2b** [A and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(2)-H(2A)...F(3)#1	0.86	2.55	3.155(4)	127.8
N(2)-H(2B)...O(2)#2	0.86	1.99	2.813(4)	160.0
N(2)-H(2A)...O(1)	0.86	2.00	2.618(4)	128.2
N(1)-H(1)....O(2)	0.898(10)	1.83(2)	2.623(4)	147(3)

Symmetry transformations used to generate equivalent atoms:
#1 -x+1,-y+2,-z #2 -x-1/2,y+1/2,-z+1/2