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The Castagnoli–Cushman reaction of bicyclic pyrrole dicarboxylic anhydrides bearing electron-withdrawing substituents

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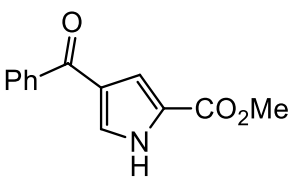
1. General information

All commercial reagents and solvents were used without further purification, unless otherwise noted. 1,2-Dichloroethane (DCE) was distilled over P_2O_5 and stored over molecular sieves 4Å. NMR spectroscopic data were recorded with a 400 MHz (400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C) spectrometer in DMSO-d_6 or in $CDCl_3$ and were referenced to residual solvent proton signals (δ_H = 2.50 and 7.26 ppm, respectively) and solvent carbon signals (δ_C = 39.5 and 77.2 ppm, respectively); multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Mass spectra were recorded with a HRMS-ESI-qTOF spectrometer (electrospray ionization mode). For TLC analysis UV254 silica gel coated plates were used. Preparative HPLC was carried out on Shimadzu LC-20AP chromatograph, equipped with spectrophotometric detector. Column: Agilent Zorbax prepHT XDB-C18, 5μm, 21.2×150mm. Eluent: H_2O–MeCN (with addition 0.1% TFA). Flow rate 12 ml min^{-1}, temperature – 40 °C, detection UV at 214 and 254 nm. Injection volume ~ 500μl.

2. Preparation of anhydrides 2a-d

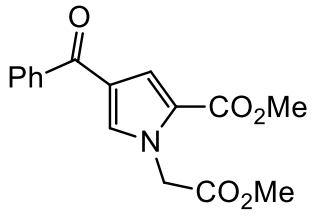
Methyl 4-benzoyl-1*H*-pyrrole-2-carboxylate [S1]



To an ice cooled solution of benzoyl chloride (5.62 g, 40 mmol, 2 equiv.) in DCE (50 ml). aluminium chloride (5.32 g, 40 mmol, 2 equiv.) was added. To the resulting solution at 0 °C,a solution of methyl 1*H*-pyrrole-2-carboxylate (2.5 g, 20 mmol) in DCE (50 ml) was added dropwise, and the mixture was slowly warmed to ambient temperature. Upon stirring for 15 min at ambient temperature, the mixture was refluxed for 2.5 hours, then cooled to ambient temperature and poured into crushed ice. The

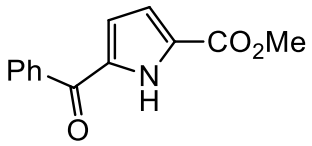
resulting suspension was extracted with EtOAc (2×50 ml), the organic phase was washed $NaHCO_3$ (30 ml), brine, dried over anhydrous Na_2SO_4. The solution was evaporated *in vacuo*. The obtained ester was used in the next step without further purification. Yield 2.7 g (60%), light grey solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.65 (br.s, 1H), 7.87 (d, *J* = 7.0 Hz, 2H), 7.61 – 7.57 (m, 2H), 7.53 – 7.48 (m, 2H), 7.38 (dd, *J* = 2.5, 1.6 Hz, 1H), 3.92 (s, 3H).

Methyl 4-benzoyl-1-(2-methoxy-2-oxoethyl)-1*H*-pyrrole-2-carboxylate



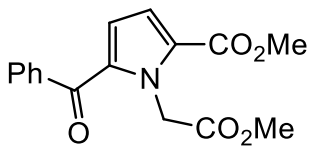
To a solution of methyl 4-benzoyl-1*H*-pyrrole-2-carboxylate (2.97 g, 13 mmol) in dry DMF (20 ml) at 0 °C, sodium hydride (60% dispersion in mineral oil, 623 mg, 15.6 mmol, 1.2 equiv.) was added. The mixture was stirred at 0 °C for 15 min, then methyl bromoacetate (2.19 g, 14.3 mmol, 1.1 equiv.) was added dropwise. The reaction mixture was stirred at 0 °C for 30 min, slowly warmed to ambient temperature, and stirred at 80 °C for 16 hours. Upon cooling to the ambient temperature, the resulting mixture was diluted with water (40 ml), and extracted with EtOAc (2×25 ml). The organic phase was washed with brine (2×15 ml), dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The obtained diester was used in the next step without further purification. Yield 3.15 g (80%), light brown viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 7.0 Hz, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 2H), 7.45 (q, *J* = 1.9 Hz, 1H), 5.11 (s, 2H), 3.85 (s, 3H), 3.82 (s, 3H).

Methyl 5-benzoyl-1*H*-pyrrole-2-carboxylate



To an ice-cooled solution of benzoyl chloride (2.8 g, 20 mmol, 2 equiv.) in DCE (5 ml) under argon, anhydrous zinc chloride (2.72 g, 20 mmol, 2 equiv.) was added. Then a solution of methyl 1*H*-pyrrole-2-carboxylate (1.25 g, 10 mmol) in DCE (15 ml) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 20 min, slowly heated to 50 °C and stirred for 20 h. Upon cooling, the resulting mixture was poured into crushed ice. The organic layer was separated, and the aqueous phase was extracted with DCM (3×20 ml). The combined organic phases were washed with HCl (1 M, 50 ml), brine (50 ml), dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The product was purified by column chromatography on silica gel eluting with *n*-hexane–EtOAc (5:1 to 3:1). Yield 1.22 g (53%), beige amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.09 (br.s, 1H), 7.93 (d, *J* = 6.9 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 2H), 6.97 (dd, *J* = 4.1, 2.6 Hz, 1H), 6.87 (dd, *J* = 4.1, 2.6 Hz, 1H), 3.95 (s, 3H).

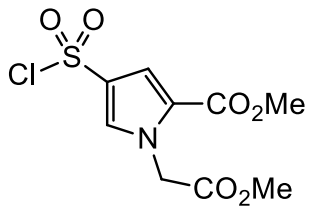
Methyl 5-benzoyl-1-(2-methoxy-2-oxoethyl)-1*H*-pyrrole-2-carboxylate



To a solution of methyl 5-benzoyl-1*H*-pyrrole-2-carboxylate (1.21 g, 5.3 mmol) in dry DMF (15 ml), NaH (60% suspension in mineral oil, 254 mg, 6.3 mmol, 1.2 equiv.) was added at 0 °C. The mixture was stirred at 0 °C for 15 min, then methyl bromoacetate (890 mg, 5.8 mmol, 1.1. equiv.) was added dropwise. The mixture was stirred at 0 °C for 30 min, slowly warmed to ambient temperature, and stirred at 80 °C for 16 hours. The resulting mixture was cooled to ambient

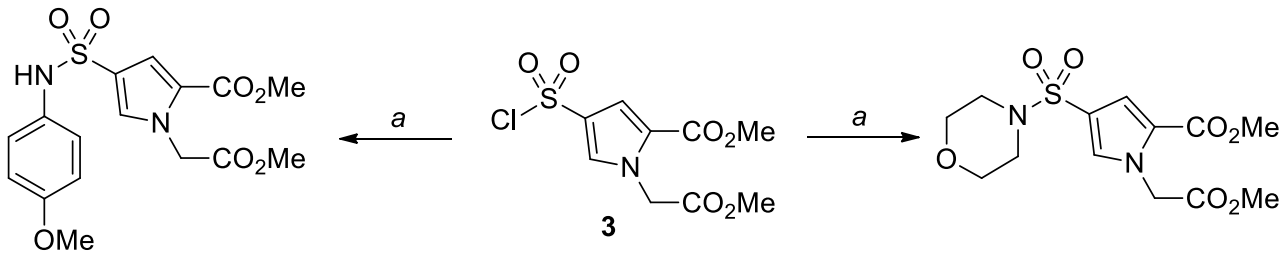
temperature, diluted with water (30 ml) and extracted with EtOAc (2×30 ml). The organic phase was washed with brine (2×15 ml), dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The obtained diester was used in the next step without further purification. Yield 1.2 g (77%), light orange amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 6.9 Hz,2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.01 (d, *J* = 4.3 Hz, 1H), 6.73 (d, *J* = 4.3 Hz, 1H), 5.74 (s, 2H), 3.89 (s, 3H), 3.81 (s, 3H).

Methyl 4-chlorosulfonyl-1-(2-methoxy-2-oxoethyl)-1*H*-pyrrole-2-carboxylate (3)



To ice-cooled chlorosulfonic acid (7.3 ml, 110 mmol, 10 equiv.) under stirring the solution of methyl 1-(2-methoxy-2-oxoethyl)-1*H*-pyrrole-2-carboxylate [S2] (2.2 g, 11 mmol) in DCM (5 ml) was added dropwise for 10 min. The resulting solution was stirred in the bath for 2.5 hours (TLC control). Thionyl chloride (1.5 ml, 22 mmol, 2 equiv.) was added, and the mixture was stirred at room temperature for 2 hours. The resulting mixture was slowly poured into crushed ice and extracted with DCM (3×25 ml). The organic phase was washed with water (2×25 ml) and brine (20 ml), dried over $CaCl_2$, filtered through a short pad of SiO_2 and evaporated. Yield 3.22 g (98%), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 1.9 Hz, 1H), 7.42 (d, *J* = 1.9 Hz, 1H), 5.12 (s, 2H), 3.88 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.4, 160.4, 131.1, 127.7, 124.5, 116.3, 53.0, 52.2, 51.1. HRMS *m/z* calcd for $C_9H_{11}ClNO_6S$ $[M+H]^+$: 295.9990, found 295.9984.

General procedure for the preparation of sulfonamides (GP1)

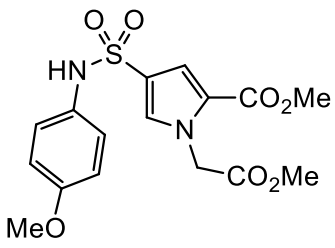


a, morpholine or *p*-anisidine, Et_3N, DCM, 0 °C to r. t.

To an ice-cooled solution of the corresponding amine (morpholine or *p*-anisidine, 3 mmol) and triethylamine (454 mg, 4.5 mmol) in DCM (10 ml), sulfonyl chloride **3** (888 mg, 3 mmol) was added under stirring. The mixture was left under stirring for 16 hours, then diluted with DCM (20 ml) and water (20 ml), the organic phase was washed with 5% HCl (15 ml), sat. aq. $NaHCO_3$ (15 ml), dried over $CaCl_2$ and evaporated to dryness. The residual crude material was crystallized from *n*-hexane–acetone mixture.

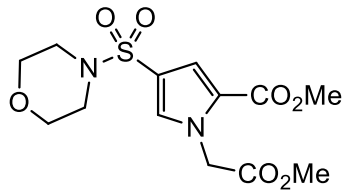
Methyl 1-(2-methoxy-2-oxoethyl)-4-[*N*-(4-methoxyphenyl)sulfamoyl]-1*H*-pyrrole-2-carboxylate

Prepared according to GP1 using *p*-anisidine; yield 825 mg (72%), light grey solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (d, *J* = 1.9 Hz, 1H), 7.09 (d, *J* = 1.9 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.49 (s, 1H), 4.98 (s, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ



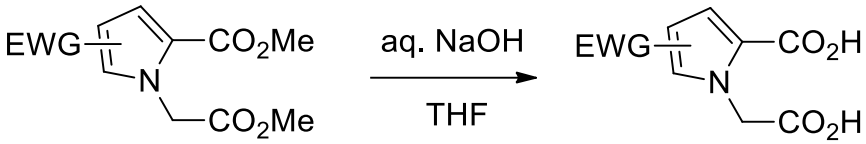
167.9, 160.8, 158.1, 131.0, 128.9, 125.8, 123.8, 122.2, 116.5, 114.5, 55.4, 52.7, 51.8, 50.7. HRMS *m/z* calcd for $C_{16}H_{18}N_2NaO_7S$ $[M+Na]^+$: 405.0727, found 405.0731.

Methyl 1-(2-methoxy-2-oxoethyl)-4-morpholinosulfonyl-1*H*-pyrrole-2-carboxylate

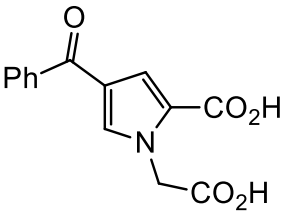


Prepared according to GP1 using morpholine; yield 802 mg (77%), white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, *J* = 1.9 Hz, 1H), 7.17 (d, *J* = 1.9 Hz, 1H), 5.10 (s, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 3.80 – 3.76 (m, 4H), 3.05 – 2.99 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9, 160.7, 131.1, 124.2, 118.0, 116.9, 66.0, 52.8, 51.9, 50.8, 45.9. HRMS *m/z* calcd for $C_{13}H_{19}N_2O_7S$ $[M+H]^+$: 347.0907, found 347.0914.

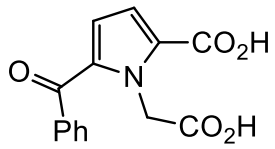
General procedure for the hydrolysis of diesters to prepare diacids (GP2)



To a solution of diester (2.0 mmol) in THF (5 ml), a solution of NaOH (240 mg, 6.0 mmol, 3 equiv.) in water (8 ml) was added. The mixture was stirred at ambient temperature for 20 hours, then 1 N HCl was added to adjust pH to 2. The resulting mixture was extracted with EtOAc (2×10 ml). The organic layer was washed brine (10 ml), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*.

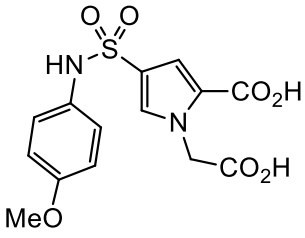


5-Benzoyl-1-carboxymethyl-1*H*-pyrrole-2-carboxylic acid was prepared according to GP2 from methyl 4-benzoyl-1-(2-methoxy-2-oxoethyl)-1*H*-pyrrole-2-carboxylate; yield 460 mg (84%), light grey solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.87 (br.s, 2H), 7.82 – 7.75 (m, 3H), 7.64 (t, *J* = 7.3 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 2H), 7.20 (d, *J* = 1.9 Hz, 1H), 5.12 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 189.2, 170.2, 162.1, 139.2, 135.7, 132.4, 129.0, 128.9, 125.0, 122.4, 118.1, 51.1. HRMS *m/z* calcd for $C_{14}H_{11}NNaO_5$ $[M+Na]^+$: 296.0529, found 296.0529.

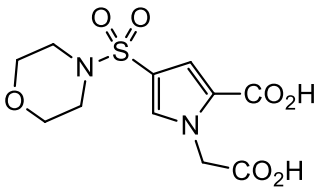


4-Benzoyl-1-carboxymethyl-1*H*-pyrrole-2-carboxylic acid was prepared according to GP2 from methyl 5-benzoyl-1-(2-methoxy-2-oxoethyl)-1*H*-pyrrole-2-carboxylate; yield 448 mg (82%), pale pink solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.00 (br.s, 2H), 7.76 (d, *J* = 6.8 Hz, 2H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 2H), 6.93 (d, *J* = 4.2 Hz, 1H), 6.68 (d, *J* = 4.2 Hz, 1H), 5.52 (s, 2H). HRMS *m/z* calcd for $C_{14}H_{11}NNaO_5$ $[M+Na]^+$: 296.0529, found 296.0533.

1-Carboxymethyl-4-[*N*-(4-methoxyphenyl)sulfamoyl]-1*H*-pyrrole-2-carboxylic acid was prepared according to GP2 from methyl 1-(2-methoxy-2-oxoethyl)-4-[*N*-(4-methoxyphenyl)sulfamoyl]-1*H*-pyrrole-2-carboxylate; yield 637 mg (90%), light lilac solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.89 (br.s, 2H), 9.63 (s, 1H), 7.51 (d, *J* = 2.0 Hz, 1H), 7.03 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 2.0 Hz,



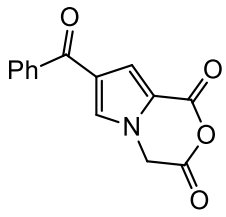
1H), 6.82 (d, *J* = 9.0 Hz, 2H), 5.02 (s, 2H), 3.69 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 169.9, 161.6, 156.8, 131.6, 131.1, 124.6, 123.7, 122.1, 115.4, 114.7, 55.6, 50.9. HRMS *m/z* calcd for $C_{14}H_{15}N_2O_7S$ $[M+H]^+$: 355.0594, found 355.0501.



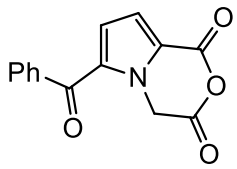
1-Carboxymethyl-4-morpholinosulfonyl-1*H*-pyrrole-2-carboxylic acid was prepared according to GP2 from methyl 1-(2-methoxy-2-oxoethyl)-4-morpholinosulfonyl-1*H*-pyrrole-2-carboxylate; yield 560 mg (88%), white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.00 (br.s, 2H), 7.70 (d, *J* = 2.0 Hz, 1H), 6.98 (d, *J* = 2.0 Hz, 1H), 5.11 (s, 2H), 3.70 – 3.60 (m, 4H), 2.89 – 2.75 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 169.9, 161.6, 132.4, 125.1, 116.2, 115.9, 65.6, 51.1, 46.3. HRMS *m/z* calcd for $C_{11}H_{14}N_2NaO_7S$ $[M+Na]^+$: 341.0414, found 341.0422.

General procedure for the preparation of anhydrides 2a-d from diacids (GP3)

To a suspension of corresponding diacid (2.0 mmol) in EtOAc (10 ml), trifluoroacetic anhydride (924 mg, 4.4 mmol, 2.2 equiv.) was added. The mixture was stirred at ambient temperature for 24 hours and evaporated *in vacuo*. The crude material was washed with *n*-hexane (2×5 ml), filtered and dried *in vacuo*.

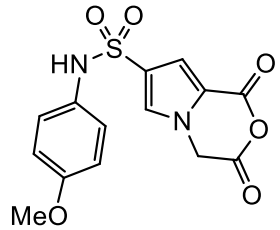


7-Benzoyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-1,3(4*H*)-dione (2a) was prepared according to GP3 from 5-benzoyl-1-carboxymethyl-1*H*-pyrrole-2-carboxylic acid; yield 450 mg (88%), pale beige solid. The fast hydrolysis takes place when NMR spectra are registered. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 7.6 Hz, 2H), 7.71 (s, 1H), 7.66 – 7.63 (m, 2H), 7.56 – 7.53 (m, 2H), 5.16 (s, 2H).



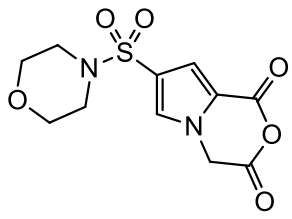
6-Benzoyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-1,3(4*H*)-dione (2b) was prepared according to GP3 from 4-benzoyl-1-(carboxymethyl)-1*H*-pyrrole-2-carboxylic acid; yield 388 mg (76%), light orange semi-solid. The fast hydrolysis takes place when NMR spectra are registered. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 – 7.84 (m, 2H), 7.69 (t, *J* = 7.4 Hz, 1H), 7.58 – 7.54 (m, 2H), 7.35 (d, *J* = 4.4 Hz, 1H), 7.01 (d, *J* = 4.4 Hz, 1H), 5.59 (s, 2H).

***N*-(4-Methoxyphenyl)-1,3-dioxo-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-7-sulfonamide (2c)**



Prepared according to GP3 from 1-(carboxymethyl)-4-(*N*-(4-methoxyphenyl)sulfamoyl)-1*H*-pyrrole-2-carboxylic acid; yield 618 mg (92%), light grey solid. The fast hydrolysis takes place when NMR spectra are registered. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.87 (s, 1H), 7.67 (d, *J* = 1.7 Hz, 1H), 7.16 (d, *J* = 1.7 Hz, 1H), 7.07 (d, *J* = 9.0 Hz, 2H), 6.85 (d, *J* = 9.0 Hz, 2H), 5.12 (s, 2H), 3.69 (s, 3H).

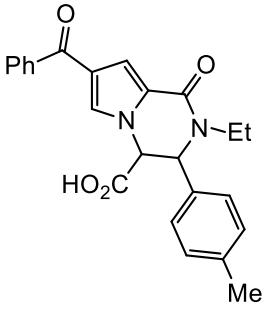
7-Morpholinosulfonyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-1,3(4*H*)-dione (2d) was prepared according to GP3 from 1-(carboxymethyl)-4-(morpholinosulfonyl)-1*H*-pyrrole-2-carboxylic acid; yield 534 mg (89%), white solid. The fast hydrolysis takes place when NMR spectra are registered. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.83 (d, *J* = 1.7 Hz, 1H), 7.35 (d, *J* = 1.7 Hz, 1H), 5.23 (s, 2H), 3.68 – 3.65 (m, 4H), 2.90 – 2.84 (m, 4H).



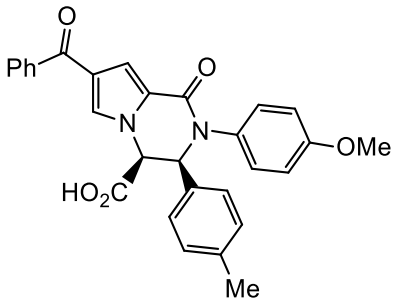
3. Preparation of compounds 5a-i (general procedure GP4)

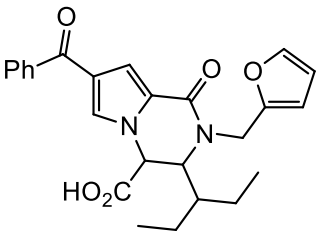
Anhydride **2** (0.2 mmol) was added to a solution of the imine **4** (0.2 mmol) in DCE (0.3 ml), and this was stirred at room temperature overnight. The mixture was then evaporated *in vacuo*. The product was purified by HPLC; eluent: A) 0.1% TFA in water, B) 0.1% TFA in acetonitrile; gradient: 20 % B (0 –5 min), 20–90 % B (5 – 40 min), 90–95 % B (40 – 50 min).

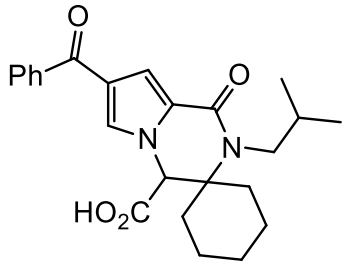
7-Benzoyl-2-ethyl-1-oxo-3-(*p*-tolyl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (5a) was prepared according to GP4 from anhydride **2a** and imine **4a** as mixture of *E*/*Z*-diastereomers (*dr* 6:1); the retention time 21–23 min; yield 51 mg (74%); colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (signals of major diastereomer) 13.93 (br.s, 1H), 7.71 (d, *J* = 6.9 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.55 (d, *J* = 1.8 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 7.06 (d, *J* = 1.8 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 2H), 5.46 (s, 1H), 5.37 (s, 1H), 3.98 (dq, *J* = 14.0, 7.1 Hz, 1H), 2.85 (dq, *J* = 14.0, 7.1 Hz, 1H), 2.24 (s, 3H), 1.05 (t, *J* = 7.1 Hz, 3H); (observed signals of minor diastereomer) 7.78 (d, *J* = 7.5 Hz, 2H), 7.09 (d, *J* = 7.9 Hz, 2H), 6.92 (d, *J* = 8.1 Hz, 2H), 5.63 (d, *J* = 5.0 Hz, 1H), 5.19 (d, *J* = 5.0 Hz, 1H), 3.78 – 3.67 (m, 1H), 3.12 – 3.01 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (signals of major diastereomer) 189.2, 169.9, 157.8, 139.2, 138.0, 135.6, 132.3, 131.1, 130.0, 129.0, 228.8, 126.4, 124.4, 112.9, 62.8, 61.1, 21.0, 13.7; (observed signals of minor diastereomer) 182.9, 167.5, 157.3, 139.3, 138.5, 135.5, 133.48, 133.47, 129.6, 129.0, 128.9, 128.04, 128.03, 126.3, 124.3, 113.0, 61.2, 21.1. HRMS *m/z* calcd for $C_{24}H_{23}N_2O_4^+$ $[M+H]^+$: 403.1652, found 403.1660.

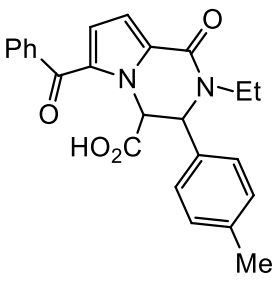


7-Benzoyl-2-(4-methoxyphenyl)-1-oxo-3-(*p*-tolyl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (5b) was prepared according to GP4 from anhydride **2a** and imine **4b** as a single *Z*-diastereomer; retention time 23–25 min; yield 45 mg (57%); colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.96 (br.s, 1H), 7.88 (d, *J* = 1.8 Hz, 1H), 7.81 (d, *J* = 6.9 Hz, 2H), 7.65 (t, 7.4 Hz, 1H), 7.56 (t, *J* = 7.4 Hz, 2 H), 7.26 (d, *J* = 1.8 Hz, 1H), 7.09 (t, *J* = 8.9 Hz, 4H), 6.90 (d, *J* = 8.7 Hz, 4H), 5.95 (d, *J* = 4.8 Hz, 1H), 5.33 (d, *J* = 4.9 Hz, 1H), 3.73 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 189.3, 167.4, 158.4, 157.3, 139.2, 138.5, 133.8, 132.9, 132.5, 131.5, 129.7, 129.1, 129.0, 128.0, 126.6, 124.5, 114.5, 114.4, 65.5, 60.5, 55.7, 21.1. HRMS *m/z* calcd for $C_{29}H_{25}N_2O_5^+$ $[M+H]^+$: 481.1758, found 481.1750.



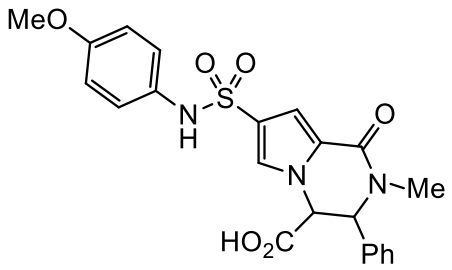
7-Benzoyl-2-(furan-2-ylmethyl)-1-oxo-3-(pentan-3-yl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (5c)  was prepared according to GP4 anhydride **2a** and imine **4c** as mixture of *E/Z*-diastereomers (5:1); retention time 23–25 min; yield 44 mg (51%), colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (signals of major diastereomer) 7.84 (d, *J* = 7.2 Hz, 2H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.49 – 7.42 (m, 3H), 7.38 (s, 1H), 7.29 (s, 1H), 7.12 (br.s, 1H), 6.29 (d, *J* = 3.1 Hz, 1H), 6.24 (s, 1H), 5.25 (br.d, *J* = 15.0 Hz, 1H), 4.87 (s,1H), 4.21 (s, 1H), 4.17 (d, *J* = 16.5 Hz, 1H), 1.57 (dt, *J* = 13.6, 6.9 Hz, 1H), 1.53 – 1.46 (m, 1H), 1.30 (dt, *J* = 13.7, 7.1 Hz, 2H), 0.94 (t, *J* = 7.2 Hz, 3H), 0.78 (t, *J* = 7.4 Hz, 3H); (observed signals of minor diastereomer) 14.13 (br.s, 1H), 8.10 (d, *J* = 1.7 Hz, 1H), 7.38 (dd, *J* = 2.9, 1.4 Hz, 2H), 6.36 – 6.34 (m, 2H), 5.57 (d, *J* = 15.6 Hz, 1H), 4.97 (d, *J* = 4.2 Hz, 1H), 4.24 (t, *J* = 4.1 Hz, 1H), 4.01 (d, *J* = 15.6 Hz, 1H), 1.44 – 1.38 (m, 1H), 1.13 (dp, *J* = 13.9, 7.0 Hz, 2H), 0.86 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (signals of major diastereomer) 191.0, 170.1, 158.7, 149.7, 149.2, 142.9, 142.8, 138.5, 138.4, 132.4, 129.30, 129.27, 128.4, 125.3, 124.8, 115.8, 110.7, 109.9, 59.6, 56.6, 43.6, 42.2, 21.9, 20.9, 11.5, 10.8; (observed signals of minor diastereomer) 191.4, 159.1, 130.7, 129.6, 125.5, 124.7, 116.5, 109.3, 77.2, 59.5, 58.1, 43.4, 22.7, 21.7, 11.7, 10.8. HRMS *m/z* calcd for $C_{25}H_{27}N_2O_5^+$ $[M+H]^+$: 435.1914, found 435.1922.

7'-Benzoyl-2'-isobutyl-1'-oxo-1',2'-dihydro-4'*H*-spiro[cyclohexane-1,3'-pyrrolo[1,2-*a*]pyrazine]-4'-carboxylic acid (5d)  was prepared according to GP4 anhydride **2a** and imine **4d**; retention time – 23–25 min; yield 16 mg (20%), colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.49 (br.s, 1H), 7.78 (dd, *J* = 10.1, 1.7 Hz, 3H), 7.64 (t, *J* = 7.3 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 2H), 6.98 (d, *J* = 1.8 Hz, 1H), 5.68 (s, 1H), 3.55 (dd, *J* = 14.2, 8.7 Hz, 1H), 3.11 (dd, *J* = 14.2, 6.4 Hz, 1H), 2.18 – 2.09 (m, 1H), 1.98 (td, *J* = 12.4, 4.6 Hz, 1H), 1.80 – 1.72 (m, 3H), 1.67 (d, *J* = 13.4 Hz, 1H), 1.57 – 1.48 (m, 3H), 1.38 (d, *J* = 8.4 Hz, 1H), 1.33 – 1.24 (m, 1H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 189.4, 169.8, 159.5, 139.4, 132.3, 129.7, 129.0, 128.9, 126.4, 124.1, 112.8, 62.8, 58.8, 46.2, 34.7, 31.7, 30.1, 24.8, 22.6, 22.3, 20.8, 20.3. HRMS *m/z* calcd for $C_{27}H_{25}N_2O_4^+$ $[M+H]^+$: 409.2122, found 409.2132.

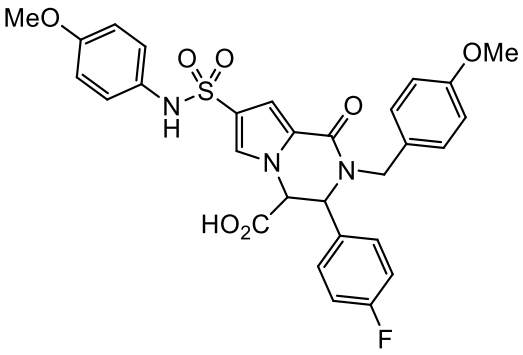
6-Benzoyl-2-ethyl-1-oxo-3-(*p*-tolyl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (5e)  was prepared according to GP4 from anhydride **2b** and imine **2a** as mixture of *E/Z*-diastereomers (9:1); retention time 23–26 min; yield 34 mg (42%), colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (signals of major diastereomer) 13.67 (br.s, 1H), 7.72 – 7.60 (m, 3H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.16 (d, *J* = 7.3 Hz, 2H), 7.06 (d, *J* = 7.9 Hz, 2H), 6.86 (d, *J* = 4.2 Hz, 1H), 6.79 (d, *J* = 4.2 Hz, 1H), 5.96 (s, 1H), 5.43 (s, 1H), 4.02 (dd, *J* = 14.0, 7.3 Hz, 1H), 2.88 (dd, *J* = 14.0, 7.3 Hz, 1H), 2.24 (s, 3H), 1.07 (t, *J* = 7.0 Hz, 3H); (observed

signals of minor diastereomer) 5.75 (d, *J* = 5.9 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 186.3, 169.9, 157.6, 138.4, 138.0, 135.6, 133.0, 131.2, 130.9, 130.0, 129.4, 129.0, 126.3, 122.0, 112.3, 62.2, 60.9, 21.0, 13.6. HRMS *m/z* calcd for $C_{24}H_{23}N_2O_4^+$ $[M+H]^+$: 403.1652, found 403.1643.

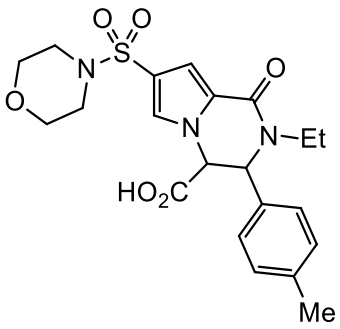
7-[*N*-(4-Methoxyphenyl)sulfamoyl]-2-methyl-1-oxo-3-phenyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]-pyrazine-4-carboxylic acid (5f) was prepared according to GP4 anhydride **2c** and imine **4e** as mixture of *E/Z*-diastereomers (5:1); retention time 21–23 min; yield 71 mg (78%), colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (signals of major diastereomer) 9.46 (s, 1H), 7.34 (d, *J* = 2.0 Hz, 1H), 7.33 (d, *J* = 2.0 Hz, 2H), 7.18 (d, *J* = 1H), 7.00 – 6.95 (m, 2H), 6.85 (d, *J* = 8.9 Hz, 2H), 6.79 (d, *J* = 1.8 Hz, 1H), 6.72 (d, *J* = 9.0 Hz, 1H), 5.38 (d, *J* = 1.5 Hz, 1H), 5.34 (s, 1H), 3.68 (s, 3H), 2.93 (s, 3H); (observed signals of minor diastereomer) 9.62 (s, 1H), 7.68 (s, 1H), 756 (d, *J* = 1.7 Hz, 1H), 7.30 – 7.24 (m, 3H), 7.04 – 7.01 (m, 2H), 6.91 – 6.89 (m, 1H), 6.82 (d, *J* = 9.0 Hz, 2H), 5.62 (d, *J* = 4.9 Hz, 1H), 5.16 (d, *J* = 5.0 Hz, 1H), 2.86 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (signals of major diastereomer) 169.7, 158.0, 157.2, 137.7, 130.6, 129.4, 128.7, 127.3, 126.3, 125.7, 125.1, 123.5, 114.5, 110.7, 63.5, 62.1, 55.6, 33.4; (observed signals of minor diastereomer) 167.3, 157.4, 157.0, 135.4, 130.9, 129.1, 127.9, 127.1, 126.1, 124.2, 123.8, 123.7, 119.8, 114.6, 63.0, 59.5, 55.6, 32.6. HRMS *m/z* calcd for $C_{22}H_{22}N_3O_6S^+$ $[M+H]^+$: 456.1224, found 456.1222.



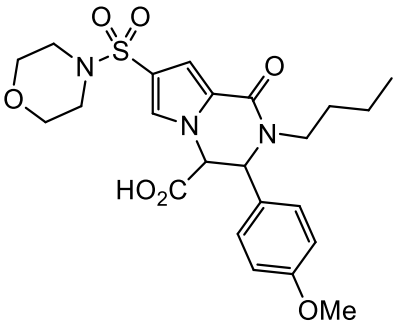
3-(4-Fluorophenyl)-2-(4-methoxybenzyl)-7-[*N*-(4-methoxyphenyl)sulfamoyl]-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (5g) was prepared according to GP4 anhydride **2c** and imine **4f** as mixture of *E/Z*-diastereomers (7:1); retention time 21–23 min; yield 77 mg (67%), colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (signals of major diastereomer) 9.50 (s, 1H), 7.18 (d, *J* = 1.8 Hz, 1H), 7.14 (d, *J* = 8.6 Hz, 2H), 6.99 (dd, *J* = 8.7, 5.4 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 1.9 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.9 Hz, 2H), 5.30 (s, 1H), 5.22 (s, 1H), 5.12 (d, *J* = 14.7 Hz, 1H), 3.75 (d, *J* = 8.2 Hz, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 2.55 (s, 3H); (observed signals of minor diastereomer) 9.67 (s, 1H), 7.56 (d, *J* = 1.8 Hz, 1H), 7.29 (s, 1H), 7.21 (d, *J* = 8.5 Hz, 2H), 7.08 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 1.8 Hz, 1H), 5.53 (d, *J* = 4.8 Hz, 1H), 4.99 (d, *J* = 4.9 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (signals of major diastereomer) 169.3, 162.3 (d, *J* = 244.8 Hz), 159.0, 157.7, 157.2, 134.1 (d, *J* = 3.0 Hz), 130.7, 129.9, 129.0, 128.6 (d, *J* = 8.5 Hz), 127.5, 125.7, 125.0, 123.8, 116.2 (d, *J* = 21.7 Hz), 114.5, 114.2, 111.0, 62.4, 60.7, 55.5, 47.5, 40.9; (observed signals of minor diastereomer) 167.1, 131.0, 127.3, 124.0, 114.7, 114.4, 113.2, 55.6. HRMS *m/z* calcd for $C_{29}H_{27}FN_3O_7S^+$ $[M+H]^+$: 580.1548, found 580.1566.



2-Ethyl-7-morpholinosulfonyl-1-oxo-3-(*p*-tolyl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (5h) was prepared according to GP4 anhydride **2d** and imine **4a** as mixture of *E/Z*-diastereomers (9:1); retention time 17–21 min; yield 55 mg (61%), colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (signals of major diastereomer) 7.44 (d, *J* = 1.7 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 2H), 6.97 (d, *J* = 7.9 Hz, 2H), 6.87 (d, *J* = 1.8 Hz, 1H), 5.45 (d, *J* = 1.5 Hz, 1H), 5.39 (s, 1H), 3.94 (dq, *J* = 14.0, 7.0 Hz, 1H), 3.62 (pd, *J* = 8.0, 4.8, 4.2 Hz, 4H), 2.88 (dq, *J* = 14.4, 7.1 Hz, 1H), 2.74 (h, *J* = 4.8, 4.3 Hz, 4H), 2.24 (s, 3H), 1.04 (t, *J* = 7.1 Hz, 3H); (observed signals of minor diastereomer) 7.65 (d, *J* = 1.8 Hz, 1H), 7.09 (d, *J* = 7.9 Hz, 2H), 5.65 (d, *J* = 4.9 Hz, 1H), 5.20 (d, *J* = 4.9 Hz, 1H), 3.71 (dd, *J* = 13.8, 7.1 Hz, 1H), 3.68 – 3.64 (m, 2H), 3.08 (dq, *J* = 13.9, 6.6 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (signals of major diastereomer) 179.3, 169.6, 157.3, 138.2, 135.4, 129.9, 127.8, 126.5, 126.3, 117.7, 111.2, 65.6, 62.9, 61.2, 46.4, 21.0, 13.6; (observed signals of minor diastereomer) 167.4, 164.6, 156.9, 138.7, 133.3, 129.7, 127.9, 126.9, 111.7, 65.6, 60.4, 21.1, 13.7. HRMS *m/z* calcd for $C_{23}H_{25}N_3O_6S^+$ $[M+H]^+$: 447.1464, found 447.1572.



2-Butyl-3-(4-methoxyphenyl)-7-morpholinosulfonyl-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]-pyrazine-4-carboxylic acid (5i) was prepared according to GP4 anhydride **2d** and imine **4g** as mixture of *E/Z*-diastereomers (9:1); retention time 20–22 min; yield 67 mg (69%), colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (signals of major diastereomer) 7.45 (d, *J* = 1.7 Hz, 1H), 6.99 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 1.7 Hz, 1H), 5.42 (d, *J* = 1.6 Hz, 1H), 5.34 (s, 1H), 3.97 (dt, *J* = 13.4, 7.7 Hz, 1H), 3.70 (s, 3H), 3.63 (t, *J* = 5.1 Hz, 4H), 2.79 – 2.68 (m, 5H), 1.46 (tq, *J* = 13.5, 6.0 Hz, 2H), 1.25 (tdt, *J* = 14.1, 10.2, 4.8 Hz, 2H), 0.87 (t, *J* = 7.4 Hz, 3H); (observed signals of minor diastereomer) 7.66 (d, *J* = 1.8 Hz, 1H), 6.84 (d, *J* = 8.9 Hz, 2H), 5.64 (d, *J* = 4.8 Hz, 1H), 5.13 (d, *J* = 4.8 Hz, 1H), 3.67 – 3.65 (m, 4 H), 2.94 – 2.82 (m, 5H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (signals of major diastereomer) 169.7, 159.6, 157.6, 129.9, 127.8, 127.7, 126.5, 117.7, 114.8, 111.2, 65.6, 62.9, 60.9, 55.5, 46.4, 44.4, 30.1, 19.8, 14.2; (observed signals of minor diastereomer) 167.4, 159.9, 157.1, 129.3, 126.8, 114.4, 111.7, 65.6, 55.5, 44.9, 30.0, 20.0, 14.1. HRMS *m/z* calcd for $C_{23}H_{30}N_3O_7S^+$ $[M+H]^+$: 492.1799, found 492.1822.

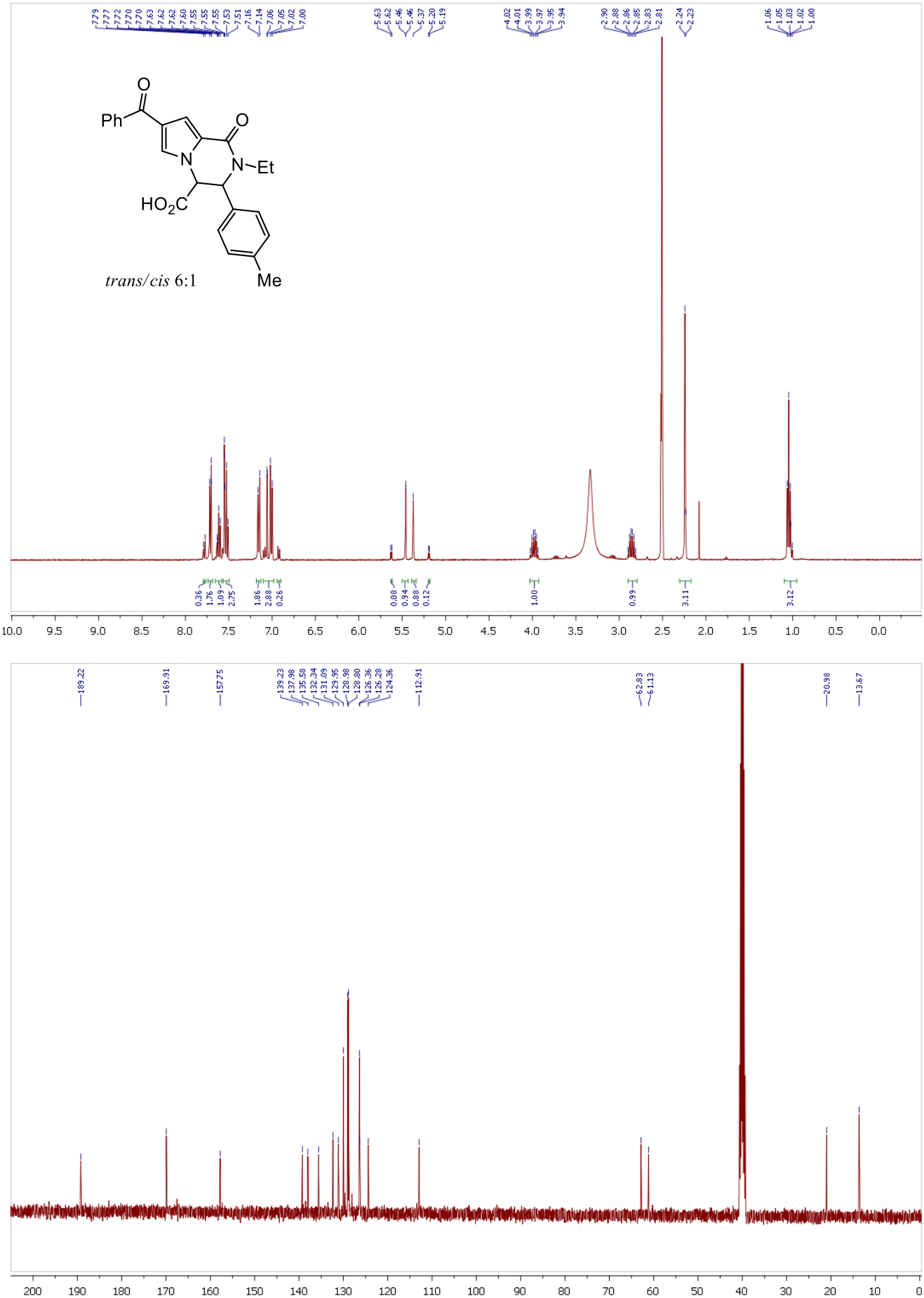


4. References

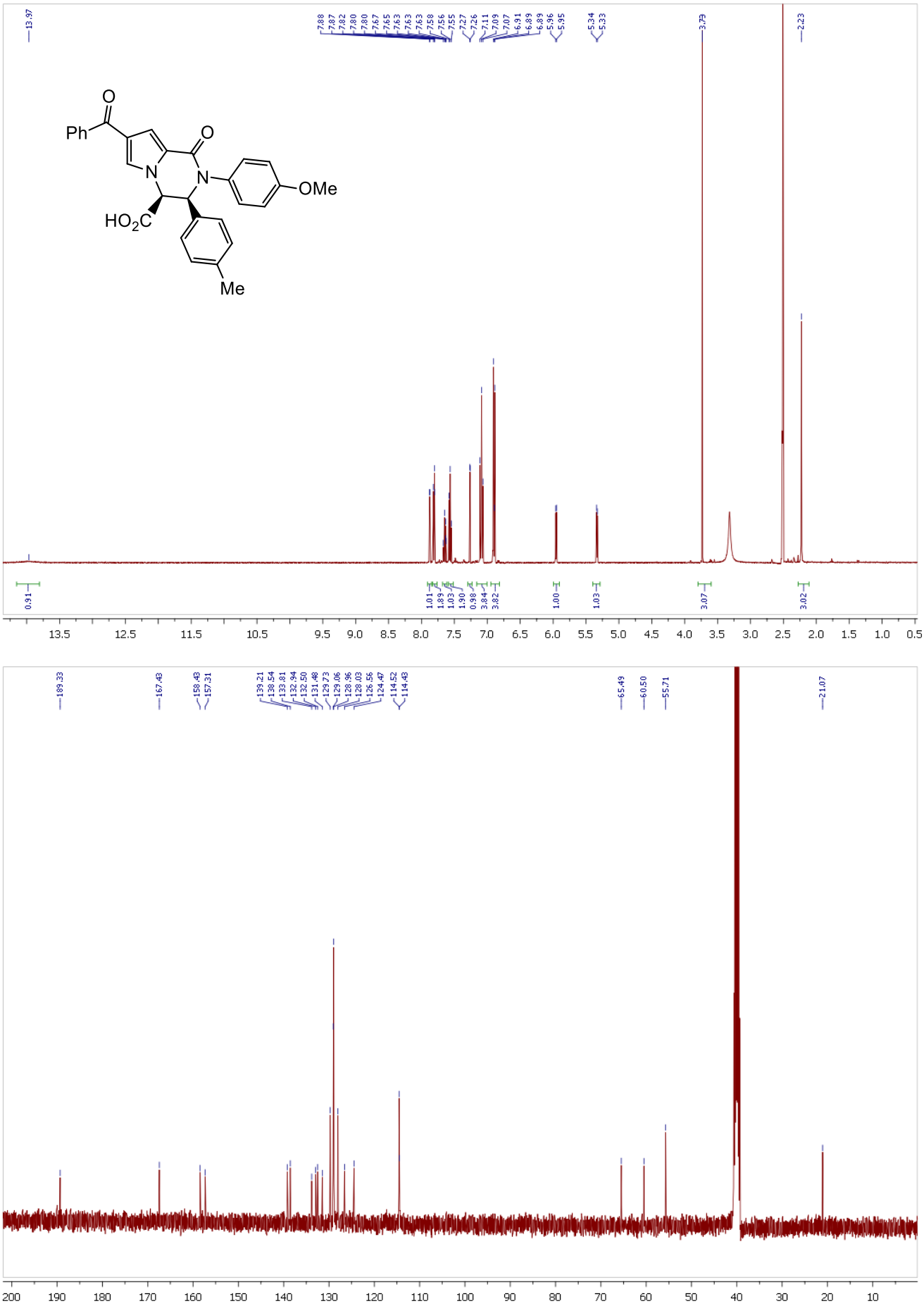
[S1] S. M. Myers, R. H. Bawn, L. C. Bisset, T. J. Blackburn, B. Cottyn, L. Molyneux, A.-C. Wong, C. Cano, W. Clegg, R. W. Harrington, H. Leung, L. Rigoreau, S. Vidot, B. T. Golding, R. J. Griffin, T. Hammonds, D. R. Newell and I. R. Hardcastle, *ACS Comb. Sci.*, 2016, **18**, 444.

[S2] M. Chizhova, O. Khoroshilova, D. Dar'in and M. Krasavin, *J. Org. Chem.*, 2018, **83**, 12722.

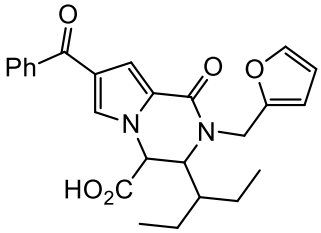
Copies of ^{1}H and ^{13}C spectra of compound **5a**



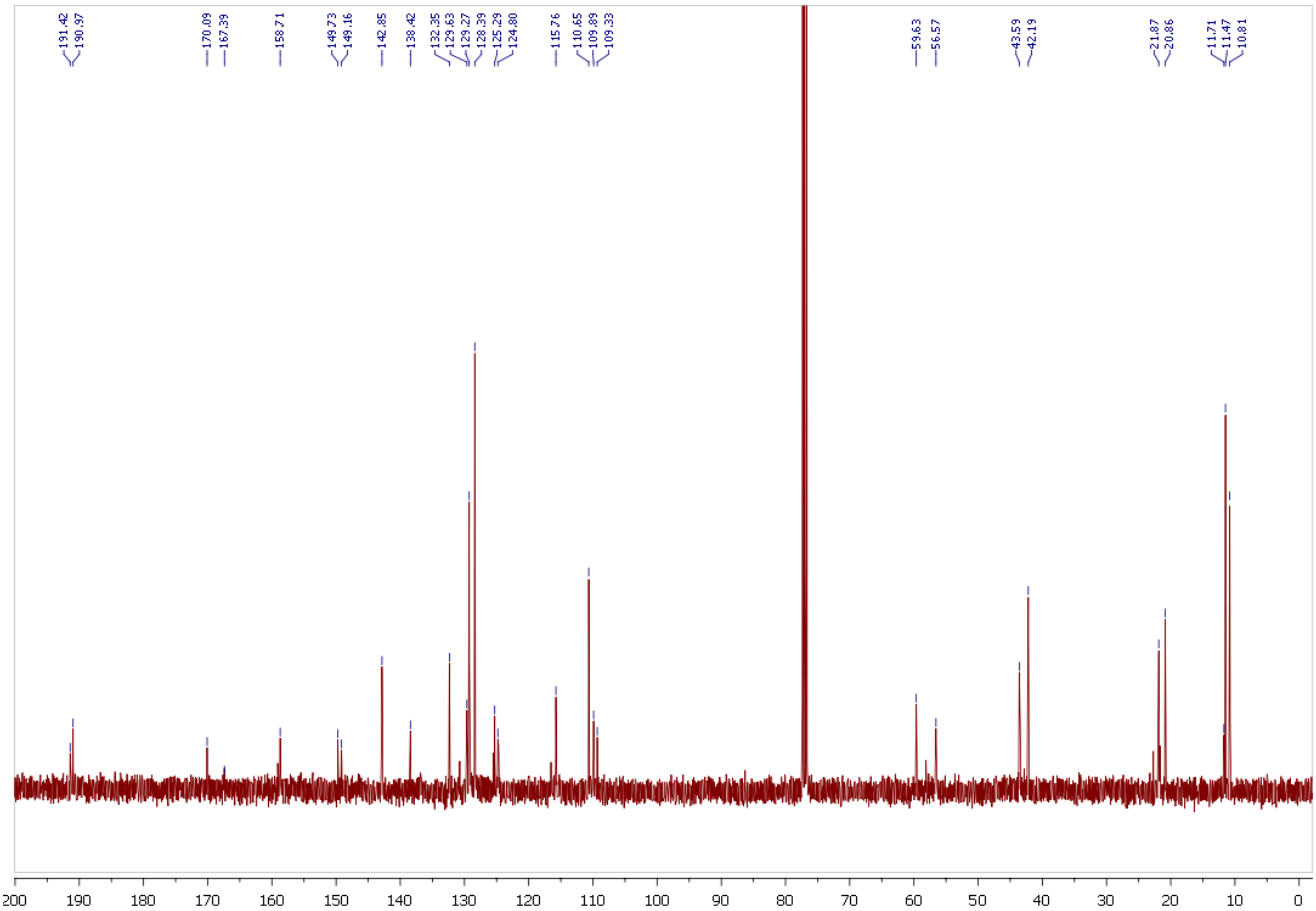
Copies of ^{1}H and ^{13}C spectra of compound **5b**



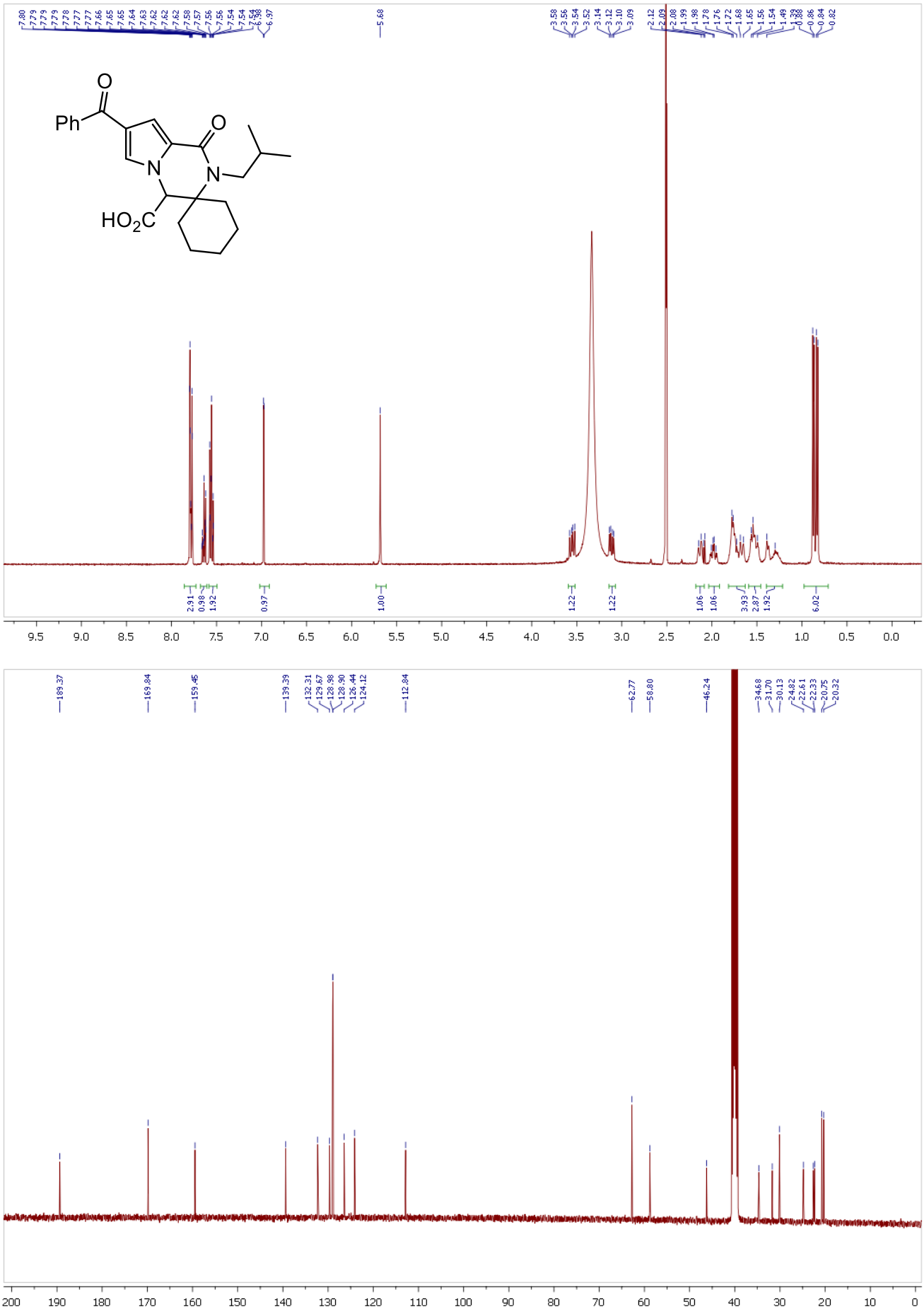
Copies of ^{1}H and ^{13}C spectra of compound **5c**



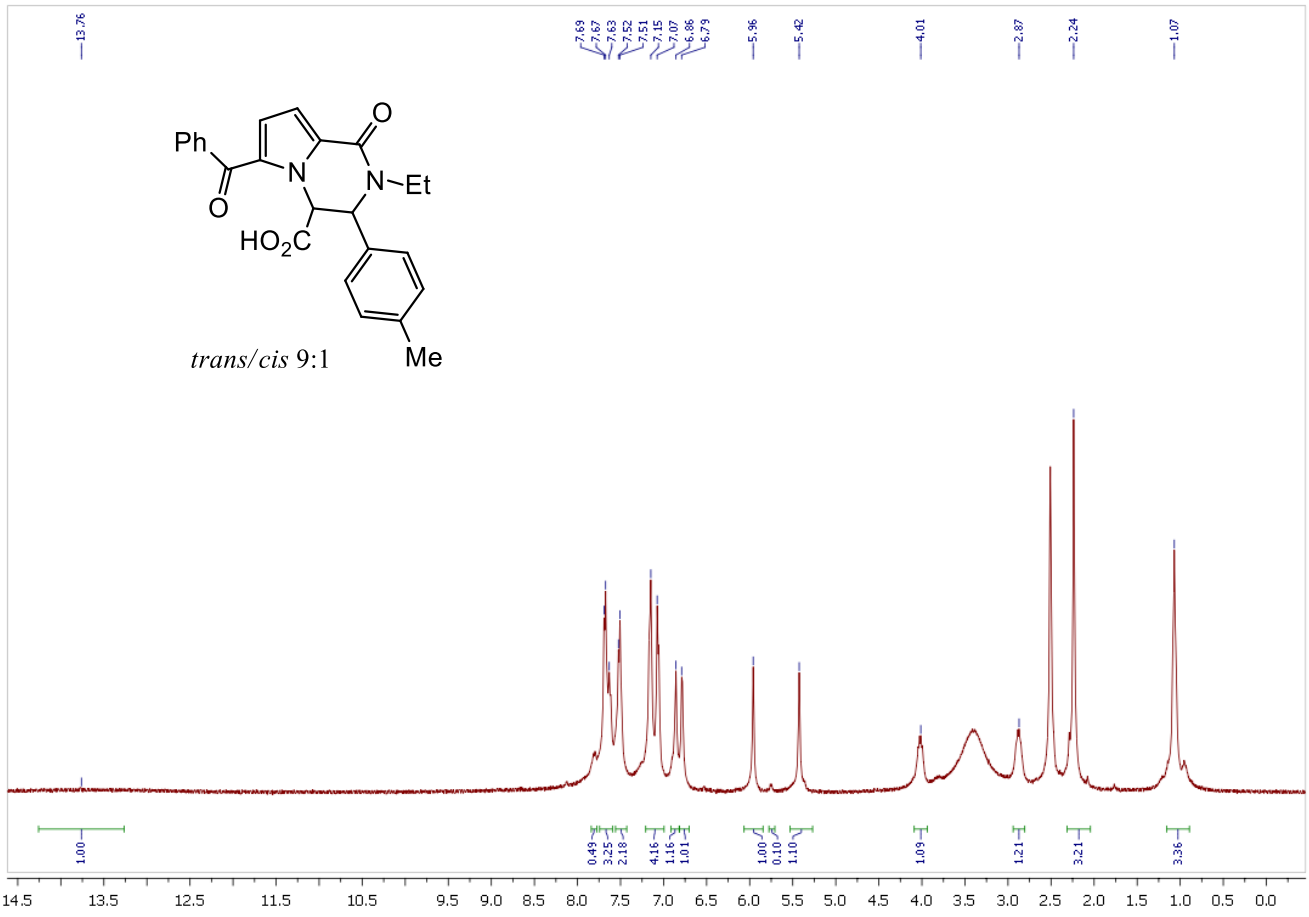
trans/cis 5:1

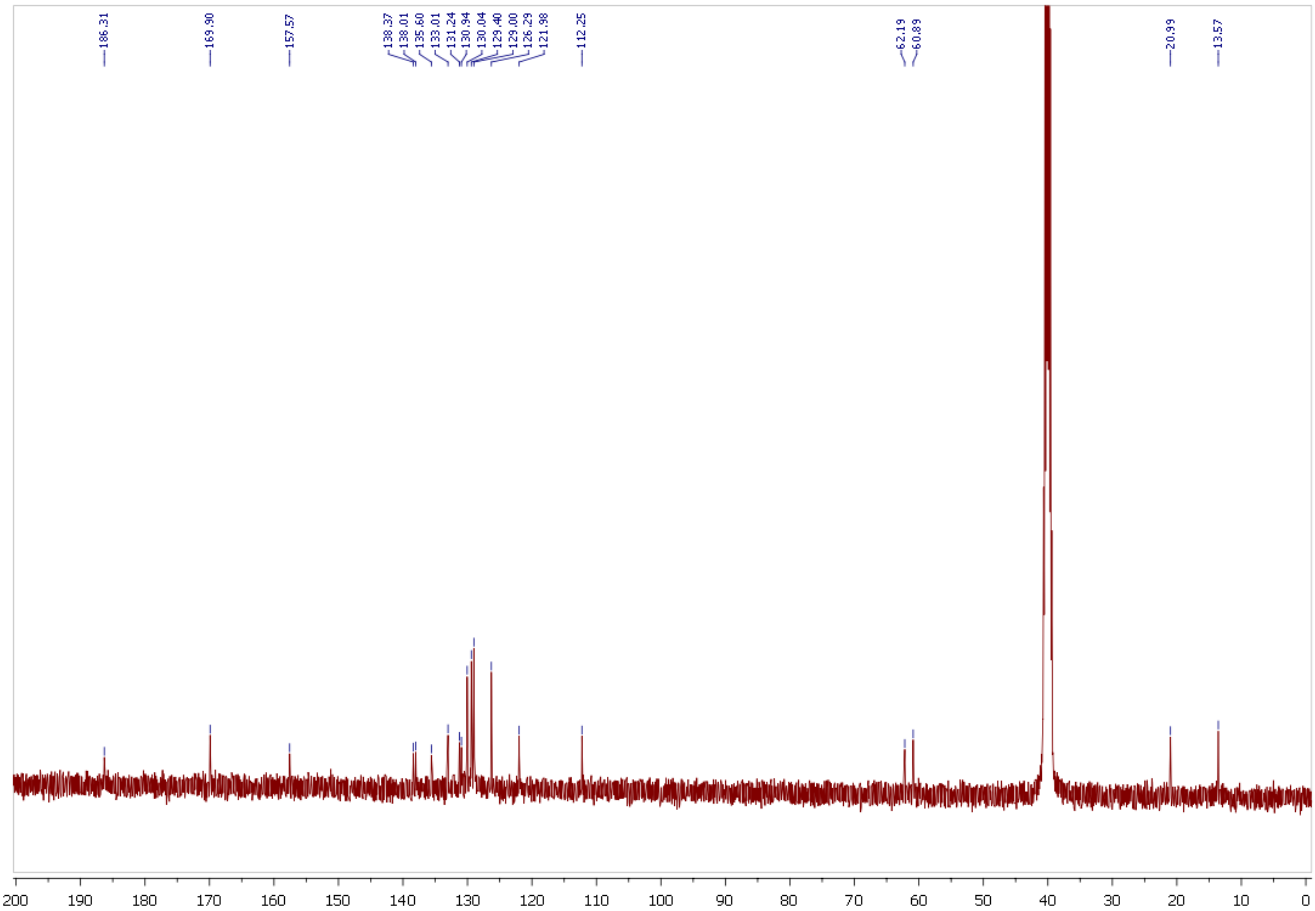


Copies of ^{1}H and ^{13}C spectra of compound **5d**

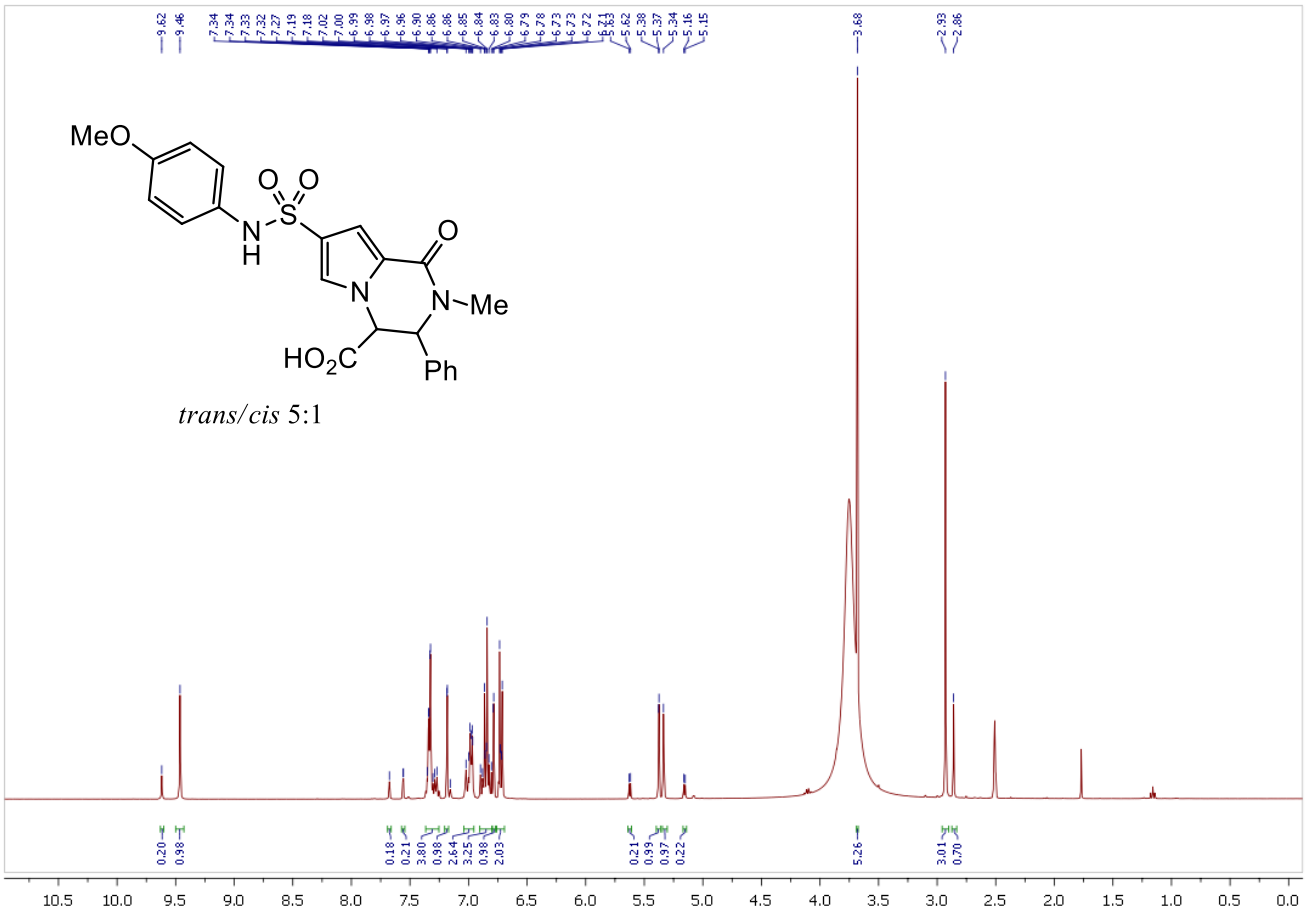


Copies of ^{1}H and ^{13}C spectra of compound **5e**

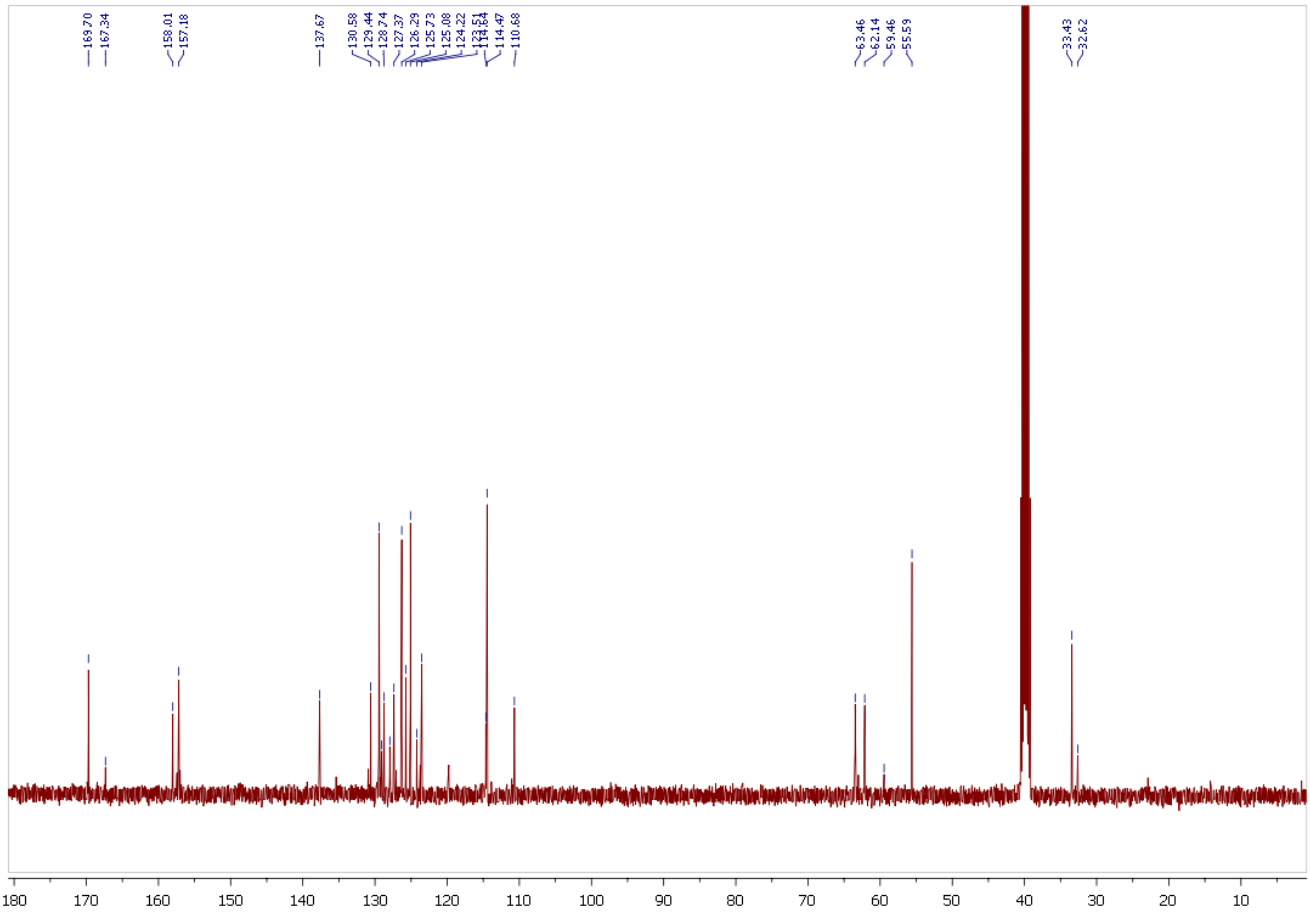




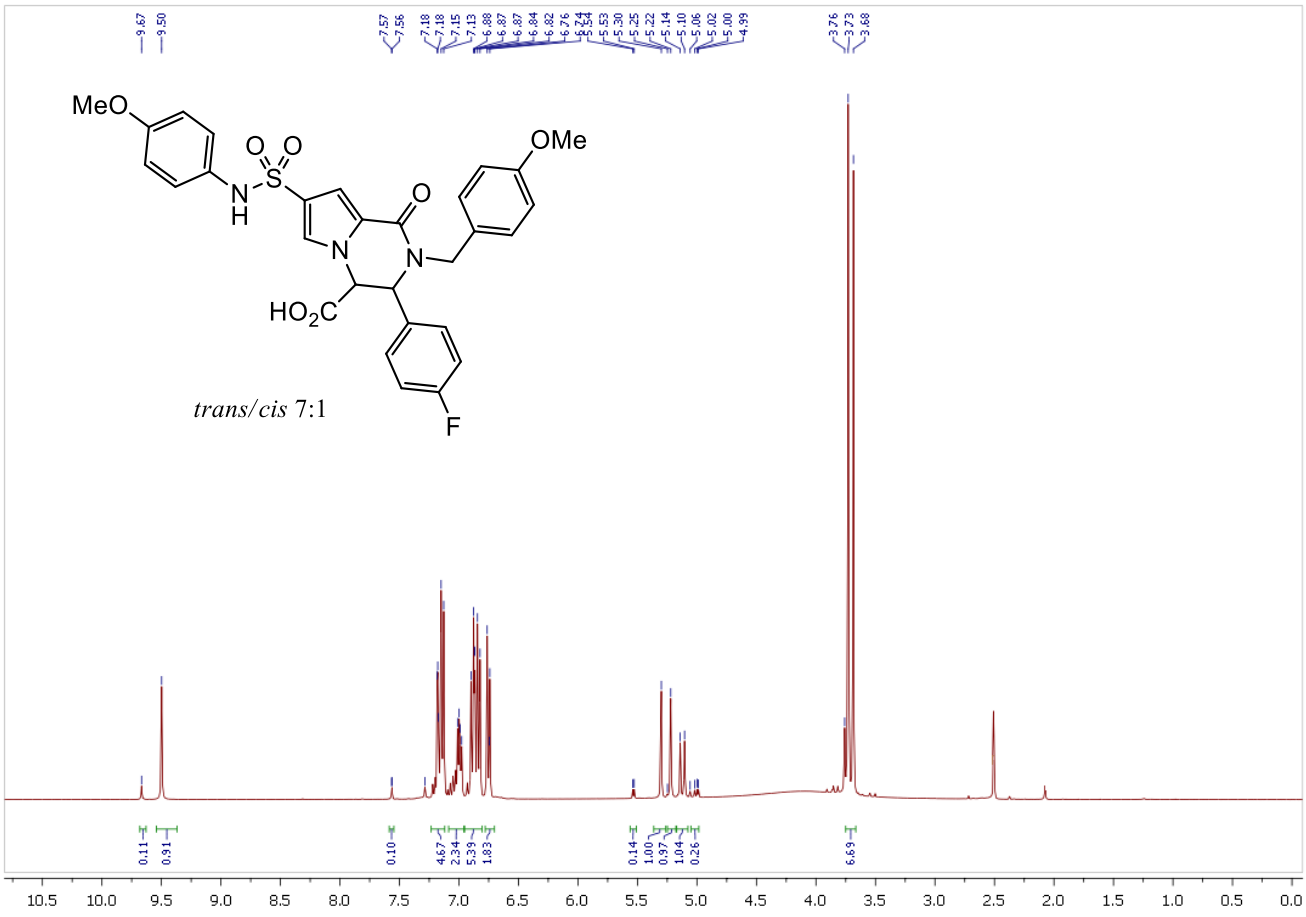
Copies of ^{1}H and ^{13}C spectra of compound **5f**

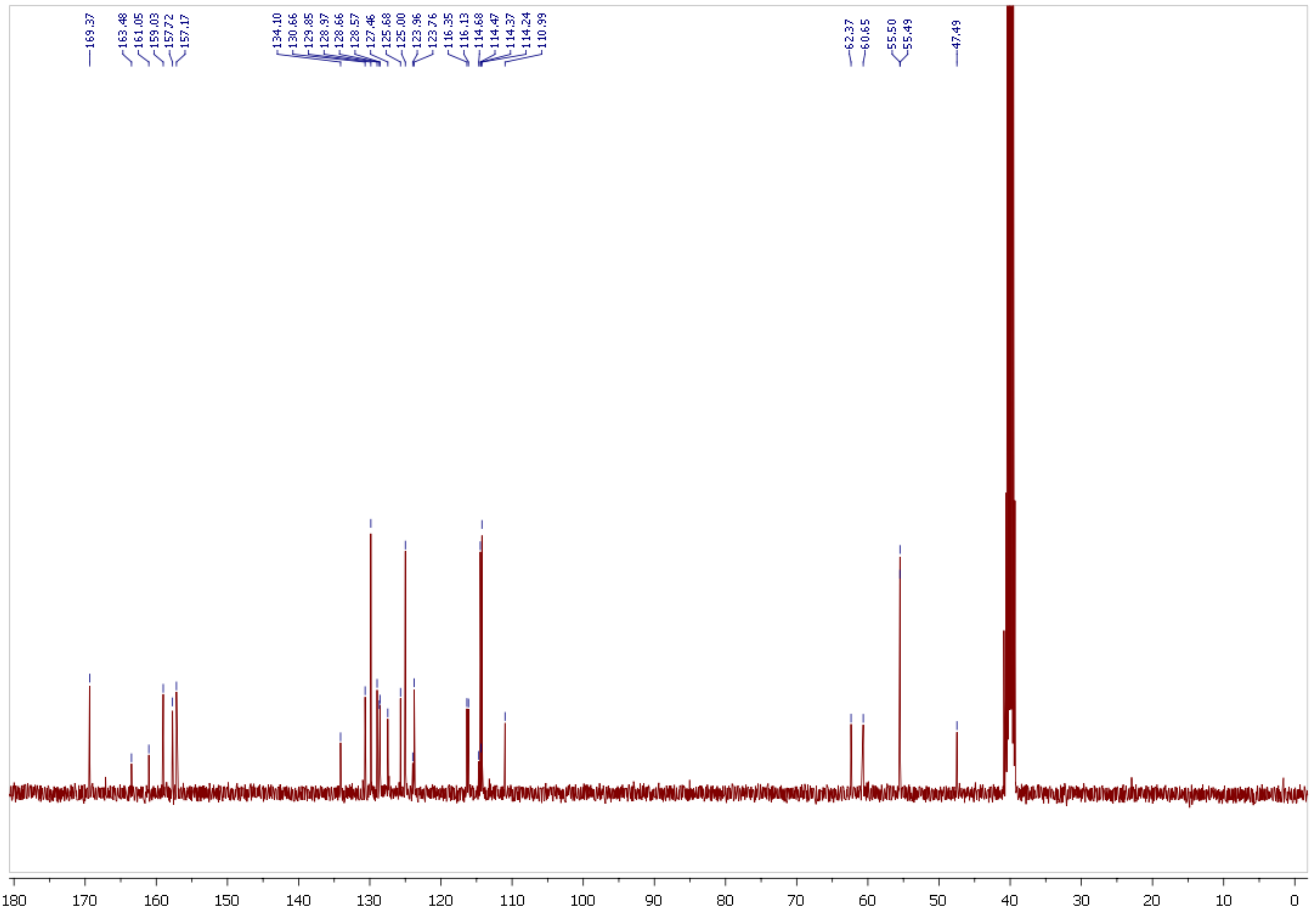


trans/cis 5:1

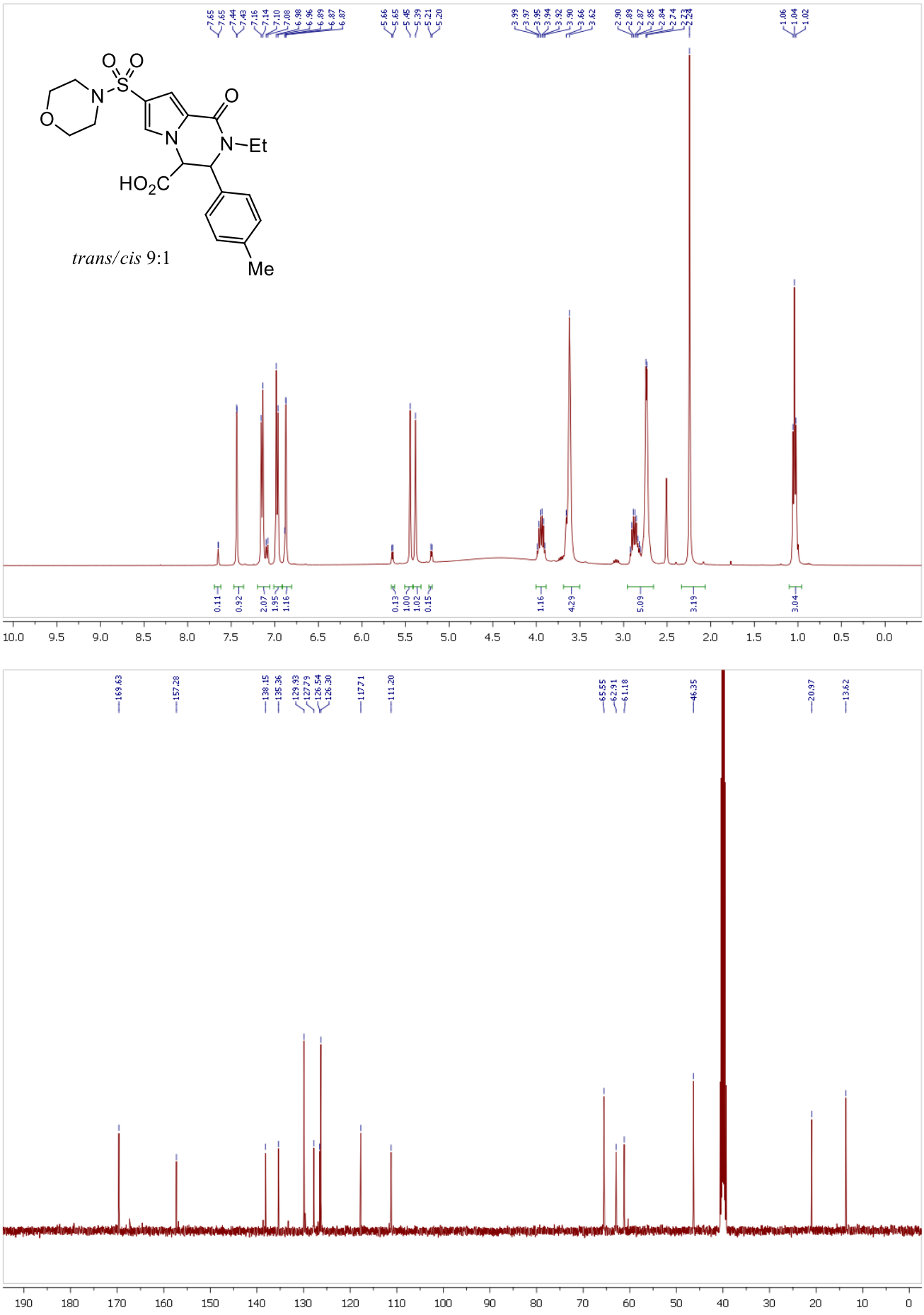


Copies of ^{1}H and ^{13}C spectra of compound **5g**





Copies of ^{1}H and ^{13}C spectra of compound **5h**



Copies of ^{1}H and ^{13}C spectra of compound **5i**