Supporting Information

Regorafenib analogues and their ferrocenic counterparts: synthesis and biological evaluation

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EXPERIMENTAL SECTION

General Considerations. Unless otherwise stated, all reactions were performed under an argon atmosphere with anhydrous solvents using Schlenk technics. THF and Et_2O were distilled over sodium/benzophenone. DMF was distilled over CaH_2 under vacuum, MeOH was distilled over magnesium and iodine, MeCN and CH_2Cl_2 were distilled over CaH_2. Unless otherwise stated, all reagents were used without prior purification. Column chromatography separations were achieved on silica gel (40-63 μm). All Thin Layer Chromatographies (TLC) were performed on aluminum backed plates pre-coated with silica gel (Merck, Silica Gel 60 F254). They were visualized by exposure to UV light. PET refers to petroleum ether. Melting points were measured on a Kofler bench. IR spectra were taken on a Perkin-Elmer Spectrum 100 spectrometer. ^{1}H, ^{13}C and ^{19}F Nuclear Magnetic Resonance (NMR) spectra were recorded either (i) on a Bruker Avance III spectrometer at 300 MHz and 75.4 MHz, respectively, or (ii) Bruker Avance III HD at 500 MHz and 126 MHz, respectively. ^{1}H chemical shifts (δ) are given in ppm relative to the solvent residual peak and ^{13}C chemical shifts are relative to the central peak of the solvent signal. Cp refers to the unsubstituted cyclopentadienyl ring of ferrocene. HPLC analyses were performed on a ThermoFisher Ultimate 3000 apparatus. Iodoferrocene was prepared according to Erb.[1] MTT assays were performed according to the manufacturer recommendations (ThermoFisher, Les Ulys, France).

Crystallography. For **6**, **7**, **19**, **31**, **35** and **39** the X-ray diffraction data were collected using D8 VENTURE Bruker AXS diffractometer at the temperature given in the crystal data. The samples were studied with monochromatized Mo-Kα radiation (λ = 0.71073 Å). The structure was solved by dual-space algorithm using the *SHELXT* program,[2] and then refined with full-matrix least-square methods based on F^2 (*SHELXL*).[3] Except hydrogen atoms linked to N atom that were introduced in the structural model through Fourier difference maps analysis, H atoms were finally included in their calculated positions and treated as riding on their parent atom with constrained thermal parameters. The molecular diagrams were generated by MERCURY (version 3.9).

4-Chloropicolinoyl chloride hydrochloride (11)

Dimethylformamide (100 μL, 94.4 mg, 1.30 mmol, 0.15 equiv) was added to a solution of thionyl chloride (3.00 mL, 4.89 g, 41.1 mmol, 5.00 equiv) in a round bottom flask under argon and the reaction mixture was heated to 45 ˚C. 2-Picolinic acid **10** (1.00 g, 8.11 mmol, 1.00 equiv) was added portionwise to control the rate of the reaction. After addition, a condenser was added to the round bottomed flask and the mixture was heated to 70 ˚C for 18 hours. The mixture was cooled to rt and toluene was added. The resulting precipitate was filtrated on a sintered glass funnel and was washed with toluene. The combined filtrates were concentrated under vacuum using a rotary evaporator. Toluene was added to the crude reaction mixture which was concentrated under vacuum. This was repeated two more times to afford the crude product as a brown solid (1.34 g, 78%) used directly in the next step. The product was already prepared by following similar protocols but not described.[4, 5]

^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 8.67 (d, J = 4.7 Hz, 1H, H6), 8.03 (s, 1H, H3), 7.75 (d, J = 3.9 Hz, 1H, H5). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 164.8 (C=O), 150.8 (ArCH), 149.8 (ArC), 144.2 (ArC), 127.0 (ArCH), 124.7 (ArCH).

4-Chloro-*N*-methylpicolinamide (9)

A solution of compound **11** (815 mg, 3.83 mmol, 1.00 equiv) in THF-MeOH (15 and 1 mL, respectively) was added dropwise to a solution of methylamine (40% aqueous solution, 10 mL, 115 mmol, 30.0 equiv) at 0 ˚C. After addition, the reaction was stirred for one hour during which time the temperature rose to 10 ˚C. Volatiles were removed under vacuum using a rotary evaporator to give the crude product. This was dissolved in ethyl acetate. The organic phase was washed three times with water and one time with brine. The organic layer was dried over $MgSO_4$, filtrated over cotton wool and concentrated under vacuum using a rotary evaporator to give the crude product. This was purified by column chromatography over SiO_2, using PET/EtOAc (60:40) to give the title product **9** as a white solid (383 mg, 59%). Analytical data analogous to those reported previously.[5]

Mp 34-40 °C. ν_{max} (film)/cm^{-1} 3343, 1667, 1529, 1404, 1291, 1267, 1180, 1089, 830, 740. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 8.83 (br s, 1H, NH), 8.61 (d, *J* = 5.3 Hz, 1H, H6), 8.01 (d, *J* = 2.1 Hz, 1H, H3), 7.73 (dd, *J* = 2.1, 5.3 Hz, 1H, H5), 2.82 (d, *J* = 4.8 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 163.1 (C=O), 151.8 (ArC), 150.0 (ArCH), 144.5 (ArC), 126.2 (ArCH), 121.8 (ArCH), 26.1 (CH_3).

4-(3-Fluorophenoxy)-*N*-methylpicolinamide (7)

Potassium *tert*-butoxide (13.7 g, 122 mmol, 2.00 equiv) and potassium carbonate (4.2 g, 30.5 mmol, 0.50 equiv) were added to a solution of 3-fluorophenol **8** (11.6 mL, 122 mmol, 2.00 equiv) in dimethylformamide (120 mL) at 0 °C and the reaction mixture was stirred for 30 min. A solution of compound **9** (10.38 g, 60.9 mmol, 1.00 equiv) in dimethylformamide (80 mL) was added. After addition, the reaction mixture was warmed to rt and then heated at 110 °C for 16h. The mixture was cooled to rt and was poured into a water (1.3 L) saturated ammonium chloride (300 mL) mixture. The resulting suspension was stirred at rt overnight. This was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtrated over cotton wool and concentrated under vacuum using a rotary evaporator to give the crude product. This was purified by column chromatography over SiO_2, using PET/EtOAc (60:40 to 50:50) to give the title product **7** as a white solid (9.14 g, 61%). Analytical data analogous to those reported previously.[4]

Mp 80-82 °C. ν_{max} (film)/cm^{-1} 3331, 1657, 1589, 1567, 1529, 1483, 1462, 1447, 1413, 1290, 1250, 1224, 1157, 1138, 1117, 961, 900, 884, 758, 732. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 8.77 (q, *J* = 4.7 Hz, 1H, NH), 8.53 (d, *J* = 5.6 Hz, 1H, ArCH), 7.55 (dd, *J* = 7.9, 7.9 Hz, 1H, ArCH), 7.44 (d, *J* = 2.6 Hz, 1H, ArCH), 7.17-7.21 (m, 3H, 3 x ArCH), 7.08 (dd, *J* = 1.8, 7.8 Hz, 1H, ArCH), 2.80 (d, *J* = 4.7 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 164.9 (s, ArC), 163.7 (C=O), 162.9 (d, *J* = 246.3 Hz, ArC), 154.5 (d, *J* = 10.9 Hz, ArC), 152.6 (s, ArC), 150.6 (s, ArC), 131.8 (d, *J* = 9.7 Hz, ArCH), 116.9 (d, *J* = 2.9 Hz, ArCH), 114.4 (s, ArCH), 112.8 (d, *J* = 21.1 Hz, ArCH), 109.4 (s, ArCH), 108.7 (d, *J* = 24.1 Hz, ArCH), 26.0 (s, CH_3). ^{19}F NMR (470 MHz, DMSO-d_6) δ (ppm) -109.9 (F).

Crystal data for 7. $C_{13}H_{11}FN_2O_2$, *M* = 246.24, *T* = 150 K; monoclinic *P 2$_1$/c (I.T.#14)*, *a* = 9.7343(10), *b* = 13.7655(14), *c* = 9.5215(10) Å, *β* = 107.930(4) °, *V* = 1213.9(2) Å^3. *Z* = 4, *d* = 1.347 g.cm^{-3}, *μ* = 0.103 mm^{-1}. A final refinement on F^2 with 2762 unique intensities and 168 parameters converged at ωR_F^2 = 0.1133 (R_F = 0.0452) for 2713 observed reflections with $I > 2\sigma(I)$. CCDC 2017024.

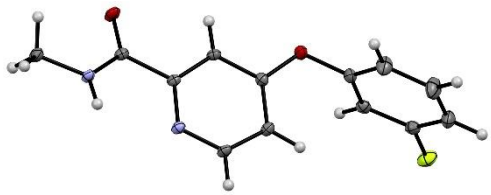


Figure 1. Molecular structure of compound **7** (thermal ellipsoids shown at the 30% probability level).

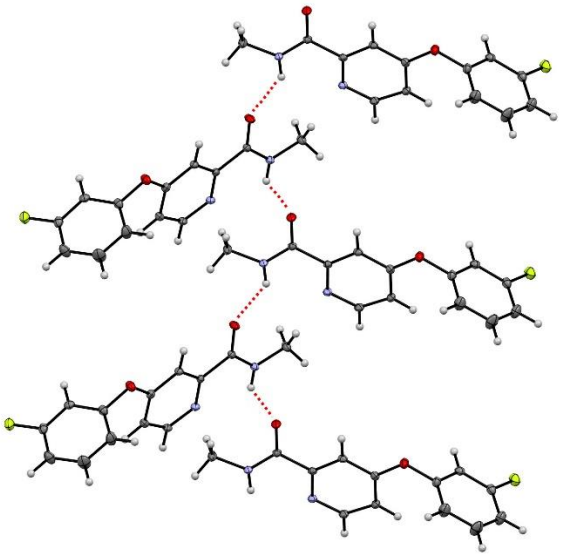


Figure 2. Hydrogen-bond network observed for compound **7** at the solid state (thermal ellipsoids shown at the 30% probability level).

4-(3-Fluoro-4-nitrophenoxy)-*N*-methylpicolinamide (12)

Compound **7** (5.02 g, 20.4 mmol, 1.00 equiv) was added portion wise to a solution of sulfuric acid (96%, 5.3 mL) in water (3 mL) at 0 °C. Sulfuric acid was added dropwise until the starting material was fully dissolved. Nitric acid (aqueous 68%, 2.6 mL, 39.6 mmol, 1.95 equiv) was added dropwise over 1 hour. The crude reaction mixture was poured into a solution of saturated sodium bicarbonate at 0 ˚C and the mixture was made slightly basic by the addition of solid sodium bicarbonate (pH 8). The reaction mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtrated over cotton wool and concentrated under vacuum using a rotary evaporator to give the crude product as an inseparable mixture of ***p*-12**/***o*-12**/**7** in a 1:0.7:0.3 ratio used directly in the next step.

4-(4-Amino-3-fluorophenoxy)-*N*-methylpicolinamide (6)

Powdered iron (5.23 g, 93.7 mmol, 4.60 equiv) was added in one portion to a solution of ammonium chloride (409 mg, 12.2 mmol, 0.60 equiv) in ethanol (21 mL), hydrochloric acid (35%, 6.4 mL) and water (14 mL) and the reaction mixture was stirred for 10 min. A solution of compounds ***p*-12**/***o*-12**/**7** from the previous step in ethanol (30 mL) was added dropwise. After addition, the reaction mixture was heated at reflux for 1h. The reaction mixture was cooled to rt and poured into a saturated solution of sodium bicarbonate. The resulting mixture was filtrated over celite® which was washed with ethanol and EtOAc. The combined filtrates were concentrated under vacuum to give a solution of the title product in water. This was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated over cotton wool and concentrated under vacuum using a rotary evaporator to give the crude product. This was purified by column chromatography over SiO_2, using

PET/EtOAc (60:40 to 40:60) with 3% of NEt_3 to give the title product which was triturated in an Et_2O/pentane mixture to afford **6** as a white solid (1.11 g, 21% over 2 steps). Analytical data analogous to those reported previously.[4]

Mp 137-139 °C. ν_{max} (film)/cm^{-1} 3396, 3295, 2943, 1667, 1585, 1569, 1536, 1507, 1470, 1282, 1223, 1141, 1115, 1073, 963, 848,803. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 8.73 (q, *J* = 4.8 Hz, 1H, NH), 8.46 (d, *J* = 8.6 Hz, 1H, ArCH), 7.37 (d, *J* = 2.6 Hz, 1H, ArCH), 7.08 (dd, *J* = 2.6, 5.6 Hz, 1H, ArCH), 7.00 (dd, *J* = 2.6, 11.8 Hz, 1H, ArCH), 6.86 (dd, *J* = 8.8, 9.9 Hz, 1H, ArCH), 6.78 (dd, *J* = 2.4, 8.8 Hz, 1H, ArCH), 5.21 (s, 2H, NH_2), 2.79 (d, *J* = 4.8 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 166.4 (s, ArC), 163.8 (C=O), 152.4 (s, ArC), 150.2 (s, ArCH), 150.1 (d, *J* = 240.0 Hz, ArC), 142.2 (d, *J* = 9.4 Hz, ArC), 134.7 (d, *J* = 12.8 Hz, ArC), 117.3 (d, *J* = 2.4 Hz, ArCH), 116.5 (d, *J* = 5.6 Hz, ArCH), 113.7 (s, ArCH), 108.9 (d, *J* = 21.1 Hz, ArCH), 108.5 (s, ArCH), 26.0 (s, CH_3). ^{19}F NMR (470 MHz, DMSO-d_6) δ (ppm) -131.1 (F).

Crystal data for 6. $C_{13}H_{12}FN_3O_2$, *M* = 261.26, *T* = 150 K; triclinic *P -1 (I.T.#2)*, *a* = 7.2126(7), *b* = 7.7988(7), *c* = 11.6303(11) Å, *α* = 108.895(3) °, *β* = 99.835(3) °, *γ* = 97.095(3) °, *V* = 598.52(10) Å^3. *Z* = 2, *d* = 1.450 g.cm^{-3}, *μ* = 0.111 mm^{-1}. A final refinement on F^2 with 2726 unique intensities and 187 parameters converged at ωR_F^2 = 0.1181 (R_F = 0.0424) for 2411 observed reflections with $I > 2\sigma(I)$. CCDC 2017023.

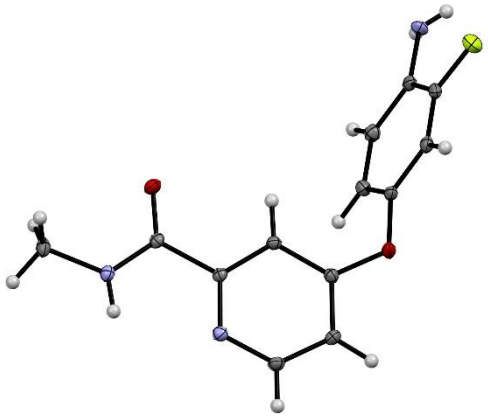


Figure 3. Molecular structure of compound **6** (thermal ellipsoids shown at the 30% probability level).

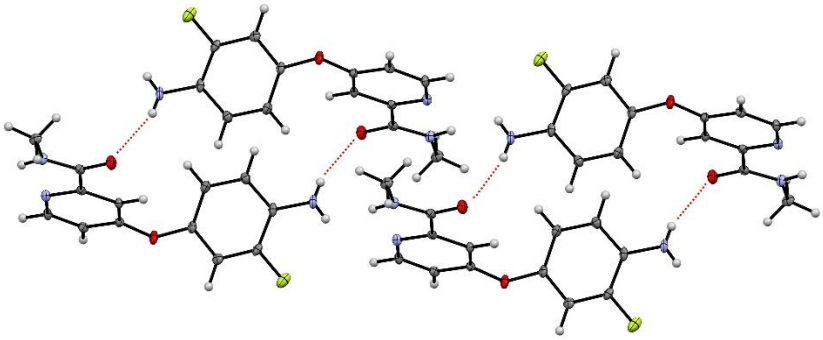


Figure 4. Hydrogen-bond network observed for compound **7** at the solid state (thermal ellipsoids shown at the 30% probability level).

1-Chloro-4-nitro-2-(trifluoromethyl)benzene (14)

Concentrated sulfuric acid (95%, 15 mL, 270 mmol, 2.60 equiv) was added dropwise to a solution of compound **13** (18.8 g, 104 mmol 1.00 equiv) at 0 °C. A solution of nitric acid (68% solution, 22 mL, 335 mmol, 3.22 equiv) and sulfuric acid (95%, 16 mL, 288 mmol, 2.80 equiv) was added dropwise during 30 min. After addition, the reaction mixture was warmed to rt and stirred for 18h. The reaction

mixture was poured into an ice/water mixture and this was extracted with EtOAc. The combined organic layers were washed with sodium bicarbonate, brine, dried over $MgSO_4$, filtrated over a plug of silica and concentrated under vacuum using a rotary evaporator to give the crude product as an oil, containing ~15% of the ortho isomer. Ethanol (4 equiv in volume) was added to the oil and this solution was kept at -20 °C for 72h. The resulting solids were filtrated to give a first crop (13.2 g) of the title product. A second crop (7.00 g) was also obtained. The title product **14** was obtained as a white solid (20.2 g, 86%). Analytical data analogous to those reported previously.[6]

Mp < 30 °C. ν_{max} (film)/cm^{-1} 1616, 1585, 1531, 1471, 1353, 1308, 1283, 1142, 1116, 1036, 916, 889, 840, 740. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.57 (d, *J* = 2.6 Hz, 1H, ArCH), 8.36 (dd, *J* = 2.6, 8.8 Hz, 1H, ArCH), 7.74 (d, *J* = 8.8 Hz, 1H, ArCH). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 146.3 (s, ArC), 139.5 (ArC), 132.9 (s, ArCH), 130.0 (q, *J* = 33.1 Hz, ArC), 127.6 (s, ArCH), 123.3 (q, *J* = 5.5 Hz, ArCH), 121.8 (q, *J* = 273.8 Hz, CF_3). ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) -63.4 (CF_3).

4-Chloro-3-(trifluoromethyl)aniline (15)

Powdered iron (15.1 g, 269 mmol, 4.60 equiv) was added in one portion to a solution of ammonium chloride (1.88 g, 35 mmol, 0.60 equiv) in ethanol (98 mL), hydrochloric acid (35%, 16 mL) and water (40 mL) at 80 °C and the reaction mixture was stirred for 5 min. A solution of compound **14** (12.5 g, 58 mmol, 1.00 equiv) in ethanol (15 mL) was added dropwise to the reaction mixture. After addition, the reaction mixture was stirred at 80 °C for 2h. The reaction mixture was cooled to rt and celite® (≈ 40 g) was added. Saturated sodium bicarbonate was added to the reaction mixture dropwise over 2h with efficient stirring. The reaction mixture was filtrated over celite® washed with EtOAc. The combined filtrates were extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, filtrated over cotton wool and concentrated under vacuum using a rotary evaporator to give the crude product. This was purified by column chromatography over SiO_2, using PET/EtOAc (90:10 to 60:40) with 2% of NEt_3 to give the title product **15** as a light yellow solid (8.79 g, 81%). Analytical data analogous to those reported previously.[7]

Mp 36-38 °C. ν_{max} (film)/cm^{-1} 3445, 3350, 1629, 1483, 1444, 1337, 1255, 1171, 1125, 1114, 1027, 872, 828. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.22 (d, *J* = 8.5 Hz, 1H, ArCH), 6.95 (d, *J* = 2.8 Hz, 1H, ArCH), 6.72 (dd, *J* = 2.8, 8.5 Hz, 1H, ArCH), 3.84 (br s, 2H, NH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 145.3 (s, ArC), 132.2 (s, ArCH), 128.8 (q, *J* = 31.1 Hz, ArC), 123.0 (q, *J* = 273.2 Hz, CF_3), 120.4 (s, ArC), 118.8 (s, ArCH), 113.7 (q, *J* = 5.4 Hz, ArCH). ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) -62.8 (CF_3).

4-(4-(3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido)-3-fluorophenoxy)-*N*-methylpicolinamide (1a)

Compound **15** (149 mg, 0.76 mmol, 1.40 equiv) in CH_2Cl_2 (1.5 mL) was added to a solution of triphosgene (249 mg, 0.83 mmol, 1.50 equiv) in CH_2Cl_2 (1.5 mL). A solution of *N*,*N*-diisopropylethylamine (280 µL, 207 mg, 1.6 mmol, 3.00 equiv) in CH_2Cl_2 (1.5 mL) was added to the suspension formed and the reaction mixture was stirred for 3h. Volatiles were removed under vacuum to give the crude product. Diethyl ether was added to precipitate diisopropylethylamine hydrochloride which was eliminated by decantation. The supernatant was removed with a syringe and was added to a solution of compound **6** (142 mg, 0.54 mmol, 1.00 equiv) in EtOAc (2 mL) and CH_2Cl_2 (0.1 ml) and the reaction mixture was stirred at rt for 18h. The white precipitate was filtrated and triturated with diethyl ether to give 89 mg of the title product **1a**. The combined filtrates were concentrated under vacuum to give the crude product. This was purified by column chromatography over SiO_2 prewashed with NEt_3,

using CH_2Cl_2/MeOH (99.5:0.5 to 98.5:1.5) to give the title product which was triturated in an Et_2O to afford the title product (80 mg). The combined title product **1a** was obtained as a white solid (169 mg, 65%). Analytical data analogous to those reported previously.[4]

Mp 211-212 °C. ν_{max} (film)/cm^{-1} 3388, 3348, 3289, 1718, 1655, 1595, 1540, 1504, 1486, 1430, 1316, 1299, 1206, 1174, 1140, 1129, 969, 870, 835, 742. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.63 (s, 1H, NH_{urea}, H22), 8.75-8.77 (br s, 2H, NH_{urea} and NH_{amide}, H23 and H24), 8.53 (d, *J* = 5.7 Hz, 1H, ArCH, H7), 8.15 (t, *J* = 9.1 Hz, 1H, ArCH, H12), 8.12 (s, 1H, ArCH, H16), 7.63 (m, 2H, 2 x ArCH, H19 and H20), 7.43 (d, *J* = 2.6 Hz, 1H, ArCH, H4), 7.33 (dd, *J* = 2.6, 11.6, 1H, ArCH, H9), 7.18 (dd, *J* = 2.6, 5.6 Hz, 1H, ArCH, H6), 7.07 (dd, *J* = 1.9, 9.0 Hz, 1H, ArCH, H13), 2.79 (d, *J* = 4.9 Hz, 3H, CH_3, H1). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 165.4 (s, ArC, C5), 163.7 (s, C=O_{amide}, C2), 152.7 (d, *J* = 245.4 Hz, ArC, C10), 152.5 (s, ArC, C3), 152.2 (s, C=O_{urea}, C14), 150.4 (s, ArCH, C7), 148.1 (d, *J* = 10.5 Hz, ArC, C8), 139.0 (s, ArC, C15), 132.1 (s, ArC, C19), 126.8 (q, *J* = 30.6 Hz, ArC, C17), 124.9 (d, *J* = 10.7 Hz, ArC, C11), 122.9 (s, ArC, C20), 122.7 (q, *J* = 272.8 Hz, CF_3, C21), 122.5 (s, 2 x ArCH, C12 and C18), 117.0 (d, *J* = 2.4 Hz, ArCH, C13), 116.6 (q, *J* = 5.5 Hz, ArCH, C16), 114.1 (s, ArCH, C6), 109.0 (d, *J* = 23.1 Hz, ArCH, C9), 108.9 (s, ArCH, C4), 25.9 (s, CH_3, C1). ^{19}F NMR (470 MHz, $CDCl_3$) δ (ppm) -61.5 (CF_3), -124.4 (F). HRMS, *m/z* 505.0662 (0 ppm) found (calcd for $C_{21}H_{15}N_4O_3F_4{}^{35}ClNa$, $[M+Na]^+$, requires 505.0661); 521.0392 (2 ppm) found (calcd for $C_{21}H_{15}N_4O_3F_4{}^{35}ClK$, $[M+K]^+$, requires 521.04004).

3,4-Dimethoxycyclobut-3-ene-1,2-dione (17)

Trimethylorthoformate (3.80 mL, 35.0 mmol, 2.00 equiv) was added to a solution of squaric acid **16** (2.00 g, 17.5 mmol, 1.00 equiv) in methanol (20 mL) and the reaction mixture was heated at reflux for 4h. The reflux condenser was replaced by a distillation head and methyl formate was distilled off during 3h. The condenser was installed back and the reaction mixture was heated at reflux overnight. Volatiles were removed under vacuum to give the crude product. This was dissolved in CH_2Cl_2 (4 mL) and Et_2O (20 mL) was slowly added. The cloudy mixture was filtrated over cotton wool. The filtrate was cooled to -80 °C during 1 min to precipitate the product. The resulting solids were filtrated and dried under high vacuum to give the title product **17** as a white solid (2.1 g, 84%). Analytical data analogous to those reported previously.[8]

Mp 57-58 °C. ν_{max} (film)/cm^{-1} 2965, 1811, 1720, 1583, 1479, 1354, 1145, 1083, 1035, 923, 829. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 4.29 (s, 6H, 2 x CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ (ppm) 189.1 (2 x C=O), 184.4 (2 x C=C), 60.9 (2 x CH_3).

3-((4-Chloro-3-(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (18)

Compound **17** (262 mg, 1.8 mmol, 1.00 equiv) was added to a solution of compound **15** (398 mg, 2.0 mmol, 1.10 equiv) in methanol (26 mL) and the mixture was stirred at rt for 18h followed by 3h at 65 ˚C. The reaction mixture was cooled to rt and was poured into of Et_2O (50 mL). The resulting yellow solid was removed by filtration and the filtrate was concentrated under vacuum to give the crude product. This was triturated in PET/Et_2O (90:10) and filtrated to give the title product **18** as a pale yellow solid (427 mg, 76% yield).

Mp 169-171 °C. ν_{max} (film)/cm^{-1} 3240, 3178, 3109, 3028, 1800, 1714, 1606, 1564, 1540, 1519, 1489, 1444, 1418, 1329, 1260, 1183, 1145, 1114, 892, 842, 754. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 11.00 (br s, 1H, NH, H13), 7.90 (s, 1H, ArCH, H2), 7.68 (d, *J* = 8.8 Hz, 1H, ArCH, H5), 7.61 (dd, *J* = 2.0, 8.8 Hz, 1H, ArCH, H6), 4.39 (s, 3H, CH_3, H12). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 187.5 (s, C=O, C10), 184.2 (s, C=O, C11), 179.4 (s, C=, C9), 168.9 (s, C=, C8), 137.7 (s, ArC, C1), 132.4 (s,

ArCH, C5), 127.2 (q, *J* = 31.1 Hz, ArC, C3), 124.7 (s, ArC, C4), 124.0 (s, ArCH, C6), 122.5 (q, *J* = 272.9 Hz, CF_3, C7), 118.2 (q, *J* = 5.5 Hz, ArCH, C2), 60.8 (s, CH_3, C12). ^{19}F NMR (470 MHz, DMSO-d_6) δ (ppm) -61.7 (CF_3).

4-(4-((2-((4-Chloro-3-(trifluoromethyl)phenyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-3-fluorophenoxy)-*N*-methylpicolinamide (1b)

Compound **6** (120 mg, 0.46 mmol, 1.00 equiv) was added to a solution of **18** (150 mg, 0.51 mmol, 1.10 equiv) in methanol (2 mL) and the reaction mixture was heated at 55 °C for 72h. The reaction mixture was cooled to rt and stirred for a further 96h. Volatiles were removed under vacuum to give the crude product. This was purified by column chromatography over SiO_2 prewashed with NEt_3, using CH_2Cl_2/MeOH (99:1 to 80:20), CH_2Cl_2/EtOH (99:1 to 90:10) and EtOAc/MeOH (99:1 to 92:8) to give a material which was further cleaned up by trituration with Et_2O and filtration to give the title product **1b** as a white solid (60.1 mg, 24%).
Mp 206-208 (decomp.) °C. ν_{max} (film)/cm^{-1} 3193, 2989, 1793, 1702, 1580, 1537, 1507, 1485, 1448, 1400, 1328, 1275, 1260, 1216, 1179, 1137, 1034, 997, 971, 909, 971, 909, 823, 750. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 10.54 (br s, 1H, $NH_{squaramide}$, H25 or H26), 9.96 (br s, 1H, $NH_{squaramide}$, H25 or H26), 8.78 (q, *J* = 4.9 Hz, 1H, NH_{amide}, H27), 8.54 (d, *J* = 5.5 Hz, 1H, ArCH, H7), 8.04 (d, *J* = 2.0 Hz, 1H, ArCH, H19), 7.96 (t, *J* = 9.3 Hz, 1H, ArCH, H12), 7.72 (d, *J* = 8.8 Hz, 1H, ArCH, H22), 7.69 (dd, *J* = 2.3, 8.8 Hz, 1H, ArCH, H23), 7.45 (d, *J* = 2.5 Hz, 1H, ArCH, H4), 7.40 (dd, *J* = 2.6, 11.8 Hz, 1H, ArCH, H9), 7.20 (dd, *J* = 2.6, 5.6 Hz, 1H, ArCH, H6), 7.16 (dd, *J* = 1.5, 8.7 Hz, 1H, ArCH, H13), 2.80 (d, *J* = 4.9 Hz, 3H, CH_3, H1). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 182.3 (s, C=$O_{squaramide}$, C15 or C16), 182.0 (s, C=$O_{squaramide}$, C15 or C16), 165.8 (s, C=$C_{squaramide}$, C14 or C17), 165.4 (s, ArC, C5), 165.2 (s, C=$C_{squaramide}$, C14 or C17), 163.6 (s, C=O_{amide}, C2), 152.9 (d, *J* = 247.7 Hz, ArC, C10), 152.5 (s, ArC, C3), 150.5 (s, ArC, C7), 149.5 (d, *J* = 9.9 Hz, ArC, C8), 138.1 (s, ArC, C18), 132.6 (s, ArCH, C22), 127.3 (q, *J* = 31.2 Hz, ArC, C20), 124.2 (d, *J* = 9.9 Hz, ArC, C11), 124.1 (s, ArC, C21), 123.5 (s, ArCH, C23), 123.1 (s, ArCH, C12), 122.6 (q, *J* = 272.8 Hz, CF_3, C24), 117.8 (q, *J* = 5.5 Hz, ArCH, C19), 117.4 (d, *J* = 2.1 Hz, ArCH, C13), 114.2 (s, ArCH, C6), 109.5 (d, *J* = 21.7 Hz, ArCH, C4), 26.0 (s, CH_3, C1). ^{19}F NMR (282 MHz, DMSO-d_6) δ (ppm) -61.5 (CF_3), -123.4 (F). HRMS, *m/z* 557.0612 (0 ppm) found (calcd for $C_{24}H_{15}N_4O_4F_4{}^{35}ClNa$, $[M+Na]^+$, requires 557.06102).

Ethyl 2-((4-chloro-3-(trifluoromethyl)phenyl)amino)-2-oxoacetate (19)

N,*N*-Diisopropylethylamine (1.28 mL, 7.34 mmol, 1.10 equiv) and ethyl chlorooxoacetate (0.965 mL, 8.70 mmol, 1.30 equiv) were added to a solution of compound **15** (1.46 g, 6.67 mmol, 1.00 equiv) in CH_2Cl_2 (12 mL) at 0 °C. After the addition, the reaction mixture was stirred at rt for 30 min before being poured into water. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with water, brine, dried over $MgSO_4$, filtrated over cotton wool and concentrated under vacuum using a rotary evaporator to give the title product **19** as a white solid (1.71 g, 87%).
Mp 128-130 °C. ν_{max} (film)/cm^{-1} 3327, 1699, 1540, 1479, 1317, 1289, 1164, 1127, 1110, 1031, 1019, 888, 851. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 11.18 (s, 1H, NH, H8), 8.32 (d, *J* = 2.5 Hz, 1H, ArCH, H2), 8.08 (dd, *J* = 2.5, 8.9 Hz, 1H, ArCH, H6), 7.72 (d, *J* = 8.9 Hz, 1H, ArCH, H5), 4.32 (q, *J* = 7.1 Hz, 2H, CH_2, H11), 1.32 (t, *J* = 7.1 Hz, 3H, CH_3, H12). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 159.9 (s, C=O_{ester}, C10), 155.6 (s, C=O_{amide}, C9), 137.0 (s, ArC, C1), 132.1 (s, ArCH, C5), 126.7 (q, *J* = 30.7 Hz, ArC, C3), 125.5 (s, ArC, C4), 125.2 (s, ArCH, C6), 122.6 (q, *J* = 273.2 Hz, CF_3, C7), 119.3 (q, *J* = 5.5 Hz, ArCH, C2), 62.6 (s, CH_2, C11), 13.8 (s, CH_3, C12). ^{19}F NMR (470 MHz, DMSO-d_6) δ (ppm) -61.6 (CF_3).

Crystal data for 19. $C_{11}H_9ClF_3NO_3$, M = 295.64, T = 150 K; monoclinic *P 2₁/c (I.T.#14)*, a = 12.3325(13), b = 11.1364(10), c = 9.0892(8) Å, β = 108.654(5) °, V = 1182.7(2) Å^3. Z = 4, d = 1.660 g.cm^{-3}, μ = 0.366 mm^{-1}. A final refinement on F^2 with 2633 unique intensities and 176 parameters converged at ωR_F^2 = 0.1064 (R_F = 0.0399) for 2155 observed reflections with $I > 2\sigma(I)$. CCDC 2017025.

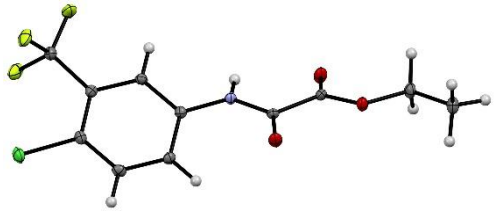


Figure 5. Molecular structure of compound **19** (thermal ellipsoids shown at the 30% probability level).

2-((4-Chloro-3-(trifluoromethyl)phenyl)amino)-2-oxoacetic acid (20)

An aqueous solution of potassium hydroxide (1M, 15 mL, 15.0 mmol, 4.20 equiv) was added to a solution of compound **19** (1.06 g, 3.58 mmol, 1.00 equiv) in THF (15 mL) at rt. After addtition, the reaction mixture was stirred at rt for 2h. Acetic acid (5 mL) was added and the reaction mixture was stirred at rt for 16h. Volatiles were removed under vacuum using a rotary evaporator. The resulting solid was filtrated and washed with water. The solid was dissolved in a CH_2Cl_2 and hydrochloric acid (2M) mixture. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated over cotton wool and concentrated under vacuum using a rotary evaporator to give the title product **20** as a white solid (599 mg, 62%).
Mp 116-121 °C. ν_{max} (film)/cm^{-1} 3334, 2925, 1684, 1535, 1480, 1424, 1321, 1259, 1166, 1126, 1112, 1035, 893, 828. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ (ppm) 11.12 (br s, 1H, CO_2H, H11), 8.36 (d, J = 2.2 Hz, 1H, ArCH, H2), 8.09 (dd, J = 2.2, 8.9 Hz, 1H, ArCH, H6), 7.71 (d, J = 8.9 Hz, 1H, ArCH, H5). ^{13}C NMR (125 MHz, DMSO-d$_6$) δ (ppm) 161.4 (s, C=O$_{acide}$, C10), 157.3 (s, C=O$_{ester}$, C9), 137.3 (s, ArC, C1), 132.1 (s, ArCH, C5), 126.7 (q, J = 30.8 Hz, ArC, C3), 125.3 (s, ArC, C6), 122.6 (q, J = 273.0 Hz, CF_3, C7), 119.1 (q, J = 5.5 Hz, ArCH, C2). ^{19}F NMR (282 MHz, DMSO-d$_6$) δ (ppm) -61.6 (CF_3).

***N*^{1}-(4-Chloro-3-(trifluoromethyl)phenyl)-*N*^{2}-(2-fluoro-4-((2-(methylcarbamoyl)pyridin-4-yl)oxy)phenyl)oxalamide (1c)**

N,*N*-Diisopropylethylamine (122 µL, 943 µmol, 4.15 equiv), EDC·HCl (310 mg, 1.64 mmol, 7.20 equiv) and HOBt (155 mg, 1.00 mmol, 4.40 equiv) were added to a solution of compound **20** (219 mg, 818 µmol, 3.60 equiv) in CH_2Cl_2 (2 mL) at rt. After addition, the reaction mixture was stirred at rt for 4h. Compound **6** (60.0 mg, 227 µmol, 1.00 equiv) was added to the reaction mixture which was stirred at rt for 8h. HBTU (380 mg, 1.0 mmol, 4.40 equiv) was added and the mixture was stirred at 50 ˚C for 14h. The reaction mixture was cooled to rt and CH_2Cl_2 (25 mL) and Et_2O (50 mL) were added. The resulting solid was filtrated and washed with water, methanol and Et_2O to give the title product **1c** as a white solid (107 mg, 33%).
Mp 260-262 °C. ν_{max} (film)/cm^{-1} 3675, 2989, 1668, 1520, 1469, 1412, 1276, 1261, 1138, 1066, 897, 826, 664, 750. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ (ppm) 11.36 (br s, 1H, NH$_{oxamide}$, H23 or H24), 10.64 (br s, 1H, NH$_{oxamide}$, H23 or H24), 8.79 (q, J = 4.9 Hz, 1H, NH$_{amide}$, H25), 8.56 (d, J = 5.6 Hz, 1H, ArCH, H7), 8.48 (d, J = 2.5 Hz, 1H, ArCH, H17), 8.19 (dd, J = 2.5, 8.8 Hz, 1H, ArCH, H21), 7.78 (t, J = 8.7 Hz, 1H, ArCH, H12), 7.76 (d, J = 8.8 Hz, 1H, ArCH, H20), 7.46 (d, J = 2.6 Hz, 1H, ArCH, H4), 7.41 (dd, J = 2.6, 10.9 Hz, 1H, ArCH, H9), 7.24 (dd, J = 2.7, 5.6 Hz, 1H, ArCH, H6), 7.16 (dd, J = 2.2, 8.8 Hz, 1H, ArCH, H13), 2.80 (d, J = 4.9 Hz, 3H, CH_3, H1). ^{13}C NMR (125 MHz, DMSO-d$_6$) δ (ppm) 164.9 (s, ArC, C5), 163.6 (s, C=O$_{amide}$, C2), 158.5 (s, C=O$_{oxamide}$, C14 or C15), 158.2 (s, C=O$_{oxamide}$, C14 or

C15), 155.7 (d, *J* = 250.7 Hz, ArC, C10), 152.6 (s, ArC, C3), 151.7 (d, *J* = 10.4 Hz, ArC, C8), 150.6 (s, ArCH, C7), 137.1 (s, ArC, C16), 132.1 (s, ArCH, C20), 127.3 (s, ArCH, C12), 126.7 (q, *J* = 30.9 Hz, ArC, C18), 125.6 (s, ArC, C19), 125.4 (s, ArCH, C21), 122.6 (q, *J* = 272.9 Hz, CF_3, C22), 122.0 (d, *J* = 12.0 Hz, ArC), 119.5 (q, *J* = 5.6 Hz, ArCH, C17), 116.9 (d, *J* = 2.3 Hz, ArCH, C13), 114.5 (s, ArCH, C6), 109.5 (d, *J* = 22.0 Hz, ArCH, C9), 109.2 (s, ArCH, C4), 26.0 (s, CH_3, C1). ^{19}F NMR (470 MHz, DMSO-d_6) δ (ppm) -61.5 (CF_3), -117.1 (F). HRMS, *m/z* 533.0614 (1 ppm) found (calcd for $C_{22}H_{15}N_4O_4F_4{}^{35}ClNa$, $[M+Na]^+$, requires 533.06102); 511.0787 (1 ppm) found (calcd for $C_{22}H_{16}N_4O_4F_4{}^{35}Cl$, $[M+H]^+$, requires 511.07907).

4-(4-(3-Ferrocenylureido)-3-fluorophenoxy)-*N*-methylpicolinamide (2a)

A solution of triphosgene (415 mg, 1.50 mmol, 4.00 equiv) in CH_2Cl_2 (2 mL) was added to a solution of compound **23** (215 mg, 1.07 mmol, 2.85 equiv) in CH_2Cl_2 (2 mL). After addition, the reaction mixture was stirred at rt for 15 min in during which a brown suspension was formed. *N*,*N*-Diisopropylethylamine (80.0 µL, 0.41 mmol, 1.10 equiv) was added and the resulting orange solution was stirred at rt for 1h. Volatiles were removed under vacuum to give the intermediate isocyanate. Et_2O was added and the reaction mixture was sonicated. The resulting yellow solution was taken by using a syringe and volatiles were removed under vacuum. The intermediate isocyanate was dissolved in THF (3.6 mL) and compound **6** (98 mg, 0,375 mmol, 1.00 equiv) was added. The reaction mixture was stirred at rt for 48h before volatiles were removed under vacuum to give the crude product. This was purified by column chromatography over SiO_2 prewashed with NEt_3, using CH_2Cl_2/MeOH (100:0 to 95:5) to give the title product which was triturated in Et_2O/PET to afford the title product **2a** as an orange solid (88.5 mg, 49%).

Mp 150-152 °C. ν_{max} (film)/cm^{-1} 3316, 3081, 2970, 1653, 1528, 1489, 1466, 1427, 1292, 1253, 1225, 1188, 1147, 1103, 996, 965, 810. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 8.77 (q, *J* = 4.8 Hz, 1H, NH_{amide}, H21), 8.52 (d, *J* = 5.6 Hz, 1H, ArCH, H7), 8.43 (d, *J* = 1.8 Hz, 1H, NH_{urea}, H20), 8.26 (d, *J* = 9.1 Hz, 1H, ArCH, H12), 8.23 (d, *J* = 1.8 Hz, 1H, NH_{urea}, H19), 7.42 (d, *J* = 2.5 Hz, 1H, ArCH, H4), 7.29 (dd, *J* = 2.5, 11.8 Hz, 1H, ArCH, H9), 7.17 (dd, *J* = 2.6, 5.6 Hz, 1H, ArCH, H6), 7.03 (dd, *J* = 1.8, 8.9 Hz, 1H, ArCH, H13), 4.51 (t, *J* = 1.8 Hz, 2H, 2 x FcCH, H16), 4.16 (s, 5H, Cp, H18), 3.97 (t, *J* = 1.8 Hz, 2H, 2 x FcCH, H17), 2.79 (d, *J* = 4.8 Hz, 3H, CH_3, H1). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 165.6 (s, ArC, C5), 163.7 (s, $C{=}O_{amide}$, C2), 152.5 (s, ArC, C3), 152.4 (s, $C{=}O_{urea}$, C14), 151.9 (d, *J* = 244.4 Hz, ArC, C10), 150.4 (s, ArCH, C7), 147.0 (d, *J* = 10.5 Hz, ArC, C8), 125.9 (d, *J* = 10.4 Hz, ArC, C11), 121.2 (s, ArCH, C12), 117.0 (d, *J* = 2.4 Hz, ArCH, C13), 114.0 (s, ArCH, C6), 108.9 (d, *J* = 21.5 Hz, ArCH, C9), 108.8 (s, ArCH, C4), 96.0 (s, FcC, C15), 68.7 (s, Cp, C18), 63.7 (s, 2 x FcCH, C17), 60.8 (s, 2 x FcCH, C16), 25.9 (s, CH_3, C1). ^{19}F NMR (470 MHz, DMSO-d_6) δ (ppm) -126.1 (F). HRMS, *m/z* 511.0844 (1 ppm) found (calcd for $C_{24}H_{21}N_4O_3FNa^{56}Fe$, $[M+Na]^+$, requires 511.08393); 488.0942 (0 ppm) found (calcd for $C_{24}H_{21}N_4O_3F^{56}Fe$, $[M]^{+\cdot}$, requires 488.09416).

Ferrocene carboxaldehyde oxime (S1)

Sodium hydroxide (6.72 g, 168 mmol, 6.00 equiv) was dissolved in ethanol (200 mL) and ferrocene carboxaldehyde (6.0 g, 28 mmol, 1.00 equiv) followed by hydroxylamine hydrochloride (3.90 g, 56 mmol, 2.00 equiv) were added before the reaction mixture was stirred at reflux for 16h. The reaction mixture was cooled to rt and volatiles were removed under vacuum to give the crude product. This was dissolved in CH_2Cl_2. The organic phase was washed with water, saturated ammonium chloride, water, brine, dried over $MgSO_4$, filtrated over cotton wool and concentrated under vacuum using a rotary

evaporator to give the title product **S1** as an orange solid (6.40 g, quant.). Analytical data analogous to those reported previously.[9]
Mp 118-120 °C. ν_{max} (film)/cm^{-1} 3178, 2987, 2867, 1795, 1630, 1440, 1375, 1298, 1250, 1202, 1103, 1046, 968, 941, 809, 783. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.12 (br s, 1H, OH, H6), 7.98 (s, 1H, =CH, H5), 4.53 (*t*, *J* = 1.8 Hz, 2H, 2 x FcCH, H2), 4.35 (*t*, *J* = 1.8 Hz, 2 x FcCH, H3), 4.22 (s, 5H, Cp, H4). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 150.1 (=CH, C5), 76.3 (FcC, C1), 70.2 (2 x FcCH, C3), 69.4 (Cp), 67.7 (2 x FcCH, C2).

(Aminomethyl)ferrocene hydrochloride (S2)

THF (180 mL) was added to lithium aluminum hydride (5.31g, 140 mmol, 5.00 equiv) at 0 °C and a solution of compound **S1** (6.40 g, 28.0 mmol, 1.00 equiv) in THF (120 mL) was added dropwise. After addition, the reaction mixture was warmed to rt and then heated at 70 °C for 16h. The reaction mixture was cooled to rt and was carefully poured onto ice before being extracted with EtOAc. The organic was washed with water, brine, dried over $MgSO_4$, filtrated over cotton wool and concentrated under vacuum using a rotary evaporator to give the crude product. This was dissolved in MeCN (50 mL) and filtrated through a pad of celite®. A solution of HCl in Et_2O (≈ 5 M) was added until no more precipitate appeared. The resulting solids were filtrated and washed with Et_2O to give the title product **S2** as a sandy brown solid (4.03 g, 58%). Analytical data analogous to those reported previously.[10]
Mp 200-204 °C (decomp.). ν_{max} (film)/cm^{-1} 2895, 2616, 2050, 1600, 1508, 1470, 1380, 1358, 1238, 1105, 1038, 1025, 910, 834, 814. ^{1}H NMR (300 MHz, CD_3OD) δ (ppm) 4.38 (s, 2H, 2 x FcCH), 4.27 (s, 2H, 2 x FcCH), 4.22 (s, 5H, Cp), 3.92 (s, 2H, CH_2). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 8.23 (br s, 3H, NH_3^+, H6), 4.37 (s, 2H, 2 x FcCH, H2), 4.21 (s, 7H, Cp + 2 x FcCH, H4 + H3), 3.75 (s, 2H, CH_2, H5). ^{13}C NMR (75.0 MHz, DMSO-d_6) δ (ppm) 79.7 (FcC, C1), 69.4 (2 x FcCH, C2), 68.6 (Cp, C4), 68.2 (2 x FcCH, C3), 38.2 (CH_2, C5).

(Aminomethyl)ferrocene (22)

The compound **S2** (350 mg, 1.40 mmol, 1.00 equiv) was mixed with Et_2O (20 mL) and 2M NaOH (10 mL) at rt and stirred for 2 min. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layer were washed with 2M NaOH, water, brine, dried over $MgSO_4$, filtrated over cotton wool and concentrated under vacuum using a rotary evaporator to give the crude product **22** (231 mg, 76%) as a low-melting solid, pure enough to be used in the next step.
Mp < 30 °C. ν_{max} (film)/cm^{-1} 3366, 3088, 2854, 1581, 1457, 1402, 1229, 1103, 1021, 999, 809. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 4.15 (t, *J* = 1.7 Hz, 2H, 2 x FcCH), 4.13 (s, 5H, Cp), 4.10 (t, *J* = 1.7 Hz, 2H, 2 x FcCH), 3.53 (s, 2H, CH_2), 1.48 (br s, 2H, NH_2). ^{13}C NMR (75.0 MHz, $CDCl_3$) δ (ppm) 91.1 (FcC), 68.4 (Cp), 67.7 (2 x FcCH), 67.2 (2 x FcCH), 41.4 (CH_2).

4-(4-(3-Ferrocenylmethylureido)-3-fluorophenoxy)-*N*-methylpicolinamide (3a)

A solution of triphosgene (239 mg, 0.80 mmol, 1.50 equiv) in CH_2Cl_2 (2 mL) was added to a solution of compound **22** (145 mg, 0.67 mmol, 1.25 equiv) in CH_2Cl_2 (2 mL). After addition, the reaction mixture was stirred at rt for 15 min in during which a brown suspension was formed. A solution of *N*,*N*-diisopropylethylamine (210 µL, 1.21 mmol, 2.25 mmol) in CH_2Cl_2 (2 mL) was added and the resulting orange solution was stirred at rt for 2h. Volatiles were removed under vacuum to give the intermediate isocyanate. Et_2O was added and the reaction mixture was sonicated. The resulting yellow solution was taken by using a syringe and volatiles were removed under vacuum. The intermediate isocyanate was

dissolved in CH_2Cl_2 (3 mL) and compound **6** (140 mg, 0.54 mmol, 1.00 equiv) was added. The reaction mixture was stirred at rt for 24h before volatiles were removed under vacuum to give the crude product. This was purified by column chromatography over SiO_2, using CH_2Cl_2/MeOH (98:2) with 1% of NEt_3 to give the product. This was further purified by preparative TLC SiO_2, using CH_2Cl_2/MeOH (98:2) with 1% of NEt_3 to give the product which was triturated in Et_2O/PET to afford the title product **3a** as a yellow solid (131 mg, 48%).

Mp 120-123 °C. ν_{max} (film)/cm^{-1} 3342, 3080, 1649, 1590, 1531, 1494, 1465, 1427, 1293, 1225, 1195, 1147, 1105, 996, 967, 811. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 8.76 (q, *J* = 4.9 Hz, 1H, NH_{amide}, H22), 8.52 (d, *J* = 5.6 Hz, 1H, ArCH, H7), 8.50 (d, *J* = 2.1 Hz, 1H, NH_{urea}, H21), 8.25 (t, *J* = 9.2 Hz, 1H, ArCH, H12), 7.41 (d, *J* = 2.5 Hz, 1H, ArCH, H4), 7.25 (dd, *J* = 2.5, 11.8 Hz, 1H, ArCH, H9), 7.15 (dd, *J* = 2.6, 5.6 Hz, 1H, ArCH, H6), 7.00 (dd, *J* = 2.4, 9.0 Hz, 1H, ArCH, H13), 6.75 (t, *J* = 5.6 Hz, 1H, NH_{urea}, H20), 4.20 (t, *J* = 1.7 Hz, 2H, 2 x FcCH, H17), 4.19 (s, 5H, Cp, H19), 4.12 (t, *J* = 1.7 Hz, 2H, 2 x FcCH, H18), 4.05 (d, *J* = 5.6 Hz, 2H, CH_2, H15), 2.79 (d, *J* = 4.9 Hz, 3H, CH_3, H1). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 165.6 (s, ArC, C5), 163.7 (s, C=O_{amide}, C2), 154.6 (s, C=O_{urea}, C14), 152.5 (s, ArC, C3), 151.7 (d, *J* = 244.0 Hz, ArC, C10), 150.4 (s, ArCH, C7), 146.6 (d, *J* = 10.3 Hz, ArC, C8), 126.4 (d, *J* = 10.5 Hz, ArC, C11), 121.2 (s, ArCH, C12), 116.9 (d, *J* = 2.3 Hz, ArCH, C13), 113.9 (s, ArCH, C6), 108.9 (s, ArCH, C4), 108.8 (d, *J* = 22.2 Hz, ArCH, C9), 86.5 (s, FcC, C16), 68.4 (s, Cp, C19), 67.5 (s, 2 x FcCH, C17 or C18), 67.4 (s, 2 x FcCH, C17 or C18), 38.2 (s, CH_2, C15), 26.0 (s, CH_3, C1). ^{19}F NMR (470 MHz, DMSO-d_6) δ (ppm) -126.2 (F). HRMS, *m/z* 502.1098 (0 ppm) found (calcd for $C_{25}H_{23}N_4O_3F^{56}Fe$, $[M]^{+\cdot}$, requires 502.10981); 525.0998 (0 ppm) found (calcd for $C_{25}H_{23}N_4O_3FNa^{56}Fe$, $[M+Na]^+$, requires 525.09958); 541.0729 (1 ppm) found (calcd for $C_{25}H_{23}N_4O_3FK^{56}Fe$, $[M+K]^+$, requires 541.07352).

Chloroferrocene (24)

tert-Butyllithium (1.6M, 27.5 mL, 44.0 mmol, 2.00 equiv) was added dropwise to a solution of ferrocene (4.09 g, 22.0 mmol, 1.00 equiv) and potassium *tert*-butoxide (246 mg, 2.20 mmol, 0.10 equiv) in THF (100 mL) at -78 ˚C. After addition, the reaction mixture was stirred at -78 °C for 75 min. A solution of hexachloroethane (10.4 g, 44.0 mmol, 2.00 equiv) in THF (20 mL) was added dropwise. After addition, the reaction mixture was warmed to rt and stirred ov. Water was added and the reaction mixture was diluted with heptane. The organic phase was washed with $FeCl_3$ (aqueous, 0.2 M), until all unreacted ferrocene was removed as monitored by NMR. The organic layer was washed with water until the aqueous does not turn blue, dried over $MgSO_4$, filtrated over cotton wool and concentrated under vacuum using a rotary evaporator to give the crude product. This was purified by sublimation (70 ˚C, 3 torr) to give the title product **24** as an orange solid (4.02 g, 85%). Analytical data analogous to those reported previously.[11]

Mp 60-62 °C. ν_{max} (film)/cm^{-1} 3092, 1410, 1358, 1345, 1166, 1104, 1018, 999, 880, 811. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.41 (t, *J* = 1.5 Hz, 2H, 2 x FcCH, H2), 4.26 (s, 5H, Cp, H4), 4.07 (t, *J* = 1.5 H, 2H, 2 x FcCH, H3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 92.4 (FcC, C1), 70.4 (Cp, C4), 68.0 (2 x FcCH, C2), 66.1 (2 x FcCH, C3).

2-Chloroferrocenecarboxylic acid (25)

sec-Butyllithium (1.2M, 13.5 mL, 16.3 mmol, 1.20 equiv) was added dropwise to a solution of compound **24** (3.01 g, 13.6 mmol, 1.00 equiv) in THF (125 mL) at -78 °C. After addition, the reaction mixture was stirred at -78 °C for 2h. Dry carbon dioxide was bubbled through the mixture for 1 hour at -78 ˚C. The reaction mixture was warmed to rt and volatiles were removed under vacuum using a rotary

evaporator to give the crude carboxylate. This was extracted with NaOH (aqueous, 2M). The aqueous phase was acidified with sulfuric acid (95%) until pH 1 was reached. The precipitate was extracted with EtOAc. The organic layer was with brine, dried over $MgSO_4$, filtrated over cotton wool and concentrated under vacuum using a rotary evaporator to give the crude product. This was purified by column chromatography over SiO_2, using CH_2Cl_2/MeOH/AcOH (94:4:2) to give the title product **25** as a yellow solid (2.82 g, 78%).
Mp 178-180 °C. ν_{max} (film)/cm^{-1} 3107, 2263, 2134, 1690, 1674, 1546, 1431, 1395, 1264, 1249, 1180, 1103, 1044, 1002, 908, 823, 739. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 11.95 (br s, 1H, CO_2H, H8), 4.82 (s, 1H, FcCH, H3 or H5), 4.72 (s, 1H, FcCH, H3 or H5), 4.38 (s, FcCH, H4), 4.34 (s, 5H, Cp, H6). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 176.8 (CO_2H, C7), 93.8 (FcC, C2), 73.1 (FcCH, C3 or C5), 72.6 (Cp, C6), 69.8 (FcCH, C3 or C5), 68.8 (FcCH, C4), 66.6 (FcC, C1).

2-Chloroferrocene acyl azide (26)

Diphenylphosphoryl azide (2.1 mL, 9.44 mmol, 1.10 equiv) was added dropwise to a solution of compound **25** (2.27 g, 8.58 mmol, 1.00 equiv) and *N*,*N*-diisopropylethylamine (1.8 mL, 10.3 mmol, 1.20 equiv) in CH_2Cl_2 (20 mL) at 0 °C. After addition, the reaction mixture was warmed to rt and stirred for 18h. Silica was added to the reaction mixture and volatiles were removed under vacuum using a rotary evaporator to give the crude product. This was purified by column chromatography over SiO_2, using PET/EtOAc (95:5) to give the title product **26** as a red solid (2.01 g, 81%).
Alternatively, compound **26** can be prepared by following this procedure. Diphenylphosphoryl azide (118 µL, 0.55 mmol, 1.10 equiv) was added dropwise to a solution of compound **25** (132 mg, 0.50 mmol, 1.00 equiv) and triethylamine (278 µL, 2.00 mmol, 4.00 equiv) in CH_2Cl_2 (2 mL) at 40 °C. After addition, the reaction mixture was stirred at 40 °C for 15 min. The reaction mixture was cooled to rt and was poured onto HCl (1 M). The reaction mixture was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtrated over cotton wool and concentrated under vacuum using a rotary evaporator to give the crude product. This was purified by column chromatography over SiO_2, using pentane/Et_2O (90:10) to give the title product **26** as a red solid (119 mg, 82%).
Mp 50-52 °C. ν_{max} (film)/cm^{-1} 3118, 2379, 2267, 2144, 1689, 1651, 1567, 1431, 1410, 1390, 1375, 1341, 1284, 1196, 1118, 1101, 1043, 1002, 909, 819, 737. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 4.74 (dd, *J* = 1.6, 2.5 Hz, 1H, FcH, H3 or H5), 4.71 (dd, *J* = 1.6, 2.9 Hz, 1H, FcH, H3 or H5), 4.38 (t, *J* = 2.7 Hz, 1H, FcCH, H4), 4.37 (s, 5H, Cp, H6). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ (ppm) 175.8 (CON_3, C7), 93.6 (FcC, C2), 73.6 (FcCH, C3 or C5), 72.6 (Cp, C6), 69.5 (FcCH, C3 or C5), 69.2 (FcCH, C4), 68.7 (FcC, C1).

1-(*tert*-Butoxycarbonyl)amino-2-chloroferrocene (27)

A degassed solution of compound **26** (1.08 g, 5.80 mmol, 1.00 equiv) and *tert*-butanol (21.4 g, 290 mmol, 50.0 equiv) in toluene (6 mL) was heated at 95 °C for 16h. The reaction mixture was cooled to rt and volatiles were removed under vacuum using a rotary evaporator to give the crude product. This was purified by column chromatography over SiO_2, using PET/EtOAc (95:5) to give the title product **27** as a yellow solid (1.77 g, 91%).
Mp 136-137 °C. ν_{max} (film)/cm^{-1} 3426, 3220, 3050, 2978, 1699, 1534, 1454, 1391, 1366, 1227, 1155, 1105, 1089, 1049, 1019, 1000, 965, 910, 893, 818, 759, 730, 692. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 8.31 (br s, 1H, NH, H10), 4.41 (br s, 1H, FcCH, H5), 4.37 (s, 1H, FcCH, H3), 4.24 (s, 5H, Cp, H6), 3.98 (s, 1H, FcCH, H4), 1.42 (s, 9H, 3 x CH_3, H9). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 154.1 (C=O, C7), 91.4 (FcC, C1), 87.1 (FcC, C2), 78.8 (C, C8), 71.1 (Cp, C6), 64.1 (FcCH, C3), 63.0 (FcCH, C5), 61.6 (FcCH, C4), 28.1 (3 x CH_3, C9).

4-(4-(3-(2-Chloroferrocenyl)ureido)-3-fluorophenoxy)-*N*-methylpicolinamide (2aCl)

A solution of HCl in Et_2O (5.5 M, 8.00 mL, 44.1 mmol, 45.0 equiv) was added to a solution of compound **27** (392 mg, 1.17 mmol, 1.20 equiv) in CH_2Cl_2 (30 mL). After addition, the reaction mixture was stirred at rt for 48h. Volatiles were removed under vacuum to give the crude hygroscopic ammonium. It was dissolved in CH_2Cl_2 (4 mL) and *N*,*N*-diisopropylethylamine (0.81 mL, 8.33 mmol, 8.50 equiv) followed by a solution of triphosgene (380 mg, 1.28 mmol, 1.30 equiv) in CH_2Cl_2 (3 mL) were added. After addition, the reaction mixture was stirred at rt for 6h. Compound **6** (240 mg, 0.98 mmol, 1.00 equiv) was added in one portion and the reaction mixture was stirred at rt for 72h. Volatiles were removed under vacuum using a rotary evaporator to give the crude product. This was purified by column chromatography over SiO_2, using CH_2Cl_2/MeOH/NEt_3 (98:1:1) to give the title product **2aCl** as a pale yellow solid after trituration in a Et_2O/pentane mixture (156 mg, 33%).
Mp 122-123˚C (decomp.). ν_{max} (film)/cm^{-1} 3328, 3005, 2989, 1656, 1591, 1542, 1499, 1429, 1394, 1339, 1276, 1261, 1227, 1198, 1149, 1106, 1066, 996, 967, 897, 822, 764, 750, 706. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 8.95 (s, 1H, NH_{urea}, H22), 8.77 (d, *J* = 4.3 Hz, 1H, NH_{amide}, H23), 8.52 (d, *J* = 5.3 Hz, 1H, ArCH, H7), 8.30 (t, *J* = 9.1 Hz, 1H, ArCH, H12), 8.27 (s, 1H, NH_{urea}, H21), 7.43 (s, 1H, ArCH, H4), 7.31 (dd, *J* = 2.2, 11.7 Hz, 1H, ArCH, H9), 7.16 (m, 1H, ArCH, H6), 7.00 (d, *J* = 8.9 Hz, 1H, ArCH, H13), 4.84 (dd, *J* = 1.6, 2.4 Hz, 1H, FcCH, H19), 4.39 (dd, *J* = 1.6, 2.4 Hz, 1H, FcCH, H17) 4.21 (s, 5H, Cp, H20), 4.00 (t, *J* = 2.4 Hz, 1H, FcCH, H18), 2.80 (d, *J* = 4.4 Hz, 3H, CH_3, H1). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 165.5 (s, ArC, C5), 163.7 (s, $C{=}O_{amide}$, C2), 152.5 (s, ArC, C3), 152.4 (s, $C{=}O_{urea}$, C14), 151.8 (d, *J* = 245.1 Hz, ArC, C10), 150.4 (s, ArCH, C7), 147.1 (d, *J* = 10.2 Hz, ArC, C8), 125.7 (d, *J* = 10.6 Hz, ArC, C11), 121.0 (s, ArCH, C12), 117.0 (s, ArCH, C13), 113.9 (s, ArCH, C6), 108.9 (d, *J* = 20.8 Hz, ArCH, C9), 108.8 (s, ArCH, C4), 92.8 (s, FcC, C15), 84.7 (s, FcC, C16), 70.9 (s, Cp, C20), 63.2 (s, FcCH, C17), 61.3 (s, FcCH, C18), 60.5 (s, FcCH, C19), 25.9 (s, CH_3, C1).
^{19}F NMR (282 MHz, DMSO-d_6) δ (ppm) -125.9 (F). HRMS, *m/z* 545.0454 (1 ppm) found (calcd for $C_{24}H_{20}N_4O_3F^{35}ClNa^{56}Fe$, $[M+Na]^+$, requires 545.04496); 522.0556 (1 ppm) found (calcd for $C_{24}H_{20}N_4O_3F^{35}Cl^{56}Fe$, $[M]^{+\cdot}$, requires 522.05519); 561.0188 (0 ppm) found (calcd for $C_{24}H_{20}N_4O_3F^{35}ClK^{56}Fe$, $[M+K]^+$, requires 561.01889).

Ethyl 2-(aminoferrocenyl)-2-oxoacetate (31)

Ethyl chlorooxoacetate (353 mg, 2.60 mmol, 1.30 mmol) and *N*,*N*-diisopropylethylamine (400 µL, 2.30 mmol, 1.15 equiv) were added dropwise to a solution of compound **23** (400 mg, 2.00 mmol, 1.00 equiv) in THF (20 mL) at 0 °C. After the addition, the reaction mixture was stirred at rt for 5 min before being poured into water. The aqueous phase was extracted with Et_2O. The combined organic layers were washed with water, brine, dried over $MgSO_4$, filtrated over cotton wool and concentrated under vacuum using a rotary evaporator to give the crude product. This was purified by column chromatography over SiO_2, using PET/EtOAc (80:20) to give the title product **31** as a yellow solid (327 mg, 55%).
Mp 112-114 °C. ν_{max} (film)/cm^{-1} 3672, 2988, 1650, 1394, 1250, 1066, 891.
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.25 (br s, 1H, NH, H9), 4.71 (s, 2H, 2 x FcCH, H2), 4.39 (q, *J* = 7.2 Hz, 2H, CH_2, H7), 4.18 (s, 5H, Cp, H4), 4.07 (s, 2H, 2 x FcCH, H3), 1.43 (t, *J* = 7.2 Hz, 3H, CH_3, H8). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ (ppm) 160.8 ($C{=}O_{ester}$, C6), 154.2 ($C{=}O_{amide}$, C5), 92.6 (FcC, C1), 69.5 (Cp, C4), 65.3 (2 x FcCH, C3), 63.6 (CH2, C7), 91.7 (2 x FcCH, C2), 14.1 (CH_3, C8).
Crystal data for 31. $C_{14}H_{15}FeNO_3$, *M* = 301.12, *T* = 150 K; monoclinic *P* $2_1/c$ (I.T.#14), *a* = 12.9052(17), *b* = 10.4423(13), *c* = 10.2490(14) Å, *β* = 108.342(5) °, *V* = 1311.0(3) $Å^3$. *Z* = 4, *d* = 1.526

g.cm^{-3}, μ = 1.153 mm^{-1}. A final refinement on F^2 with 2963 unique intensities and 176 parameters converged at ωR_F^2 = 0.1077 (R_F = 0.0419) for 2471 observed reflections with $I > 2\sigma(I)$. CCDC 2017026.

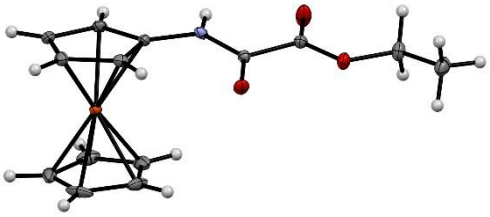


Figure 6. Molecular structure of compound **31** (thermal ellipsoids shown at the 30% probability level).

Ethyl 2-(aminomethylferrocenyl)-2-oxoacetate (32)

Ethyl chlorooxoacetate (290 µL, 2.6 mmol, 1.30 equiv) and *N*,*N*-diisopropylethylamine (1.39 mL, 8.0 mmol, 4.00 equiv) were added dropwise to a solution of compound **22.HCl** (503 mg, 2.0 mmol, 1.00 equi) in THF (20 mL) and CH_2Cl_2 (0.2 mL) at 0 °C. After the addition, the reaction mixture was stirred at rt for 15 min before being poured into water. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with water, brine, dried over $MgSO_4$, filtrated over cotton wool and concentrated under vacuum using a rotary evaporator to give the crude product. This was purified by column chromatography over SiO_2, using PET/EtOAc (90:10 to 70:30) to give the title product **32** as a yellow solid (458 mg, 73%).
Mp 128-130 °C. ν_{max} (film)/cm^{-1} 3253, 2983, 1733, 1672, 1524, 1463, 1433, 1372, 1343, 1303, 1257, 1210, 1198, 1105, 1020, 1003, 823, 806, 765. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.34 (br s, 1H, NH, H10), 4.36 (q, *J* = 7.2 Hz, 2H, CH_2, H8), 4.19-4.20 (m, 8H, Cp + 2 x FcCH + C*H*H, 4 + H2 or H3 + H5), 4.16-4.18 (m, 3H, 2 x FcCH + CH*H*, H2 or H3 + H5), 1.39 (t, *J* = 7.2 Hz, 3H, CH_3, H9). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 160.8 ($C{=}O_{ester}$, C7), 156.0 ($C{=}O_{amide}$, C6), 83.8 (FcC, C1), 68.7 (Cp, C4), 68.5 (2 x FcCH, C2 or C3), 68.4 (2 x FcCH, C2 or C3), 63.4 (CH_2, C8), 39.2 (CH2, C5), 14.1 (CH_3, C9).

2-(Ferrocenylamino)-2-oxoacetic acid (33)

An aqueous solution of potassium hydroxide (2M, 1.70 mL, 3.40 mmol, 5.80 mmol) was added to a solution of compound **31** (172 mg, 0.59 mmol, 1.00 equiv) in THF (2 mL) at rt. After addtition, the reaction mixture was stirred at rt for 6h. Hydrochloric acid (1M) was added until neutral pH was reached. The reaction mixture was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtrated over cotton wool and concentrated under vacuum using a rotary evaporator to give the title product **33** as a tan solid (151 mg, 93%).
Mp 182-185 °C. ν_{max} (film)/cm^{-1} 3457, 3389, 3352, 2983, 1669, 1582, 1563, 1507, 1469, 1410, 1340, 1291, 1261, 1230, 1139, 1040, 998, 958, 892, 810. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 10.24 (br s, 1H, NH, H7), 4.78 (t, *J* = 1.6 Hz, 2H, 2 x FcCH, H2), 4.11 (s, 5H, Cp, H4), 4.02 (t, *J* = 1.6 Hz, 2H, 2 x FcCH, H3). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 161.8 ($C{=}O_{acide}$, C6), 156.4 ($C{=}O_{amide}$, C5), 93.8 (FcC, C1), 68.9 (Cp, C4), 64.4 (2 x FcCH, C3), 61.4 (2 x FcCH, C2).

2-(Aminomethylferrocenyl)-2-oxoacetic acid (34)

An aqueous solution of potassium hydroxide (1M, 3 mL, 3.00 mmol, 2.70 equiv) was added to a solution of compound **32** (348 mg, 1.1 mmol, 1.00 equiv) in THF (5 mL) at rt. After addition, the reaction mixture was stirred at rt for 6h. Hydrochloric acid (1M) was added until neutral pH was reached. The reaction mixture was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtrated over

cotton wool and concentrated under vacuum using a rotary evaporator to give the title product **34** as a yellow solid (315 mg, quant.).
Mp 89-91 °C. ν_{max} (film)/cm^{-1} 3398, 3091, 2926, 1679, 1547, 1516, 1448, 1400, 1380, 1330, 1265, 1234, 1154, 1105, 1039, 1025, 1001, 898, 865, 813, 733, 701. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 8.97 (t, *J* = 6.0 Hz, 1H, NH, H8), 4.19 (t, *J* = 1.8 Hz, 2H, 2 x FcCH, H2), 4.17 (s, 5H, Cp, H4), 4.09 (t, *J* = 1.8 Hz, 2H, 2 x FcCH, H3), 4.03 (d, *J* = 6.2 Hz, 2H, CH_2, H5). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 162.3 (C=O_{acide}, C7), 157.9 (C=O_{amide}, C6), 85.1 (FcC, C1), 68.3 (Cp, C4), 68.2 (2 x FcCH, C2), 67.4 (2 x FcCH, C3), 37.8 (CH_2, C5).

<u>*N*^{1}-Ferrocenyl-*N*^{2}-(2-fluoro-4-((2-(methylcarbamoyl)pyridin-4-yl)oxy)phenyl)oxalamide (2c)</u>

N,*N*-Diisopropylethylamine (108 µL, 622 µmol, 2.50 equiv) was added to a solution of compound **33** (62.0 mg, 227 µmol, 1.00 equiv) and HBTU (94.8 mg, 250 µmol, 1.10 equiv) in CH_2Cl_2 (0.6 mL) at rt and the reaction mixture was stirred for 15 min. Compound **6** (60.0 mg, 227 µmol, 1.00 equiv) was added to the reaction mixture which was stirred for 48h at rt. Volatiles were removed under vacuum using a rotary evaporator to give the crude product. This was further purified by column chromatography over SiO_2, using CH_2Cl_2/MeOH (99.1:0.1 to 98:2) to give the title **2c** as a yellow solid (60.2 mg, 51%).
Mp 235-237 °C. ν_{max} (film)/cm^{-1} 3193, 2988, 1792, 1701, 1580, 1537, 1507, 1484, 1448, 1402, 1327, 1274, 1259, 1215, 1178, 1136, 1116, 1033, 971, 764, 749. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 10.50 (br s, 1H, $NH_{oxamide}$, H20), 10.45 (br s, 1H, $NH_{oxamide}$, H21), 8.79 (q, *J* = 4.6 Hz, 1H, NH_{amide}, H22), 8.56 (d, *J* = 5.5 Hz, 1H, ArCH, H7), 7.84 (t, *J* = 8.6 Hz, 1H, ArCH, H12), 7.45 (d, *J* = 2.3 Hz, 1H, ArCH, H4), 7.40 (dd, *J* = 2.2, 10.9 Hz, 1H, H9), 7.23 (dd, *J* = 2.4, 5.6 Hz, 1H, ArCH, H6), 7.16 (dd, *J* = 1.7, 8.7 Hz, 1H, ArCH, H13), 4.89 (s, 2H, 2 x FcCH, H17), 4.15 (s, 5H, Cp, H19), 4.06 (s, 2H, 2 x FcCH, H18), 2.80 (d, *J* = 4.8 Hz, 3H, CH_3, H1). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 165.0 (s, ArC, C5), 163.6 (s, C=O_{amide}, C2), 158.4 (s, C=$O_{oxamide}$, C14 or C15), 157.6 (s, C=$O_{oxamide}$, C14 or C15), 155.4 (d, *J* = 250.5 Hz, ArC, C10), 152.6 (s, ArC, C3), 151.3 (d, *J* = 10.2 Hz, ArC, C8), 150.6 (s, ArCH, C7), 126.7 (s, ArCH, C12), 122.3 (d, *J* = 11.8 Hz, ArC, C11), 116.9 (s, ArCH, C13), 114.5 (s, ArCH, C6), 109.4 (d, *J* = 22.4 Hz, ArCH, C9), 109.2 (s, ArCH, C4), 93.6 (s, FcC, C16), 68.9 (s, Cp, C19), 64.5 (s, 2 x FcCH, C18), 61.5 (s, 2 x FcCH, C17), 26.0 (s, CH_3, C1). ^{19}F NMR (282 MHz, DMSO-d_6) δ (ppm) -117.8 (F). HRMS, *m/z* 516.0894 (1 ppm) found (calcd for $C_{25}H_{21}N_4O_4F^{56}Fe$, $[M]^{+\cdot}$, requires 516.08907); 539.0789 (0 ppm) found (calcd for $C_{25}H_{21}N_4O_4FNa^{56}Fe$, $[M+Na]^+$, requires 539.07884); 555.0520 (1 ppm) found (calcd for $C_{25}H_{21}N_4O_4FK^{56}Fe$, $[M+K]^+$, requires 555.05278).

<u>*N*^{1}-(2-Fluoro-4-((2-(methylcarbamoyl)pyridin-4-yl)oxy)phenyl)-*N*^{2}-(methylferrocenyl)oxalamide (3c)</u>

N,*N*-Diisopropylethylamine (236 µL, 1.36 mmol, 3.00 equiv) was added to a solution of compound **34** (156 mg, 0.54 mmol, 1.20 equiv) and HBTU (215 mg, 566 µmol, 1.25 equiv) in CH_2Cl_2 (1 mL) at rt and the reaction mixture was stirred for 2h. Compound **6** (118 mg, 452 µmol, 1.00 equiv) was added to the reaction mixture which was stirred for 18h at rt. Volatiles were removed under vacuum using a rotary evaporator to give the crude product. This was further purified by column chromatography over SiO_2, using CH_2Cl_2/MeOH (99.1:0.1 to 98:2) to give a material triturated in an EtOAc/Et_2O mixture to give the title product **3c** (38.1 mg, 16%) as a yellow solid.
Mp 178-180 °C. ν_{max} (film)/cm^{-1} 3193, 2988, 1792, 1701, 1580, 1537, 1507, 1484, 1448, 1402, 1327, 1274, 1259, 1215, 1178, 1136, 1116, 1033, 971, 764, 749. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 9.51 (br s, 1H, $NH_{oxamide}$, H22), 8.41 (d, *J* = 5.5 Hz, 1H, ArCH, H7), 8.39 (d, *J* = 8.8 Hz, 1H, ArCH, H12), 7.99 (q, *J* = 3.8 Hz, 1H, NH_{amide}, H23), 7.76 (t, *J* = 4.9 Hz, 1H, $NH_{oxamide}$, H21), 7.73 (d, *J* = 2.1 Hz, 1H,

ArCH, H4), 6.98 (dd, *J* = 2.1, 5.2 Hz, 1H, ArCH, H6), 6.95 (s, 1H, ArCH, H9), 6.93 (s, 1H, ArCH, H13), 4.23 (s, 9H, CH_2 and 2 x FcCH and Cp, H16 and H18 or H19 and H20), 4.19 (s, 2H, 2 x FcCH, H18 or H19), 3.01 (d, *J* = 5.0 Hz, 3H, CH_3, H1). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 165.0 (s, ArC, C5), 164.4 (s, C=O_{amide}, C2), 158.7 (s, C=$O_{oxamide}$, C14), 157.8 (s, C=$O_{oxamide}$, C15), 153.4 (d, *J* = 249.7 Hz, ArC, C10), 152.7 (s, ArC, C3), 150.9 (d, *J* = 10.1 Hz, ArC, C8), 150.0 (s, ArCH, C7), 122.8 (d *J* = 10.6 Hz, ArC, C11), 112.6 (s, ArCH, C12), 116.9 (d J = 3.3 Hz, ArCH, C13), 114.5 (s, ArCH, C6), 110.6 (s, ArCH, C4), 108.9 (d, *J* = 21.6 Hz, ArCH, C9), 83.8 (s, FcC, C17), 68.8 (s, Cp, C20), 68.6 (s, 2 x FcCH, C18 or C19), 68.3 (s, 2 x FcCH, C18 or C19), 39.4 (s, CH_2, C16), 26.3 (s, CH_3, C1). ^{19}F NMR (282 MHz, DMSO-d_6) δ (ppm) -117.8 (F). HRMS, *m/z* 530.1053 (1 ppm) found (calcd for $C_{26}H_{23}N_4O_4F^{56}Fe$, $[M]^{+\cdot}$, requires 530.10472); 553.0950 (1 ppm) found (calcd for $C_{26}H_{23}N_4O_4FNa^{56}Fe$, $[M+Na]^+$, requires 553.09449); 569.0681 (1 ppm) found (calcd for $C_{26}H_{23}N_4O_4FK^{56}Fe$, $[M+K]^+$, requires 569.06843).

4-Chloro-*N*-ferrocenylpicolinamide (35)

A solution of compound **11** (1.04 g, 4.93 mmol, 1.30 equiv) in CH_2Cl_2 (35 mL) was added dropwise to a solution of compound **23** (768 mg, 3.79 mmol, 1.00 equiv) and *N*,*N*-diisopropylethylamine (994 µL, 3.79 mmol, 1.00 equiv) in CH_2Cl_2 (35 mL) at 0 °C. After addition, the reaction mixture was stirred at the same temperature for 20 min. Ethanol was added and volatiles were removed under vacuum using a rotary evaporator to give the crude product. It was dissolved in EtOAc and the organic phase was washed with water, NaOH (2M), saturated sodium bicarbonate, brine, dried over $MgSO_4$, filtrated over cotton wool and concentrated under vacuum using a rotary evaporator to give the crude product. This was purified by column chromatography over SiO_2, using PET/EtOAc (95:5) followed by CH_2Cl_2/PET/NEt_3 (50:48:2) to give the title product **35** (564 mg, 42%) as a red solid.
Mp 196-200 °C. ν_{max} (film)/cm^{-1} 3193, 2988, 1792, 1701, 1580, 1537, 1507, 1484, 1448, 1402, 1327, 1274, 1259, 1215, 1178, 1136, 1116, 1033, 971, 764, 749. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.17 (br s, 1H, NH, H11), 8.49 (d, *J* = 5.3 Hz, 1H, ArCH, H10), 8.25 (d, *J* = 2.0 Hz, 1H, ArCH, H7), 7.47 (dd, *J* = 2.0, 5.3 Hz, 1H, ArCH, H9), 4.8 (t, *J* = 1.7 Hz, 2H, 2 x FcCH, H2), 4.18 (s, 5H, Cp, C4), 4.08 (t, *J* = 1.7 Hz, 2H, 2 x FcCH, H3). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ (ppm) 161.1 (C=O, C5), 151.3 (ArC, C6), 149.0 (ArCH, C10), 146.6 (ArC, C8), 126.5 (ArCH, C9), 122.8 (ArCH, C7), 94.2 (FcC, C1), 69.4 (Cp, C4), 65.1 (2 x FcCH, C3), 61.6 (2 x FcCH, C2).
Crystal data for 35. $C_{16}H_{13}ClFeN_2O$, *M* = 340.58, *T* = 150 K; orthorhombic *P n a 2₁* (I.T.#33), *a* = 13.2083(11), *b* = 9.7083(8), *c* = 10.6102(7) Å, *V* = 1360.55(18) Å^3. *Z* = 4, *d* = 1.663 g.cm^{-3}, μ = 1.303 mm^{-1}. A final refinement on F^2 with 2980 unique intensities and 193 parameters converged at ωR_F^2 = 0.0633 (R_F = 0.0236) for 2882 observed reflections with $I > 2\sigma(I)$. CCDC 2017027.

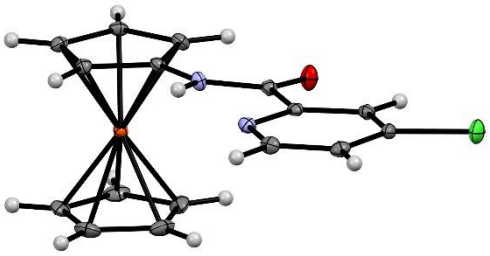


Figure 7. Molecular structure of compound **35** (thermal ellipsoids shown at the 30% probability level).

4-Chloro-*N*-(ferrocenylmethyl)picolinamide (36)

N,*N*-Diisopropylethylamine (2.00 mL, 11.5 mmol, 3.75 equiv) was added to a solution of **22.HCl** (770 mg, 3.08 mmol, 1.00 equiv) and compound **11** (851 mg, 4.00 mmol, 1.30 equiv) CH_2Cl_2 (20 mL) at 0

˚C. After addition, the reaction mixture was warmed to rt and stirred for 2h. Volatiles were removed under vacuum using a rotary evaporator to give the crude product. It was dissolved in EtOAc and the organic phase was washed with NaOH (40%), water, brine, dried over $MgSO_4$, filtrated over cotton wool and concentrated under vacuum using a rotary evaporator to give the crude product. This was purified by column chromatography over SiO_2, using PET/EtOAc (95:5) to give the title product **36** (609 mg, 56%) as a red solid.

Mp 126-128 °C. ν_{max} (film)/cm^{-1} 3372, 3090, 1673, 1555, 1511, 1455, 1329, 1001, 902, 839, 813, 781, 753. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 8.96 (t, *J* = 5.7 Hz, 1H, NH, H12), 8.64 (d, *J* = 5.3 Hz, 1H, ArCH, H11), 8.06 (d, *J* = 1.8 Hz, 1H, ArCH, H8), 7.76 (dd, *J* = 1.8, 5.3 Hz, 1H, ArCH, H10), 4.25 (s, 2H, 2 x FcCH, H2), 4.21-4.19 (m, 7H, CH_2 + Cp, H4 + H5), 4.09 (s, 2H, 2 x FcCH, H3). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 162.0 (C=O, C6), 151.7 (ArC, C7), 150.0 (ArCH, C11), 144.6 (ArC, C9), 126.4 (ArCH, C10), 121.9 (ArCH, C8), 85.7 (FcC, C1), 68.3 (Cp, C4), 68.2 (2 x FcCH, C2), 67.4 (2 x FcCH, C3), 37.8 (CH_2, C5).

4-Amino-3-fluorophenol (37)

A mixture of 3-fluoro-4-nitrophenol (1.57 g, 10.0 mmol, 1.00 equiv) and Pd/C (10%, 106 mg) in EtOH (50.0 mL) was vigorously stirred overnight under an atmosphere of hydrogen at rt. The reaction mixture was filtrated over celite® which was washed with EtOAc. The combined filtrates were concentrated under vacuum using a rotary evaporator to give the crude product as a grey solid, pure enough to the used in the next step (1.13 g, 89%).

Mp 139-140 °C. ν_{max} (film)/cm^{-1} 3381, 3295, 2936, 2806, 2611, 1610, 1508, 1360, 1297, 1259, 1214, 1138, 1077, 959, 897, 835, 768, 726. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.79 (br s, 1H, OH), 6.61 (dd, *J* = 8.5, 10.5 Hz, 1H, ArCH), 6.45 (dd, *J* = 2.6, 12.8 Hz, 1H, ArCH), 6.36 (dd, *J* = 0.9, 8.5 Hz, 1H, ArCH), 4.37 (br s, 2H, NH_2). ^{13}C NMR (75.0 MHz, $CDCl_3$) δ (ppm) 151.0 (d, *J* = 236.9 Hz, ArC), 148.6 (d, *J* = 10.0 Hz, ArC), 127.9 (d, *J* = 13.2 Hz, ArC), 117.2 (d, *J* = 5.8 Hz, ArCH), 111.1 (d, *J* = 2.6 Hz, ArCH), 102.9 (d, *J* = 21.0 Hz, ArCH).

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(2-fluoro-4-hydroxyphenyl)urea (38a)

A solution of compound **15** (1.00 g, 5.10 mmol, 1.00 equiv) in CH_2Cl_2 (5 mL) was added to a solution of triphosgene (1.82 g, 6.12 mmol, 1.20 equiv) in CH_2Cl_2 (5 mL). A solution of *N*,*N*-diisopropylethylamine (2.67 mL, 15.3 mmol, 3.00 equiv) in CH_2Cl_2 (5 mL) was added dropwise at 0 °C. After addition, the reaction mixture was warmed to rt and stirred for 1h. Compound **37** (650 mg, 5.10 mmol, 1.00 equiv) was added in one portion and the reaction mixture was stirred at rt for 16h. Volatiles were removed under vacuum using a rotary evaporator to give the crude product. This was purified by column chromatography over SiO_2, using PET/EtOAc (80:20). This was further purified by column chromatography over SiO_2, using CH_2Cl_2/MeOH (97:3) to give the title product **38a** as a light brown solid (401 mg, 22% yield). Analytical data analogous to those reported previously.[12, 13]

Mp 229-231 °C. ν_{max} (film)/cm^{-1} 3294, 1674, 1595, 1559, 1518, 1460, 1322, 1178, 1142, 1122, 110, 1032, 966, 814. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 9.64 (s, 1H, OH, H17), 9.30 (s, 1H, NH, H15), 8.24 (s, 1H, NH, H16), 8.09 (d, *J* = 2.0 Hz, 1H, ArCH, H9), 7.62 (d, *J* = 9.1 Hz, 1H, ArCH, H5), 7.57-7.59 (m, 2H, 2 x ArCH, H12 and H13), 6.63 (dd, *J* = 2.6, 12.5 Hz, 1H, ArCH, H2), 6.57 (dd, *J* = 2.4, 8.7 Hz, 1H, ArCH, H6). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 154.5 (d, *J* = 10.9 Hz, ArC, C1), 154.4 (d, *J* = 242.5 Hz, ArC, C3), 152.6 (s, C=O, C7), 139.4 (s, ArC, C11), 131.9 (s, ArCH, C12), 126.7 (q, *J* = 30.6 Hz, ArC, C10), 124.5 (d, *J* = 2.5 Hz, ArCH, C5), 122.8 (q, *J* = 273.0 Hz, CF_3, C14), 122.7 (s, ArCH, C13), 122.1 (s, ArC, C8), 117.6 (d, *J* = 11.8 Hz, ArC, C4), 116.5 (q, *J* = 5.7 Hz, ArCH, C9),

110.9 (d, *J* = 2.2 Hz, ArCH, C6), 102.6 (d, *J* = 21.9 Hz, ArCH, H2). ^{19}F NMR (470 MHz, DMSO-d_6) δ (ppm) -61.5 (CF_3), -125.3 (F). HRMS, *m/z* 371.0180 (0 ppm) found (calcd for $C_{14}H_9N_2O_2F_4{}^{35}ClNa$, $[M+Na]^+$, requires 371.01809).

3-((4-Chloro-3-(trifluoromethyl)phenyl)amino)-4-((2-fluoro-4-hydroxyphenyl)amino)cyclobut-3-ene-1,2-dione (38b)

Compound **37** (462 mg, 3.62 mmol, 1.20 equiv) was added to a solution of compound **18** (924 mg, 3.02 mmol, 1.00 equiv) in methanol (3 mL) and the reaction mixture was stirred at rt for 48h and then at 60 °C for 3h. The reaction mixture was cooled to rt and volatiles were removed under vacuum using a rotary evaporator to give the crude product. This was purified by column chromatography over SiO_2, using PET/EtOAc (50:50) to EtOAc/MeOH (98:2) to CH_2Cl_2/MeOH (90:10) to give a material which was triturated in a Et_2O/pentane (50:50) mixture to give the title product **38b** (722 mg, 60%) as a white solid.

Mp 170-172 °C. ν_{max} (film)/cm^{-1} 3196, 1794, 1692, 1607, 1582, 1551, 1522, 1482, 1448, 1325, 1303, 1260, 1236, 1170, 1144, 1129, 1108, 1098, 1031, 967, 883, 853, 840. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 10.3 (br s, 1H, NH, H18 or H19), 9.83 (br s, 1H, OH, H20), 9.61 (br s, 1H, NH, H18 or H19), 7.97 (s, 1H, ArCH, H12), 7.64-7.59 (m, 2H, 2 x ArCH, H15 and H16), 7.53 (t, *J* = 9.5 Hz, 1H, ArCH, H5), 6.66 (dd, *J* = 2.4, 12.7 Hz, 1H, ArCH, H2), 6.59 (dd, *J* = 2.1, 8.8 Hz, 1H, ArCH, H6). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 182.1 (s, C=O, C8 or C9), 181.5 (s, C=O, C8 or C9), 166.2 (s, C=C, C7 or C10), 164.4 (s, C=C, C7 or C10), 155.4 (d, *J* = 10.6 Hz, ArC, C1), 153.7 (d, *J* = 243.5 Hz, ArC, C3), 138.3 (s, ArC, C14), 132.5 (s, ArCH, C15), 127.4 (q, *J* = 31.2 Hz, ArC, C13), 123.7 (s, ArC, C11), 123.4 (s, ArCH, C16), 123.0 (s, ArCH, C5), 122.6 (q, *J* = 273.5 Hz, CF_3, C17), 117.5 (s, ArC, C4), 117.4 (q, *J* = 5.6 Hz, ArCH, C12), 111.4 (d, *J* = 1.5 Hz, ArCH, C6), 102.9 (d, *J* = 21.5 Hz, ArCH, C2). ^{19}F NMR (470 MHz, DMSO-d_6) δ (ppm) -61.6 (CF_3), -125.5 (F). HRMS, *m/z* 423.0130 (0 ppm) found (calcd for $C_{17}H_9N_2O_3F_4{}^{35}ClNa$, $[M+Na]^+$, requires 423.0130).

4-(4-Amino-3-fluorophenoxy)-*N*-ferrocenylpicolinamide (39)

A solution of potassium *tert*-butoxide (210 mg, 1.71 mmol, 1.40 equiv) in THF (1.3 mL) was added to a solution of compound **37** (248 mg, 1.71 mmol, 1.40 equiv) in NMP (4 mL) at 0 °C. The reaction mixture was warmed to rt and stirred for 2h. A solution of compound **35** (436 mg, 1.22 mmol, 1.00 equiv) in THF (10 mL) was added. A distillation head was added and the reaction mixture was heated at 120 °C. After all the THF was distilled, the distillation head was removed and the reaction mixture was heated at 120 °C for 16h. The reaction mixture was cooled to rt, silica was added and volatiles were removed under vacuum using a rotary evaporator to give the crude product. This was purified by column chromatography over SiO_2, using PET/EtOAc (70:30 to 50:50) to CH_2Cl_2/ EtOAc (95:5) to give the title product **39** (279 mg, 52%) as a yellow solid.

Mp 166-168 °C. ν_{max} (film)/cm^{-1} 3454, 3347, 2976, 1666, 1589, 1506, 1471, 1411, 1291, 1226, 1105, 1066, 997, 968. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 10.08 (br s, 1H, NH, H18), 8.54 (d, J = 5.6 Hz, 1H, ArCH), 7.43 (d, *J* = 2.1 Hz, 1H, ArCH, H7), 7.15 (dd, *J* = 2.3, 5.2 Hz, 1H, ArCH, H9), 7.04 (dd, *J* = 1.9, 11.6 Hz, 1H, ArCH, H12), 6.88 (m, 1H, ArCH, H15), 6.81 (dd, *J* = 2.0, 8.7 Hz, 1H, ArCH H16), 5.24 (s, 2H, NH_2, H17), 4.92 (s, 2H, 2 x FcCH, H2), 4.09 (s, 5H, Cp, H4), 4.01 (s, 2H, 2 x FcCH, H3). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 166.6 (s, ArC, C8), 161.6 (s, C=O, C5), 152.0 (s, ArC, C6), 150.2 (s, ArCH, C10), 150.1 (d, *J* = 240.2 Hz, ArC, C13), 142.1 (d, *J* = 9.4 Hz, ArC, C11), 134.7 (d, *J* = 12.8 Hz, ArC, C14), 117.4 (d, *J* = 2.1 Hz, ArCH, C16), 116.5 (d, *J* = 5.6 Hz, ArCH, C15), 113.9 (s, ArCH, C9), 109.0 (d, *J* = 21.0 Hz, ArCH, C12), 108.5 (s, ArCH, C7), 94.7 (s, FcC, C1), 68.8 (s, Cp,

C4), 64.1 (s, 2 x FcCH, C3), 61.3 (s, 2 x FcCH, C2). ^{19}F NMR (282 MHz, DMSO-d_6) δ (ppm) -131.1 (F).

Crystal data for 39. $C_{22}H_{18}FFeN_3O_2$, M = 431.24, T = 150 K; triclinic *P -1 (I.T.#2)*, a = 11.2927(11), b = 13.7746(14), c = 14.1675(15) Å, α = 65.688(3) °, β = 68.371(4) °, γ = 88.915(4) °, V = 1843.9(3) Å^3. Z = 4, d = 1.553 g.cm^{-3}, μ = 0.852 mm^{-1}. A final refinement on F^2 with 8364 unique intensities and 526 parameters converged at ωR_F^2 = 0.0991 (R_F = 0.0466) for 6413 observed reflections with $I > 2\sigma(I)$. CCDC 2017028.

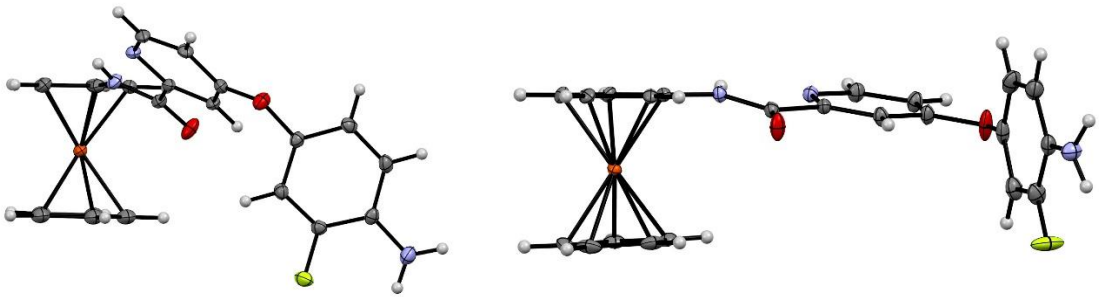


Figure 8. Molecular structures of compound **39** (thermal ellipsoids shown at the 30% probability level). Two molecules were found in the asymmetric unit.

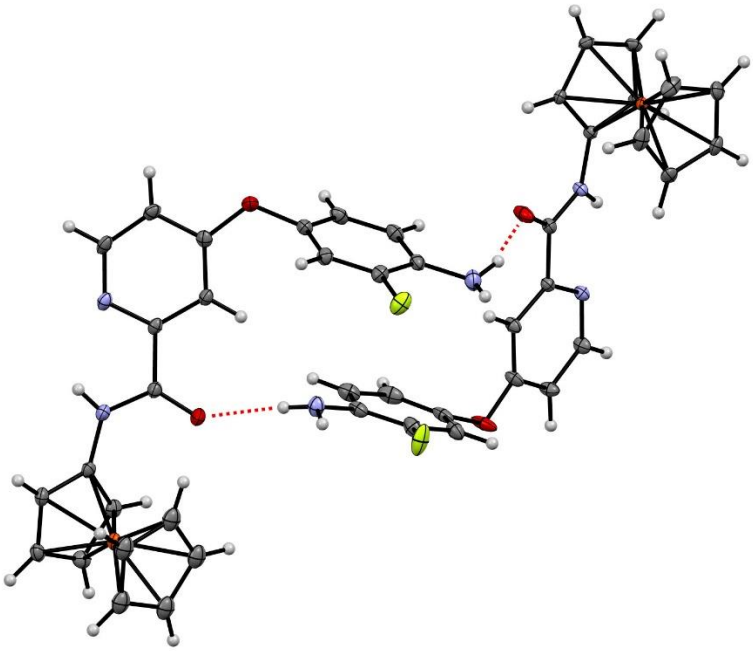


Figure 9. Hydrogen-bond network observed for compound **39** at the solid state (thermal ellipsoids shown at the 30% probability level).

4-(4-Amino-3-fluorophenoxy)-*N*-(ferrocenylmethyl)picolinamide (40)

A solution of potassium *tert*-butoxide (118 mg, 0.92 mmol, 1.40 equiv) in THF (1 mL) was added to a solution of compound **37** (118 mg, 0.92 mmol, 1.40 equiv) in NMP (1 mL) at 0 °C. The reaction mixture was warmed to rt and stirred for 3h. Compound **36** (236 mg, 0.66 mmol, 1.00 equiv) was added and the reaction mixture was heated at 115 °C for 16h. The reaction mixture was cooled to rt, silica was added and volatiles were removed under vacuum using a rotary evaporator to give the crude product. This was purified by column chromatography over SiO_2, using PET/EtOAc (70:30 to 50:50) to give the product

contaminated with NMP. The product was precipitated by the addition of water and isolated by filtration to give the title product **40** as a pale yellow solid (210 mg, 71% yield).
Mp 156-158 °C. ν_{max} (film)/cm^{-1} 3457, 3390, 3354, 3180, 3080, 1670, 1629, 1583, 1563, 1511, 1470, 1436, 1413, 1340, 1291, 1263, 1232, 1140, 1117, 997, 959, 930, 893, 859, 821. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 8.87 (t, *J* = 6.1 Hz, 1H, NH, H19), 8.50 (d, *J* = 5.6 Hz, 1H, ArCH, H11), 7.39 (d, *J* = 2.6 Hz, 1H, ArCH, H8), 7.11 (dd, *J* = 2.7, 5.6 Hz, 1H, ArCH, H10), 7.02 (dd, *J* = 2.5, 11.8 Hz, 1H, ArCH, H13), 6.86 (t, *J* = 9.2 Hz, 1H, ArCH, H16), 6.79 (dd, *J* = 2.5, 8.7 Hz, 1H, ArCH, H17), 5.22 (br s, 2H, NH2, H18), 4.22 (t, *J* = 1.7 Hz, 2H, 2 x FcCH, H2), 4.19 (s, 5H, Cp, H4), 4.16 (d, *J* = 6.1 Hz, 2H, CH_2, H5), 4.09 (t, *J* = 1.7 Hz, 2H, 2 x FcCH, H3). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 166.4 (s, ArC, C9), 162.6 (s, C=O, C6), 152.2 (s, ArC, C7), 150.3 (s, ArCH, C11), 150.1 (d, *J* = 240.7 Hz, ArC, C14), 142.1 (d, *J* = 9.4 Hz, ArC, C12), 134.7 (d, *J* = 12.8 Hz, ArC, C15), 117.3 (d, *J* = 2.5 Hz, ArCH, C17), 116.5 (d, *J* = 5.7 Hz, ArCH, C16), 113.8 (s, ArCH, C10), 108.9 (d, *J* = 21.0 Hz, ArCH, C13), 108.6 (s, ArCH, C8), 85.8 (s, FcC, C1), 68.3 (s, Cp, C4), 68.1 (s, 2 x FcCH, C2), 67.4 (s, 2 x FcCH, C3), 37.7 (s, CH_2, C5). ^{19}F NMR (282 MHz, DMSO-d_6) δ (ppm) -131.1 (F).

4-(4-(3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido)-3-fluorophenoxy)-*N*-ferrocenylpicolinamide (4a)

A solution of triphosgene (115 mg, 389 µmol, 1.30 equiv) in CH_2Cl_2 (1.5 mL) was added to a solution of compound **39** (129 mg, 299 µmol, 1.00 equiv) in CH_2Cl_2 (1.5 mL). After addition, the reaction mixture was stirred at rt for 15 min in during which a red suspension formed. A solution of *N*,*N*-diisopropylethylamine (156 µL, 0.90 mmol, 3.00 equiv) in CH_2Cl_2 (1.5 mL) was added and the reaction mixture was stirred for at rt for 2h. Triphosgene (100 mg, 329 µmol, 1.10 equiv) was added and the reaction mixture was stirred for 1h. Compound **15** (176 mg, 0.90 mmol, 3.00 equiv) was added and the reaction mixture was stirred at rt for 48h. Silica was added to the reaction mixture and volatiles were removed under vacuum to give the title product. This was purified by column chromatography over SiO_2 prewashed with NEt_3, using CH_2Cl_2/MeOH (99:1) to give the title product **4a** as a yellow solid (54 mg, 28%).
Mp 158-160 °C. ν_{max} (film)/cm^{-1} 3328, 2989, 1657, 1592, 1541, 1500, 1483, 1420, 1321, 1276, 1261, 1222, 1198, 1176, 1140, 1104, 1047, 974, 870, 824, 764, 750. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 10.12 (br s, 1H, NH_{amide}, H27), 9.58 (br s, 1H, NH_{urea}, H25), 8.76 (br s, 1H, NH_{urea}, H26), 8.60 (d, *J* = 5.5 Hz, 1H, ArCH, H10), 8.18 (t, *J* = 9.0 Hz, 1H, ArCH, H15), 8.13 (s, 1H, ArCH, H19), 7.63 (s, 2H, 2 x ArCH, H22 and H23), 7.49 (d, *J* = 2.4 Hz, 1H, ArCH, H7), 7.37 (dd, *J* = 2.4, 11.5 Hz, 1H, ArCH, H12), 7.25 (dd, *J* = 2.4, 5.5 Hz, 1H, ArCH, H9), 7.11 (dd, *J* = 1.5, 9.0 Hz, 1H, ArCH, H16), 4.93 (s, 2H, 2 x FcCH, H2), 4.09 (s, 5H, Cp, H4), 4.02 (s, 2H, 2 x FcCH, H3). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 165.7 (s, ArC, C8), 161.5 (s, C=O_{amide}, C5), 152.8 (d, *J* = 245.4 Hz, ArC, C13), 152.2 and 152.1 (2 x s, C=O_{urea} and ArC, C17 and C6), 150.4 (s, ArCH, C10), 148.1 (d, *J* = 10.2 Hz, ArC, C11), 139.0 (s, ArC, C18), 132.1 (s, ArCH, C22), 126.8 (q, *J* = 30.4 Hz, ArC, C20), 124.9 (d, *J* = 10.7 Hz, ArC, C14), 122.9 (s, ArCH, C23), 122.7 (q, *J* = 273.5 Hz, CF_3, C24), 122.6 (s, ArCH, C15), 122.5 (s, ArC, C21), 117.2 (d, *J* = 2.3 Hz, ArCH, C16), 116.6 (q, *J* = 5.7 Hz, ArCH, C19), 114.4 (s, ArCH, C9), 109.2 (d, *J* = 22.0 Hz, ArCH, C12), 108.9 (s, ArCH, C7), 94.7 (s, FcC, C1), 68.8 (s, Cp, C4), 64.1 (s, 2 x FcCH, C3), 61.3 (s, 2 x FcCH, C2). ^{19}F NMR (282 MHz, DMSO-d_6) δ (ppm) -61.5 (CF_3), -124.3 (F). HRMS, *m/z* 652.0579 (0 ppm) found (calcd for $C_{30}H_{21}N_4O_3F_4{}^{35}Cl{}^{56}Fe$, $[M]^{+\cdot}$, requires 652.05822); 675.0476 (1 ppm) found (calcd for $C_{30}H_{21}N_4O_3F_4{}^{35}ClNa{}^{56}Fe$, $[M+Na]^+$, requires 675.04799); 691.0208 (2 ppm) found (calcd for $C_{30}H_{21}N_4O_3F_4{}^{35}ClK{}^{56}Fe$, $[M+K]^+$, requires 691.02193).

4-(4-(3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido)-3-fluorophenoxy)-*N*-(ferrocenylmethyl)picolinamide (5a)

A solution of triphosgene (80.0 mg, 269 µmol, 1.20 equiv) in CH_2Cl_2 (0.5 mL) was added to a solution of compound **40** (100 mg, 224 µmol, 1.00 equiv) in CH_2Cl_2 (0.5 mL). After addition, the reaction mixture was stirred at rt for 25 min in during which an orange suspension formed. A solution of *N*,*N*-diisopropylethylamine (148 µL, 851 mmol, 3.80 equiv) in CH_2Cl_2 (0.5 mL) was added and the reaction mixture was stirred for at rt for 90 min. Compound **15** (162 mg, 828 µmol, 3.70 equiv) was added and the reaction mixture was stirred at rt for 48h. Volatiles were removed under vacuum to give the title product. This was purified by a first column chromatography over SiO_2, using CH_2Cl_2/MeOH (99:1 to 98:2) with 2% NEt_3 and a second column chromatography over SiO_2, using PET/EtOAc (60:40) with 2% NEt_3 to give the title product **5a** as a yellow solid (49 mg, 33%).

Alternatively, the following protocol can also be followed. A solution of triphosgene (267 mg, 0.90 mmol, 3.00 equiv) in CH_2Cl_2 (2.0 mL) was added to a solution of compound **15** (117 mg, 0.60 mmol, 2.00 equiv) in CH_2Cl_2 (2.0 mL). After addition, the reaction mixture was stirred at rt for 15 min in during which an orange suspension formed. *N*,*N*-Diisopropylethylamine (209 µL, 1.20 mmol, 4.00 equiv) was added and the reaction mixture was stirred for at rt for 60 min. Volatiles were removed under vacuum and diethyl ether was added to the residue which was sonicated. The solution was transferred into another round-bottom flask and volatiles were removed under vacuum. THF (4.0 mL) was added to the residue and compound **40** (134 mg, 0.30 mmol, 1.00 equiv) was added in one portion. The reaction mixture was stirred at rt for 16h. Volatiles were removed under vacuum to give the crude product. This was purified by a first column chromatography over SiO_2, using CH_2Cl_2/MeOH (99:1) with 1% NEt_3 to give the product. Final trituration in pentane afforded the title product **5a** as a yellow solid (170 mg, 85%).

Mp 208-211 °C. ν_{max} (film)/cm^{-1} 3340, 1715, 1655, 1598, 1530, 1481, 1417, 1281, 1260, 1191, 1174, 1126, 1107, 1028, 999, 969, 874, 822. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 9.58 (br s, 1H, NH_{urea}, H26), 8.90 (t, J = 5.8 Hz, 1H, NH_{amide}, H28), 8.75 (br s, 1H, NH_{urea}, H27), 8.55 (d, *J* = 5.6 Hz, 1H, ArCH, H11), 8.16 (t, *J* = 9.0 Hz, 1H, ArCH, H16), 8.13 (s, 1H, ArCH, H20), 7.62 (s, 2H, 2 x ArCH, H23 and H24), 7.46 (d, *J* = 2.2 Hz, 1H, ArCH, H8), 7.33 (dd, *J* = 1.9, 11.5 Hz, 1H, ArCH, H13), 7.20 (dd, *J* = 2.1, 5.3 Hz, 1H, ArCH, H10, 7.07 (d, *J* = 8.8 Hz, 1H, ArCH, H17), 4.23 (s, 2H, 2 x FcCH, H2), 4.19 (s, 5H, Cp, H4), 4.17 (d, *J* = 6.1 Hz, 2H, CH_2, H5), 4.09 (s, 2H, 2 x FcCH, H3). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 165.6 (s, ArC, C9), 162.5 (s, $C{=}O_{amide}$, C6), 152.8 (d, *J* = 245.4 Hz, ArC, C14), 152.4 (s, $C{=}O_{urea}$, C18), 152.2 (s, ArC, C7), 150.6 (s, ArCH, C11), 148.1 (d, *J* = 10.6 Hz, ArC, C12), 139.0 (s, ArC, C19), 132.1 (s, ArCH, C23), 126.8 (q, *J* = 30.6 Hz, ArC, C21), 124.9 (d, *J* = 10.7 Hz, ArC, C15), 122.9 (s, ArCH, C24), 122.8 (q, *J* = 273.0 Hz, CF_3, C25), 122.6 (s, ArCH and ArC, C16 and C22), 117.1 (d, *J* = 1.4 Hz, ArCH, C17), 116.6 (q, *J* = 5.4 Hz, ArCH, C20), 114.3 (s, ArCH, C10), 109.1 (d, *J* = 22.1 Hz, ArCH, C13), 109.0 (s, ArCH, C8), 85.8 (s, FcC, C1), 68.3 (s, Cp, C4), 68.2 (s, 2 x FcCH, C2), 67.4 (s, 2 x FcCH, C3), 37. (s, CH_2, C5). ^{19}F NMR (470 MHz, DMSO-d_6) δ (ppm) -61.5 (CF_3), -124.4 (F). HRMS, *m/z* 652.0579 (0 ppm) found (calcd for $C_{31}H_{23}N_4O_3F_4{}^{35}Cl{}^{56}Fe$, $[M]^{+\cdot}$, requires 666.07387); 689.0640 (0 ppm) found (calcd for $C_{31}H_{23}N_4O_3F_4{}^{35}ClNa{}^{56}Fe$, $[M+Na]^+$, requires 689.06364).

Kinase inhibition assays

Kinase assays were performed in 384-well plates using the ADP-Glo™ assay kit (Promega, Madison, WI) according to the recommendations of the manufacturer. As described by Zegzouti et al.,[14] this assay is a luminescent ADP detection assay that provides an homogeneous and high-throughput screening method to measure kinase activity by quantifying the amount of ADP produced during a kinase reaction. Briefly, the reactions were carried out in a final volume of 6 µl for 30 min at 30°C in appropriate kinase buffer, with either protein or peptide as substrate in the presence of 10µM ATP (see hereafter). After that, 6 µl of ADP-Glo™ Kinase Reagent was added to stop the kinase reaction. After an incubation time of 50 min at room temperature (RT), 12 µl of Kinase Detection Reagent was added for one hour at RT. The transmitted signal was measured using the Envision (PerkinElmer, Waltham, MA) microplate luminometer and expressed in Relative Light Unit (RLU). The kinase assays were performed in duplicate (n=2) in the absence or presence of 1µM and 10µM of the tested compounds. Kinase activities are expressed in % of maximal activity, i.e. measured in the absence of inhibitor. To validate each kinase assay, the following model inhibitors were used under the same conditions than the tested compounds: Staurosporine from *Streptomyces* sp. (#S5921, Sigma-Aldrich) for CK1ε; Indirubin-3'-oxime (#I0404, Sigma-Aldrich) for CDK5/p25, CDK9/CyclinT, *Rn*DYRK1A and *Mm*CLK1; CHR-6494 (#SML0648, Sigma-Aldrich) for HASPIN; Tofacitinib (CP-690550, #S2789, Selleckchem) for JAK3; Imatinib mesylate (STI571, #S1026, Selleckchem) for ABL1; SGI-1776 (#S2198, Selleckchem) for Pim1; Regorafenib (BAY 73-4506, Selleckchem) for VEGFR2.

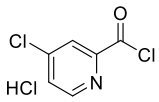
Table S1: Experimental conditions used for protein kinase assays.

Protein Kinase	Enzyme Description	Substrate* *(Working concentration)*	Buffer used**
CDK5/p25	Human, recombinant, expressed in bacteria	Histone H1 (*37.2µM*)	**A**
CDK9/CyclinT	Human, recombinant, expressed by baculovirus in Sf9 insect cells	Peptide: YSPTSPSYSPTSPSYSPTSPSKKKK (*83µM*)	**A**
CLK1	From *Mus musculus*, recombinant, expressed in bacteria	Peptide: GRSRSRSRSRSR (57.3µM)	**A**
DYRK1A	From *Rattus norvegicus*, amino acids 1 to 499 including the kinase domain, recombinant, expressed in bacteria, DNA vector kindly provided by Dr. W. Becker, Aachen, Germany	Peptide: KKISGRLSPIMTEQ (*10.7µM*)	**A**
PIM1	Human proto-oncogene, recombinant, expressed in bacteria	Histone H1 (*18.6µM*)	**A**
GSK3b	Human, recombinant, expressed by baculovirus in Sf9 insect cells	GS-1 peptide: YRRAAVPPSPSLSRHSSPHQSpEDEEE ******* (*20µM*)	**A**
HASPIN	Human, kinase domain, amino acids 470 to 798, recombinant, expressed in bacteria	Histone H3 peptide (1-21): ARTKQTARKSTGGKAPRKQLA (*8µM*)	**A**
CK1ε	Human, recombinant, expressed by baculovirus in Sf9 insect cells	Peptide: RRKHAAIGSpAYSITA *** (*170µM*)	**A**
ABL1	Human, recombinant, expressed by baculovirus in Sf9 insect cells	Peptide: EAIYAAPFAKKK (127µM)	**A**
EGFR	Human, recombinant, expressed by baculovirus in Sf9 insect cells	Poly(L-glutamic acid – L-tyrosine) sodium salt (0.17µg/µL)	**A**
VEGFR2	Human, recombinant, expressed by baculovirus in Sf9 insect cells	Poly(L-glutamic acid – L-tyrosine) sodium salt (0.17µg/µL)	**A**
JAK3	Human, recombinant, expressed by baculovirus in Sf9 insect cells	Peptide: GGEEEEYFELVKKKK (94µM)	**A**

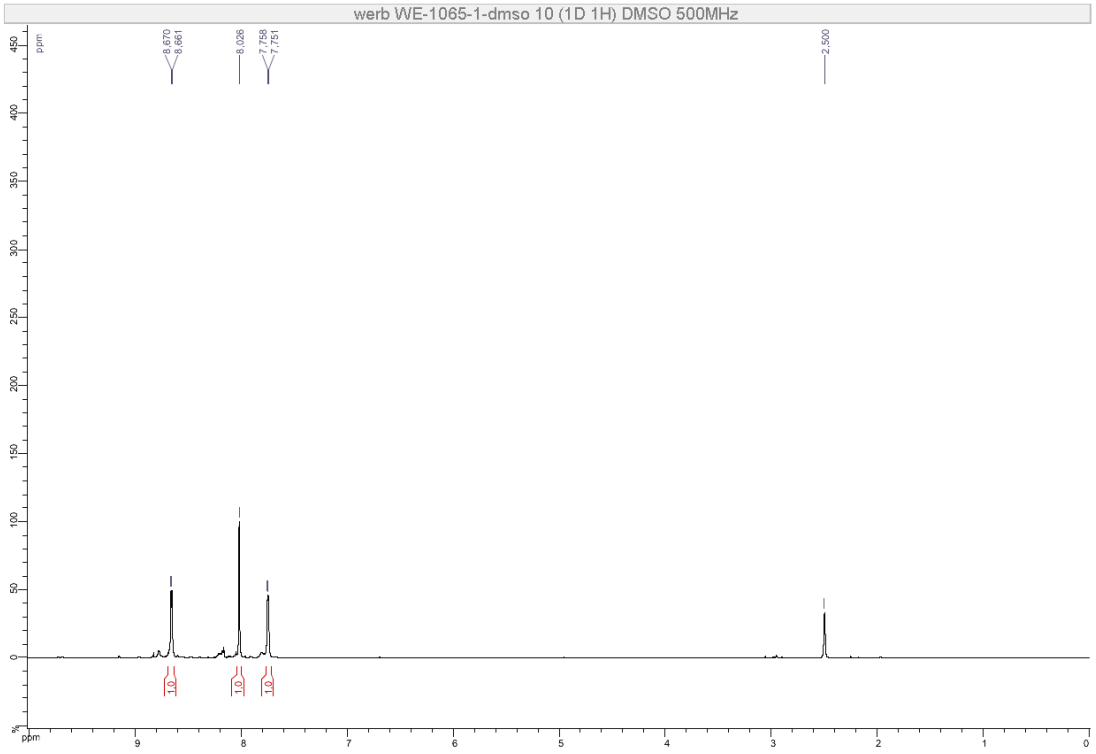
* Peptide substrates were obtained from ProteoGenix (Schiltigheim, France) or Sigma for Histone H1 and Poly (L-glutamic acid – L-tyrosine) sodium salt; ** composition of the buffer A: 10 mM $MgCl_2$, 1 mM EGTA, 1 mM DTT, 25 mM Tris-HCl pH 7.5, 50 µg/mL heparin; *** "Sp" stands for phosphorylated serine.

NMR Spectra

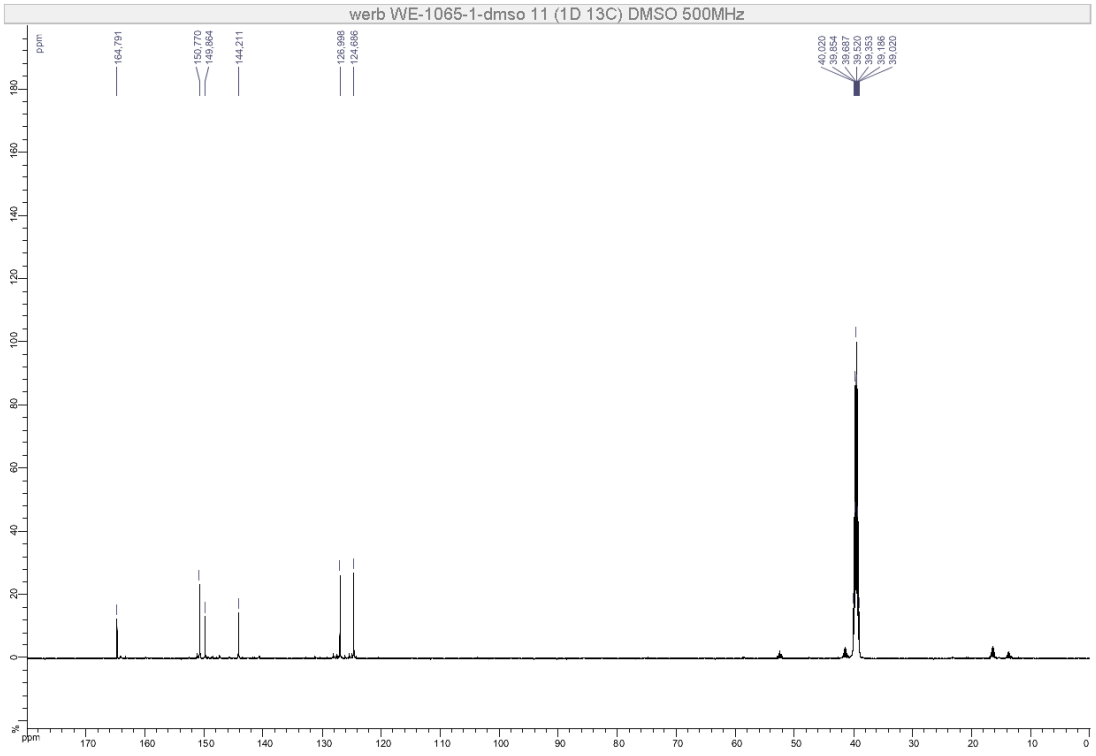
Compound 11



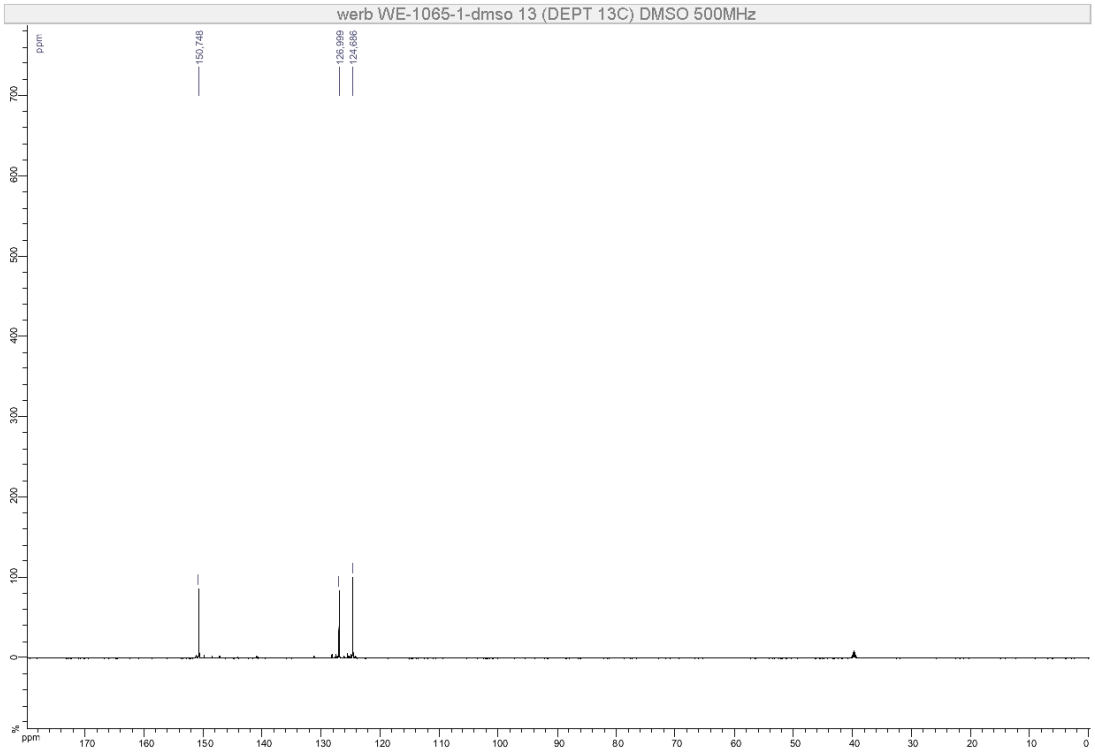
^{1}H NMR



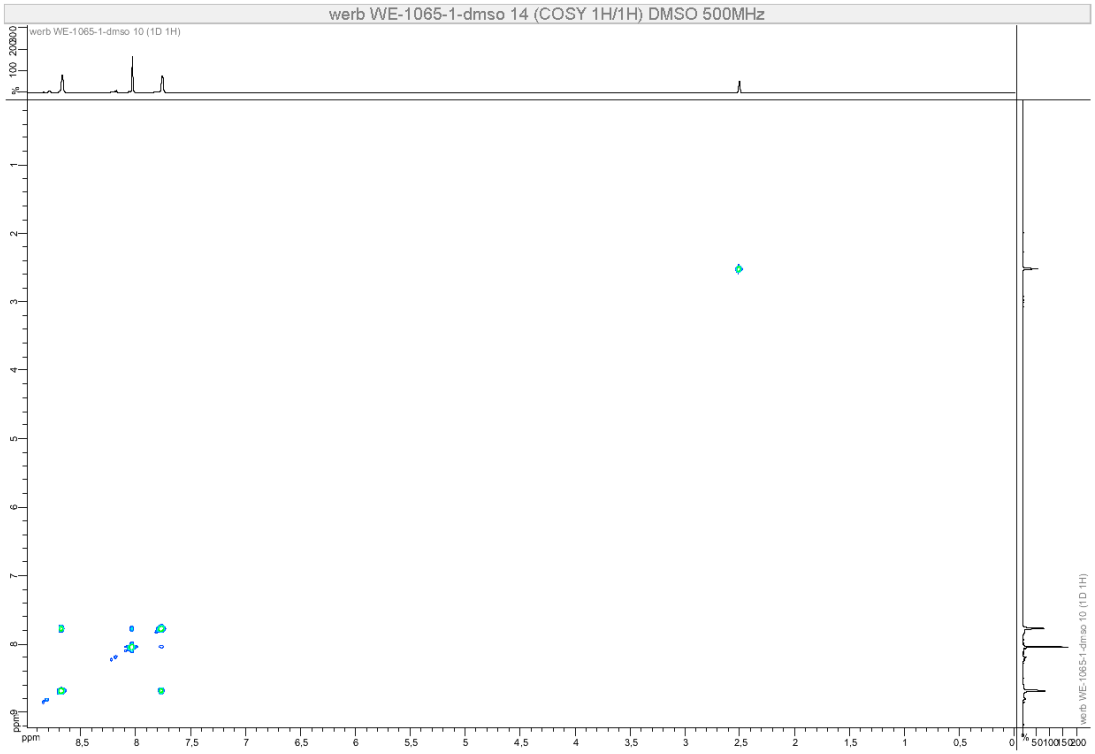
^{13}C NMR



DEPT 135 NMR



COSY NMR



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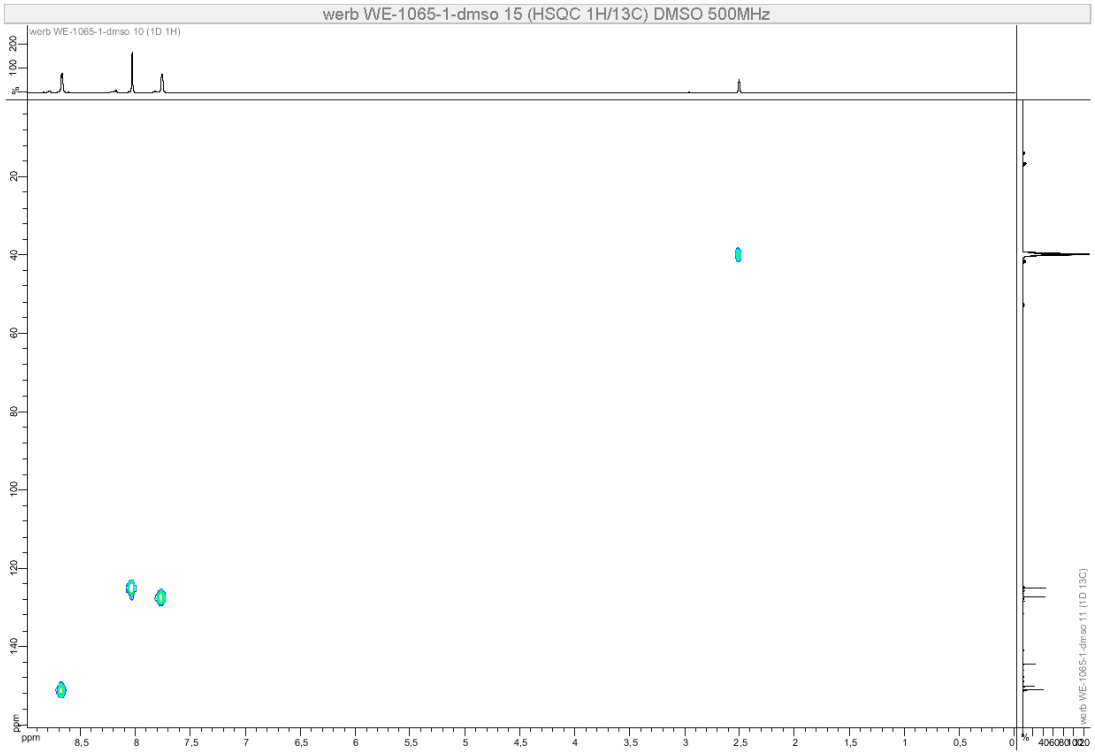
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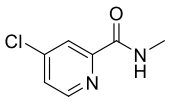
Compound 9



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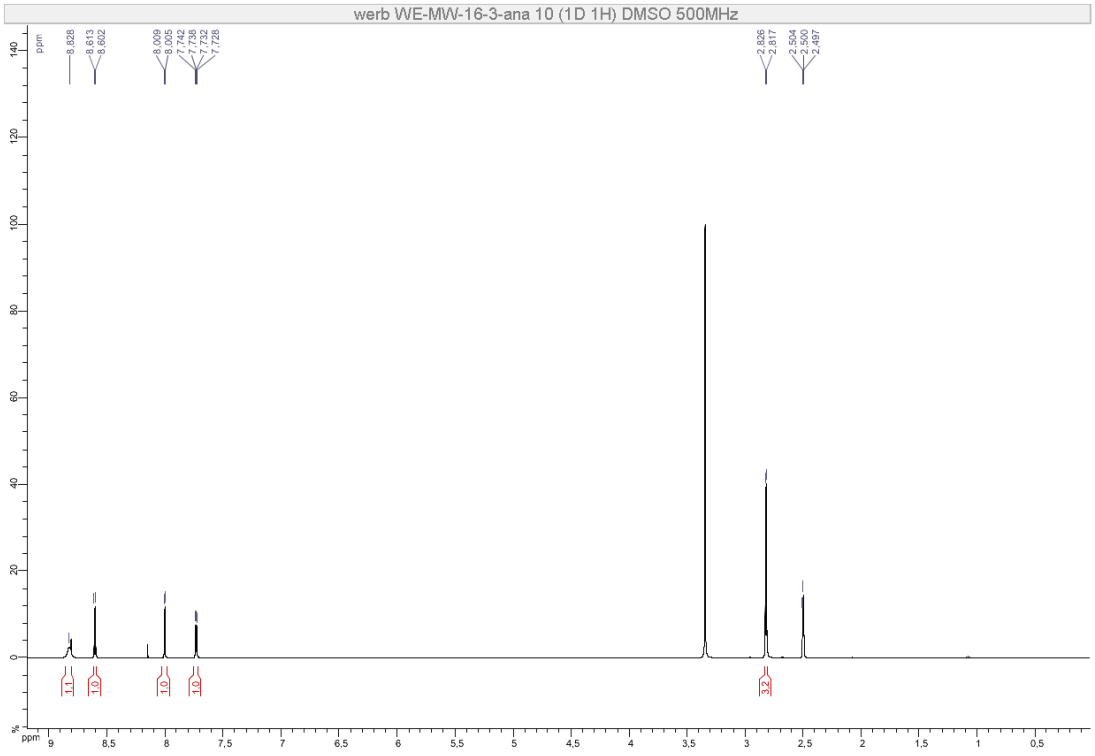

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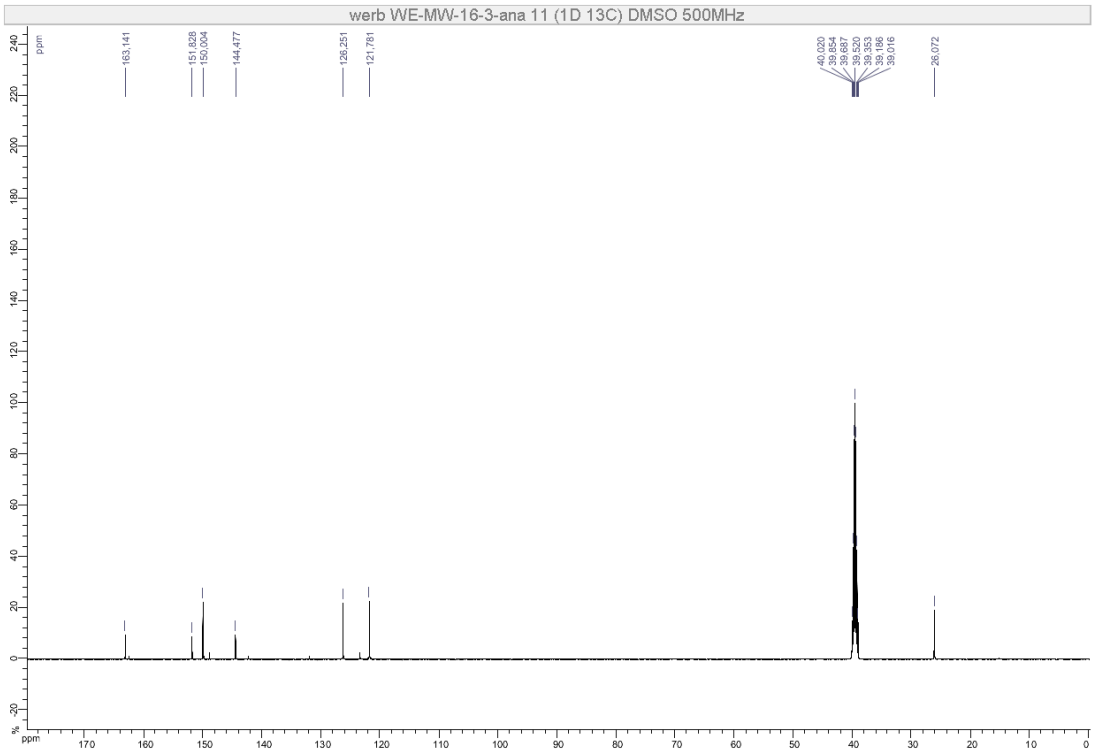
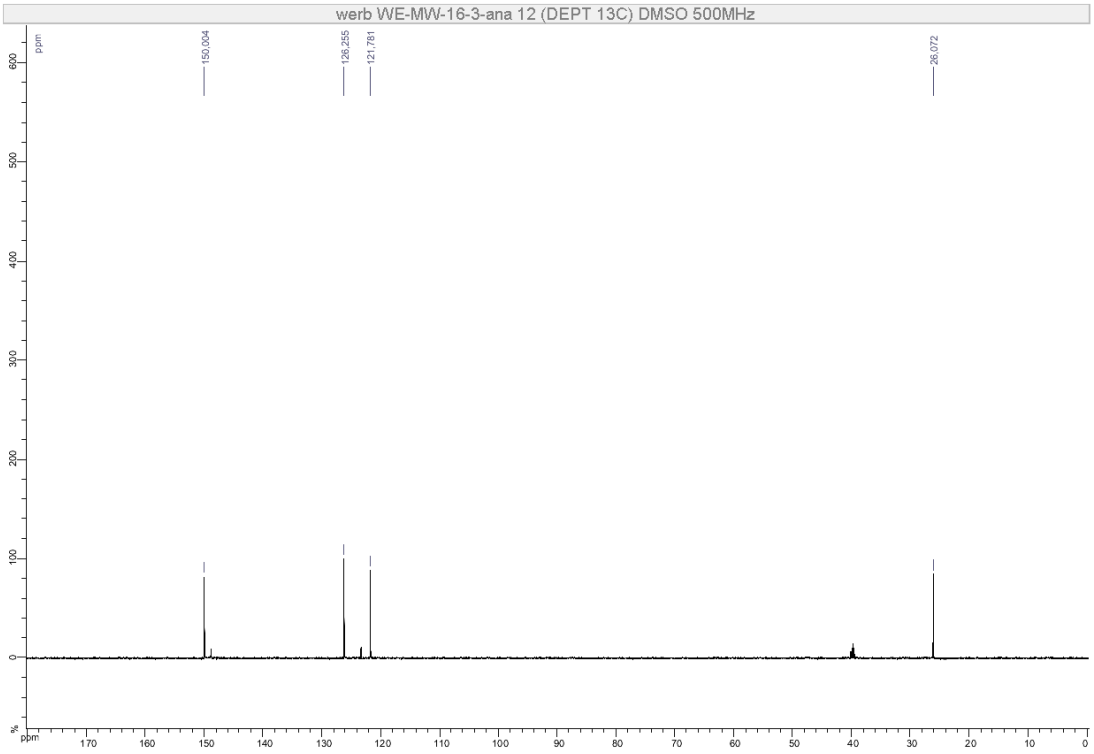


DEPT 135 NMR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%
ppm
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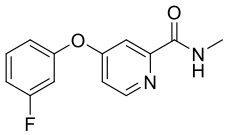
Compound 7



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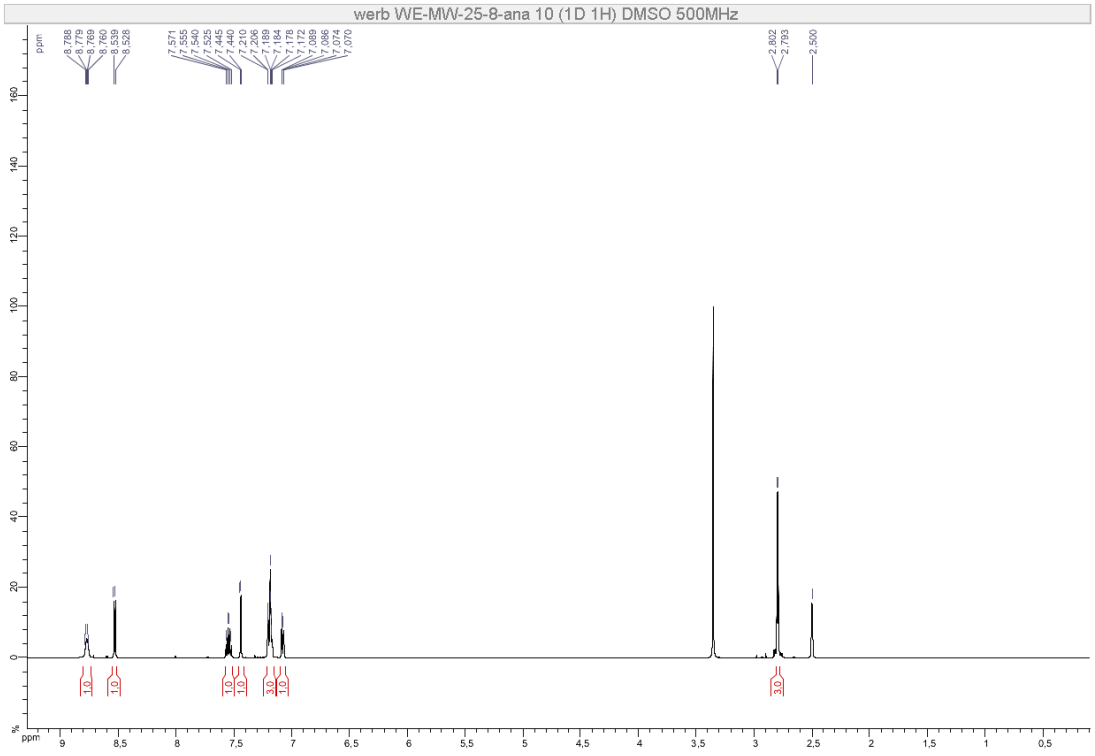

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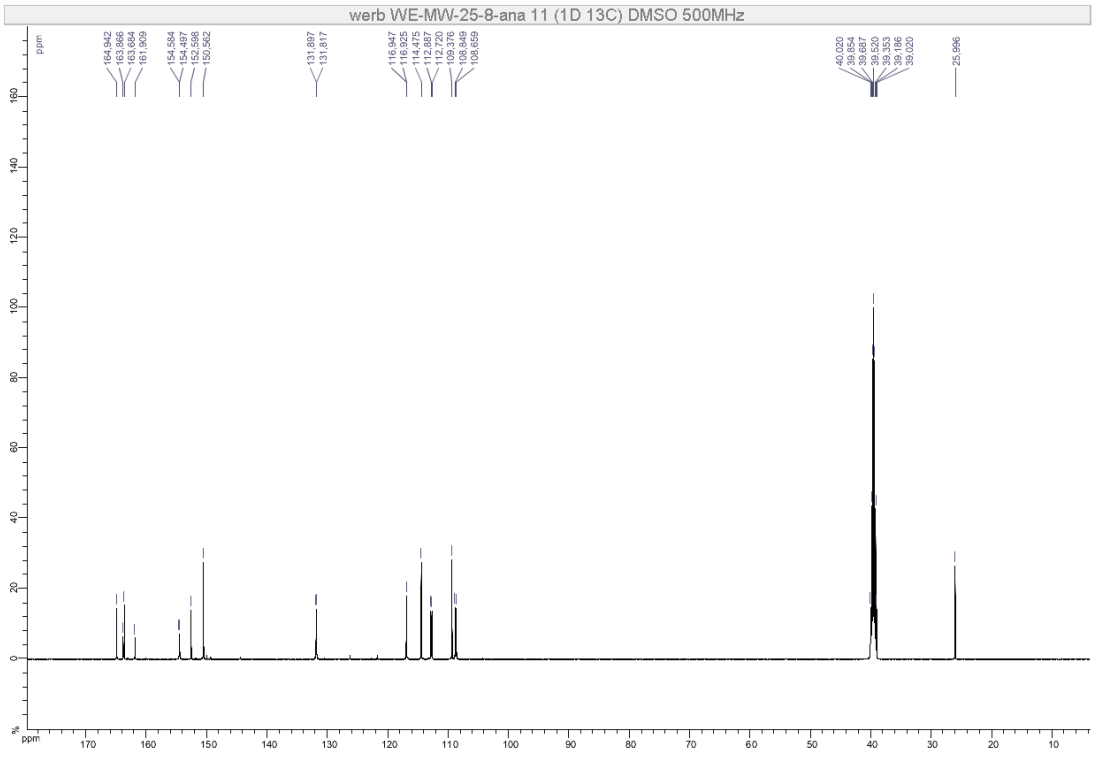

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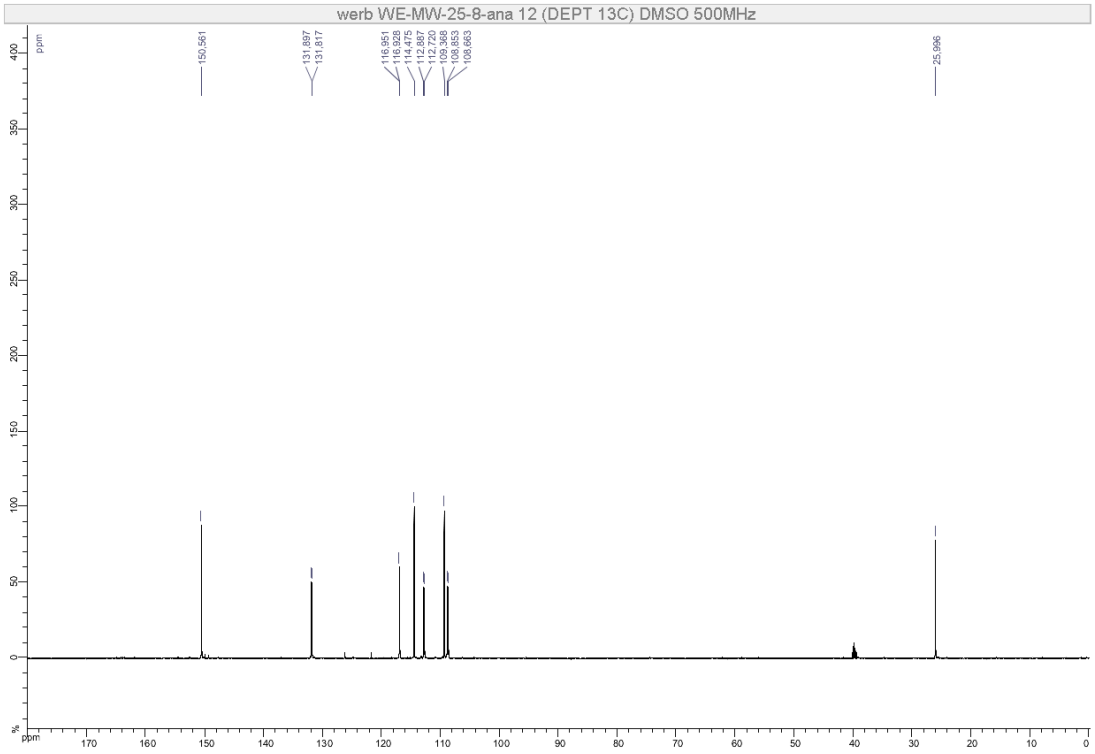
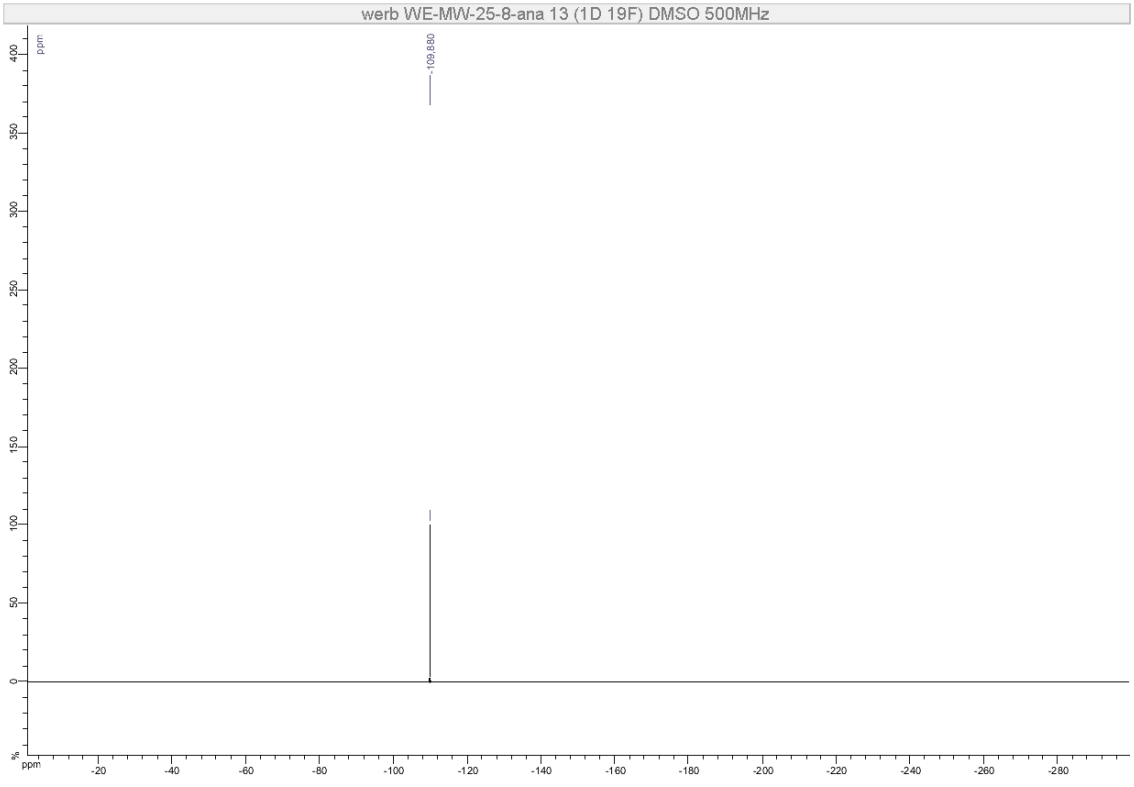
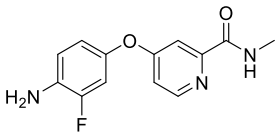


^{19}F NMR



Compound 6



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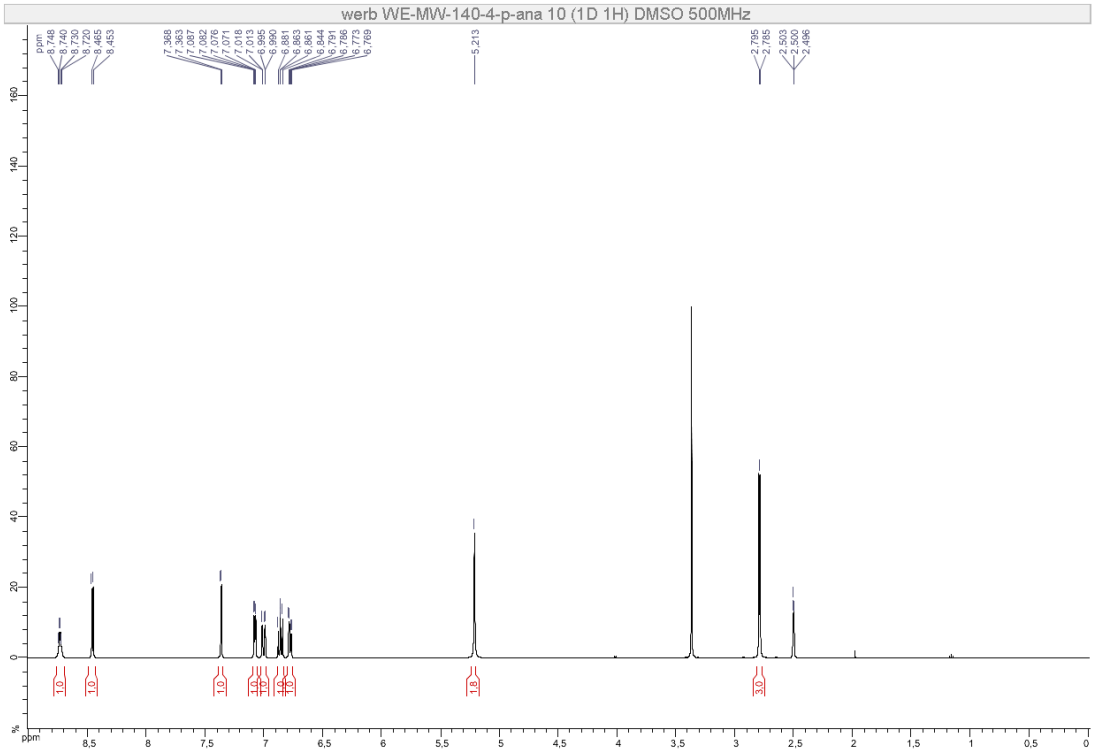

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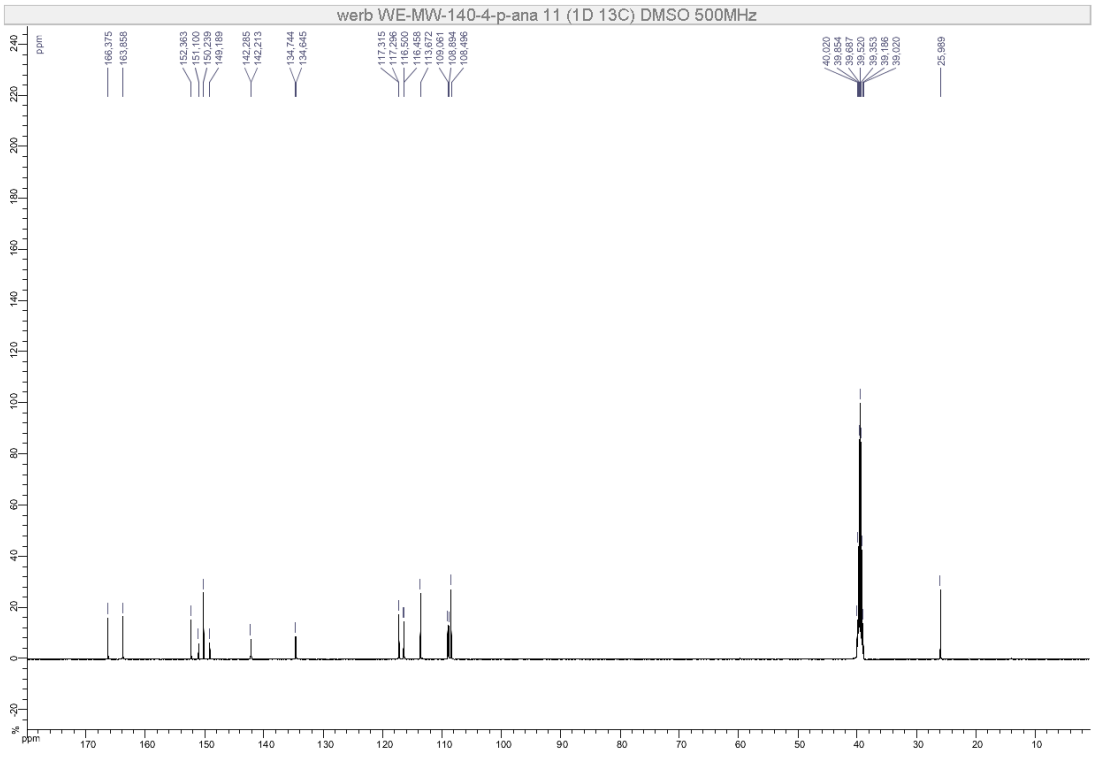

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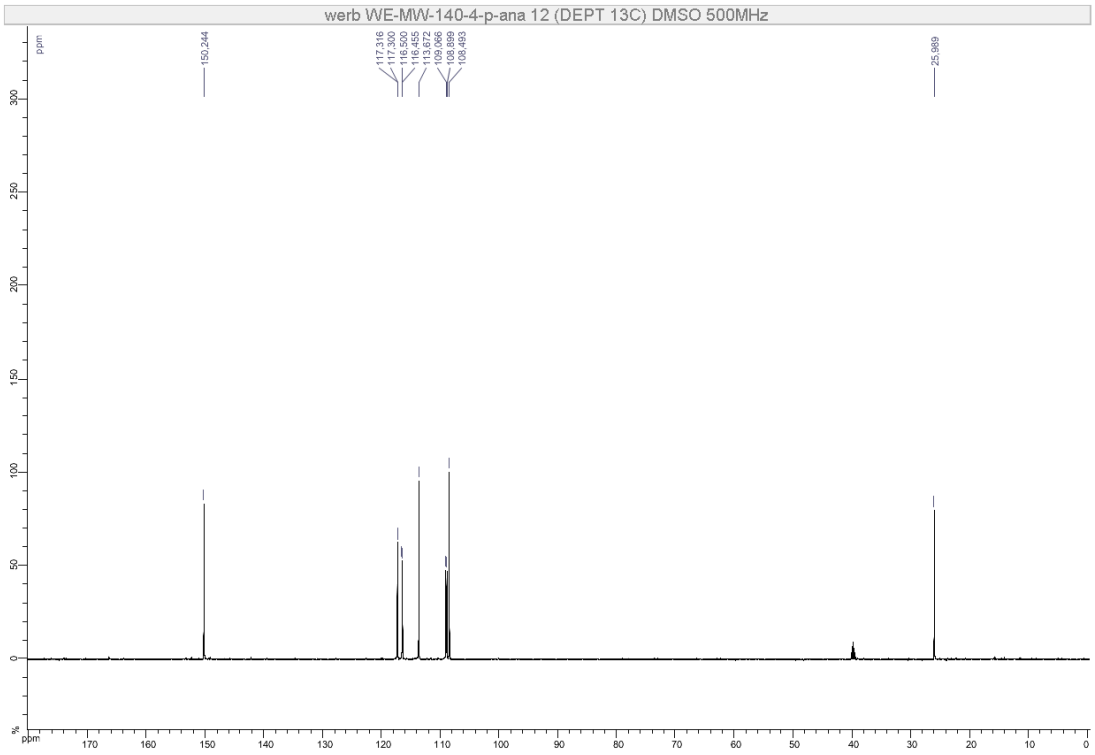

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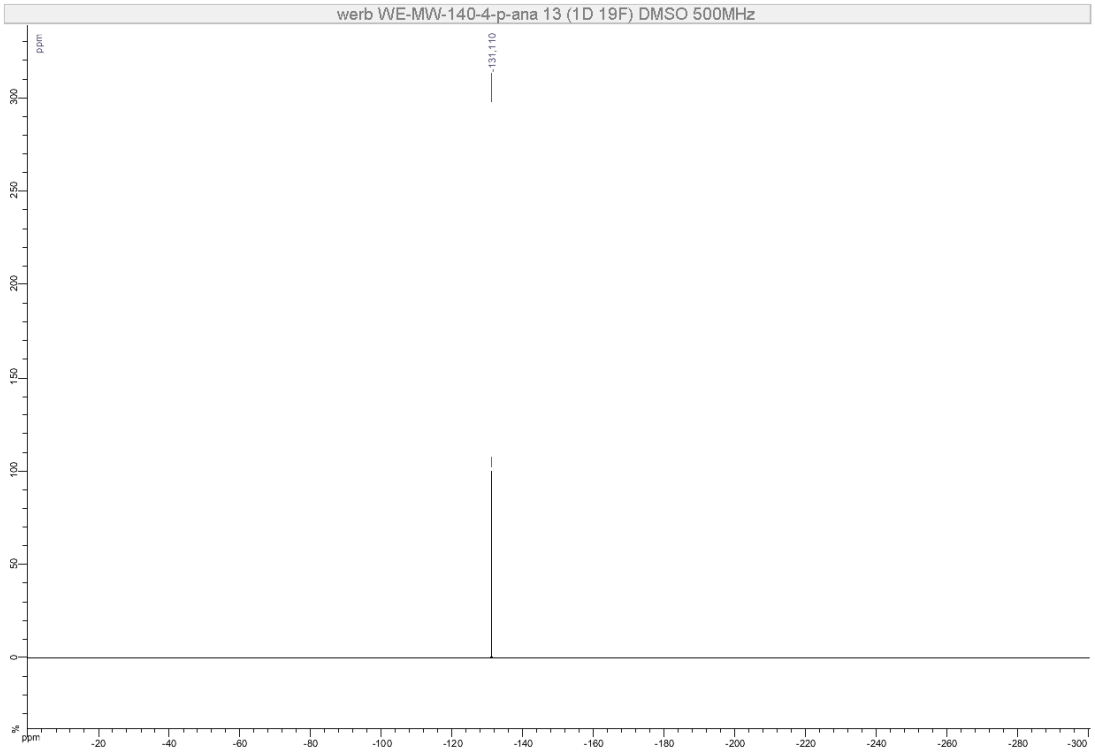
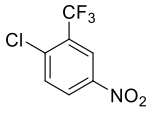
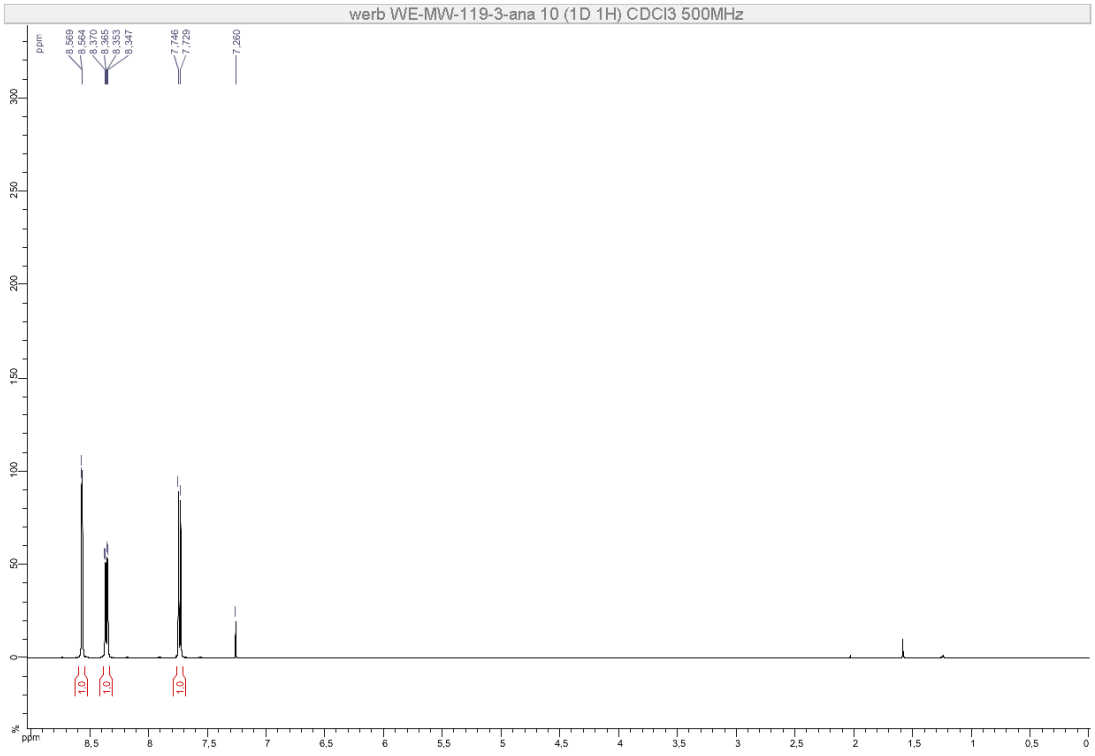


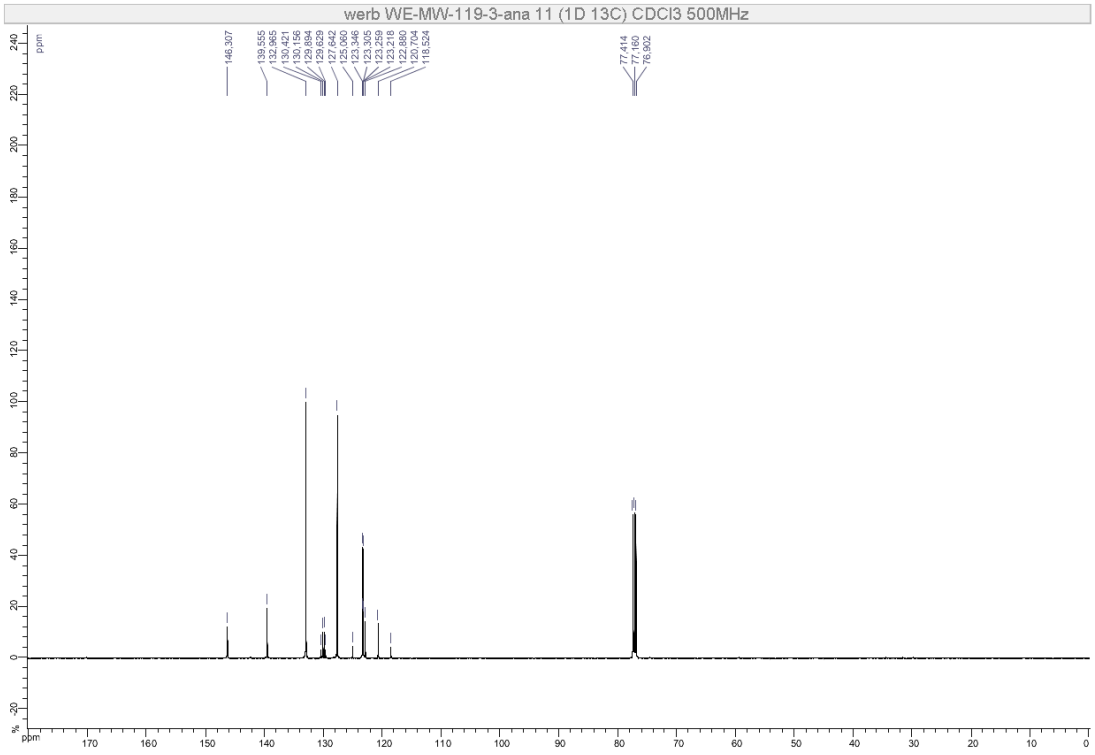
Compound 14



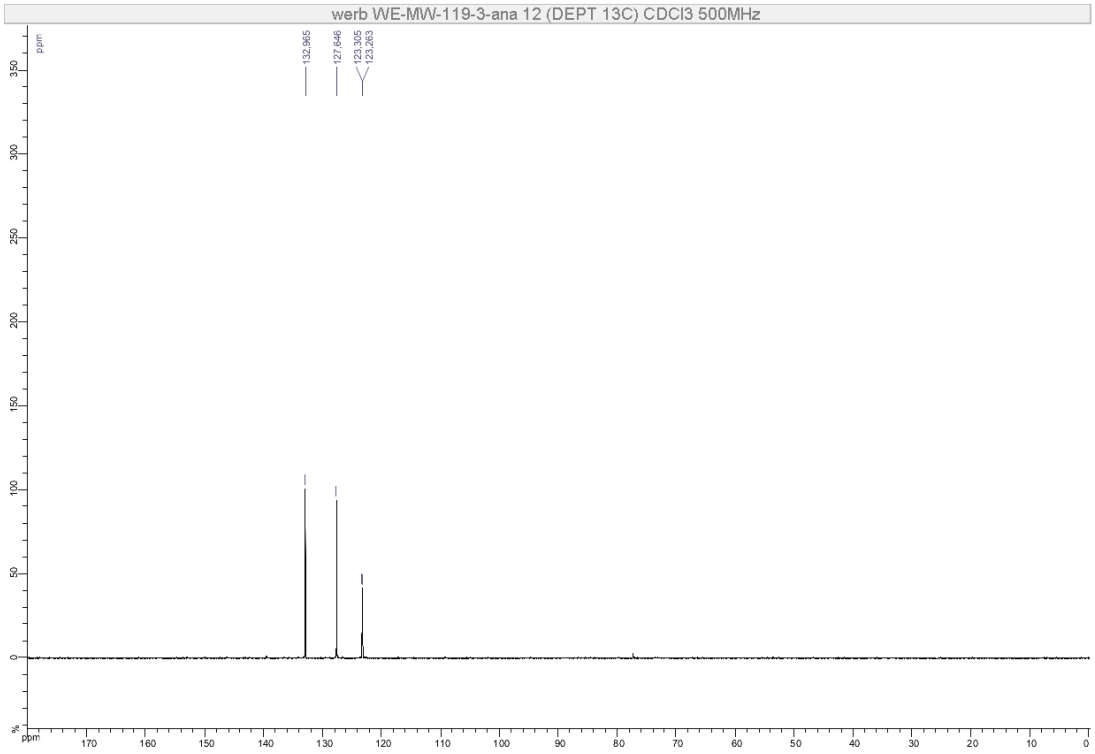
^{1}H NMR



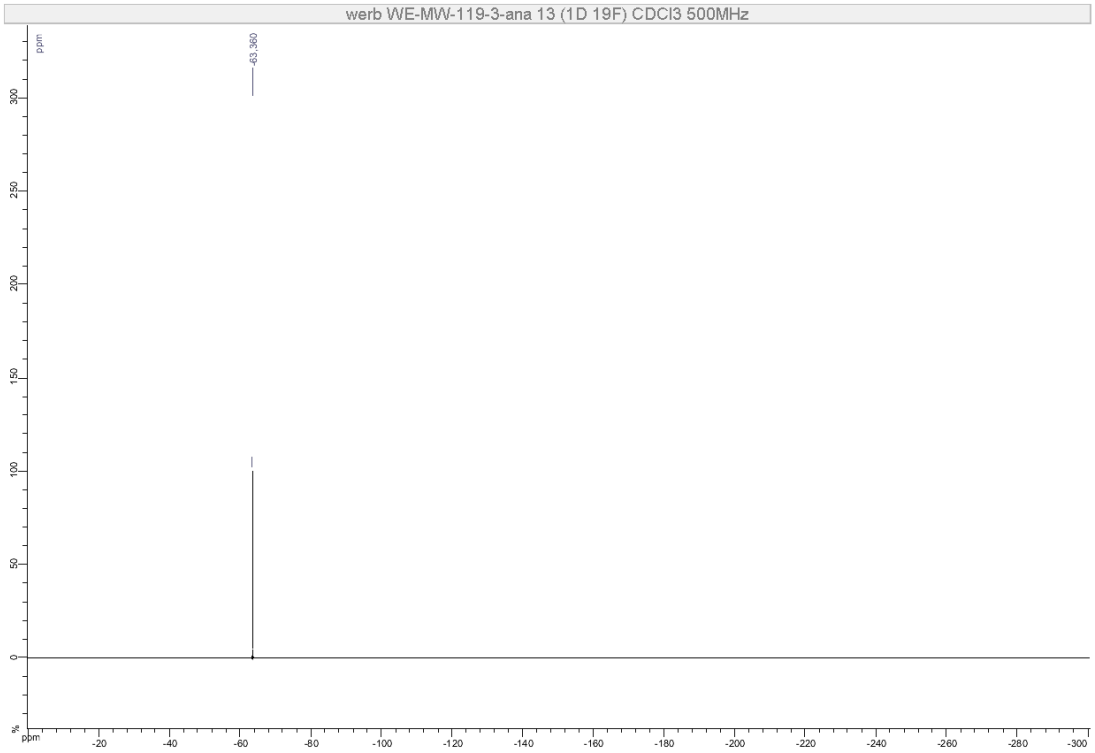
^{13}C NMR



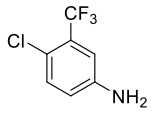
DEPT 135 NMR



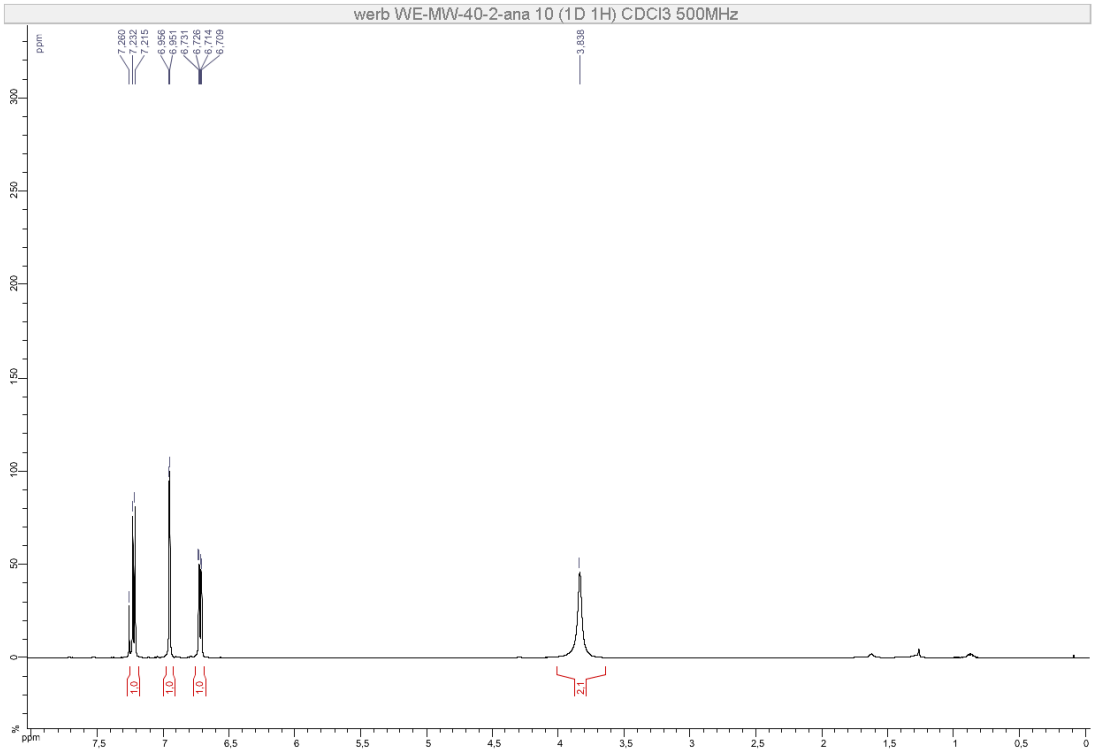
^{19}F NMR



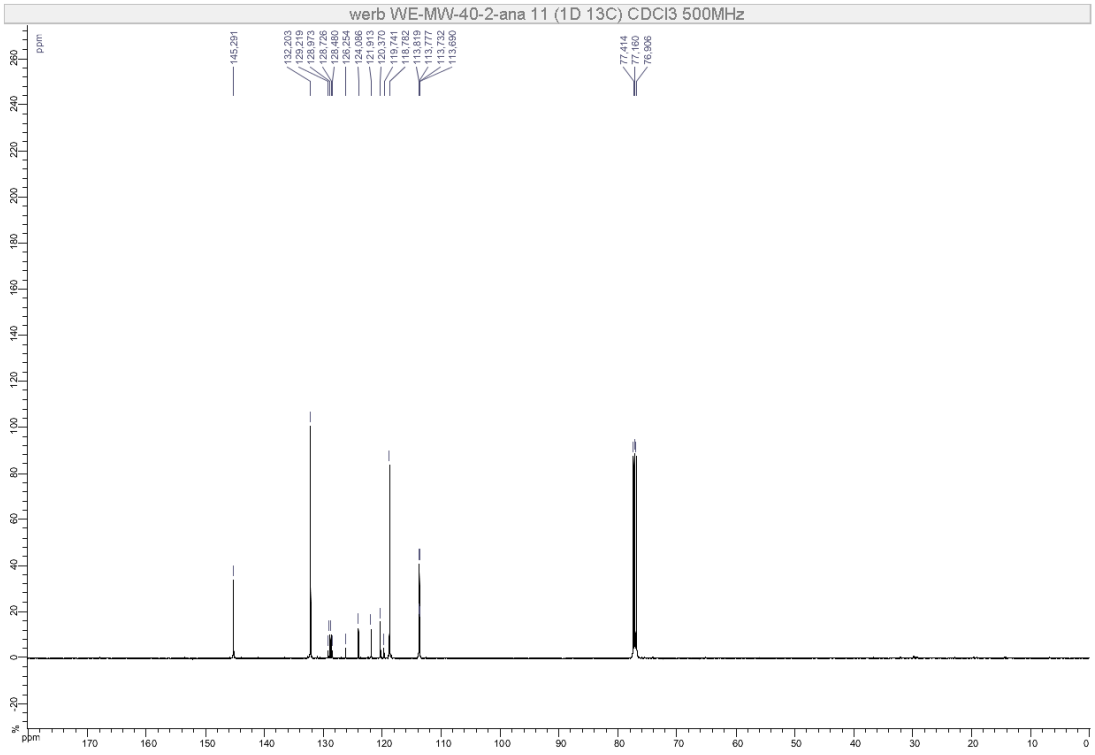
Compound 15



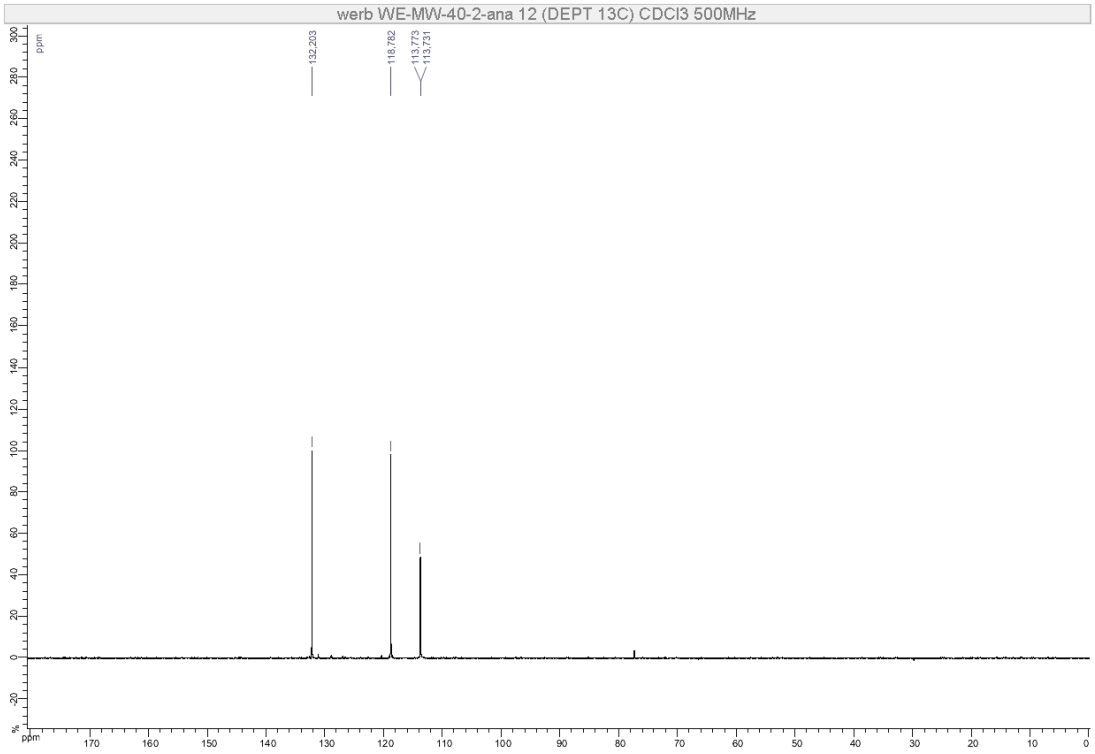
^{1}H NMR



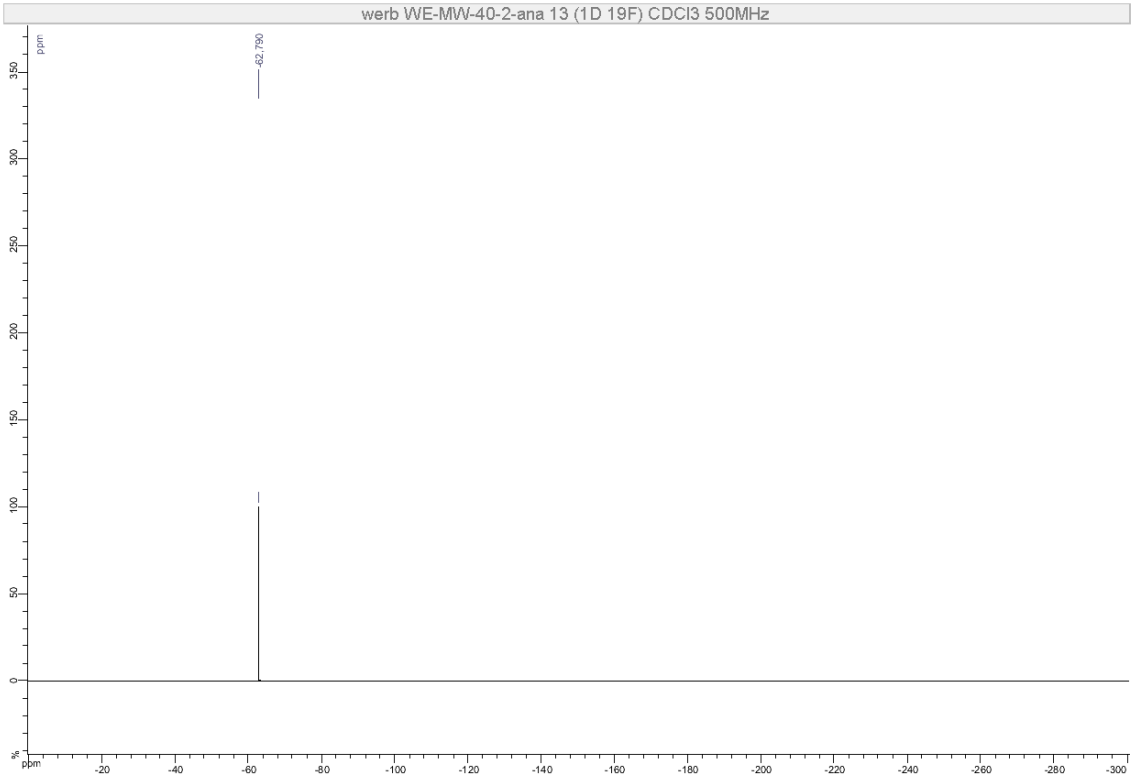
^{13}C NMR



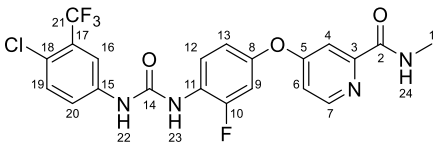
DEPT 135 NMR



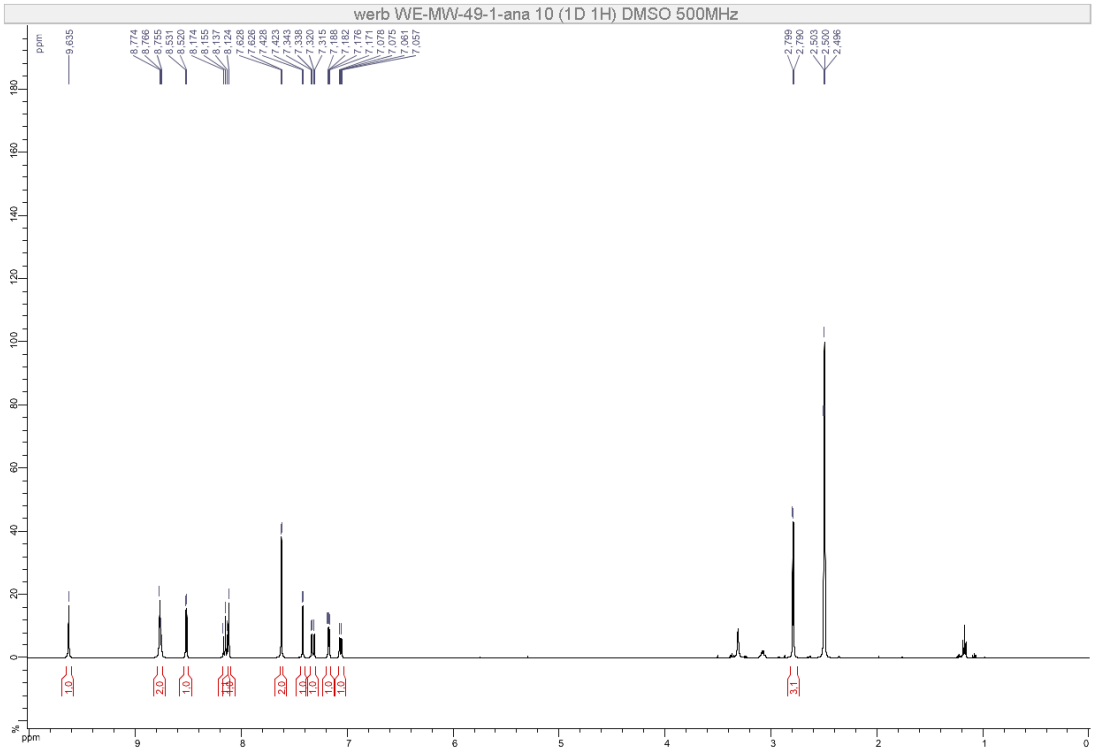
^{19}F NMR



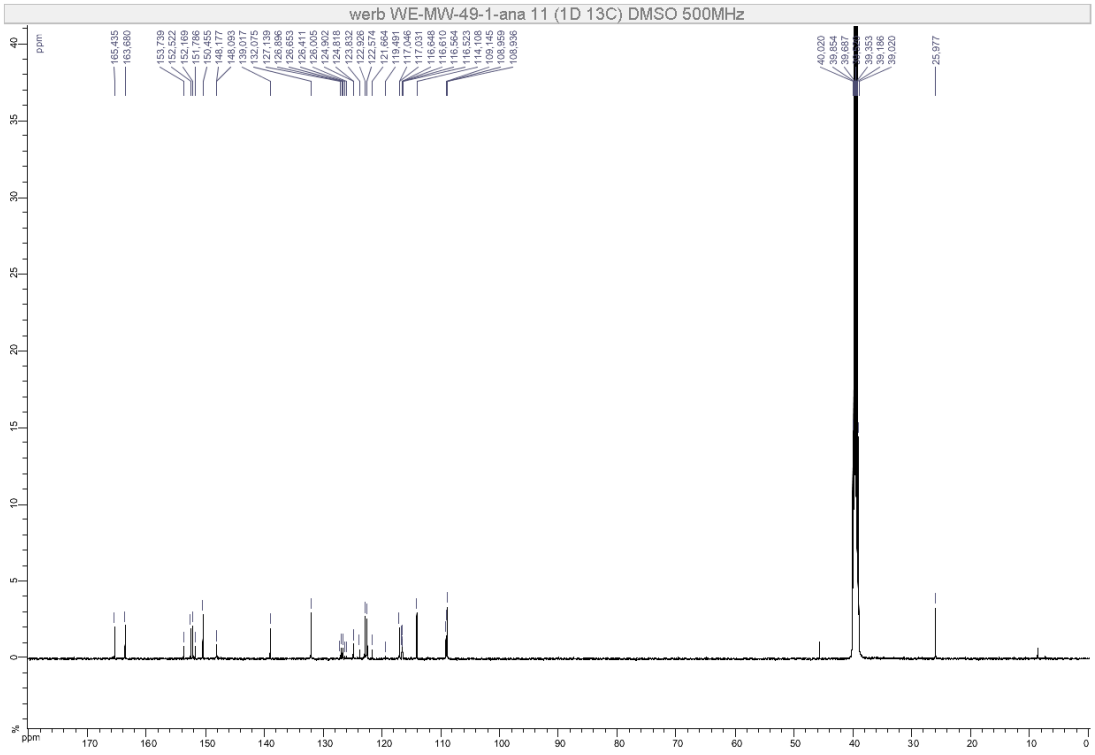
Compound 1a



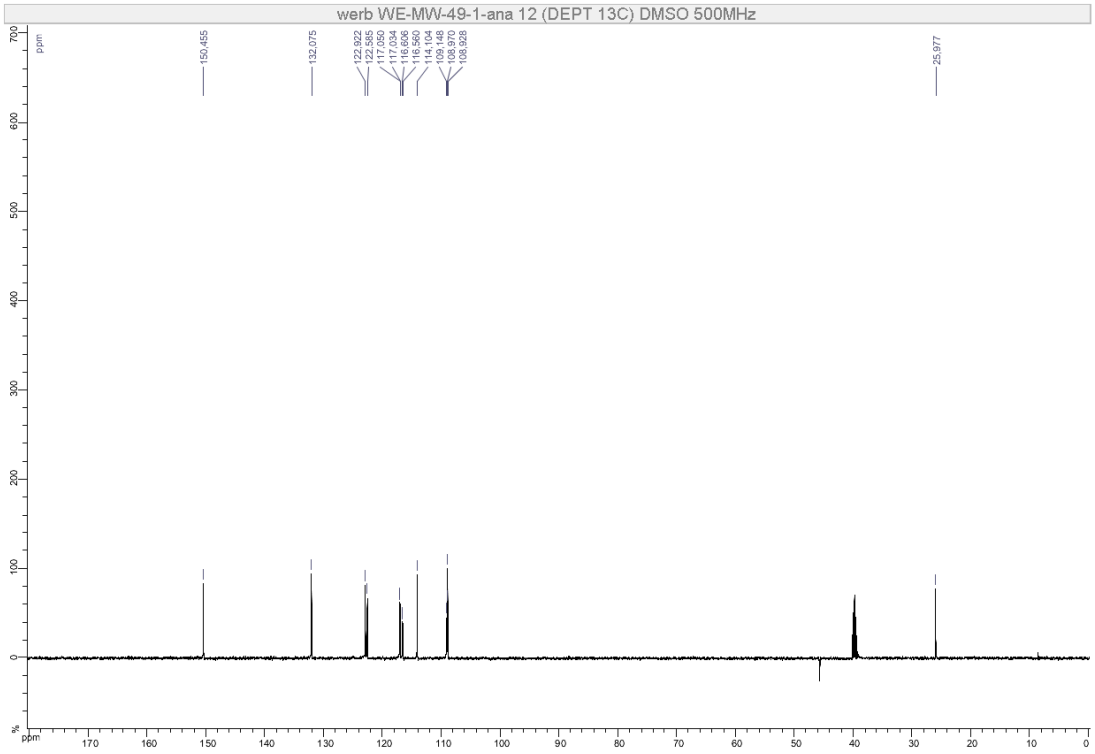
^{1}H NMR



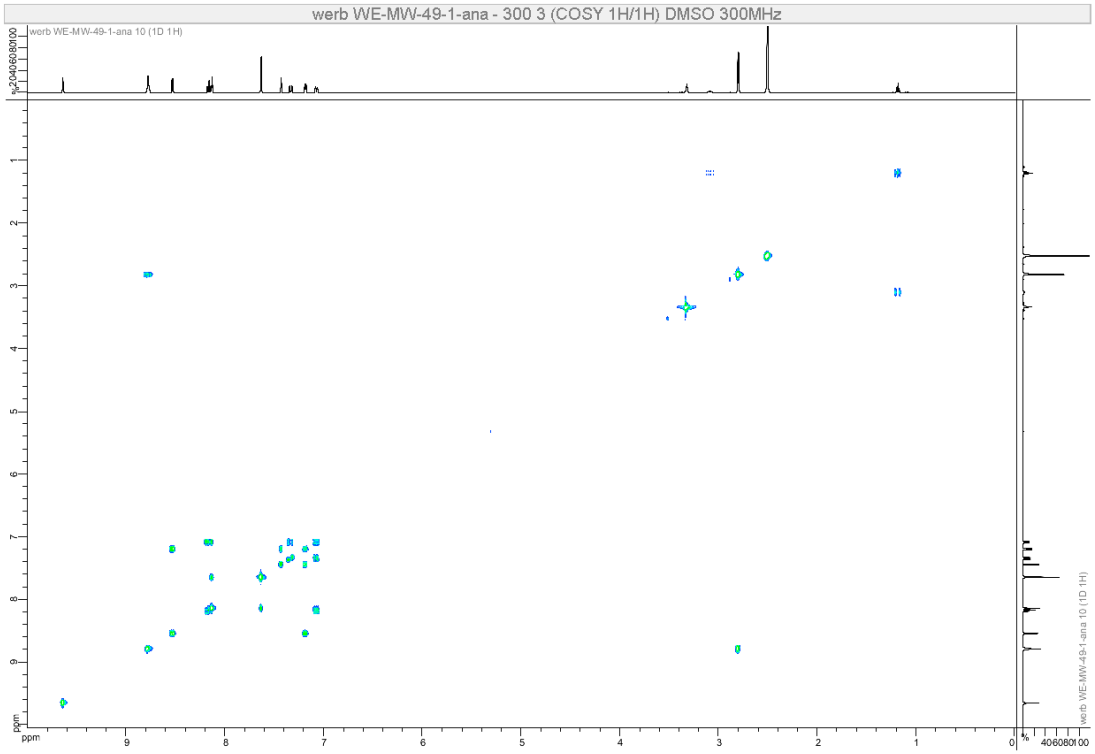
^{13}C NMR



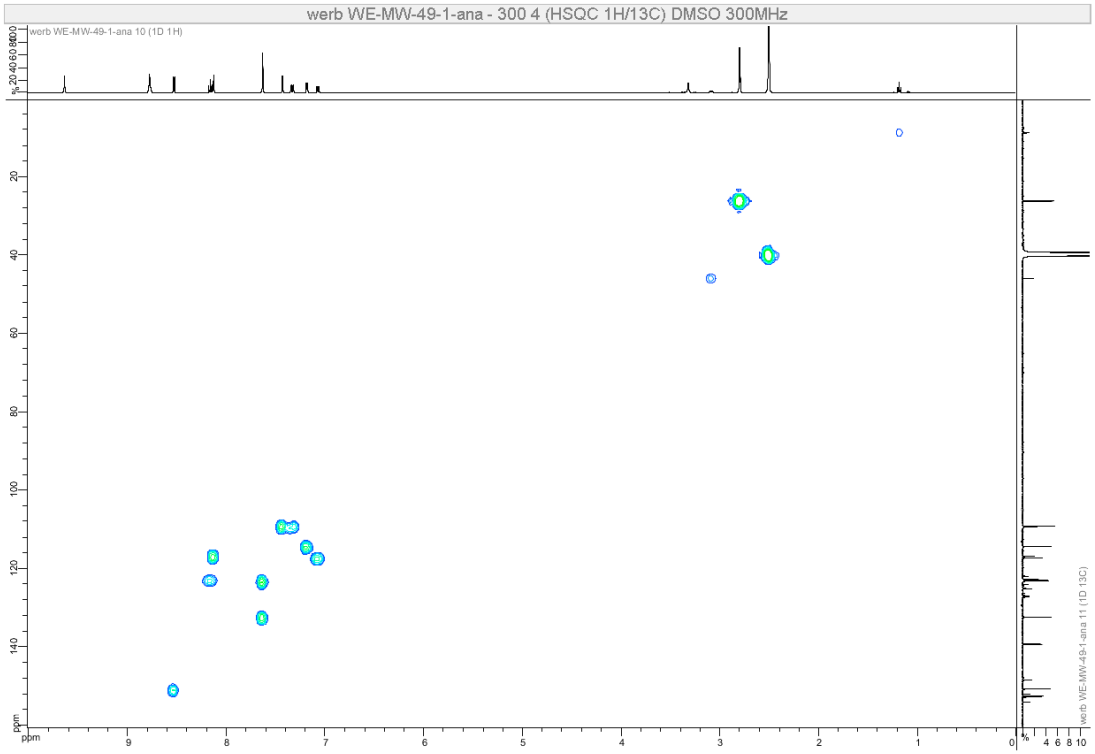
DEPT 135 NMR



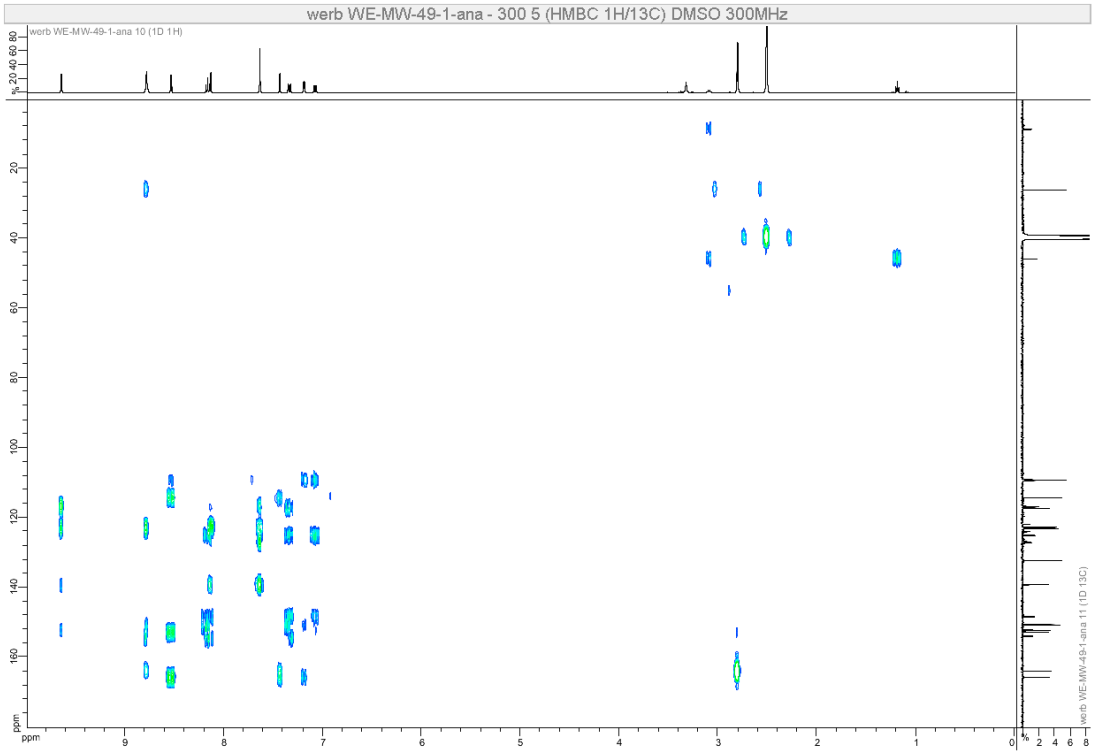
COSY NMR



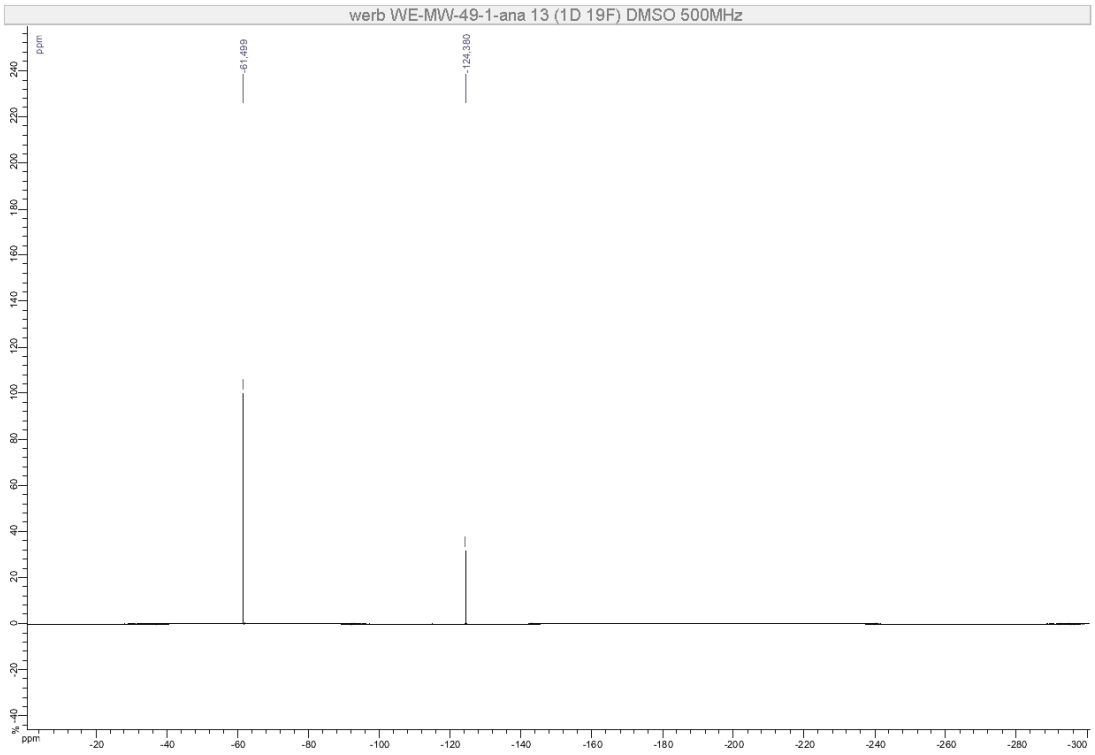
HSQC NMR



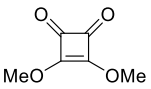
HMBC NMR



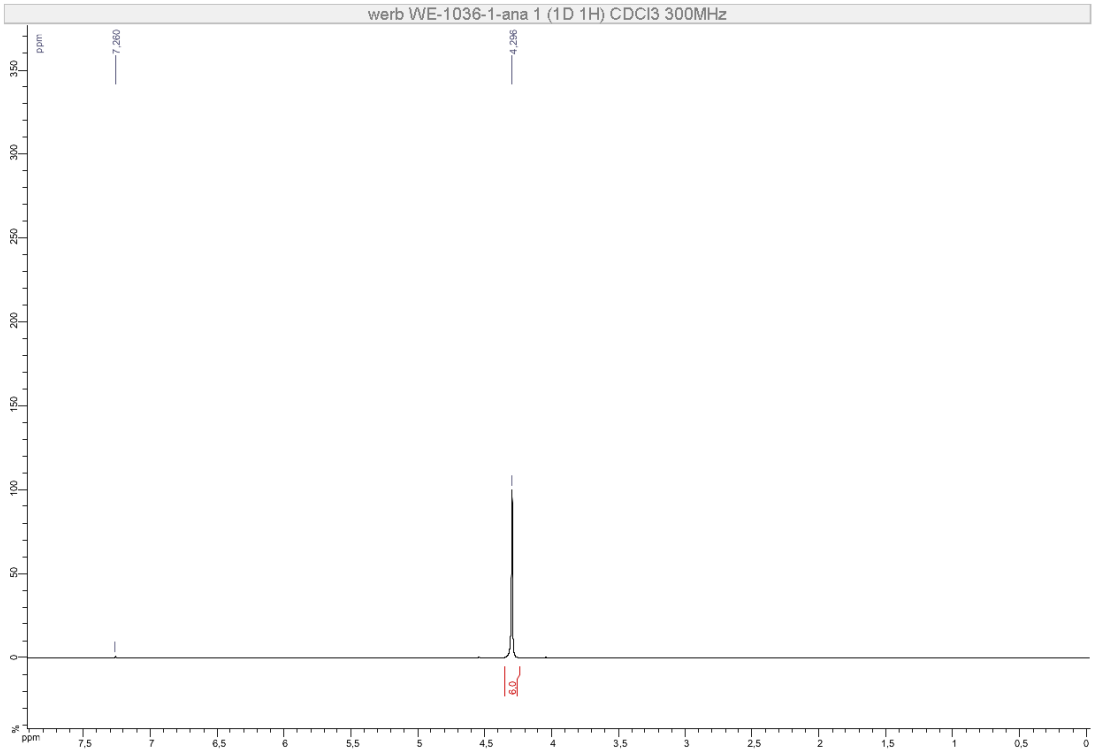
^{19}F NMR


werb WE-MW-49-1-ana 13 (1D 19F) DMSO 500MHz
ppm
-61,499
-124,380
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
%
ppm
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
-260
-280
-300

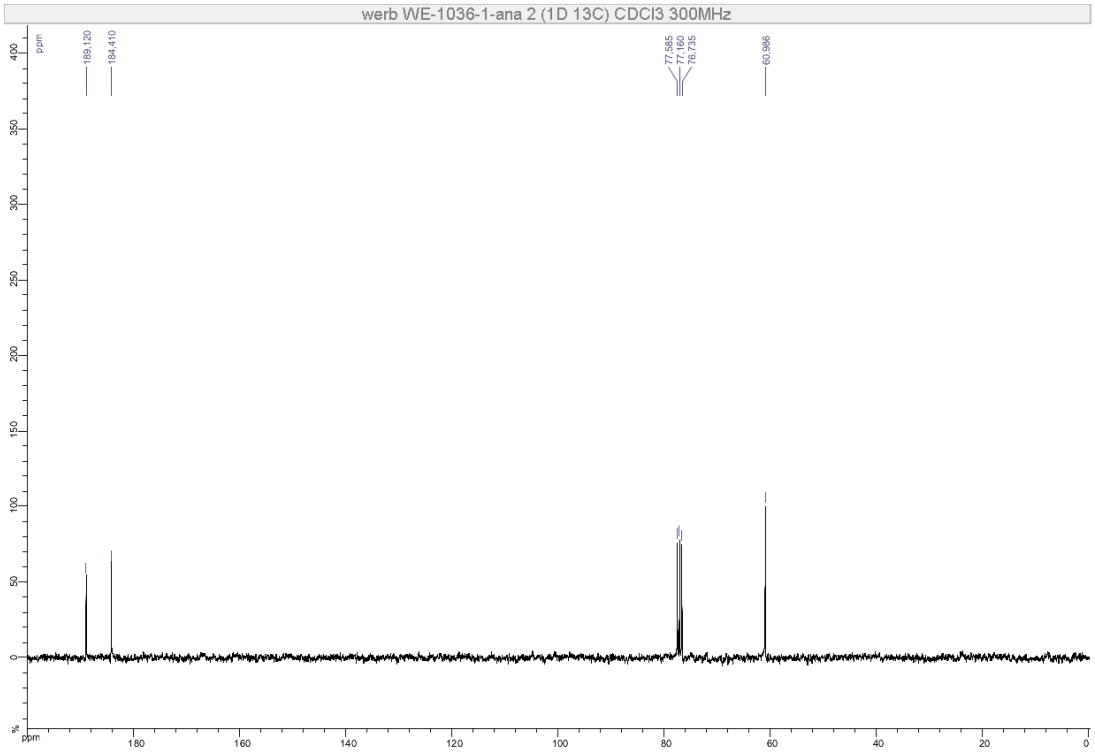
Compound 17



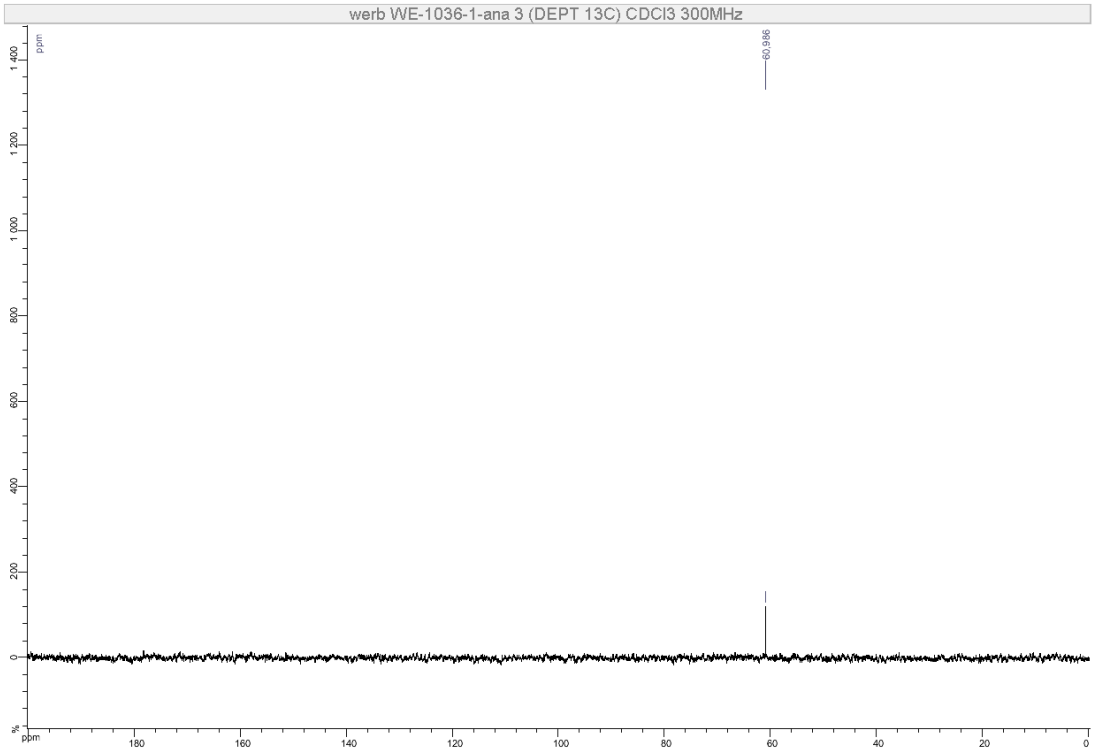
^{1}H NMR



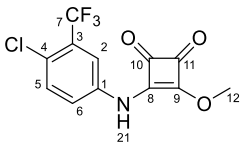
^{13}C NMR



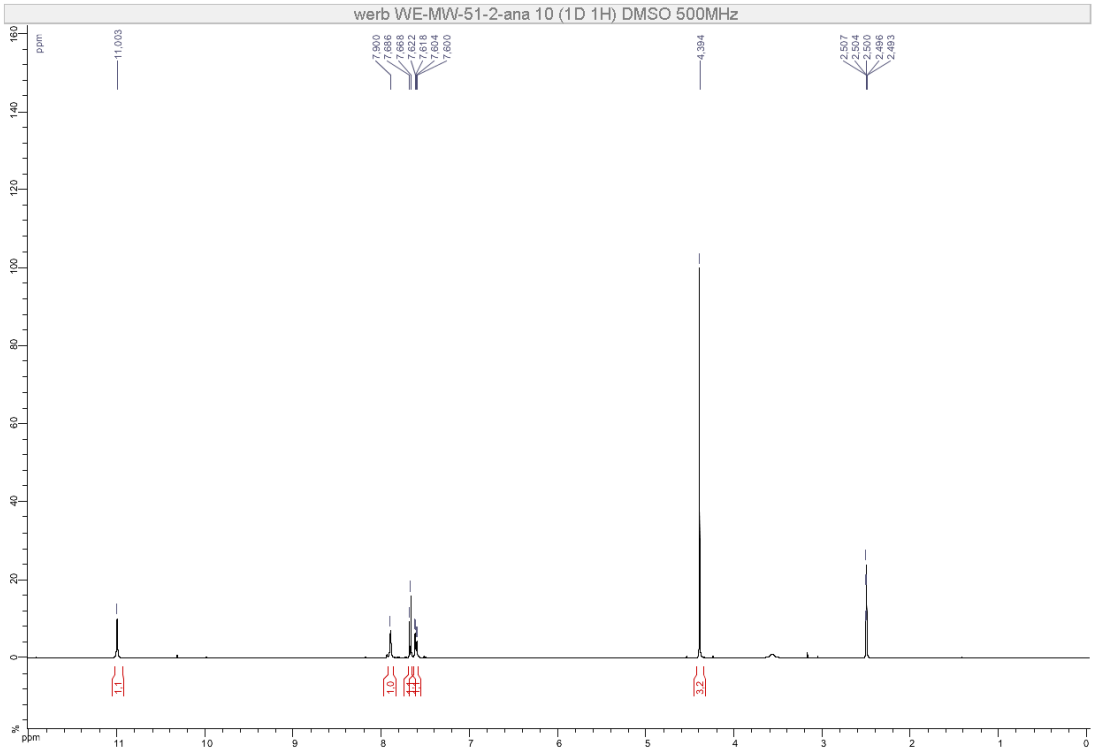
DEPT 135 NMR


werb WE-1036-1-ana 3 (DEPT 13C) CDCl3 300MHz
60.986
ppm
1.400
1.200
1.000
800
600
400
200
0
%
ppm
180
160
140
120
100
80
60
40
20
0

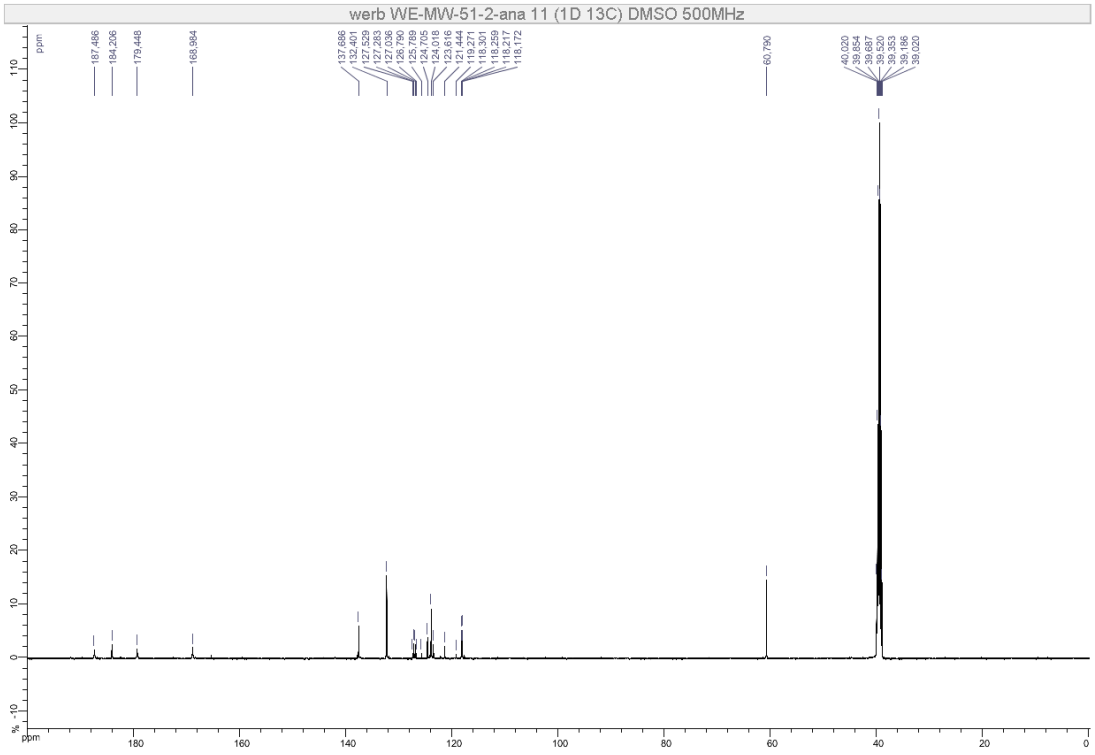
Compound 18



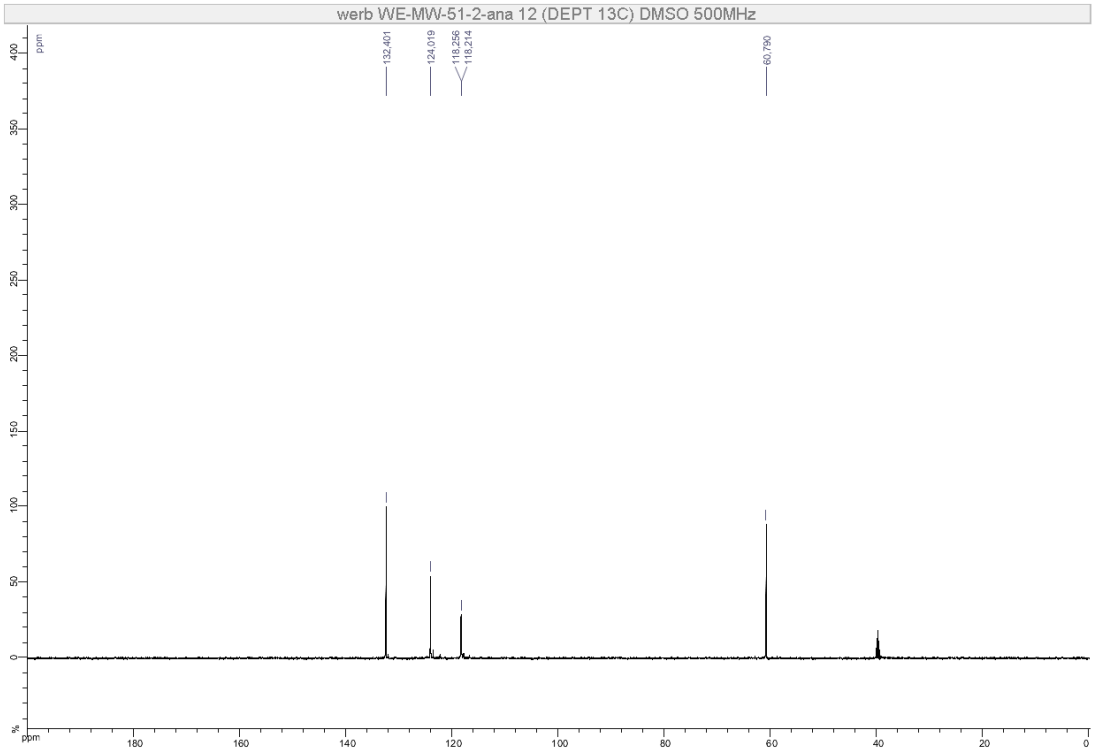
^{1}H NMR



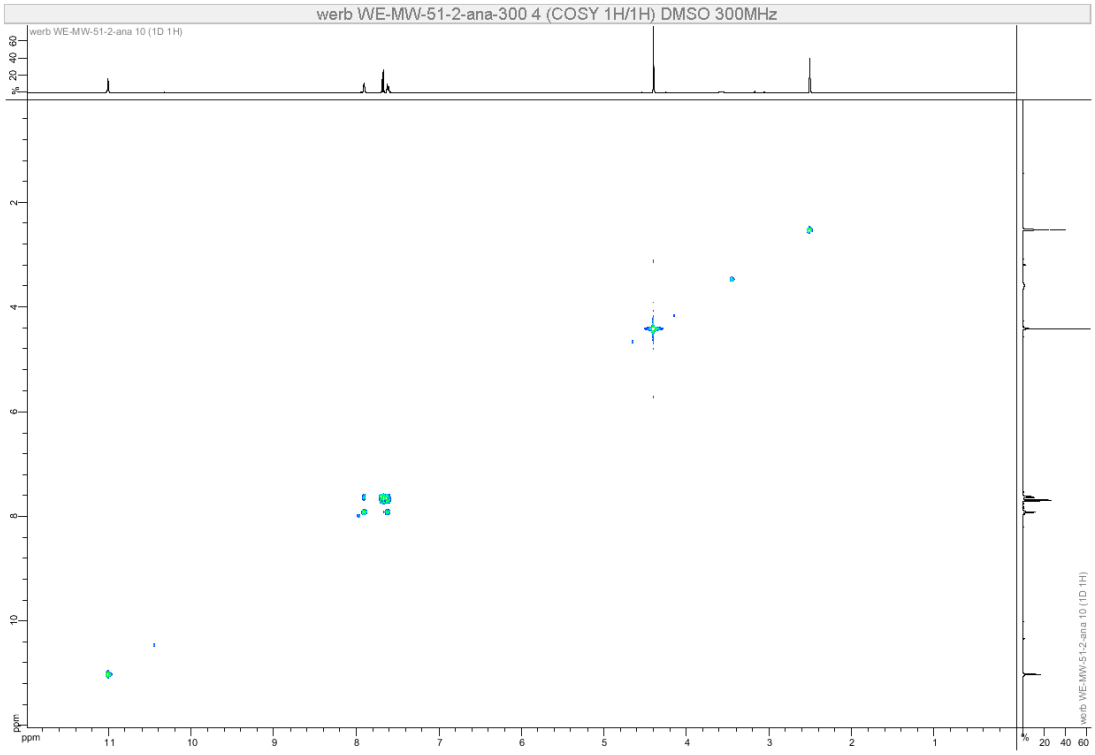
^{13}C NMR



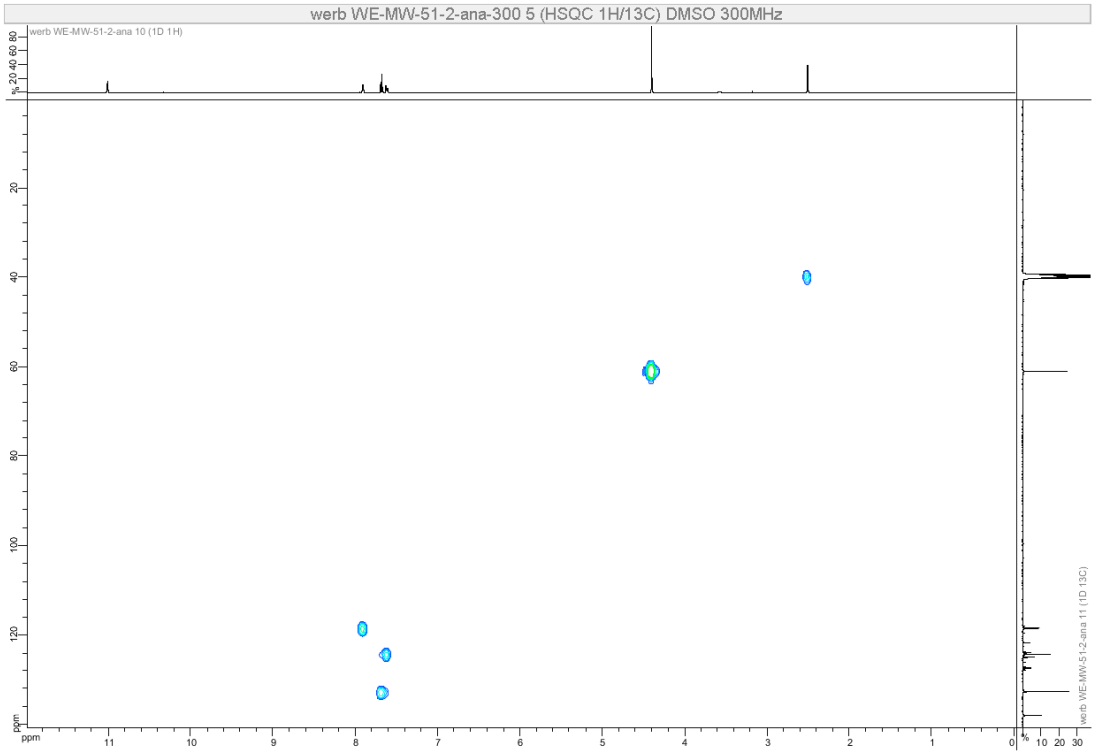
DEPT 135 NMR



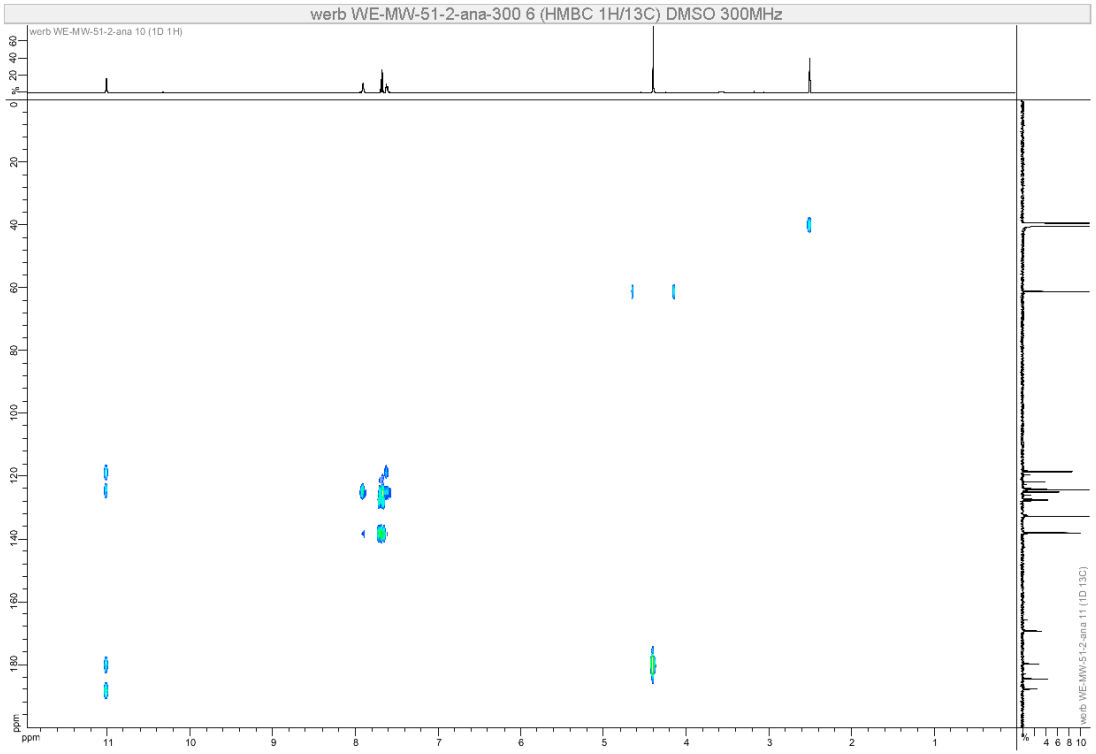
COSY NMR



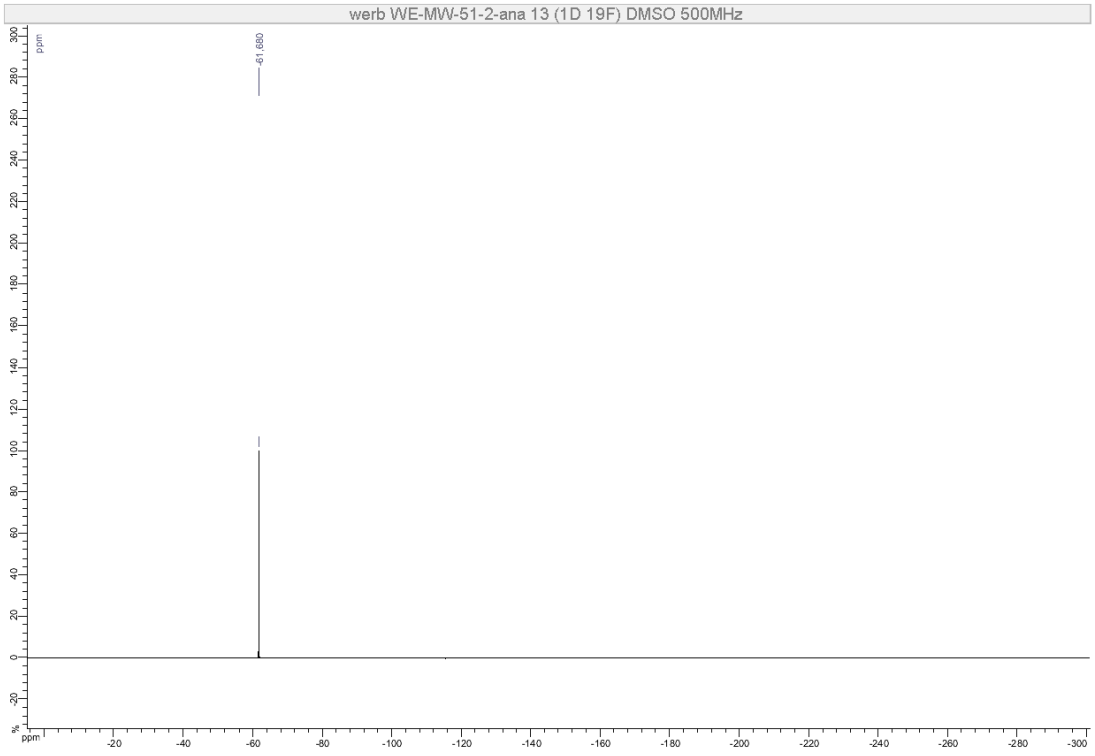
HSQC NMR



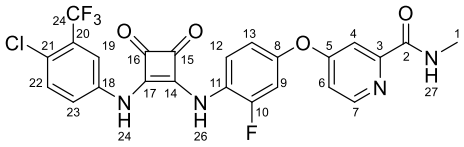
HMBC NMR



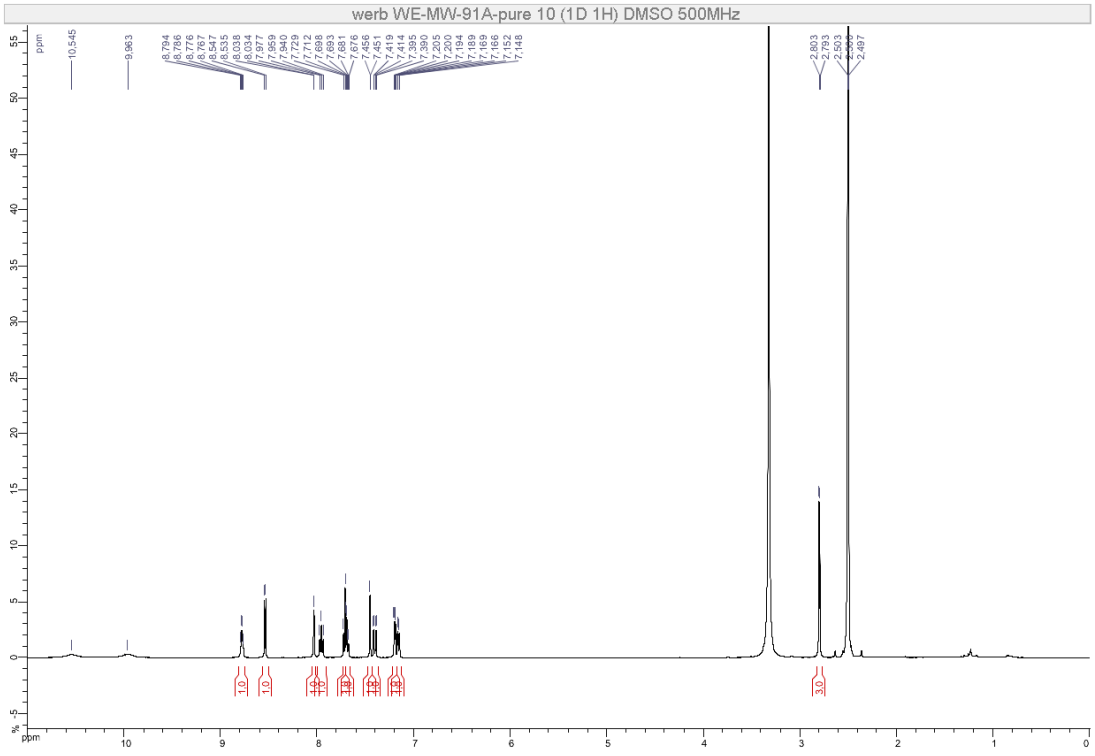
^{19}F NMR


werb WE-MW-51-2-ana 13 (1D 19F) DMSO 500MHz
ppm
-61,680
ppm
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
-260
-280
-300

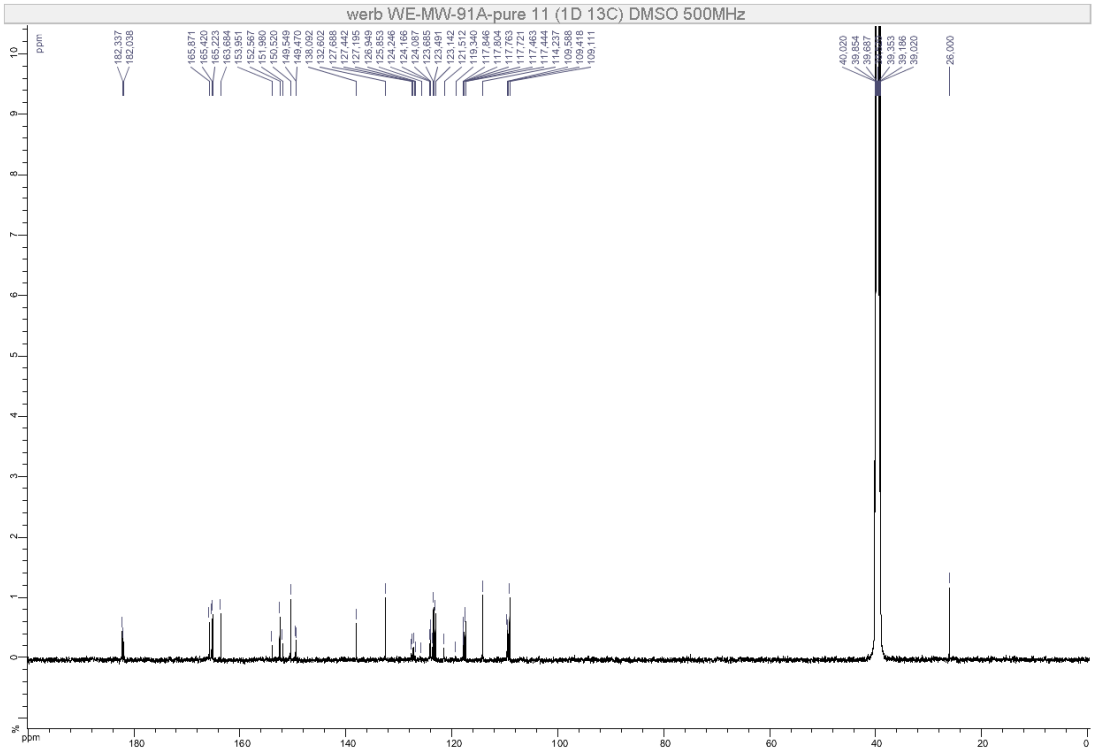
Compound 1b



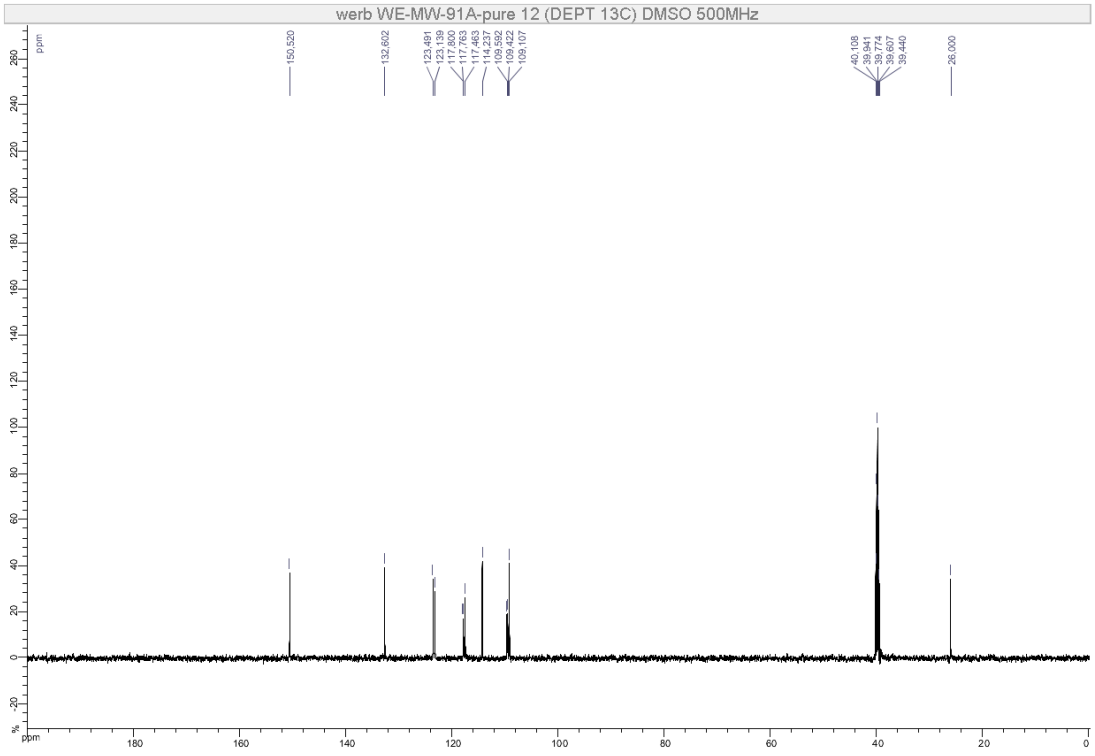
^{1}H NMR



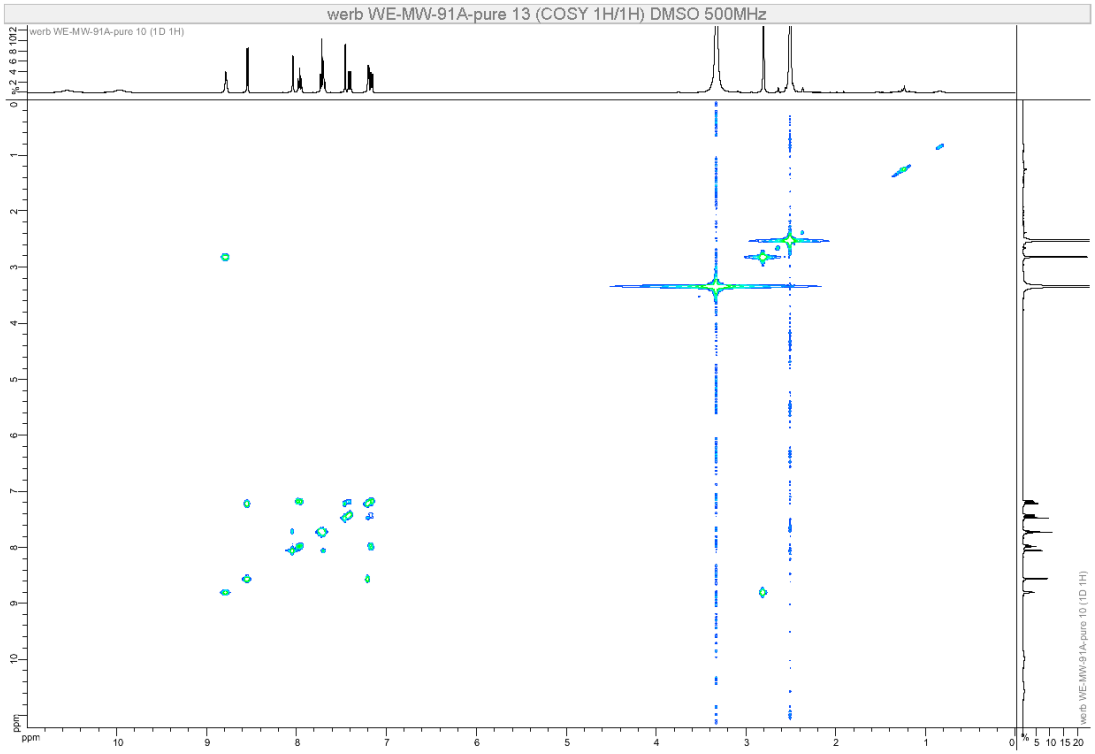
^{13}C NMR



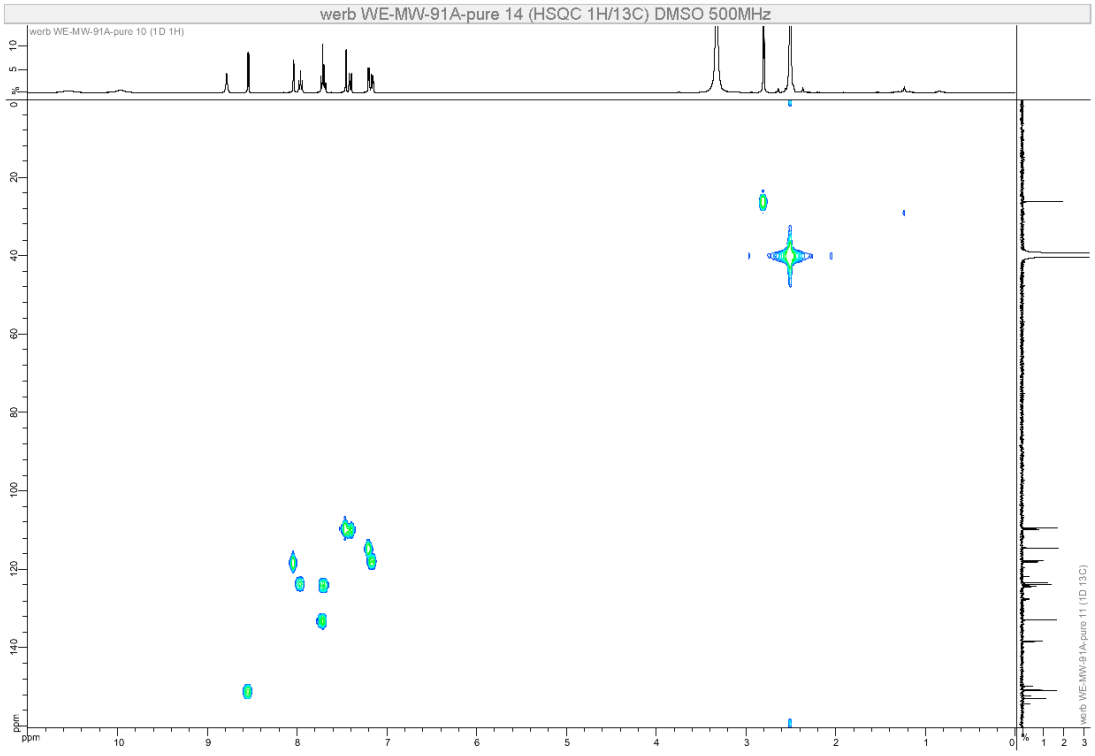
DEPT 135 NMR



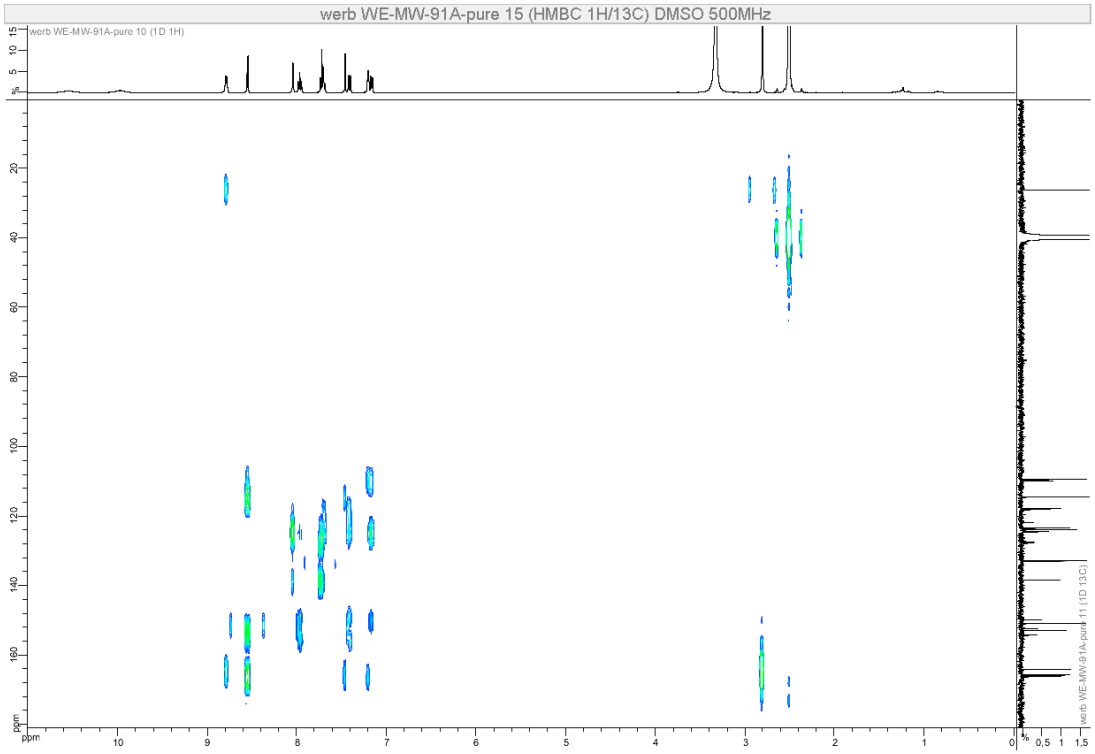
COSY NMR



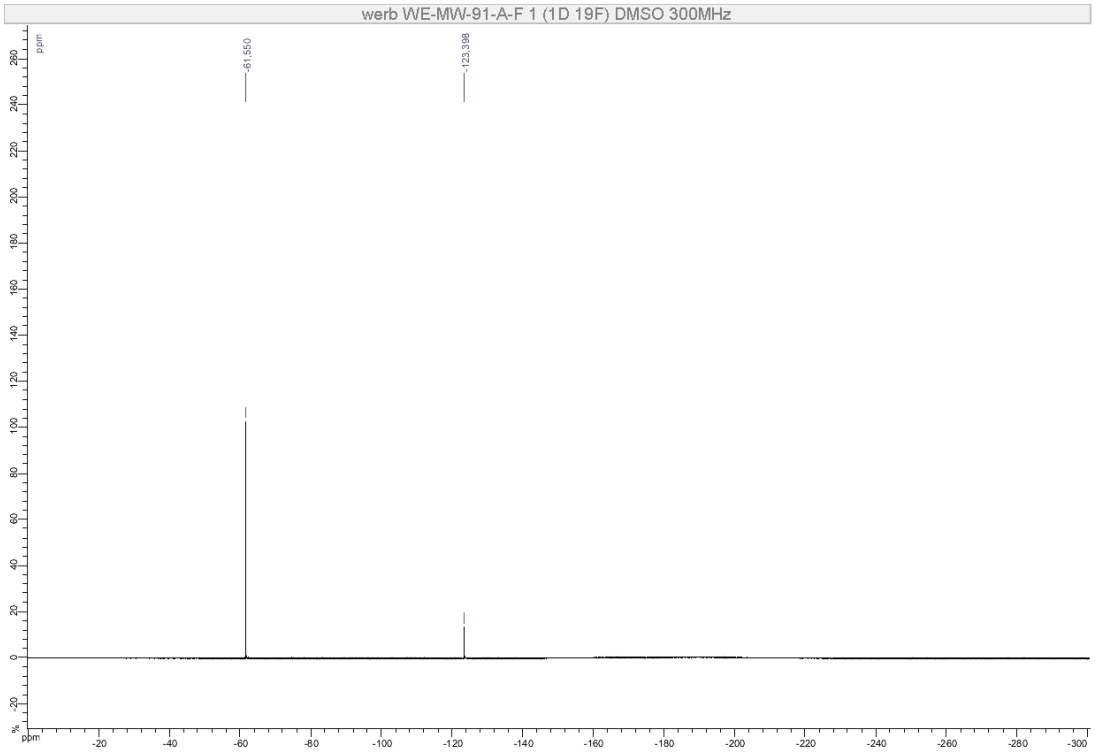
HSQC NMR



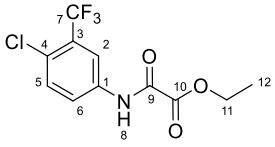
HMBC NMR



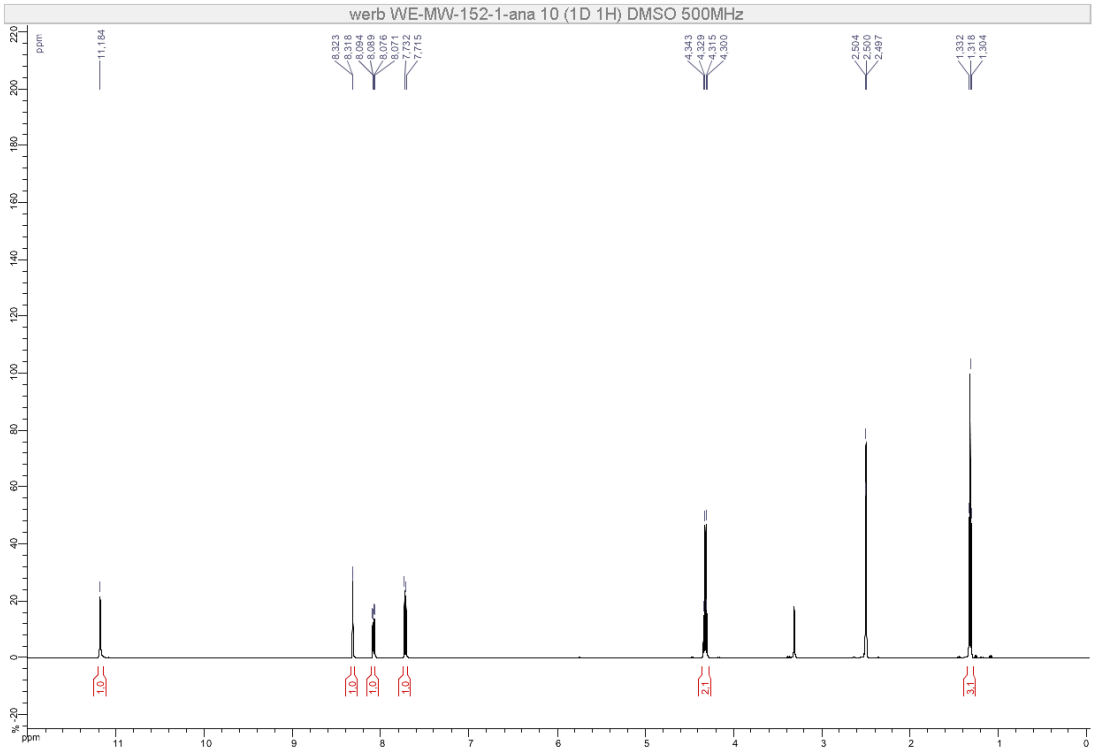
^{19}F NMR



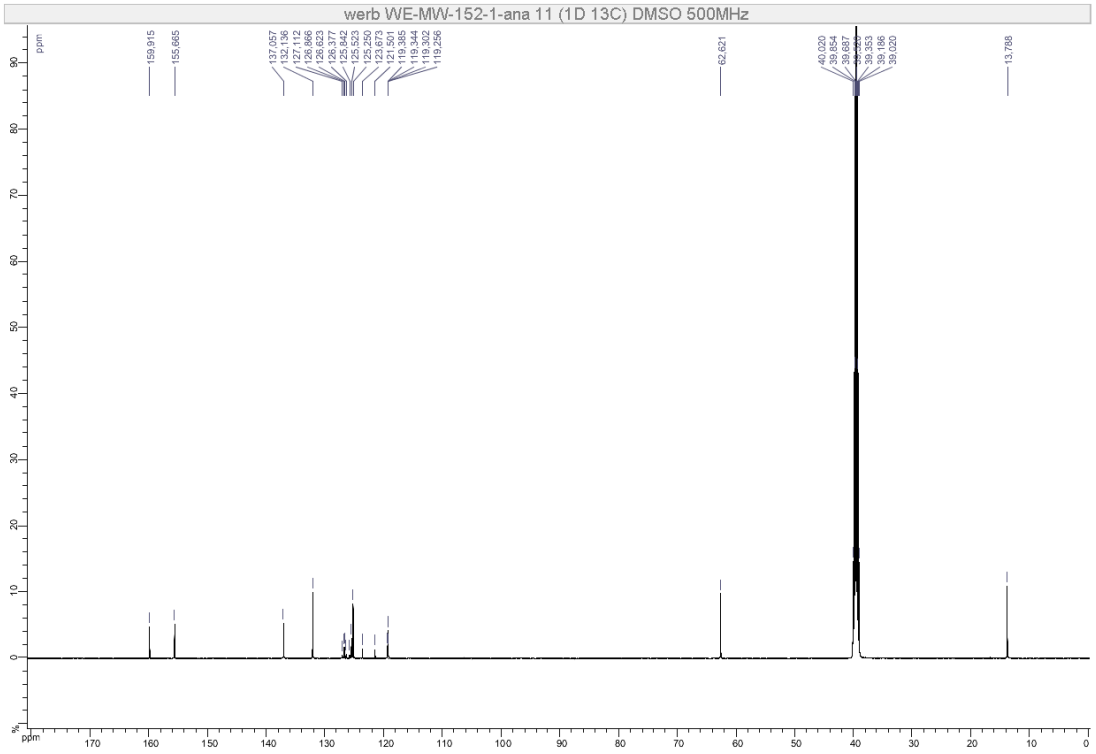
Compound 19



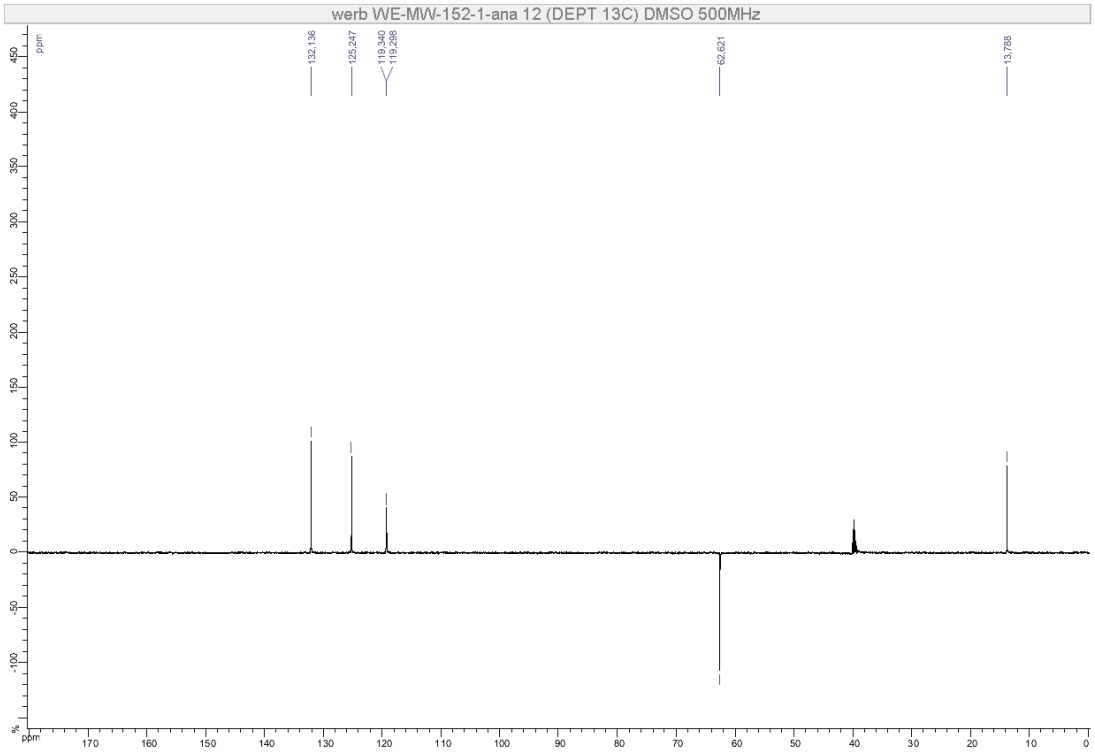
^{1}H NMR



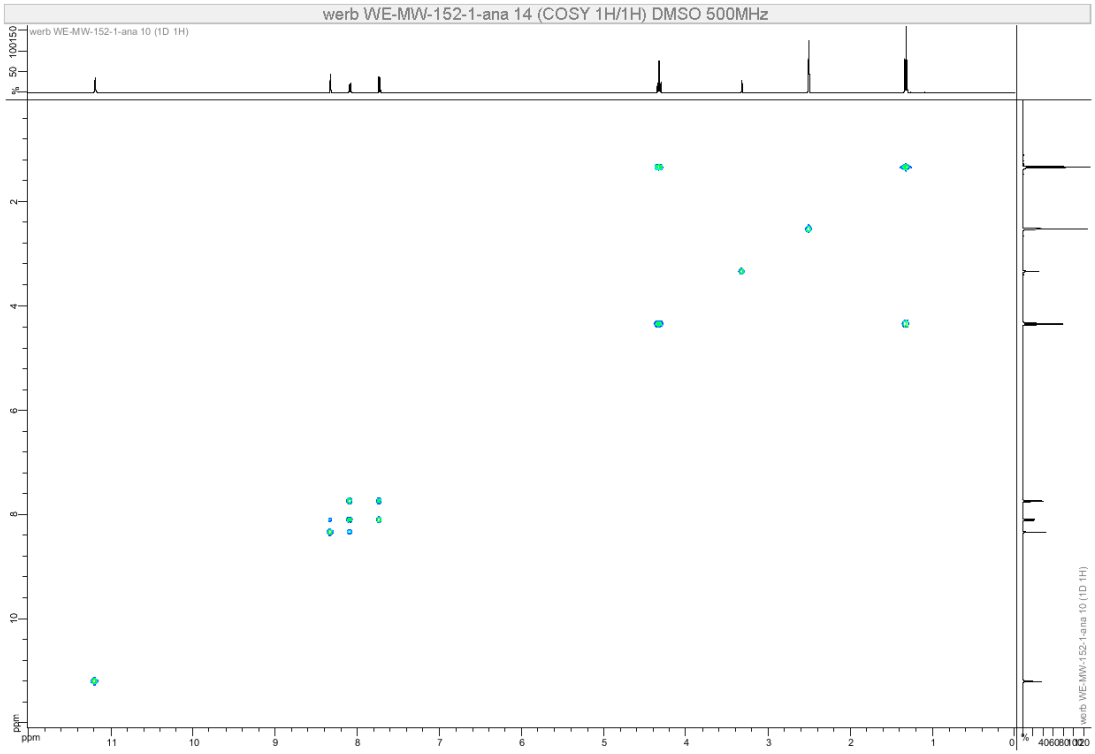
^{13}C NMR



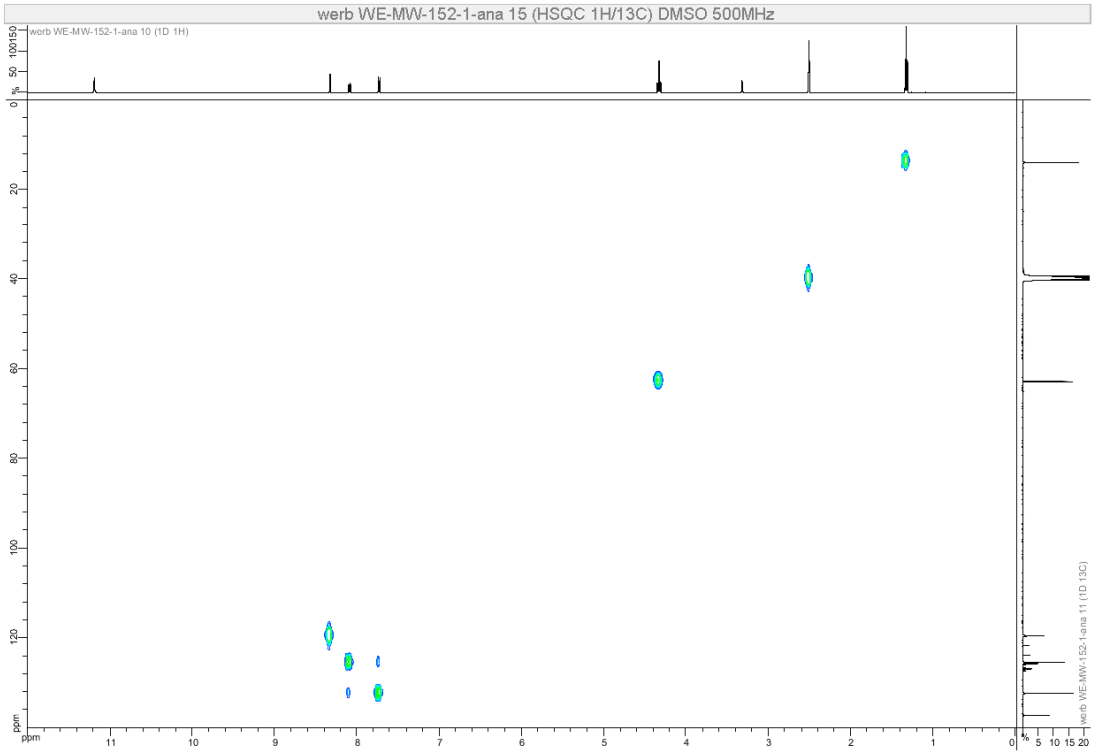
DEPT 135 NMR



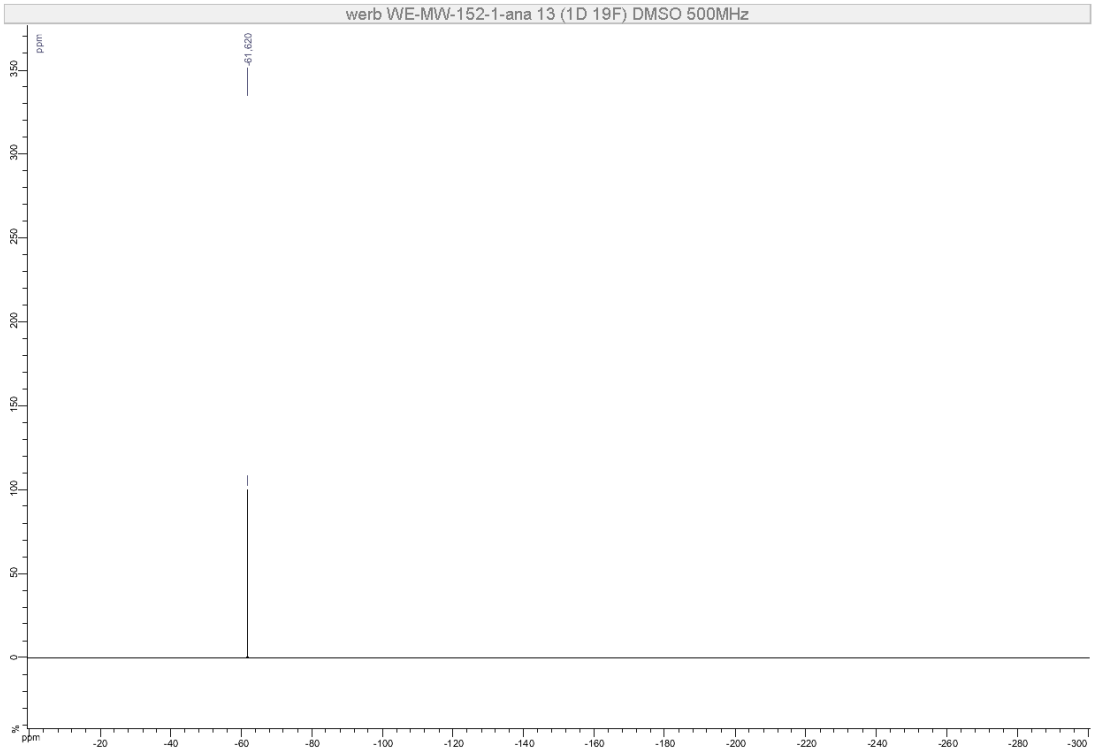
COSY NMR



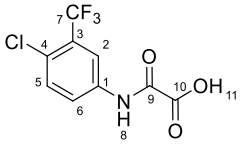
HSQC NMR



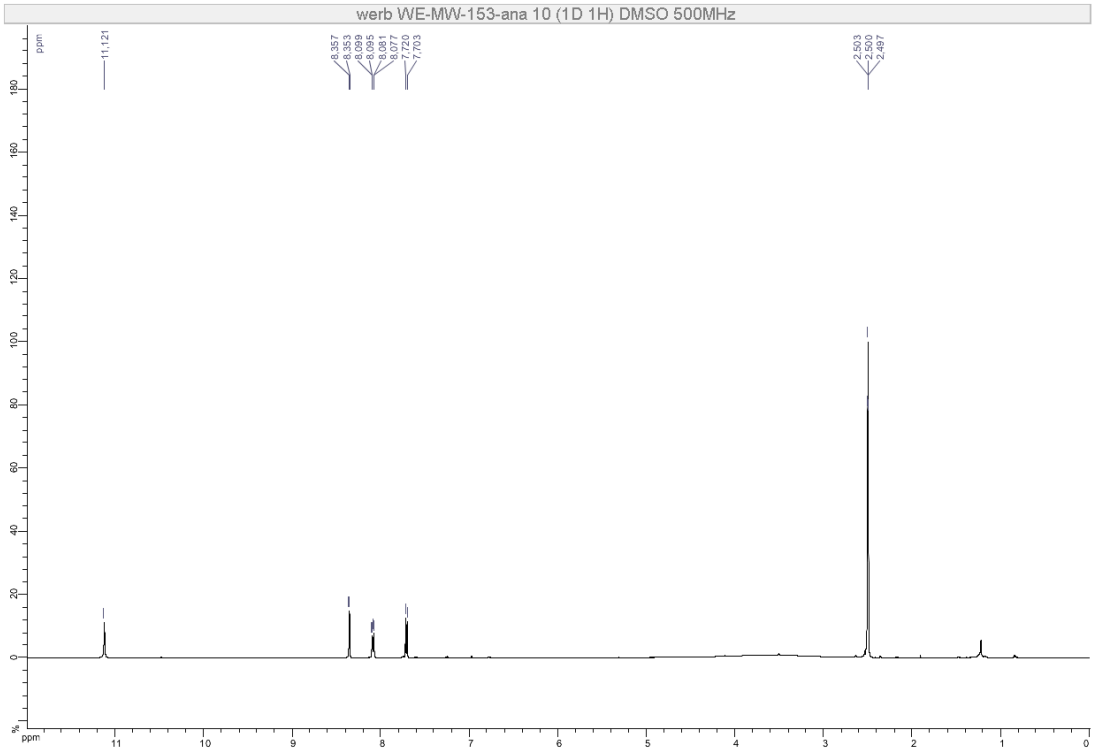
^{19}F NMR



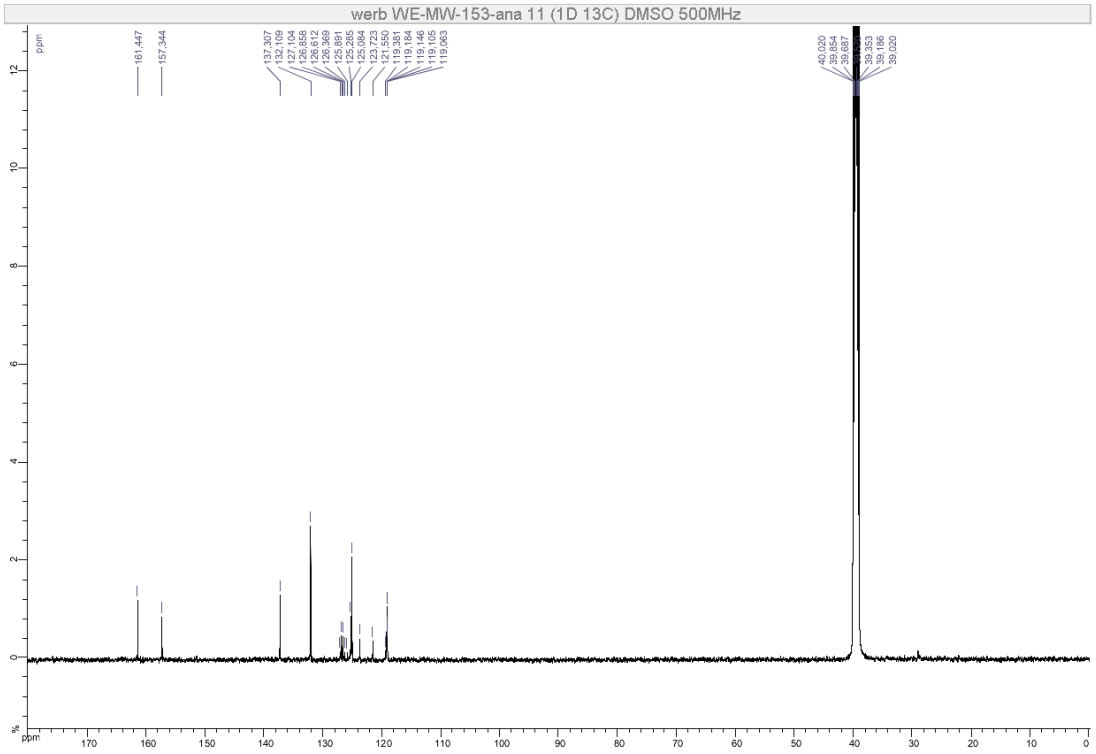
Compound 20



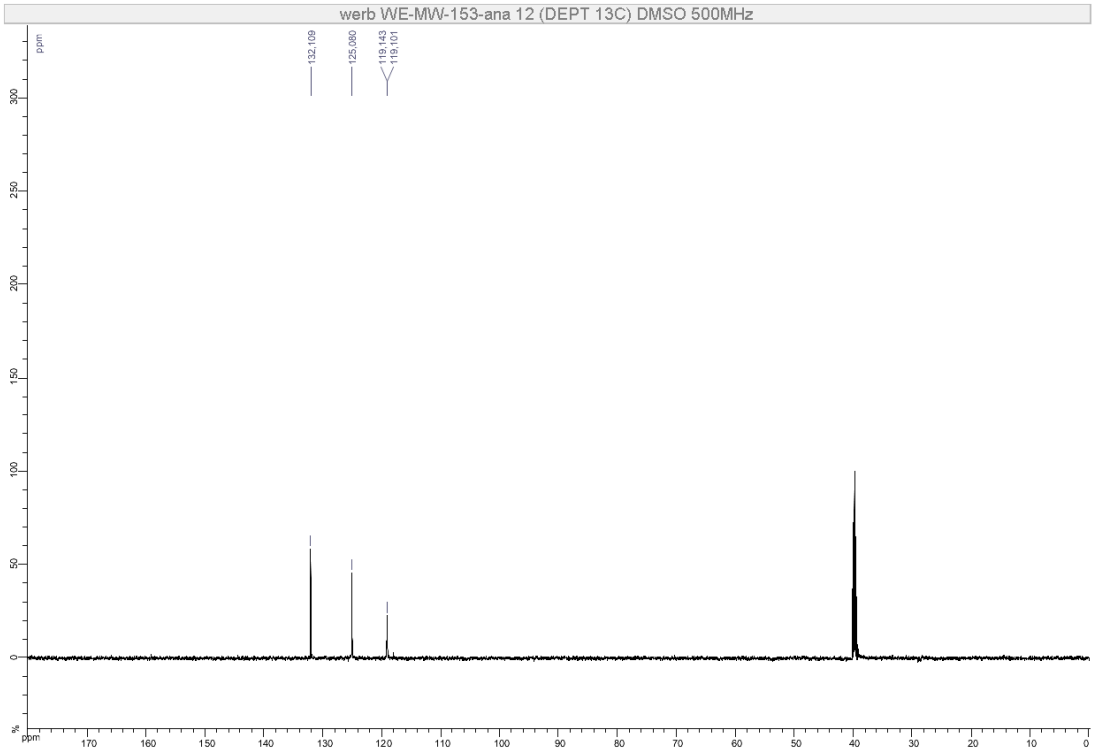
^{1}H NMR



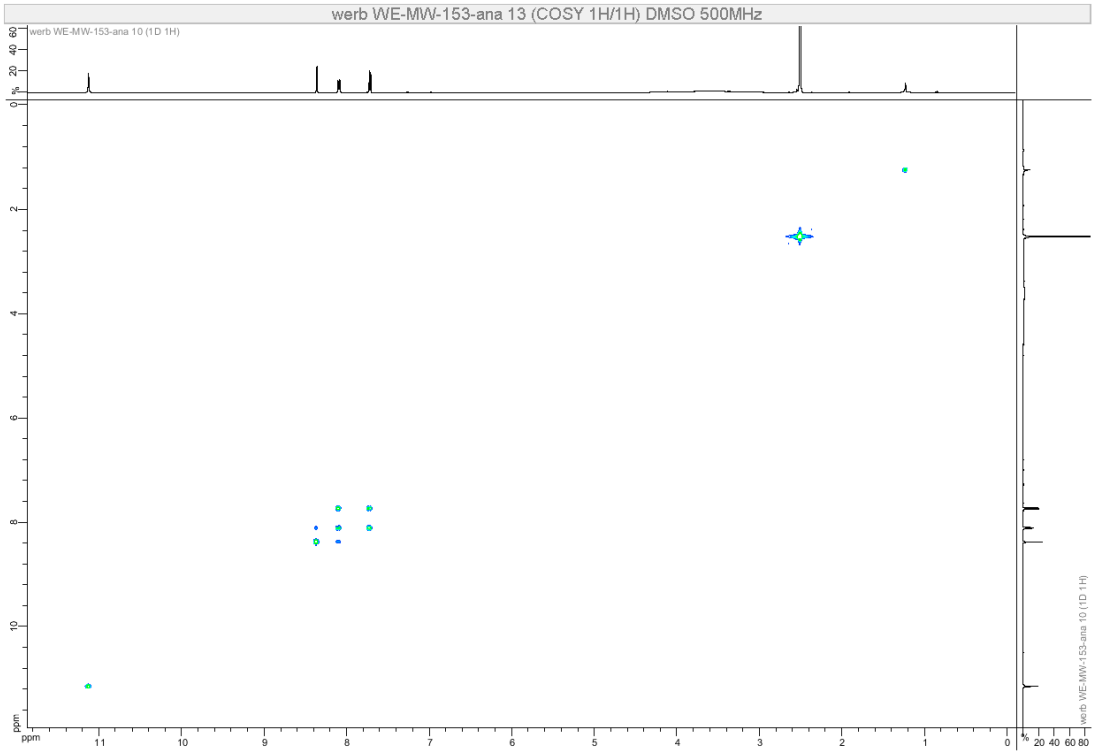
^{13}C NMR



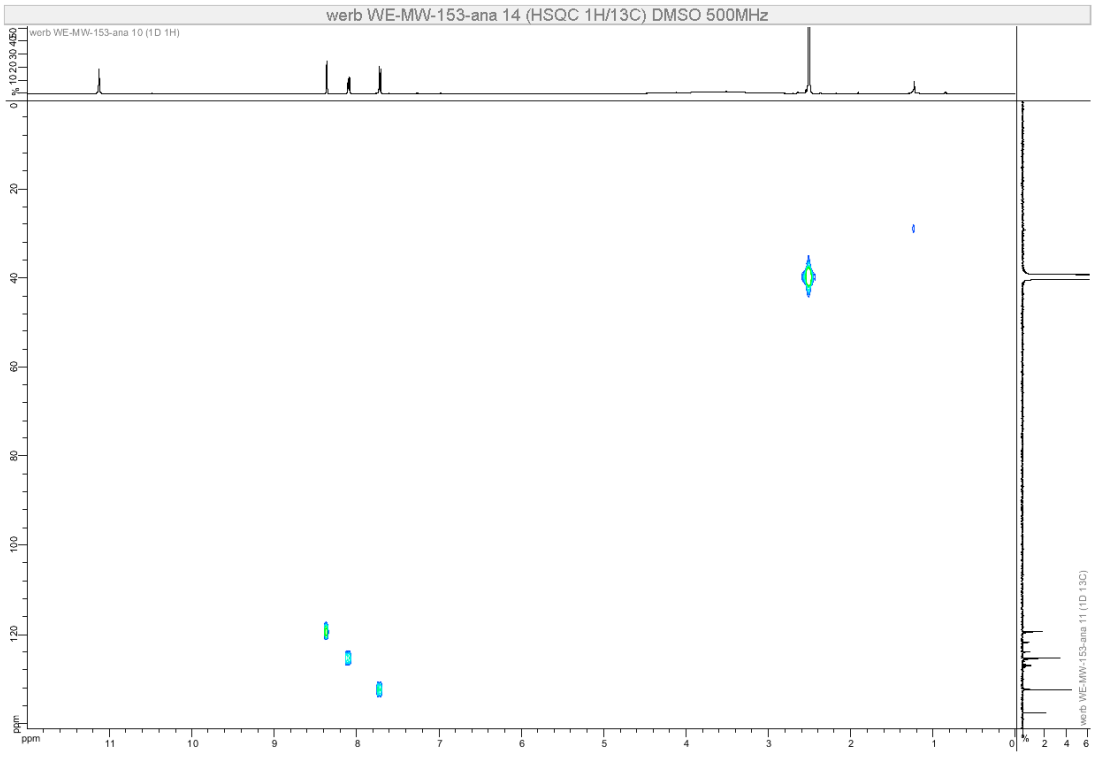
DEPT 135 NMR



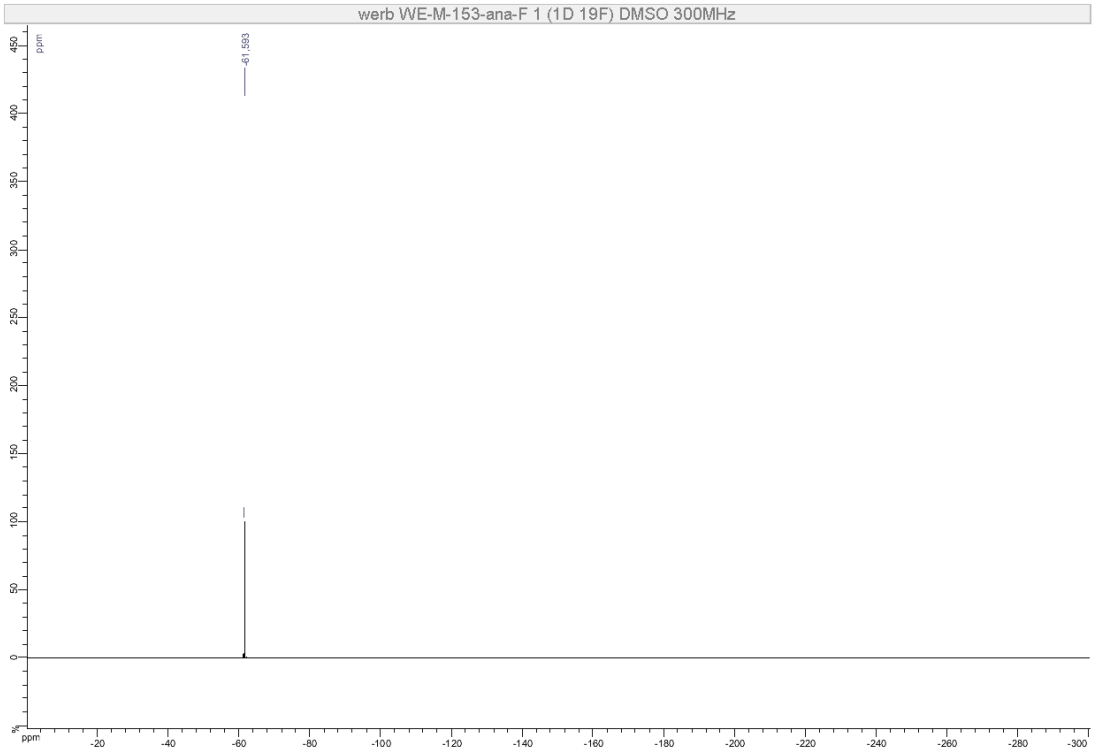
COSY NMR



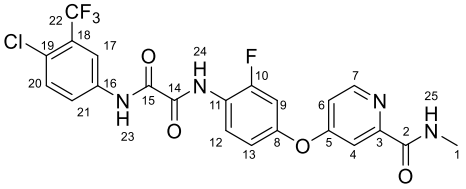
HSQC NMR



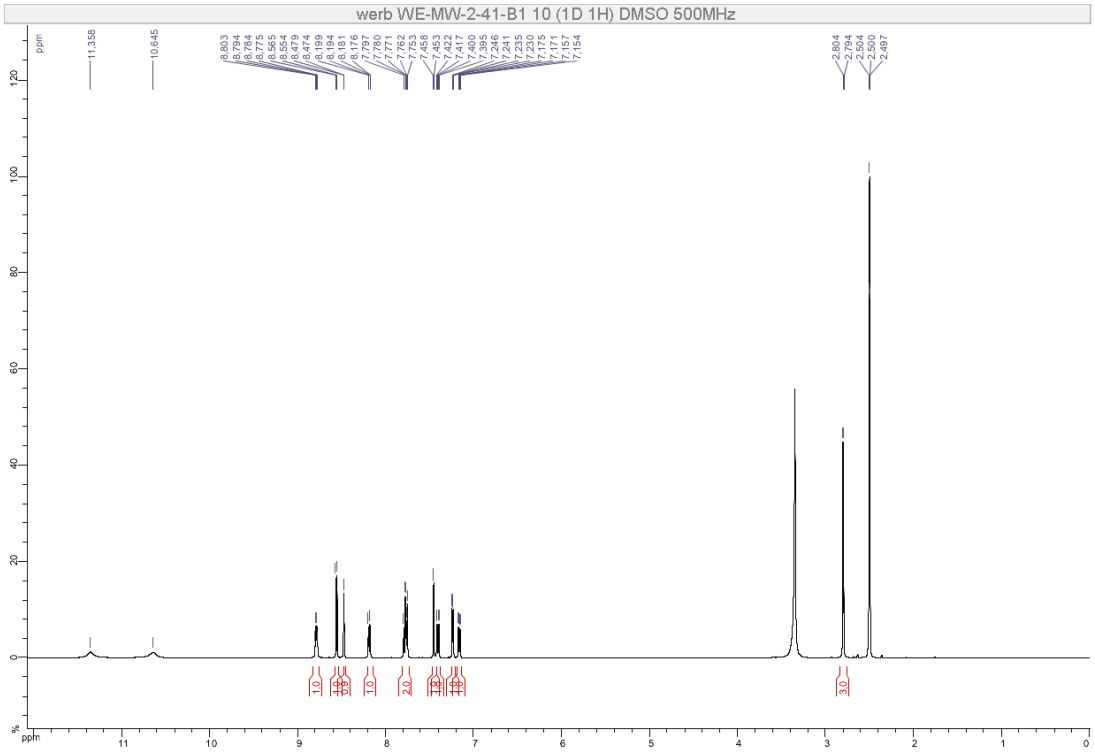
^{19}F NMR



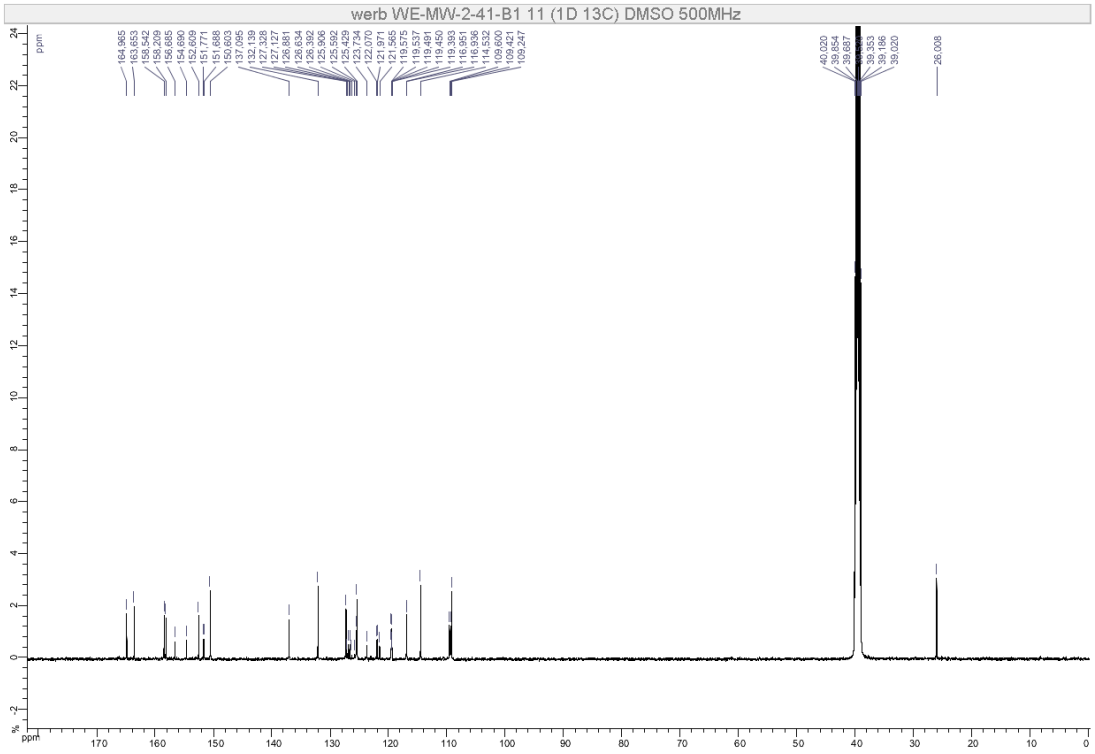
Compound 1c



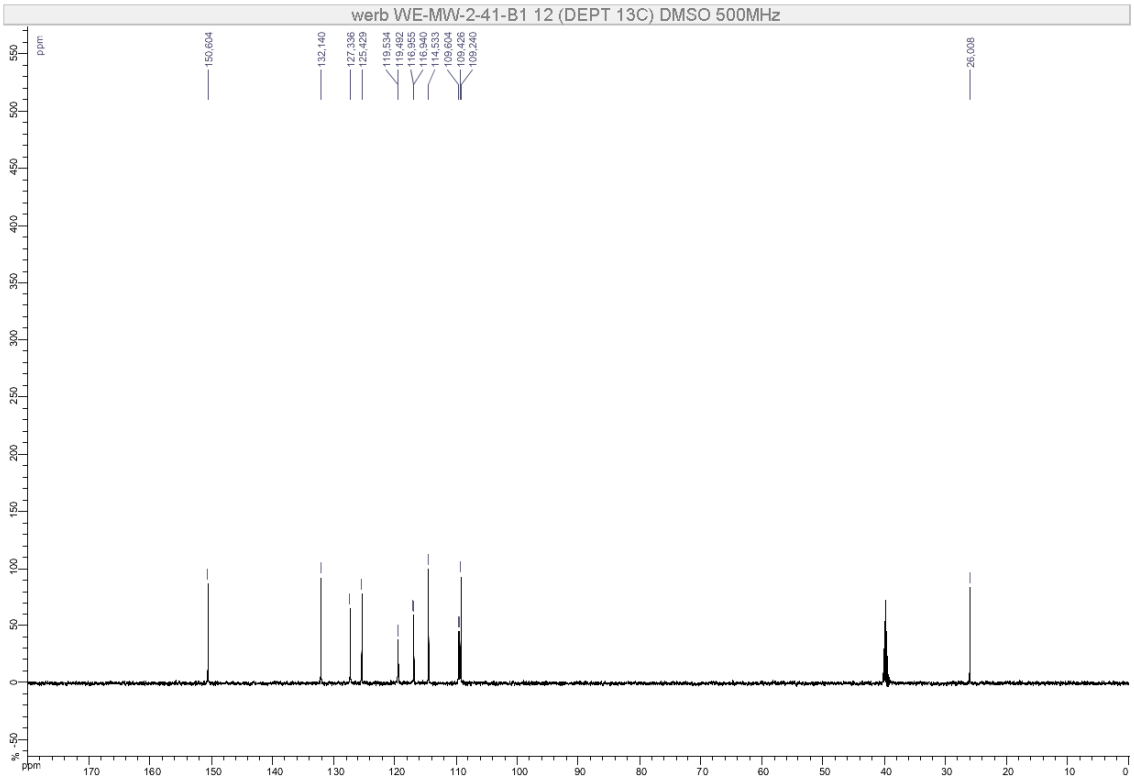
^{1}H NMR



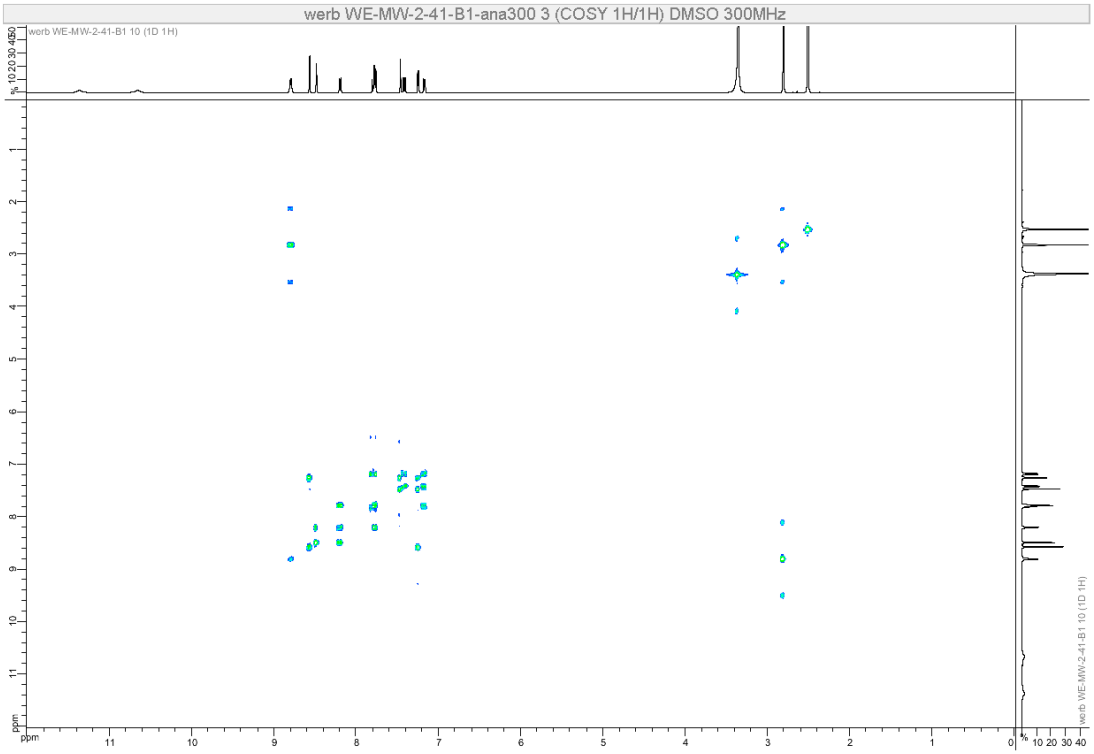
^{13}C NMR



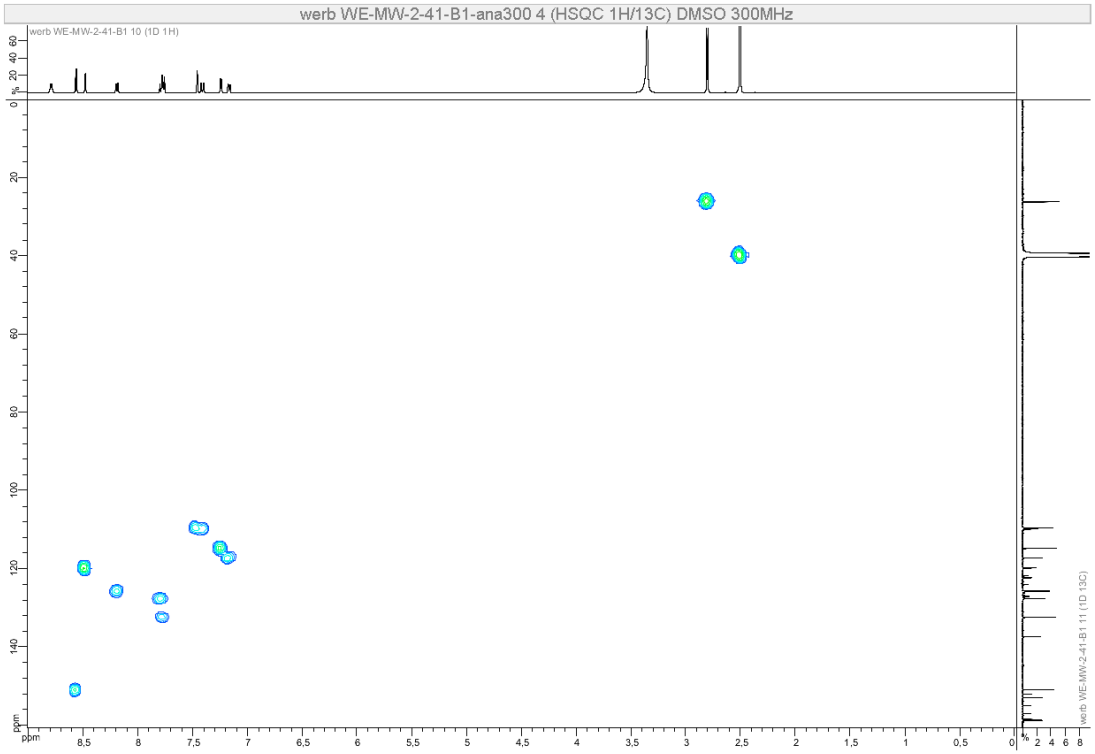
DEPT 135 NMR



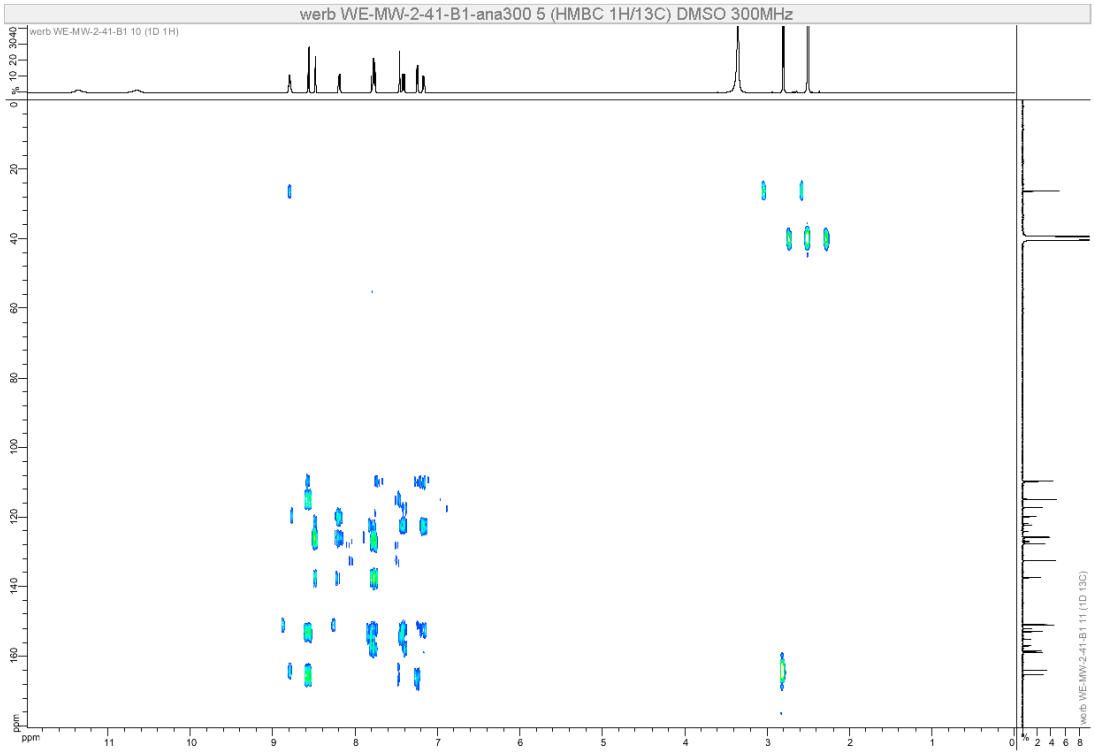
COSY NMR



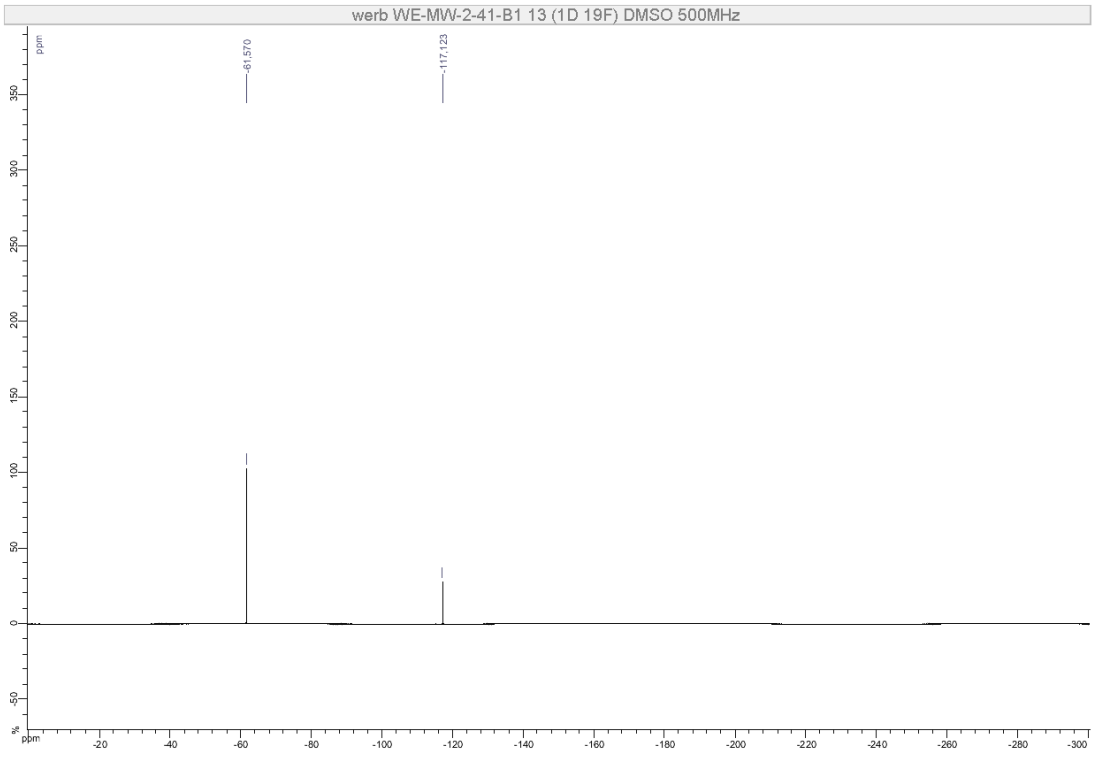
HSQC NMR



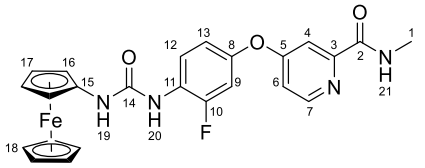
HMBC NMR



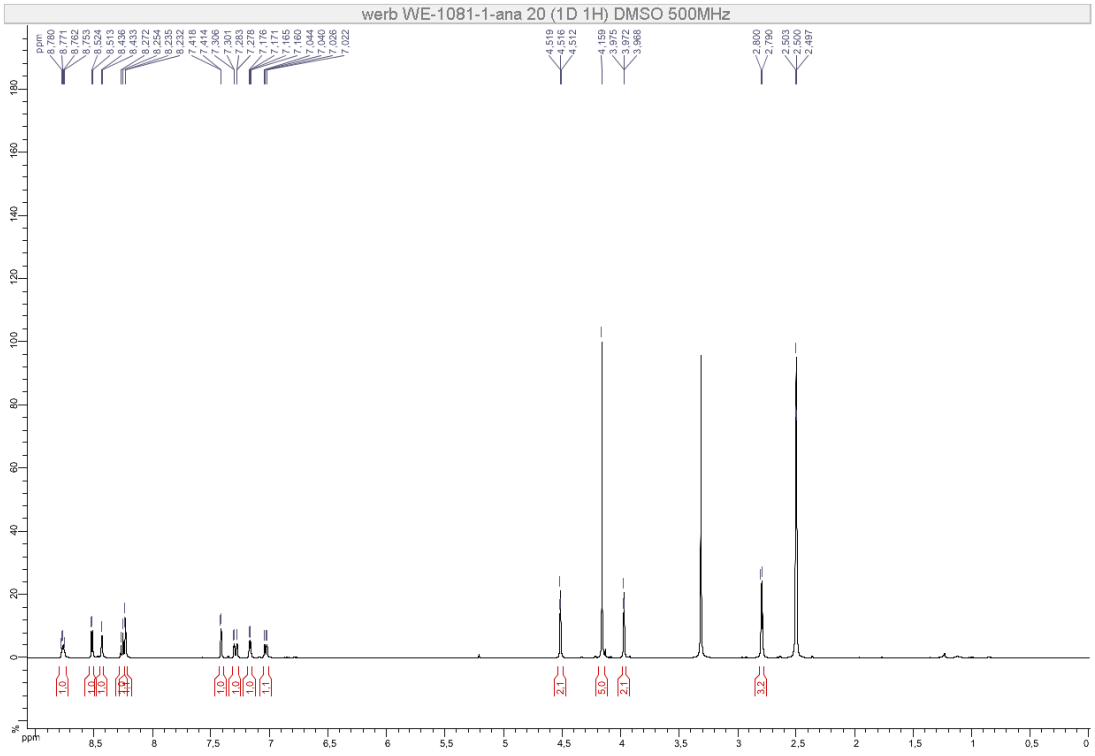
^{19}F NMR


werb WE-MW-2-41-B1 13 (1D 19F) DMSO 500MHz
ppm
-61,570
-117,123
%
ppm
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
-260
-280
-300

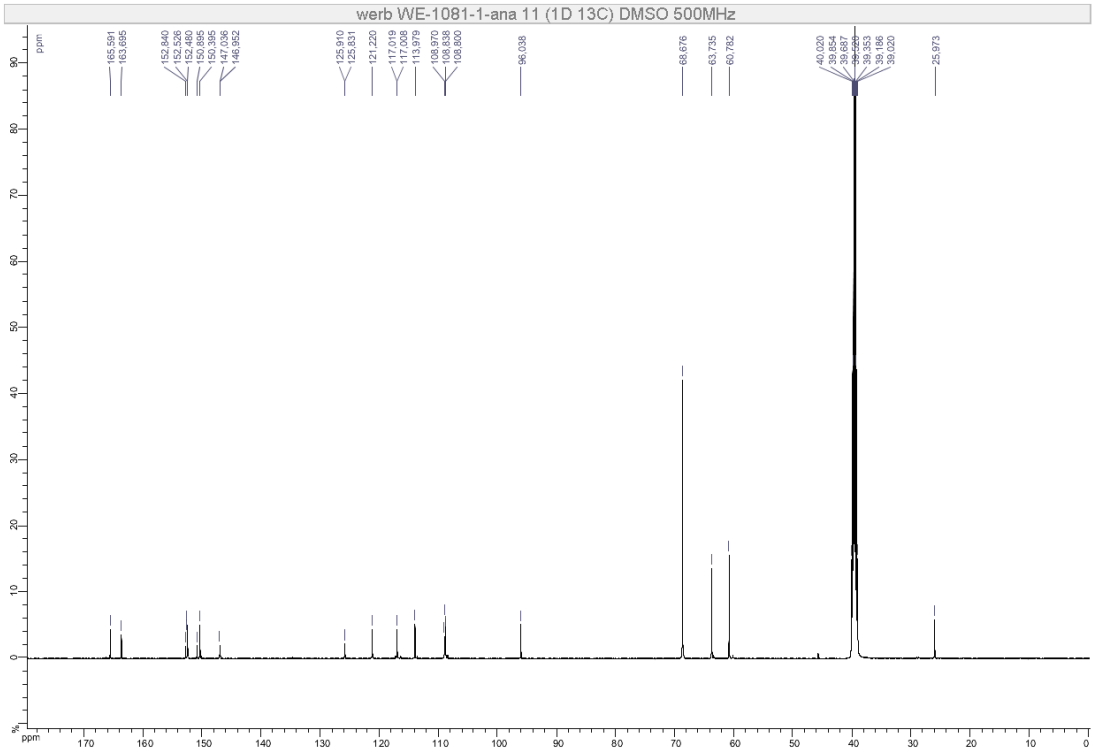
Compound 2a



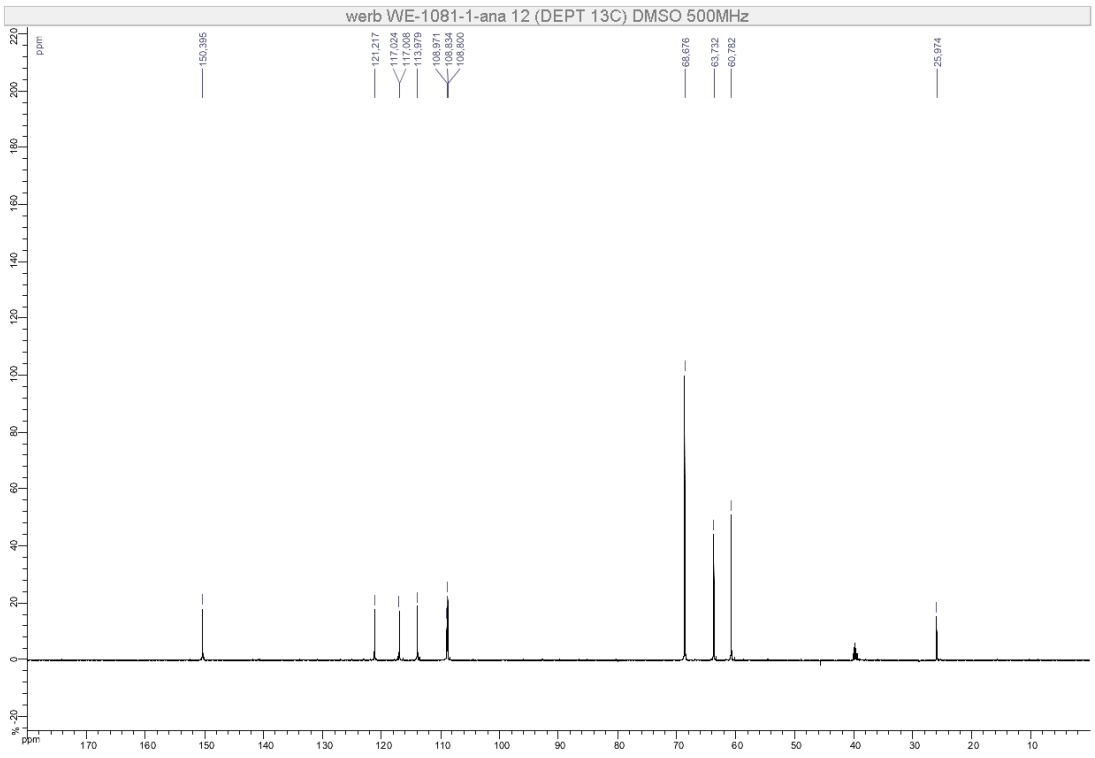
^{1}H NMR



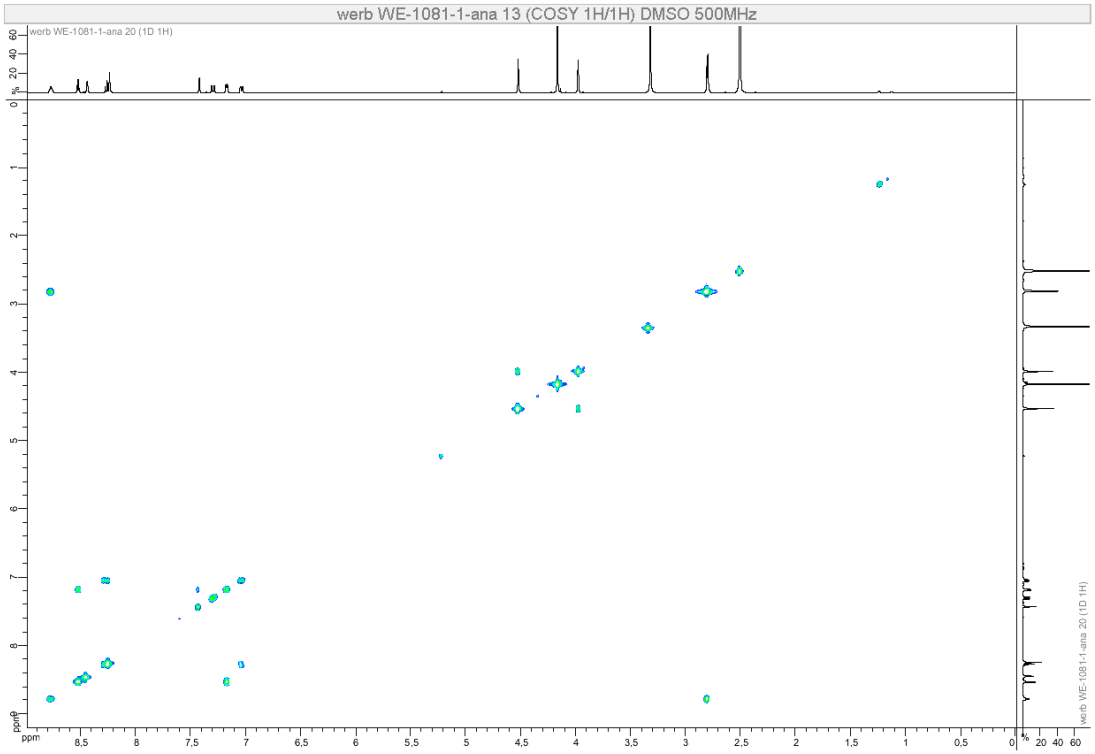
^{13}C NMR



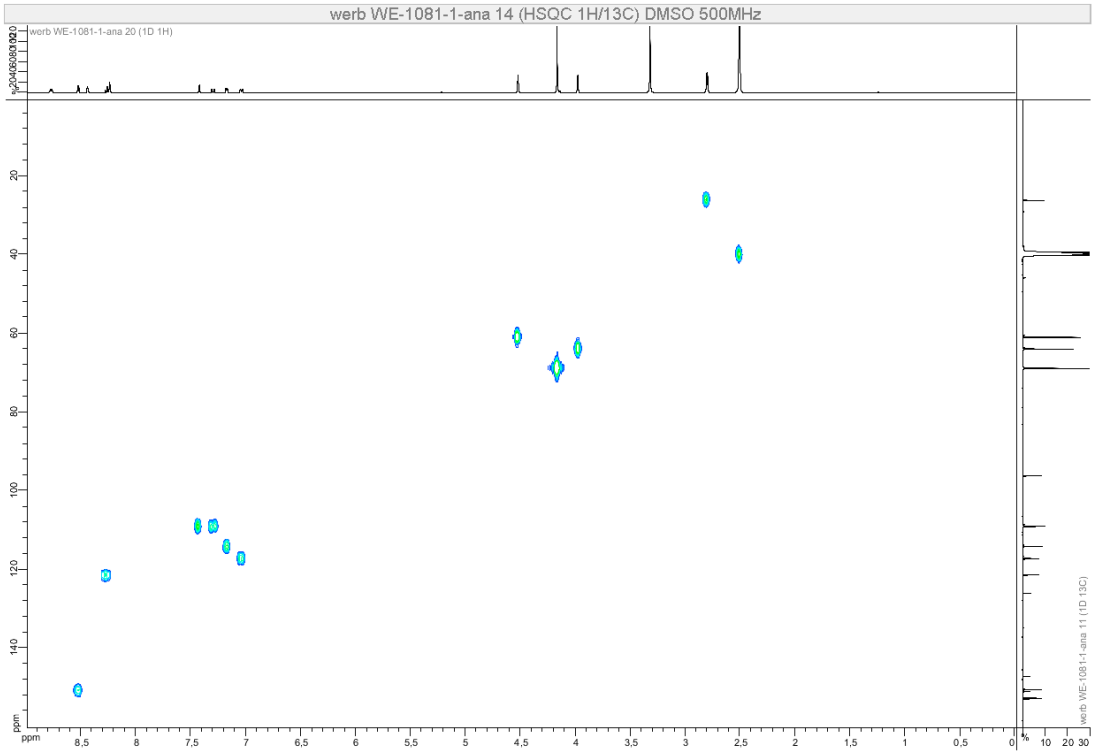
DEPT 135 NMR



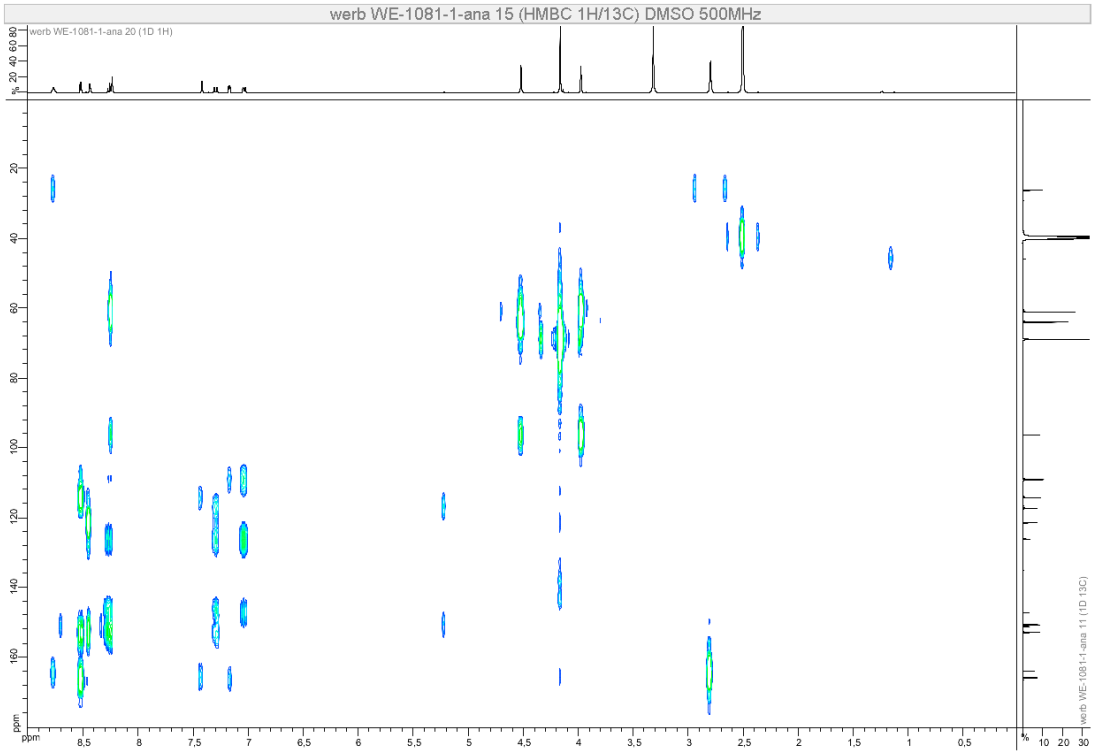
COSY NMR



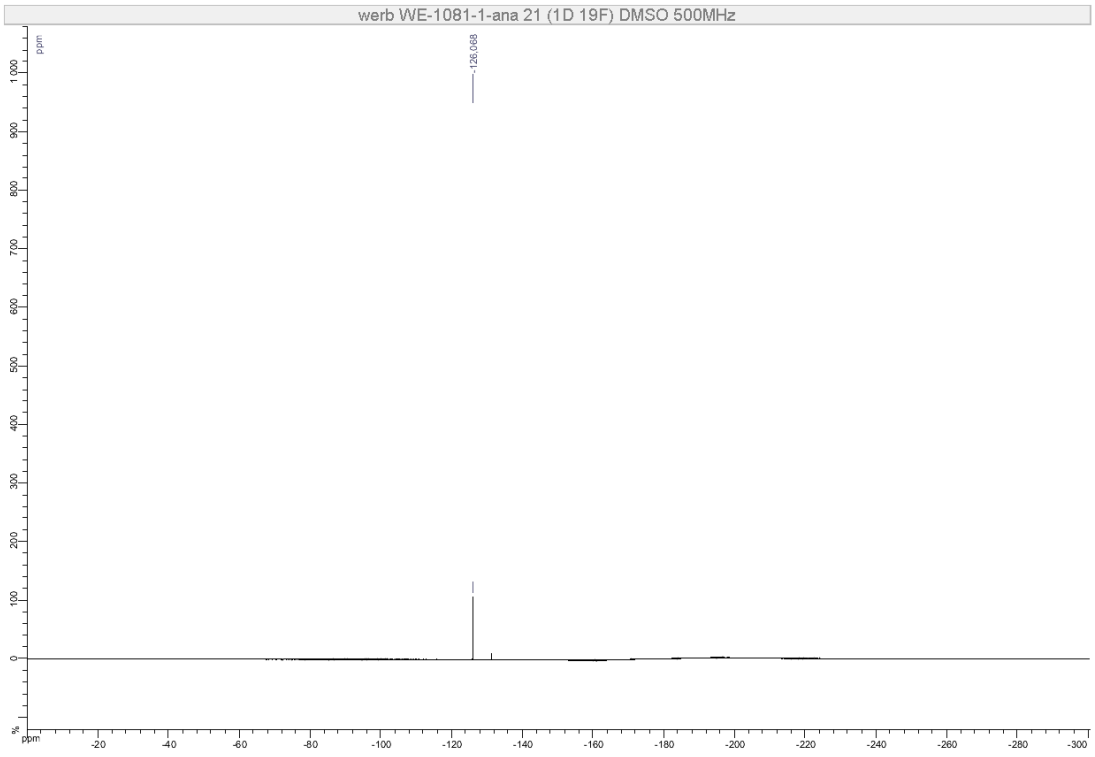
HSQC NMR



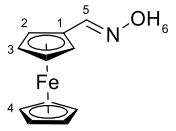
HMBC NMR



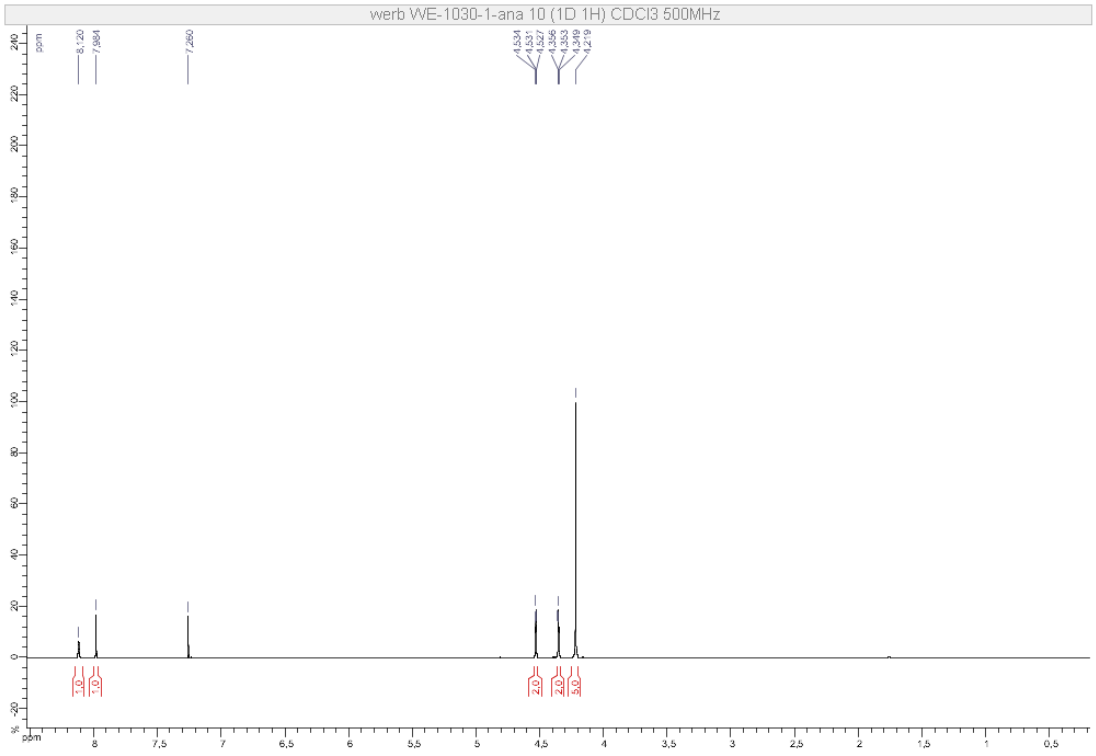
^{19}F NMR


werb WE-1081-1-ana 21 (1D 19F) DMSO 500MHz
-126.068
ppm
1 000
900
800
700
600
500
400
300
200
100
0
%
ppm
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
-260
-280
-300

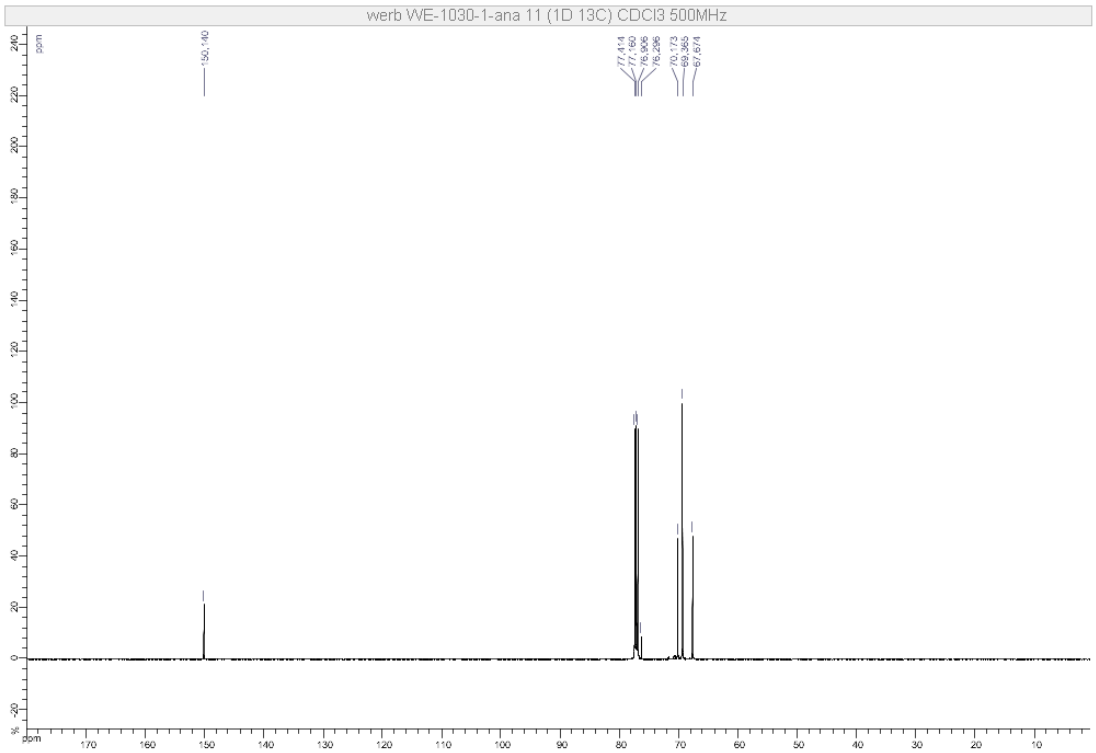
Compound S1



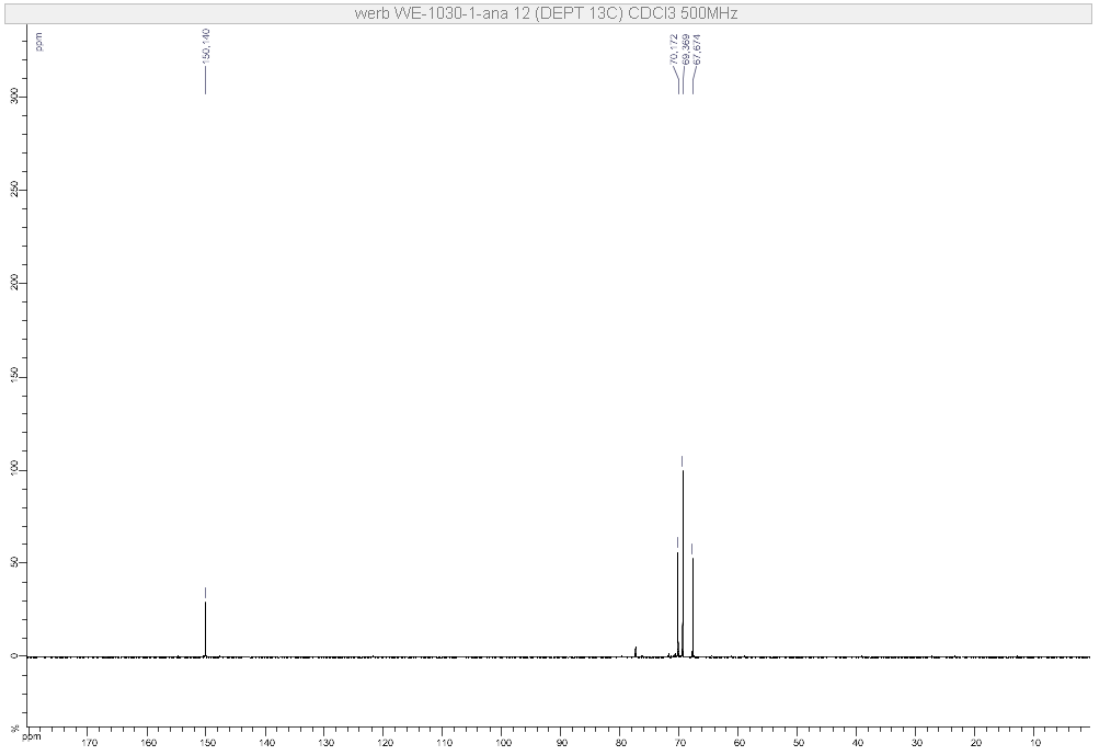
^{1}H NMR



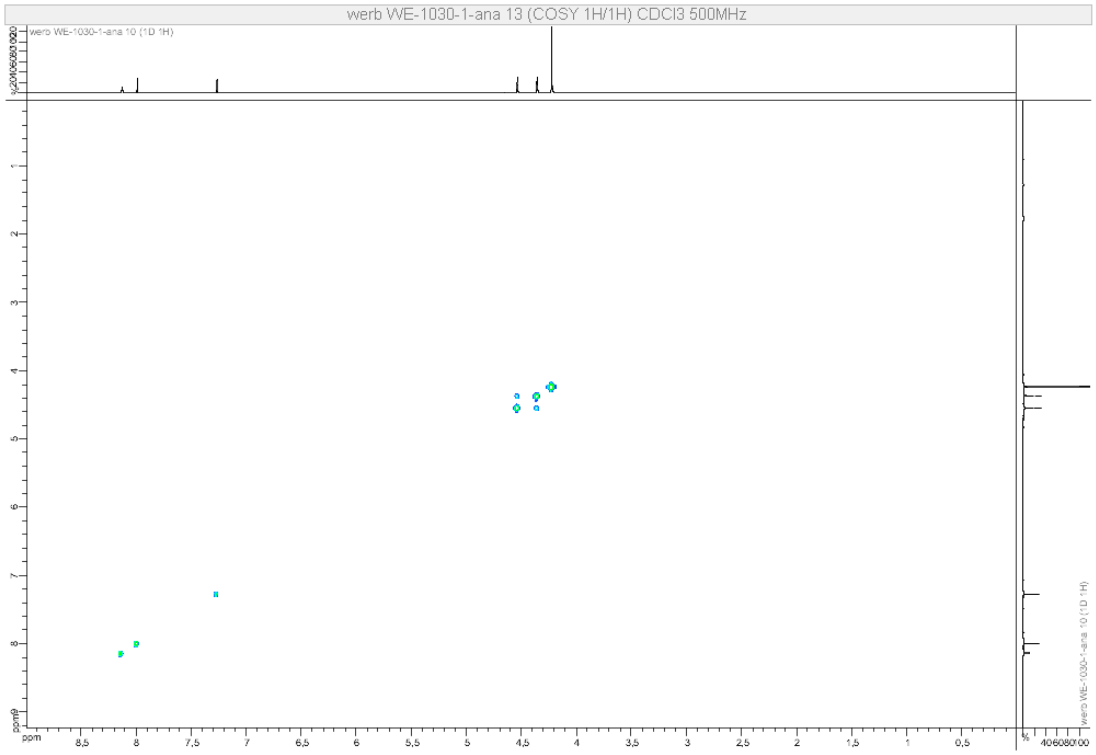
^{13}C NMR



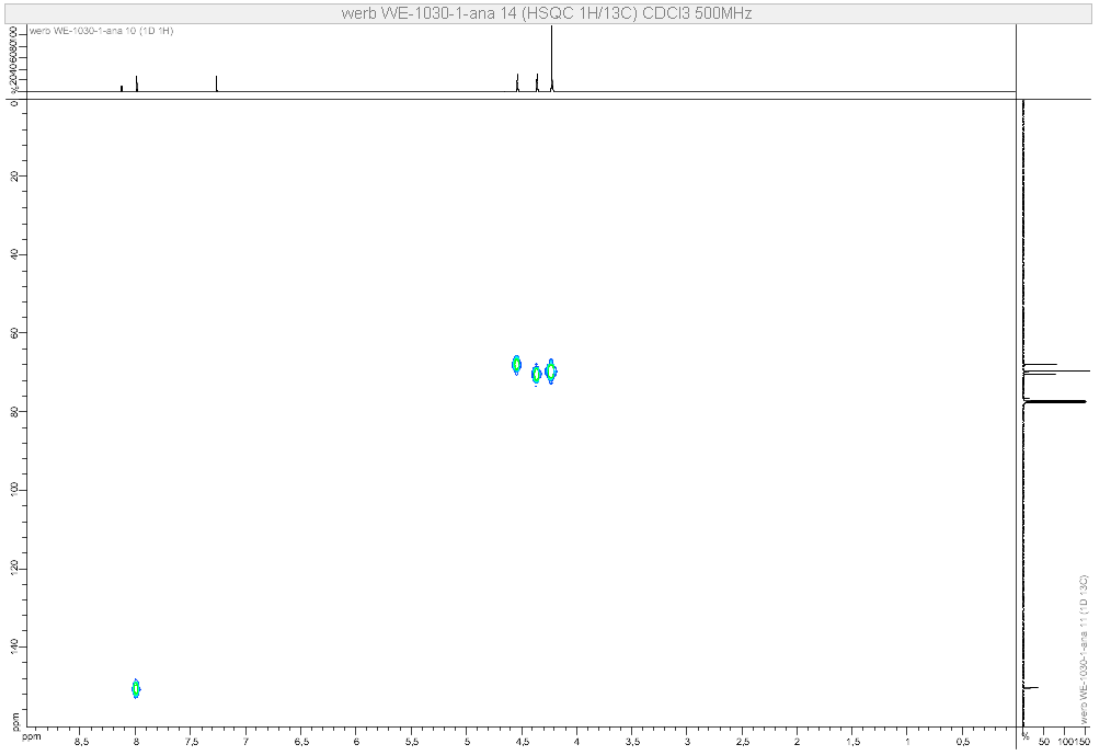
DEPT 135 NMR



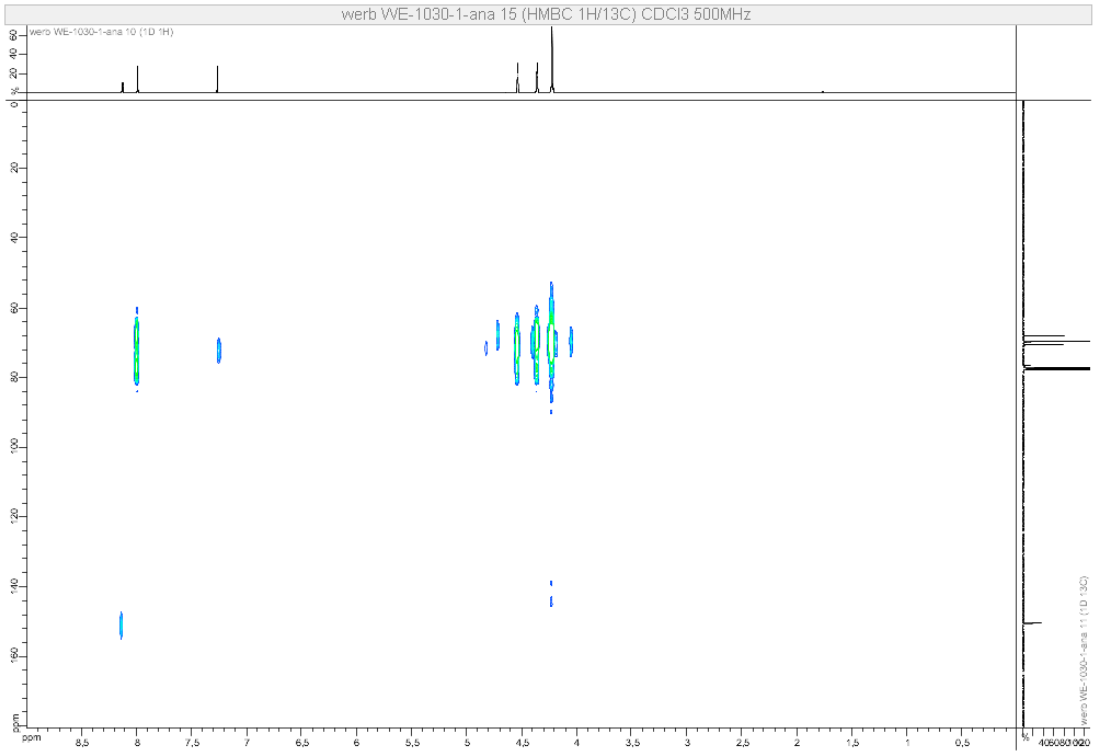
COSY NMR



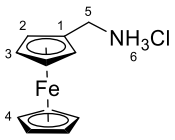
HSQC NMR



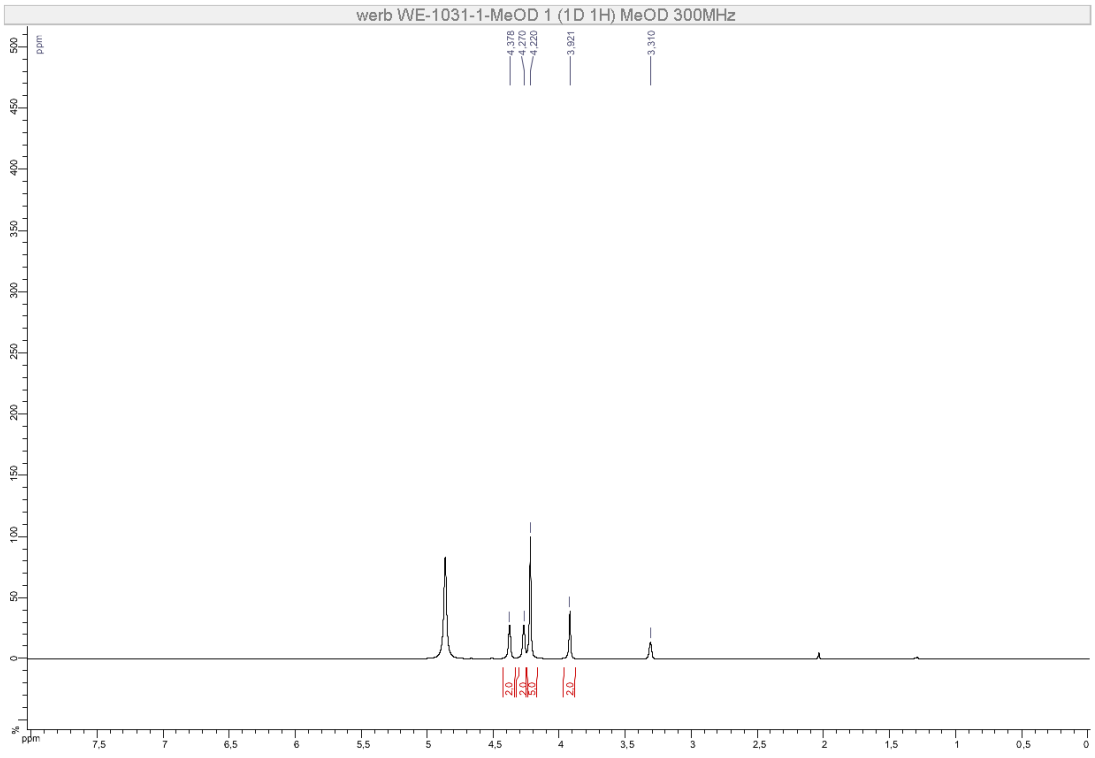
HMBC NMR



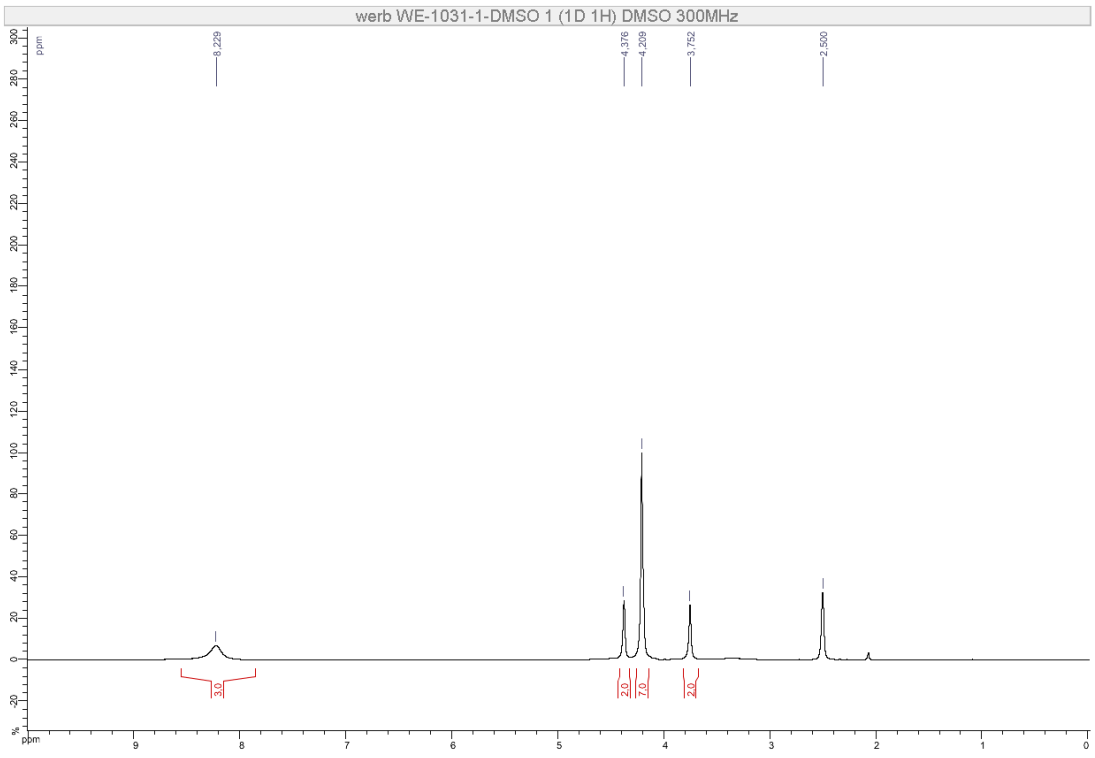
Aminomethylferrocene hydrochloride (S2)



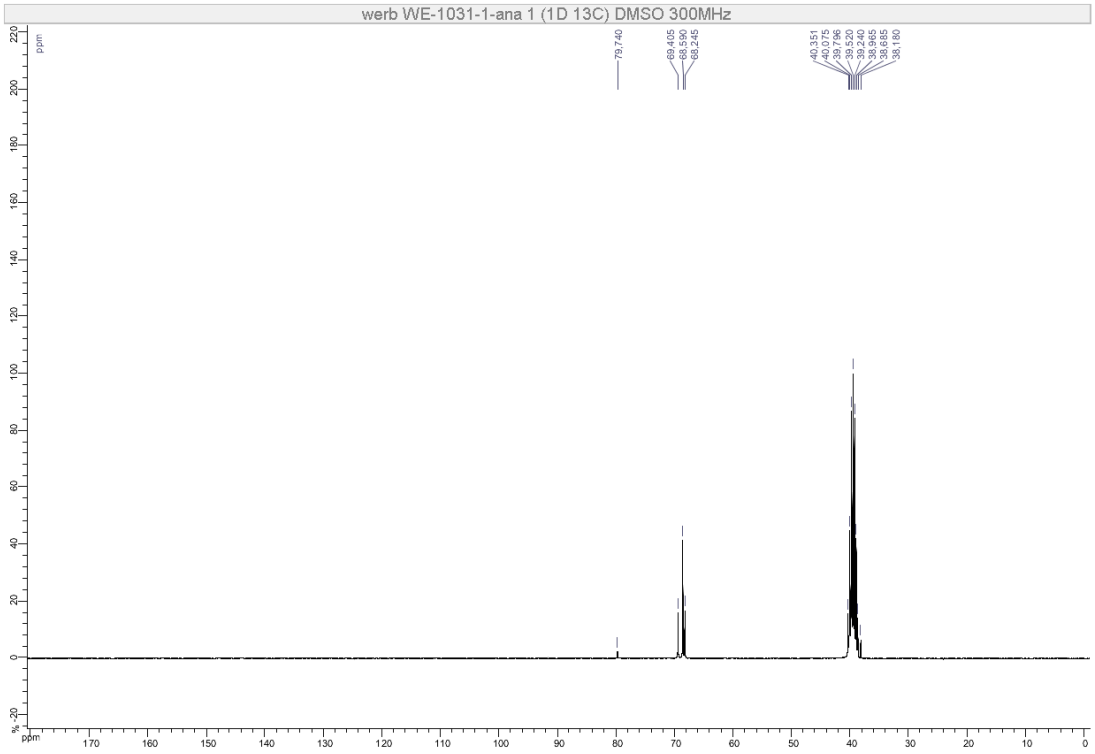
^{1}H NMR



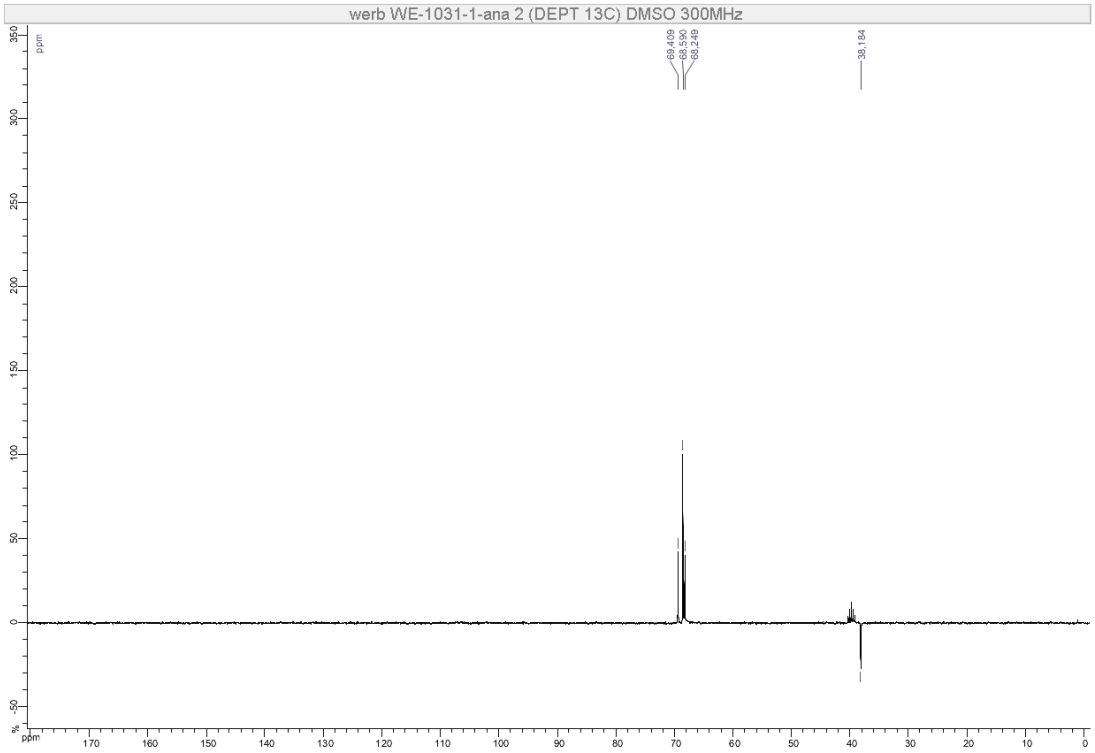
^{1}H NMR



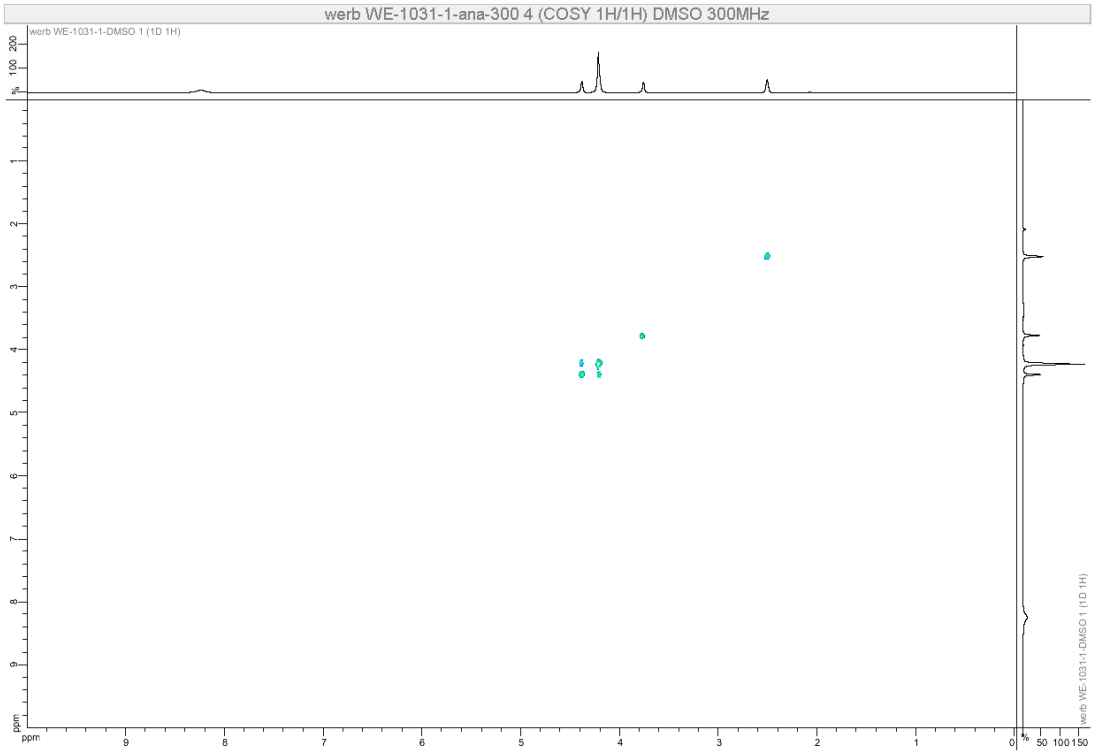
^{13}C NMR



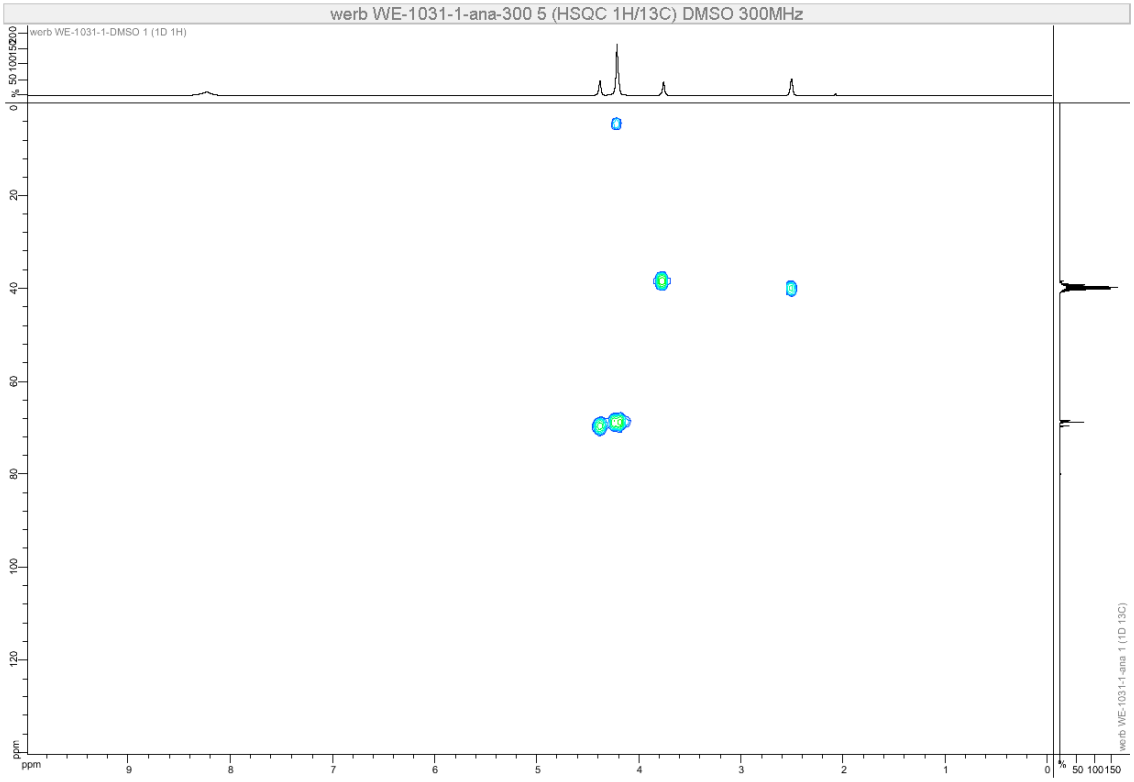
DEPT 135 NMR



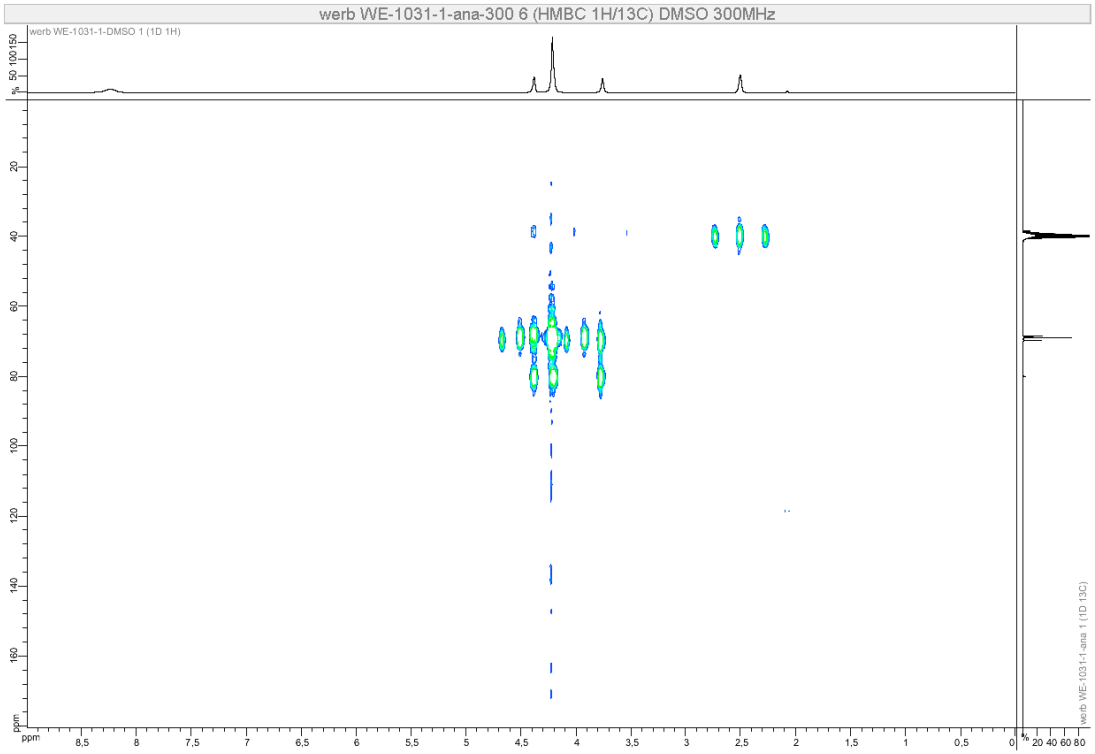
COSY NMR



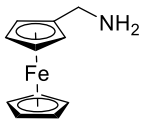
HSQC NMR



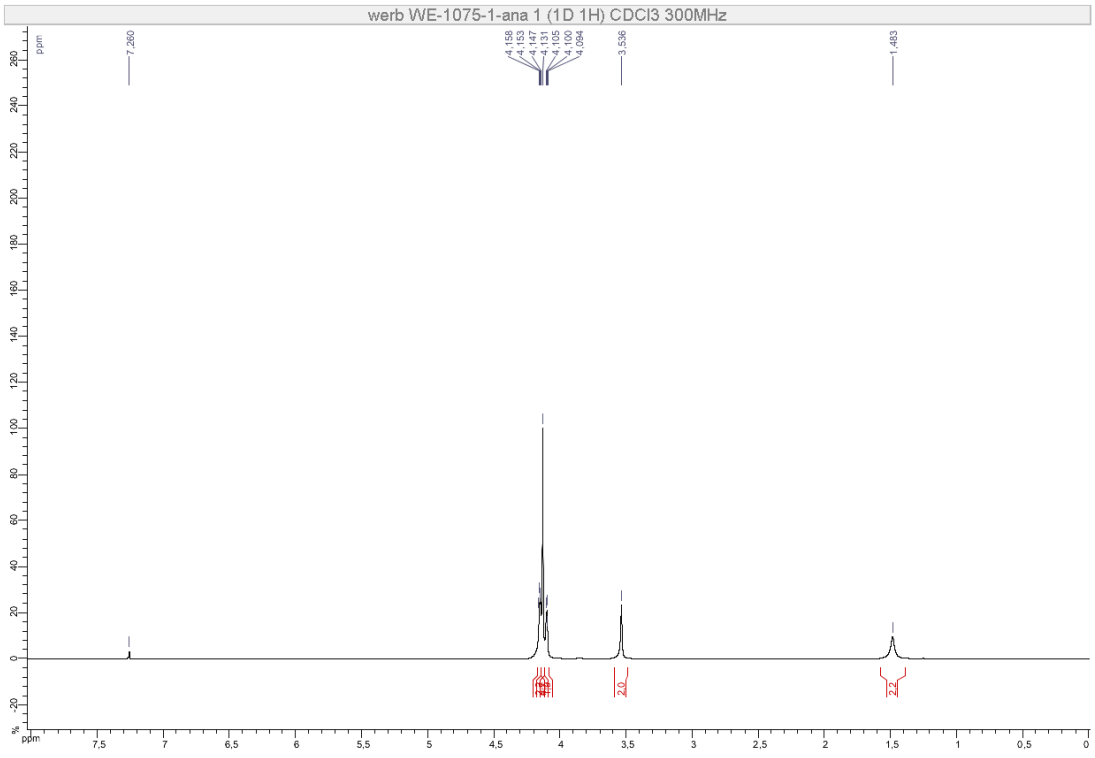
HMBC NMR


werb WE-1031-1-ana-300 6 (HMBC 1H/13C) DMSO 300MHz
werb WE-1031-1-DMSO 1 (1D 1H)
ppm
werb WE-1031-1-ana 1 (1D 13C)

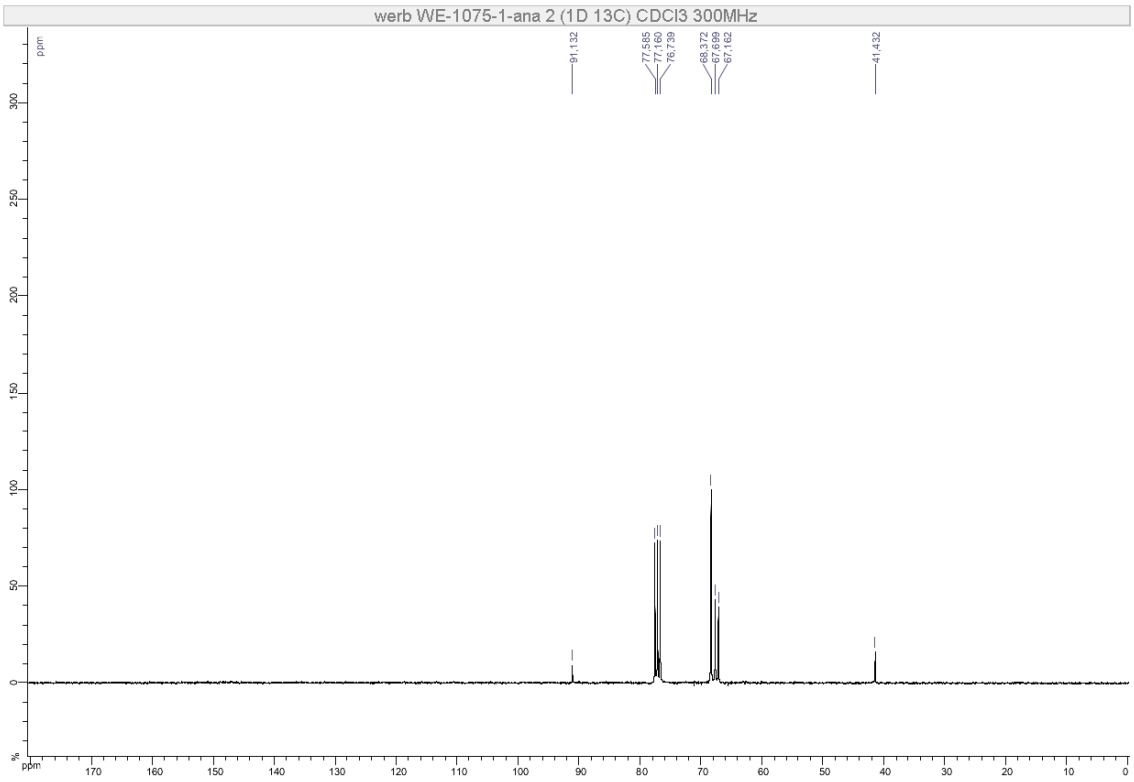
Aminomethylferrocene (22)



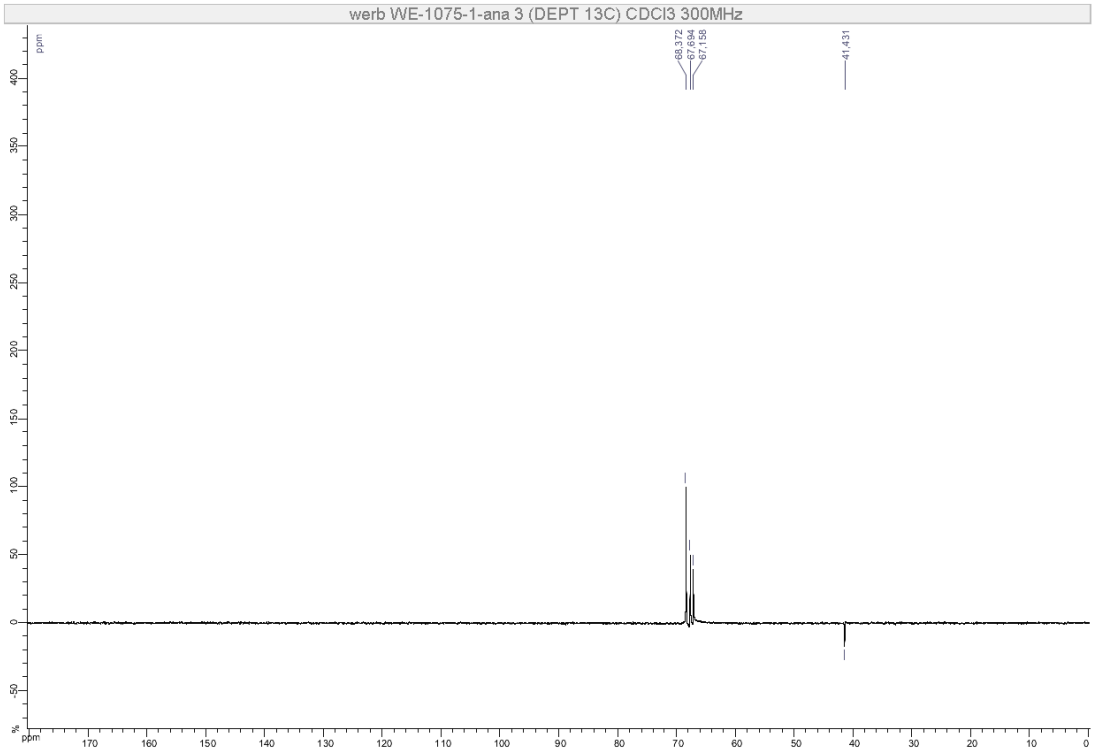
^{1}H NMR



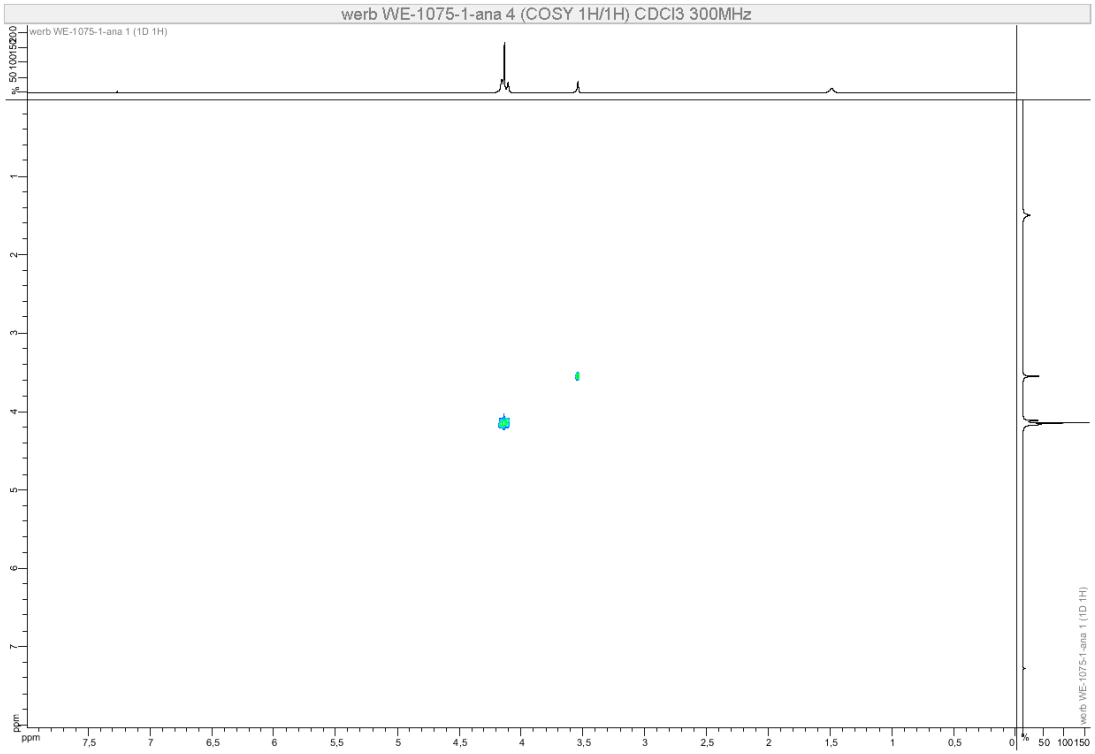
^{13}C NMR



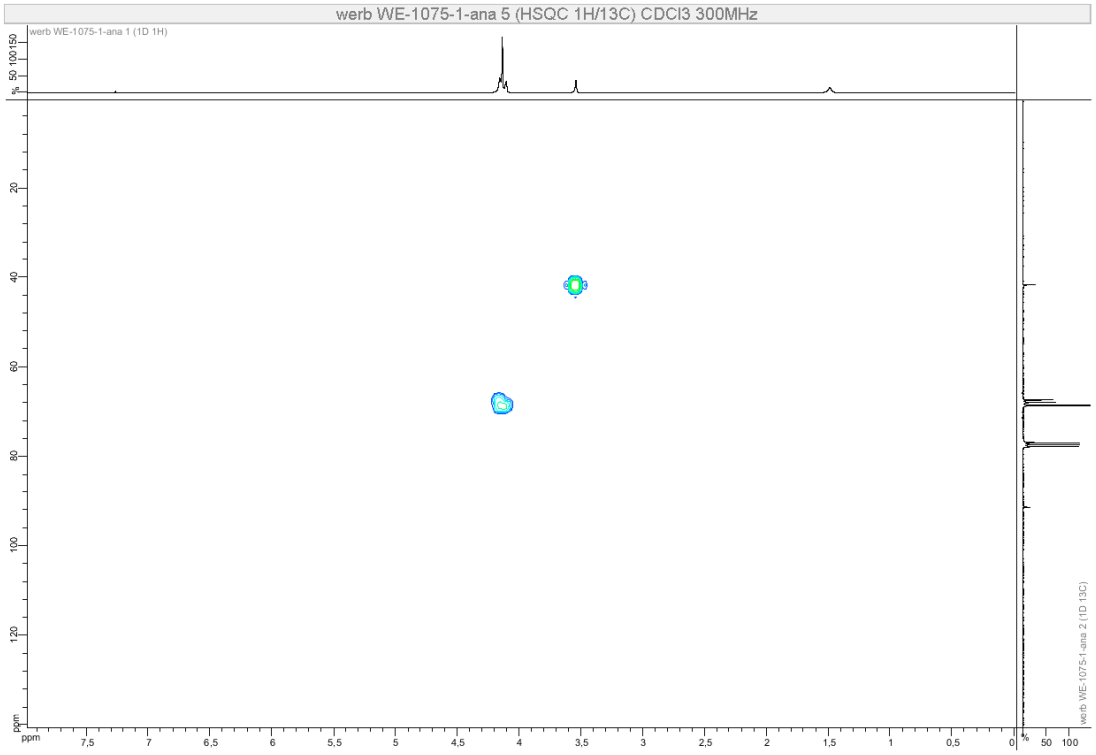
DEPT 135 NMR



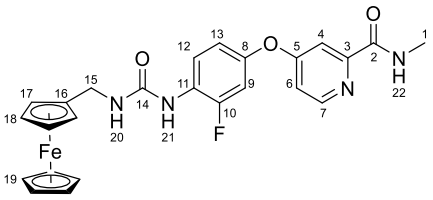
COSY NMR



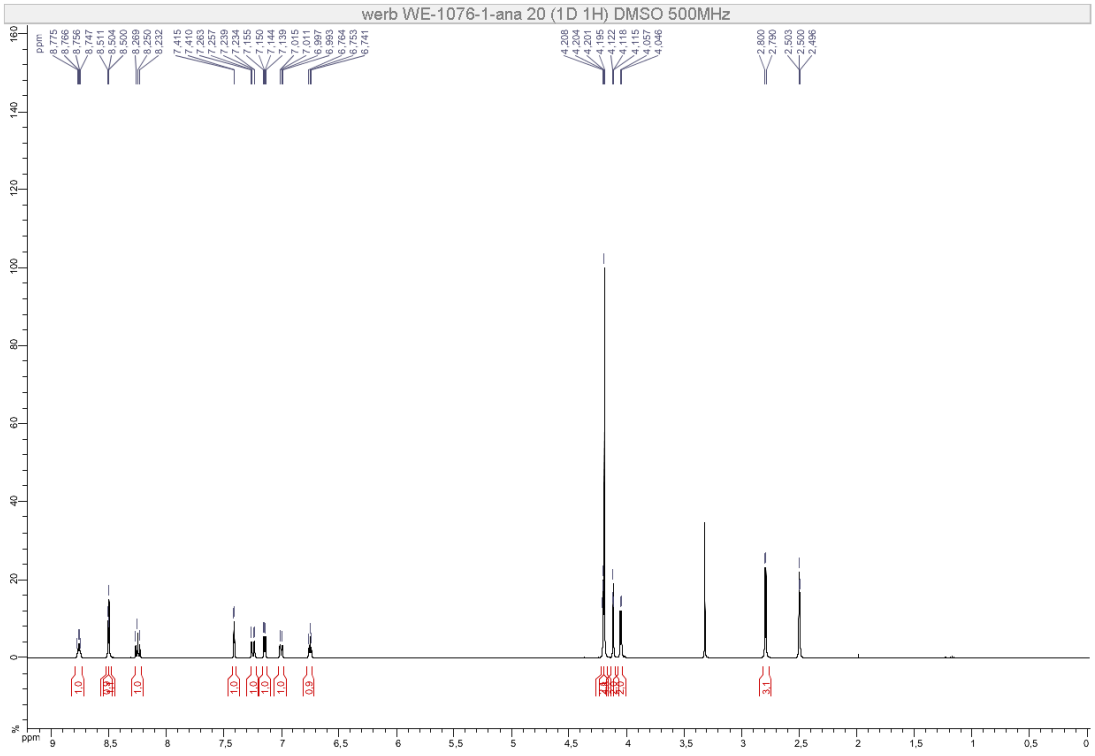
HSQC NMR


werb WE-1075-1-ana 5 (HSQC 1H/13C) CDCl3 300MHz
werb WE-1075-1-ana 1 (1D 1H)
werb WE-1075-1-ana 2 (1D 13C)
ppm
%

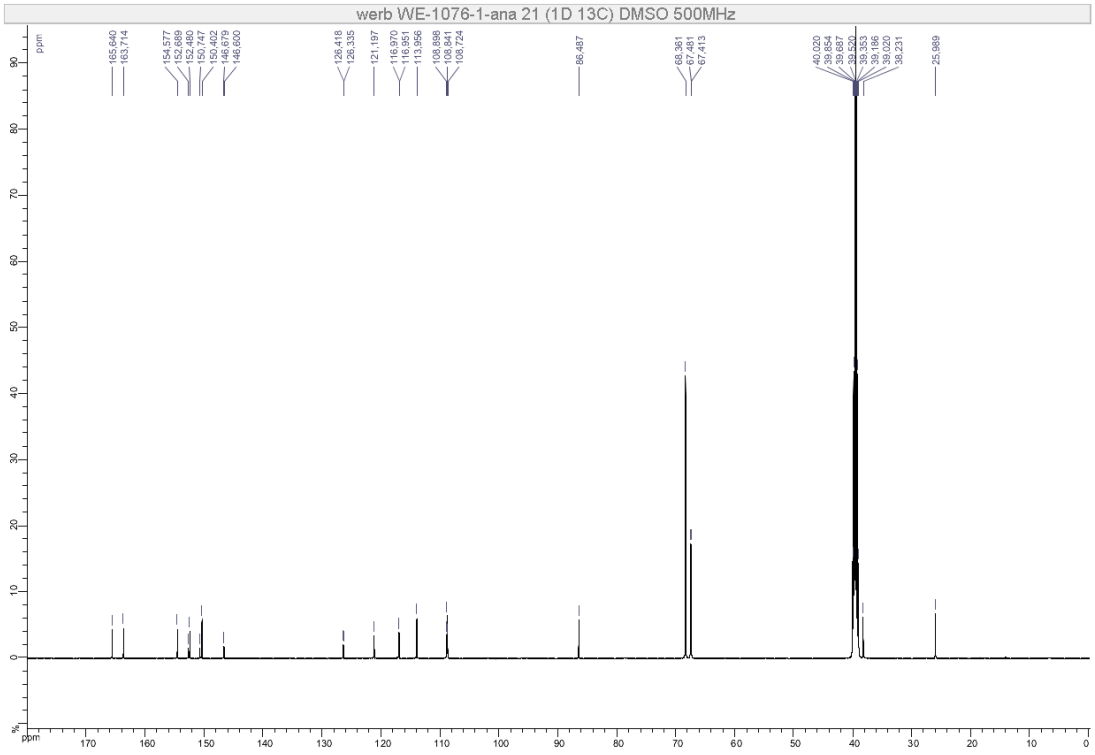
Compound 3a



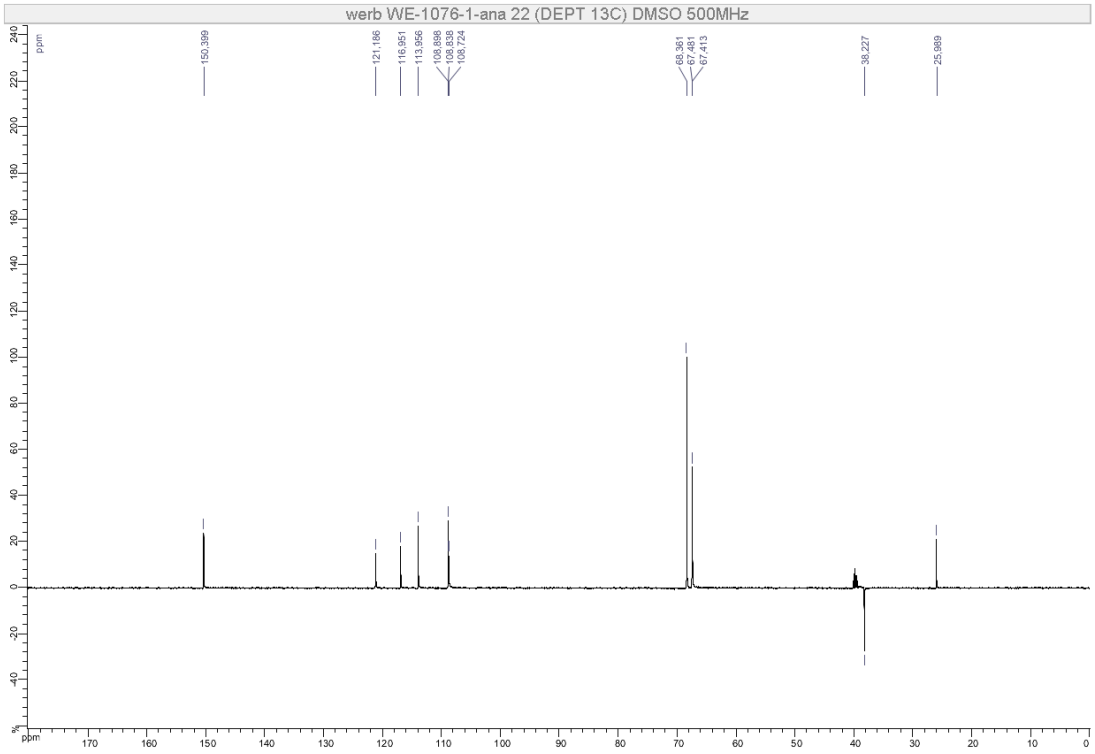
^{1}H NMR



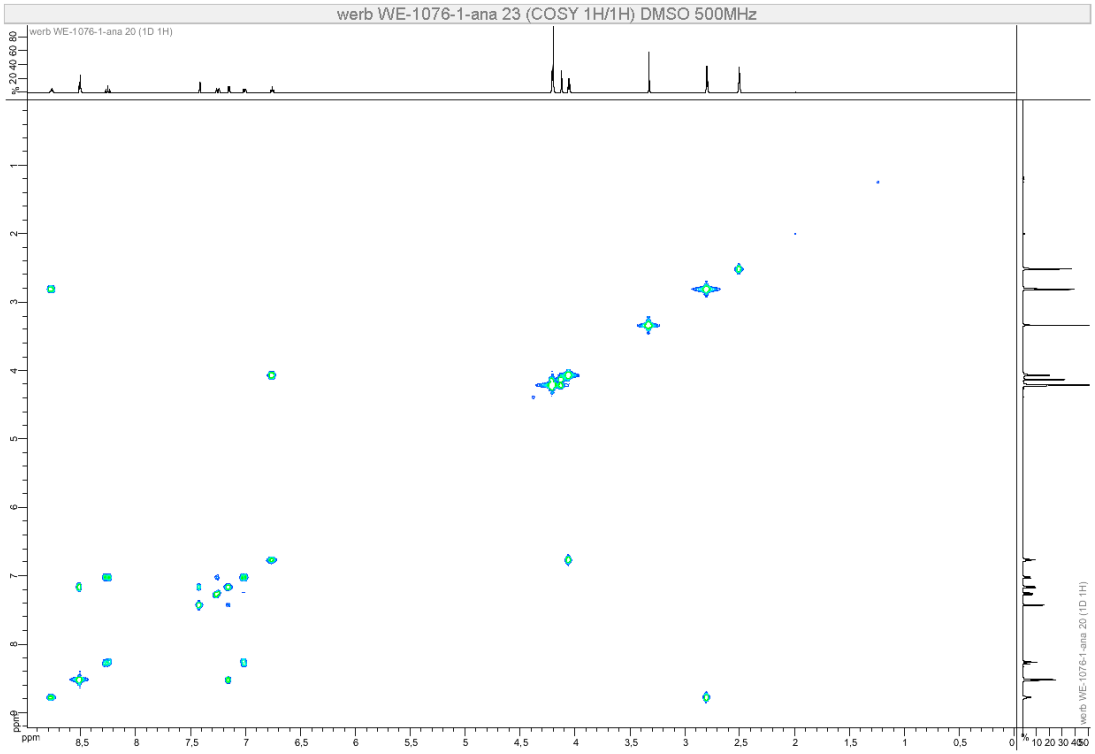
^{13}C NMR



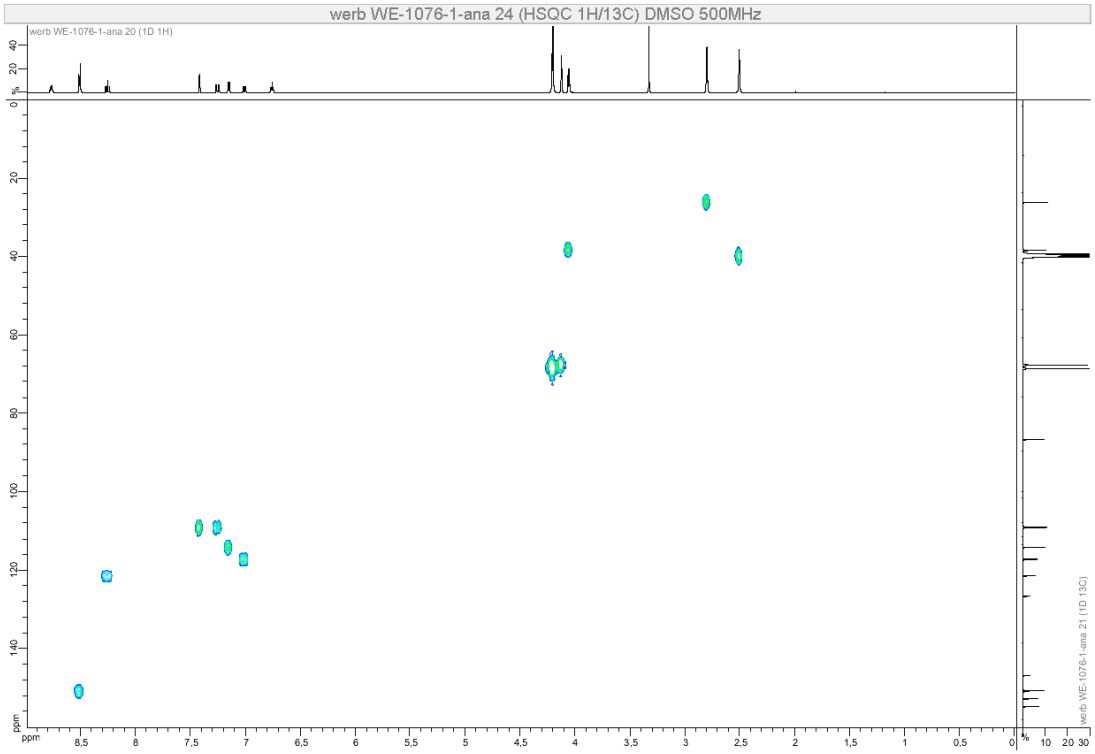
DEPT 135 NMR



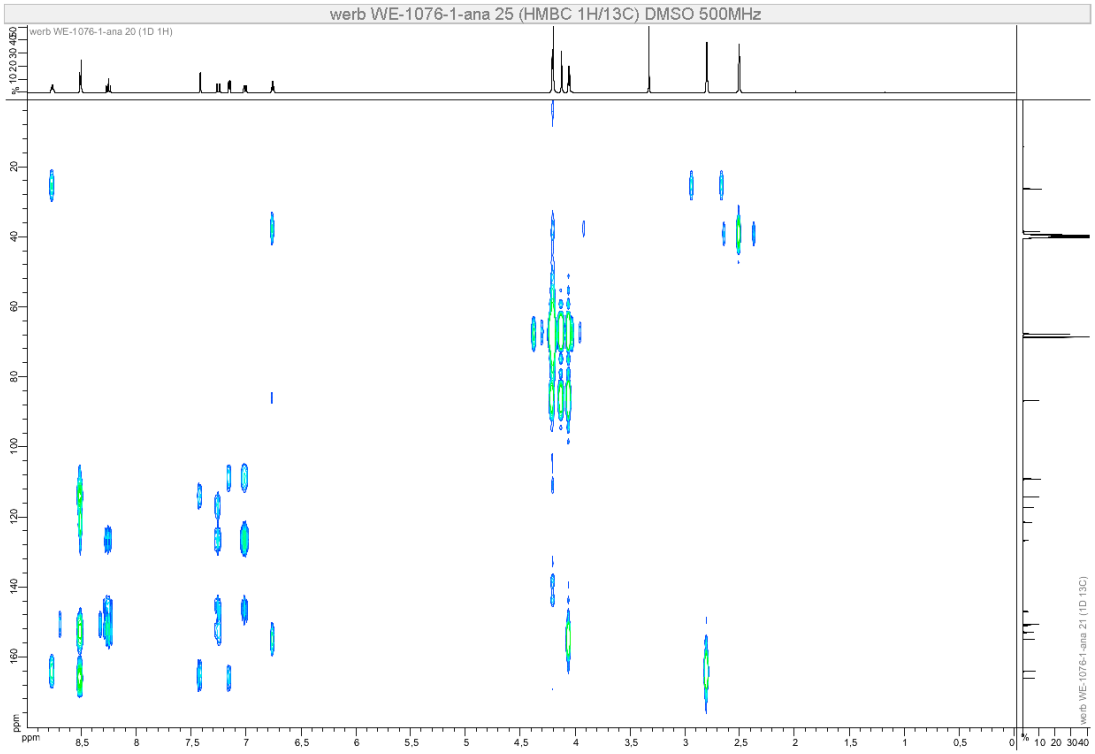
COSY NMR



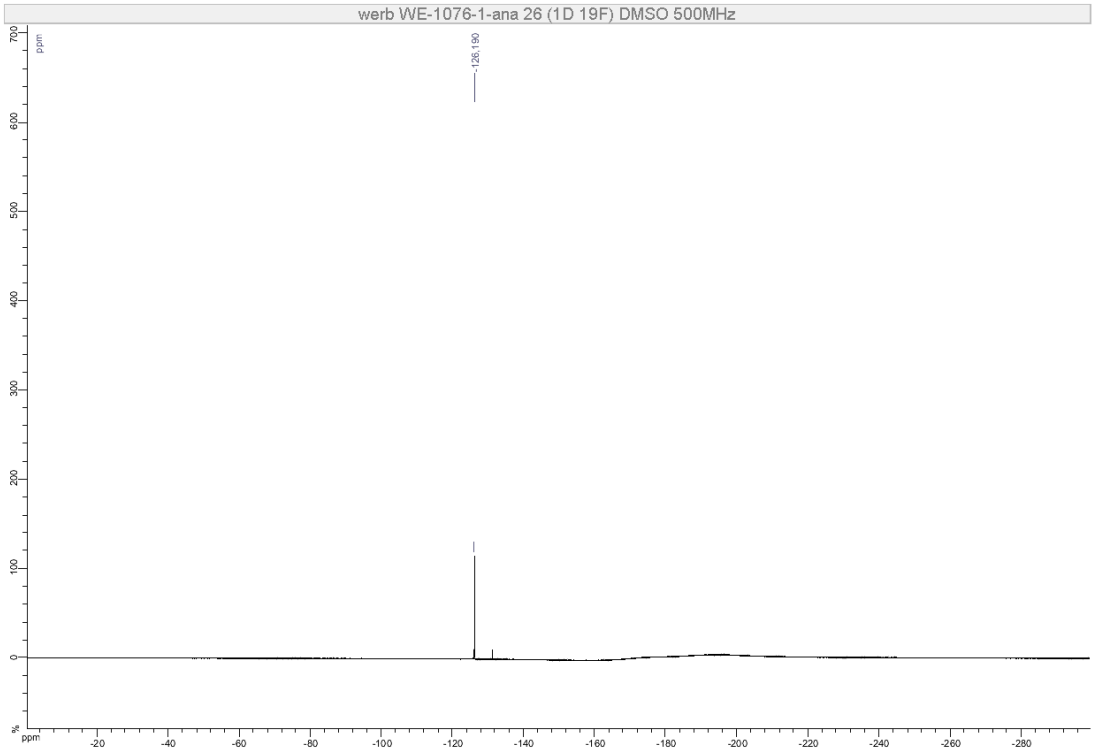
HSQC NMR



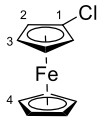
HMBC NMR



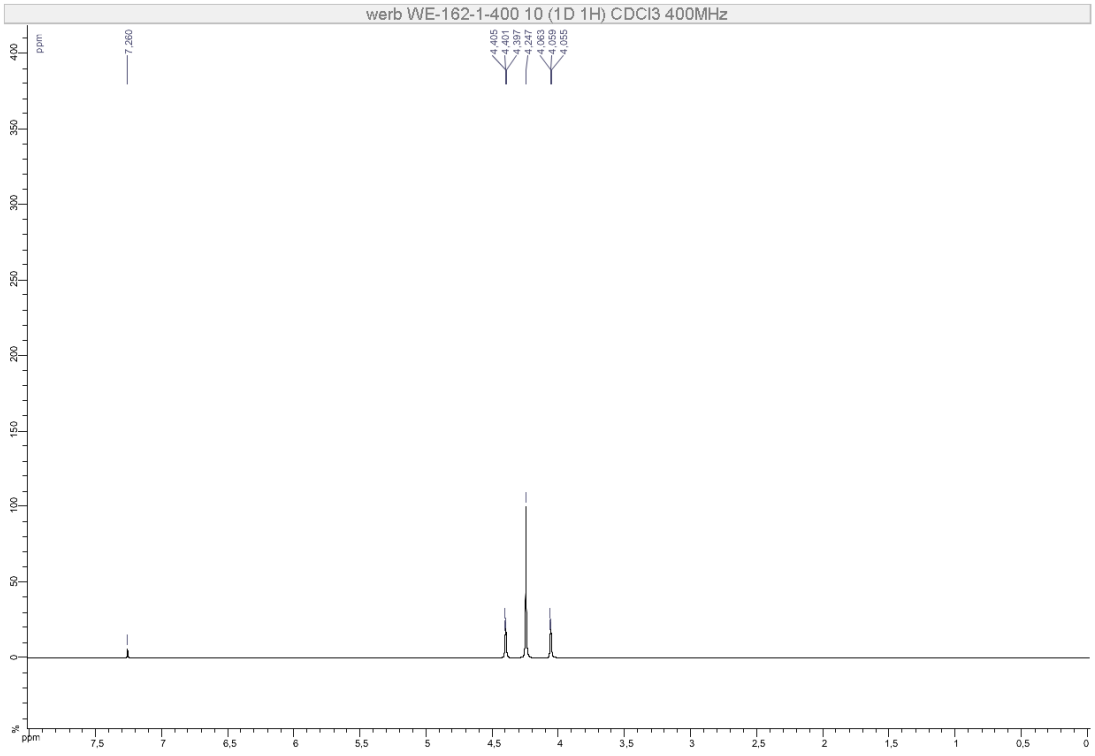
^{19}F NMR


werb WE-1076-1-ana 26 (1D 19F) DMSO 500MHz
-126.190
ppm
%
700
600
500
400
300
200
100
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
-260
-280

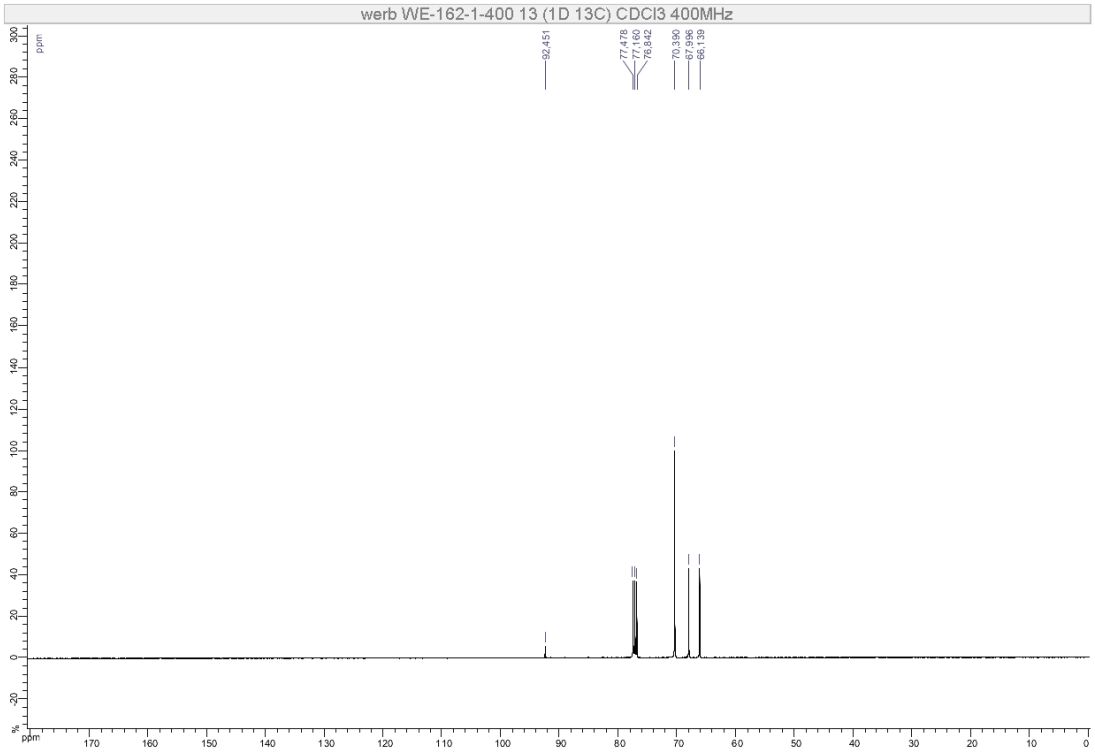
Compound 24



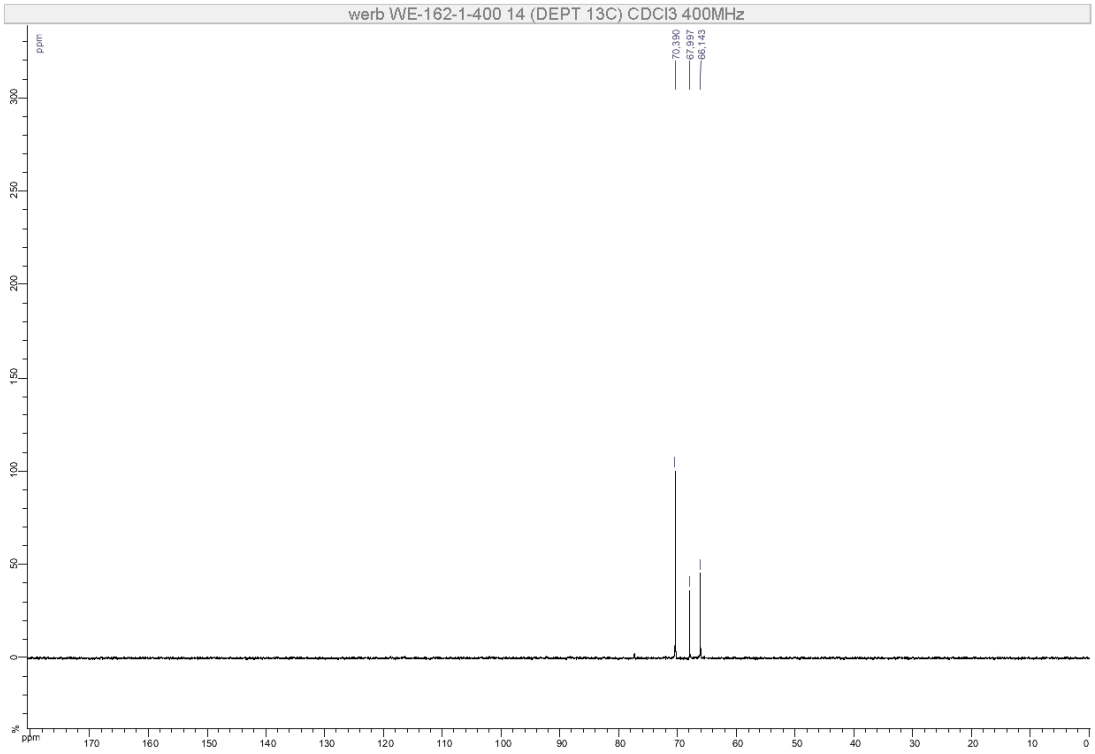
^{1}H NMR



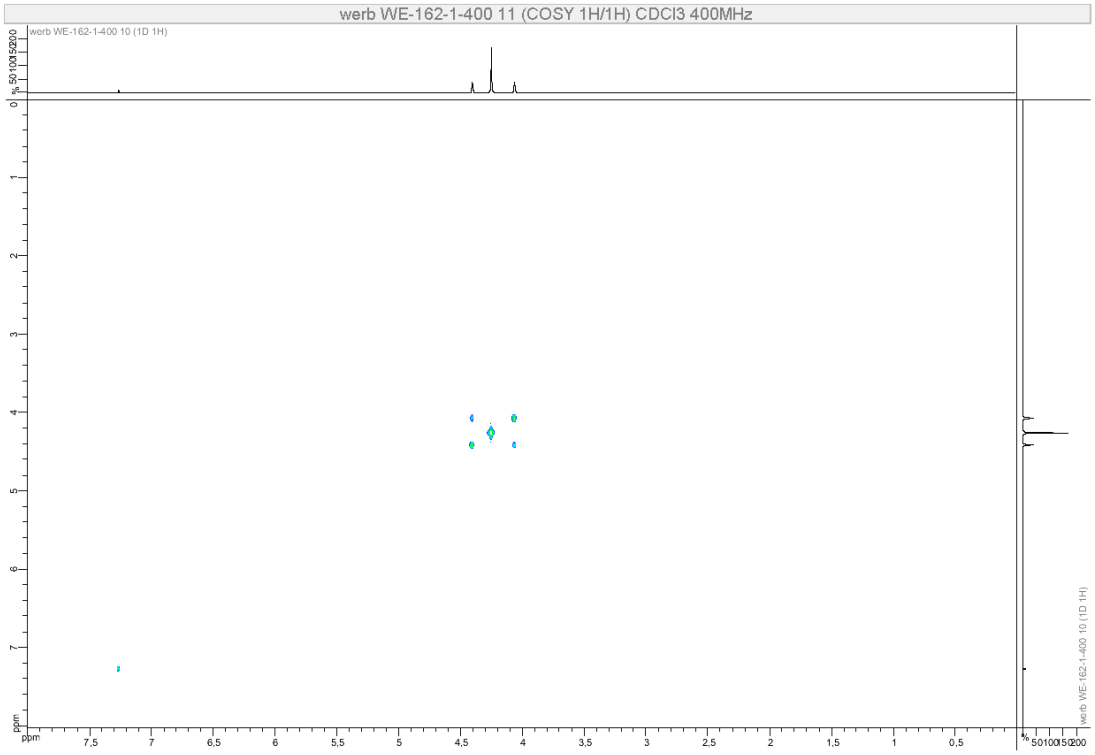
^{13}C NMR



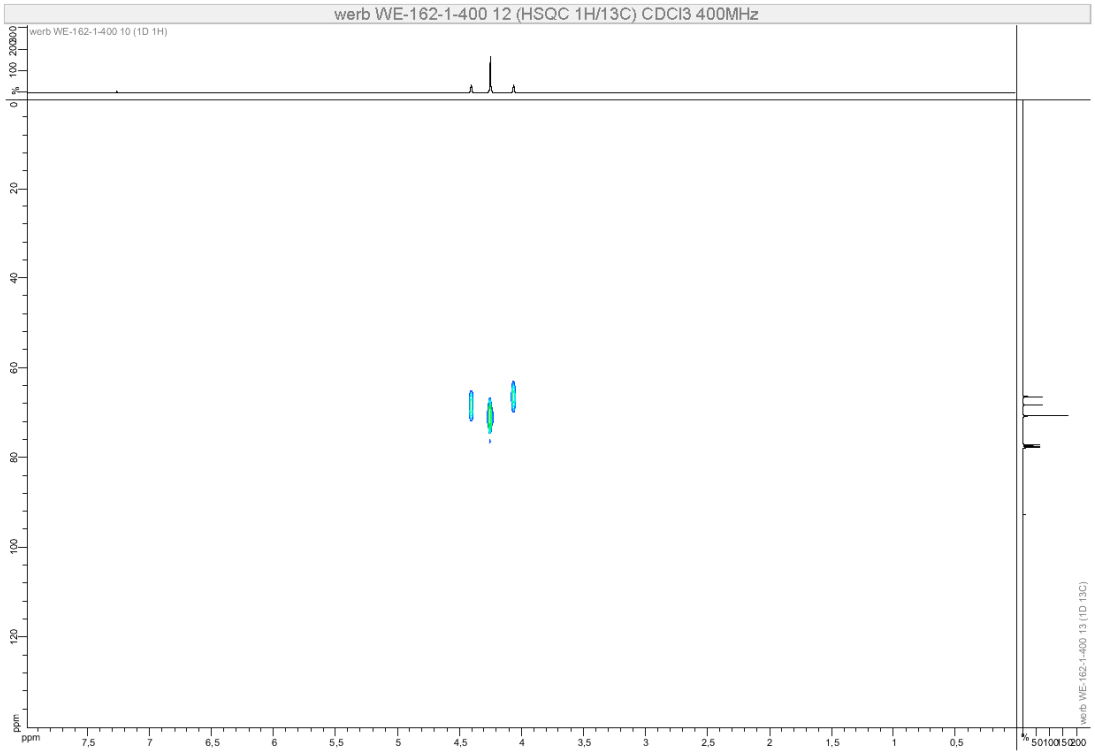
DEPT 135 NMR



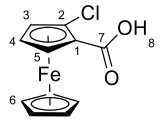
COSY NMR



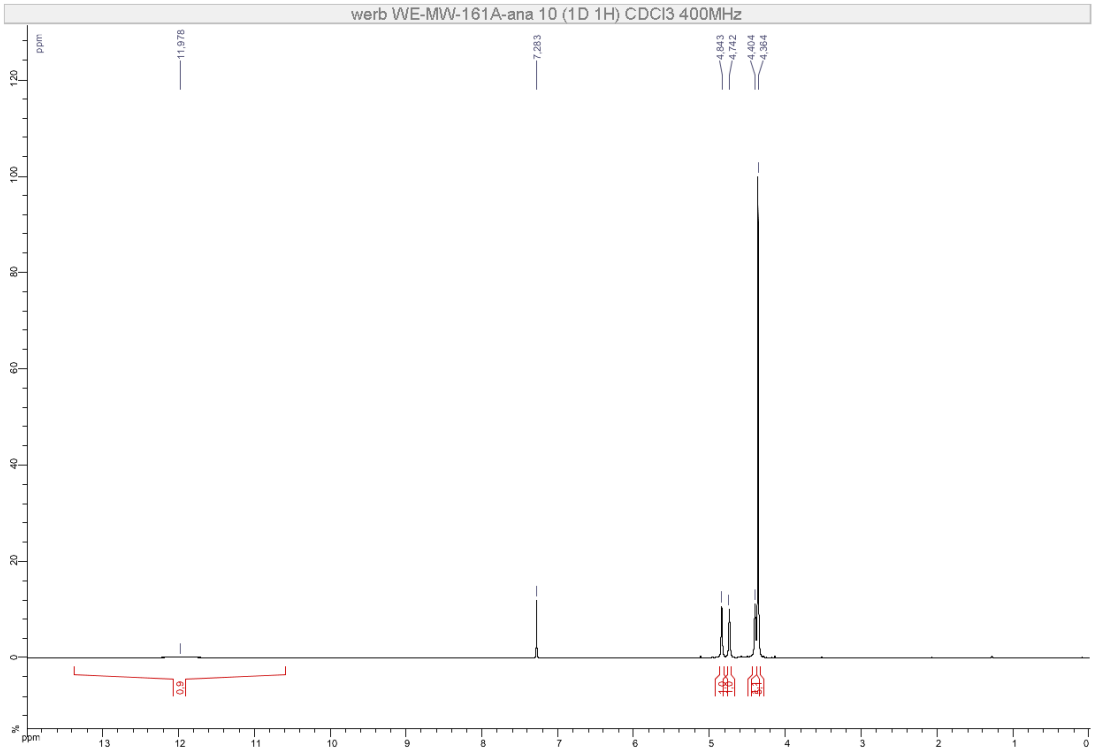
HSQC NMR


werb WE-162-1-400 12 (HSQC 1H/13C) CDCl3 400MHz
werb WE-162-1-400 10 (1D 1H)
ppm
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
%
werb WE-162-1-400 13 (1D 13C)

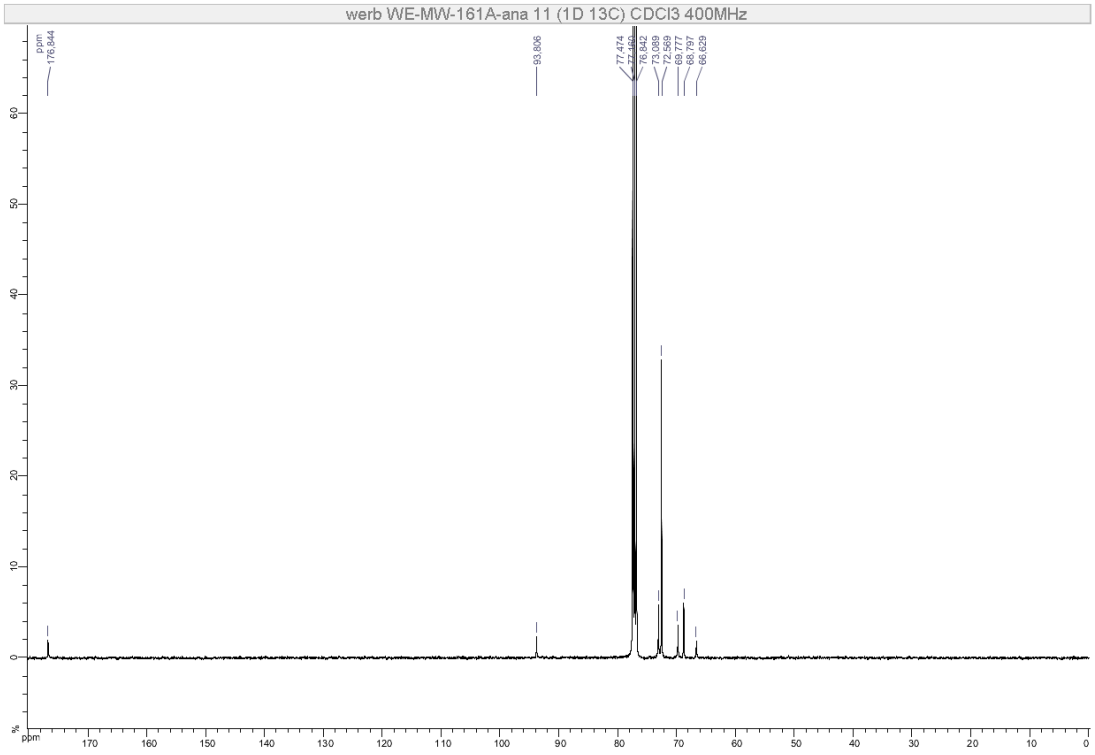
Compound 25



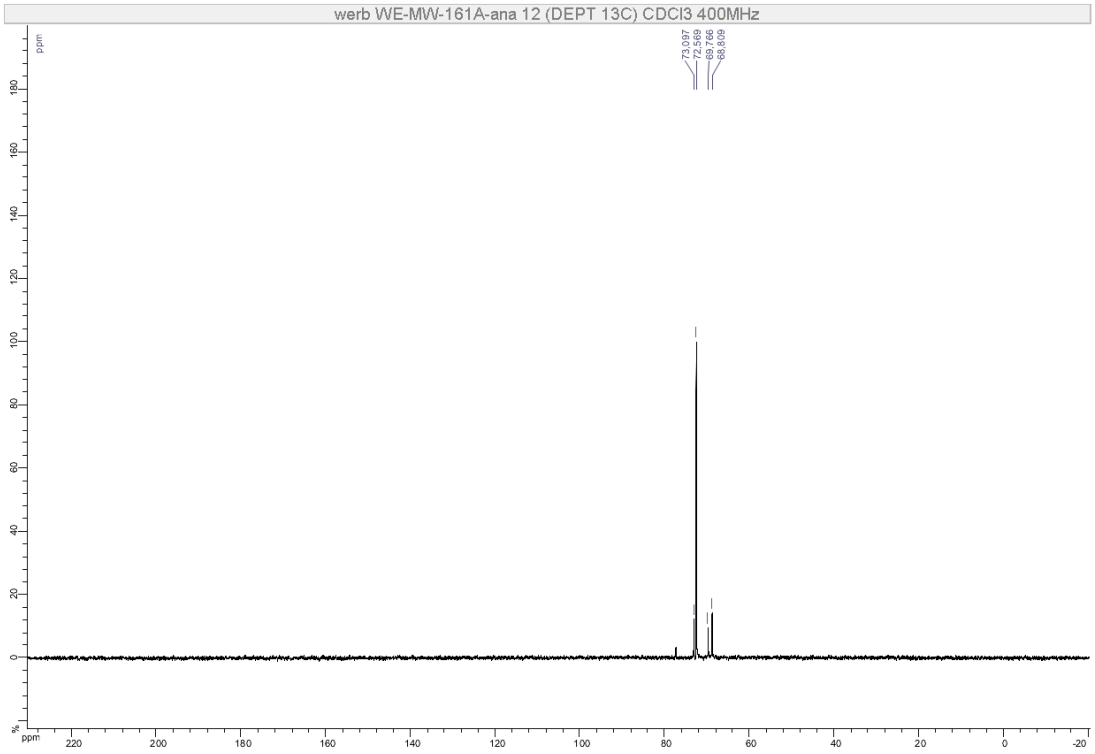
^{1}H NMR



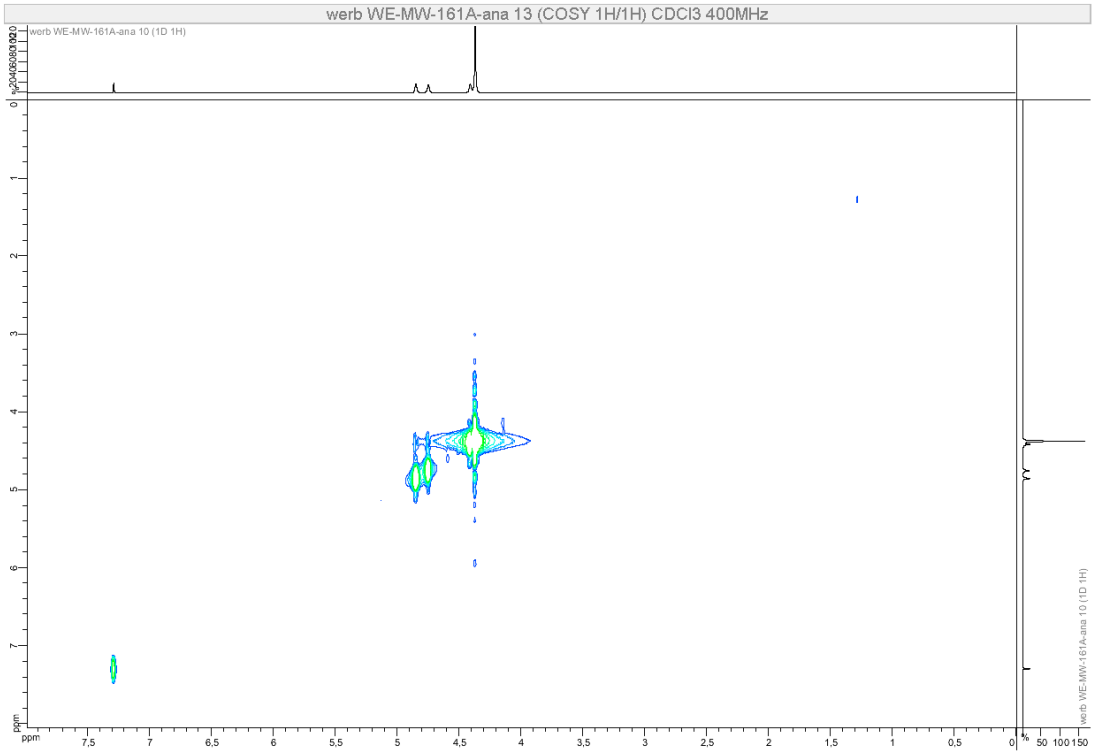
^{13}C NMR



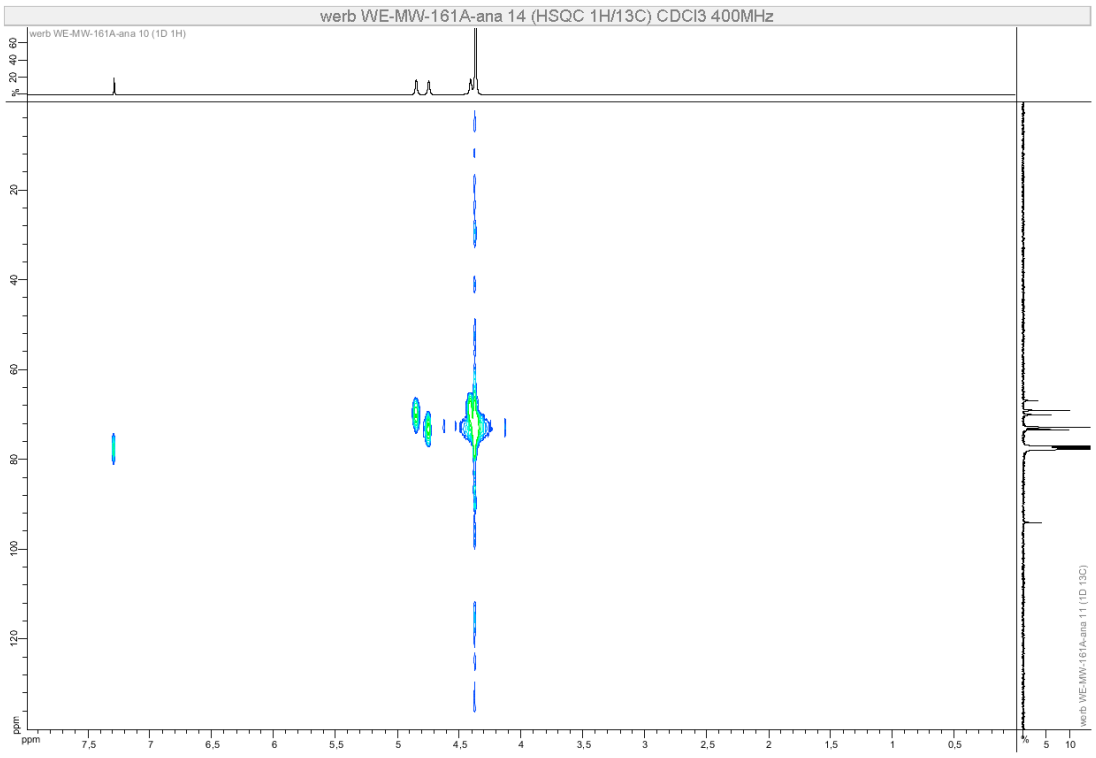
DEPT 135 NMR



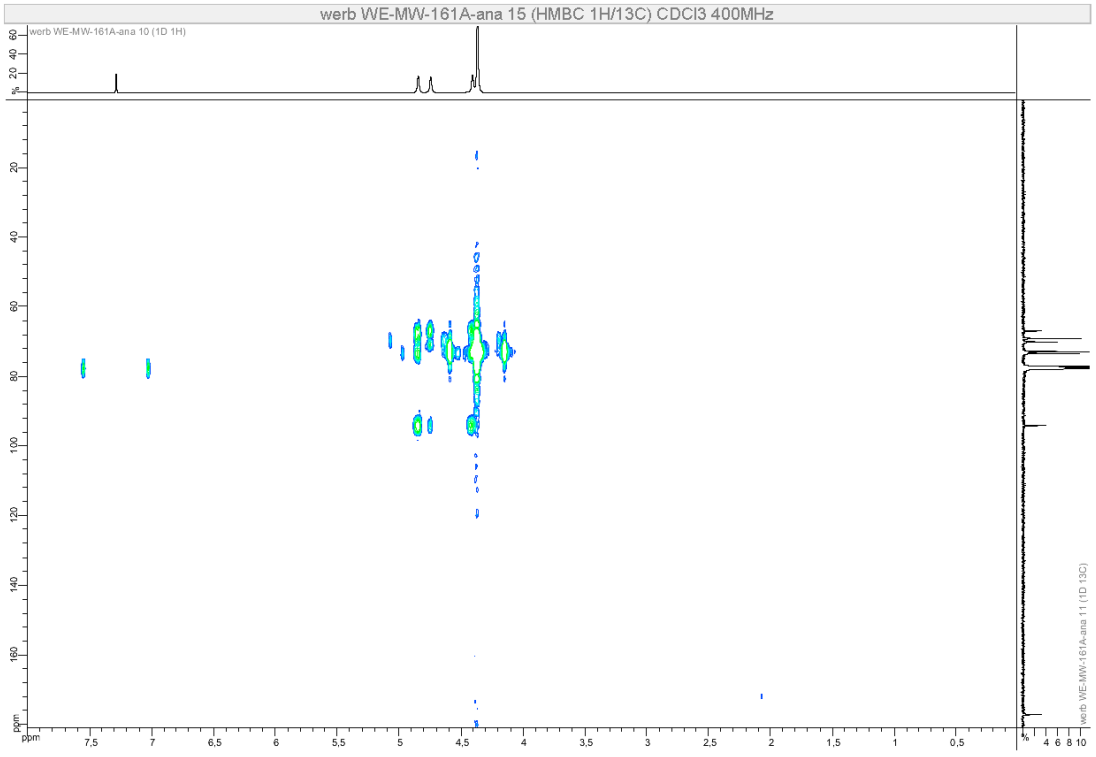
COSY NMR



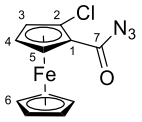
HSQC NMR



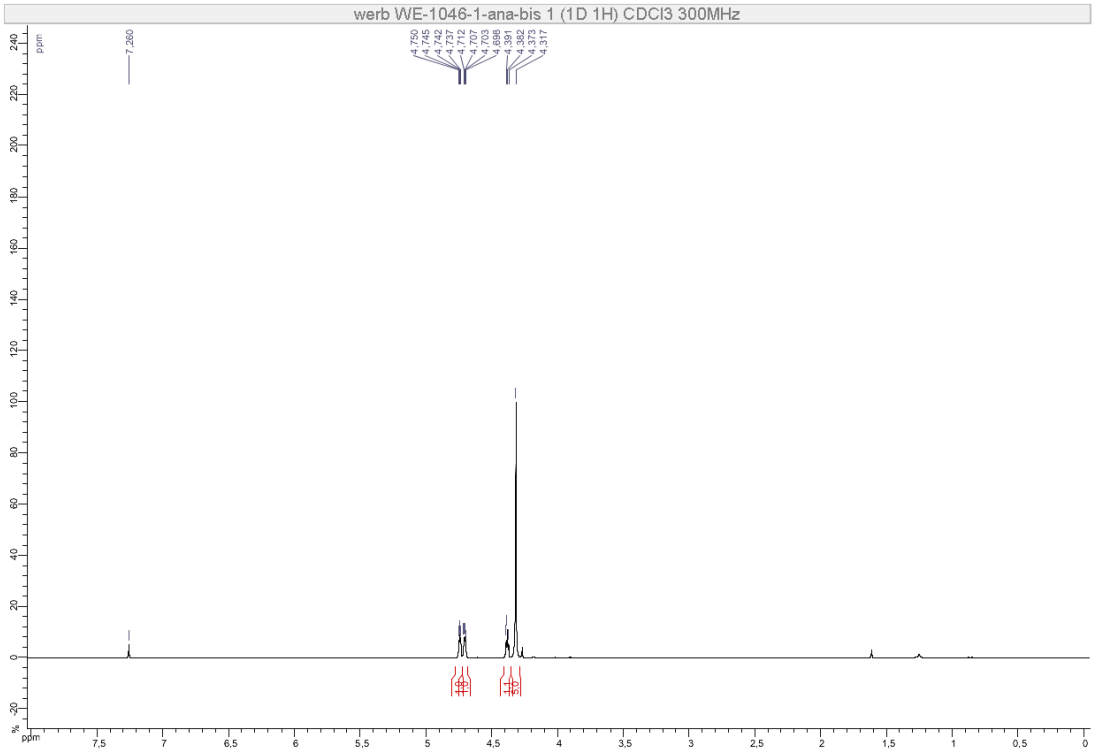
HMBC NMR



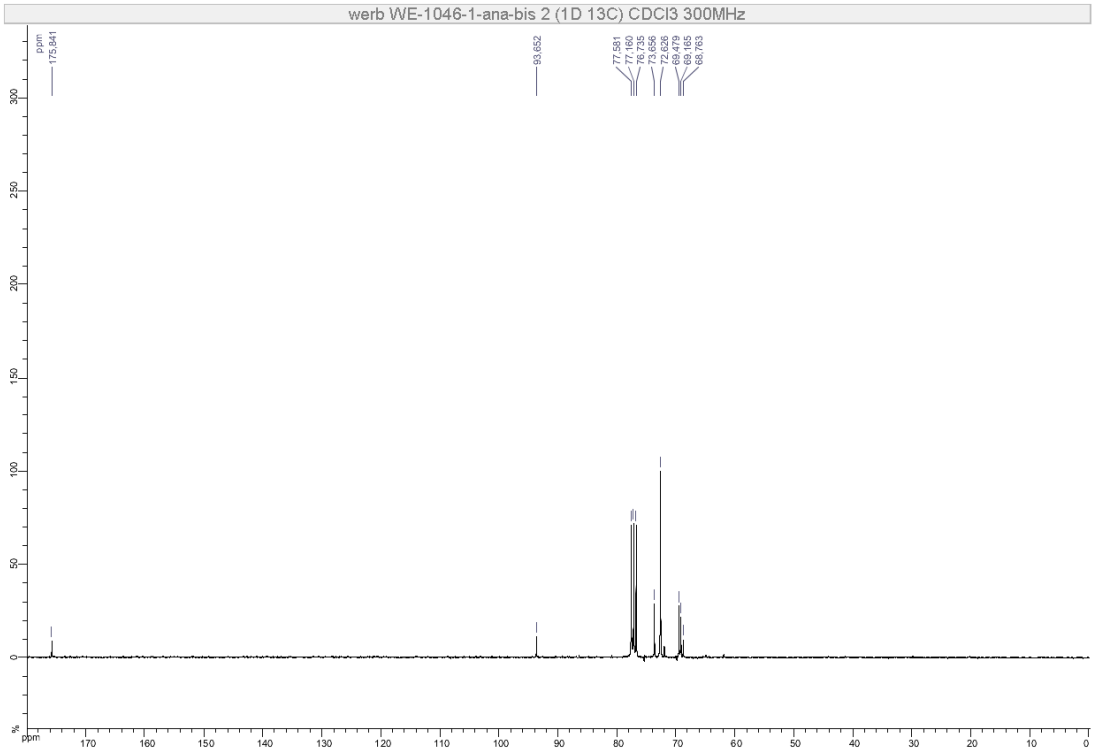
Compound 26



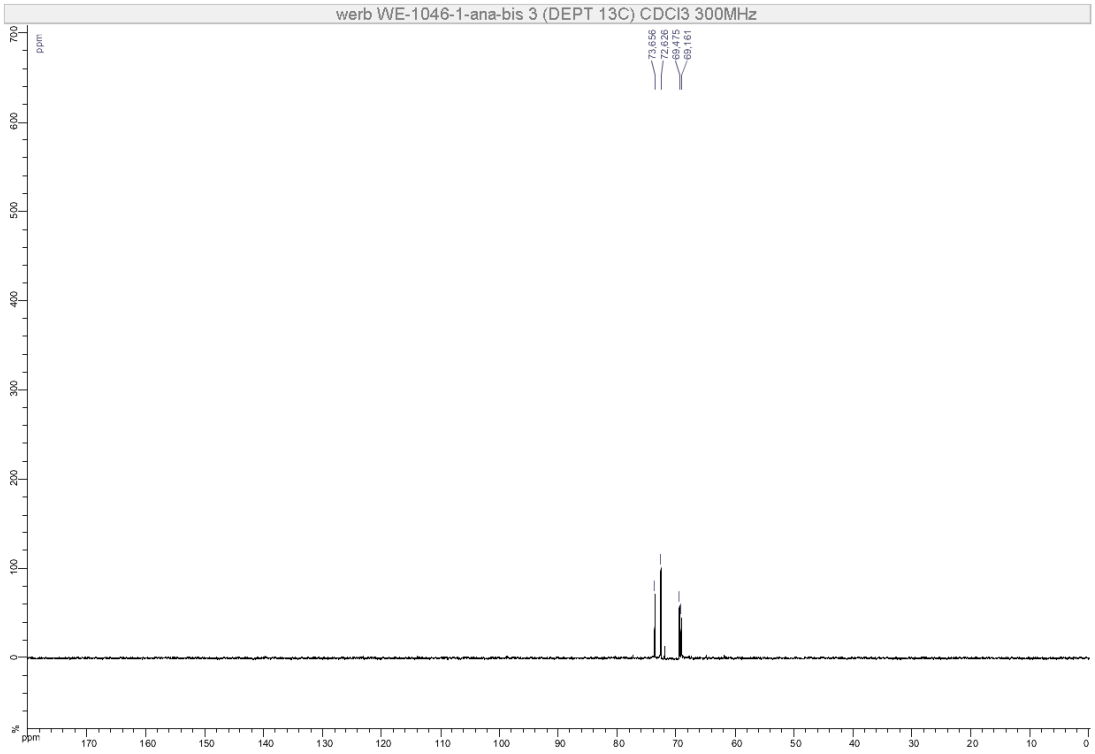
^{1}H NMR



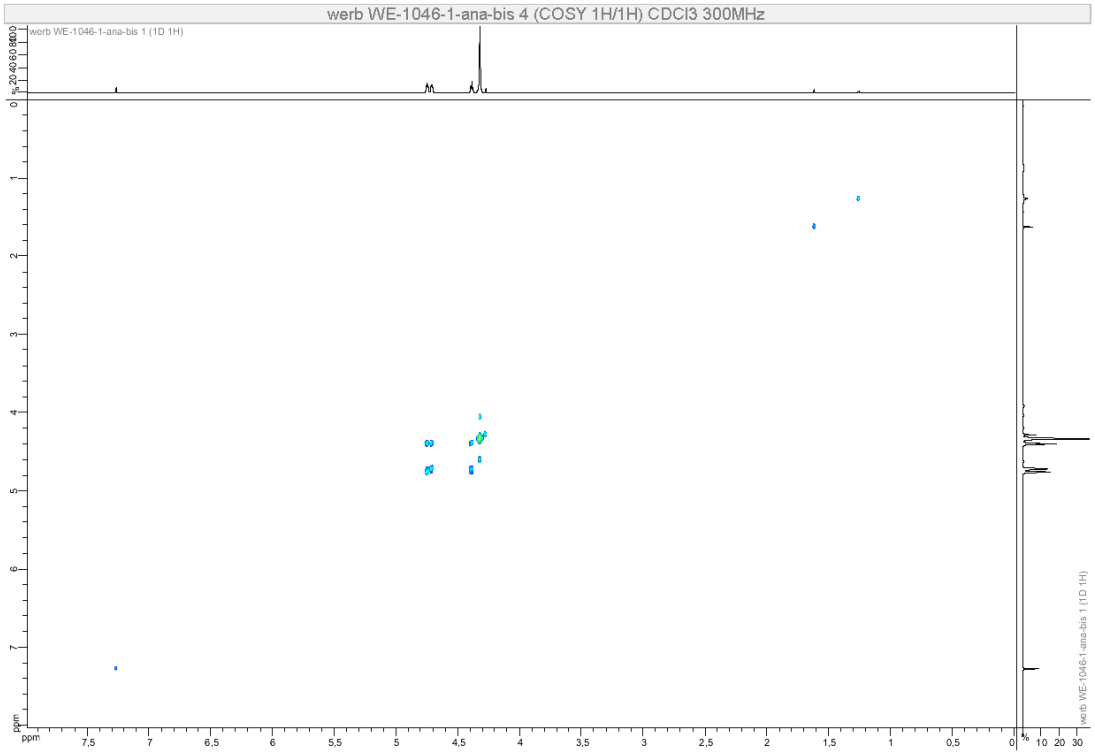
^{13}C NMR



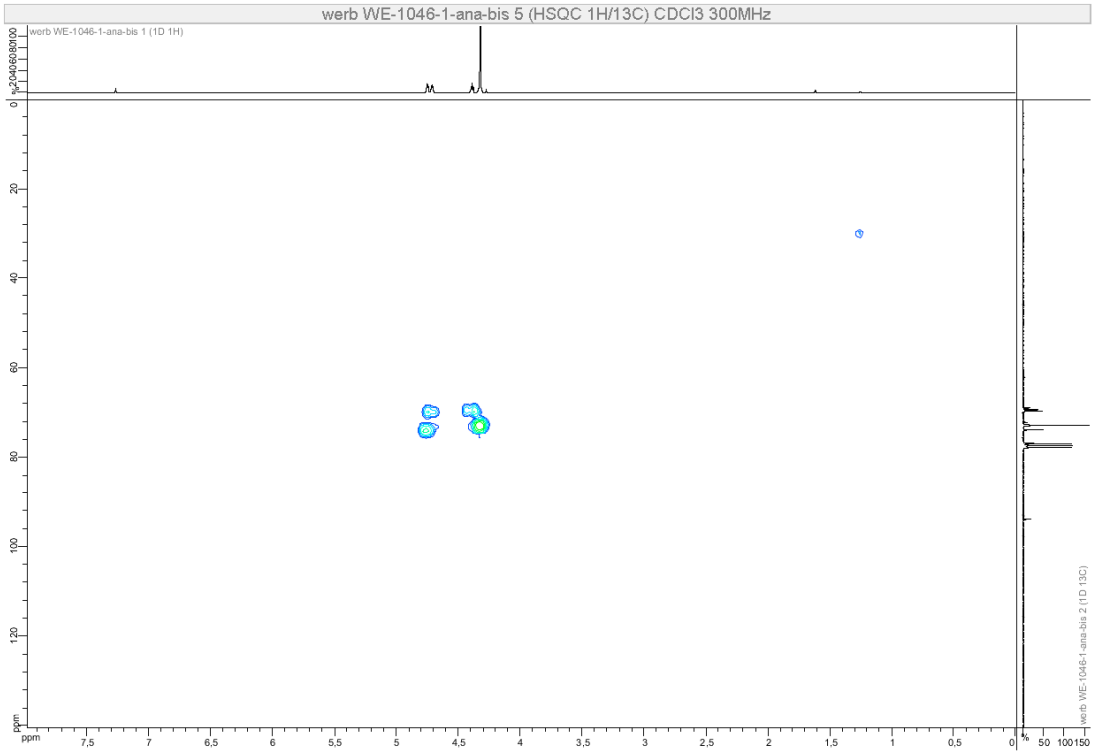
DEPT 135 NMR



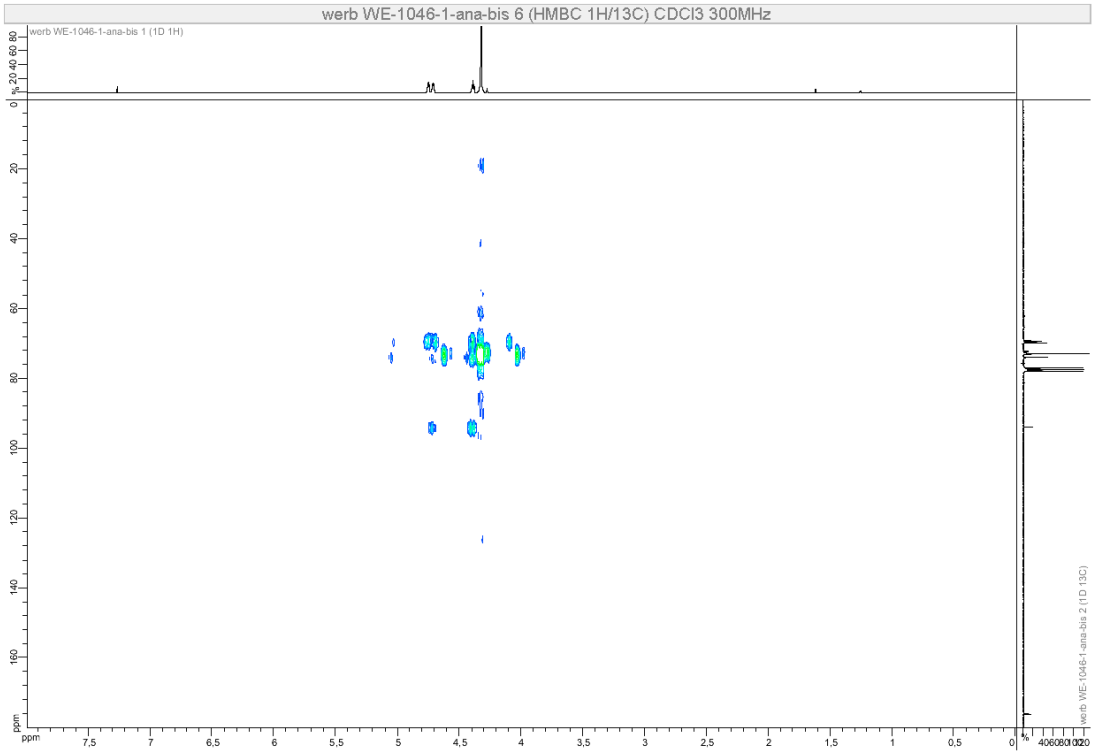
COSY NMR



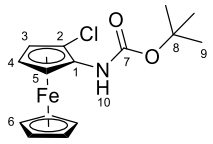
HSQC NMR



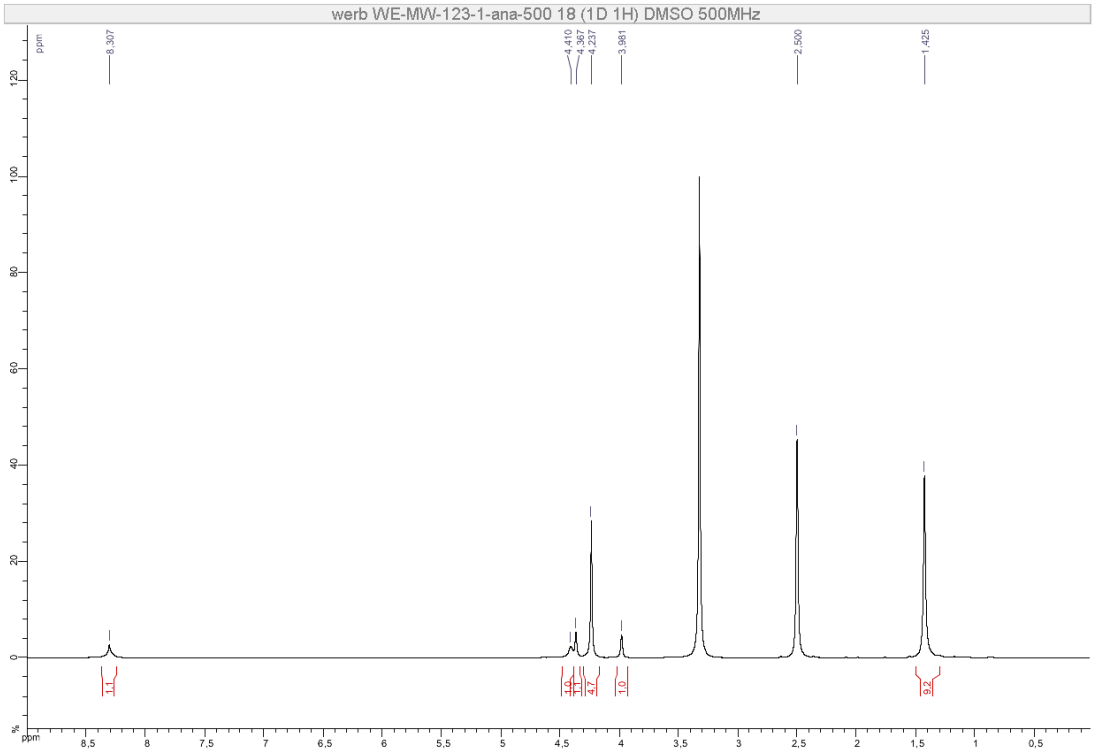
HMBC NMR



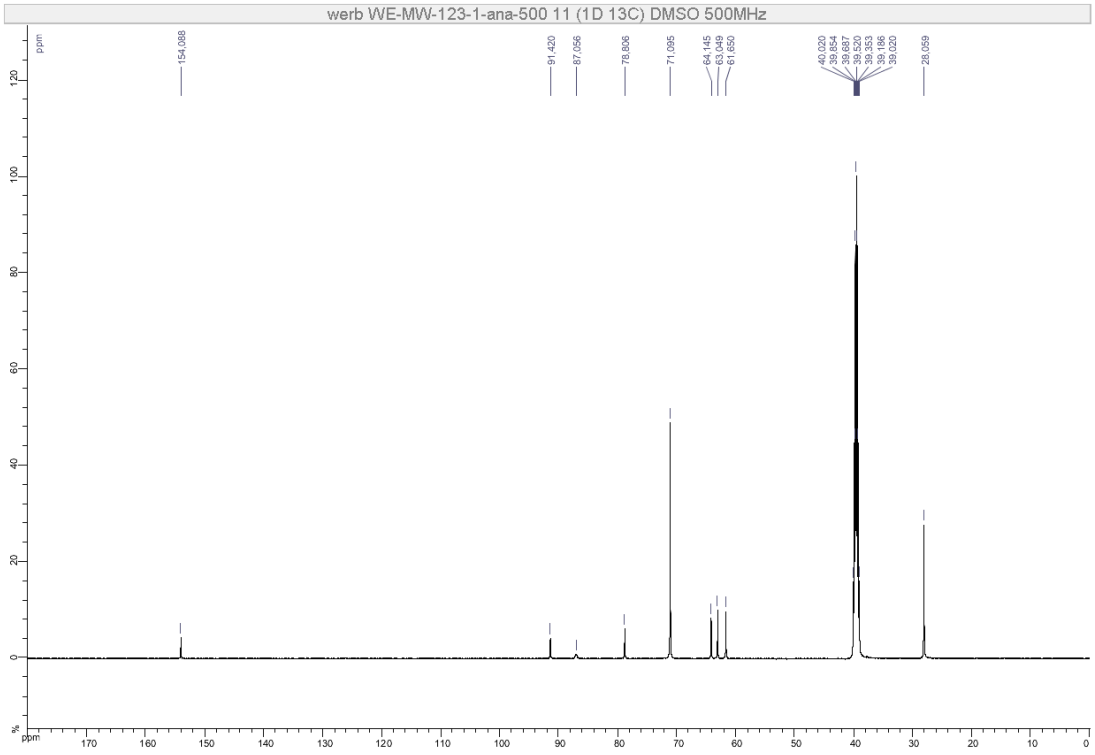
Compound 27



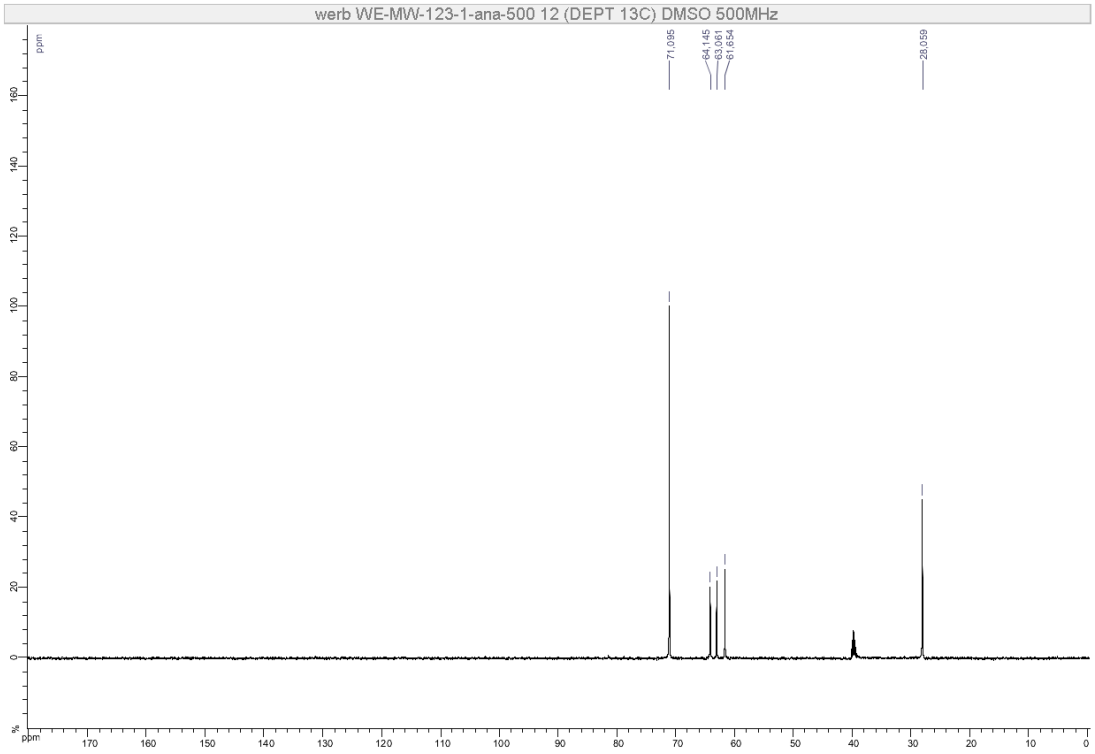
^{1}H NMR



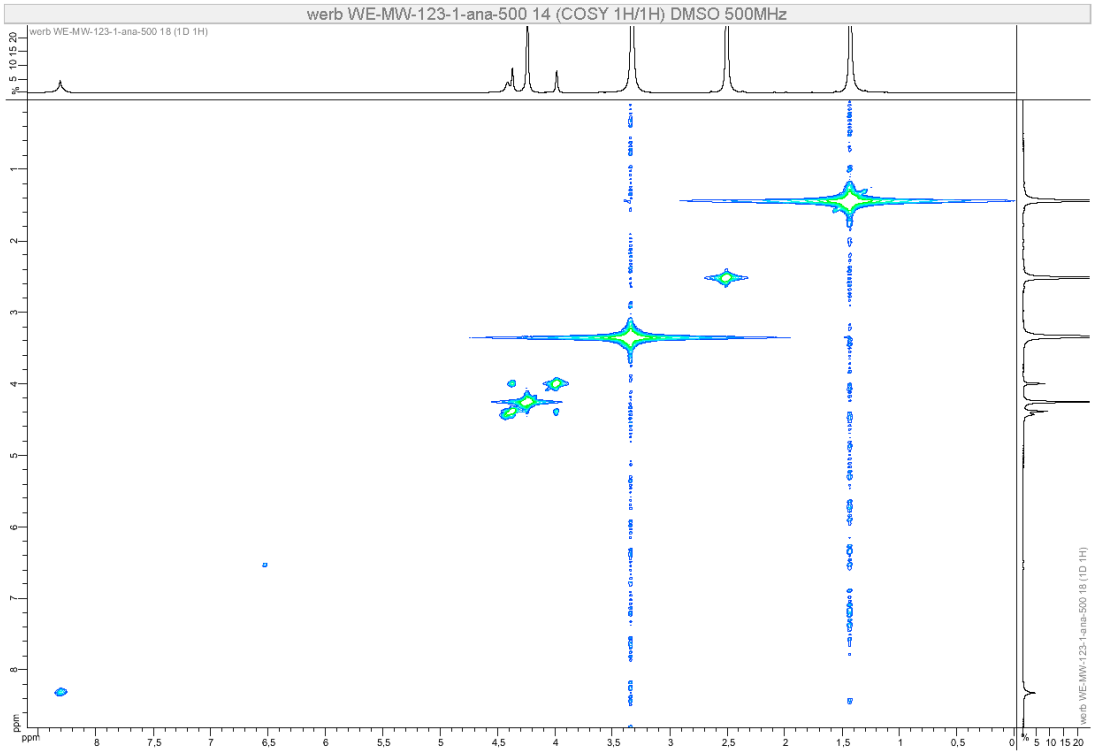
^{13}C NMR



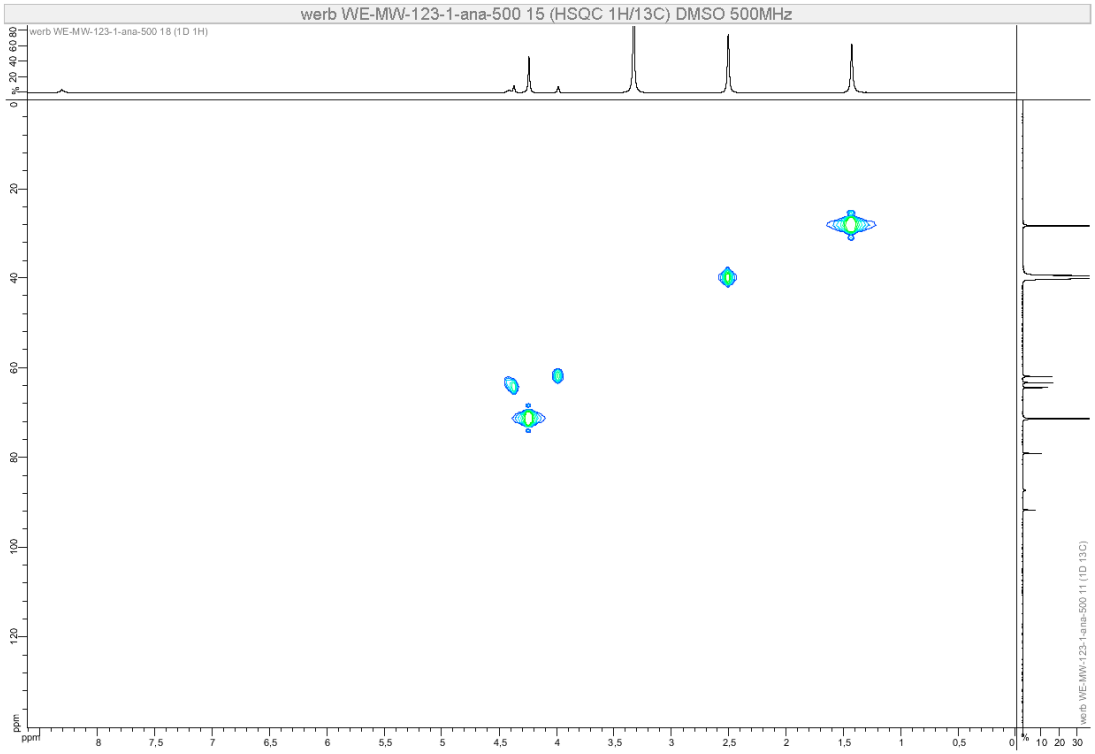
DEPT 135 NMR



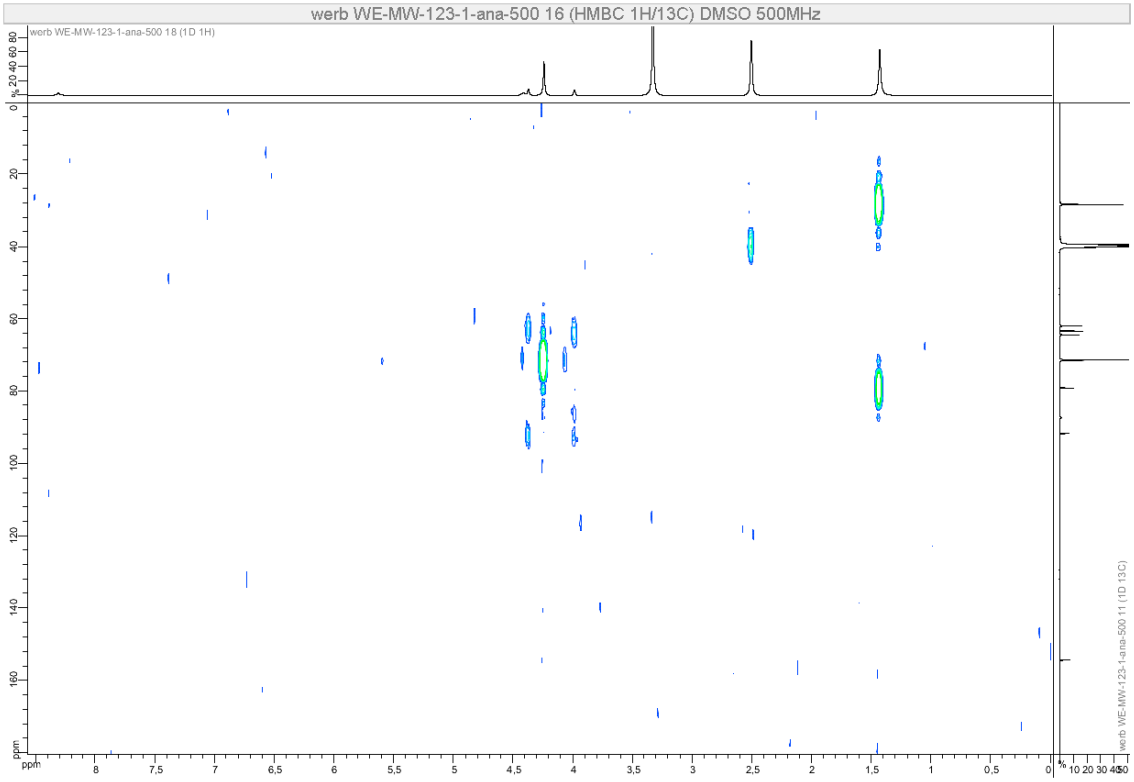
COSY NMR



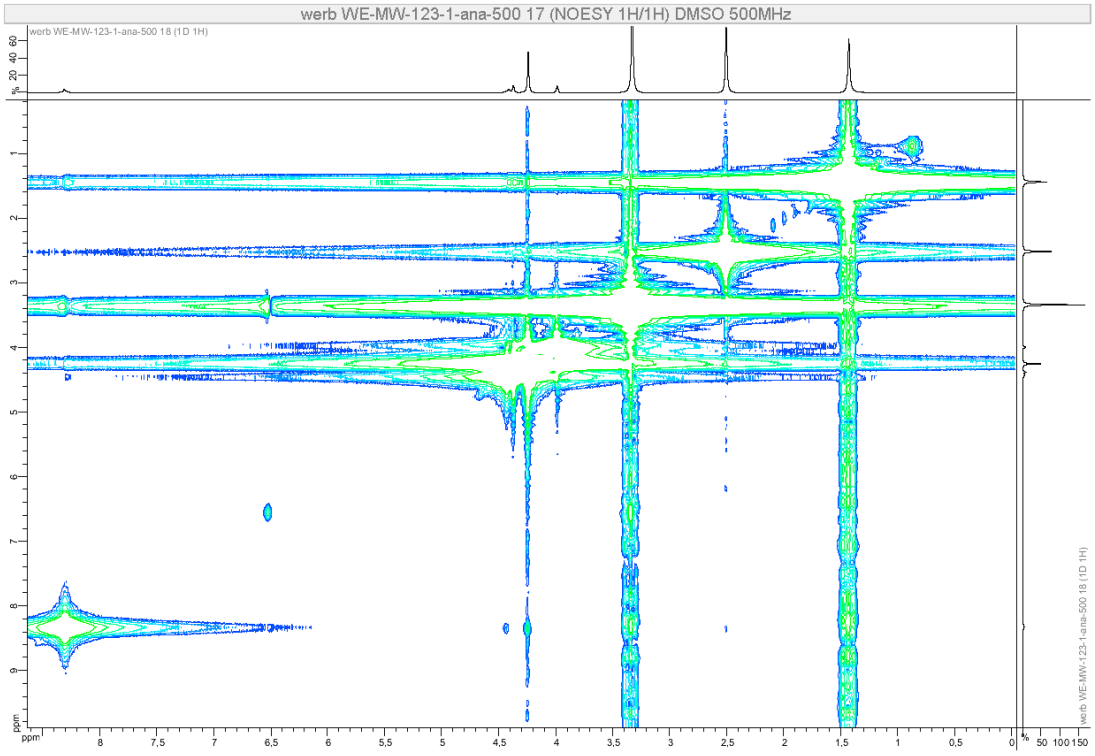
HSQC NMR



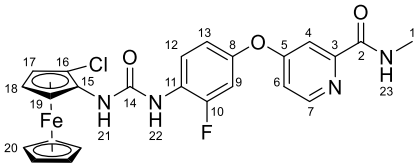
HMBC NMR



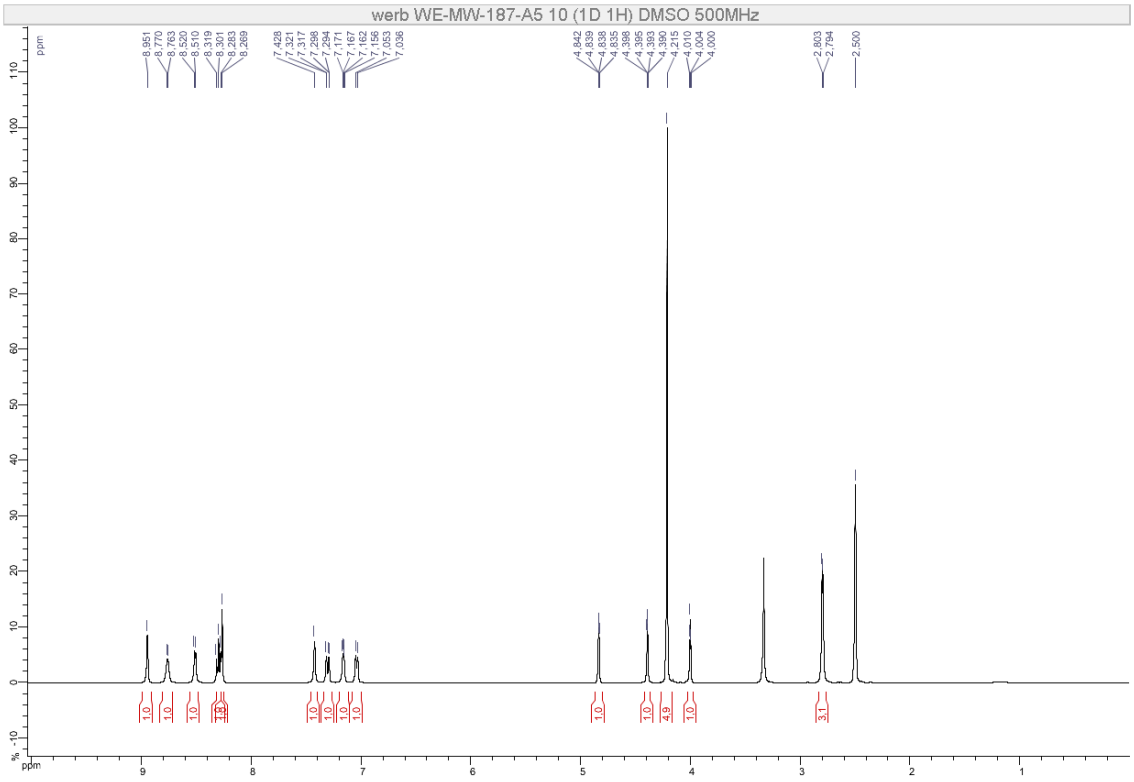
NOESY NMR


werb WE-MW-123-1-ana-500 17 (NOESY 1H/1H) DMSO 500MHz
werb WE-MW-123-1-ana-500 18 (1D 1H)
ppm
%

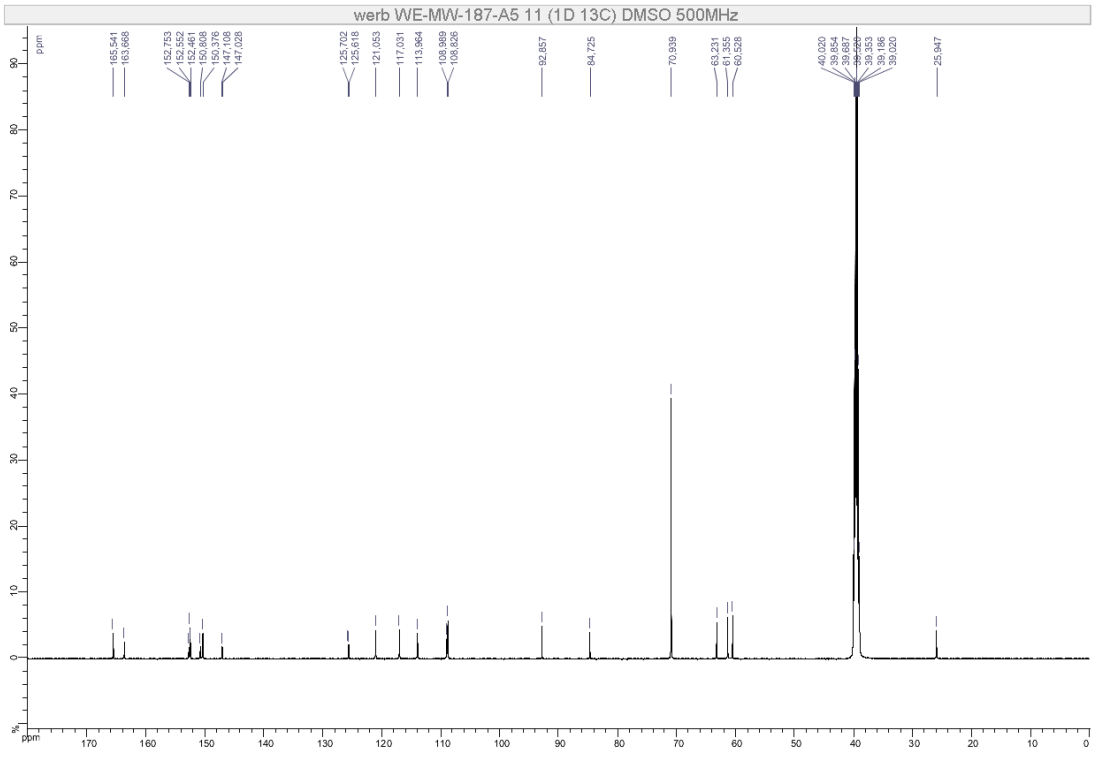
Compound 2aCl



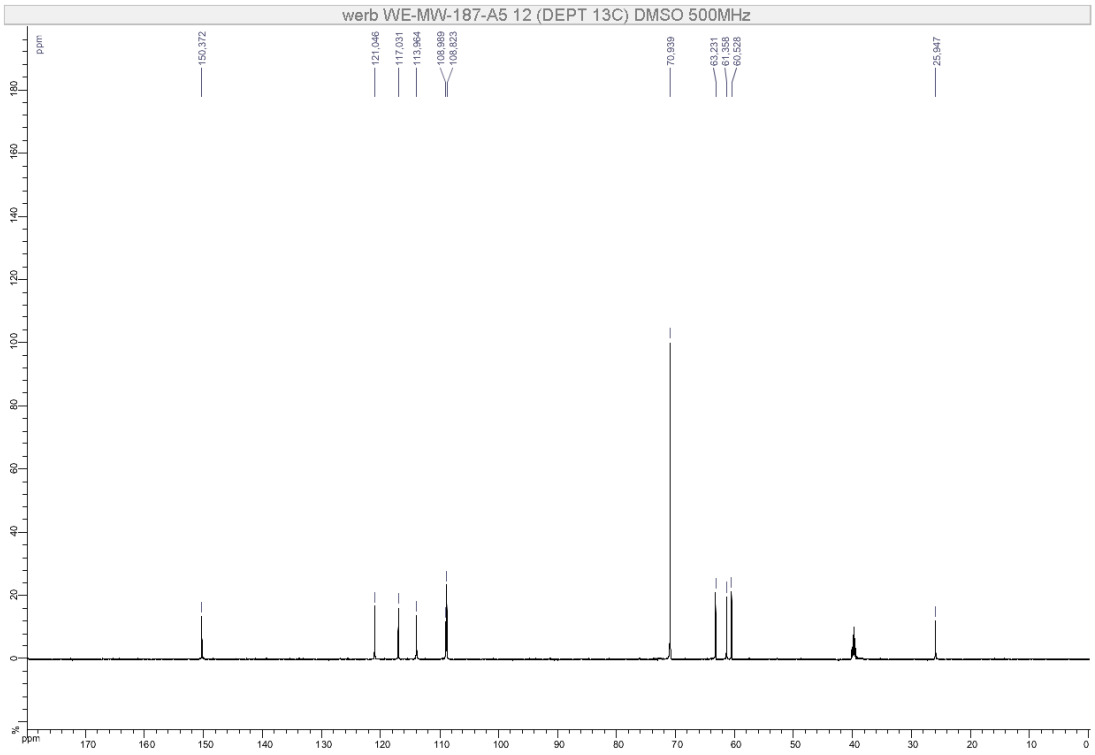
^{1}H NMR



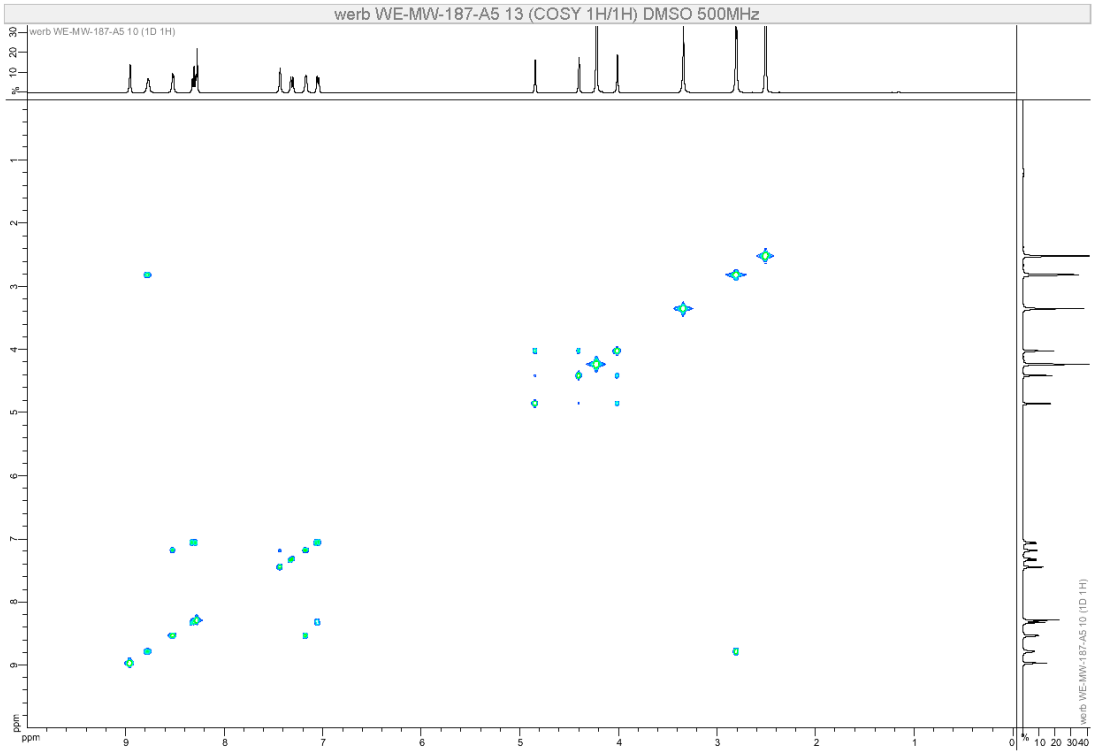
^{13}C NMR



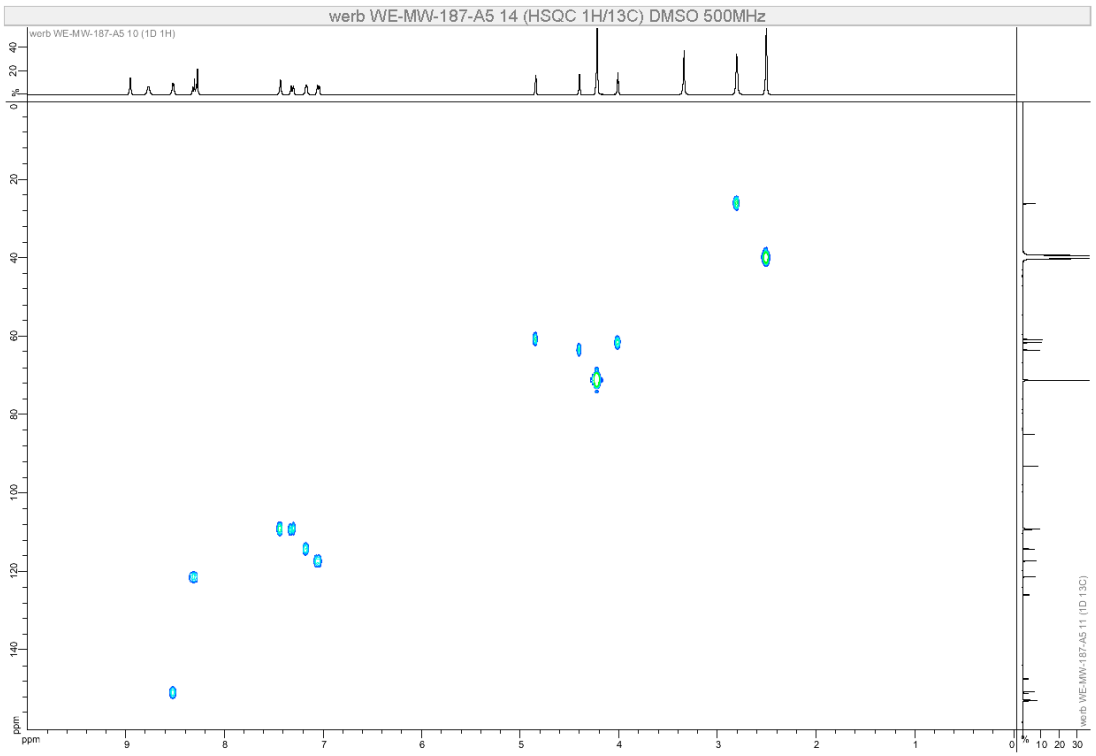
DEPT 135 NMR



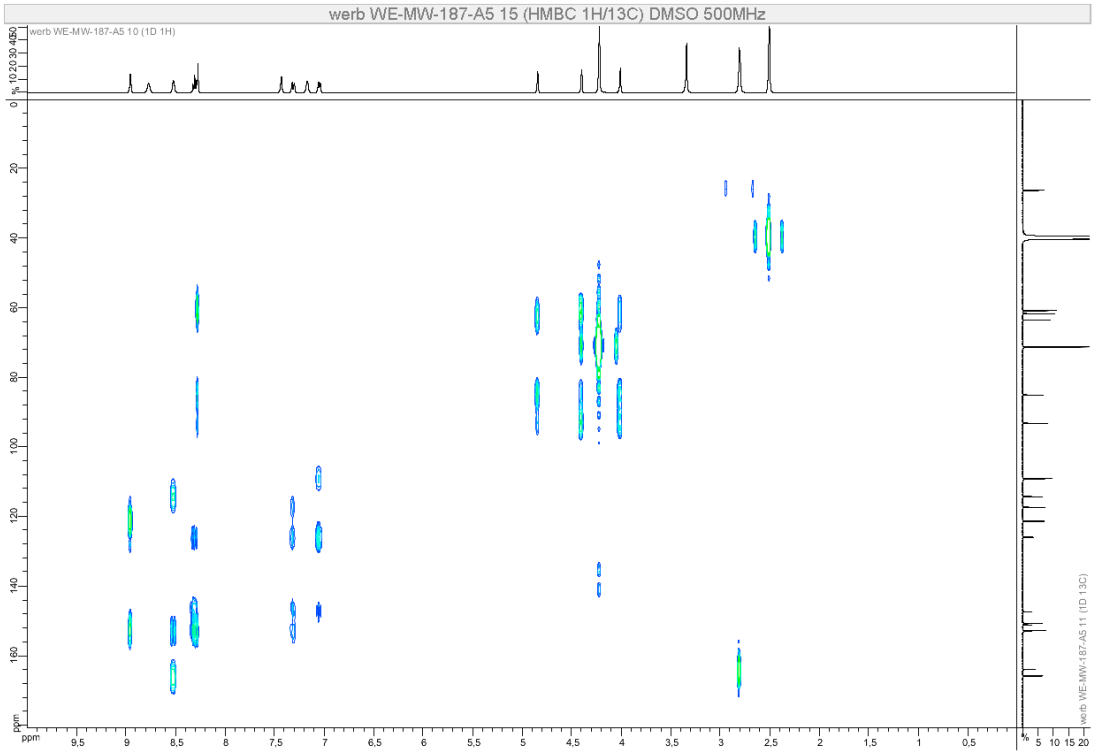
COSY NMR



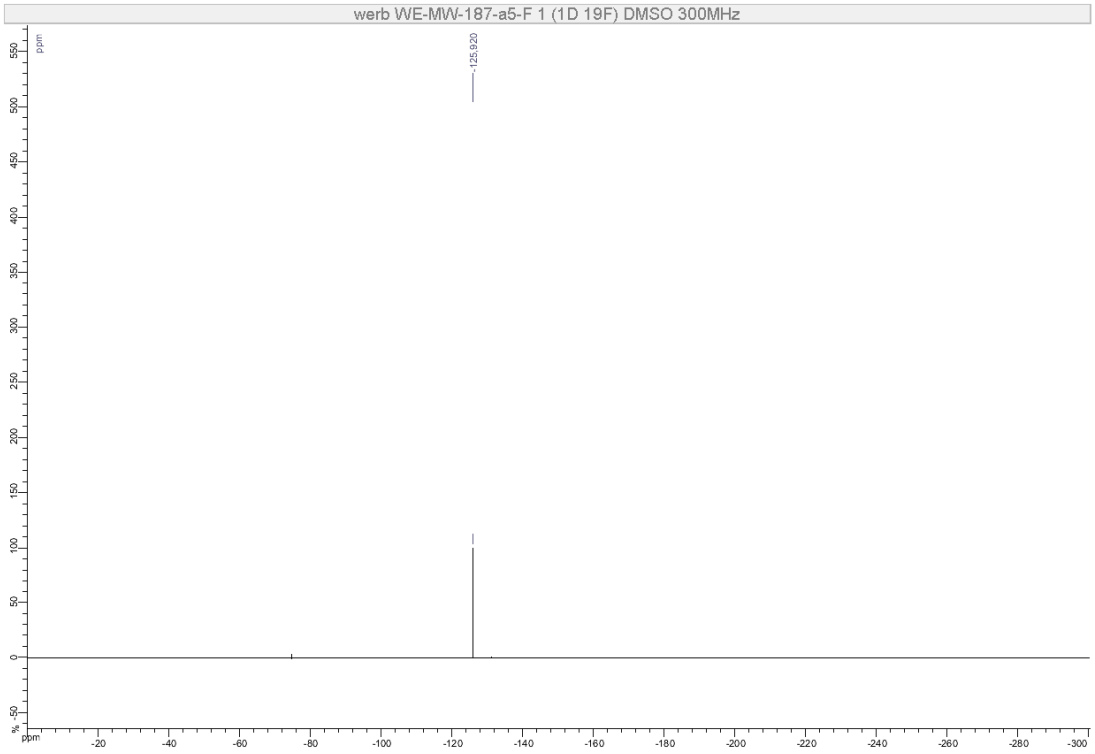
HSQC NMR



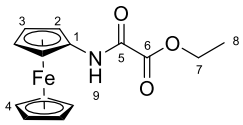
HMBC NMR



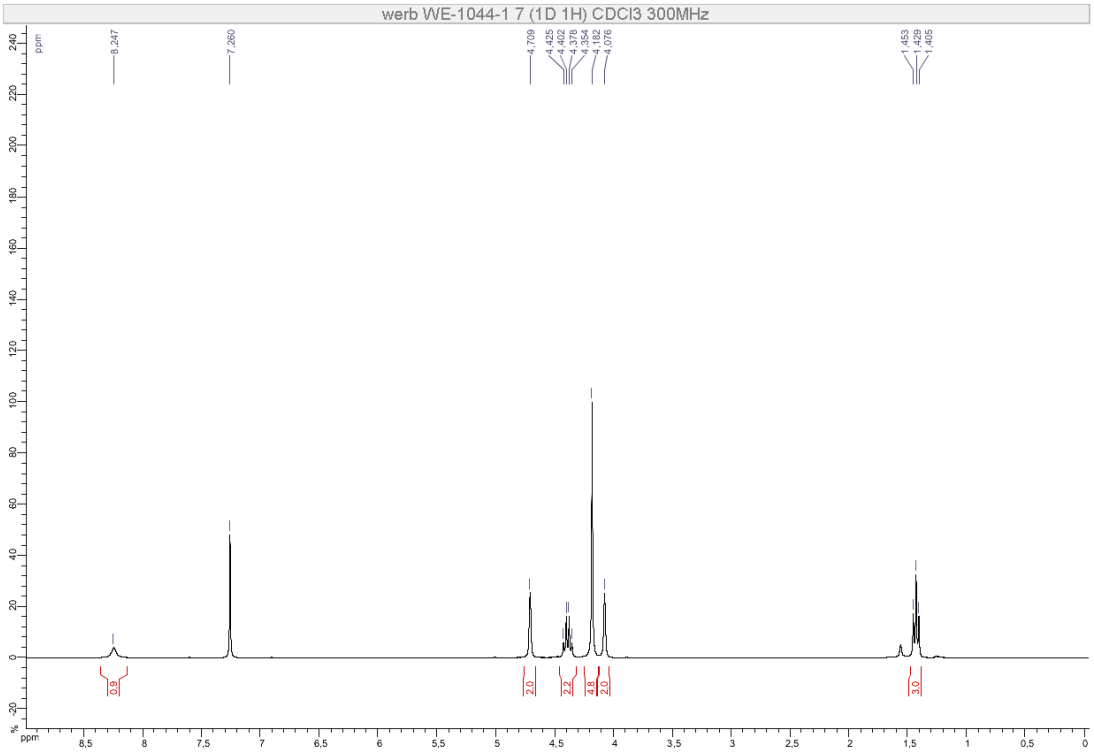
^{19}F NMR


werb WE-MW-187-a5-F 1 (1D 19F) DMSO 300MHz
-125.920
ppm
% 550 500 450 400 350 300 250 200 150 100 50 0 -50
ppm -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 -220 -240 -260 -280 -300

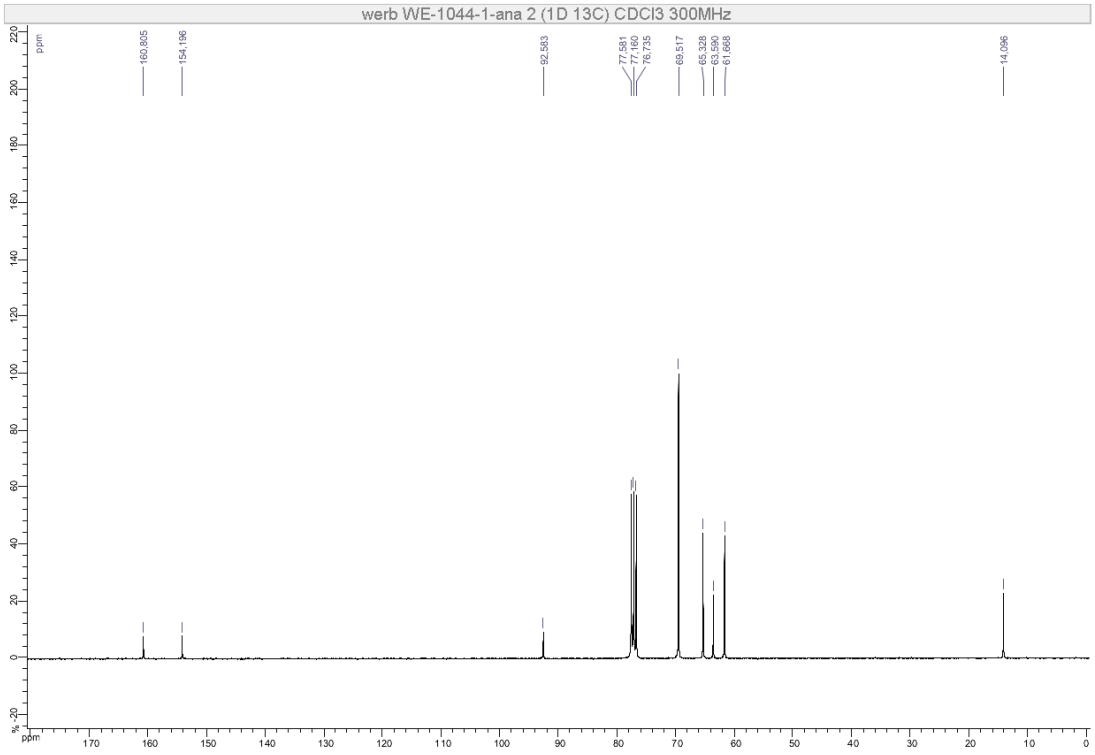
Compound 31



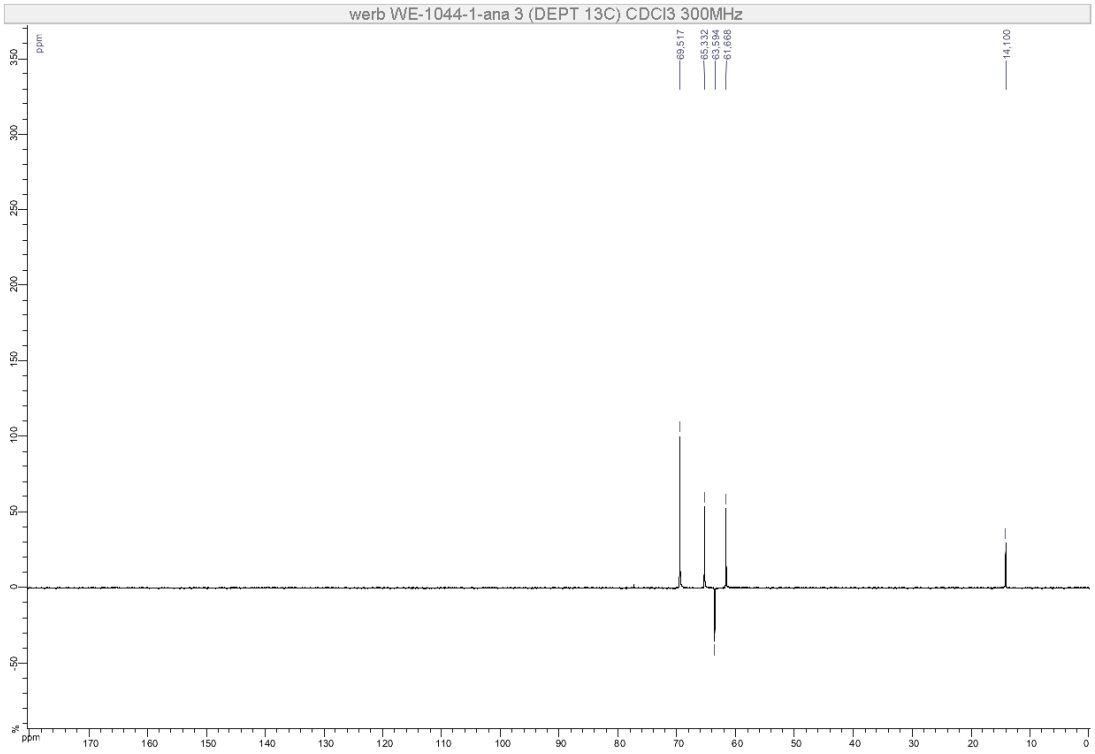
^{1}H NMR



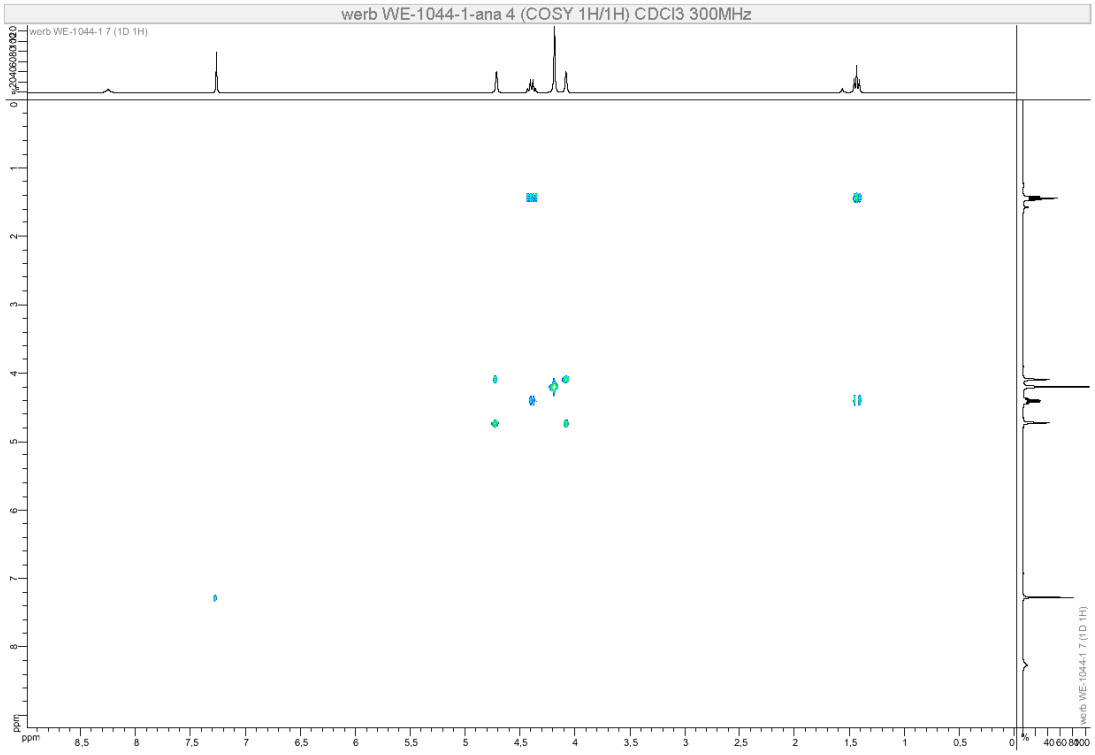
^{13}C NMR



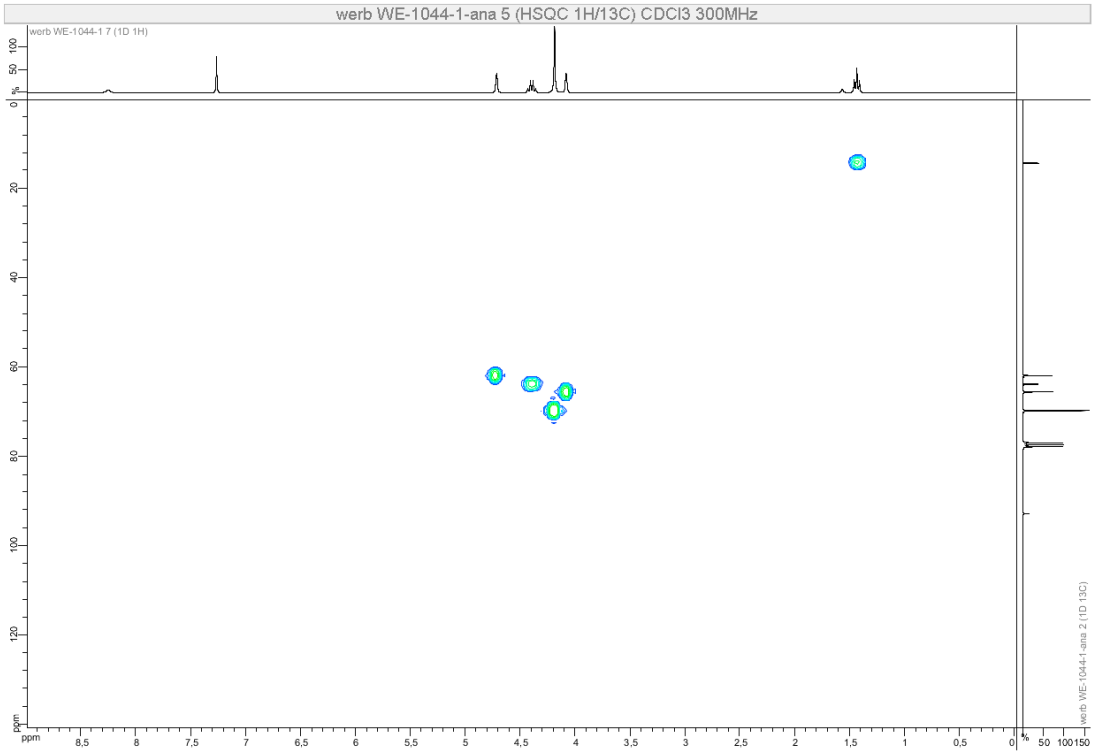
DEPT 135 NMR



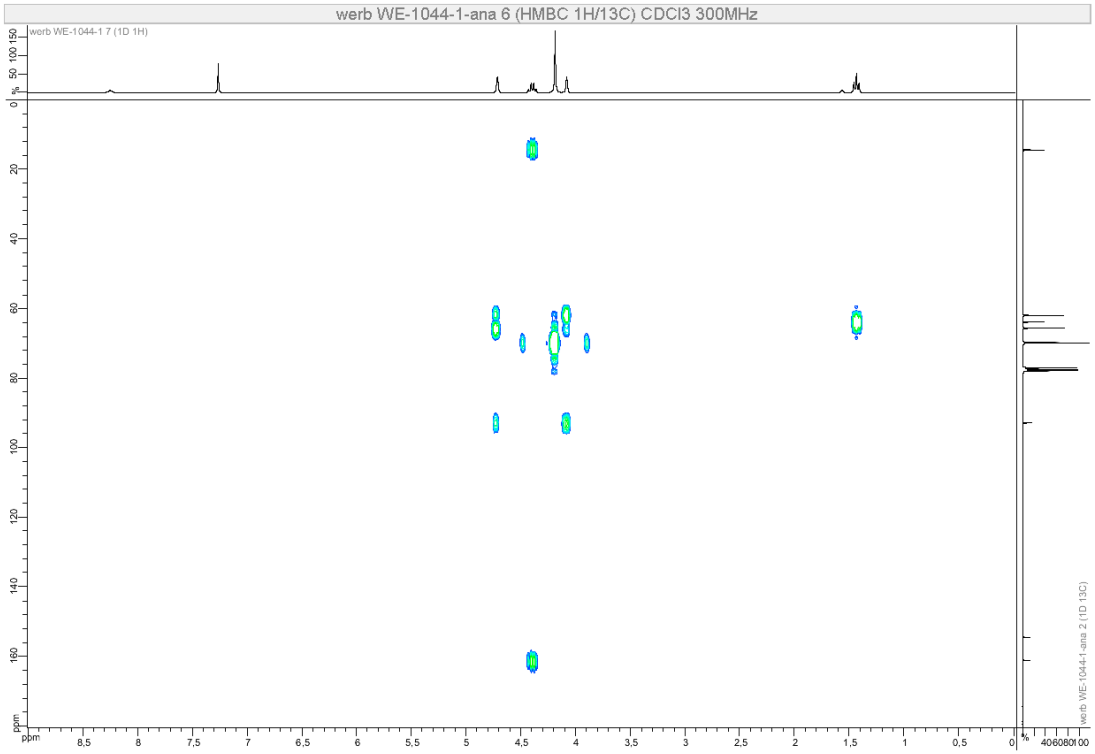
COSY NMR



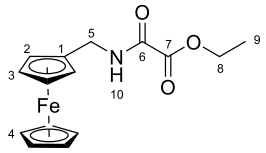
HSQC NMR



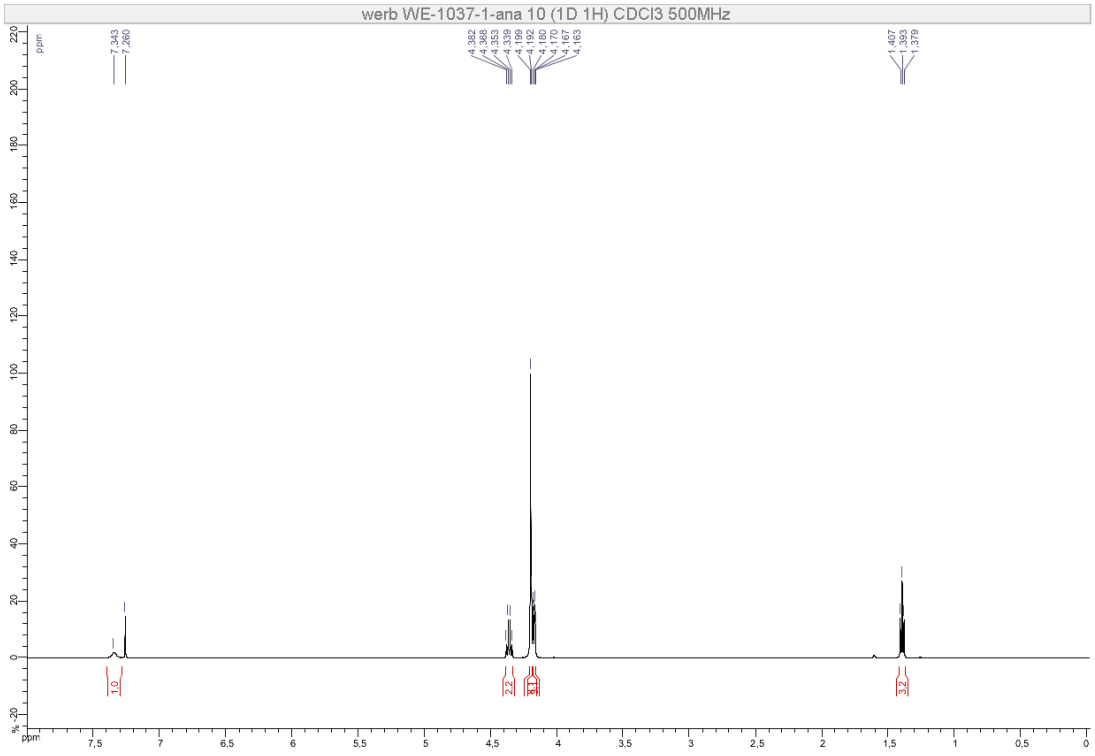
HMBC NMR



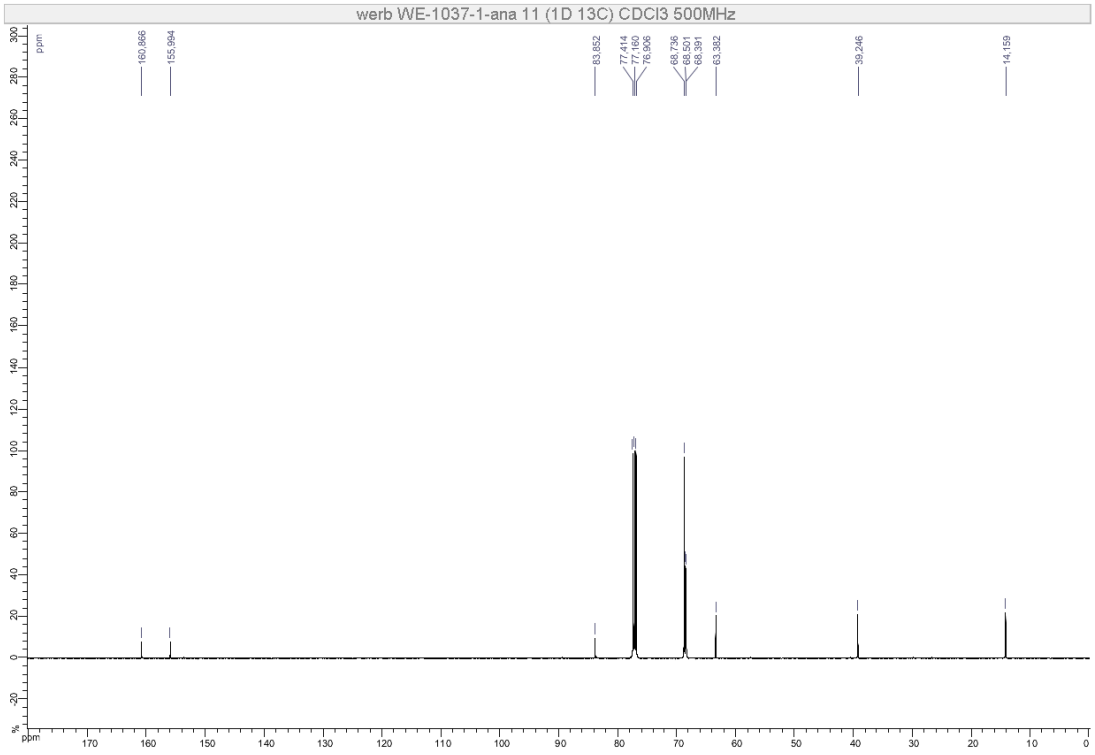
Compound 32



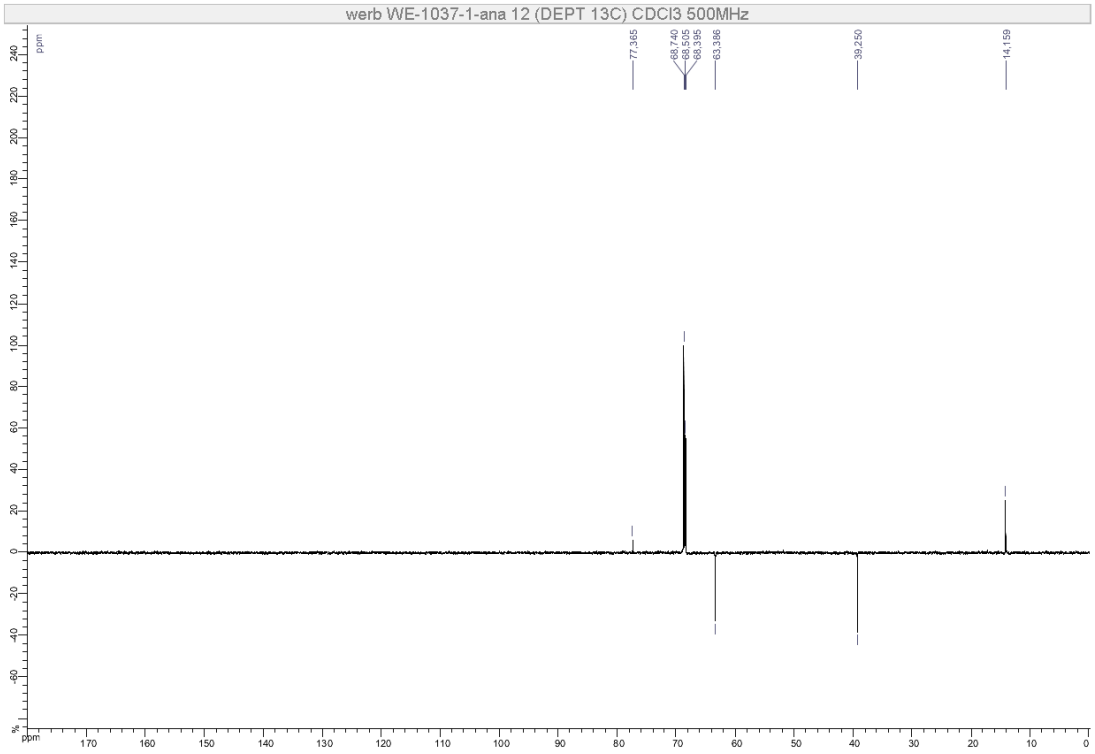
^{1}H NMR



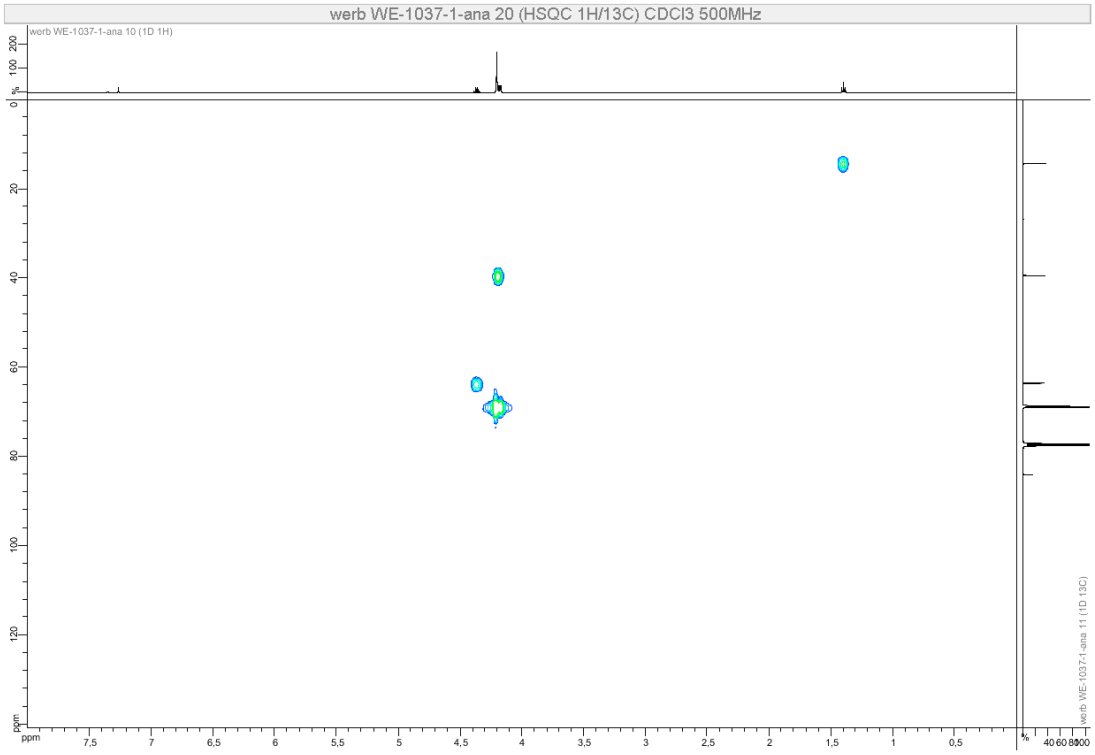
^{13}C NMR



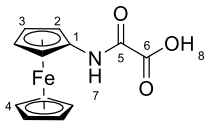
DEPT 135 NMR



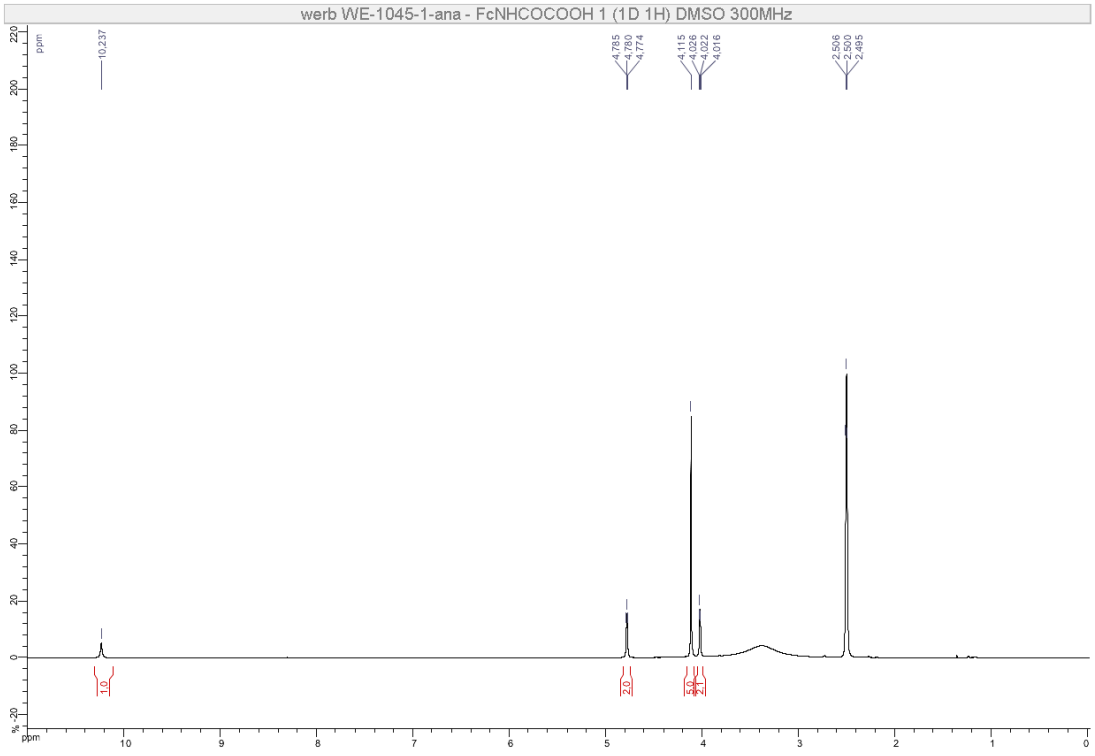
HSQC NMR



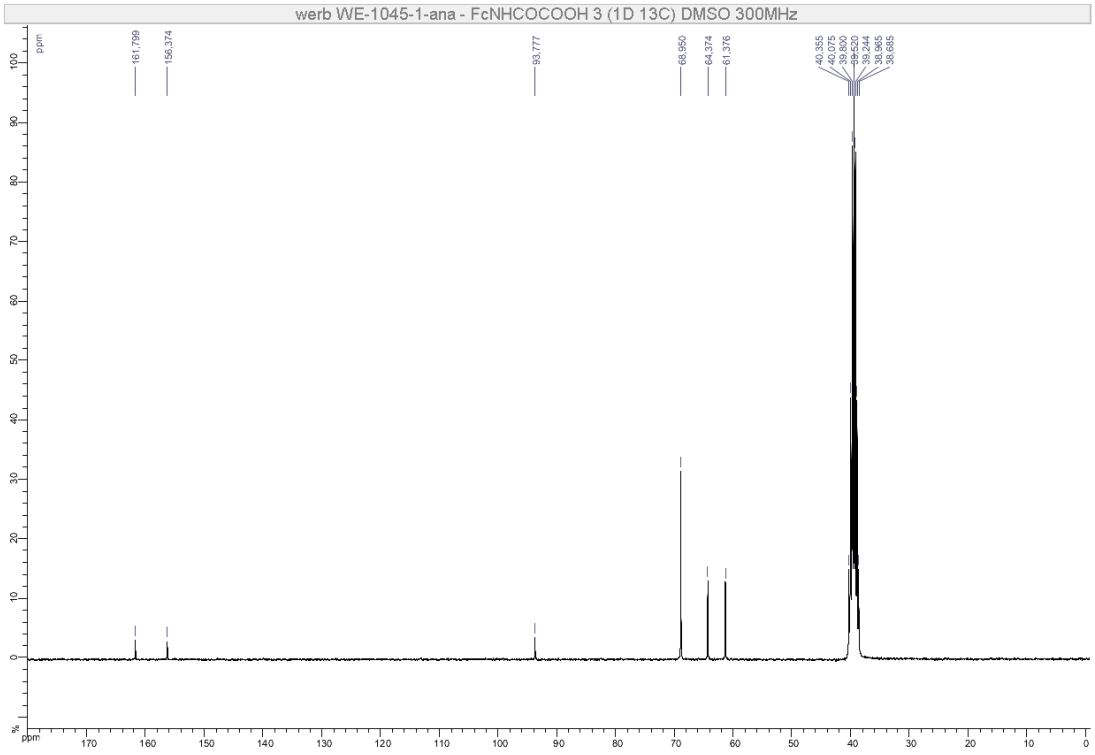
Compound 33



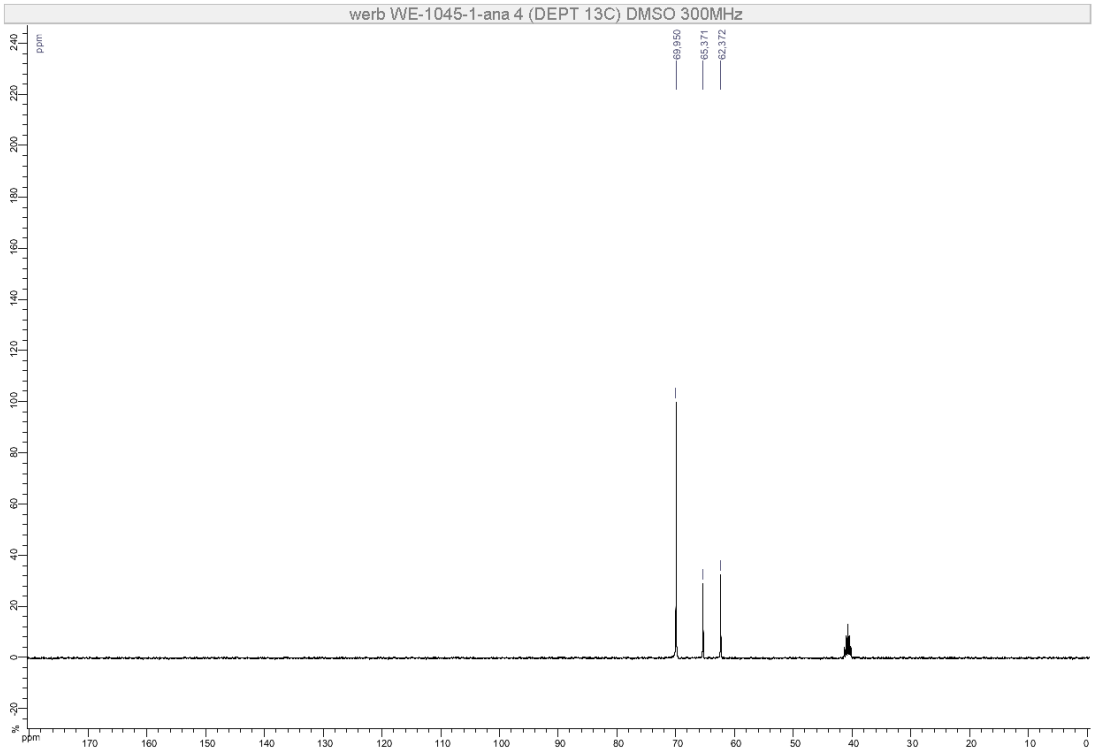
^{1}H NMR



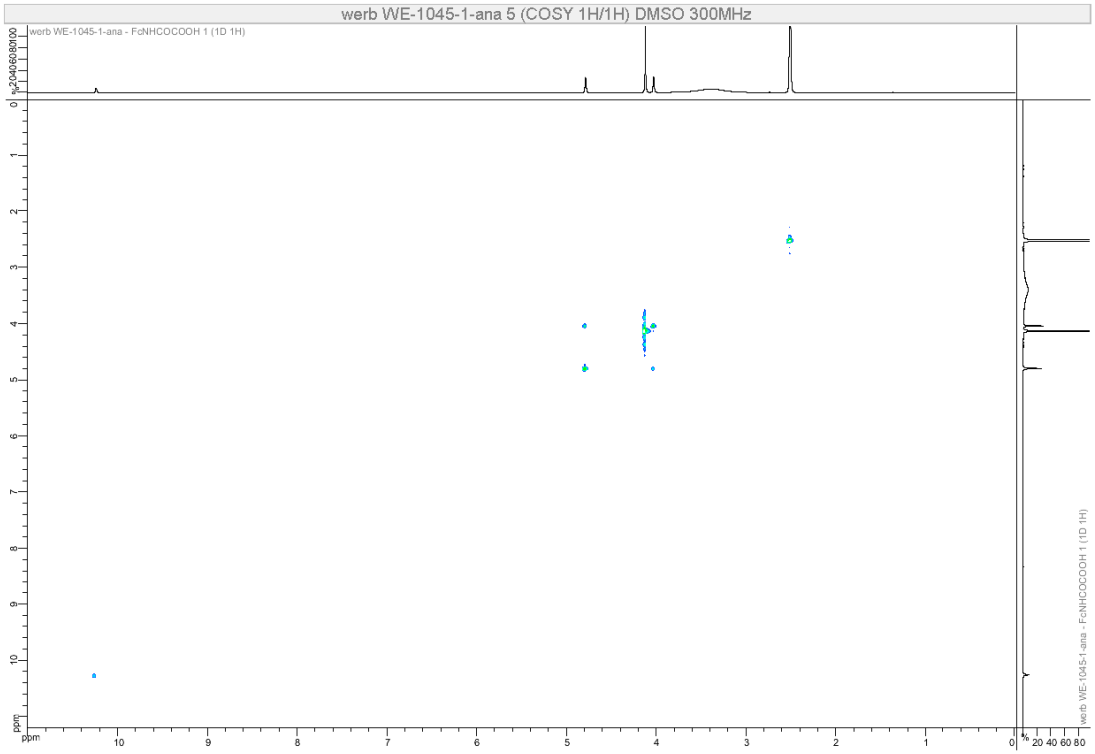
^{13}C NMR



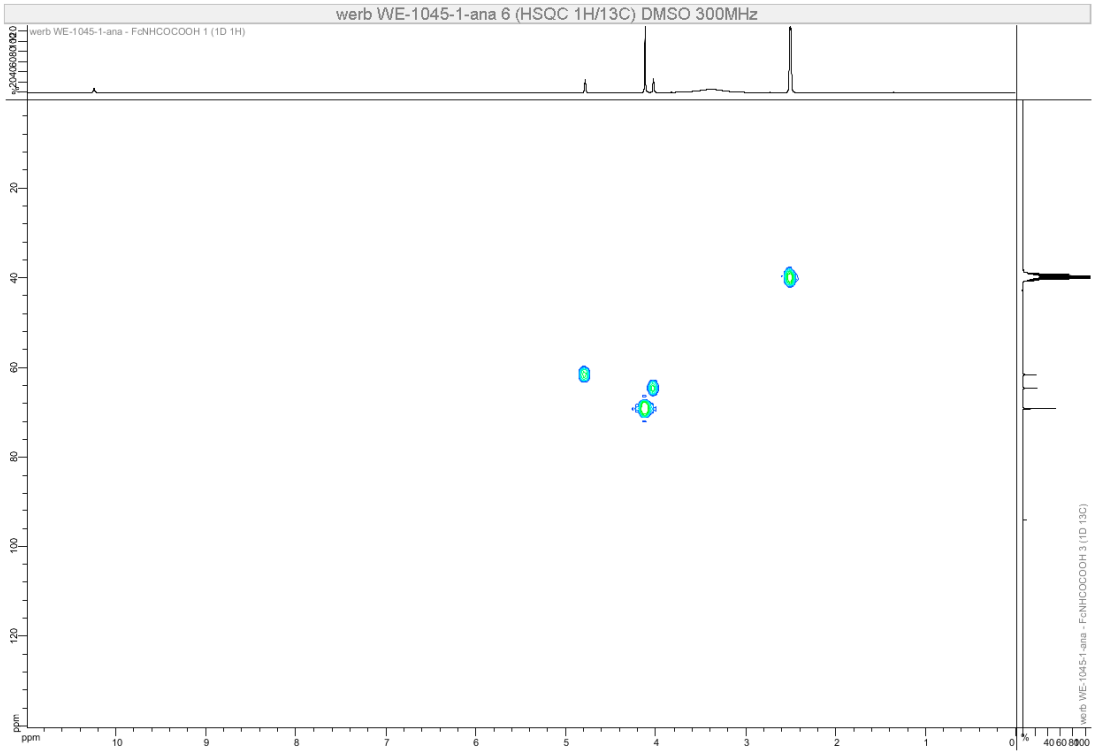
DEPT 135 NMR



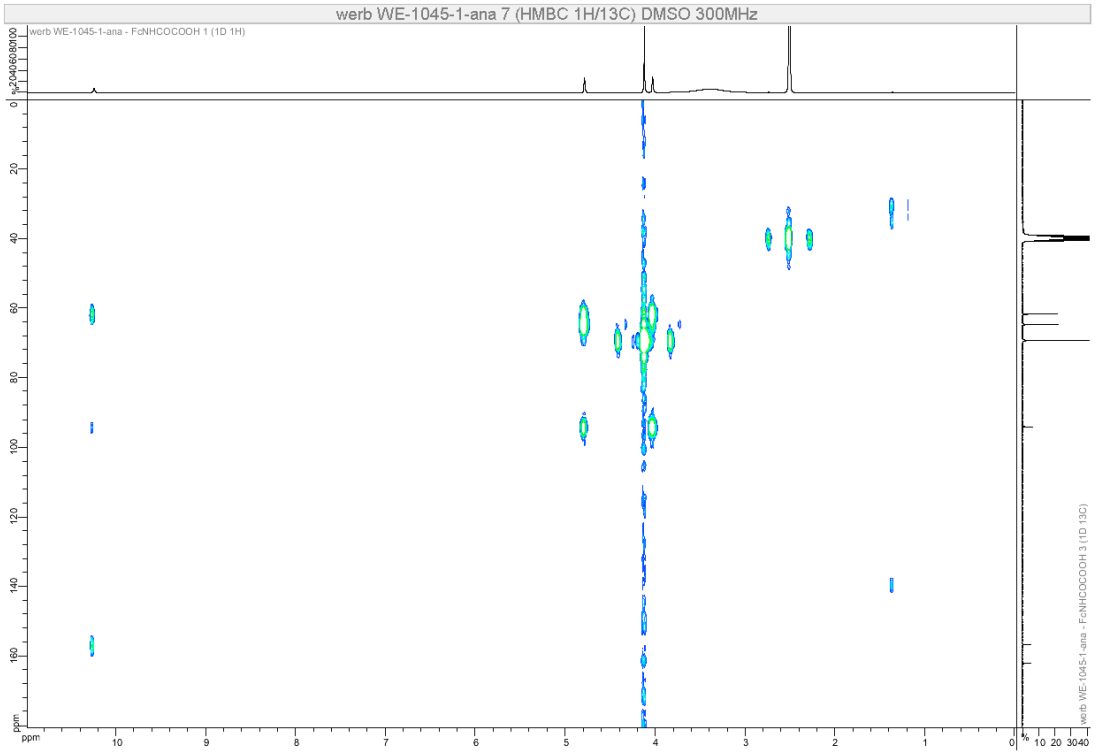
COSY NMR



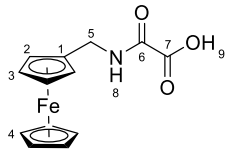
HSQC NMR



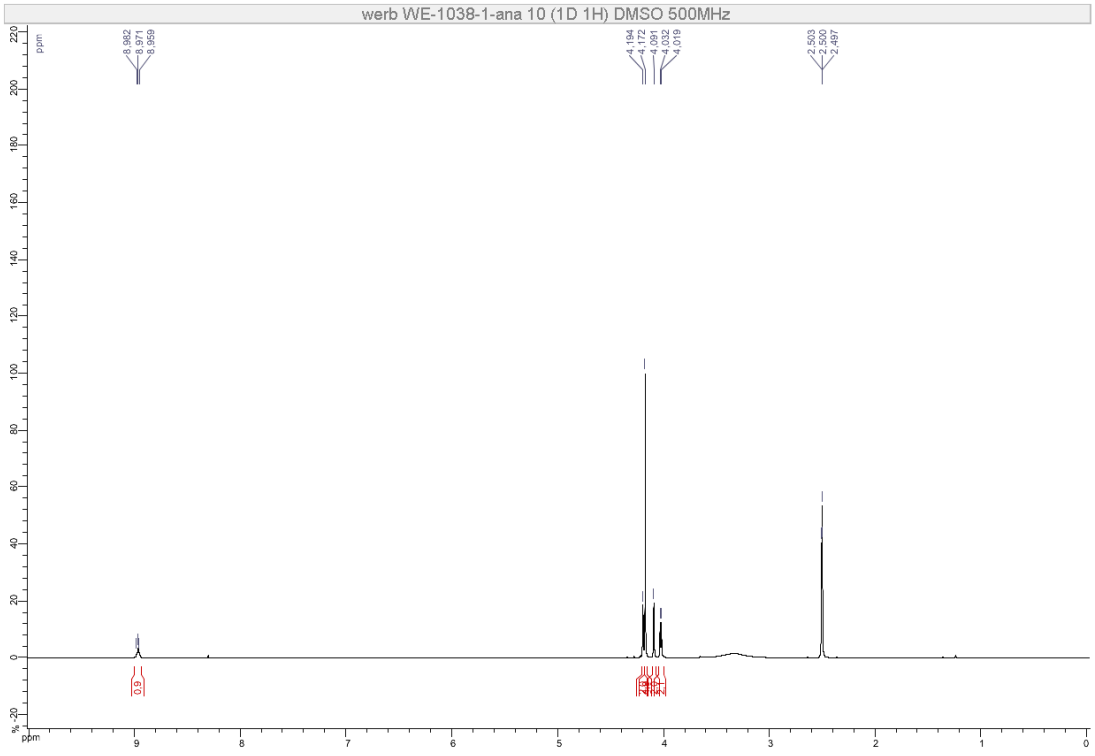
HMBC NMR



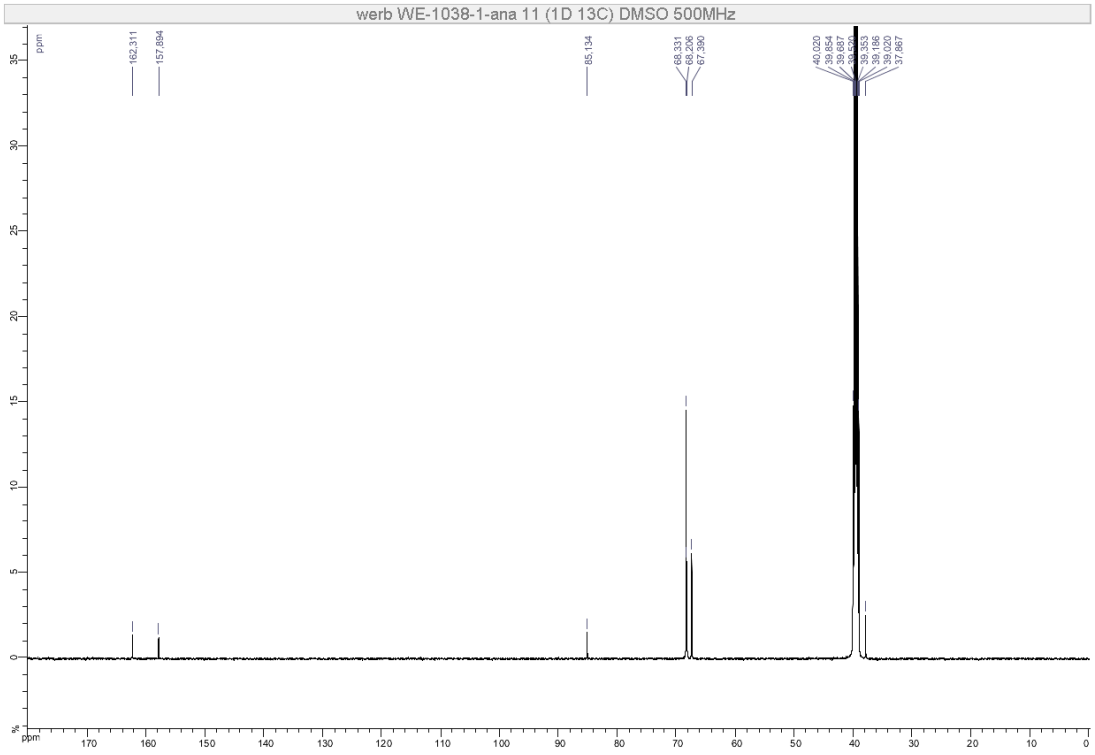
Compound 34



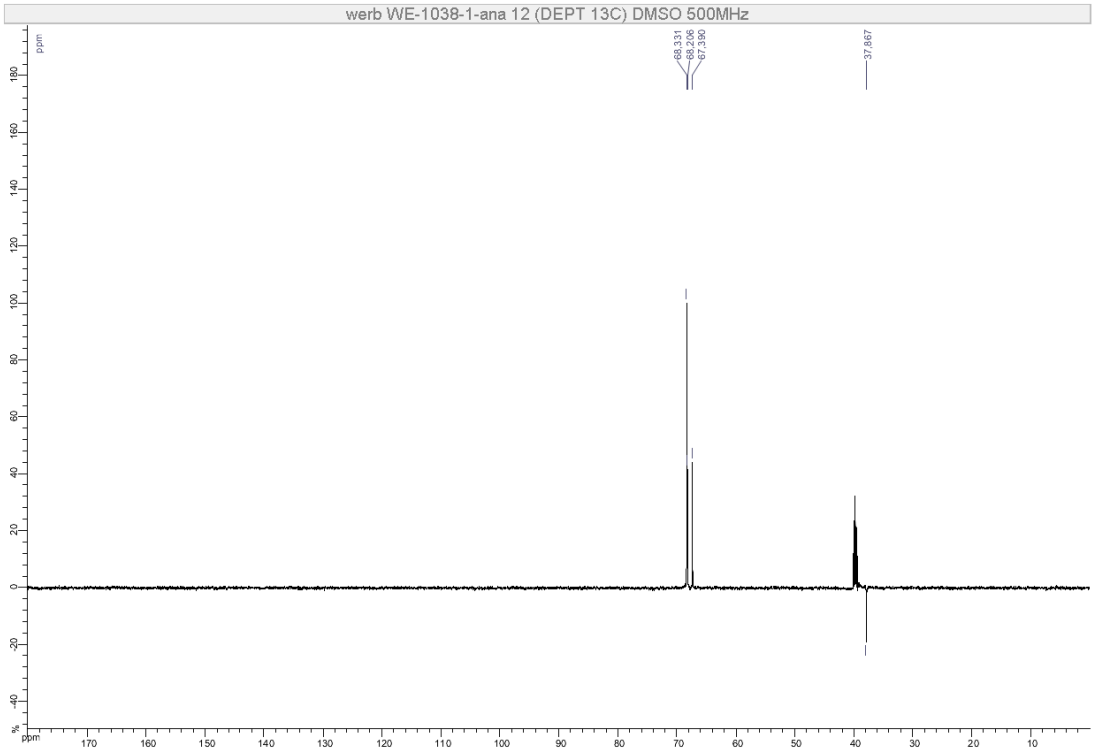
^{1}H NMR



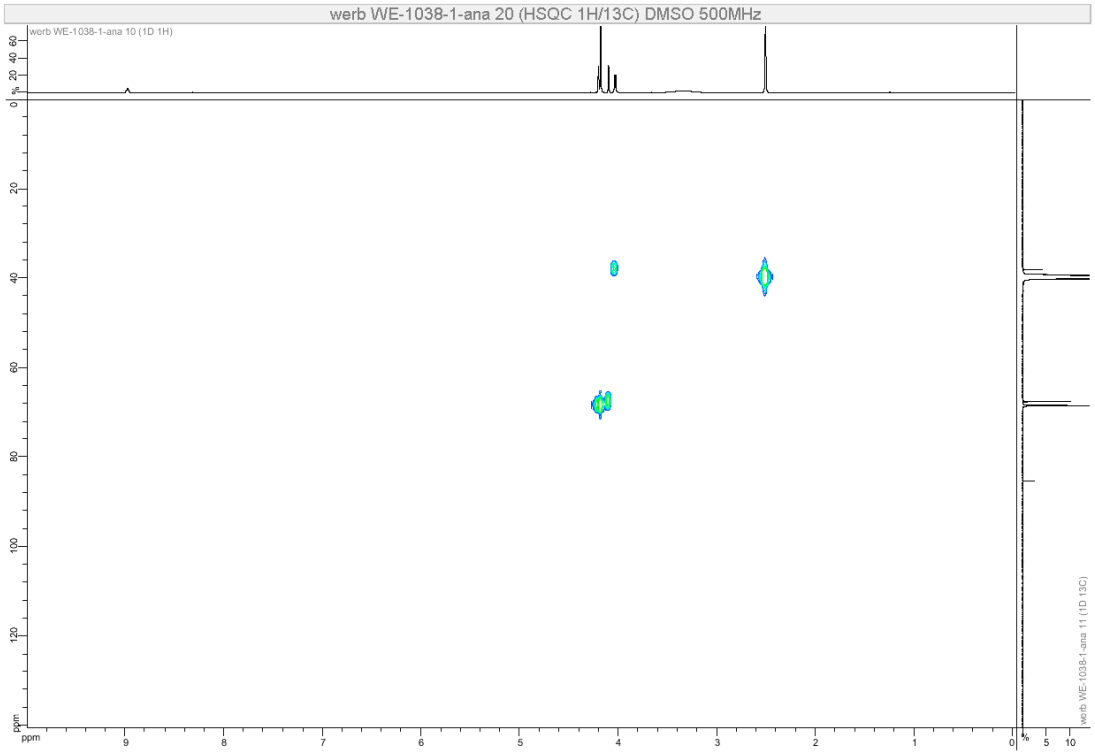
^{13}C NMR



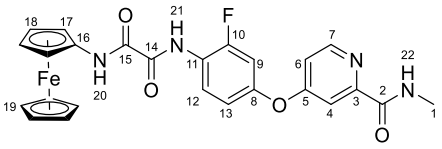
DEPT 135 NMR



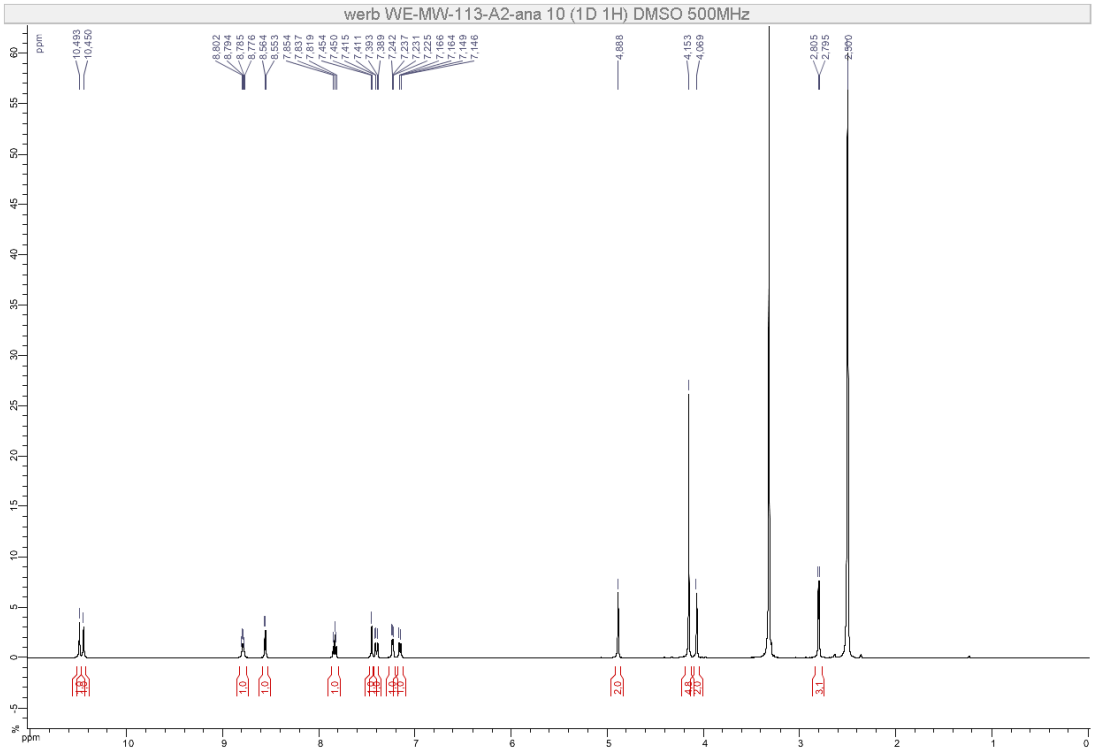
HSQC NMR



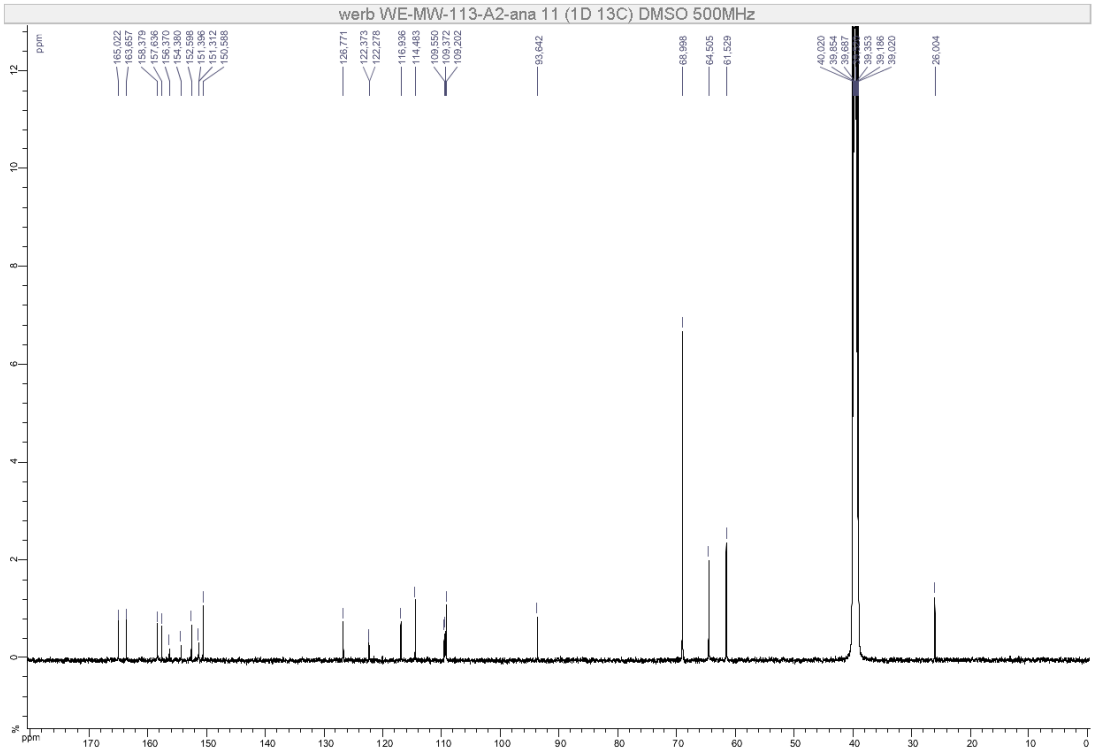
Compound 2c



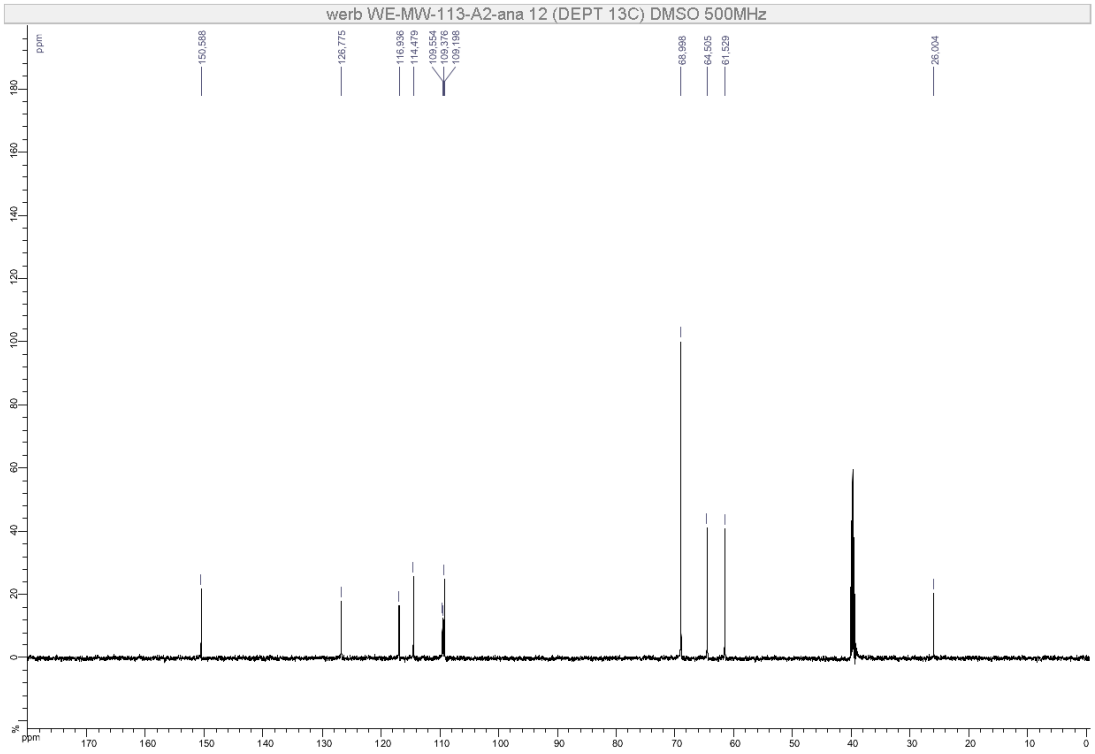
^{1}H NMR



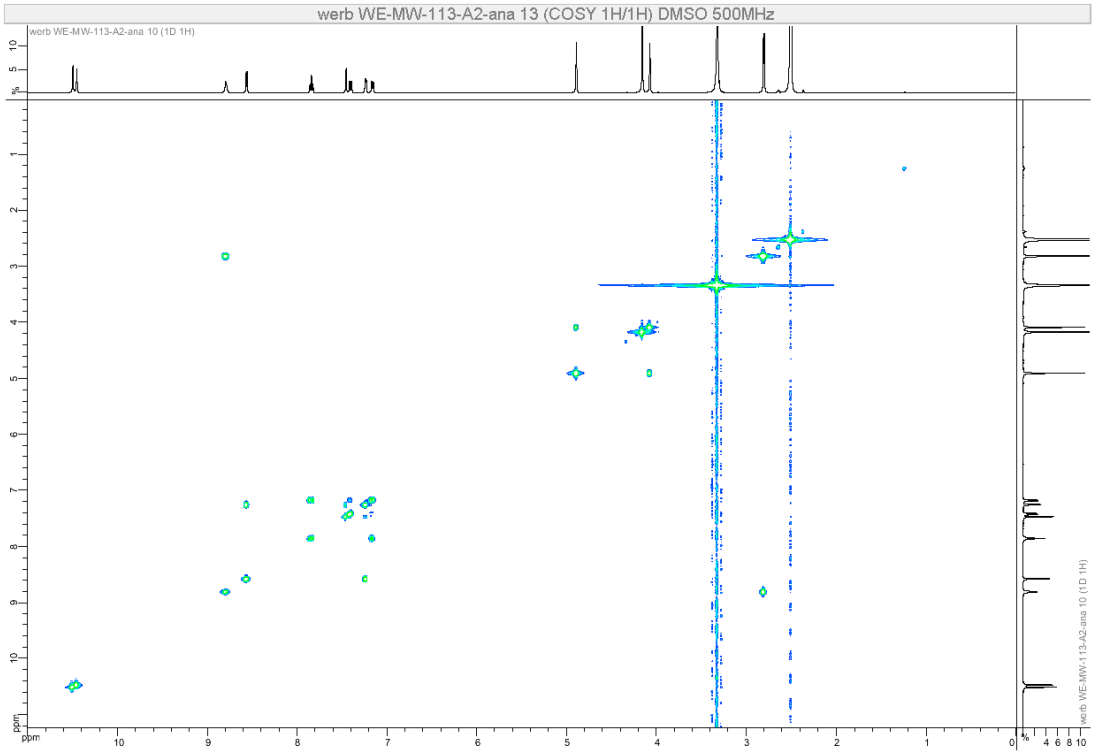
^{13}C NMR



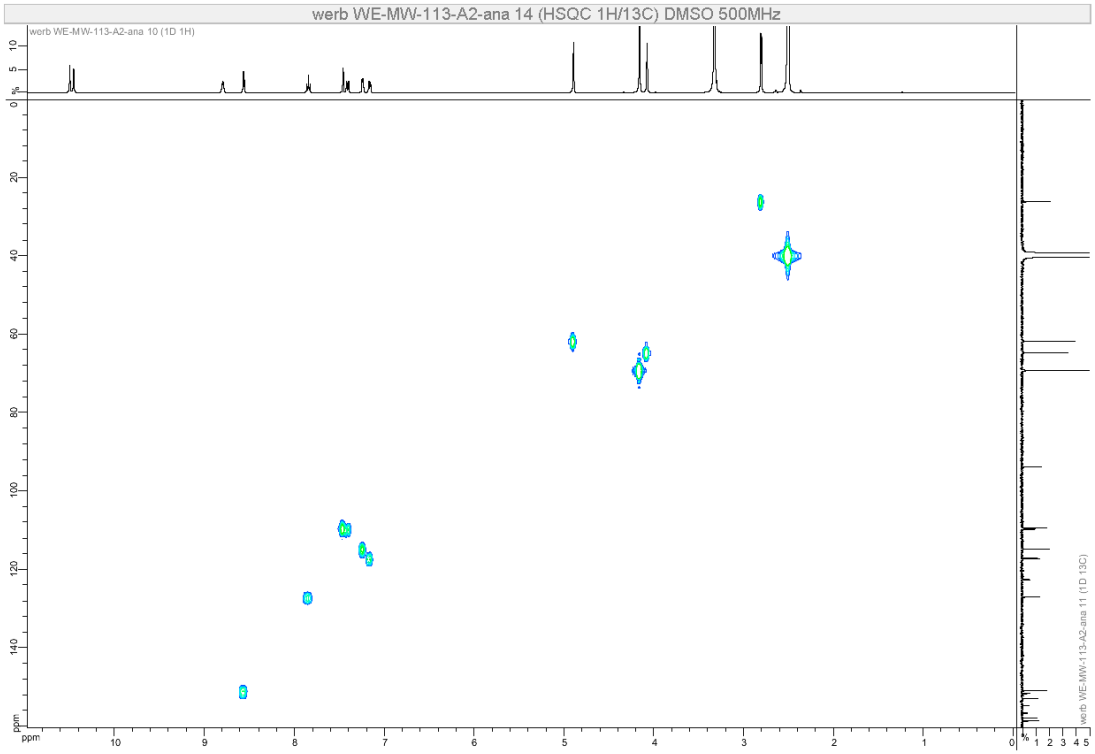
DEPT 135 NMR



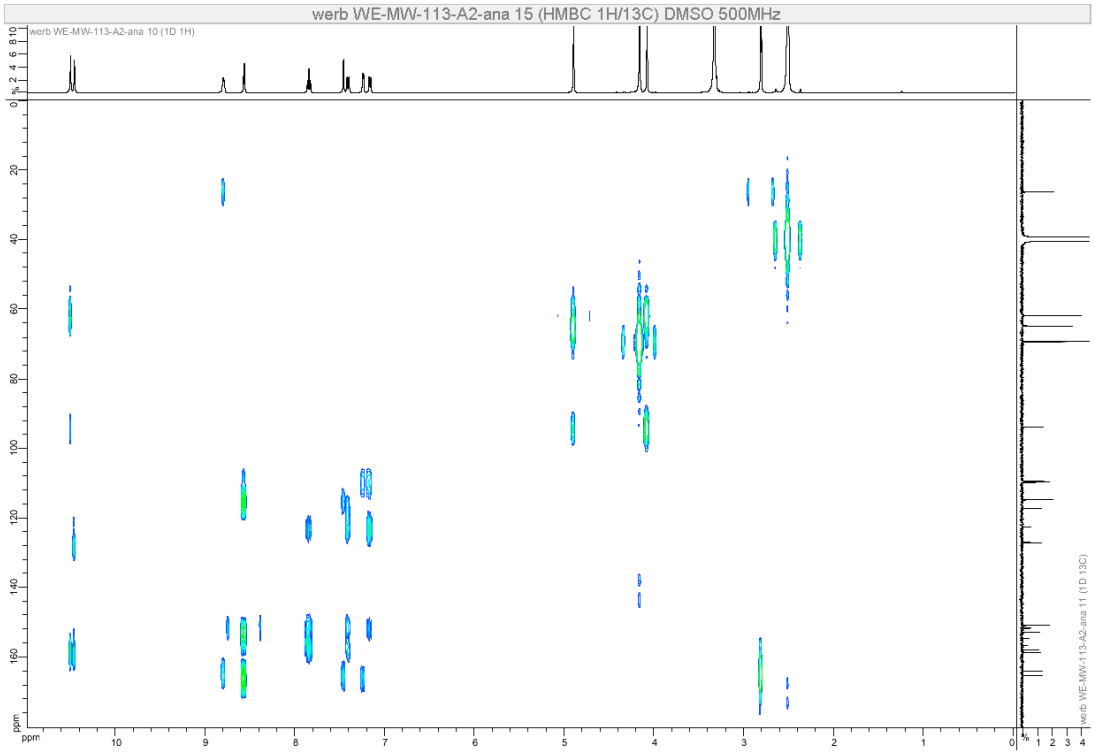
COSY NMR



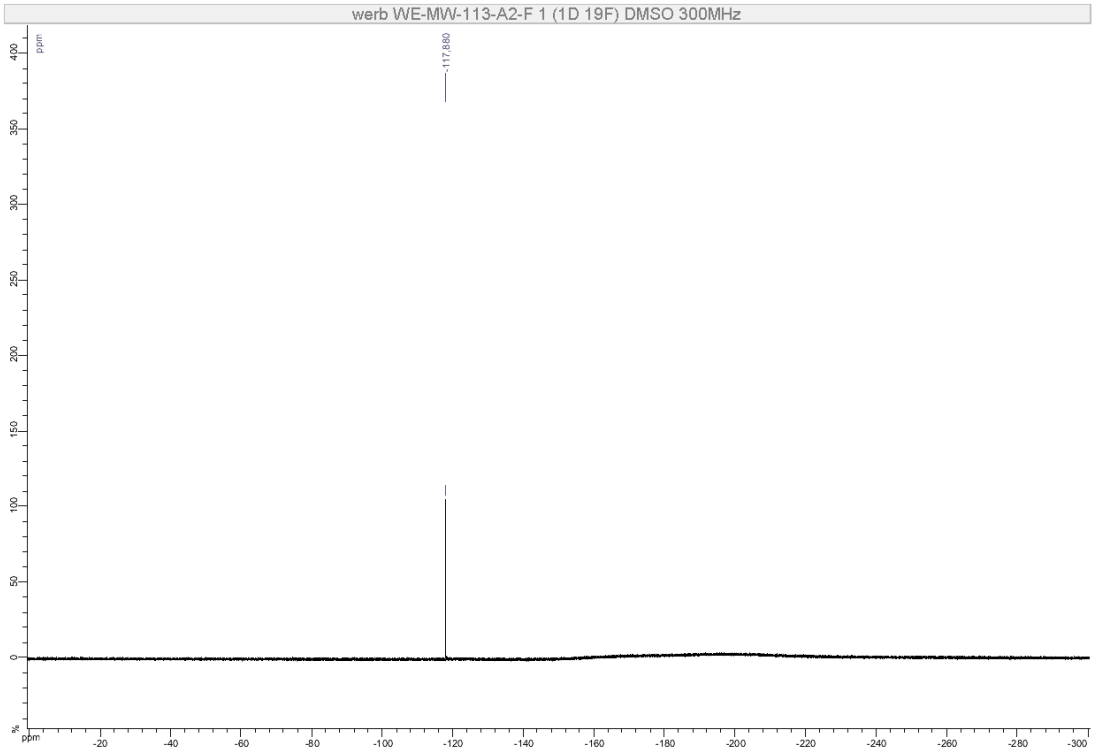
HSQC NMR



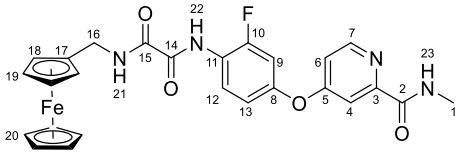
HMBC NMR



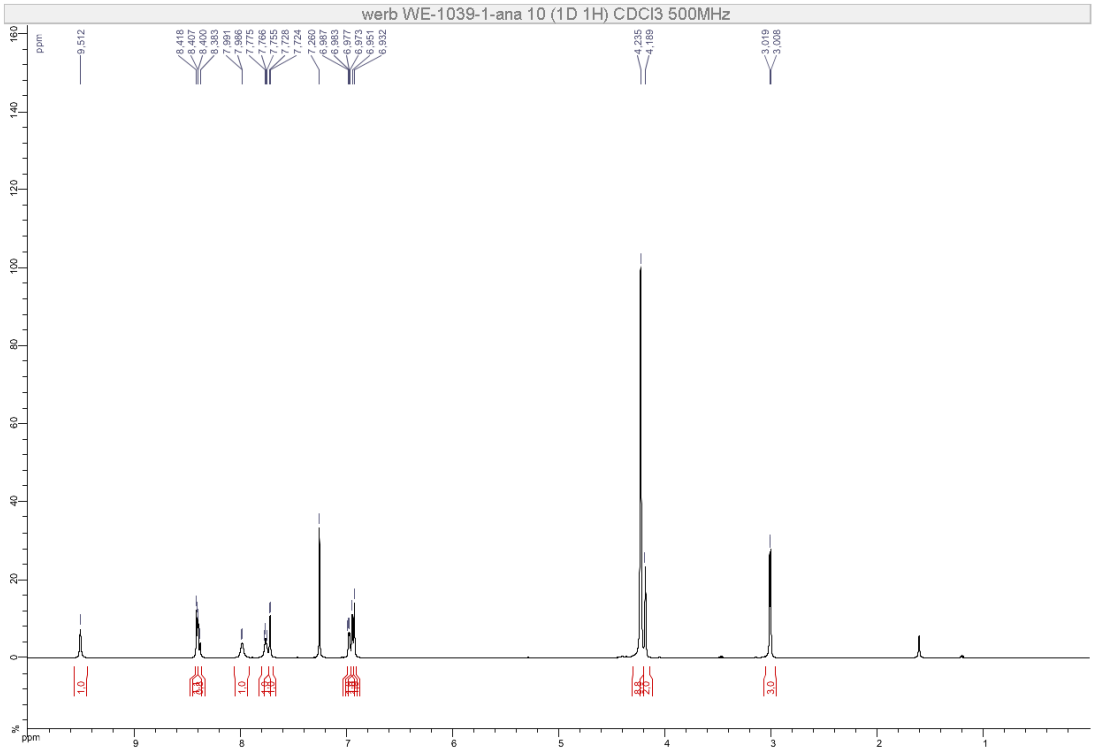
^{19}F NMR


werb WE-MW-113-A2-F 1 (1D 19F) DMSO 300MHz
ppm
-117.880
400
350
300
250
200
150
100
50
0
%
ppm
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
-260
-280
-300

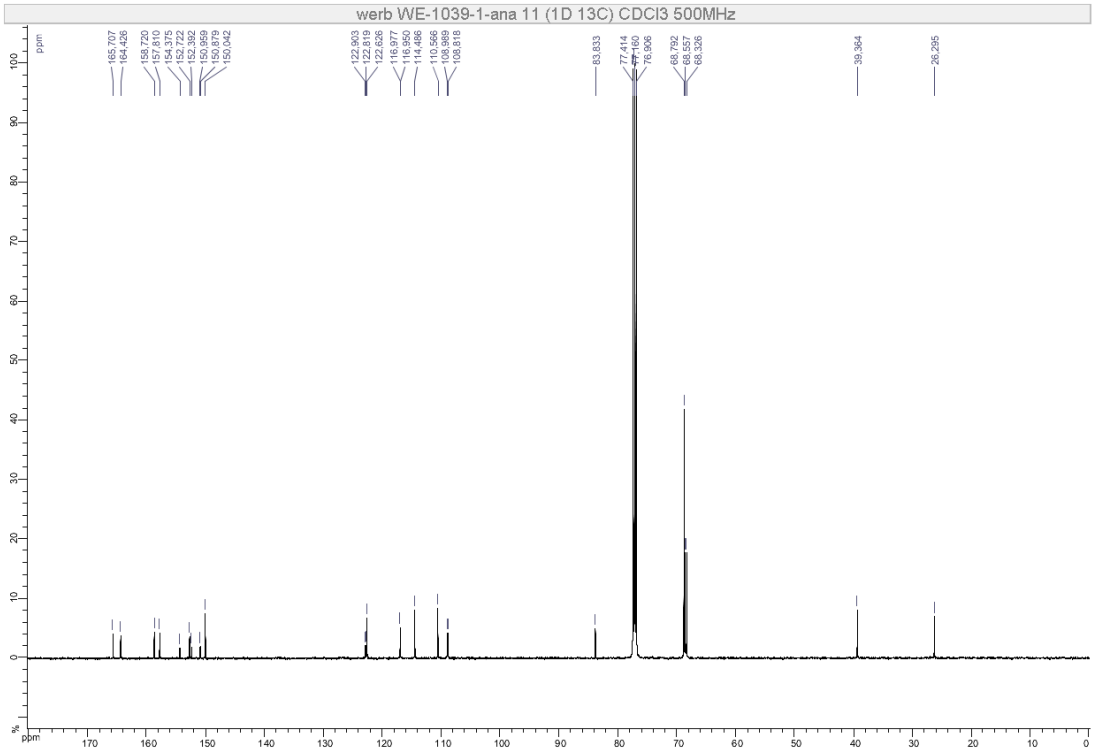
Compound 3c



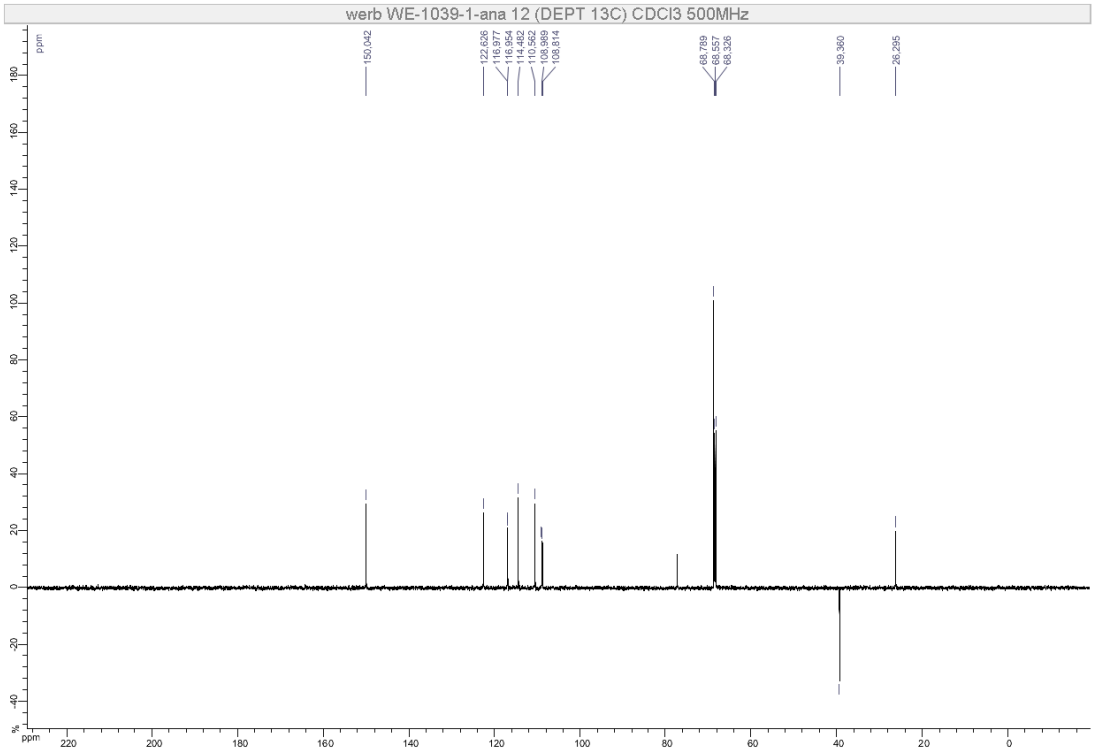
^{1}H NMR



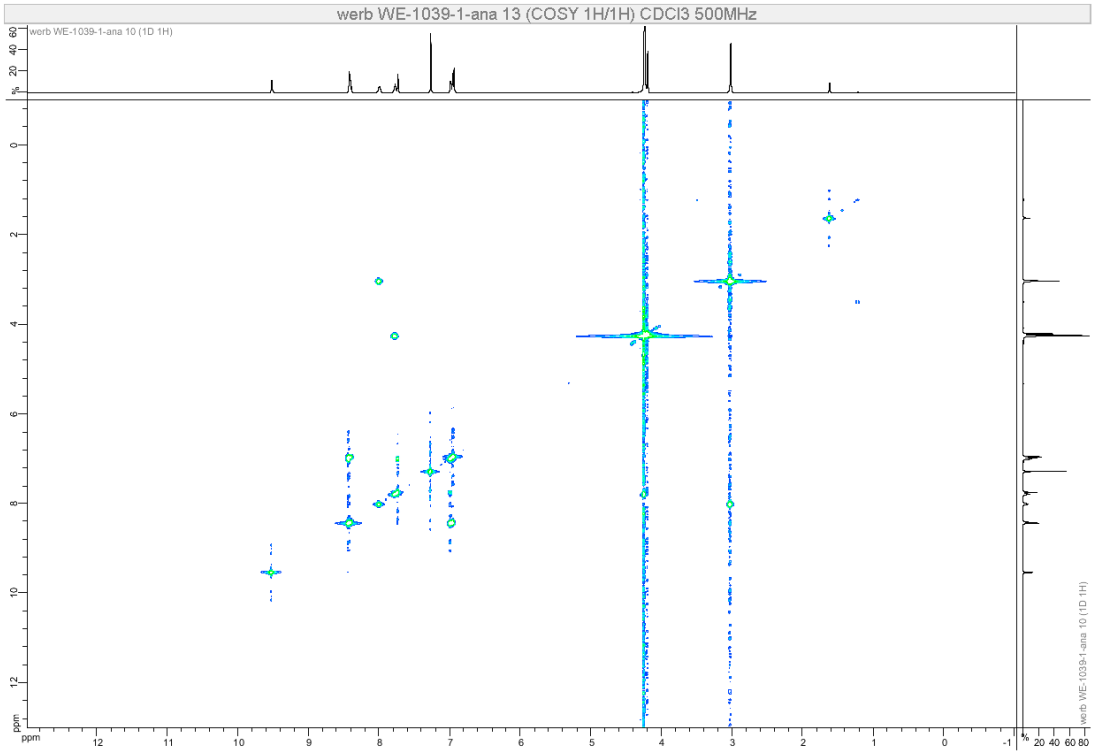
^{13}C NMR



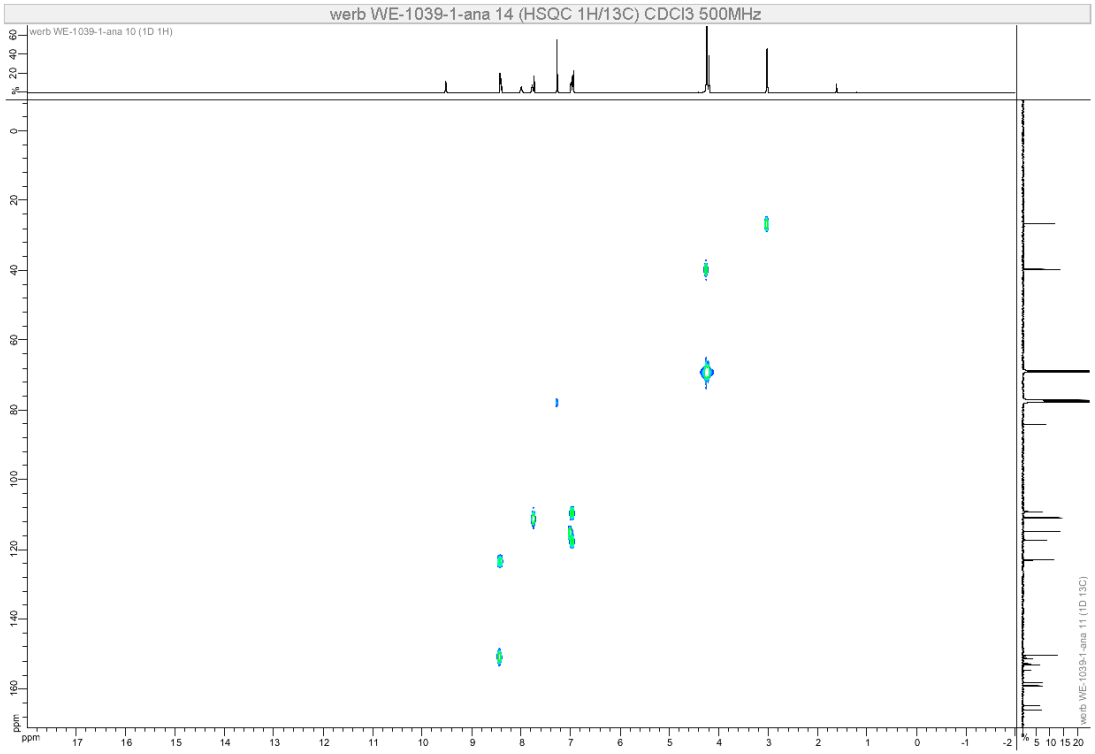
DEPT 135 NMR



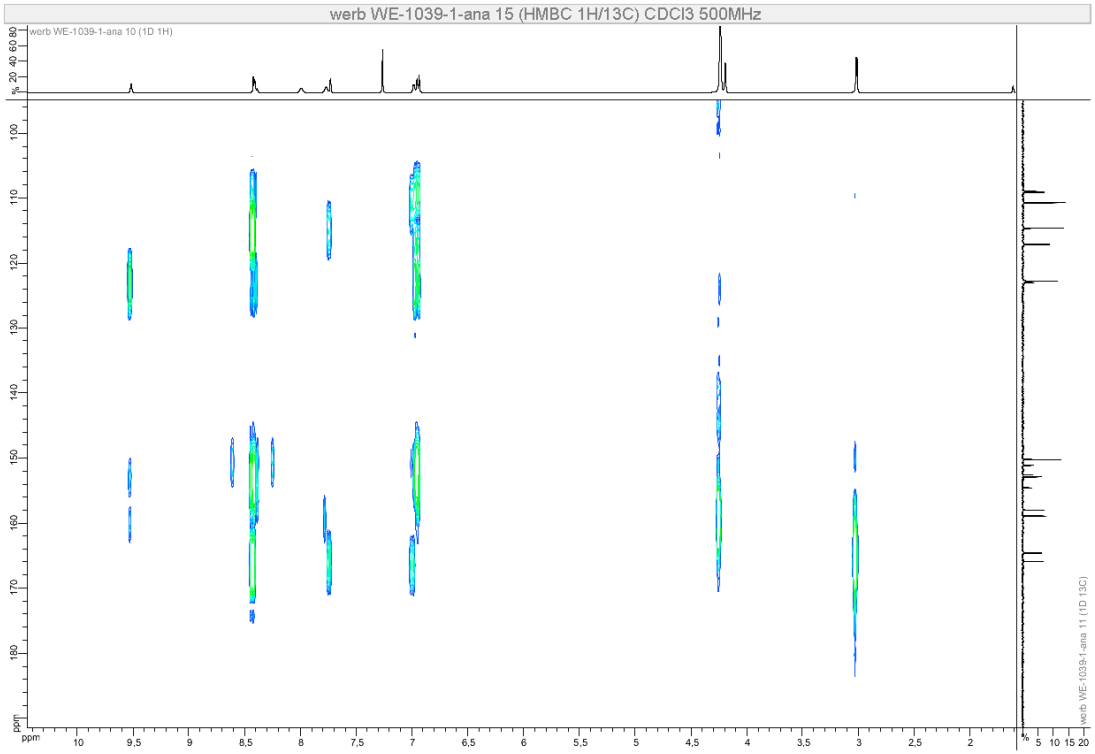
COSY NMR



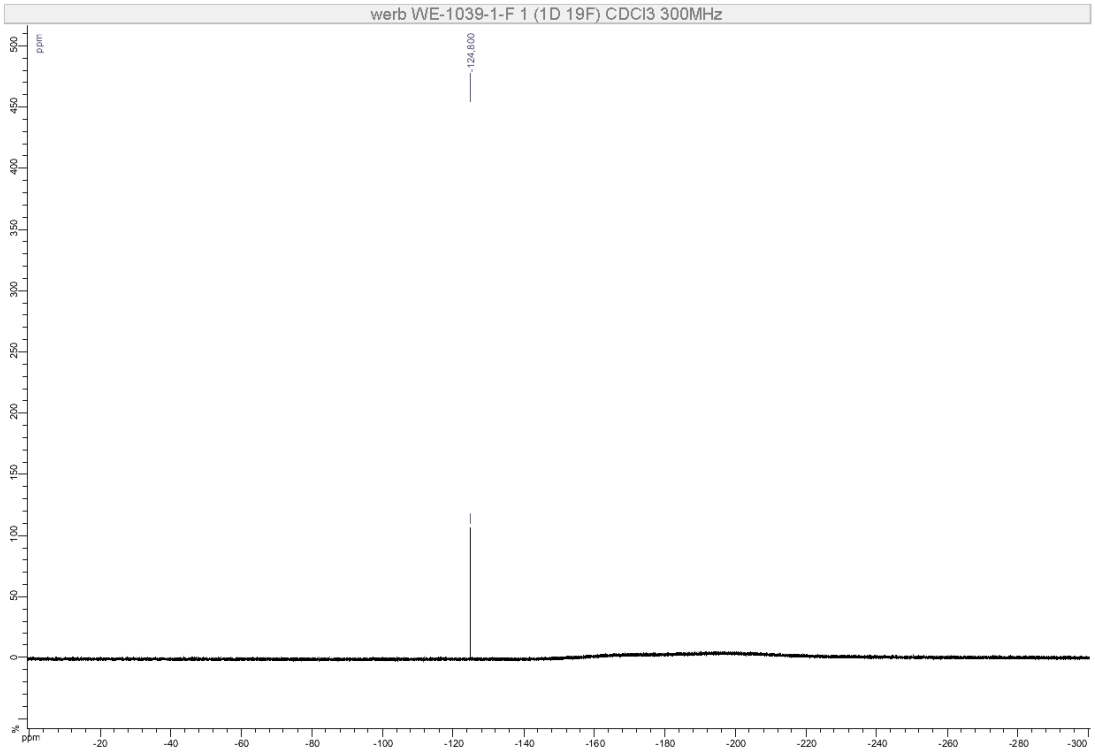
HSQC NMR



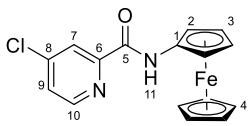
HMBC NMR



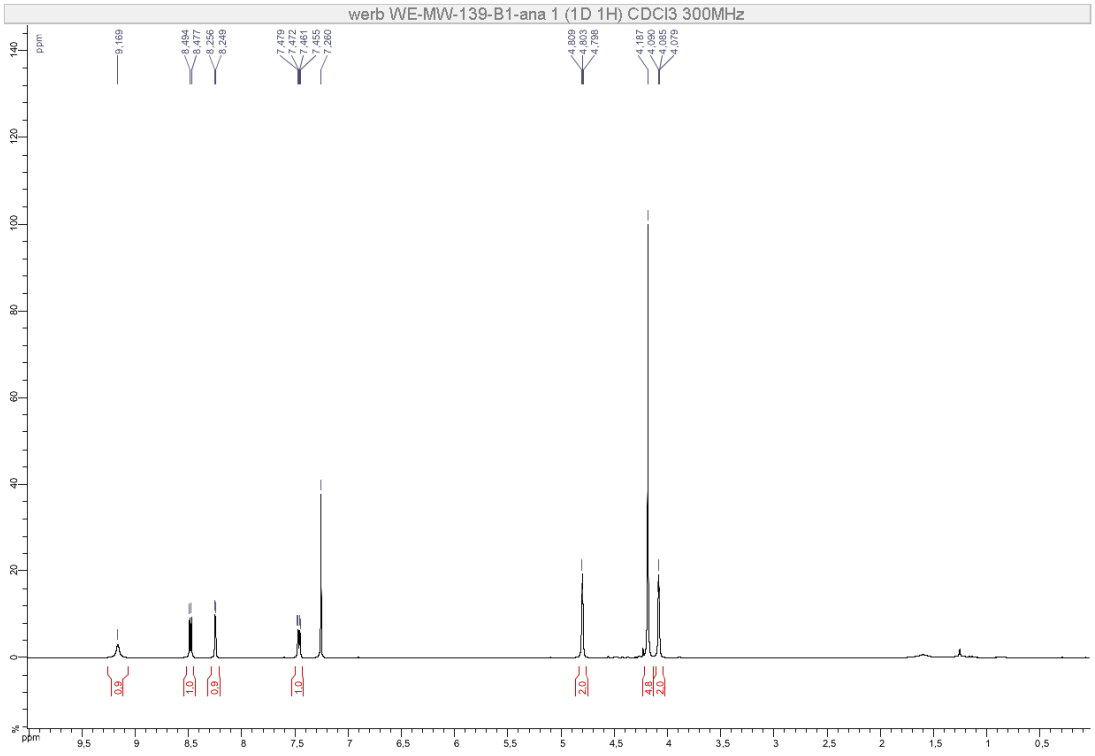
^{19}F NMR


werb WE-1039-1-F 1 (1D 19F) CDCl3 300MHz
ppm
-124.800
500
450
400
350
300
250
200
150
100
50
0
%
ppm
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
-260
-280
-300

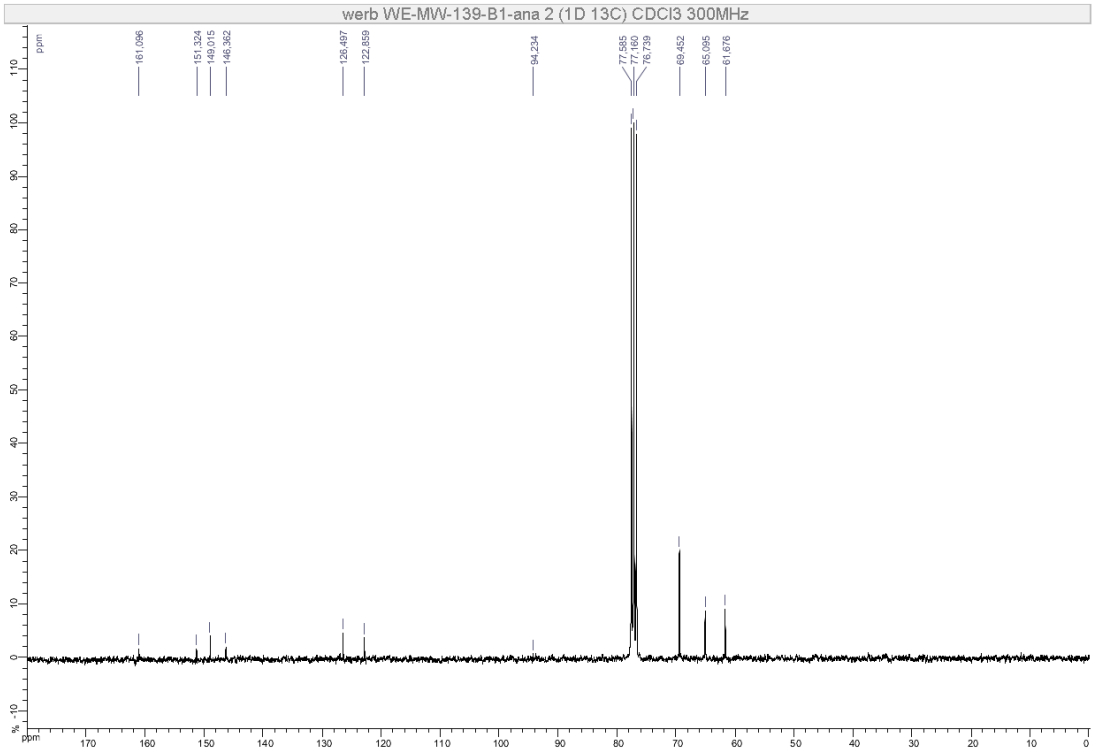
Compound 35



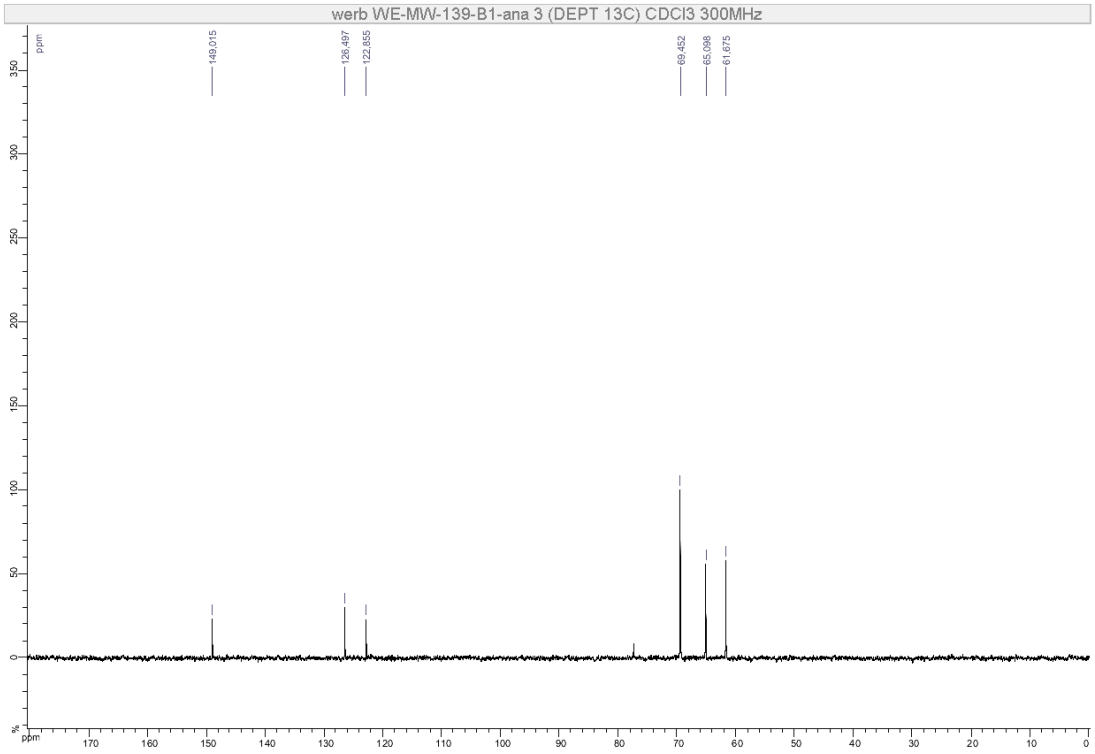
^{1}H NMR



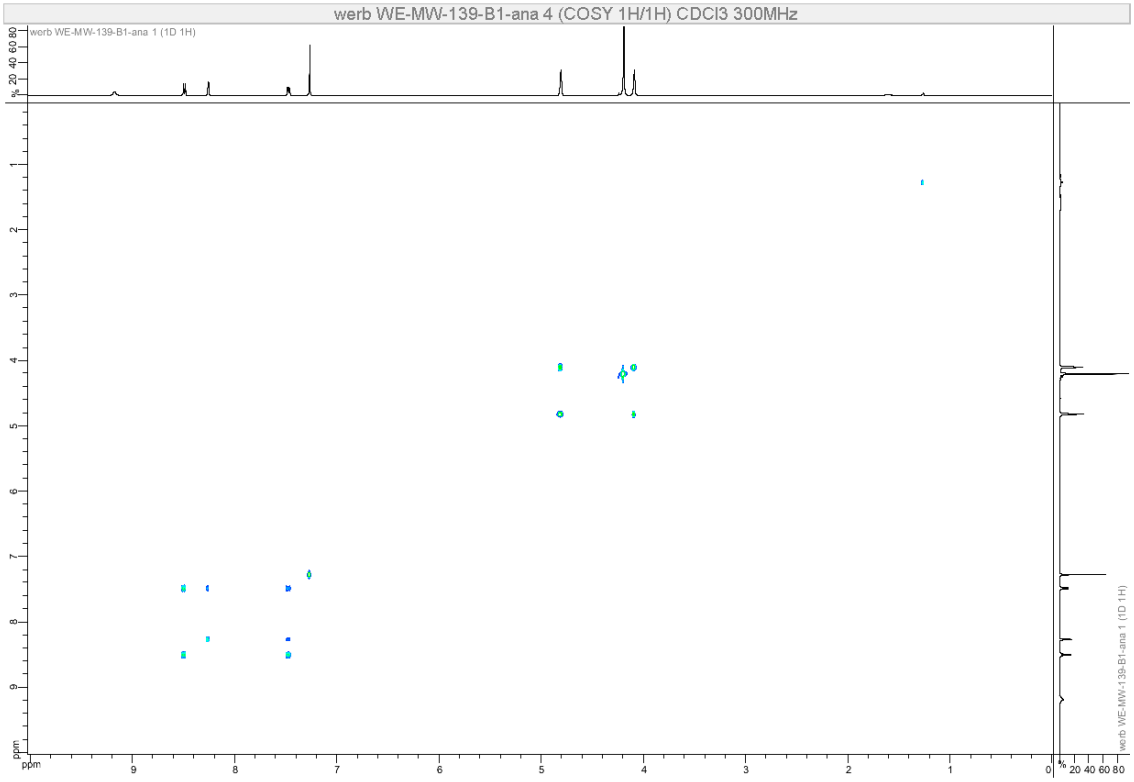
^{13}C NMR



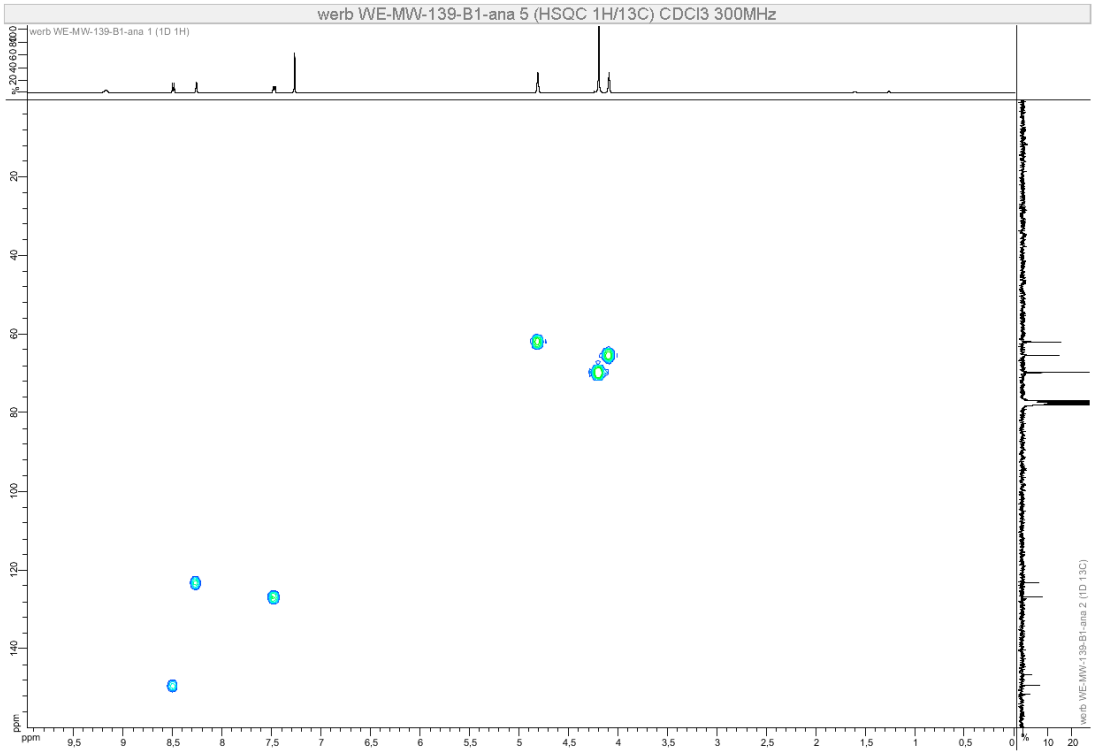
DEPT 135 NMR



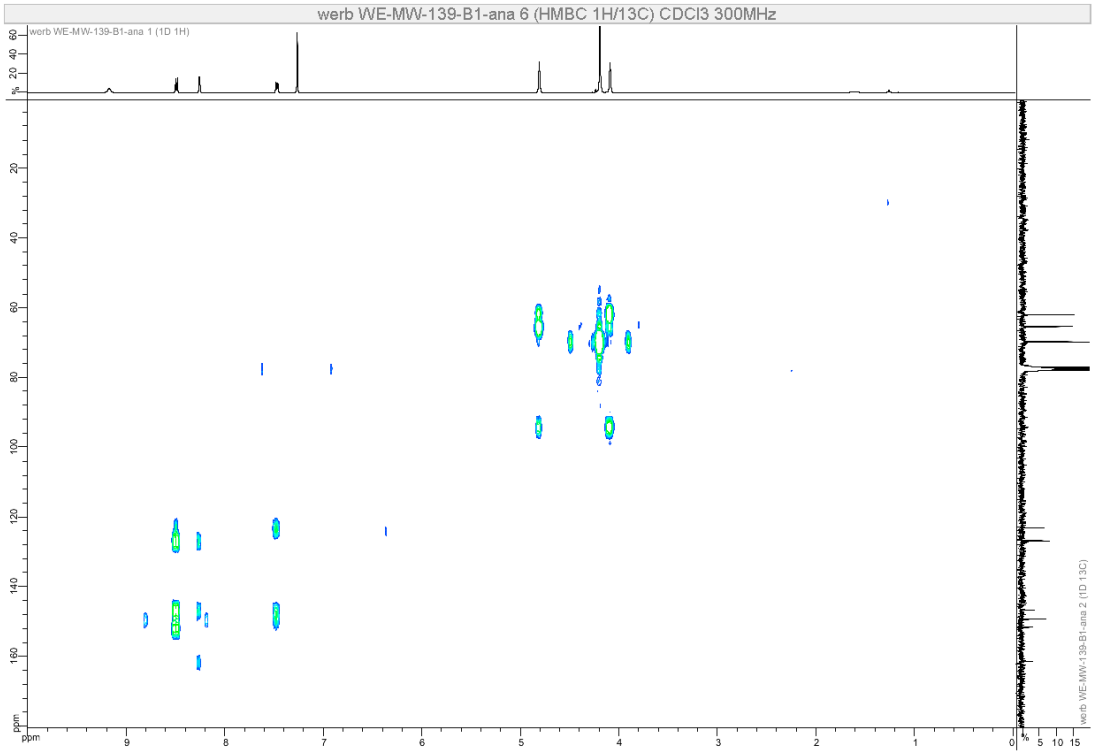
COSY NMR



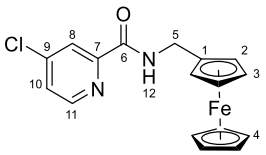
HSQC NMR



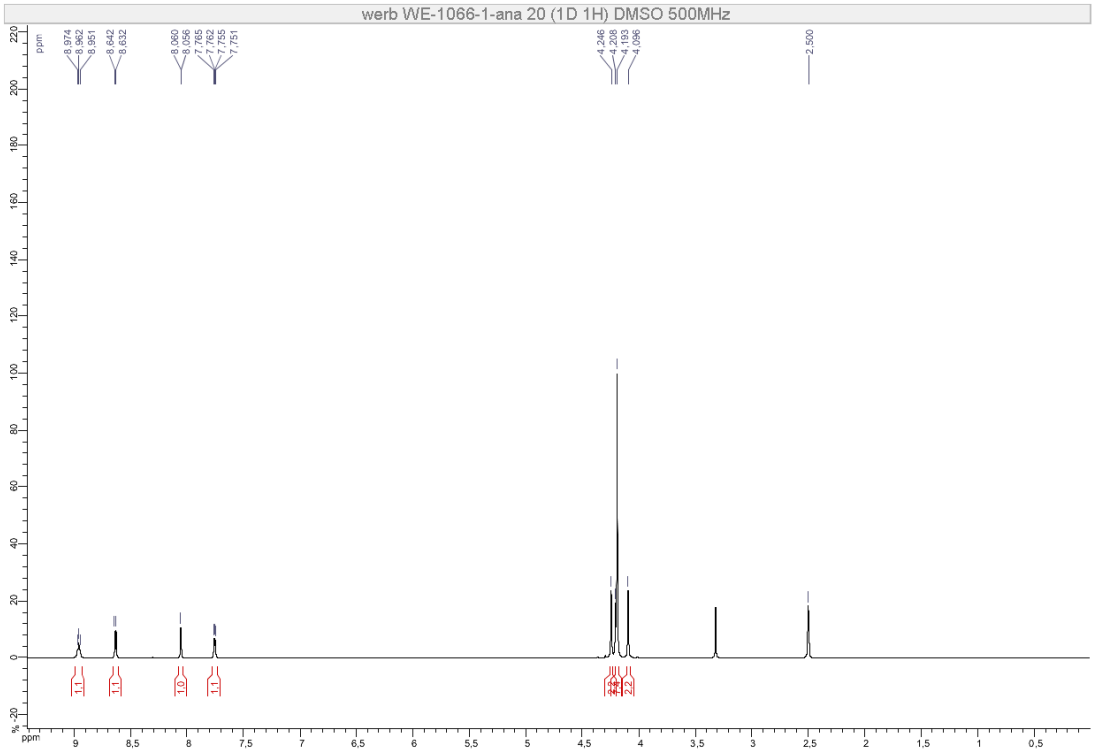
HMBC NMR



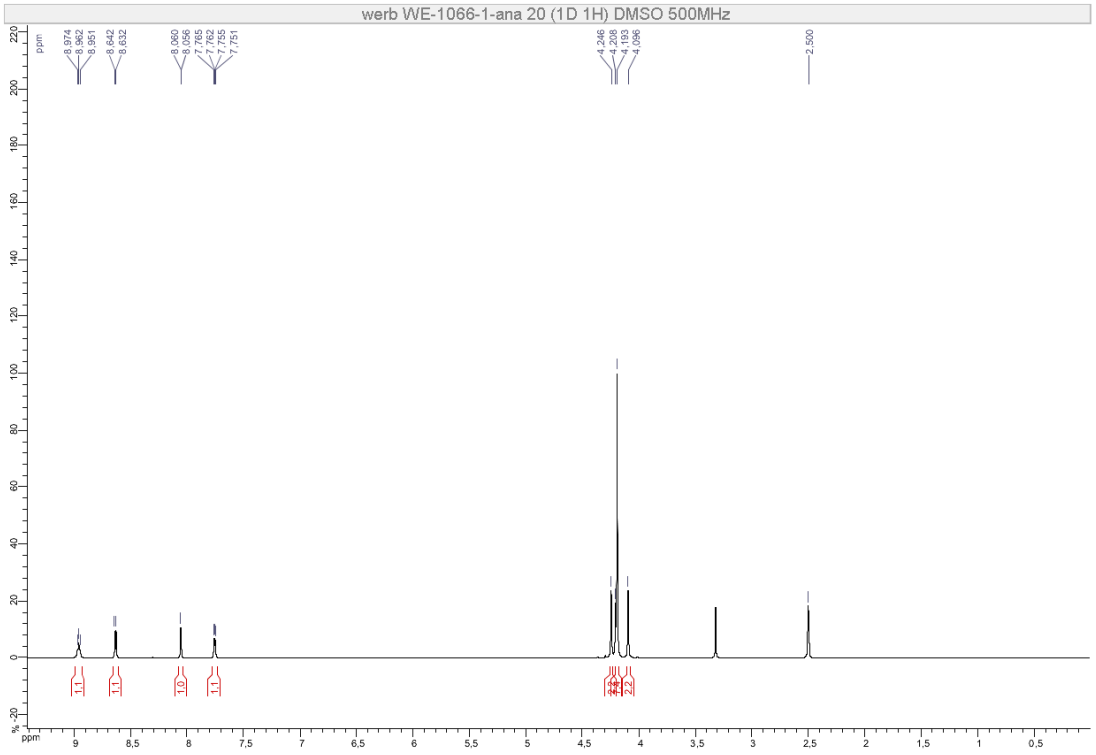
Compound 36



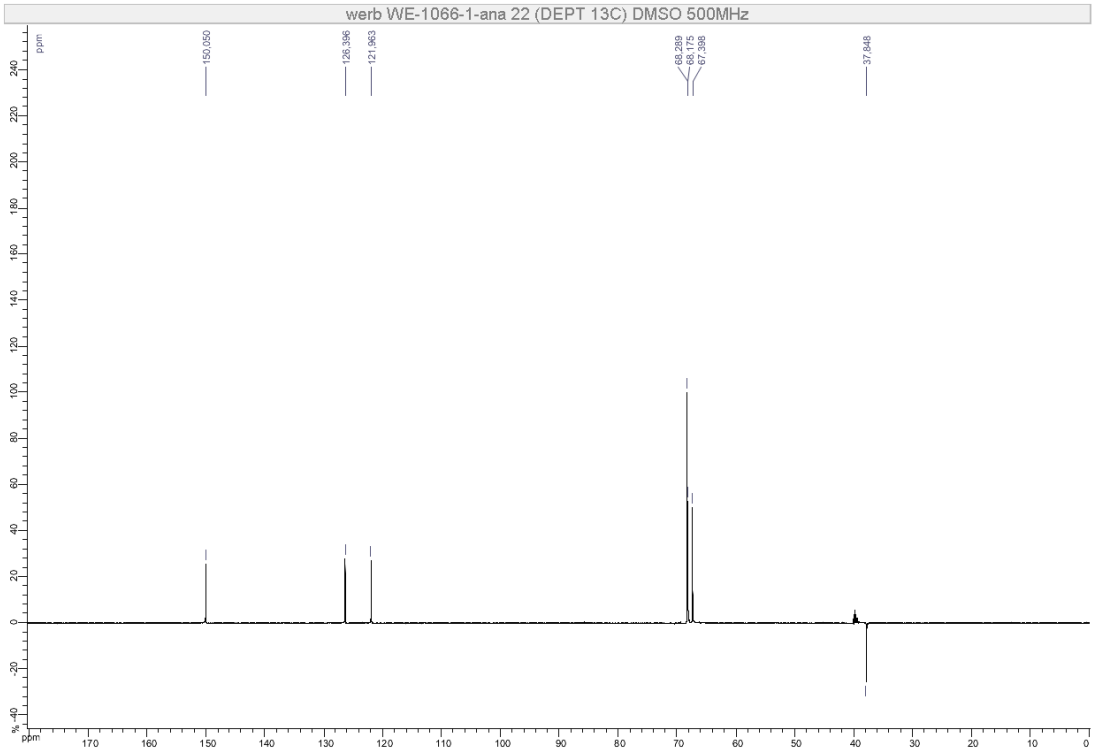
^{1}H NMR



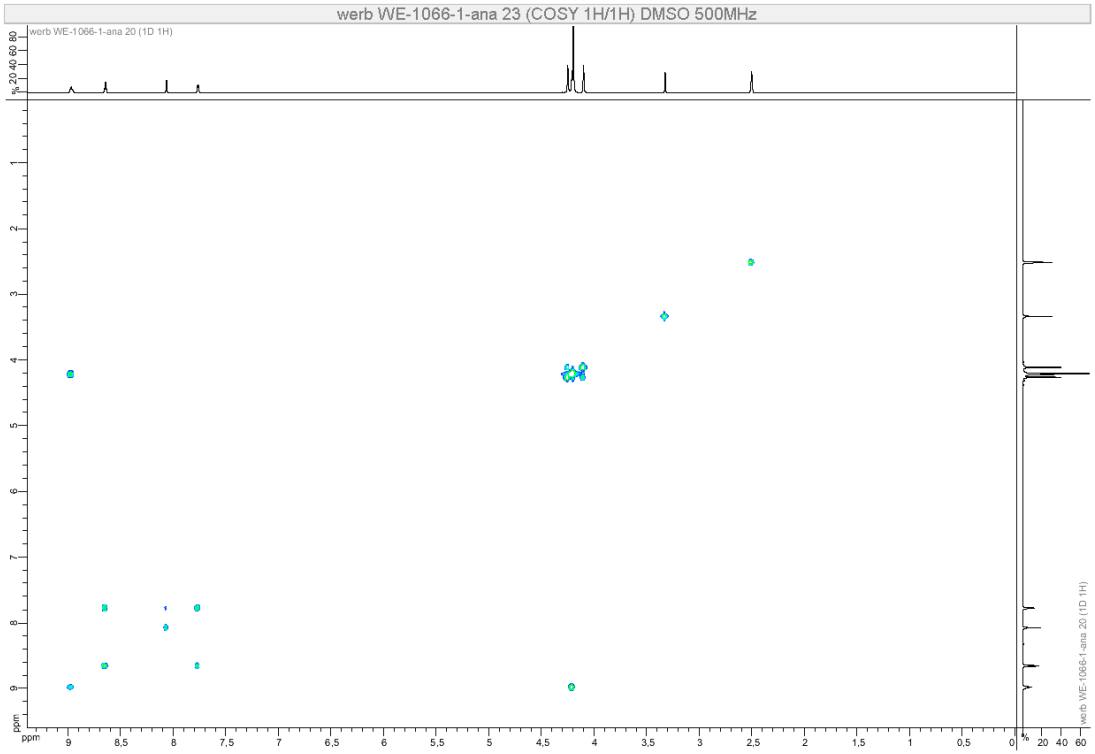
^{13}C NMR



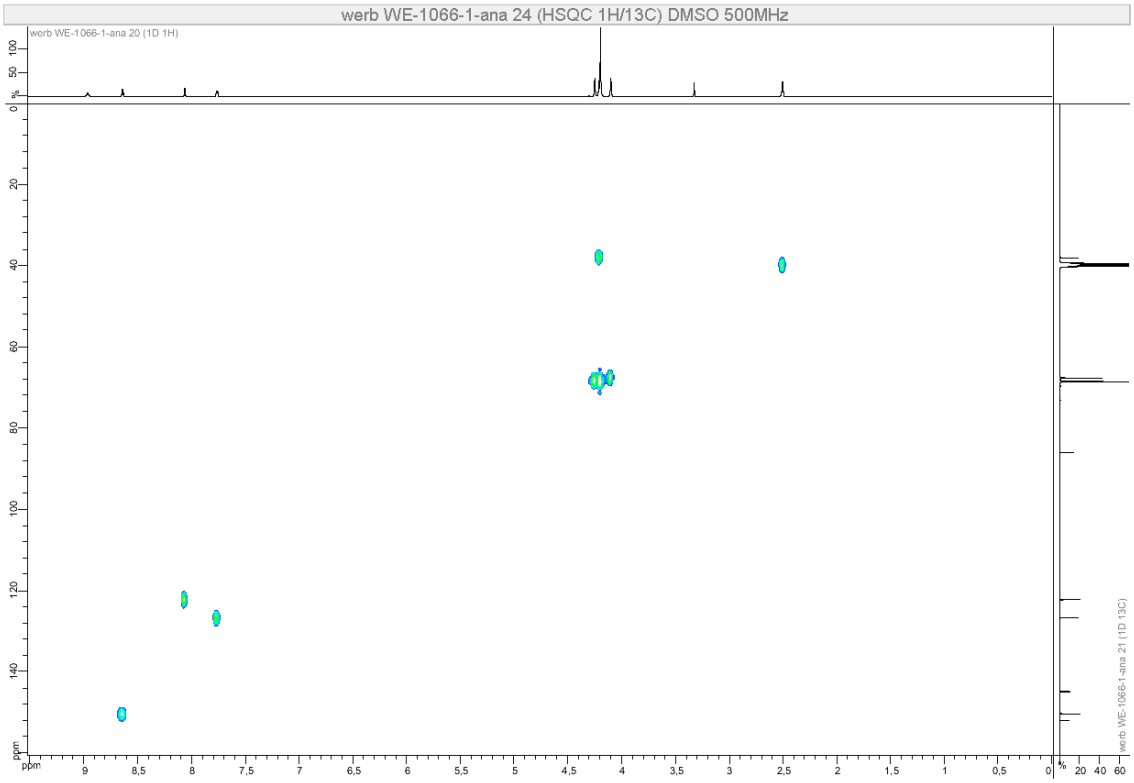
DEPT 135 NMR



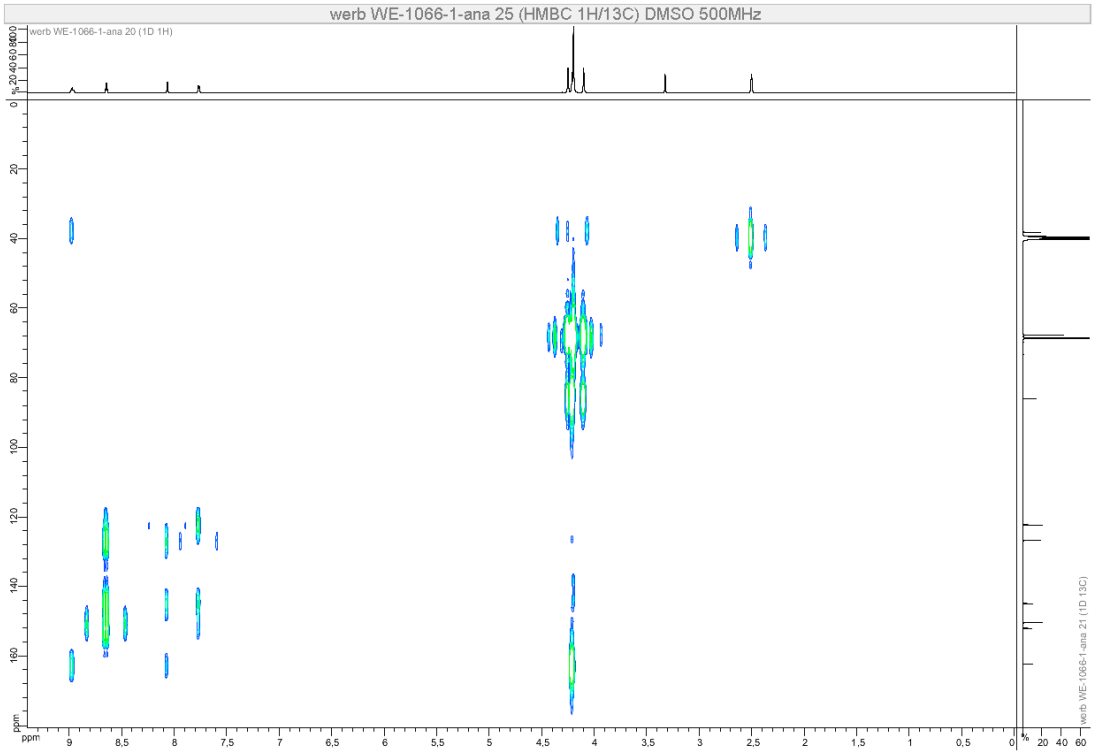
COSY NMR



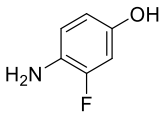
HSQC NMR



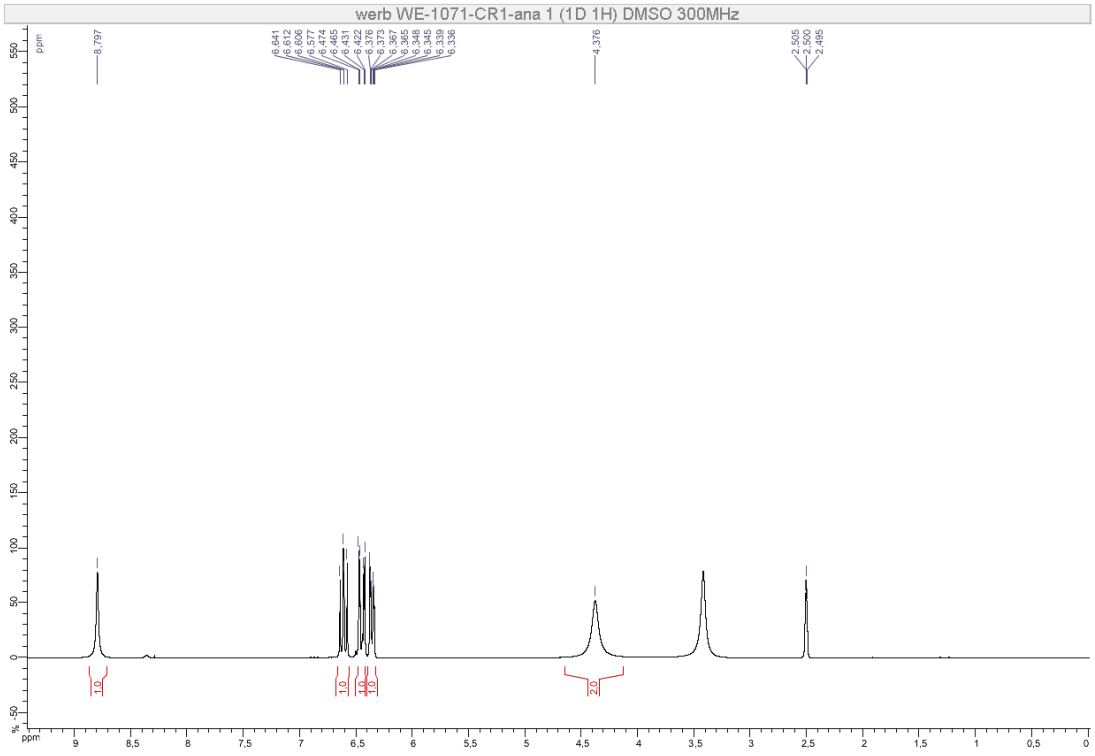
HMBC NMR



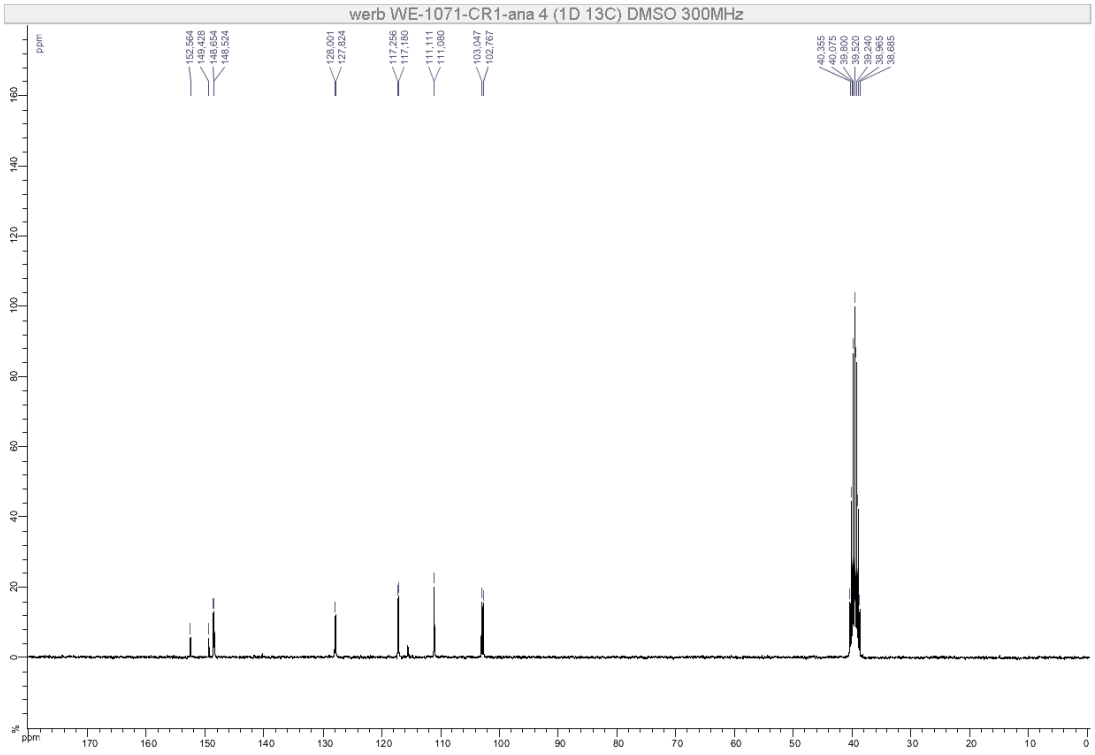
4-Amino-3-fluorophenol (37)



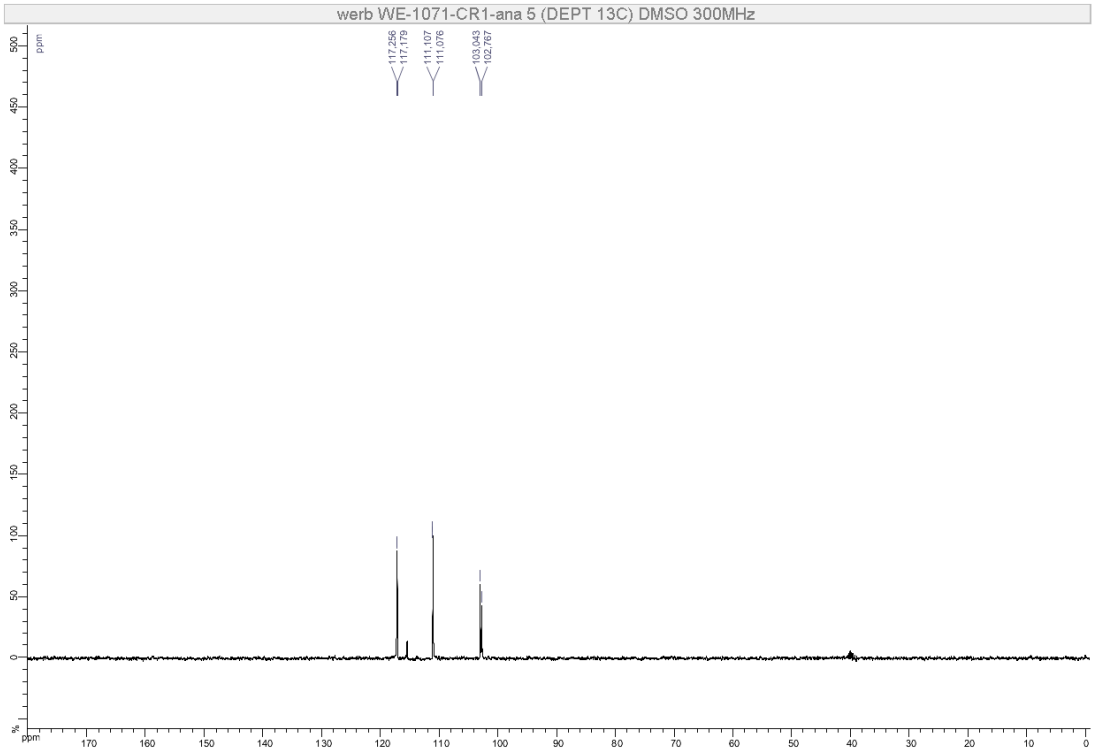
^{1}H NMR



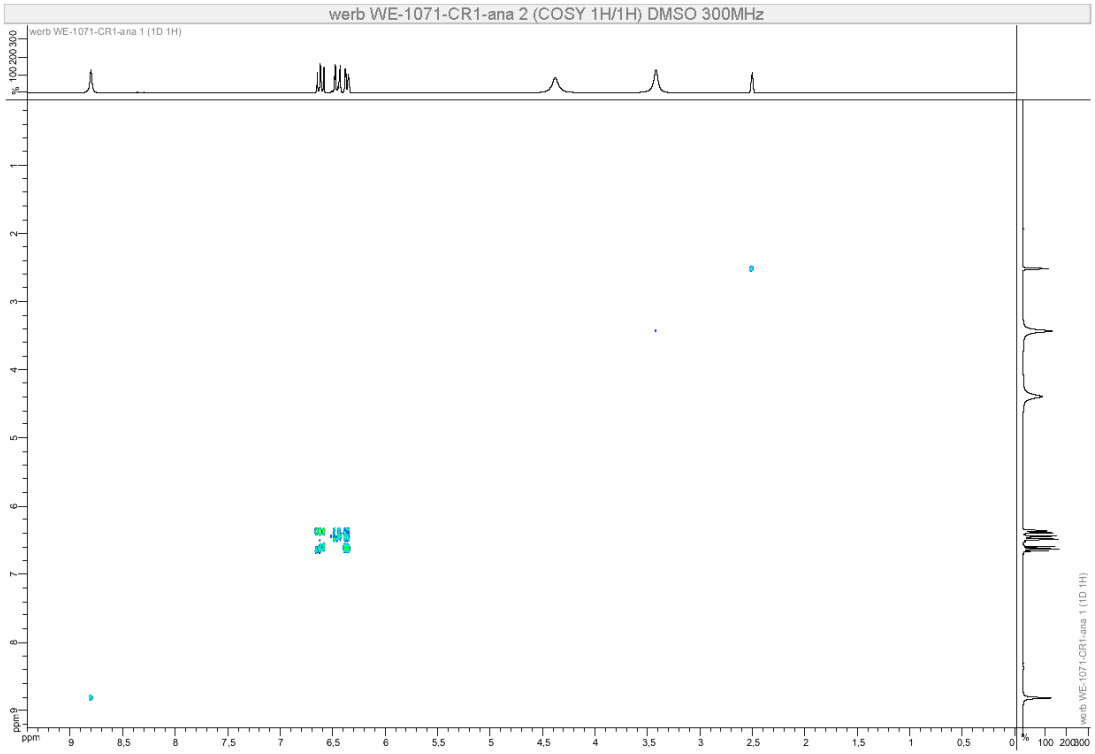
^{13}C NMR



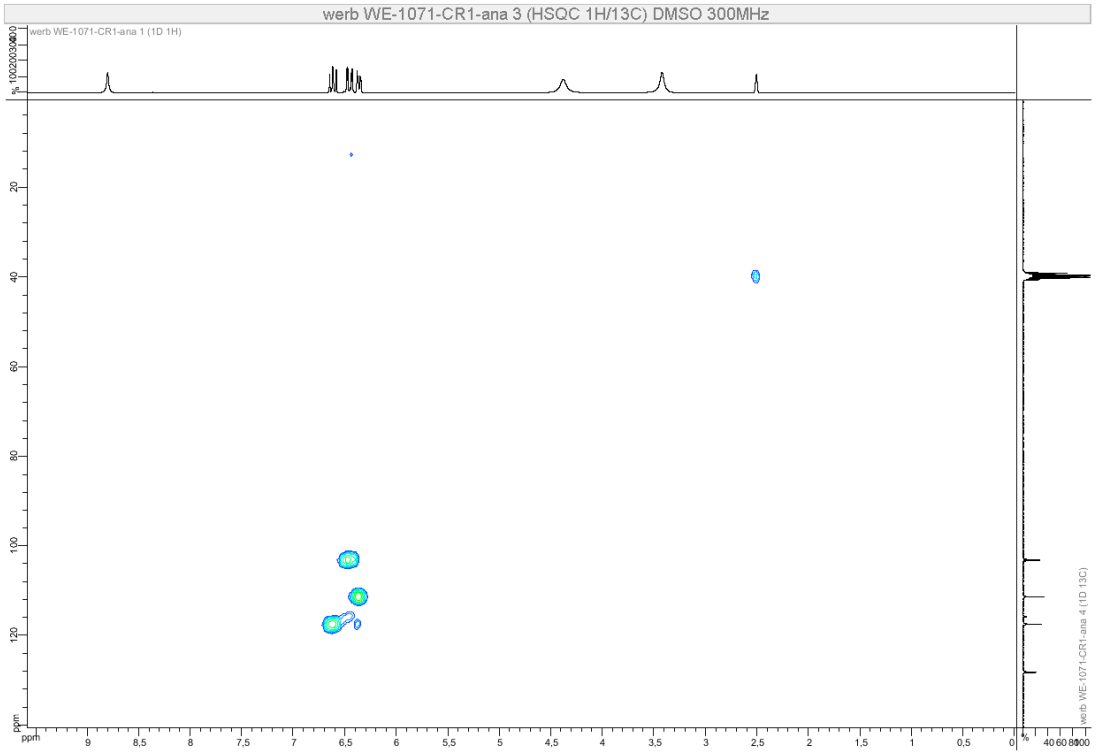
DEPT 135 NMR



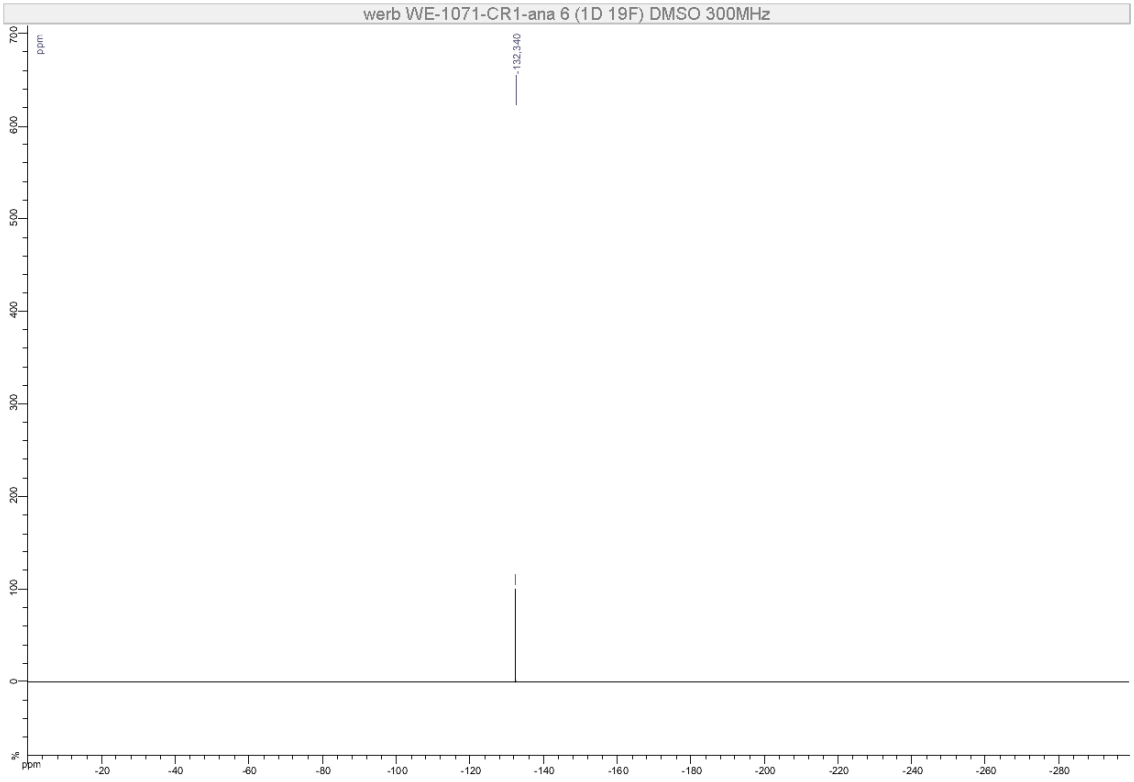
COSY NMR



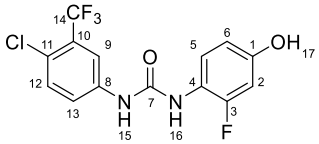
HSQC NMR



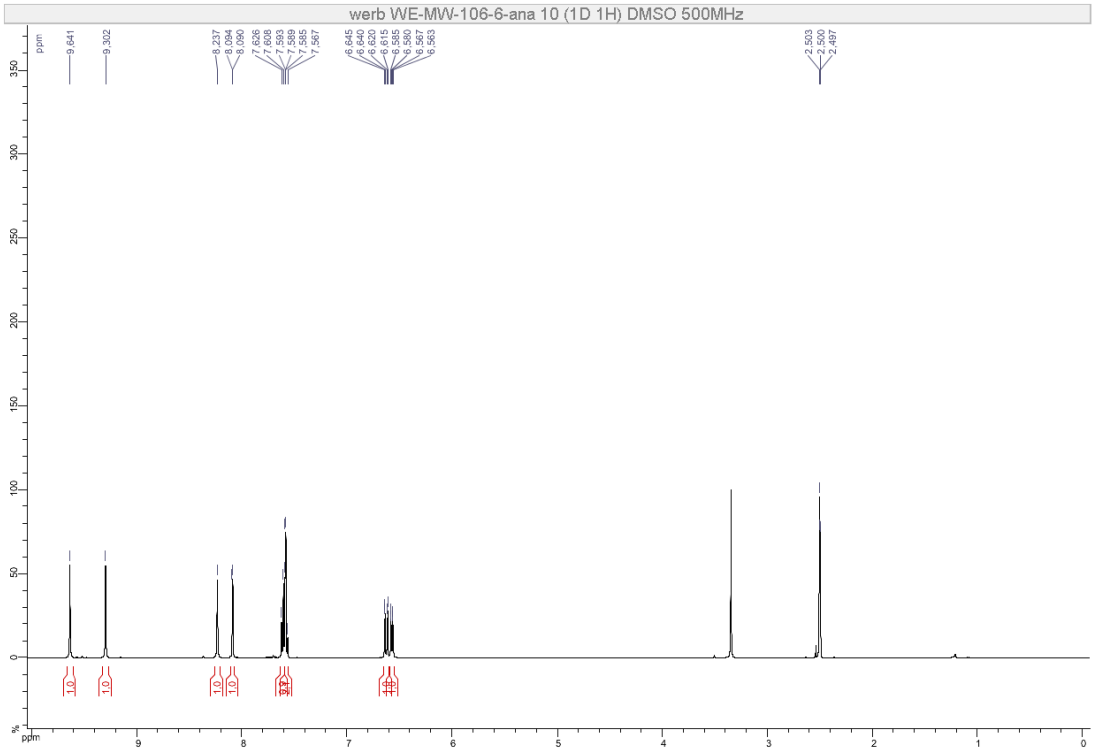
^{19}F NMR



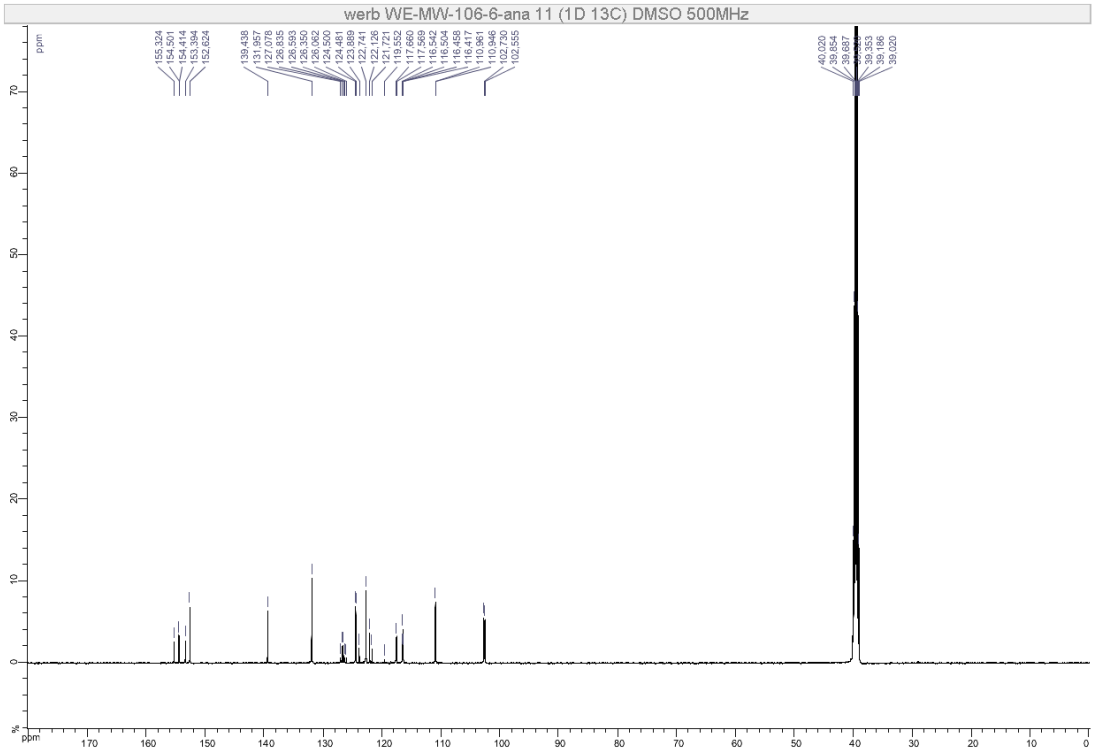
Compound 38a



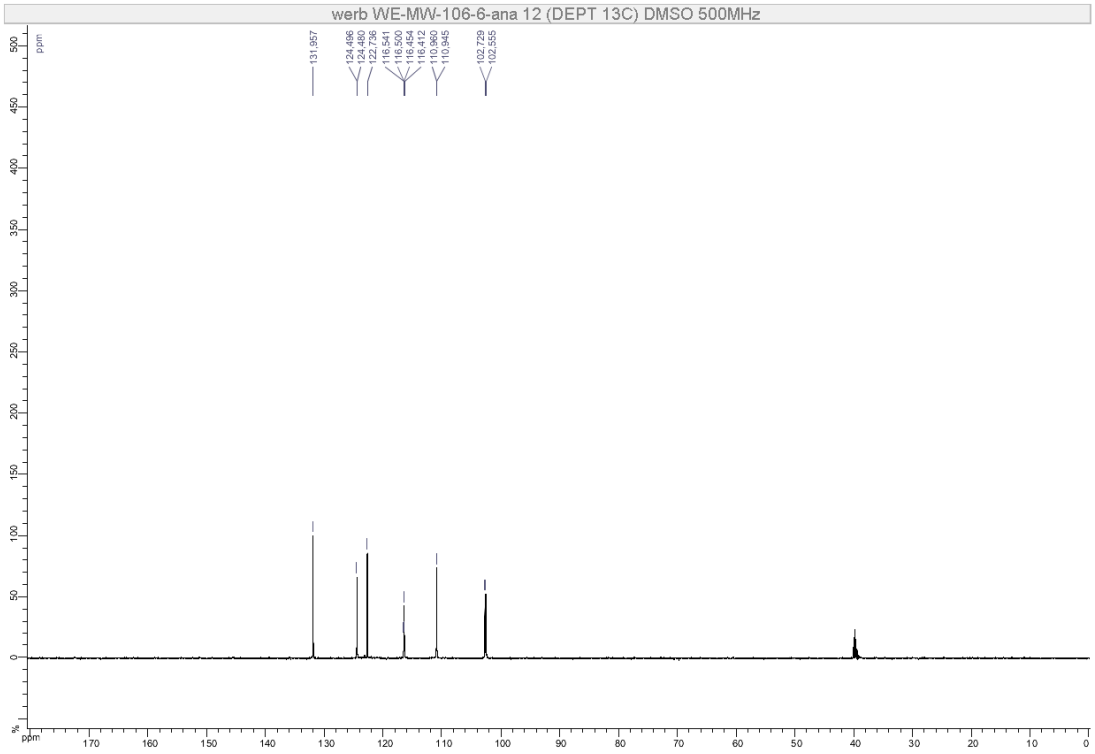
^{1}H NMR



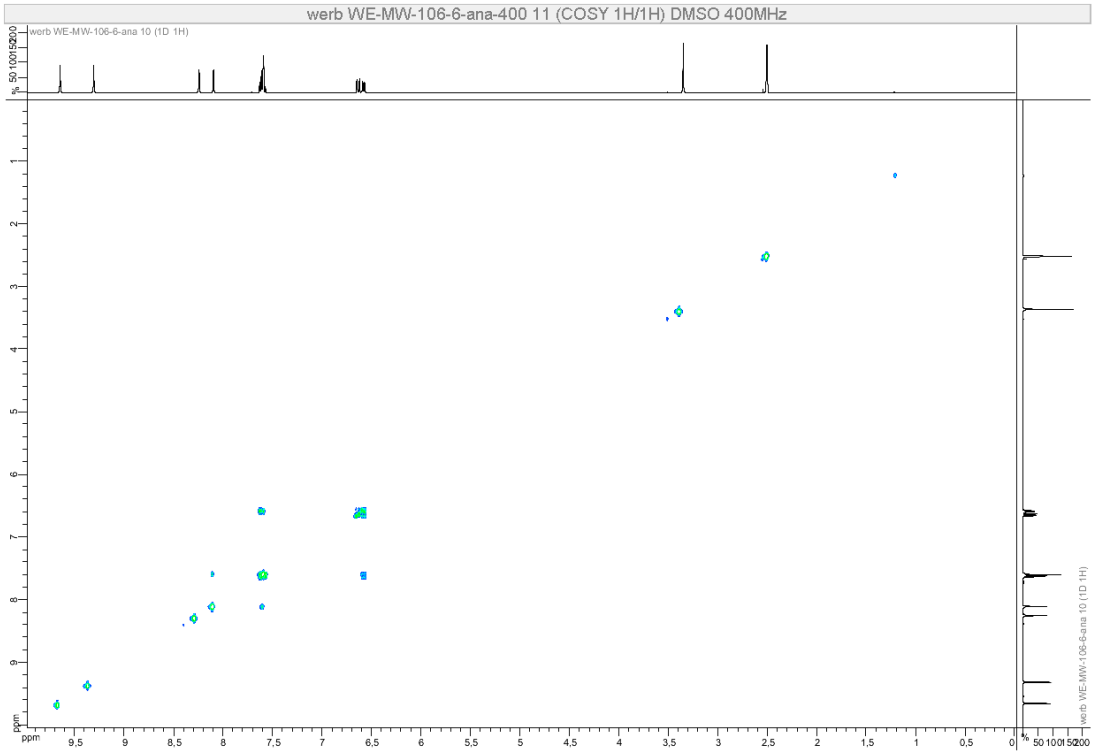
^{13}C NMR



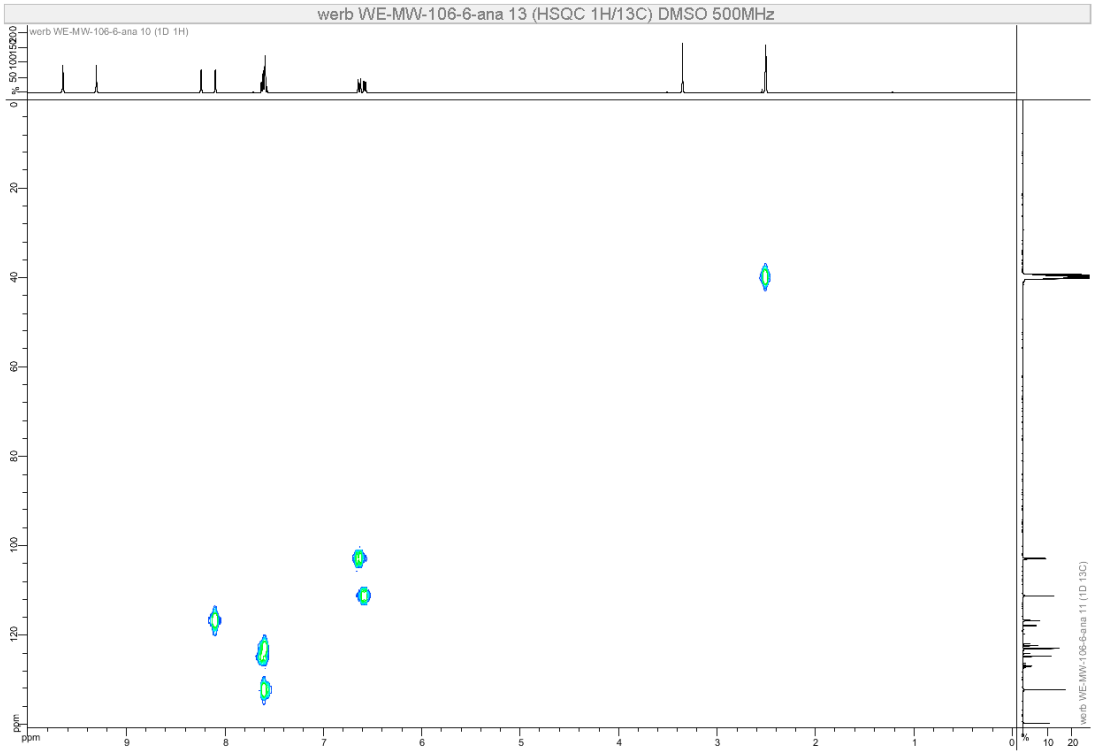
DEPT 135 NMR



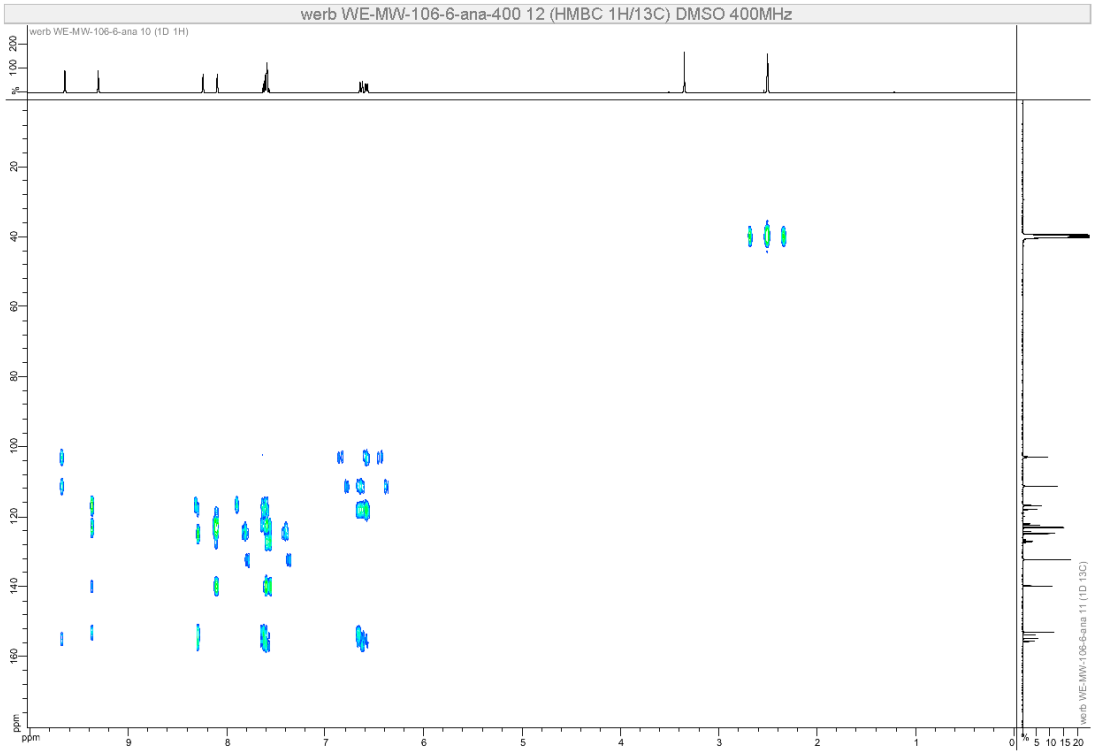
COSY NMR



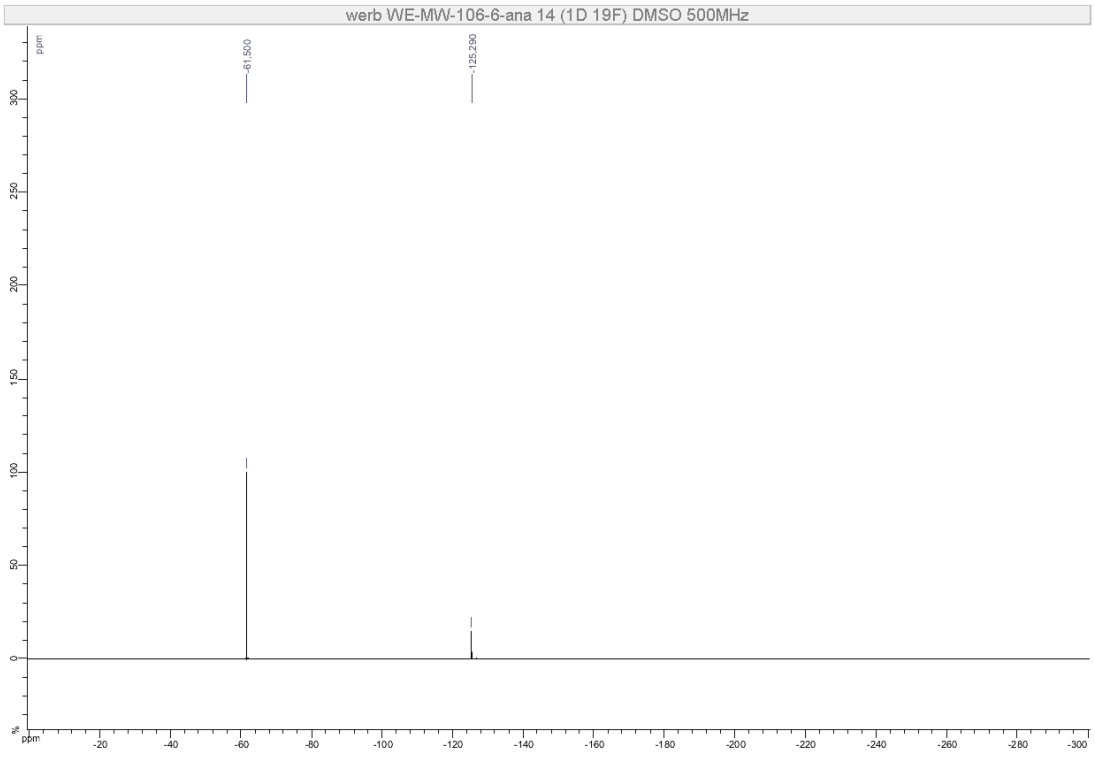
HSQC NMR



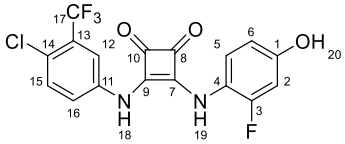
HMBC NMR



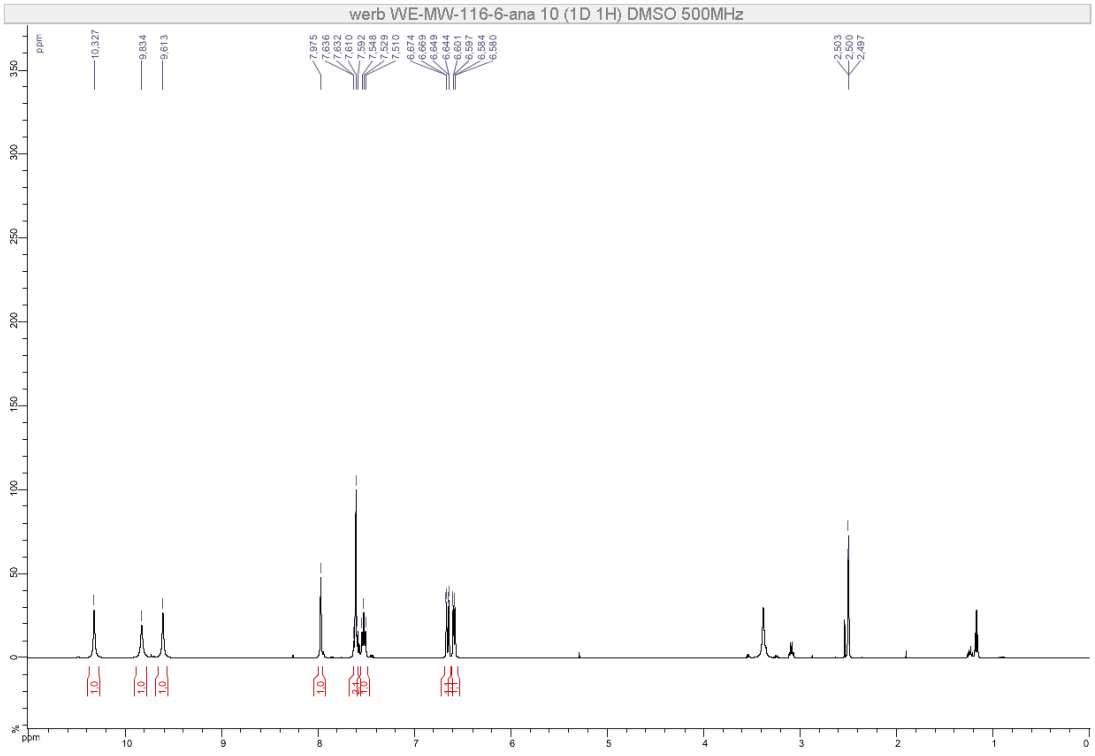
^{19}F NMR


werb WE-MW-106-6-ana 14 (1D 19F) DMSO 500MHz
ppm
-61,500
-125,290
300
250
200
150
100
50
0
%
ppm
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
-260
-280
-300

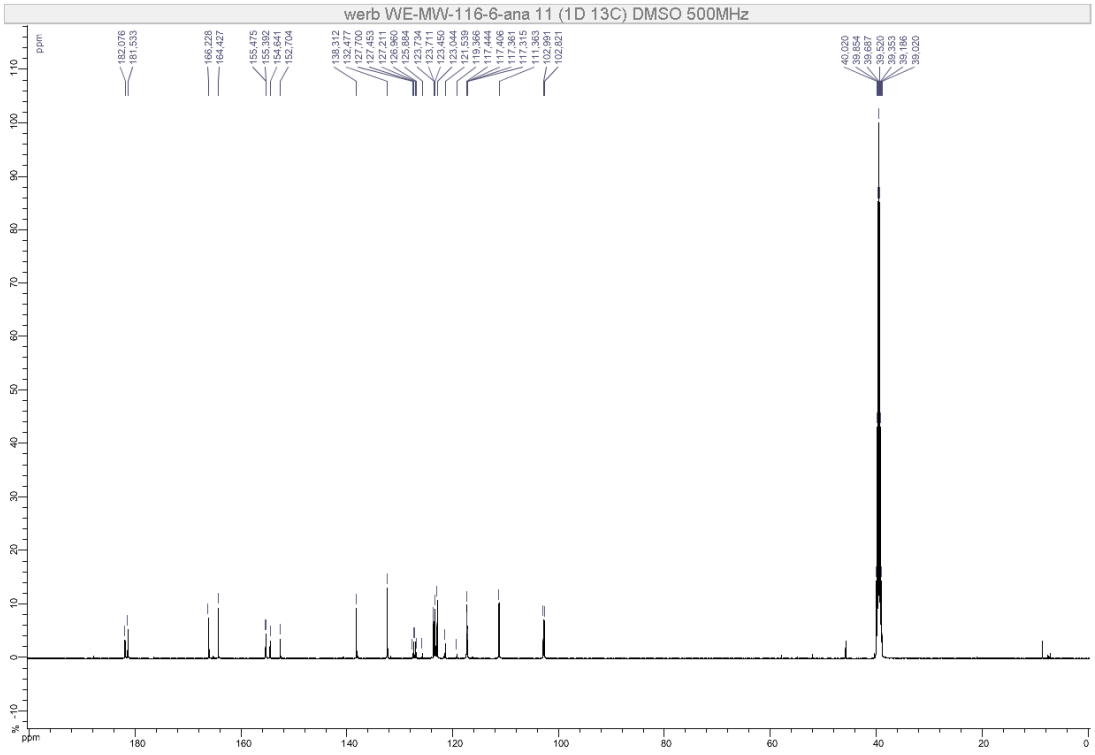
Compound 38b



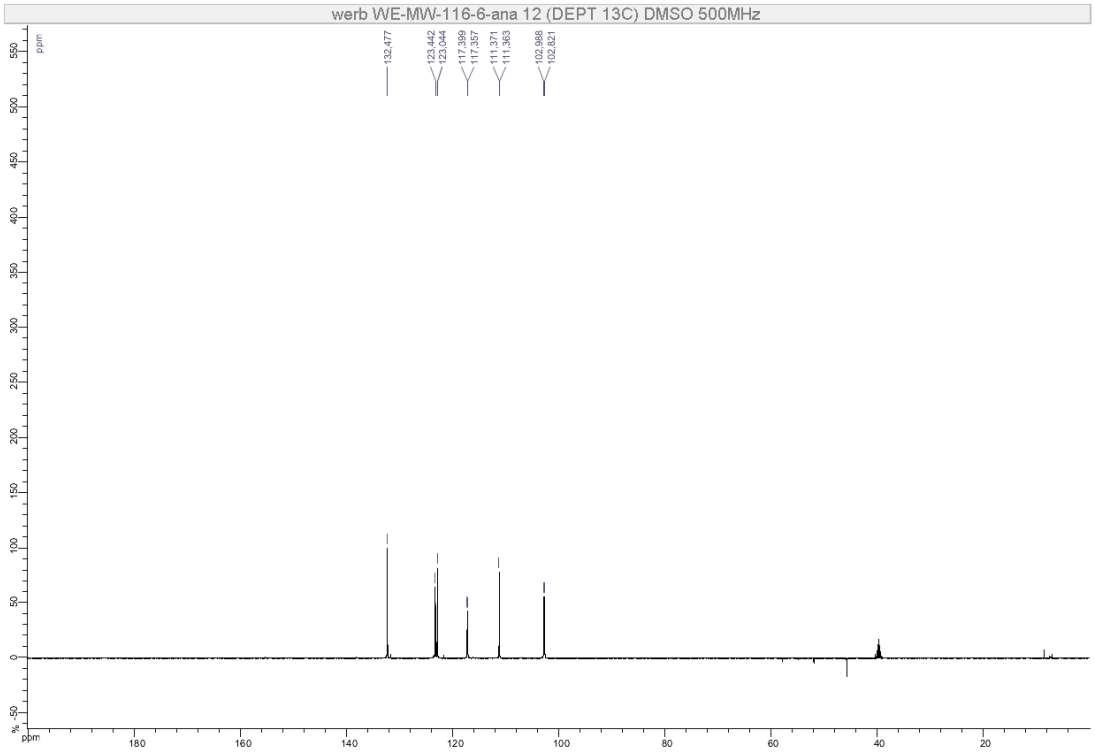
^{1}H NMR



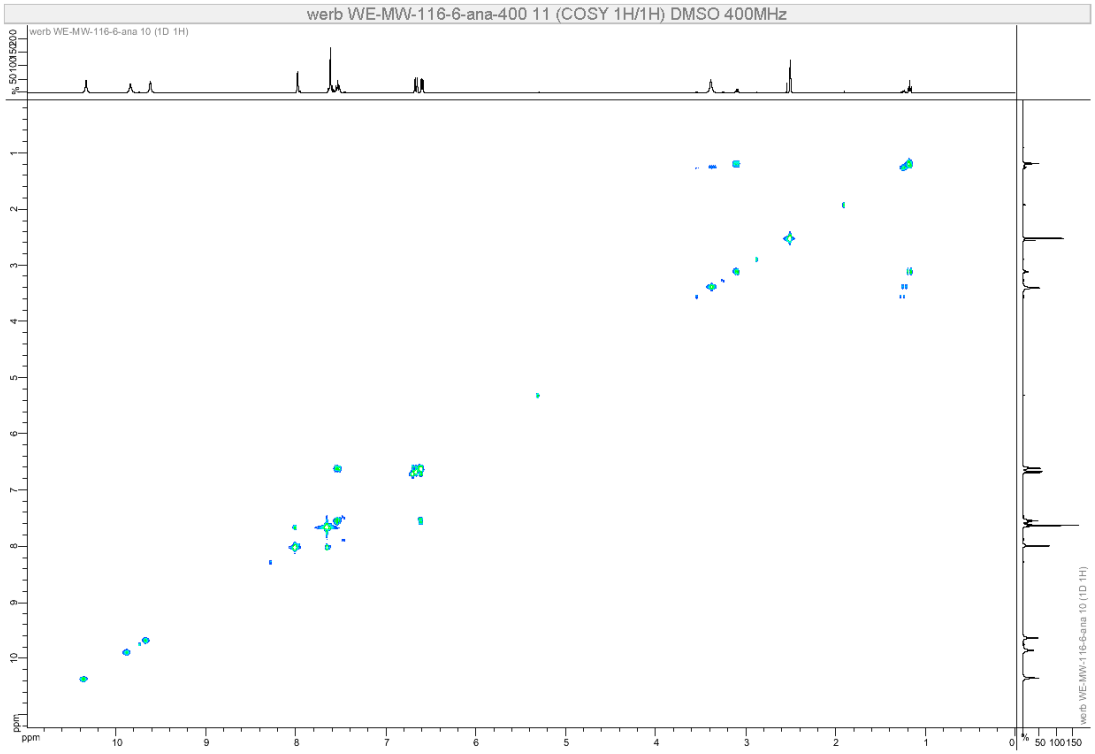
^{13}C NMR



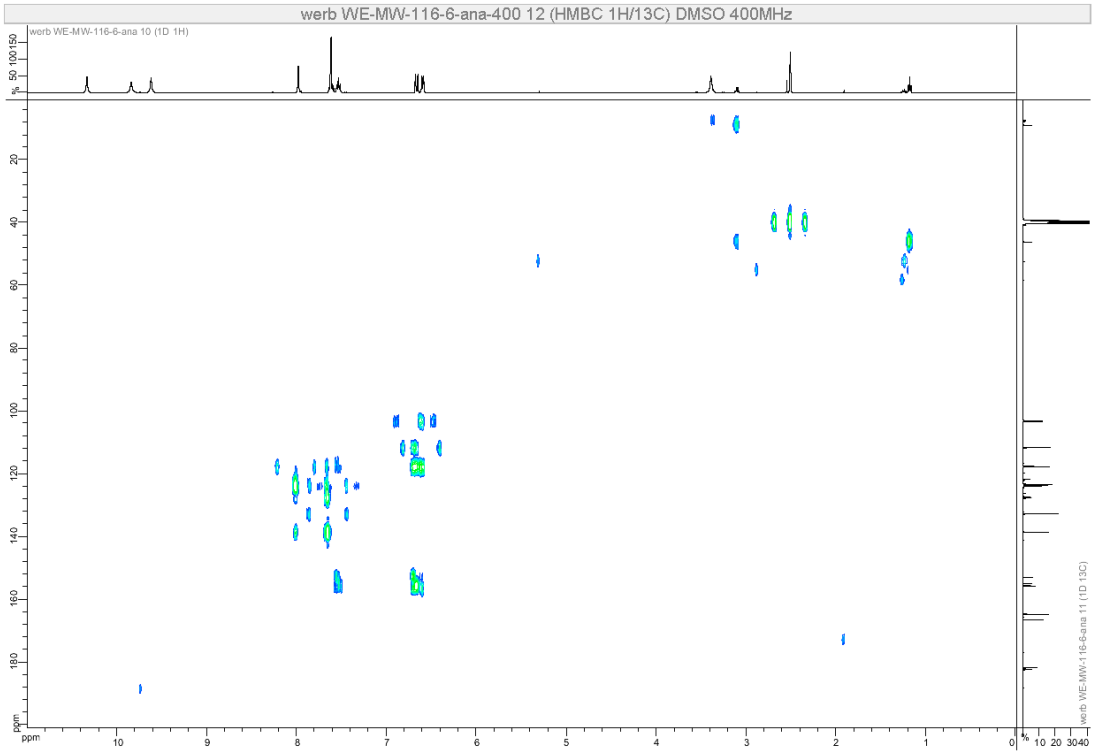
DEPT 135 NMR



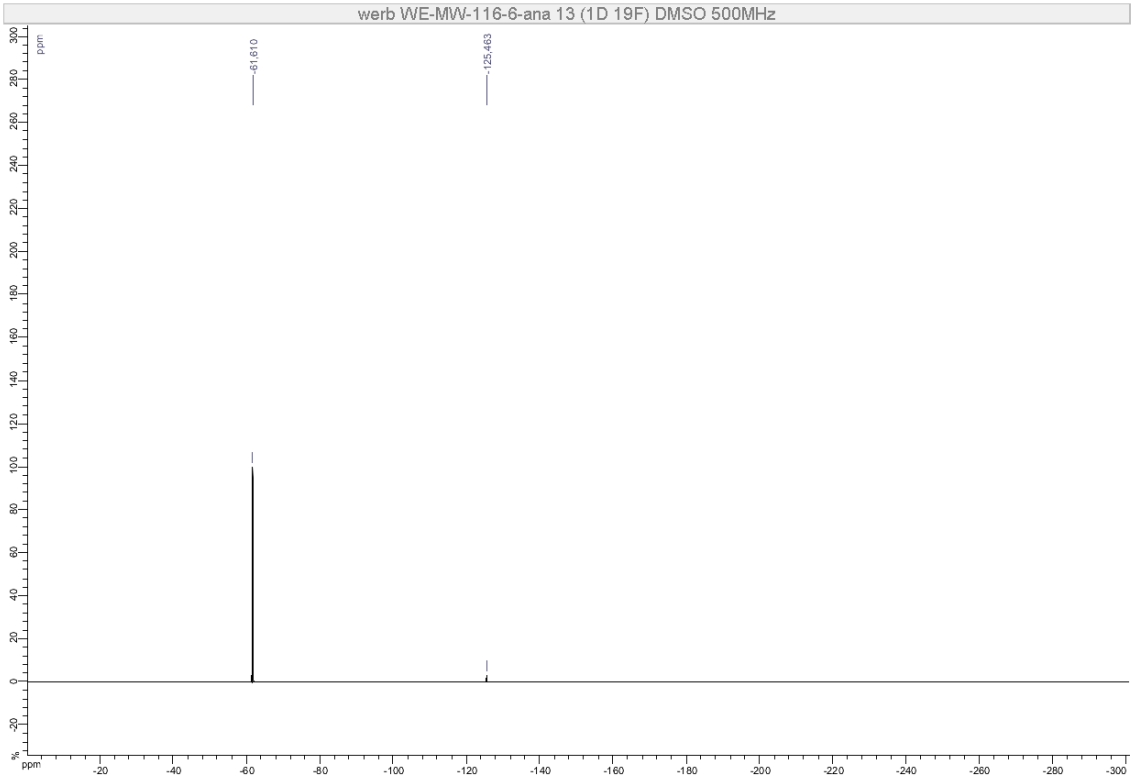
COSY NMR



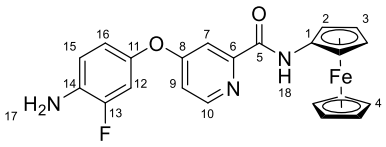
HMBC NMR



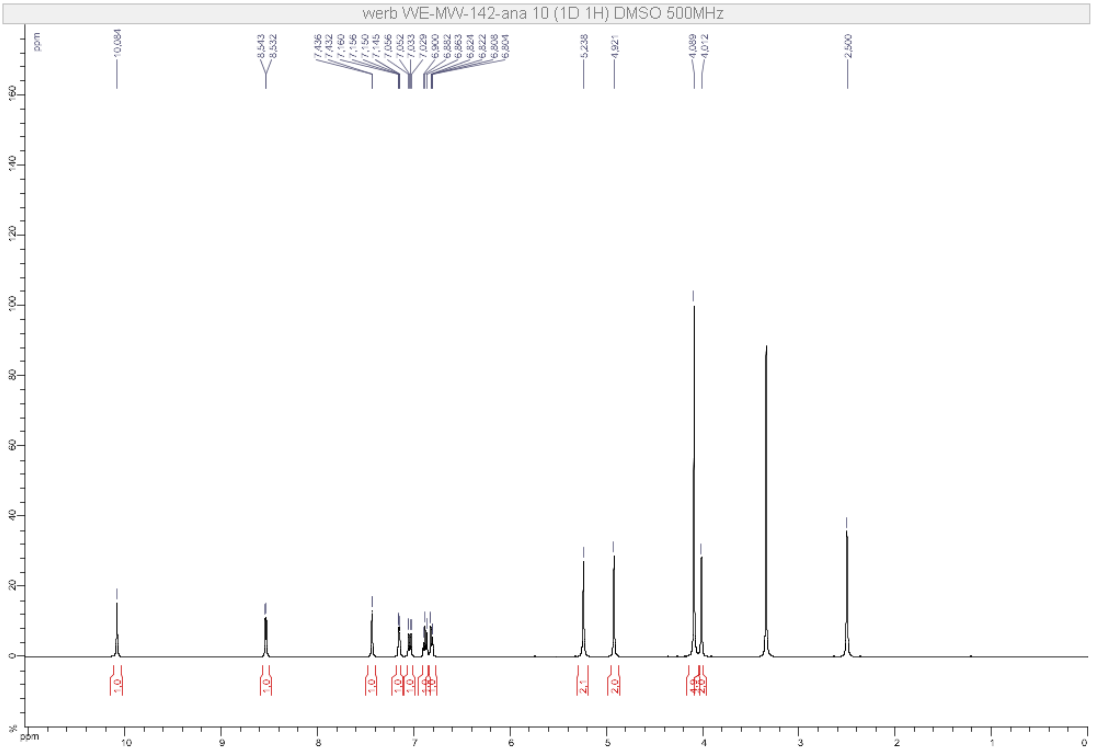
^{19}F NMR



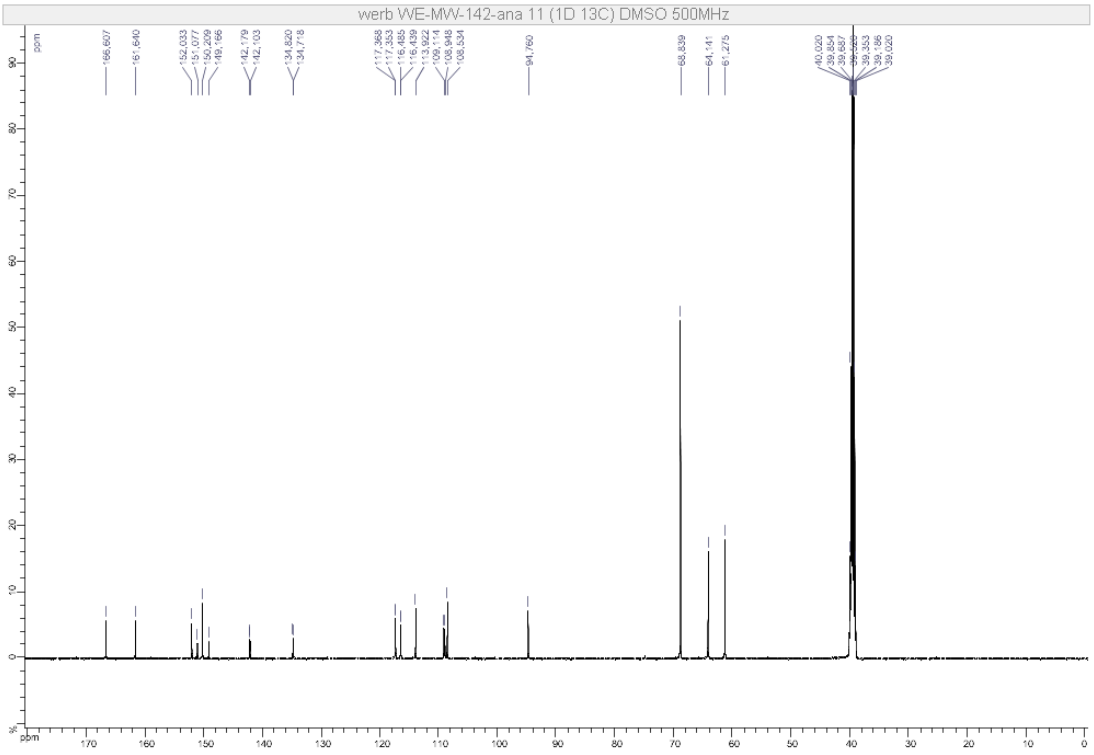
Compound 39



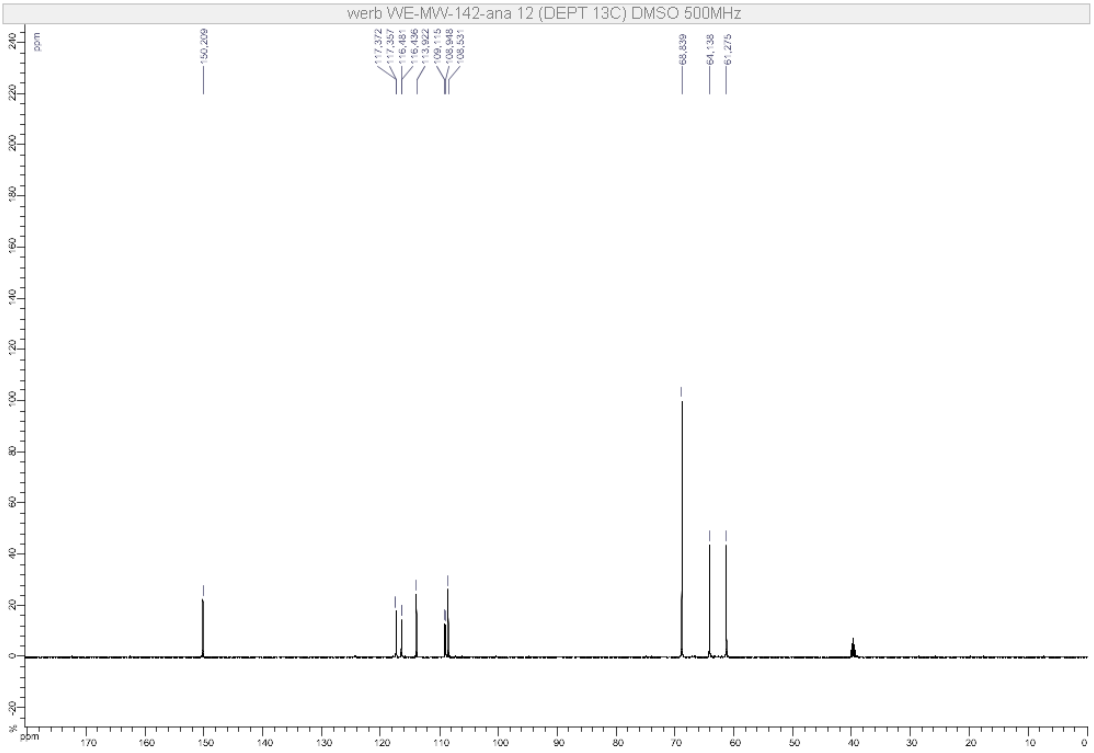
^{1}H NMR



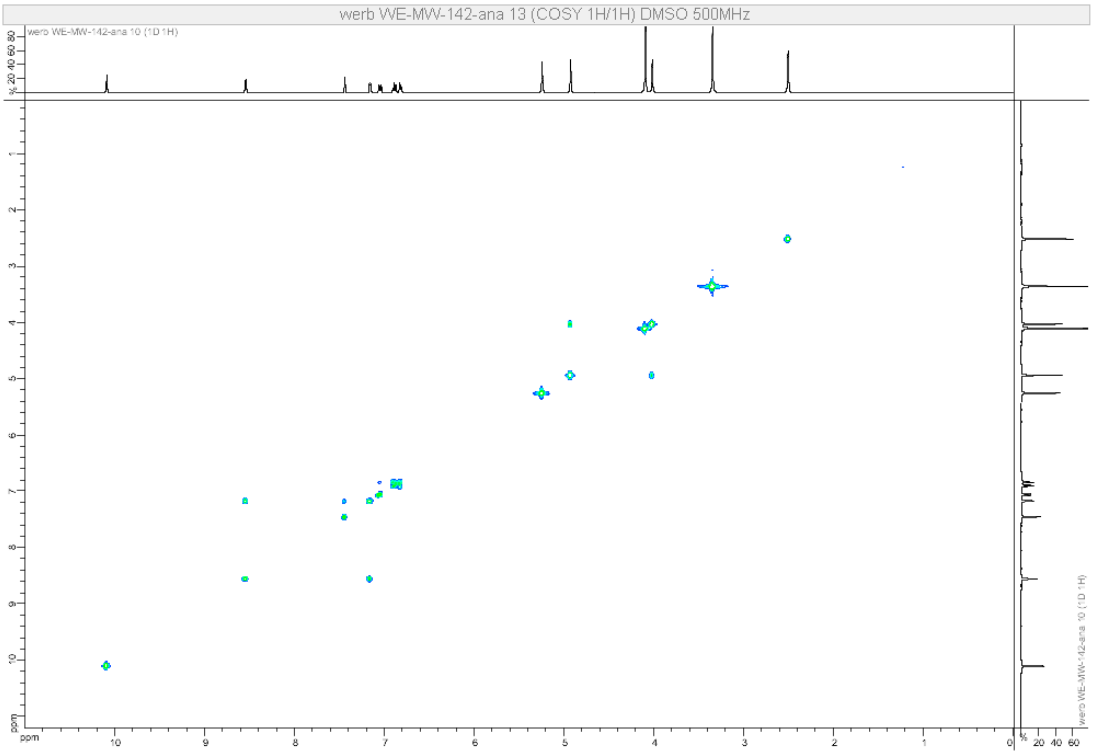
^{13}C NMR



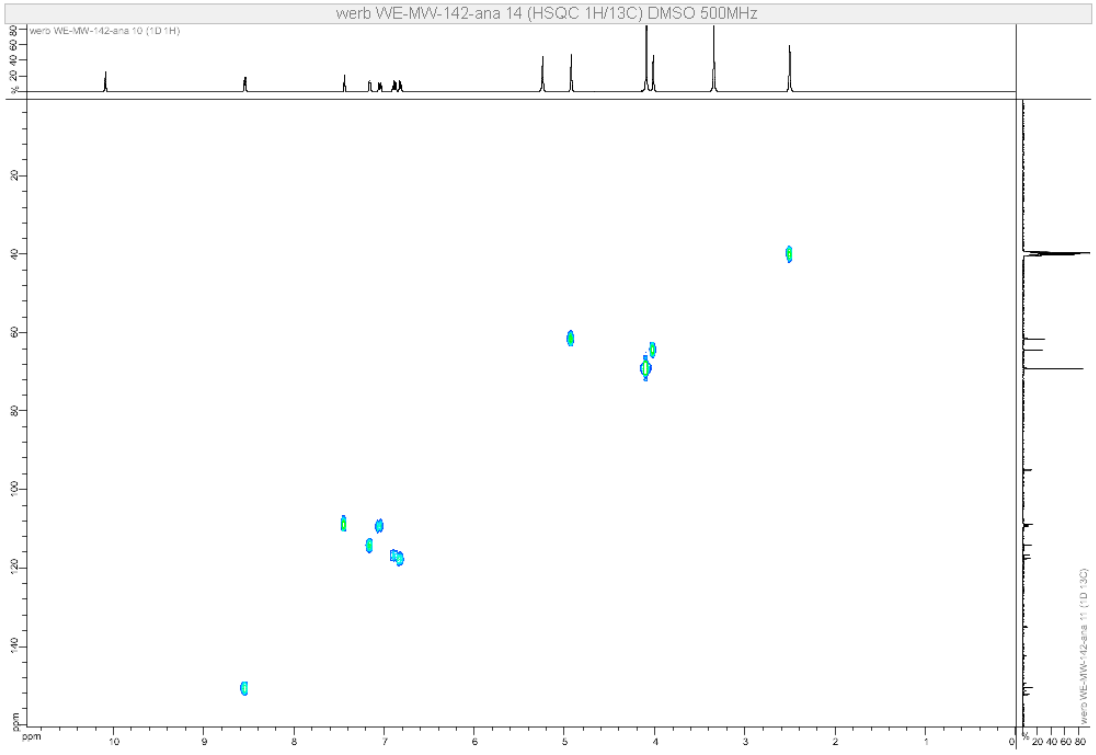
DEPT 135 NMR



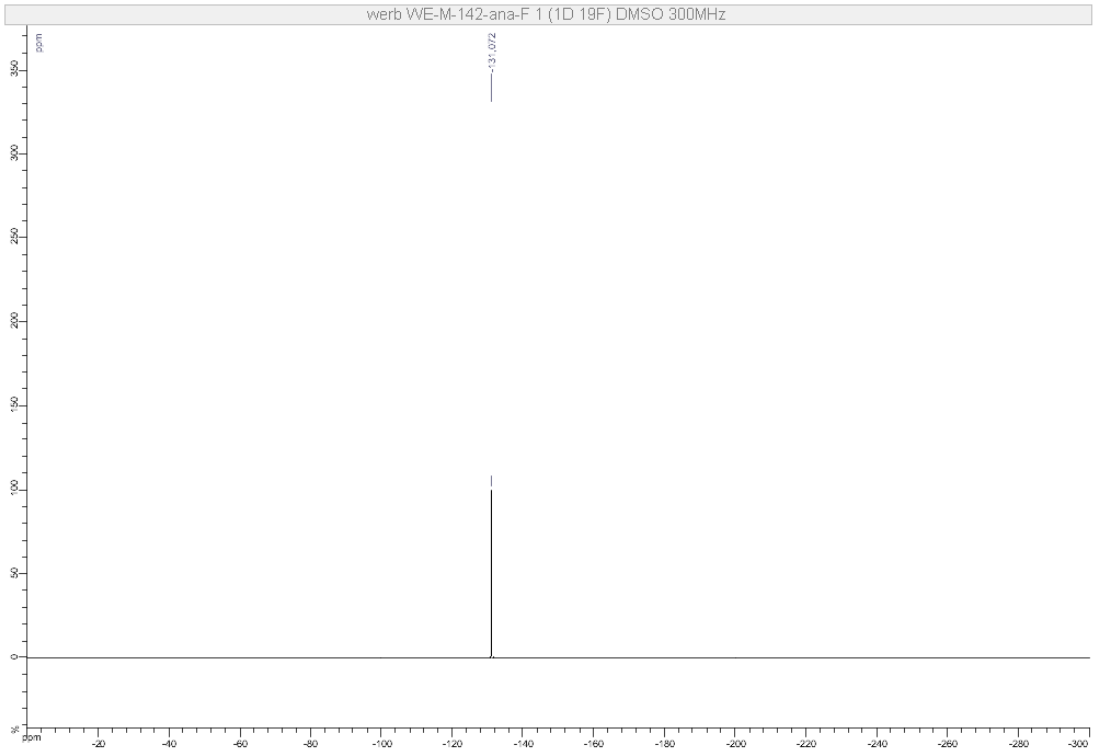
COSY NMR



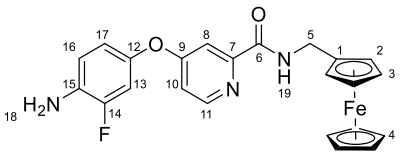
HSQC NMR



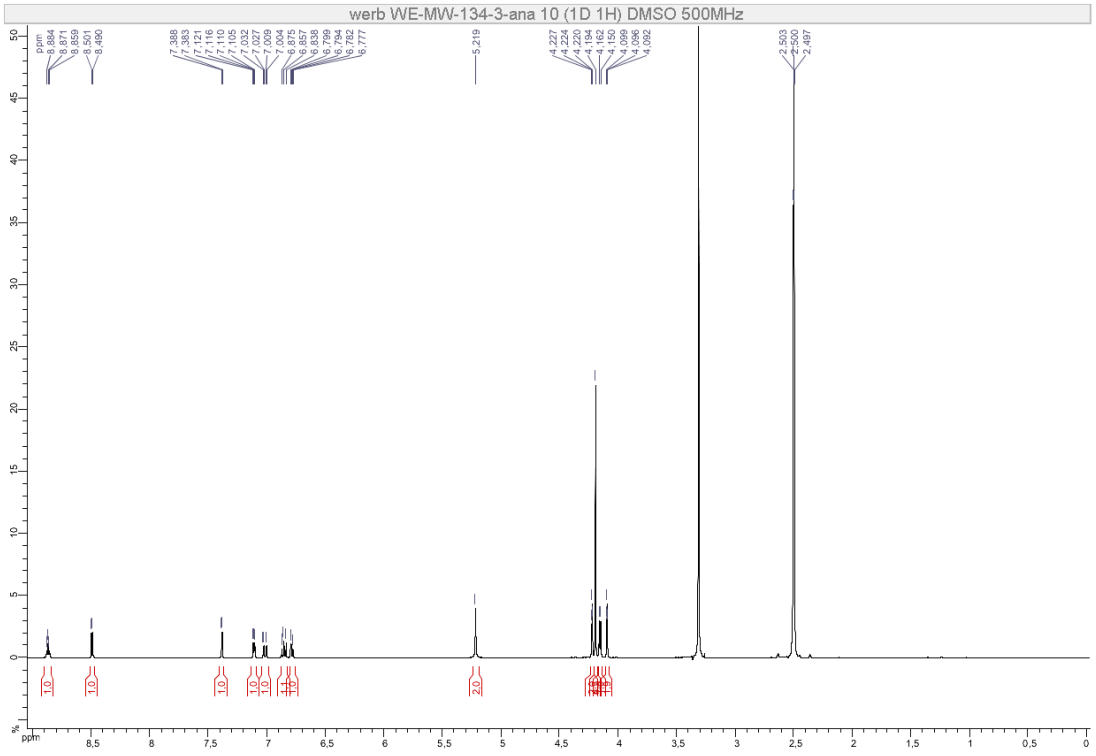
^{19}F NMR



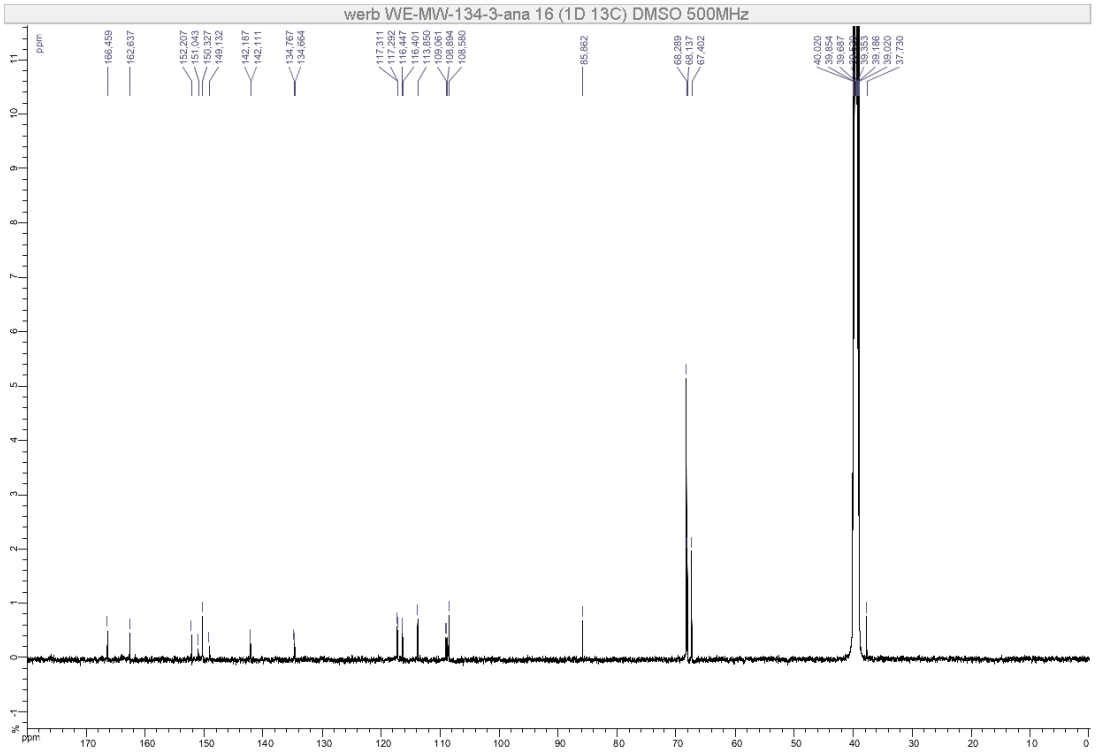
Compound 40



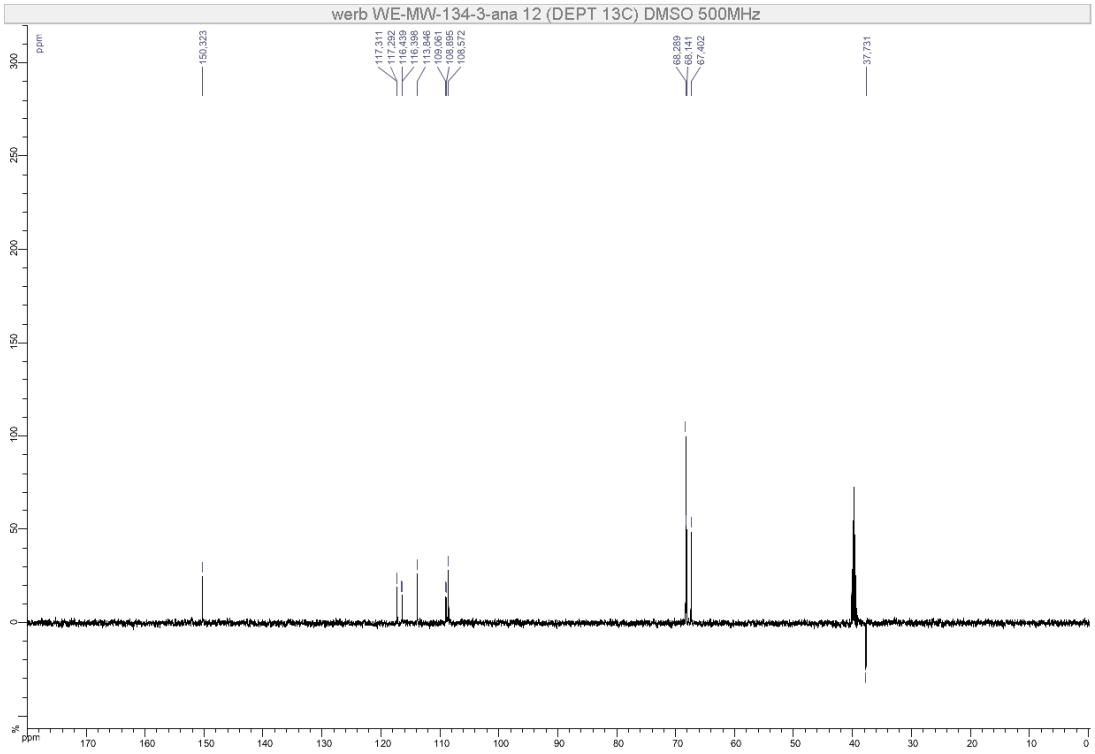
^{1}H NMR



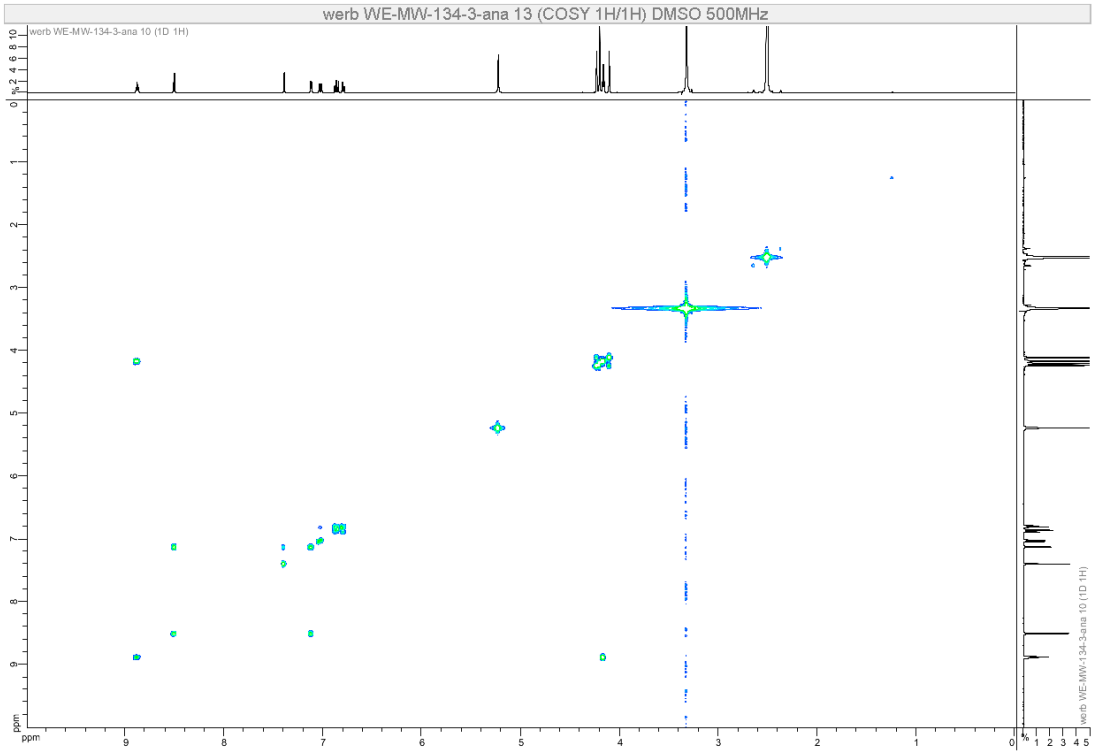
^{13}C NMR



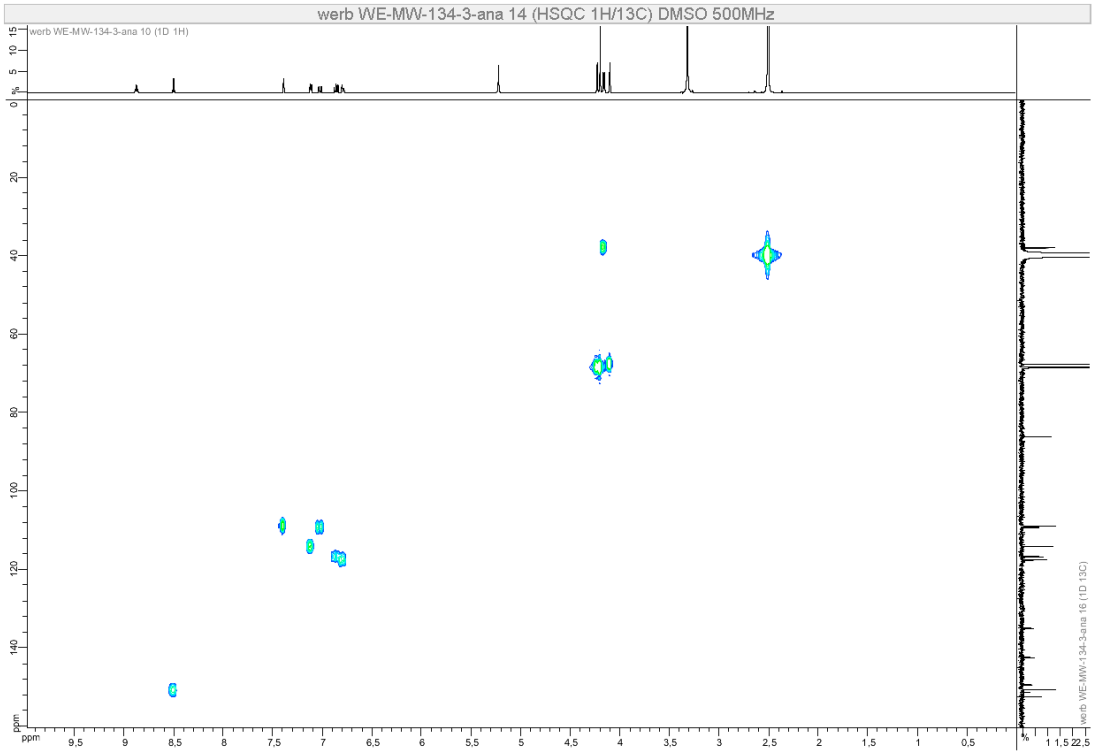
DEPT 135 NMR



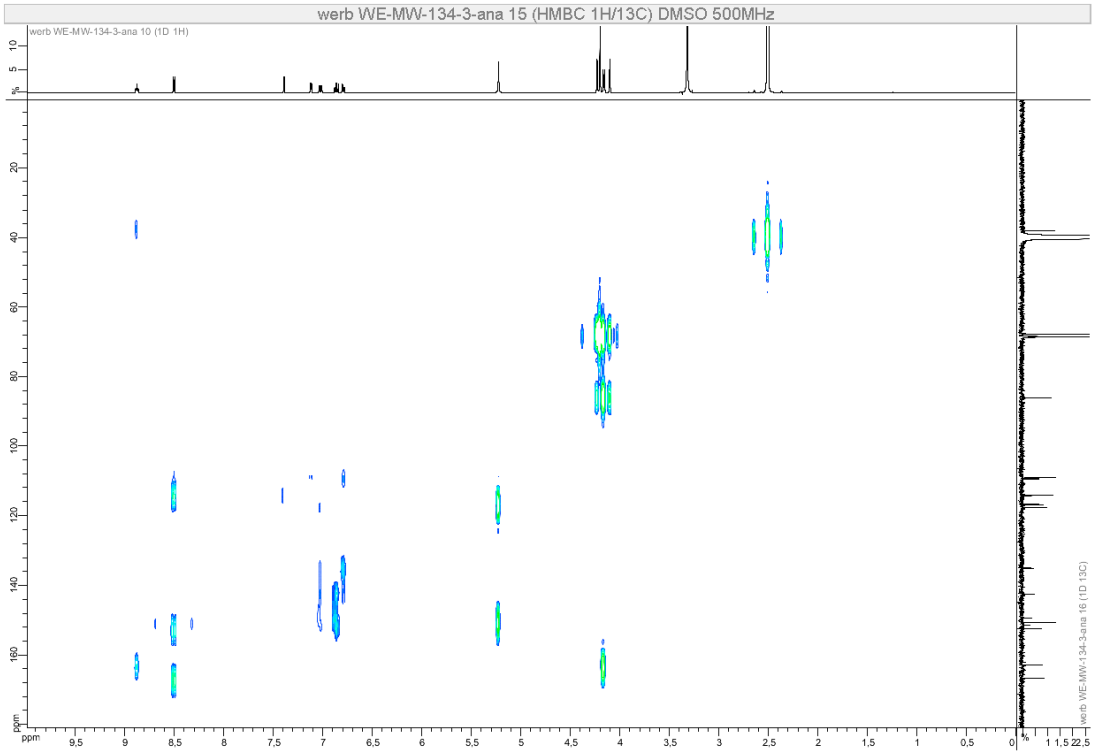
COSY NMR



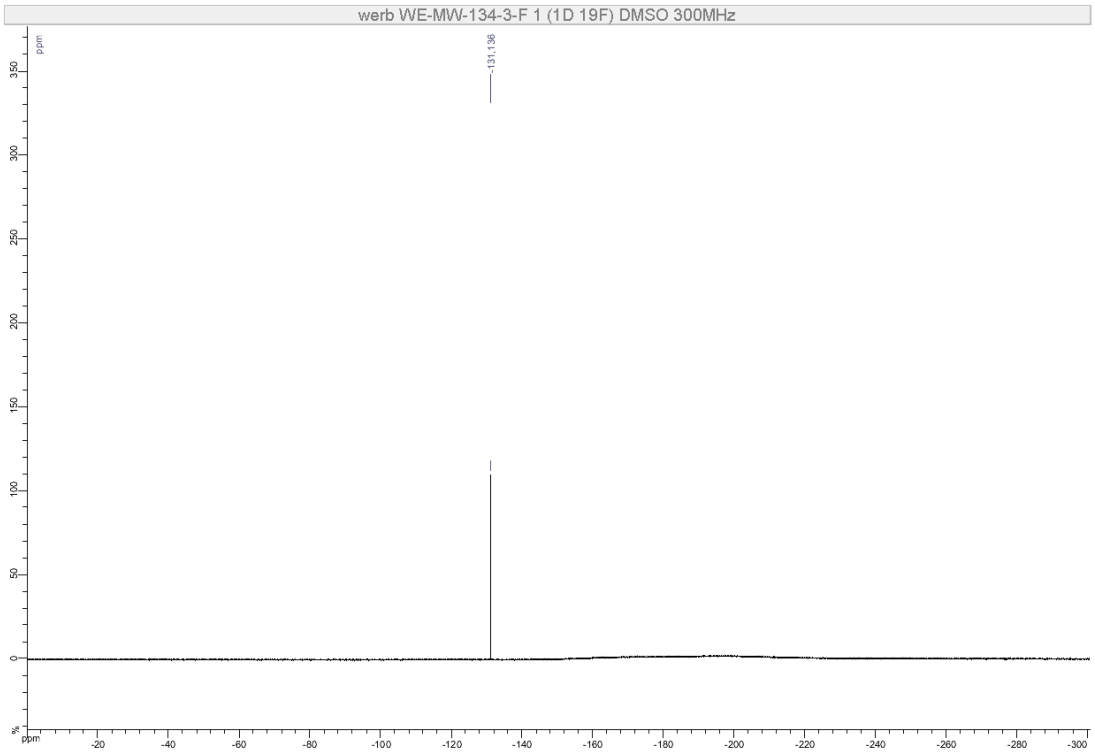
HSQC NMR



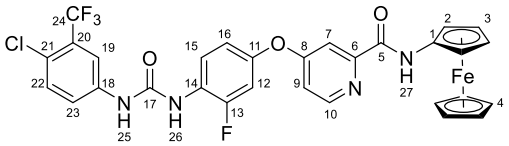
HMBC NMR



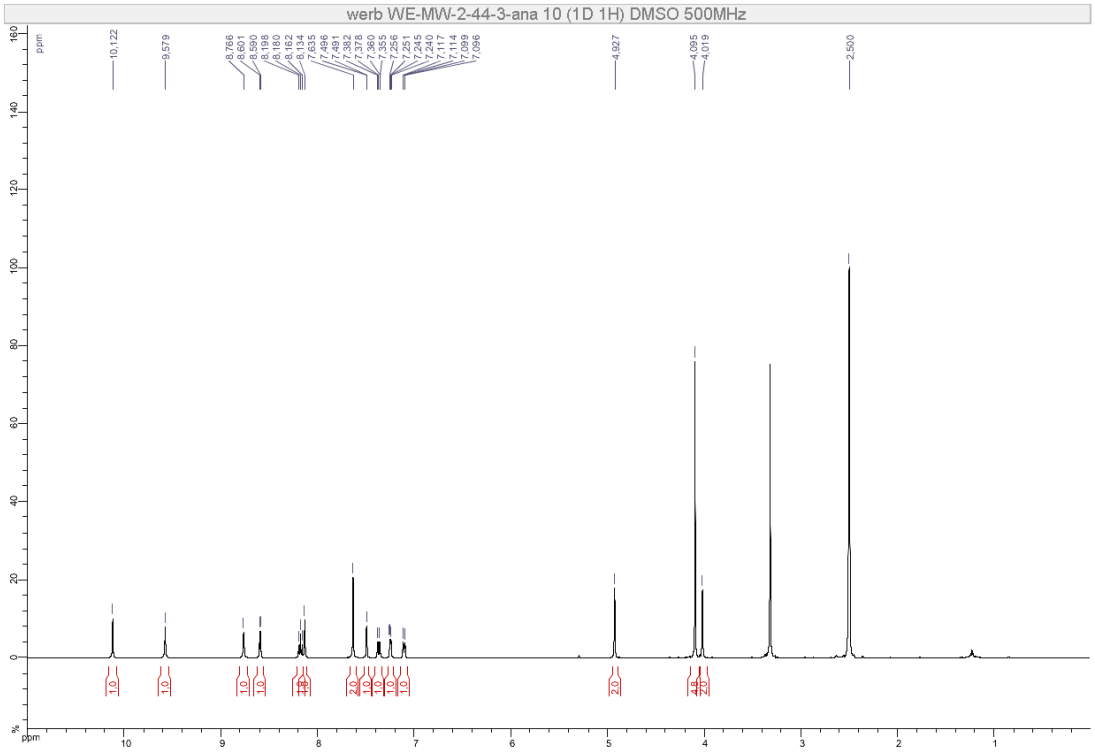
^{19}F NMR


werb WE-MW-134-3-F 1 (1D 19F) DMSO 300MHz
ppm
-131.136
350
300
250
200
150
100
50
0
%
ppm
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
-260
-280
-300

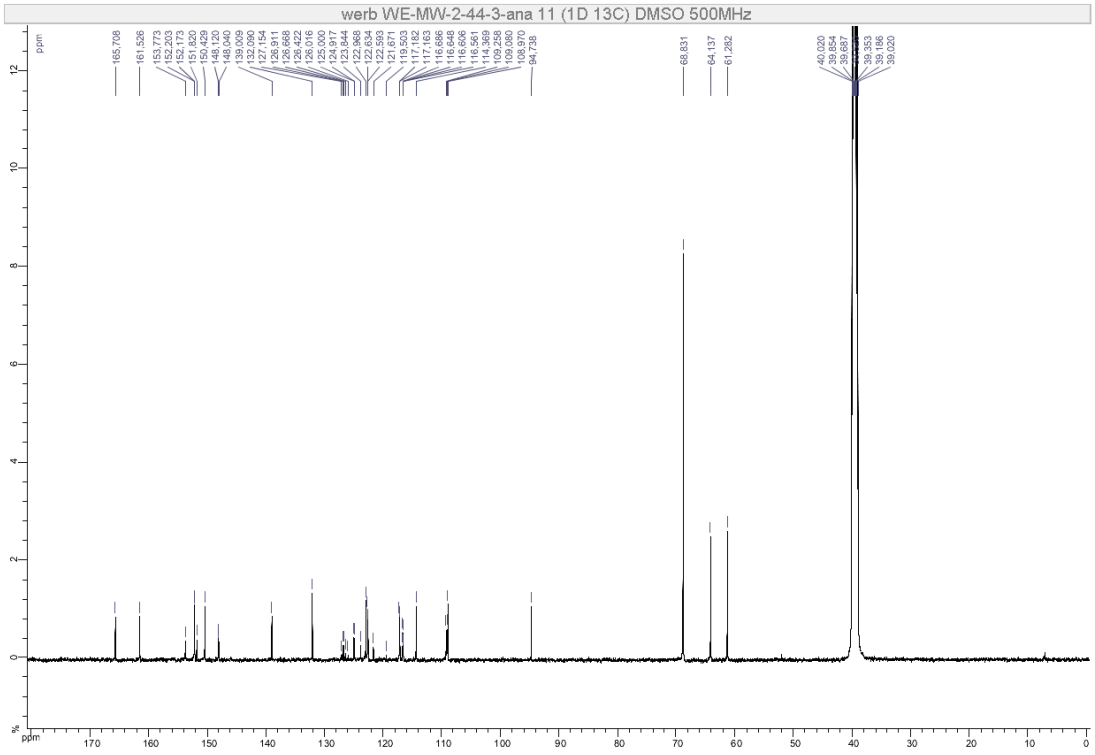
Compound 4a



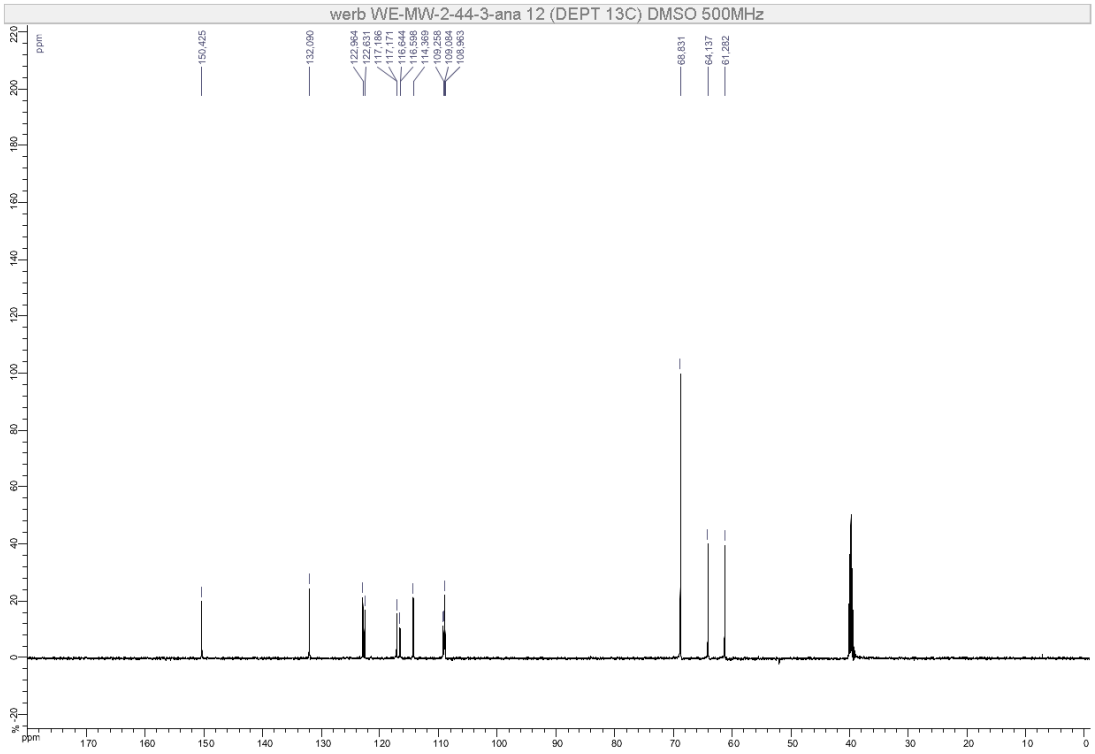
^{1}H NMR



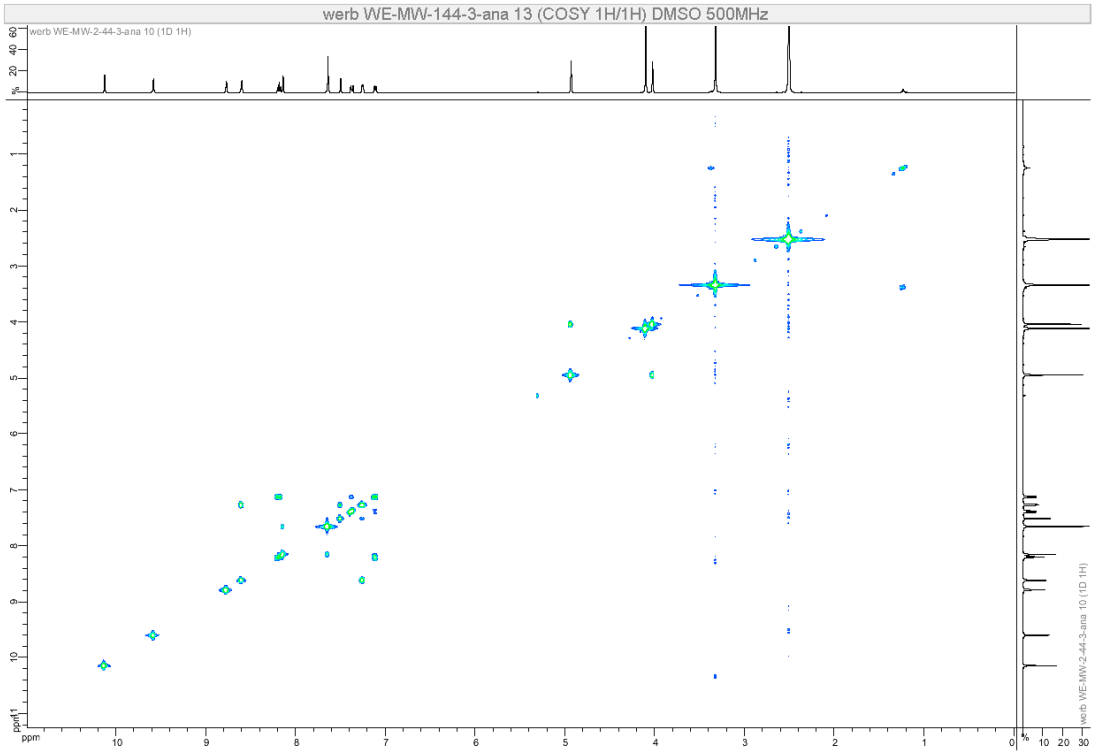
^{13}C NMR



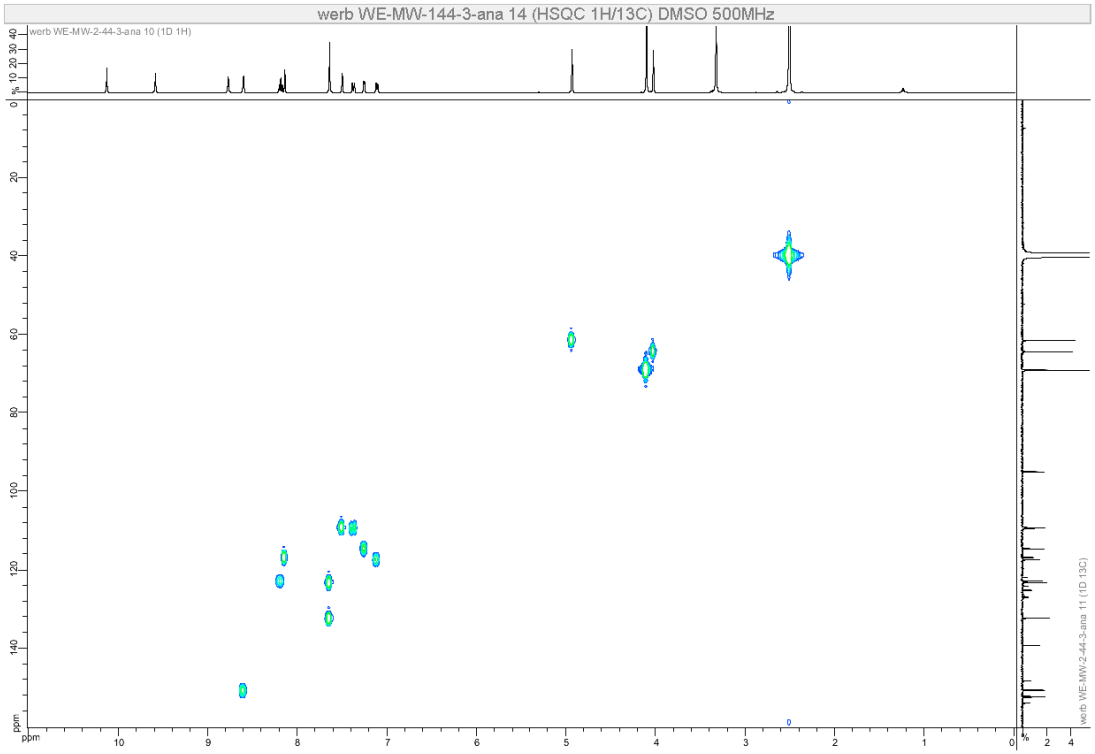
DEPT 135 NMR



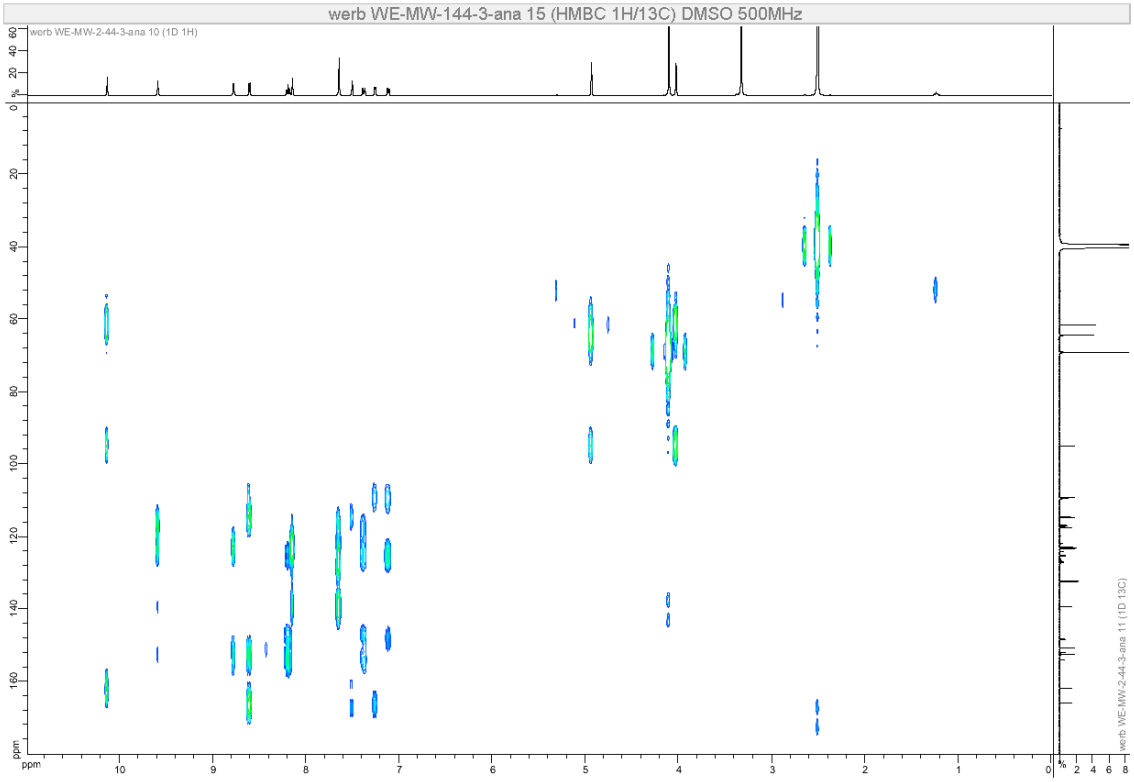
COSY NMR



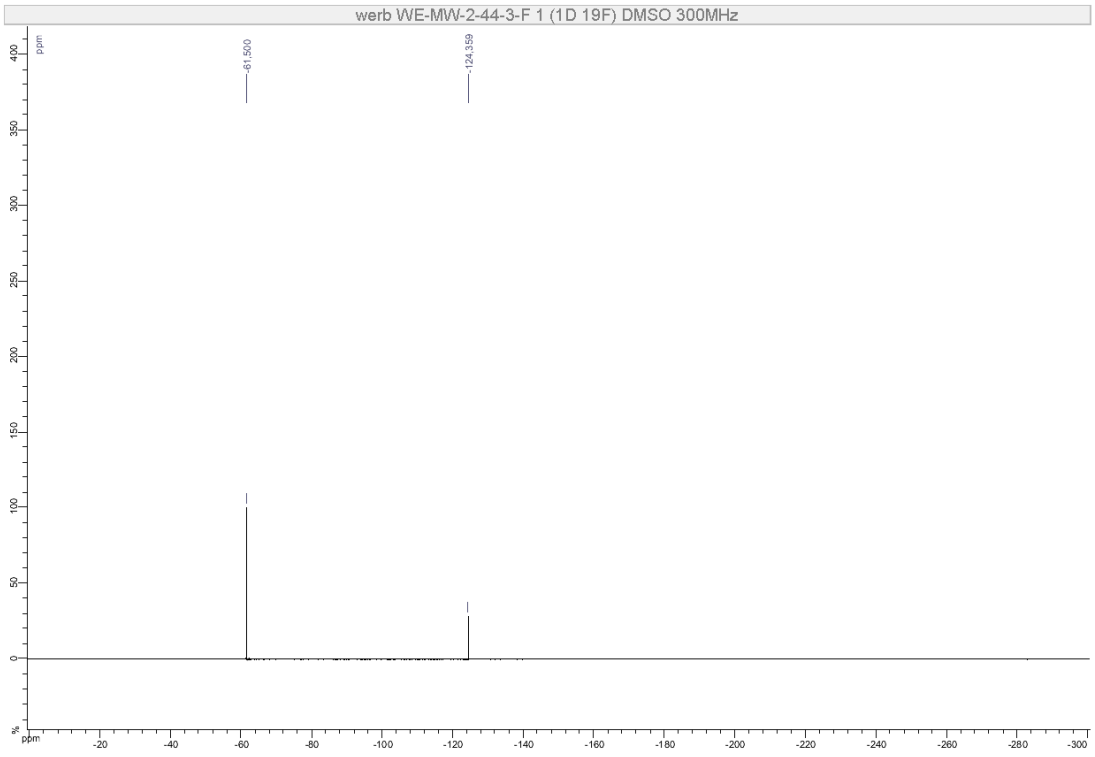
HSQC NMR



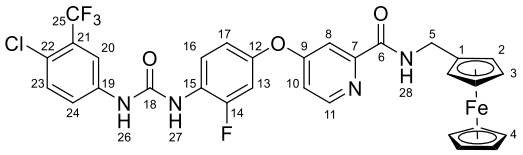
HMBC NMR



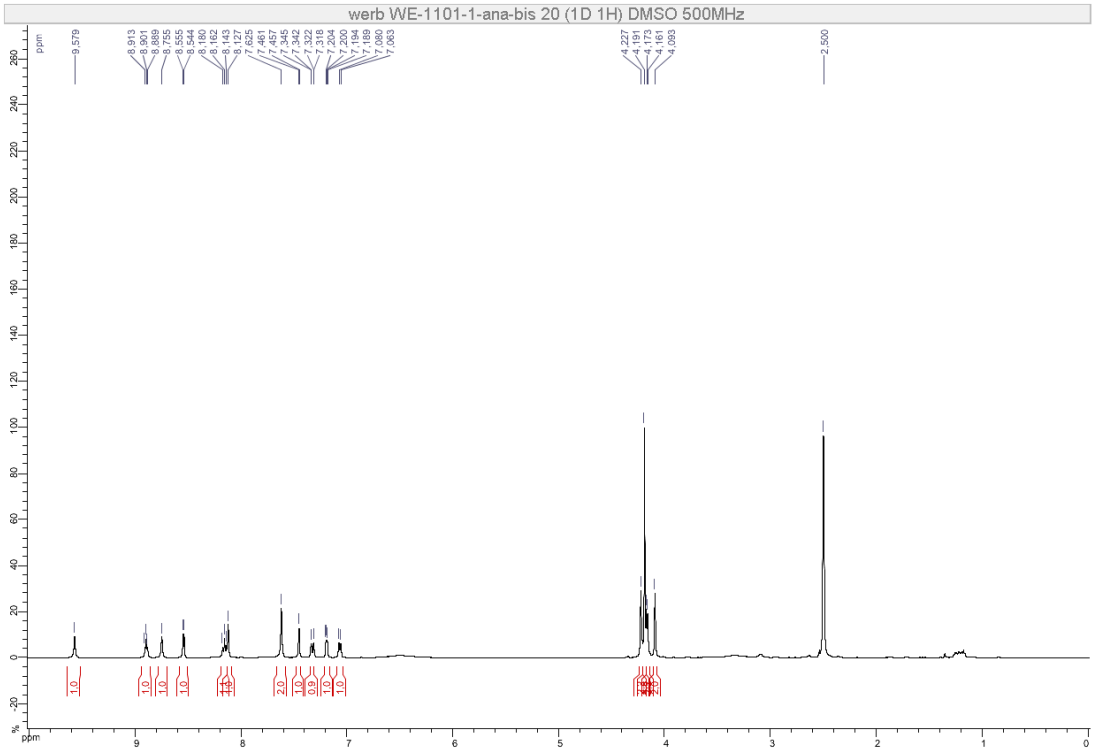
^{19}F NMR


werb WE-MW-2-44-3-F 1 (1D 19F) DMSO 300MHz
ppm
-61,500
-124,359
400
350
300
250
200
150
100
50
0
%
ppm
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
-260
-280
-300

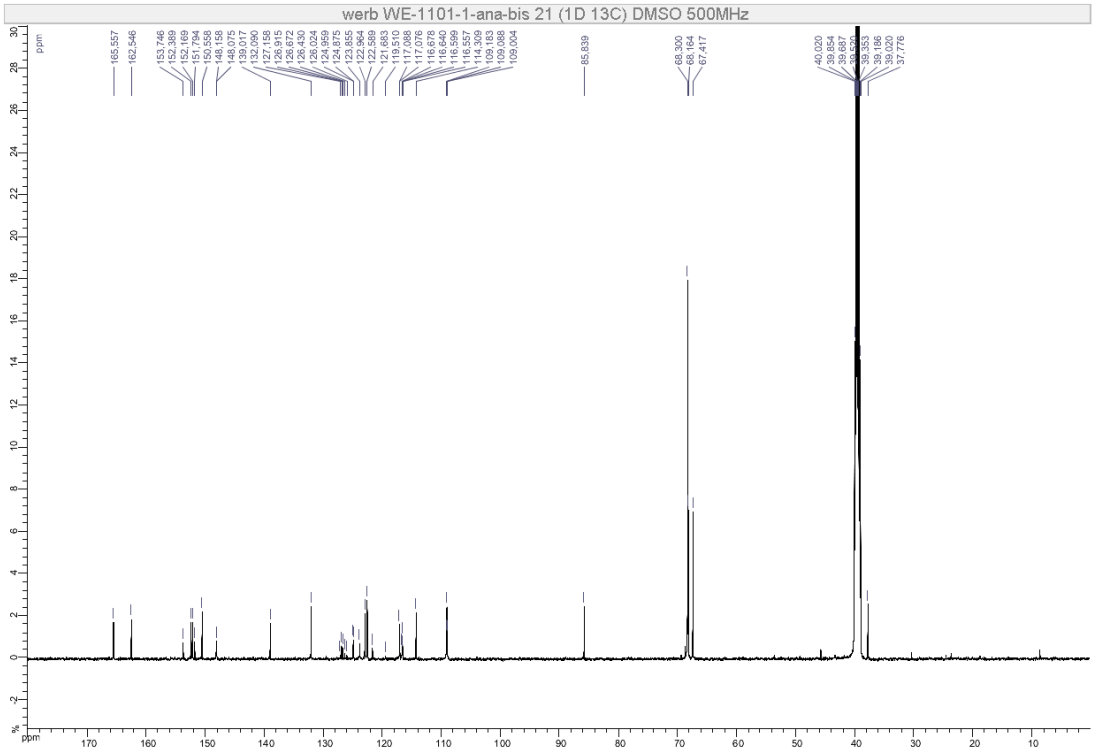
Compound 5a



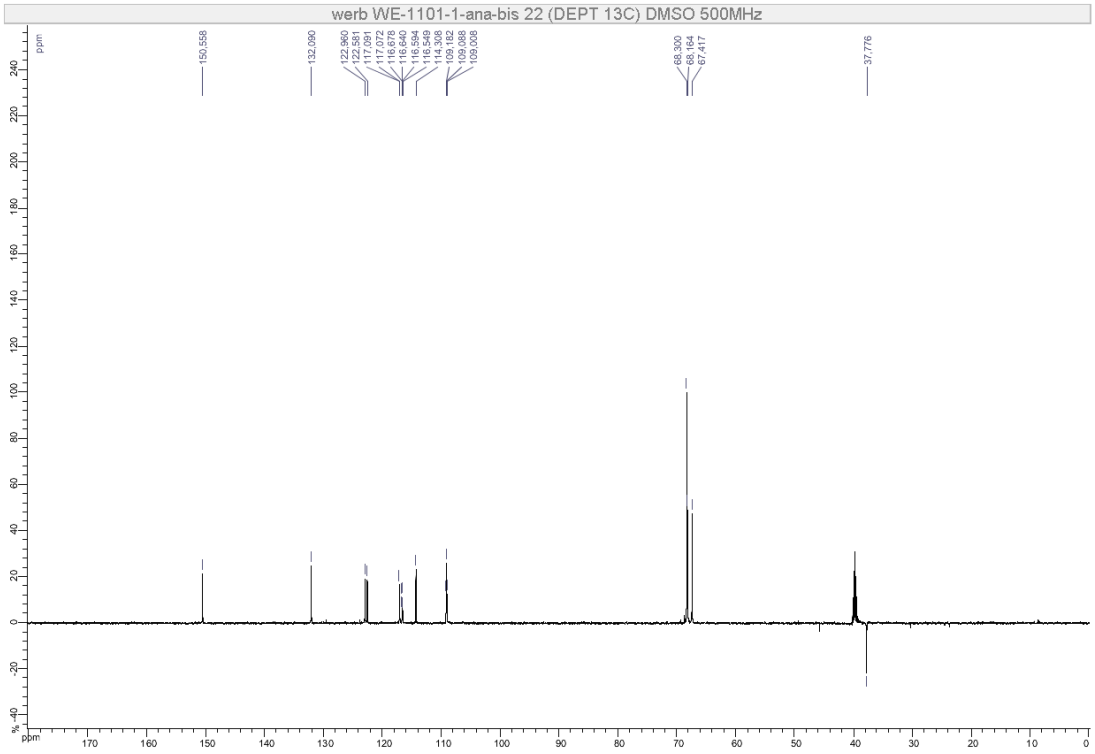
^{1}H NMR



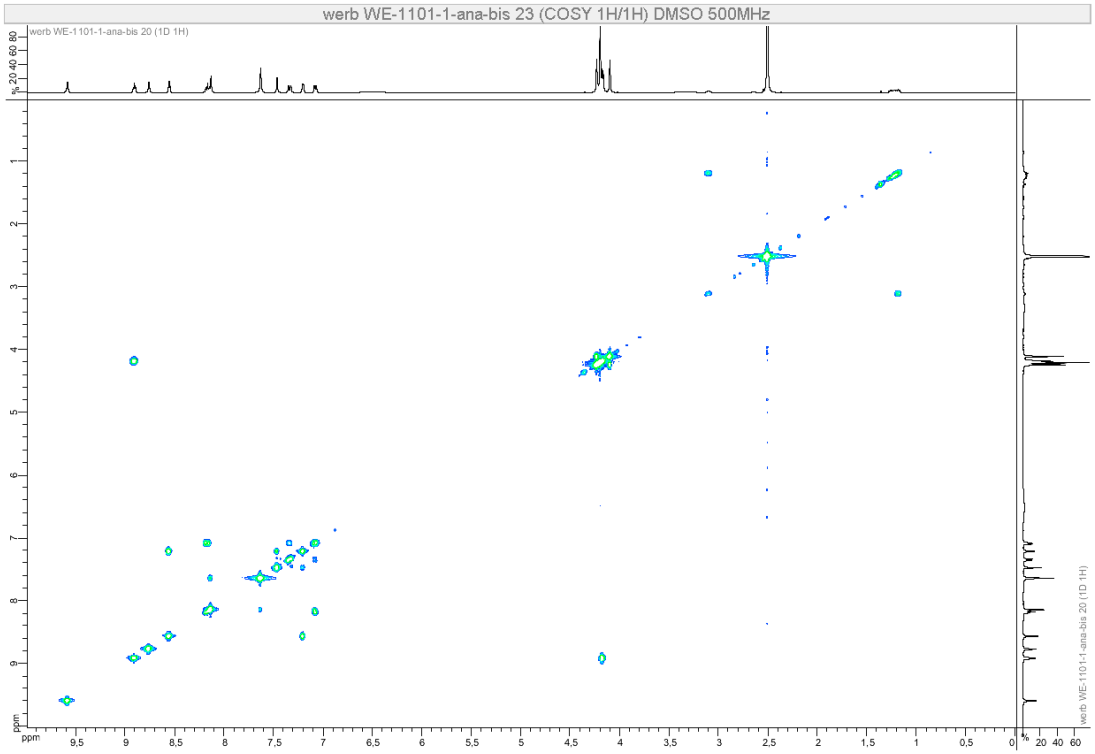
^{13}C NMR



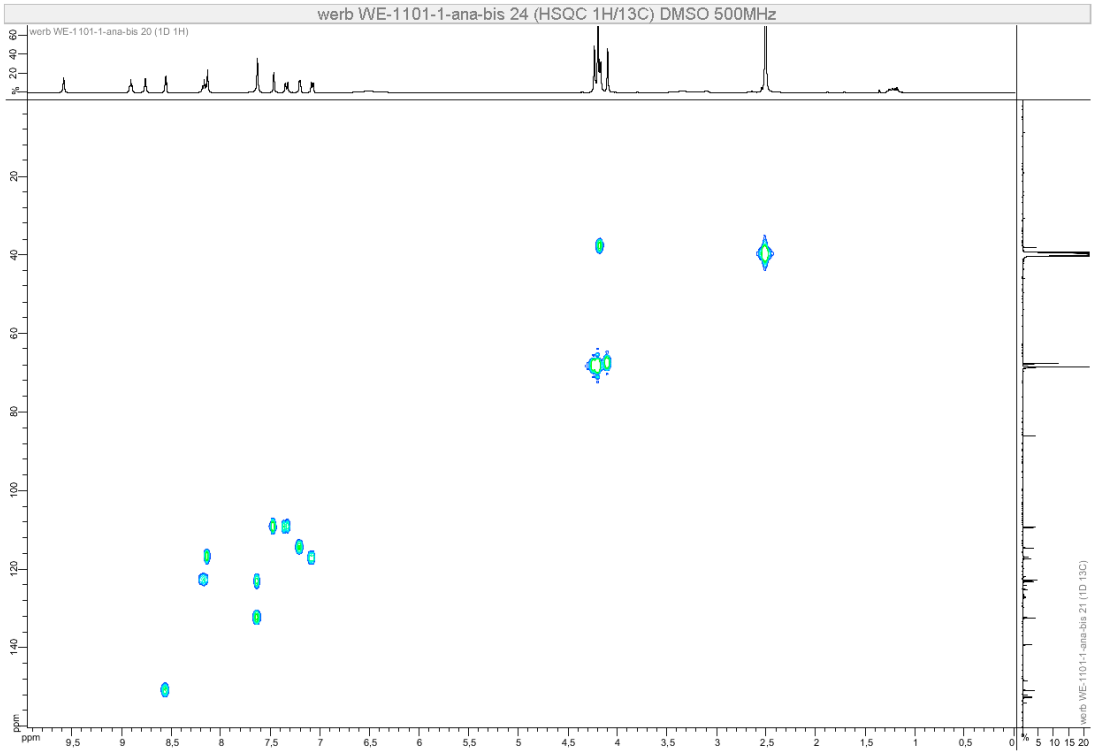
DEPT 135 NMR



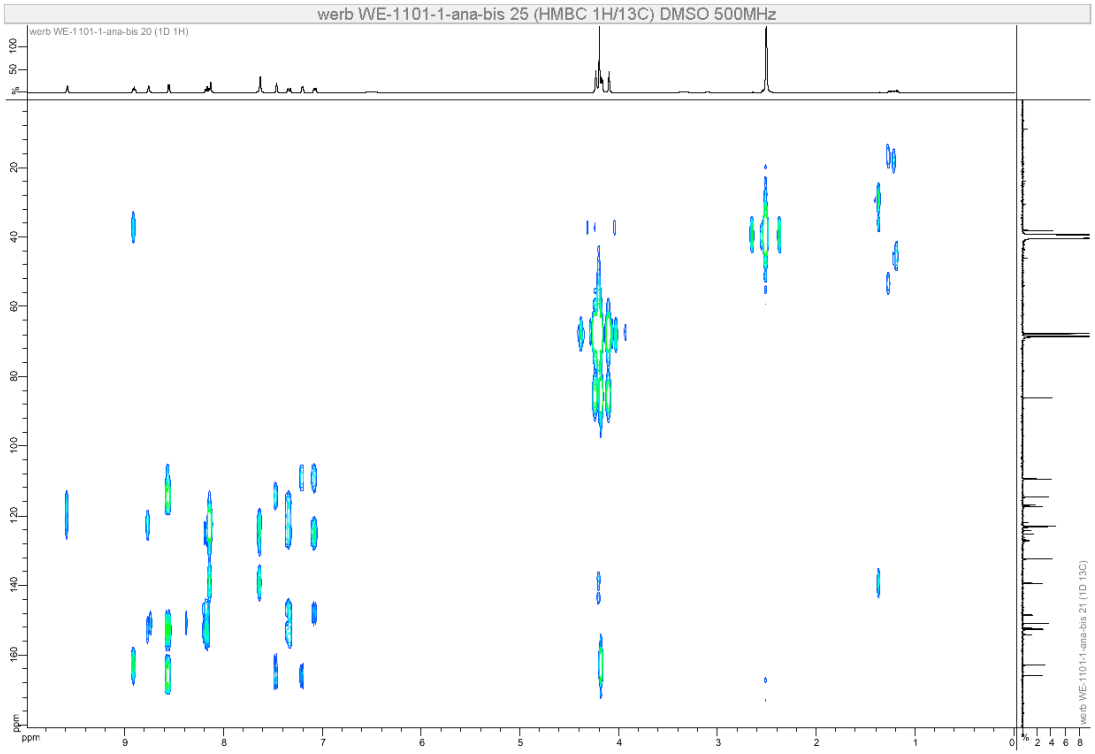
COSY NMR



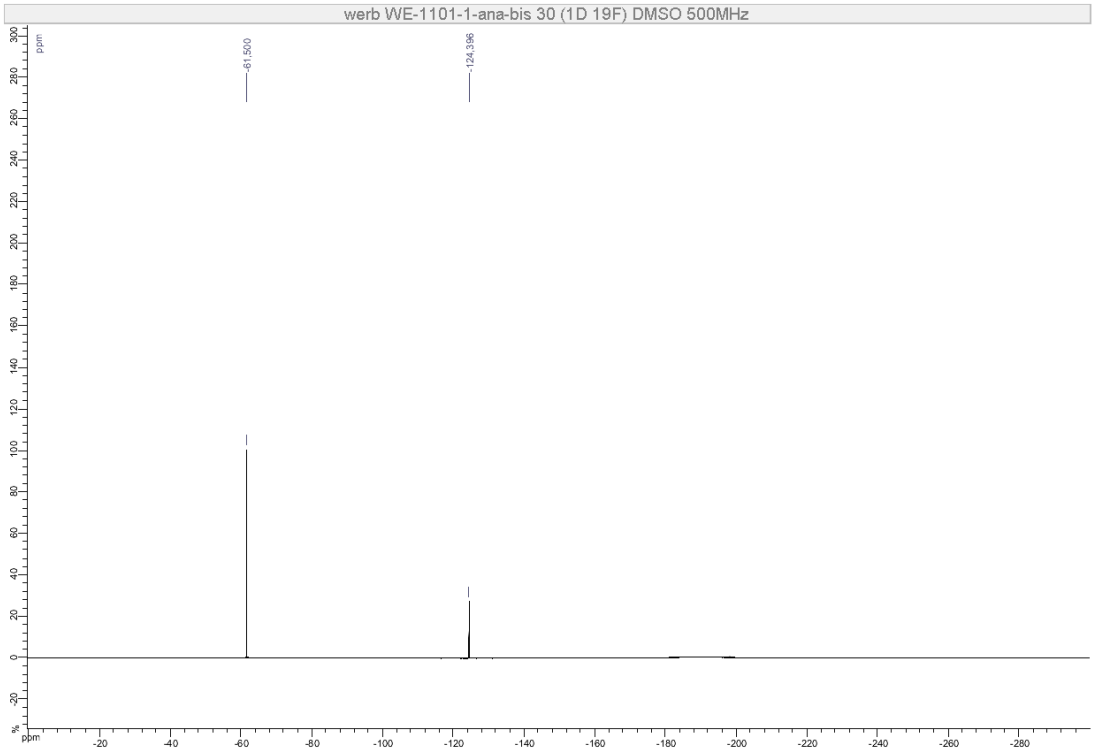
HSQC NMR



HMBC NMR

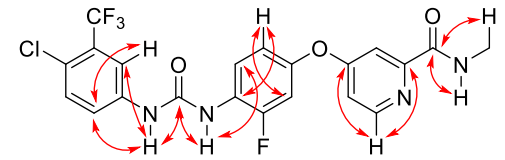


^{19}F NMR

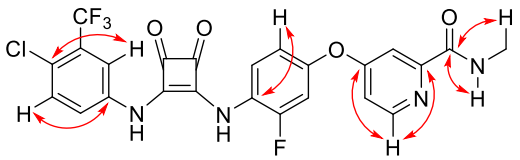

werb WE-1101-1-ana-bis 30 (1D 19F) DMSO 500MHz
ppm
-61,500
-124,396
ppm
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
-260
-280

Key HMBC correlations observed for the final compounds and selected synthetic intermediates.

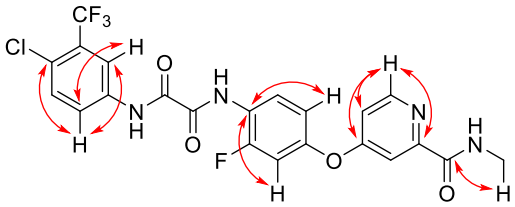
Compound 1a



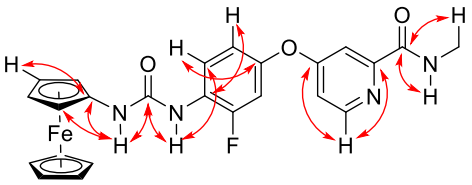
Compound 1b



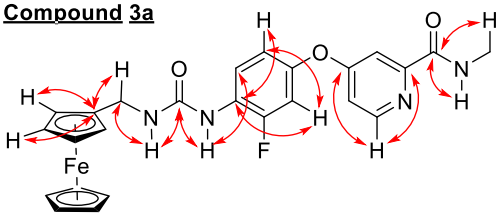
Compound 1c



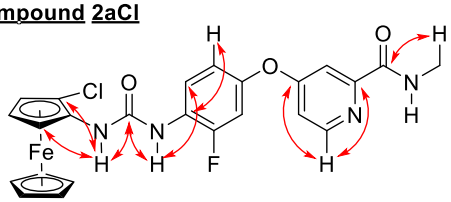
Compound 2a



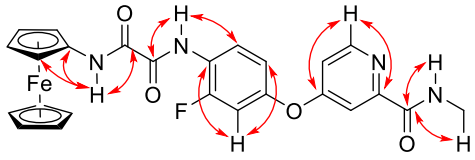
Compound 3a



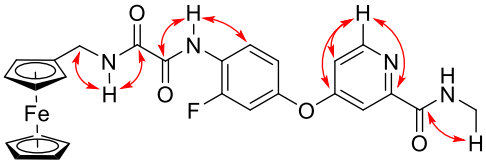
Compound 2aCl



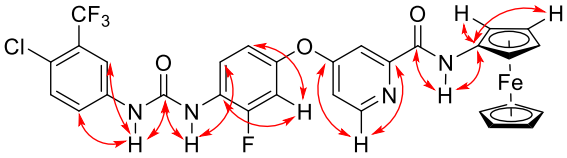
Compound 2c



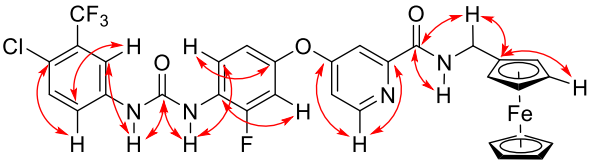
Compound 3c



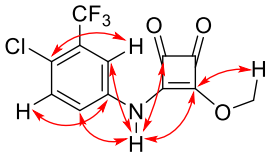
Compound 4a



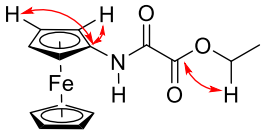
Compound 5a



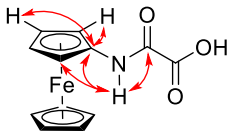
Compound 18



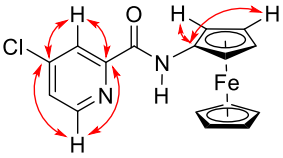
Compound 31



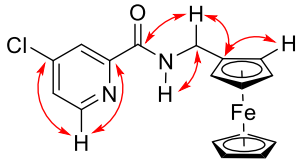
Compound 33



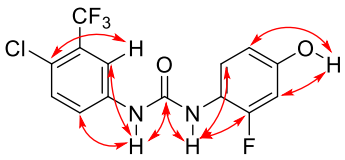
Compound 35



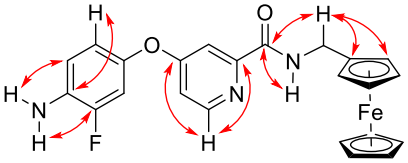
Compound 36



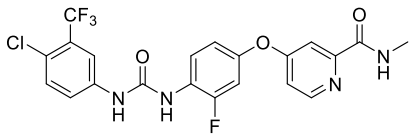
Compound 38a



Compound 40



HPLC Chromatograms



Compound 1a

Chimie Organique et Interfaces (CORINT)

Chromatogram and Results

General informations

Sequence Name:	2018-03-23
Instrument:	U3000
Logiciel used:	Chromeleon
Column used:	CHIRALPAK IC-3 DAICEL CHIRALPAK IC DAICEL

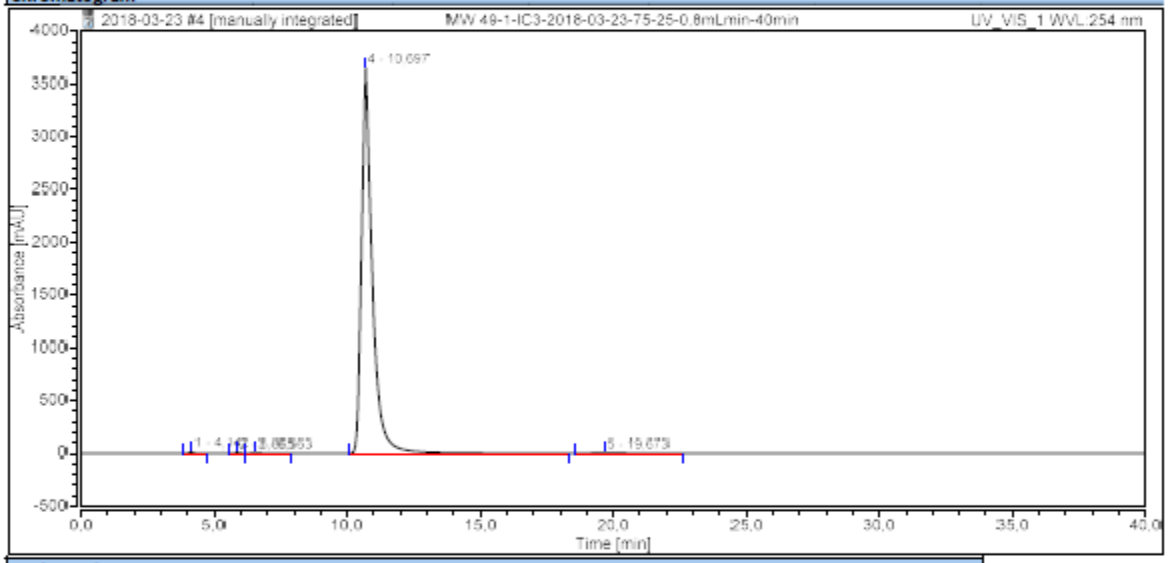
Injection Details

Injection Name:	MW 49-1-IC3-2018-03-23-75-25-0,8mLmin-40min	*Run Time:*	40,00 min
Instrument Method:	Madani-IC3-75-25-0,8mLmin-40min	*Injection Volume:*	5,00 µL
Injection Date/Time:	23/mars/18 11:33	*Channel:* UV_VIS_1	
		Wavelength:	254 nm

Instrument Method Details

Instrument Method:	Madani-IC3-75-25-0,8mLmin-40min			
%A	Isopropanol	25 %		
%B	Hexane	75 %	*Température du four:*	20,0 °C
	Debit:	0,800 mL/min	*Pression:*	87 bars

Chromatogram



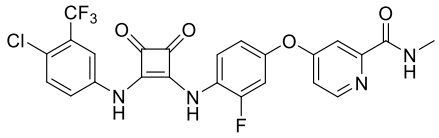
Peak Results

No.	Peak Name	Retention Time min	Width (50%) min	Resolution (EP)	Asymmetry (EP)	Plates (EP)
1		4,142	0,230	4,58	1,14	1790
2		5,865	0,213	1,38	n.a.	4181
3		6,563	0,383	6,30	n.a.	1630
4		10,697	0,392	6,36	1,57	4123
5		19,673	1,273	n.a.	1,85	1322

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %
1		4,142	2,447	10,582	0,14	0,29
2		5,865	2,215	9,709	0,13	0,26
3		6,563	4,112	9,086	0,24	0,25
4		10,697	1713,886	3650,238	99,00	99,04
5		19,673	8,601	5,860	0,50	0,16
Total:			**1731,261**	**3685,475**	**100,00**	**100,00**

Compound 1b



Chimie Organique et Interfaces (CORINT)

Chromatogram and Results

General informations

Sequence Name:	2018-03-30
Instrument:	U3000
Logiciel used:	Chromeleon
Column used:	CHIRALPAK IC-3 DAICEL CHIRALPAK IC DAICEL

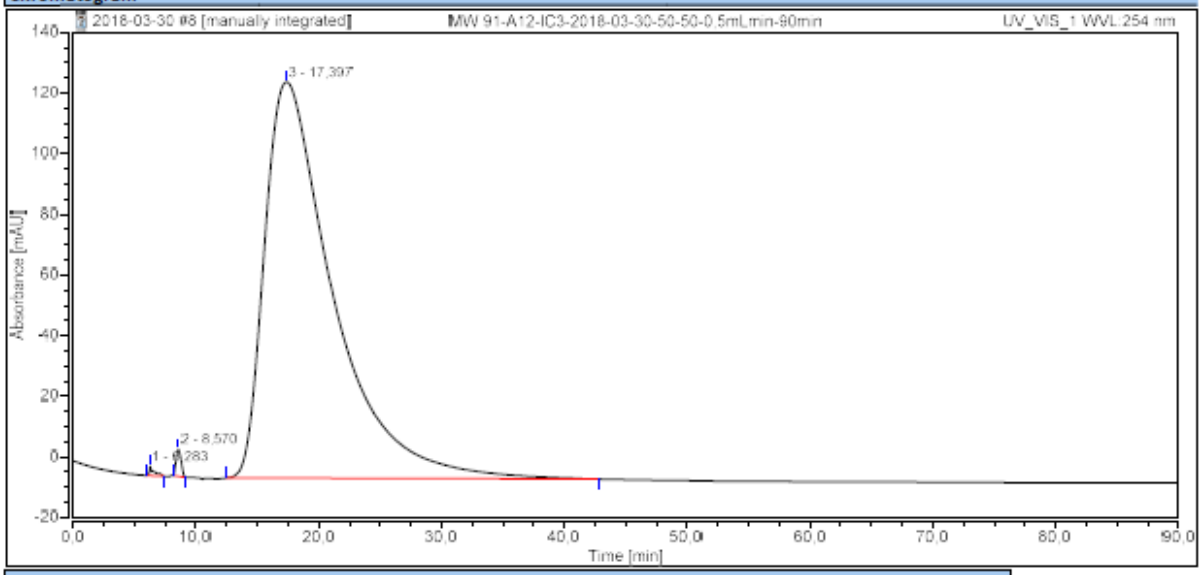
Injection Details

Injection Name:	MW 91-A12-IC3-2018-03-30-50-50-0,5mLmin-90min	*Run Time:*	90,00 min
Instrument Method:	Madani-IC3-50-50-0,5mLmin-90min	*Injection Volume:*	10,00 µL
Injection Date/Time:	30/mars/18 17:29	*Channel:*	UV_VIS_1
		Wavelength:	254 nm

Instrument Method Details

Instrument Method:	Madani-IC3-50-50-0,5mLmin-90min		
%A Isopropanol	50 %		
%B Hexane	50 %	*Température du four:*	20,0 °C
Débit:	0,500 mL/min	*Pression:*	95 bars

Chromatogram



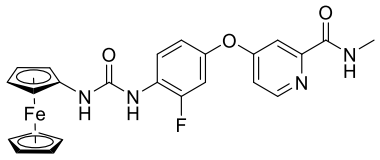
Peak Results

No.	Peak Name	Retention Time min	Width (50%) min	Resolution (EP)	Asymmetry (EP)	Plates (EP)
1		6,283	0,124	4,47	2,41	14134
2		8,570	0,479	1,74	1,22	1770
3		17,397	5,506	n.a.	2,13	55

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %
1		6,283	1,314	3,196	0,15	2,24
2		8,570	4,220	8,956	0,50	6,27
3		17,397	842,274	130,701	99,35	91,49
Total:			**847,808**	**142,854**	**100,00**	**100,00**

Compound 2a



Chimie Organique et Interfaces (CORINT)

Chromatogram and Results

General informations

Sequence Name:	**2018-04-10**
Instrument:	**U3000**
Logiciel used:	**Chromeleon**
Column used:	**CHIRALPAK IC-3 DAICEL** **CHIRALPAK IC DAICEL**

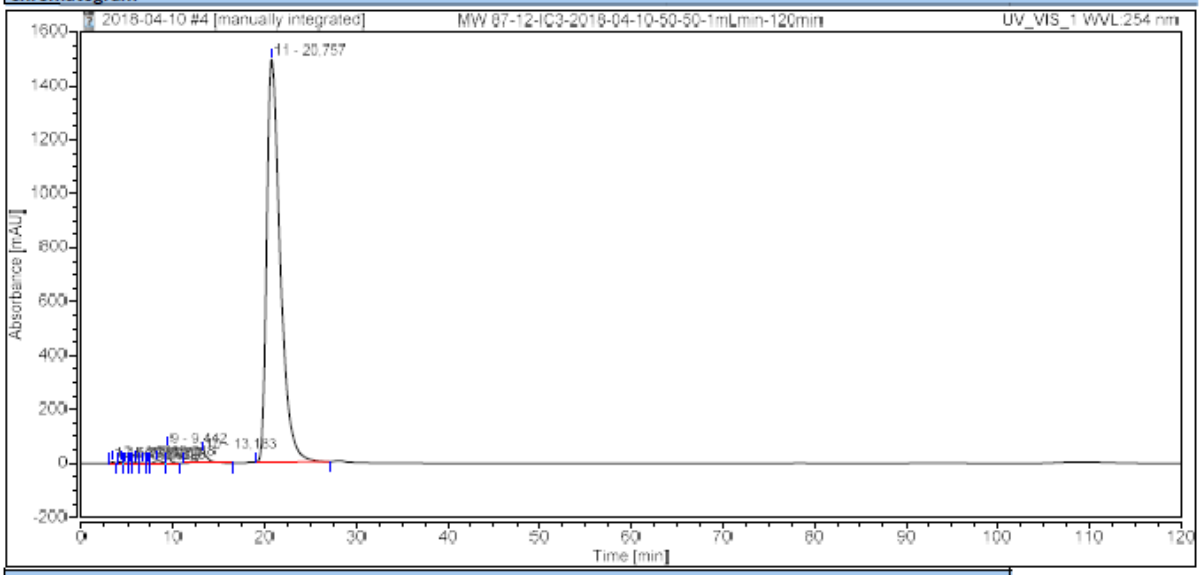
Injection Details

Injection Name:	**MW 87-12-IC3-2018-04-10-50-50-1mLmin-120min**	*Run Time:*	**120,00 min**
Instrument Method:	**Madani-IC3-50-50-1mLmin-120min**	*Injection Volume:*	**10,00 µL**
Injection Date/Time:	**10/avr./18 21:40**	*Channel:*	**UV_VIS_1**
		Wavelength:	**254 nm**

Instrument Method Details

Instrument Method:	**Madani-IC3-50-50-1mLmin-120min**				
%A	**Isopropanol**	**50 %**			
%B	**Hexane**	**50 %**	*Température du four:*	**20,0 °C**	
	Débit:	**1,000 mL/min**	*Pression:*	**200 bars**	

Chromatogram



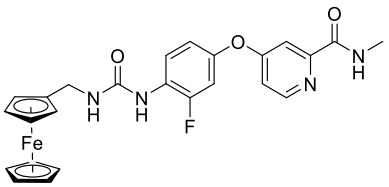
Peak Results

No.	Peak Name	Retention Time min	Width (50%) min	Resolution (EP)	Asymmetry (EP)	Plates (EP)
1		3,332	0,320	1,92	0,95	599
2		4,303	0,278	n.a.	n.a.	1327
3		4,658	n.a.	n.a.	n.a.	n.a.
4		5,278	0,113	2,02	1,14	12019
5		5,820	0,202	2,19	1,71	4581
6		6,677	0,259	1,49	n.a.	3669
7		7,220	0,170	1,14	1,06	9937
8		8,248	0,895	1,19	n.a.	471
9		9,442	0,286	3,31	1,64	6055
10		13,183	1,047	3,46	1,29	878
11		20,757	1,534	n.a.	1,63	1014

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %
1		3,332	1,679	5,180	0,06	0,32
2		4,303	1,764	6,448	0,07	0,40
3		4,658	0,198	0,633	0,01	0,04
4		5,278	0,072	0,622	0,00	0,04
5		5,820	1,123	4,334	0,04	0,27
6		6,677	0,245	1,005	0,01	0,06
7		7,220	0,208	1,174	0,01	0,07
8		8,248	8,427	9,636	0,32	0,60
9		9,442	20,026	58,540	0,76	3,62
10		13,183	47,885	36,693	1,82	2,27
11		20,757	2549,412	1493,796	96,90	92,32
Total:			**2631,039**	**1618,060**	**100,00**	**100,00**

Compound 3a



Chimie Organique et Interfaces (CORINT)

Chromatogram and Results

General informations

Sequence Name:	2018-04-10
Instrument:	U3000
Logiciel used:	Chromeleon
Column used:	CHIRALPAK IC-3 DAICEL

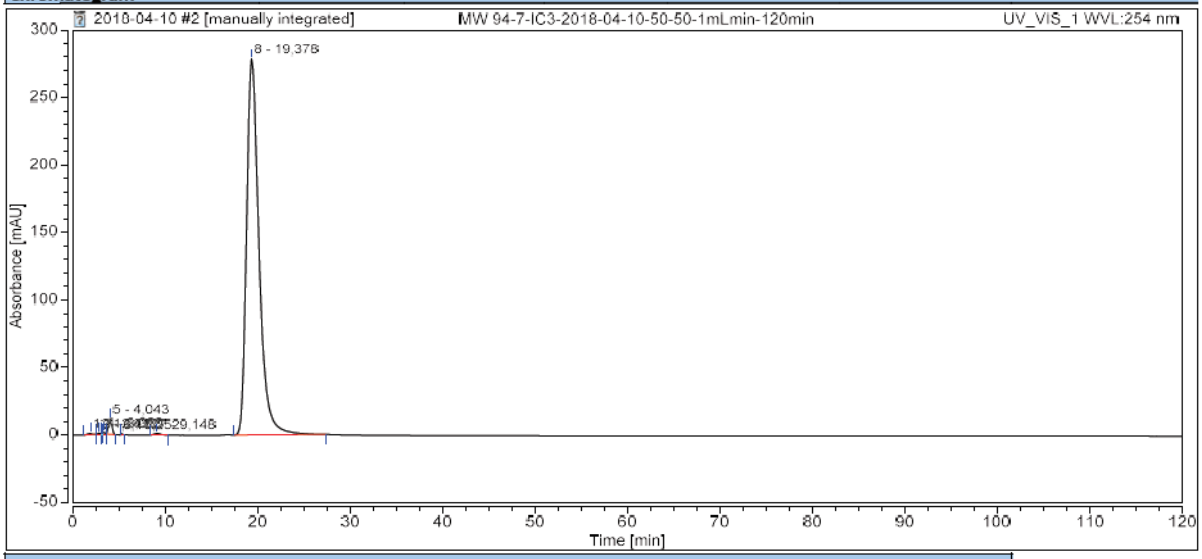
Injection Details

Injection Name:	MW 94-7-IC3-2018-04-10-50-50-1mLmin-120min	*Run Time:*	120,00 min
Instrument Method:	Madani-IC3-50-50-1mLmin-120min	*Injection Volume:*	10,00 µL
Injection Date/Time:	10/avr./18 17:39	*Channel:* UV_VIS_1	
		Wavelength:	254 nm

Instrument Method Details

Instrument Method:	Madani-IC3-50-50-1mLmin-120min				
%A	Isopropanol	50 %			
%B	Hexane	50 %	*Température du four:*	20,0 °C	
	Débit:	1,000 mL/min	*Pression:*	199 bars	

Chromatogram



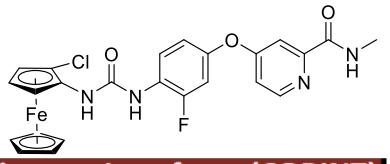
Peak Results

No.	Peak Name	Retention Time min	Width (50%) min	Resolution (EP)	Asymmetry (EP)	Plates (EP)
1		1,942	0,413	1,59	0,99	123
2		2,818	0,239	n.a.	n.a.	770
3		3,112	n.a.	n.a.	n.a.	n.a.
4		3,360	0,279	1,07	n.a.	805
5		4,043	0,475	2,31	1,15	401
6		5,252	0,142	4,88	1,47	7576
7		9,148	0,801	5,55	1,24	723
8		19,378	1,375	n.a.	1,41	1100

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %
1		1,942	0,424	1,055	0,10	0,36
2		2,818	0,228	0,988	0,05	0,33
3		3,112	0,080	0,705	0,02	0,24
4		3,360	0,392	1,447	0,09	0,49
5		4,043	4,479	11,445	1,02	3,86
6		5,252	0,163	1,092	0,04	0,37
7		9,148	0,890	1,125	0,20	0,38
8		19,378	433,349	278,827	98,49	93,98
Total:			**440,005**	**296,684**	**100,00**	**100,00**

Compound 2aCl



Chimie Organique et Interfaces (CORINT)

Chromatogram and Results

General informations

Sequence Name:	**2018-04-26**
Instrument:	**U3000**
Logiciel used:	**Chromeleon**
Column used:	**CHIRALPAK IC-3 DAICEL CHIRALPAK IC DAICEL**

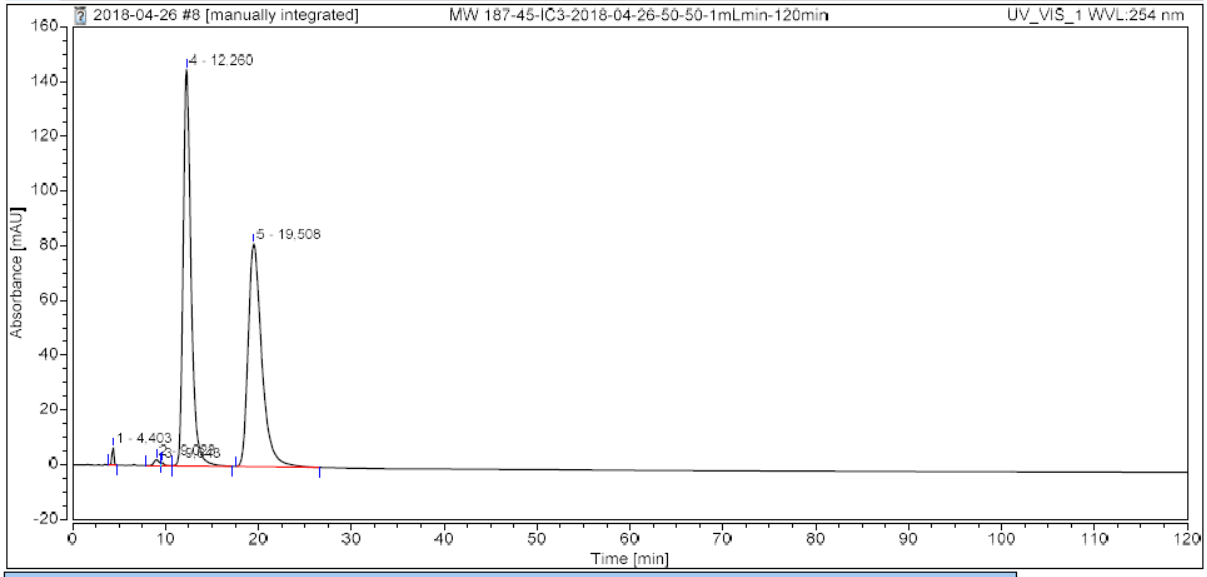
Injection Details

Injection Name:	**MW 187-45-IC3-2018-04-26-50-50-1mLmin-120min**	*Run Time:*	**120,00 min**
Instrument Method:	**Madani-IC3-50-50-1mLmin-120min**	*Injection Volume:*	**10,00 µL**
Injection Date/Time:	**26/avr./18 18:42**	*Channel:*	**UV_VIS_1**
		Wavelength:	**254 nm**

Instrument Method Details

Instrument Method:		**Madani-IC3-50-50-1mLmin-120min**			
%A	**Isopropanol**	**50 %**			
%B	**Hexane**	**50 %**	*Température du four:*	**20,0 °C**	
	Débit:	**1,000 mL/min**	*Pression:*	**199 bars**	

Chromatogram



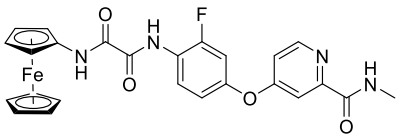
Peak Results

No.	Peak Name	Retention Time min	Width (50%) min	Resolution (EP)	Asymmetry (EP)	Plates (EP)
1		4,403	0,285	5,88	0,79	1324
2		9,023	0,643	n.a.	n.a.	1091
3		9,643	n.a.	n.a.	n.a.	n.a.
4		12,260	0,868	3,61	1,38	1105
5		19,508	1,500	n.a.	1,45	936

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %
1		4,403	1,734	6,341	0,61	2,69
2		9,023	1,429	2,180	0,50	0,92
3		9,643	0,447	1,183	0,16	0,50
4		12,260	143,018	144,948	50,13	61,39
5		19,508	138,693	81,476	48,61	34,50
Total:			**285,321**	**236,128**	**100,00**	**100,00**

Compound 2c



Chimie Organique et Interfaces (CORINT)

Chromatogram and Results

General informations

Sequence Name:	**2018-04-10**
Instrument:	**U3000**
Logiciel used:	**Chromeleon**
Column used:	**CHIRALPAK IC-3 DAICEL CHIRALPAK IC DAICEL**

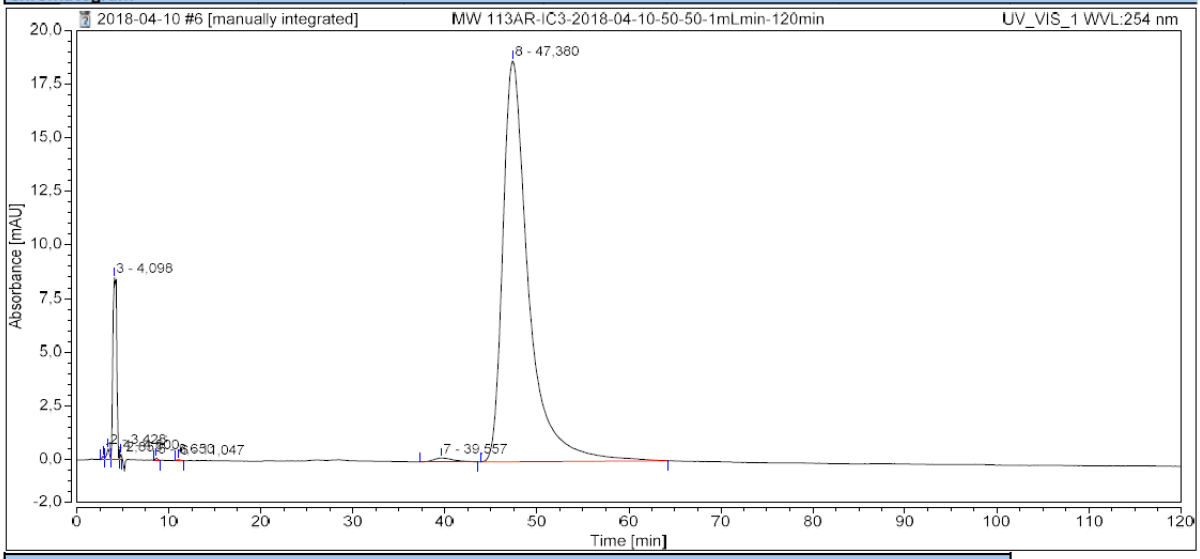
Injection Details

Injection Name:	**MW 113AR-IC3-2018-04-10-50-50-1mLmin-120min**	*Run Time:*	**120,00 min**
Instrument Method:	**Madani-IC3-50-50-1mLmin-120min**	*Injection Volume:*	**10,00 µL**
Injection Date/Time:	**11/avr./18 01:42**	*Channel:*	**UV_VIS_1**
		Wavelength:	**254 nm**

Instrument Method Details

Instrument Method:		**Madani-IC3-50-50-1mLmin-120min**			
%A	**Isopropanol**	**50 %**			
%B	**Hexane**	**50 %**	*Température du four:*	**20,0 °C**	
	Débit:	**1,000 mL/min**	*Pression:*	**201 bars**	

Chromatogram



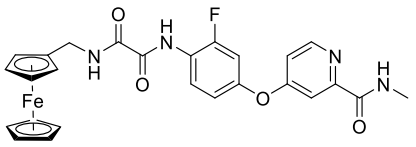
Peak Results

No.	Peak Name	Retention Time min	Width (50%) min	Resolution (EP)	Asymmetry (EP)	Plates (EP)
1		2,853	0,180	1,42	n.a.	1386
2		3,428	0,297	0,96	n.a.	736
3		4,098	0,522	1,28	1,16	341
4		4,800	0,126	12,23	n.a.	8040
5		8,650	0,245	5,21	1,17	6887
6		11,047	0,298	12,97	1,31	7617
7		39,557	2,296	1,86	1,49	1645
8		47,380	2,679	n.a.	1,72	1733

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %
1		2,853	0,035	0,160	0,05	0,56
2		3,428	0,157	0,504	0,24	1,77
3		4,098	4,266	8,463	6,53	29,82
4		4,800	0,034	0,248	0,05	0,87
5		8,650	0,029	0,105	0,04	0,37
6		11,047	0,016	0,045	0,02	0,16
7		39,557	0,483	0,188	0,74	0,66
8		47,380	60,344	18,672	92,32	65,78
Total:			**65,365**	**28,384**	**100,00**	**100,00**

Compound 3c



Chimie Organique et Interfaces (CORINT)

Chromatogram and Results

General informations

Sequence Name:	**2018-04-03**
Instrument:	**U3000**
Logiciel used:	**Chromeleon**
Column used:	**CHIRALPAK IC-3 DAICEL** **CHIRALPAK IC DAICEL**

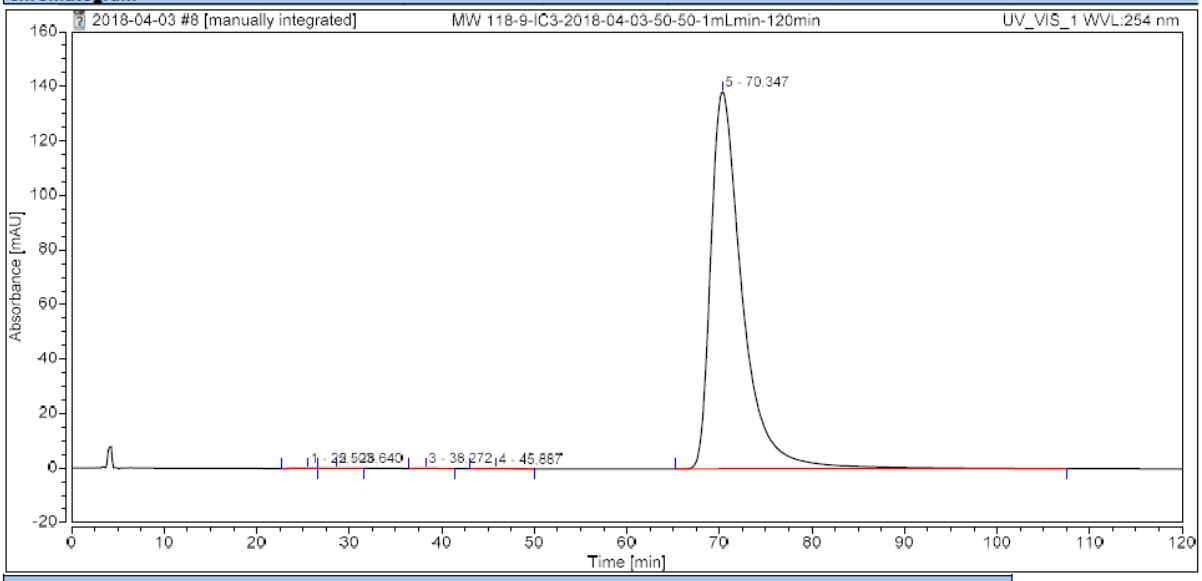
Injection Details

Injection Name:	**MW 118-9-IC3-2018-04-03-50-50-1mLmin-120min**	*Run Time:*	**120,00 min**
Instrument Method:	**Madani-IC3-50-50-1mLmin-120min**	*Injection Volume:*	**10,00 µL**
Injection Date/Time:	**03/avr./18 15:27**	*Channel:*	**UV_VIS_1**
		Wavelength:	**254 nm**

Instrument Method Details

Instrument Method:		**Madani-IC3-50-50-1mLmin-120min**			
%A	**Isopropanol**	**50 %**			
%B	**Hexane**	**50 %**	*Température du four:*	**20,0 °C**	
	Débit:	**1,000 mL/min**	*Pression:*	**200 bars**	

Chromatogram



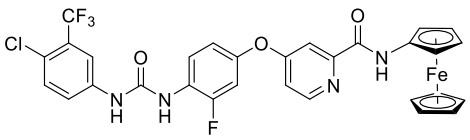
Peak Results

No.	Peak Name	Retention Time min	Width (50%) min	Resolution (EP)	Asymmetry (EP)	Plates (EP)
1		25,503	1,300	0,99	n.a.	2132
2		28,640	2,451	2,56	n.a.	756
3		38,272	1,994	2,63	1,30	2041
4		45,887	1,419	6,02	0,99	5793
5		70,347	3,373	n.a.	1,70	2410

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %
1		25,503	0,101	0,061	0,02	0,04
2		28,640	0,136	0,064	0,02	0,05
3		38,272	0,213	0,105	0,04	0,08
4		45,887	0,085	0,036	0,02	0,03
5		70,347	546,934	138,383	99,90	99,81
Total:			**547,469**	**138,649**	**100,00**	**100,00**

Compound 4a



Chimie Organique et Interfaces (CORINT)

Chromatogram and Results

General informations

Sequence Name:	**2018-03-30**
Instrument:	**U3000**
Logiciel used:	**Chromeleon**
Column used:	**CHIRALPAK IC-3 DAICEL** **CHIRALPAK IC DAICEL**

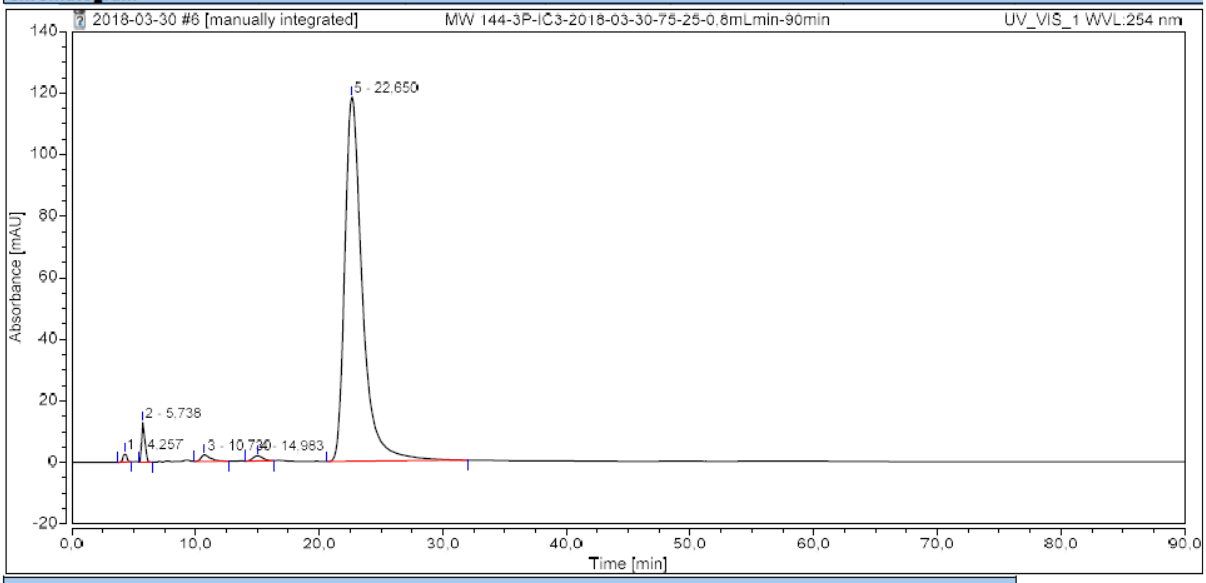
Injection Details

Injection Name:	**MW 144-3P-IC3-2018-03-30-75-25-0,8mLmin-90min**	*Run Time:*	**90,00 min**
Instrument Method:	**Madani-IC3-75-25-0,8mLmin-90min**	*Injection Volume:*	**10,00 µL**
Injection Date/Time:	**30/mars/18 15:28**	*Channel:*	**UV_VIS_1**
		Wavelength:	**254 nm**

Instrument Method Details

Instrument Method:	**Madani-IC3-75-25-0,8mLmin-90min**				
%A	**Isopropanol**	**25 %**			
%B	**Hexane**	**75 %**	*Température du four:*	**20,0 °C**	
	Débit:	**0,800 mL/min**	*Pression:*	**88 bars**	

Chromatogram



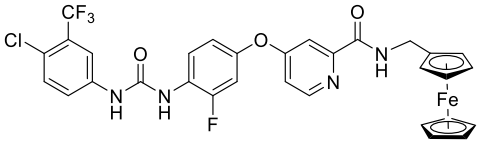
Peak Results

No.	Peak Name	Retention Time min	Width (50%) min	Resolution (EP)	Asymmetry (EP)	Plates (EP)
1		4,257	0,383	2,63	1,01	683
2		5,738	0,282	5,68	1,48	2297
3		10,730	0,754	3,13	1,71	1121
4		14,983	0,850	3,99	1,19	1722
5		22,650	1,416	n.a.	1,50	1418

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %
1		4,257	1,006	2,668	0,49	1,94
2		5,738	3,798	12,840	1,87	9,32
3		10,730	1,865	2,103	0,92	1,53
4		14,983	1,480	1,659	0,73	1,20
5		22,650	195,445	118,422	96,00	86,01
Total:			**203,594**	**137,692**	**100,00**	**100,00**

Compound 5a



Chimie Organique et Interfaces (CORINT)

Chromatogram and Results

General informations

Sequence Name:	**2018-04-10**
Instrument:	**U3000**
Logiciel used:	**Chromeleon**
Column used:	**CHIRALPAK IC-3 DAICEL** **CHIRALPAK IC DAICEL**

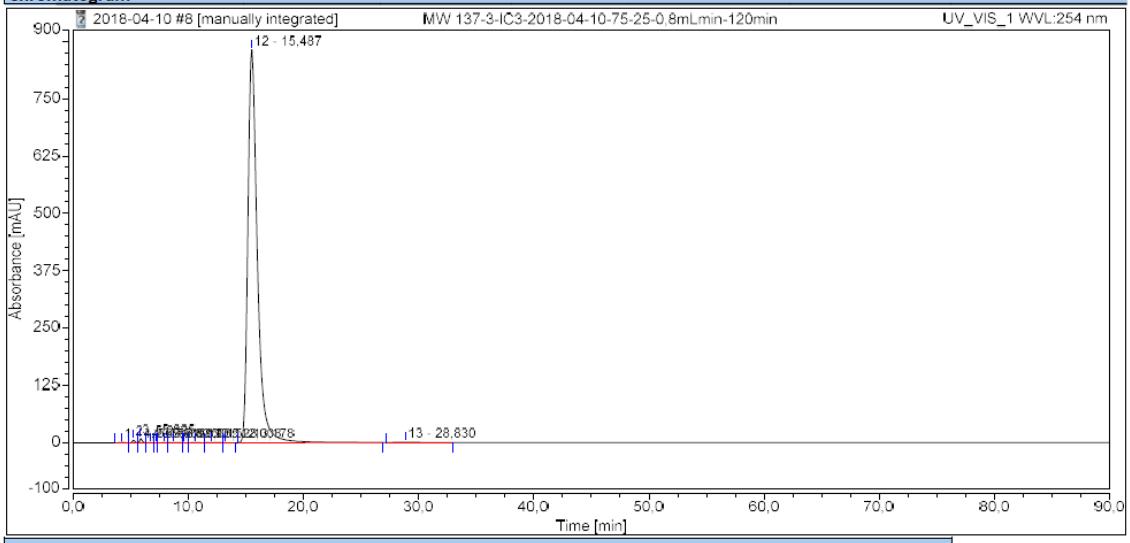
Injection Details

Injection Name:	**MW 137-3-IC3-2018-04-10-75-25-0,8mLmin-120min**	*Run Time:*	**90,00 min**
Instrument Method:	**Madani-IC3-75-25-0,8mLmin-90min**	*Injection Volume:*	**10,00 µL**
Injection Date/Time:	**11/avr./18 05:13**	*Channel:*	**UV_VIS_1**
		Wavelength:	**254 nm**

Instrument Method Details

Instrument Method:	**Madani-IC3-75-25-0,8mLmin-90min**			
%A	**Isopropanol**	**25 %**		
%B	**Hexane**	**75 %**	*Température du four:*	**20,0 °C**
	Débit:	**0,800 mL/min**	*Pression:*	**88 bars**

Chromatogram



Peak Results

No.	Peak Name	Retention Time min	Width (50%) min	Resolution (EP)	Asymmetry (EP)	Plates (EP)
1		4,205	0,338	2,25	n.a.	859
2		5,213	0,191	1,81	n.a.	4132
3		5,825	0,207	1,78	1,16	4377
4		6,665	0,351	0,93	n.a.	1997
5		7,132	0,242	1,37	n.a.	4804
6		7,835	0,366	0,98	n.a.	2541
7		8,637	0,600	1,32	n.a.	1150
8		9,565	0,233	1,38	n.a.	9298
9		10,528	0,593	1,12	n.a.	1749
10		12,008	0,970	n.a.	n.a.	849
11		13,178	n.a.	n.a.	n.a.	n.a.
12		15,487	0,828	6,07	1,48	1938
13		28,830	1,764	n.a.	1,41	1480

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %
1		4,205	0,406	0,997	0,05	0,11
2		5,213	1,478	6,533	0,18	0,74
3		5,825	2,164	9,621	0,26	1,10
4		6,665	0,139	0,370	0,02	0,04
5		7,132	0,034	0,166	0,00	0,02
6		7,835	0,258	0,656	0,03	0,07
7		8,637	0,475	0,696	0,06	0,08
8		9,565	0,088	0,312	0,01	0,04
9		10,528	0,400	0,585	0,05	0,07
10		12,008	0,358	0,358	0,04	0,04
11		13,178	0,078	0,123	0,01	0,01
12		15,487	821,094	856,454	99,09	97,57
13		28,830	1,688	0,872	0,20	0,10
Total:			**828,662**	**877,743**	**100,00**	**100,00**

Titration curves for IC_{50} determination

Compound 1a

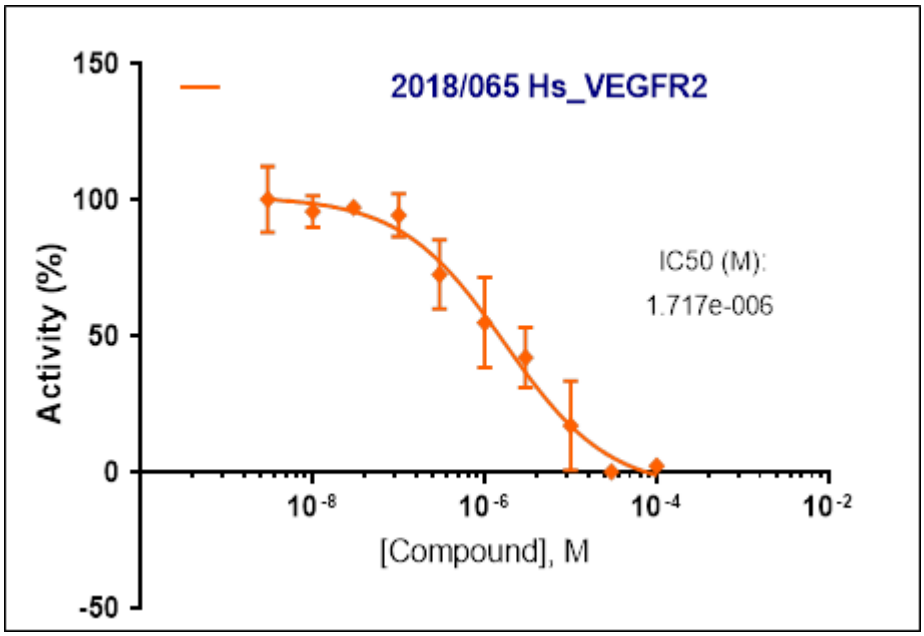


Figure 10.

Compound 2aCl

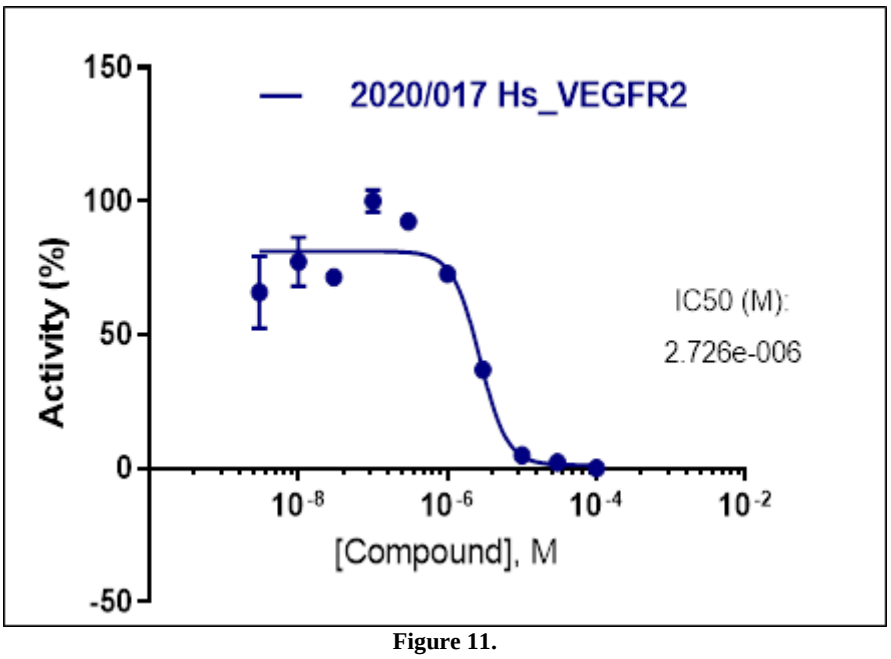


Figure 11.

Compound 3a

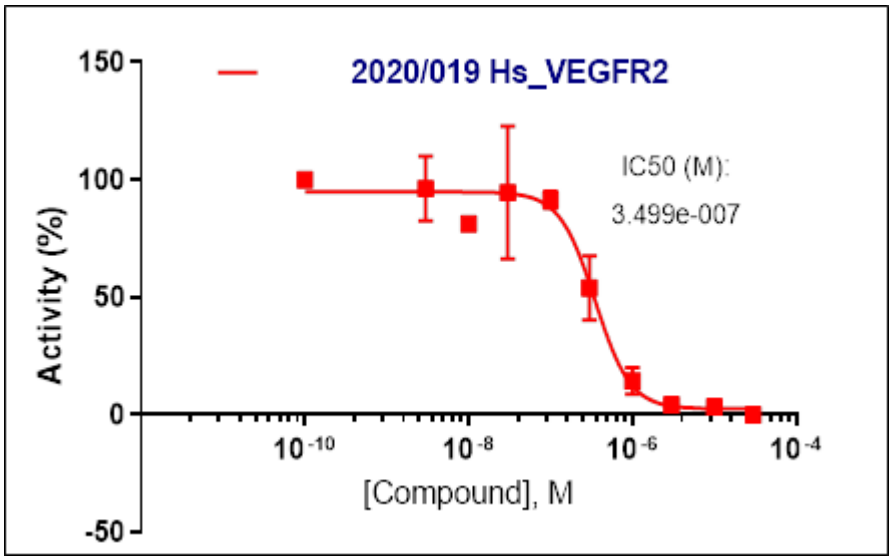


Figure 12.

Compound 4a

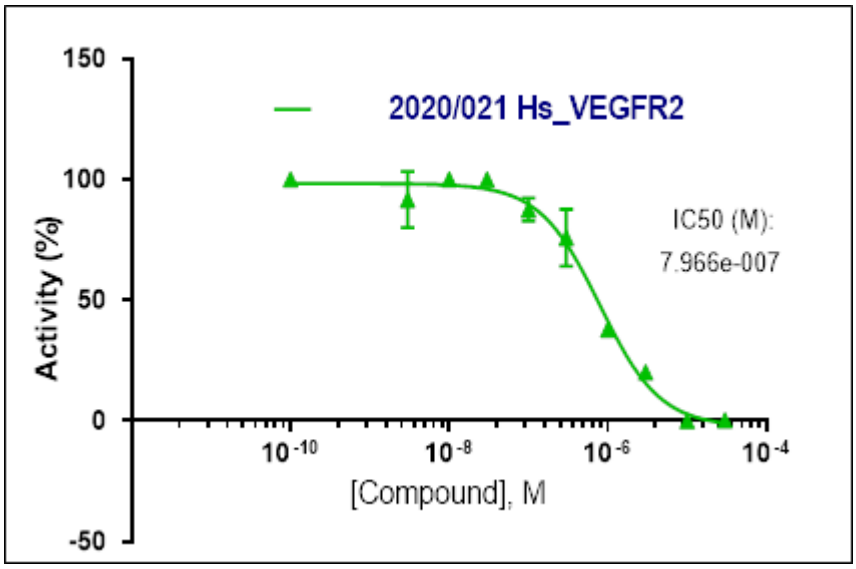


Figure 13.

Compound 5a

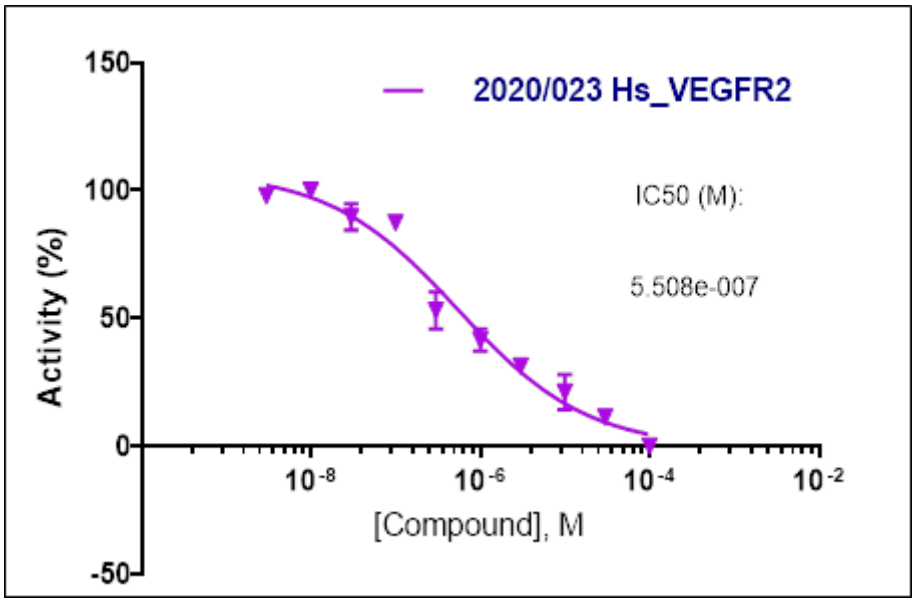


Figure 14.

Activity curves on cell lines

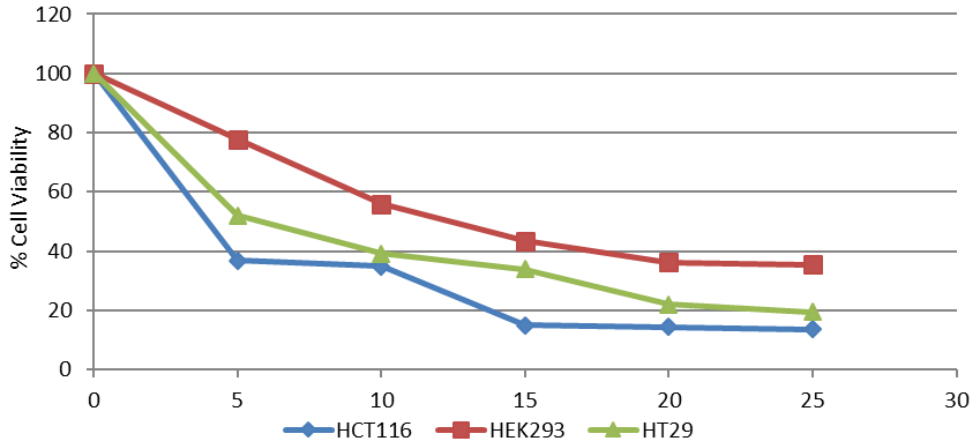


Figure 15. Cell viability (% of control) was measured using the MTT test after exposure of the cells to compound **1a** at the concentrations indicated for 48h.

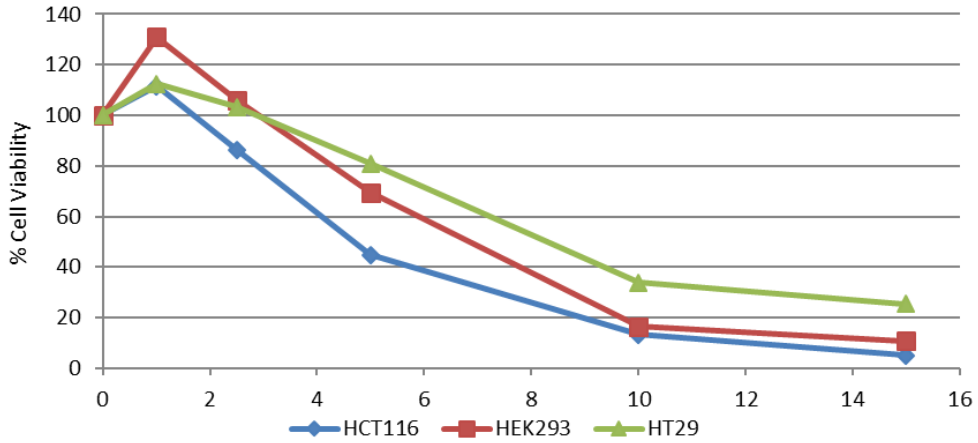


Figure 16. Cell viability (% of control) was measured using the MTT test after exposure of the cells to compound **1b** at the concentrations indicated for 48h.

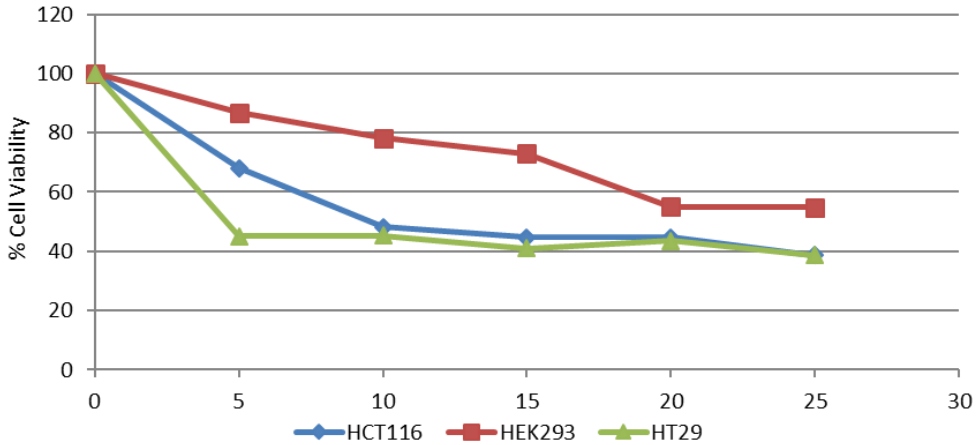


Figure 17. Cell viability (% of control) was measured using the MTT test after exposure of the cells to compound **3a** at the concentrations indicated for 48h.

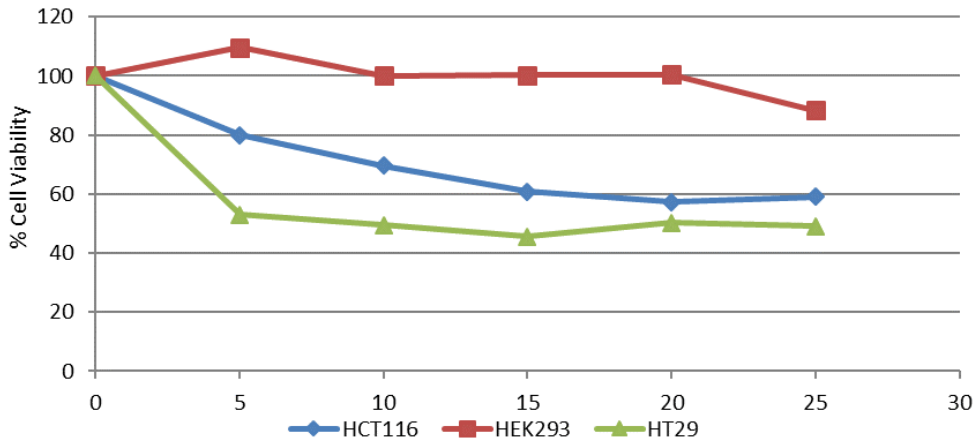


Figure 18. Cell viability (% of control) was measured using the MTT test after exposure of the cells to compound **2aCl** at the concentrations indicated for 48h.

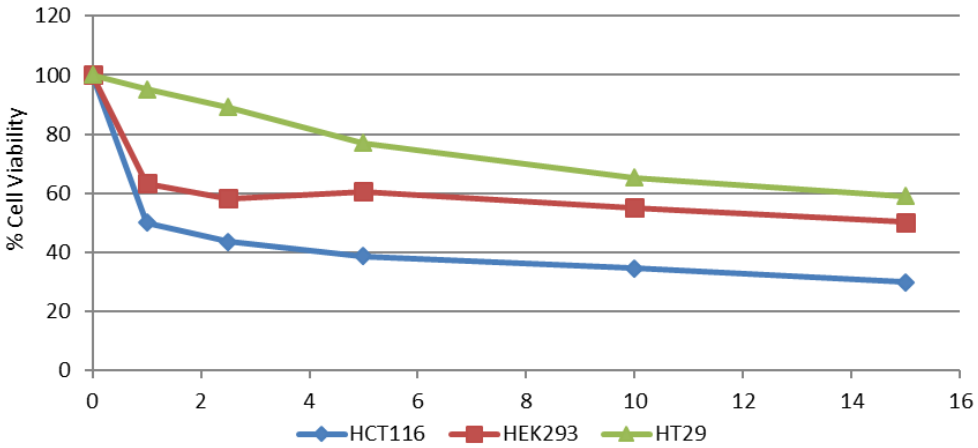


Figure 19. Cell viability (% of control) was measured using the MTT test after exposure of the cells to compound **3c** at the concentrations indicated for 48h.

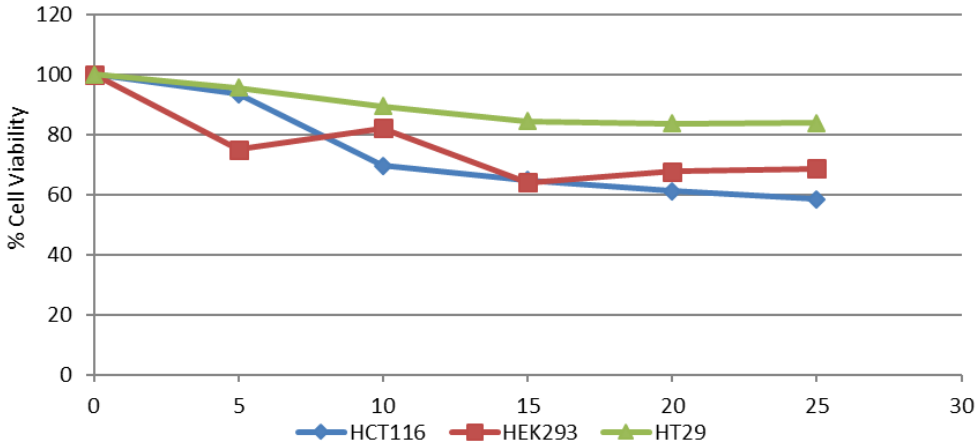


Figure 20. Cell viability (% of control) was measured using the MTT test after exposure of the cells to compound **4a** at the concentrations indicated for 48h.

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