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Supporting information for

The first solvent-free synthesis of privileged γ- and δ-lactams via the Castagnoli-Cushman reaction

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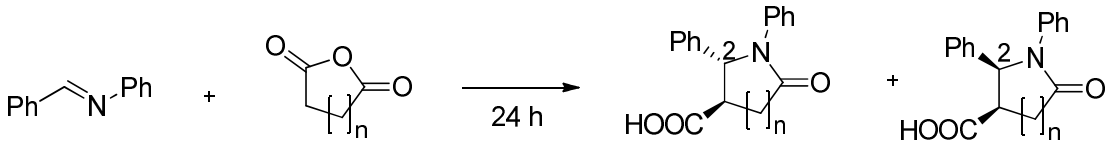
1. General Information

NMR spectra were recorded on a Bruker Avance III 400 spectrometer (^{1}H: 400.13 MHz; ^{13}C: 100.61 MHz; chemical shifts are reported as parts per million (δ, ppm); the residual solvent peaks were used as internal standards: 7.28 and 2.50 ppm for ^{1}H in $CDCl_3$ and DMSO-d_6 respectively, 40.01 and 77.02 ppm for ^{13}C in DMSO-d_6 and $CDCl_3$ respectively; multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constants, *J*, are reported in Hz. Mass spectra were recorded on a Bruker micrOTOF spectrometer (ESI ionization). Melting points were determined in open capillary tubes on Stuart SMP30 Melting Point Apparatus.

2. Experimental procedures and analytical data

Table S1. Screening of temperature regimens for the solvent-free reaction *N*-benzylidene aniline with succinic (**2**) and glutaric (**3**) anhydrides.[a]



2, n = 1
3, n = 2

***trans*-6a**, n = 1
***trans*-7a**, n = 2

***cis*-6a**, n = 1
***cis*-7a**, n = 2

Temperature	Yield (n = 2)	Conversion of imine	Yield (n = 1)	Conversion of imine
90 °C	< 20%	~40%	< 20%	~50%
110 °C	24%	~50%	22%	~60%
130 °C	42%	98%	36%	100%
150 °C	**65%**	100%	**48%**	100%
170 °C	**66%**	100%	**50%**	100%

[a]The data represent NMR yield of the product (*trans*+*cis*).

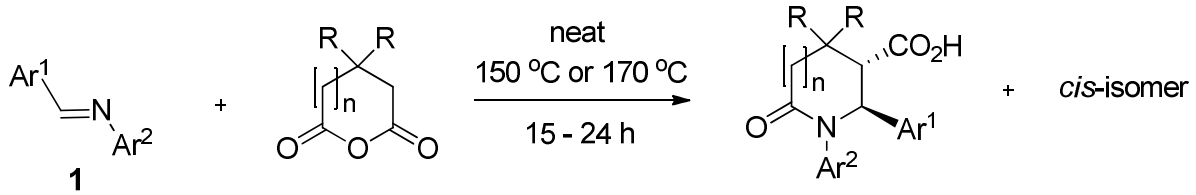
Sample preparation: Anhydride **2** or **3** (20 mg) and *N*-(benzylidene)aniline (1 equiv.) were grounded together and placed in a glass test tube with a screw cap, placed in a pre-heated bath and kept at corresponding temperature for 24 hours. After cooling to ambient temperature the reaction mixture was dissolved in $CDCl_3$ (with addition of a few drops of DMSO-d_6) and transferred into NMR test-tube. *n*-Tetradecane was added as internal standard (0.4–0.7 equiv.). The intensity of 2-CH protons of **6a** or **7a** was determined relative to intensity of CH_3 protons signals in *n*-tetradecane (integrated from 0.92 to 0.80 ppm equal 6). The NMR yield of **6a** or **7a** was calculated from equation:

$$NMR\ yield = \frac{I \times n(st)}{0.1136 \times 0.88} \times 100\%$$

n(st) – amount of added *n*-tetradecane (mmol)

The factor of 0.9 was determined from ^{1}H NMR integration experiments of solutions containing known concentrations of **6a** or **7a** and *n*-tetradecane to reflect the difference in relaxation times of 2-CH protons in **6a** or **6a** and the protons of terminal methyl groups in *n*-tetradecane.

Preparation of Castagnoli-Cushman lactams 6, 7, 8 and 9.



2, n = 0, R = H
3, n = 1, R = H
4, n = 1, R = Me
5, n = 1, R+R = $(CH_2)_4$

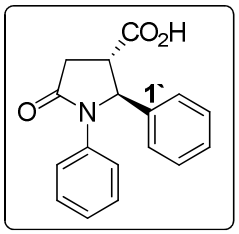
6, n = 0, R = H
7, n = 1, R = H
8, n = 1, R = Me
9, n = 1, R+R = $(CH_2)_4$

General procedure (scale – 2 mmol for **2**, 1.75 mmol for **3** and 1 mmol for **4**,**5**)**.** The corresponding cyclic anhydride (1 equiv.) and imine **1** (1 equiv.) were grounded together and placed in a glass test tube with a screw cap, placed in a pre-heated bath (150 °C or 170 °C) and kept at this temperature for indicated period of time.

Method A (this was used, unless otherwise stated). After cooling to ambient temperature 10% aqueous $KHCO_3$ (8 mL) was added and mixture was stirred vigorously for 10–16 hours. Filtration through a pad of Celite afforded clear aqueous solution which was acidified with conc. HCl to pH ~ 2 and stirred for 1–2 h in ice bath. The crystalline precipitate was collected and dried in air to yield product as diastereomeric mixture (*dr* varies from 10:1 to 3:1) with purity not less than 95%. Recrystallization from aqueous ethanol was used for additional purification and isolation of pure *trans*-isomer in some cases.

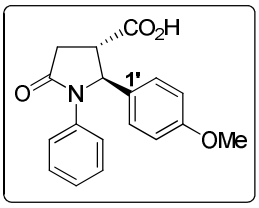
Method B. After cooling to ambient temperature reaction mixture was dissolved in a minimum amount of boiling ethanol and water was gradually added to the stirred hot solution till opacity appears. After cooling in ice bath the crystals formed was filtered and dried in air.

***trans/cis*-5-Oxo-1,2-diphenylpyrrolidine-3-carboxylic acid (6a).** Yield 280 mg (50%), *dr* 7:1;



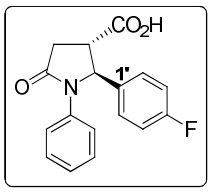
crystallization from aqueous ethanol afforded *dr* 10:1; Beige solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ for *trans*-isomer:[1] 12.89 (br.s, 1H, COOH), 7.41 (d, *J* = 8.0 Hz, 2H), 7.35 – 7.21 (m, 7H), 7.05 (t, *J* = 7.4 Hz, 1H), 5.58 (d, *J* = 5.3 Hz, 1H, 2-H), 3.10 (ddd, *J* = 9.5, 6.6, 5.3 Hz, 1H, 3-H), 2.97 (dd, *J* = 17.0, 9.5 Hz, 1H, 4-H), 2.76 (dd, *J* = 17.0, 6.6 Hz, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ for *trans*-isomer: 174.0, 172.3, 140.8, 138.1, 129.2, 128.9, 128.3, 127.2, 125.3, 123.2, 65.2, 46.2, 34.6. HRMS (ESI), *m/z* calcd for $C_{17}H_{15}NO_3$ $[M+Na]^+$ 304.0944, found 304.0943.

***trans/cis*-2-(4-Methoxyphenyl)-5-oxo-1-phenylpyrrolidine-3-carboxylic acid (6b).** Yield 306 mg



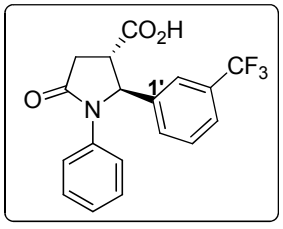
(50%), *dr* 5:1; crystallization from aqueous ethanol afforded *dr* 7:1; Beige solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ for *trans*-isomer: 12.80 (br.s, 1H, COOH), 7.39 (d, *J* = 7.8 Hz, 2H, *o*-Ph), 7.29 – 7.20 (m, 4H, 2',6'-H and *m*-Ph), 7.05 (t, *J* = 7.4 Hz, 1H, *p*-Ph), 6.84 (d, *J* = 8.7 Hz, 2H, 3',5'-H), 5.50 (d, *J* = 5.5 Hz, 1H, 2-H),), 3.69 (s, 3H, OCH_3), 3.08 (ddd, *J* = 9.4, 6.9, 5.5 Hz, 1H, 3-H), 2.95 (dd, *J* = 16.9, 9.4 Hz, 1H, 4-H), 2.74 (dd, *J* = 16.9, 6.9 Hz, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ for *trans*-isomer: 174.1, 172.2, 159.2, 138.2, 132.5, 128.9, 128.5, 125.3, 123.4, 114.5, 64.8, 55.5, 46.4, 34.6. HRMS (ESI), *m/z* calcd for $C_{18}H_{17}NO_4$ $[M+Na]^+$ 334.1050, found 334.1056.

***trans/cis*-2-(4-Fluorophenyl)-5-oxo-1-phenylpyrrolidine-3-carboxylic acid (6c).** Crystallization



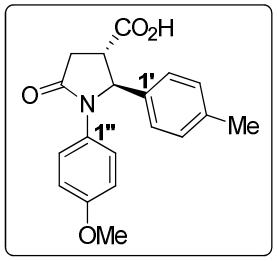
from aqueous ethanol afforded 234 mg (40%), *dr* 7:1; Beige solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ for *trans*-isomer:[1] 12.85 (br.s, 1H, COOH), 7.41 – 7.35 (m, 4H, 2',6'-H and *o*-Ph), 7.25 (t, *J* = 7.6 Hz, 2H, *m*-Ph), 7.12 (t, *J* = 8.8 Hz, 2H, 3',5'-H), 7.06 (t, *J* = 7.4 Hz, 1H, *p*-Ph), 5.59 (d, *J* = 5.8 Hz, 1H, 2-H), 3.12 (ddd, *J* = 9.5, 7.2, 5.7 Hz, 1H, 3-H), 2.96 (dd, *J* = 17.0, 9.5 Hz, 1H, 4-H), 2.76 (dd, *J* = 17.0, 7.2 Hz, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ for *trans*-isomer: 173.9, 172.2, 162.0 (d, *J* = 243.8 Hz), 138.0, 136.9 (d, *J* = 3.0 Hz), 129.5 (d, *J* = 8.4 Hz), 128.9, 125.4, 123.5, 115.9 (d, *J* = 21.5 Hz), 64.5, 46.2, 34.5. HRMS (ESI), *m/z* calcd for $C_{17}H_{14}FNO_3$ $[M+Na]^+$ 322.0850, found 322.0849.

***trans*-5-Oxo-1-phenyl-2-(3-(trifluoromethyl)phenyl)pyrrolidine-3-carboxylic acid (6d).** Yield



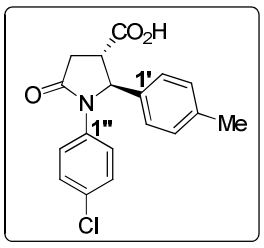
239 mg (35%), *dr* 9:1; crystallization from aqueous ethanol afforded pure *trans*-isomer; Beige solid; Mp 169−170 °C (EtOH-H_2O); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.92 (br.s, 1H, COOH), 7.74 (s, 1H, 2'-H), 7.65 (d, *J* = 7.6 Hz, 1H, 4'-H), 7.58 (d, *J* = 7.9 Hz, 1H, 6'-H), 7.52 (t, *J* = 7.7 Hz, 1H, 5'-H), 7.40 (d, *J* = 7.8 Hz, 2H, *o*-Ph), 7.25 (t, *J* = 7.8 Hz, 2H, *m*-Ph), 7.06 (t, *J* = 7.6 Hz, 1H, *p*-Ph), 5.73 (d, *J* = 6.2 Hz, 1H, 2-H), 3.21 (ddd, *J* = 9.5, 7.5, 6.2 Hz, 1H, 3-H), 2.97 (dd, *J* = 17.0, 9.5 Hz, 1H, 4-H), 2.80 (dd, *J* = 17.0, 7.5 Hz, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.7, 172.3, 142.2, 137.8, 131.6, 130.1, 129.7 (q, *J* = 31.7 Hz), 125.6, 125.1 (q, *J* = 3.7 Hz), 124.5 (q, *J* = 272.4 Hz), 124.4 (q, *J* = 4.1 Hz), 123.6, 64.5, 45.9, 34.5. HRMS (ESI), *m/z* calcd for $C_{18}H_{14}F_3NO_3$ $[M+H]^+$ 350.0999, found 350.1002.

***trans/cis*-1-(4-Methoxyphenyl)-5-oxo-2-(*p*-tolyl)pyrrolidine-3-carboxylic acid (6e).** Crystallization



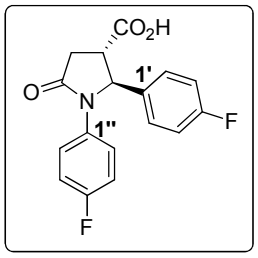
from aqueous ethanol afforded 220 mg (35%), *dr* 9:1; additional crystallization afforded *dr* 16:1; Beige solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.80 (br.s, 1H, COOH), 7.26 (d, J = 9.0 Hz, 2H, 2",6"-H), 7.19 (d, J = 8.1 Hz, 2H, 2',6'-H), 7.09 (d, J = 8.0 Hz, 2H, 3',5'-H), 6.80 (d, J = 9.0 Hz, 2H, 3",5"-H), 5.42 (d, J = 5.6 Hz, 1H, 2-H), 3.67 (s, 3H, OCH_3), 3.06 (ddd, J = 9.5, 7.0, 5.6 Hz, 1H, 3-H), 2.92 (dd, J = 16.9, 9.5 Hz, 1H, 4-H), 2.72 (dd, J = 16.9, 7.0 Hz, 1H, 4-H), 2.23 (s, 3H, 4'-CH_3). ^{13}C NMR (101 MHz, DMSO) δ 174.1, 172.0, 156.8, 137.8, 137.5, 131.1, 129.7, 127.3, 125.2, 114.1, 65.5, 55.5, 46.3, 34.5, 21.1. HRMS (ESI), *m/z* calcd for $C_{19}H_{19}NO_4$ $[M+Na]^+$ 348.1206, found 348.1215.

***trans/cis*-1-(4-Chlorophenyl)-5-oxo-2-(p-tolyl)pyrrolidine-3-carboxylic acid (6f).** Crystallization



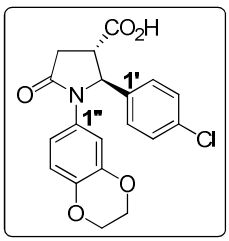
from aqueous ethanol afforded 148 mg (24%), *dr* 9:1; Beige solid; ^{1}H NMR (400 MHz, DMSO) δ for *trans*-isomer: 12.87 (br.s, 1H, COOH), 7.43 (d, J = 8.9 Hz, 2H, 2",6"-H), 7.30 (d, J = 8.9 Hz, 2H, 3",5"-H), 7.20 (d, J = 8.1 Hz, 2H, 2',6'-H), 7.10 (d, J = 8.1 Hz, 2H, 3',5'-H), 5.52 (d, J = 5.5 Hz, 1H, 2-H), 3.08 (ddd, J = 9.4, 6.9, 5.5 Hz, 1H, 3-H), 2.95 (dd, J = 17.0, 9.4 Hz, 1H, 4-H), 2.76 (dd, J = 17.0, 6.9 Hz, 1H, 4-H), 2.23 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ for *trans*-isomer: 173.9, 172.4, 137.6, 137.4, 137.1, 129.8, 129.2, 128.8, 127.1, 124.8, 64.9, 46.2, 34.6, 21.1. HRMS (ESI), *m/z* calcd for $C_{18}H_{16}ClNO_3$ $[M+Na]^+$ 352.0711, found 352.0716.

***trans/cis*-1,2-Bis(4-fluorophenyl)-5-oxopyrrolidine-3-carboxylic acid (6g).** Crystallization from



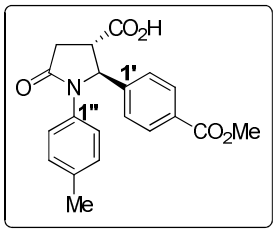
aqueous ethanol afforded 220 mg (36%), *dr* 7:1; Beige solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ for *trans*-isomer: 12.86 (br.s, 1H, COOH), 7.41 – 7.37 (m, 4H, 2',6'-H and 2",6"-H), 7.15 – 7.06 (m, 4H, 3',5'-H and 3",5"-H), 5.55 (d, J = 6.1 Hz, 1H, 2-H), 3.16 – 3.10 (m, 1H, 3-H), 2.94 (dd, J = 17.0, 9.5 Hz, 1H, 4-H), 2.76 (dd, J = 17.0, 7.6 Hz, 1H, 4-H).^{13}C NMR (101 MHz, DMSO-d_6) δ for *trans*-isomer: 173.8, 172.2, 162.0 (d, J = 250.9 Hz), 159.6 (d, J = 249.0 Hz), 136.70 (d, J = 3.0 Hz), 134.26 (d, J = 2.7 Hz), 129.65 (d, J = 8.4 Hz), 125.78 (d, J = 8.3 Hz), 115.91 (d, J = 21.6 Hz), 115.65 (d, J = 22.4 Hz), 64.7, 46.2, 34.5. HRMS (ESI), *m/z* calcd for $C_{17}H_{13}F_2NO_3$ $[M+Na]^+$ 340.0756, found 340.0743.

***trans*-2-(4-Chlorophenyl)-1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-5-oxopyrrolidine-3-carboxylic**



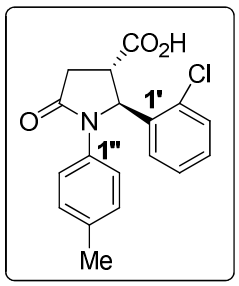
acid (6h). Method **A**: crystallization from aqueous ethanol afforded 209 mg (28%), *dr* 10:1. Method **B**: yield 373 mg (50%), pure *trans*-isomer; Beige solid; Mp 210−211 °C (EtOH-H_2O); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 (br.s, 1H, COOH), 7.39 – 7.34 (m, 4H, ArH'), 6.93 (d, J = 2.4 Hz, 1H, 2"-H), 6.78 (dd, J = 8.7, 2.4 Hz, 1H, 6"-H), 6.71 (d, J = 8.7 Hz, 1H, 5"-H), 5.47 (d, J = 5.7 Hz, 1H, 2-H), 4.19 – 4.14 (m, 4H, OCH_2CH_2O), 3.07 (ddd, J = 9.5, 7.1, 5.7 Hz, 1H, 3-H), 2.90 (dd, J = 17.0, 9.5 Hz, 1H, 4-H), 2.72 (dd, J = 17.0, 7.1 Hz, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.8, 172.1, 143.3, 141.3, 139.9, 132.8, 131.3, 129.4, 129.1, 117.0, 116.7, 113.0, 64.7, 64.5, 64.3, 46.0, 34.3. HRMS (ESI), *m/z* calcd for $C_{19}H_{16}ClNO_5$ $[M+H]^+$ 374.0790, found 374.0795.

***trans/cis*-2-(4-(Methoxycarbonyl)phenyl)-5-oxo-1-(*p*-tolyl)pyrrolidine-3-carboxylic acid (6i).**



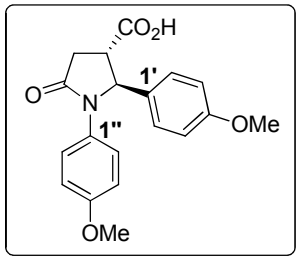
Method **A**: crystallization from aqueous ethanol afforded 261 mg (37%), *dr* 10:1. Method **B**: yield 380 mg (54%), *dr* 11:1; Beige solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ for *trans*-isomer: 12.91 (br.s, 1H, COOH), 7.87 (d, J = 8.3 Hz, 1H, 3',5'-H), 7.48 (d, J = 8.3 Hz, 1H, 2',6'-H), 7.27 (d, J = 8.4 Hz, 1H, 2",6"-H), 7.04 (d, J = 8.4 Hz, 1H, 3",5"-H), 5.62 (d, J = 5.7 Hz, 1H, 2-H), 3.81 (s, 3H, CO_2CH_3), 3.13 (ddd, J = 9.6, 7.1, 5.7 Hz, 1H, 3-H), 2.94 (dd, J = 17.0, 9.6 Hz, 1H, 4-H), 2.77 (dd, J = 17.0, 7.1 Hz, 1H, 4-H), 2.18 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ for *trans*-isomer: 173.7, 172.1, 166.3, 146.3, 135.4, 134.7, 130.0, 129.6, 129.4, 127.8, 123.3, 64.9, 52.6, 45.8, 34.4, 20.8. HRMS (ESI), *m/z* calcd for $C_{20}H_{19}NO_5$ $[M+Na]^+$ 376.1155, found 376.1139.

***trans/cis*-2-(2-Chlorophenyl)-5-oxo-1-(p-tolyl)pyrrolidine-3-carboxylic acid (6j).** Crystallization



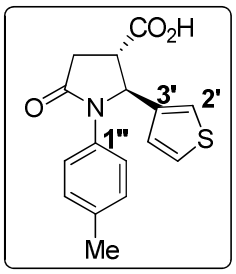
from aqueous ethanol afforded 228 mg (37%), *dr* 10:1; Beige solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ for *trans*-isomer: 13.00 (br.s, 1H, COOH), 7.46 – 7.43 (m, 1H, 6'-H), 7.32 – 7.27 (m, 5H, 3',4',5'-H and 2",6"-H), 7.08 (d, J = 8.4 Hz, 2H, 3",5"-H), 5.86 (d, J = 4.0 Hz, 1H, 2-H), 3.16 – 3.07 (m, 1H, 3-H), 2.98 (dd, J = 17.2, 9.6 Hz, 1H, 4-H), 2.74 (dd, J = 17.2, 4.9 Hz, 1H, 4-H), 2.20 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ for *trans*-isomer: 174.0, 172.3, 137.2, 135.5, 134.7, 132.5, 130.5, 130.5, 130.1, 129.6, 128.2, 122.4, 62.6, 44.4, 34.6, 20.8. HRMS (ESI), *m/z* calcd for $C_{18}H_{16}ClNO_3$ $[M+H]^+$ 330.0891, found 330.0894.

***trans/cis*-1,2-Bis(4-methoxyphenyl)-5-oxopyrrolidine-3-carboxylic acid (6k).** Crystallization from



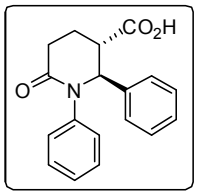
aqueous ethanol afforded 237 mg (37%), *dr* 10:1; Beige solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ for *trans*-isomer: 12.76 (br.s, 1H, COOH), 7.25 (d, J = 9.0 Hz, 2H, 2",6"-H), 7.23 (d, J = 8.7 Hz, 2H, 2',6'-H), 6.84 (d, J = 8.7 Hz, 2H, 3',5'-H), 6.80 (d, J = 9.0 Hz, 2H, 3",5"-H), 5.40 (d, J = 5.8 Hz, 1H, 2-H), 3.69 (s, 3H, 4'-CH_3), 3.67 (s, 3H, 4"-CH_3), 3.08 (ddd, J = 9.5, 7.2, 5.8 Hz, 1H, 3-H), 2.92 (dd, J = 16.9, 9.5 Hz, 1H, 4-H), 2.72 (dd, J = 16.9, 7.2 Hz, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ for *trans*-isomer: 174.1, 171.9, 159.2, 156.9, 132.6, 131.0, 128.7, 125.4, 114.4, 114.1, 65.3, 55.5, 55.4, 46.4, 34.5. HRMS (ESI), *m/z* calcd for $C_{19}H_{19}NO_5$ $[M+Na]^+$ 364.1155, found 364.1155

***trans/cis*-5-Oxo-2-(thiophen-3-yl)-1-(*p*-tolyl)pyrrolidine-3-carboxylic acid (6l).** Method **A**:



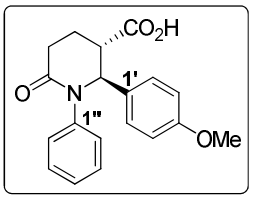
crystallization from aqueous ethanol afforded 209 mg (35%), *dr* 6:1. Method **B**: yield 377 mg (63%) *dr* 7:1; Beige solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ for *trans*-isomer: 12.82 (br.s, 1H, COOH), 7.45 (dd, J = 4.9, 3.0 Hz, 1H, 4'-H), 7.42 (dd, J = 3.0, 1.3 Hz, 1H, 2'-H), 7.27 (d, J = 8.5 Hz, 2H, 2",6"-H), 7.09 – 7.05 (m, 3H, 5'-H and 3",5"-H), 5.61 (d, J = 5.0 Hz, 1H, 2-H), 3.14 (ddd, J = 9.5, 6.3, 5.0 Hz, 1H, 3-H), 2.97 (dd, J = 17.0, 9.5 Hz, 1H, 4-H), 2.71 (dd, J = 17.0, 6.3 Hz, 1H, 4-H), 2.21 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ for *trans*-isomer: 174.1, 171.8, 141.9, 135.6, 134.7, 129.4, 127.5, 126.5, 123.8, 123.5, 61.4, 45.3, 34.6, 20.9. HRMS (ESI), *m/z* calcd for $C_{16}H_{15}NO_3SNa$ $[M+Na]^+$ 324.0665, found 324.0670.

***trans*-6-Oxo-1,2-diphenylpiperidine-3-carboxylic acid (7a).** Yield 400 mg (67%), *dr* 6:1;



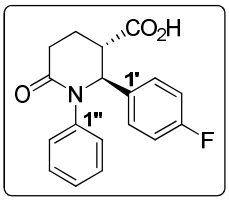
crystallization from aqueous ethanol afforded pure *trans*-isomer; Colorless solid; Mp 258–259 °C (EtOH-H_2O) (lit[1] Mp 200 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.56 (br.s, 1H, COOH), 7.33 – 7.30 (m, 4H, ArH), 7.28 – 7.21 (m, 3H, ArH), 7.19 – 7.10 (m, 3H, ArH), 5.37 (d, *J* = 4.4 Hz, 1H, 2-H), 3.00 (dt, *J* = 5.8, 4.5 Hz, 1H, 3-H), 2.67 (ddd, *J* = 18.0, 6.8, 5.6 Hz, 1H, 5-H), 2.56 – 2.48 (m, 1H, 5-H), 2.16 – 2.06 (m, 1H, 4-H), 2.03 – 1.94 (m, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.8, 169.1, 143.0, 141.0, 128.85, 128.80, 127.87, 127.85, 127.5, 126.6, 65.8, 46.8, 30.4, 20.3. HRMS (ESI), *m/z* calcd for $C_{18}H_{17}NO_3$ $[M+Na]^+$ 318.1101, found 318.1097.

***trans*-2-(4-Methoxyphenyl)-6-oxo-1-phenylpiperidine-3-carboxylic acid (7b).** Yield 373 mg (65%),



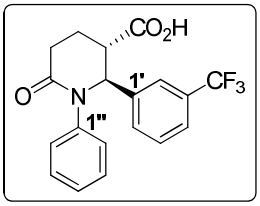
dr 7:1; crystallization from aqueous ethanol afforded pure *trans*-isomer; Colorless solid; Mp 224−225 °C (EtOH-H_2O); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.49 (br.s, 1H, COOH), 7.27 – 7.20 (m, 4H, 2',6'-H and *m*-Ph), 7.17 – 7.10 (m, 3H, *o*-Ph and *p*-Ph), 6.87 (d, *J* = 8.5 Hz, 2H, 3',5'-H), 5.30 (d, *J* = 4.7 Hz, 1H, 2-H), 3.73 (s, 3H, OCH_3), 2.96 (dt, *J* = 6.2, 4.5 Hz, 1H, 3-H), 2.67 (ddd, *J* = 17.9, 7.0, 5.6 Hz, 1H, 5-H), 2.55 – 2.46 (m, 1H, 5-H), 2.14 – 2.05 (m, 1H, 4-H), 2.04 – 1.96 (m, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.8, 169.1, 159.1, 143.1, 132.9, 128.8, 128.7, 127.9, 126.6, 114.4, 65.4, 55.6, 47.0, 30.5, 20.4. HRMS (ESI), *m/z* calcd for $C_{19}H_{19}NO_4$ $[M+Na]^+$ 348.1206, found 348.1199.

***trans/cis*-2-(4-Fluorophenyl)-6-oxo-1-phenylpiperidine-3-carboxylic acid (7c).** Yield 390 mg



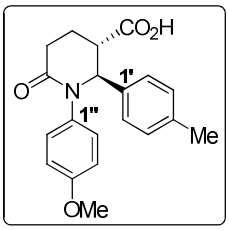
(72%), *dr* 8:1; crystallization from aqueous ethanol afforded *dr* 13:1; Beige solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ for *trans*-isomer: 12.53 (br.s, 1H, COOH), 7.37 – 7.34 (m, 2H, 2',6'-H), 7.27 – 7.23 (m, 2H, *m*-Ph), 7.18 – 7.07 (m, 5H, 3',5'-H, *o*-Ph and *p*-Ph), 5.36 (d, *J* = 5.0 Hz, 1H, 2-H), 3.00 (dt, *J* = 6.4, 4.6 Hz, 1H, 3-H), 2.68 (dt, *J* = 17.9, 6.4 Hz, 1H, 5-H), 2.55 – 2.46 (m, 1H, 5-H), 2.17 – 2.08 (m, 1H, 4-H), 2.05 – 1.96 (m, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ for *trans*-isomer: 173.7, 169.0, 161.9 (d, *J* = 243.9 Hz), 142.8, 137.0 (d, *J* = 3.1 Hz), 129.7 (d, *J* = 8.3 Hz), 128.8, 128.0, 126.7, 115.5 (d, *J* = 21.5 Hz), 65.2, 47.0, 30.6, 20.7. HRMS (ESI), *m/z* calcd for $C_{18}H_{16}FNO_3$ $[M+Na]^+$ 336.1006, found 336.1009.

***trans/cis*-6-Oxo-1-phenyl-2-(3-(trifluoromethyl)phenyl)piperidine-3-carboxylic acid (7d).** Yield

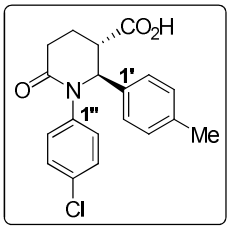


417 mg (66%), *dr* 6:1; crystallization from aqueous ethanol afforded *dr* 10:1; Beige solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ for *trans*-isomer: 12.55 (br.s, 1H, COOH), 7.68 – 7.63 (m, 2H, Ar'H), 7.58 – 7.52 (m, 2H, Ar'H), 7.25 (t, *J* = 7.8 Hz, 2H, *m*-Ph), 7.15 (d, *J* = 7.6 Hz, 2H, *o*-Ph), 7.12 (t, *J* = 7.6 Hz, 1H, *p*-Ph), 5.48 (d, *J* = 5.3 Hz, 1H, 2-H), 3.09 (dt, *J* = 6.6, 4.7 Hz, 1H, 3-H), 2.73 (dt, *J* = 17.9, 6.6 Hz, 1H, 5-H), 2.56 – 2.48 (m, 1H, 5-H), 2.19 – 2.10 (m, 1H, 4-H), 2.05 – 1.94 (m, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ for *trans*-isomer: 173.8, 169.1, 142.4, 142.2, 132.1, 129.9, 129.5 (q, *J* = 31.6 Hz), 129.0, 128.1, 126.9, 124.7 (q, *J* = 3.8 Hz), 124.6 (q, *J* = 3.8 Hz), 124.5 (q, *J* = 272.4 Hz), 65.1, 46.6, 30.5, 20.8. HRMS (ESI), *m/z* calcd for $C_{19}H_{16}F_3NO_3$ $[M+Na]^+$ 386.0974, found 386.0967.

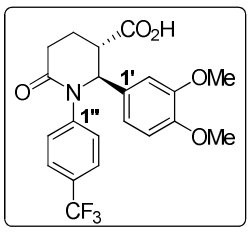
***trans/cis*-1-(4-Methoxyphenyl)-6-oxo-2-*p*-tolylpiperidine-3-carboxylic acid (7e).** Yield 413 mg (70%) *dr* 6.5:1; Beige solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ for *trans*-isomer: 12.48 (br.s, 1H, COOH), 7.19 (d, *J* = 8.3 Hz, 2H, Ar'H), 7.13 (d, *J* = 8.3 Hz, 2H, Ar'H), 7.05 (d, *J* = 8.9 Hz, 2H, Ar"H), 6.80 (d, *J* = 8.9 Hz, 2H, Ar"H), 5.26 (d, *J* = 4.3 Hz, 1H, 2-H), 3.70 (s, 3H, OCH_3), 2.93 (dt, *J* = 6.0, 4.3 Hz, 1H, 3-H), 2.62 (ddd, *J* = 18.0, 6.8, 5.4 Hz, 1H, 5-H), 2.54 – 2.44 (m, 1H, 5-H), 2.27 (s, 3H, 4'-CH_3), 2.13 – 2.04 (m, 1H, 4-H), 2.02 – 1.93 (m, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ for *trans*-isomer: 173.8, 169.1, 157.9, 138.1, 137.0, 135.9, 129.4, 128.9, 127.4, 114.3, 65.9, 55.7, 46.9, 30.4, 20.9, 20.3. HRMS (ESI), *m/z* calcd for $C_{20}H_{21}NO_4$ $[M+Na]^+$ 362.1363, found 362.1356.



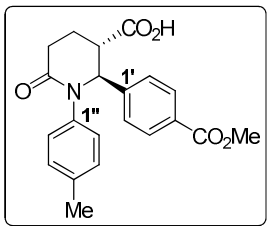
***trans/cis*-1-(4-Chlorophenyl)-6-oxo-2-*p*-tolylpiperidine-3-carboxylic acid (7f).** Yield 383 mg (64%) *dr* 7:1; Beige solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ for *trans*-isomer:12.49 (br.s, 1H, COOH), 7.29 (d, *J* = 8.7 Hz, 2H, 3",5"-H), 7.19 (d, *J* = 8.0 Hz, 2H, Ar'H), 7.17 (d, *J* = 8.7 Hz, 2H, 2",6"-H), 7.13 (d, *J* = 8.0 Hz, 2H, Ar'H), 5.30 (d, *J* = 4.7 Hz, 1H, 2-H), 2.97 (dt, *J* = 6.1, 4.6 Hz, 1H, 3-H), 2.66 (ddd, *J* = 18.0, 6.9, 5.7 Hz, 1H, 5-H), 2.55 – 2.45 (m, 1H, 5-H), 2.26 (s, 3H, 4'-CH_3), 2.14 – 2.05 (m, 1H, 4-H), 2.04 – 1.94 (m, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ for *trans*-isomer: 173.7, 169.2, 141.8, 137.7, 137.2, 131.1, 129.6, 129.5, 128.8, 127.5, 65.5, 46.9, 30.5, 20.9, 20.5. HRMS (ESI), *m/z* calcd for $C_{19}H_{18}ClNO_3$ $[M+Na]^+$ 366.0867, found 366.0867.

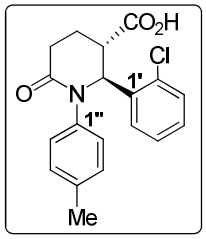


***trans*-2-(3,4-Dimethoxyphenyl)-6-oxo-1-(4-(trifluoromethyl)phenyl)piperidine-3-carboxylic acid (7g).** Crystallization from aqueous ethanol afforded 378 mg (51%) *dr* 8:1; pure *trans*-isomer was obtained after crystallization from aqueous ethanol; Beige solid; Mp 194−195 °C (EtOH-H_2O); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.53 (br.s, 1H, COOH), 7.63 (d, *J* = 8.5 Hz, 2H, 3",5"-H), 7.43 (d, *J* = 8.5 Hz, 2H, 2",6"-H), 6.90 (d, *J* = 2.2 Hz, 1H, 2'-H), 6.88 (d, *J* = 8.3 Hz, 1H, 5'-H), 6.83 (dd, *J* = 8.3, 2.2 Hz, 1H, 6'-H), 5.36 (d, *J* = 4.7 Hz, 1H, 2-H), 3.75 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.06 (dt, *J* = 6.2, 4.5 Hz, 1H, 3-H), 2.70 (ddd, *J* = 18.1, 6.9, 5.6 Hz, 1H, 5-H), 2.56 – 2.47 (m, 1H, 5-H), 2.17 – 2.07 (m, 1H, 4-H), 2.06 – 1.97 (m, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.8, 169.4, 149.7, 149.1, 146.6, 133.0, 128.5, 127.1 (q, *J* = 32.0 Hz), 125.9 (q, *J* = 3.7 Hz), 124.5 (q, *J* = 272.0 Hz), 119.9, 112.8, 112.1, 65.1, 56.4, 56.3, 46.8, 30.5, 20.5. HRMS (ESI), *m/z* calcd for $C_{21}H_{20}F_3NO_5$ $[M+Na]^+$ 446.1186, found 446.1197.

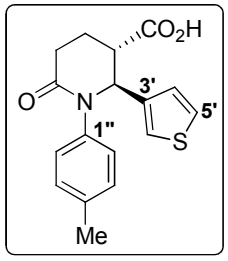


***trans*-2-(4-(Methoxycarbonyl)phenyl)-6-oxo-1-*p*-tolylpiperidine-3-carboxylic acid (7h).** Yield 465 mg (74%), *dr* 6:1; pure *trans*-isomer was obtained after crystallization from aqueous ethanol; Beige solid; Mp 230−231 °C (EtOH-H_2O); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.57 (br.s, 1H, COOH), 7.90 (d, *J* = 8.2 Hz, 2H, 3',5'-H), 7.48 (d, *J* = 8.2 Hz, 2H, 2',6'-H), 7.05 (s, 4H, Ar"H), 5.41 (d, *J* = 4.6 Hz, 1H, 2-H), 3.85 (s, 3H, CO_2CH_3), 3.01 (dt, *J* = 6.2, 4.5 Hz, 1H, 3-H), 2.67 (ddd, *J* = 17.9, 6.8, 5.6 Hz, 1H, 5-H), 2.55 – 2.46 (m, 1H, 5-H), 2.21 (s, 3H, 4"-CH_3), 2.17 – 2.07 (m, 1H, 4-H), 2.03 – 1.93 (m, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.5, 169.1, 166.4, 146.4, 140.2, 136.1, 129.7, 129.5, 129.4, 128.1, 127.7, 65.7, 52.4, 46.7, 30.5, 20.8, 20.5. HRMS (ESI), *m/z* calcd for $C_{21}H_{21}NO_5$ $[M+Na]^+$ 390.1312, found 390.1311.

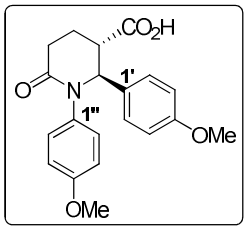


***trans*-2-(2-Chlorophenyl)-6-oxo-1-*p*-tolylpiperidine-3-carboxylic acid (7i).** Yield 486 mg (80%), *dr* 7:1; pure *trans*-isomer was obtained after crystallization from aqueous ethanol; 

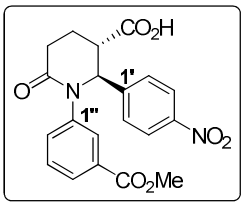
Beige solid; Mp 264−265 °C (EtOH-H_2O); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.73 (br.s, 1H, COOH), 7.58 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar'H), 7.44 – 7.39 (m, 1H, Ar'H), 7.37 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar'H), 7.33 – 7.26 (m, 1H, Ar'H), 7.10 – 7.03 (m, 4H, Ar"H), 5.75 (d, *J* = 3.4 Hz, 1H, 2-H), 3.00 (dt, *J* = 4.5, 3.7 Hz, 1H, 3-H), 2.67 (ddd, *J* = 18.2, 6.8, 3.9 Hz, 1H, 5-H), 2.56 – 2.45 (m, 1H, 5-H), 2.23 (s, 3H, 4"-CH_3), 2.17 – 2.08 (m, 1H, 4-H), 2.01 – 1.90 (m, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.5, 169.1, 140.4, 137.7, 136.3, 132.1, 130.3, 129.81, 129.80, 129.5, 127.7, 127.4, 63.1, 43.8, 30.0, 20.9, 19.7. HRMS (ESI), *m/z* calcd for $C_{19}H_{18}ClNO_3$ $[M+Na]^+$ 366.0867, found 366.0869.

***trans/cis*-6-Oxo-2-(thiophen-3-yl)-1-p-tolylpiperidine-3-carboxylic acid (7j).** Yield 353 mg (64%), 

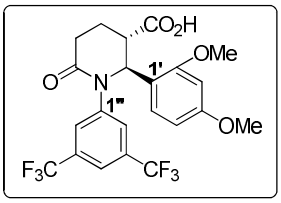
dr 4:1; crystallization from aqueous ethanol afforded *dr* 8:1; Beige solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ for *trans*-isomer: 12.52 (br.s, 1H, COOH), 7.45 (dd, *J* = 5.0, 3.0 Hz, 1H, 4'-H), 7.35 (ddd, *J* = 3.0, 1.4, 0.8 Hz, 1H, 2'-H), 7.10 – 7.05 (m, 5H, 5'-H and Ar"H), 5.40 (d, *J* = 4.1 Hz, 1H, 2-H), 3.85 (s, 3H, CO_2CH_3), 3.03 (dt, *J* = 5.5, 4.3 Hz, 1H, 3-H), 2.59 (ddd, *J* = 17.9, 7.2, 4.9 Hz, 1H, 5-H), 2.53 – 2.42 (m, 1H, 5-H), 2.25 (s, 3H, 4"-CH_3), 2.16 – 2.06 (m, 1H, 4-H), 2.05 – 1.94 (m, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ for *trans*-isomer: 173.7, 168.7, 142.6, 140.6, 135.9, 129.3, 127.5, 127.1, 127.0, 123.2, 62.2, 46.0, 30.2, 20.9, 20.4. HRMS (ESI), *m/z* calcd for $C_{17}H_{17}NO_3S$ $[M+Na]^+$ 338.0821, found 338.0828.

***trans/cis*-1,2-Bis(4-methoxyphenyl)-6-oxopiperidine-3-carboxylic acid (7k).** Yield 444 mg (72%), 

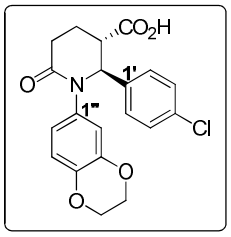
dr 6:1; Beige solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ for *trans*-isomer: 12.43 (br.s, 1H, COOH), 7.21 (d, *J* = 8.6 Hz, 2H, 2',6'-H), 7.04 (d, *J* = 8.9 Hz, 2H, Ar"H), 6.87 (d, *J* = 8.6 Hz, 2H, 3',5'-H), 6.80 (d, *J* = 8.9 Hz, 2H, Ar"H), 5.23 (d, *J* = 4.6 Hz, 1H, 2-H), 3.74 (s, 3H, 4'-OCH_3), 3.70 (s, 3H, 4"-OCH_3), 2.93 (dt, *J* = 6.1, 4.5 Hz, 1H, 3-H), 2.62 (ddd, *J* = 17.9, 6.9, 5.5 Hz, 1H, 5-H), 2.53 – 2.43 (m, 1H, 5-H), 2.12 – 2.04 (m, 1H, 4-H), 2.03 – 1.94 (m, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ for *trans*-isomer: 173.8, 169.1, 159.1, 157.9, 135.9, 133.0, 128.9, 128.7, 114.4, 114.3, 65.6, 55.7, 55.6, 47.0, 30.5, 20.5. HRMS (ESI), *m/z* calcd for $C_{20}H_{21}NO_5$ $[M-H]^-$ 354.1336, found 354.1345.

***trans*-1-(3-(Methoxycarbonyl)phenyl)-2-(4-nitrophenyl)-6-oxopiperidine-3-carboxylic acid (7l).** 

Yield 387 mg (56%), *dr* 6:1; pure *trans*-isomer was obtained after crystallization from aqueous ethanol; Beige solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.64 (br.s, 1H, COOH), 8.13 (d, *J* = 8.8 Hz, 2H, 3',5'-H), 7.83 (t, *J* = 2.0 Hz, 1H, 2"-H), 7.73 (dt, *J* = 7.5, 1.5 Hz, 1H, 6"-H), 7.67 (d, *J* = 8.8 Hz, 2H, 2',6'-H), 7.46 (ddd, *J* = 8.0, 2.2, 1.5 Hz, 1H, 4"-H). 7.40 (t, *J* = 7.9 Hz, 1H, 5"-H), 5.58 (d, *J* = 5.1 Hz, 1H, 2-H), 3.84 (s, 3H, CO_2CH_3), 3.10 (ddd, *J* = 6.8, 5.1, 4.1 Hz, 1H, 3-H), 2.76 (dt, *J* = 17.9, 6.5 Hz, 1H, 5-H), 2.58 – 2.47 (m, 1H, 5-H), 2.24 – 2.14 (m, 1H, 4-H), 2.08 – 1.98 (m, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.3, 169.3, 166.1, 148.2, 147.6, 142.8, 132.7, 130.9, 129.4, 129.3, 128.8, 127.6, 123.9, 65.2, 52.5, 46.6, 30.6, 20.8. HRMS (ESI), *m/z* calcd for $C_{20}H_{18}N_2O_7$ $[M-H]^-$ 397.1030, found 397.1045.

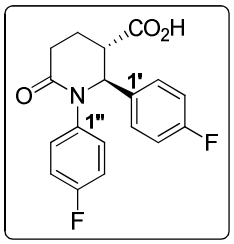
***trans*-1-(3,5-Bis(trifluoromethyl)phenyl)-2-(2,4-dimethoxyphenyl)-6-oxopiperidine-3-carboxylic acid (7m).** 

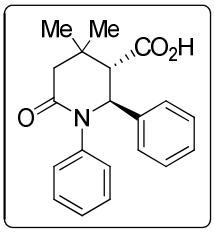
Method **B:** yield 502 mg (59%); Beige solid; Mp 234−235 °C (EtOH-H_2O); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.81 (br.s, 1H, COOH), 7.79 (s, 1H, 4''-H), 7.76 (s, 2H, 2'',6''-H), 7.19 (d, J = 8.3 Hz, 1H, 6'-H), 6.47 (dd, J = 8.3, 2.2 Hz, 1H, 5'-H), 6.45 (d, J = 2.2 Hz, 1H, 3'-H), 5.55 (d, J = 6.4 Hz, 1H, 2-H), 3.71 (s, 6H, 2'-OCH_3 and 4'-OCH_3), 3.12 (ddd, J = 7.9, 6.4, 4.1 Hz, 1H), 2.70 (ddd, J = 17.9, 7.9, 6.6 Hz, 1H), 2.58 – 2.51 (m, 1H, 5-H) 2.23 – 2.13 (m, 1H, 4-H), 2.11 – 2.04 (m, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.9, 169.9, 161.1, 157.9, 144.5, 130.86 (q, J = 33.2 Hz), 129.9, 128.9 (q, J = 4.8 Hz), 123.4 (q, J = 272.7 Hz), 120.2 – 119.8 (m), 119.3, 105.7, 99.3, 61.0, 56.0, 55.7, 45.0, 31.0, 22.0. HRMS (ESI), *m/z* calcd for $C_{22}H_{19}FNO_5$ $[M+H]^+$ 492.1240, found 492.1252.

***trans/cis*-2-(4-Chlorophenyl)-1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-6-oxopiperidine-3-carboxylic acid (7n).** 

Yield 601 mg (89%), *dr* 5:1; Beige solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ for *trans*-isomer: 12.51 (br.s, 1H, COOH), 7.40 – 7.32 (m, 4H, ArH'), 6.71 (d, J = 8.6 Hz, 1H, 5''-H), 6.65 (d, J = 2.3 Hz, 1H, 2''-H), 6.60 (dd, J = 8.5, 2.3 Hz, 1H, 6''-H), 5.28 (d, J = 4.5 Hz, 1H, 2-H), 4.18 (s, 4H, OCH_2CH_2O), 2.94 (dt, J = 5.6, 4.5 Hz, 1H, 3-H), 2.69 – 2.57 (m, 1H, 5-H), 2.54 – 2.41 (m, 1H, 5-H), 2.16 – 2.01 (m, 1H, 4-H), 2.01 – 1.86 (m, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ for *trans*-isomer: 173.6, 169.1, 143.4, 142.4, 140.1, 136.1, 132.6, 129.5, 128.8, 120.7, 116.9, 116.9, 65.4, 64.5, 64.5, 46.6, 30.3, 20.2. HRMS (ESI), *m/z* calcd for $C_{20}H_{18}ClNO_5$ $[M+Na]^+$ 410.0766, found 410.0762.

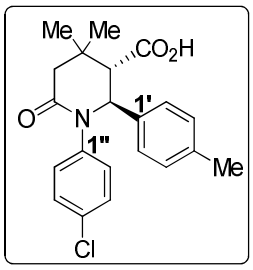
***trans/cis*-1,2-Bis(4-fluorophenyl)-6-oxopiperidine-3-carboxylic acid (7o).** Yield 419 mg (73%), *dr* 6:1; Beige solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ for *trans*-isomer: 12.49 (br.s, 1H, COOH), 7.35 (dd, J = 8.8, 5.3 Hz, 2H), 7.16 (dd, J = 9.0, 5.1 Hz, 2H), 7.10 (t, J = 8.8 Hz, 2H), 7.05 (t, J = 8.9 Hz, 2H), 5.31 (d, J = 5.3 Hz, 1H, 2-H), 3.00 (ddd, J = 6.9, 5.3, 4.2 Hz, 1H, 3-H), 2.69 (dt, J = 17.8, 6.6 Hz, 1H, 5-H), 2.55 – 2.45 (m, 1H, 5-H), 2.17 – 2.08 (m, 1H, 4-H), 2.07 – 1.98 (m, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ for *trans*-isomer: 173.6, 169.2, 162.5 (d, J = 128.2 Hz), 160.1 (d, J = 127.6 Hz), 138.9 (d, J = 3.1 Hz), 136.8 (d, J = 3.0 Hz), 130.1 (d, J = 8.6 Hz), 129.9 (d, J = 8.3 Hz), 115.7 (d, J = 0.8 Hz), 115.5 (d, J = 2.0 Hz), 65.4, 47.0, 30.6, 20.9. HRMS (ESI), *m/z* calcd for $C_{18}H_{15}F_2NO_3$ $[M-H]^-$ 330.0936, found 330.0948.



***trans*-4,4-Dimethyl-6-oxo-1,2-diphenylpiperidine-3-carboxylic acid (8a).** 

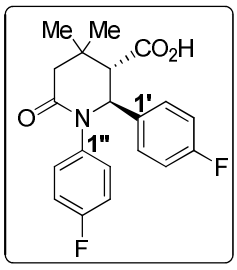
Yield 222 mg (69%), *dr* 4:1; pure *trans*-isomer was obtained after crystallization from aqueous ethanol; Colorless solid; Mp 287−288 °C (EtOH-H_2O); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.41 (br.s, 1H, COOH), 7.27 – 7.08 (m, 7H, ArH), 7.06 – 7.00 (m, 3H, ArH), 5.10 (d, J = 11.0 Hz, 1H, 2-H), 2.99 (d, J = 11.0 Hz, 1H, 3-H), 2.82 (d, J = 16.5 Hz, 1H, 5-H), 2.27 (d, J = 16.5 Hz, 1H, 5-H), 1.27 (s, 3H, 4-CH_3), 1.09 (s, 3H, 4-CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.5, 168.9, 141.2, 140.1, 128.74, 128.73, 128.72, 128.5, 128.0, 126.7, 64.6, 58.2, 47.5, 33.1, 28.8, 21.3. HRMS (ESI), *m/z* calcd for $C_{20}H_{21}NO_3$ $[M+H]^+$ 324.1594, found 324.1612.

***trans/cis*-1-(4-Chlorophenyl)-4,4-dimethyl-6-oxo-2-(*p*-tolyl)piperidine-3-carboxylic acid (8b).**



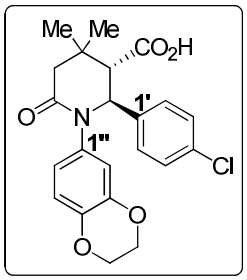
Yield 133 mg (36%), *dr* 5:1; crystallization from aqueous ethanol afforded *dr* 7:1; Colorless solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ for *trans*-isomer: 12.37 (br.s, 1H, COOH), 7.22 (d, J = 8.7 Hz, 2H, 2",6"-H), 7.11 (d, J = 8.0 Hz, 2H, 2',6'-H), 7.07 (d, J = 8.7 Hz, 2H, 3",5"-H), 6.99 (d, J = 8.0 Hz, 2H, 3',5'-H), 5.06 (d, J = 11.0 Hz, 1H, 2-H), 2.96 (d, J = 11.0 Hz, 1H, 3-H), 2.81 (d, J = 16.5 Hz, 1H, 5-H), 2.26 (d, J = 16.5 Hz, 1H, 5-H), 2.18 (s, 3H, 4'-CH_3), 1.24 (s, 3H, 4-CH_3), 1.07 (s, 3H, 4-CH_3); signals of *cis*-isomer: 5.52 (d, J = 5.6 Hz, 1H, 2-H), 3.04 (d, J = 17.1 Hz, 1H, 5-H), 2.16 (s, 3H, 4'-CH_3), 1.32 (s, 3H, 4-CH_3), 1.03 (s, 3H, 4-CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ for *trans*-isomer: 172.4, 169.1, 140.2, 137.2, 136.8, 130.9, 130.5, 129.2, 128.7, 128.6, 64.0, 58.1, 47.4, 33.0, 28.7, 21.3, 21.1. HRMS (ESI), *m/z* calcd for $C_{21}H_{22}ClNO_3$ $[M+H]^+$ 394.1180, found 394.1196.

***trans/cis*-1,2-Bis(4-fluorophenyl)-4,4-dimethyl-6-oxopiperidine-3-carboxylic acid (8c).** Yield



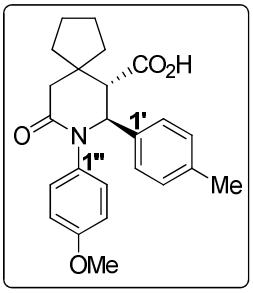
208 mg (58%), *dr* 4:1; Colorless solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ for *trans*-isomer: 12.42 (br.s, 1H, COOH), 7.32 – 7.21 (m, 2H, ArH), 7.10 – 6.94 (m, 6H, ArH), 5.10 (d, J = 11.1 Hz, 1H, 2-H), 3.02 (d, J = 11.1 Hz, 1H, 3-H), 2.82 (d, J = 16.6 Hz, 1H, 5-H), 2.27 (d, J = 16.6 Hz, 1H, 5-H), 1.26 (s, 3H, 4-CH_3), 1.09 (s, 3H, 4-CH_3); signals of *cis*-isomer: 5.58 (d, J = 5.7 Hz, 1H, 2-H), 3.06 (d, J = 17.0 Hz, 1H, 5-H), 2.86 (dd, J = 5.7, 1.6 Hz, 1H, 3-H), 2.16 (dd, J = 17.0, 1.6 Hz, 1H, 5-H), 1.33 (s, 3H, 4-CH_3), 1.04 (s, 3H, 4-CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ for *trans*-isomer: 172.4, 169.1, 161.8 (d, J = 243.9 Hz), 160.5 (d, J = 243.2 Hz), 137.3 (d, J = 2.9 Hz), 136.1 (d, J = 3.0 Hz), 131.0 (d, J = 8.3 Hz), 130.7 (d, J = 8.6 Hz), 115.6 (d, J = 16.9 Hz), 115.4 (d, J = 15.8 Hz), 63.8, 57.9, 47.4, 33.0, 28.7, 21.4; signals of *cis*-isomer: 173.0, 170.6, 162.5 (d, J = 243.5 Hz), 161.44 (d, J = 243.2 Hz), 137.5 (d, J = 2.9 Hz), 134.6 (d, J = 3.2 Hz), 130.1 (d, J = 8.6 Hz), 114.9 (d, J = 21.3 Hz), 61.0, 56.3, 42.5, 32.2, 28.2, 27.7. HRMS (ESI), *m/z* calcd for $C_{20}H_{19}F_2NO_3$ $[M+Na]^+$ 382.1225, found 382.1227.

***trans*-2-(4-Chlorophenyl)-1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-4,4-dimethyl-6-oxopiperidine-**



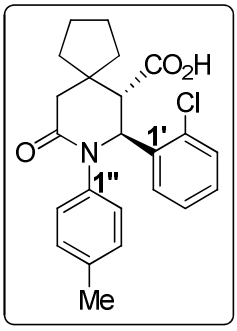
3-carboxylic acid (8d). Yield 207 mg (50%), *dr* 7:1; pure *trans*-isomer was obtained after crystallization from aqueous ethanol; Colorless solid; Mp 295−296 °C (EtOH-H_2O); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.45 (br.s, 1H, COOH), 7.30 – 7.22 (m, 4H, ArH'), 6.65 (d, J = 9.0 Hz, 1H, 5"-H), 6.52 – 6.46 (m, 2H, 2"-H and 6"-H), 5.01 (d, J = 11.0 Hz, 1H, 2-H), 4.17 – 4.10 (m, 4H, OCH_2CH_2O), 2.92 (d, J = 11.0 Hz, 1H, 3-H), 2.77 (d, J = 16.5 Hz, 1H, 5-H), 2.24 (d, J = 16.5 Hz, 1H, 5-H), 1.22 (s, 3H, 4-CH_3), 1.06 (s, 3H, 4-CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.3, 169.1, 143.2, 142.1, 139.4, 134.2, 132.5, 130.6, 128.6, 121.3, 117.6, 116.9, 64.3, 64.0, 58.1, 47.4, 33.1, 28.7, 21.3. HRMS (ESI), *m/z* calcd for $C_{22}H_{22}ClNO_5$ $[M+Na]^+$ 438.1079, found 438.1064.

***trans*-8-(4-Methoxyphenyl)-9-oxo-7-(*p*-tolyl)-8-azaspiro[4.5]decane-6-carboxylic acid (9a).** Yield



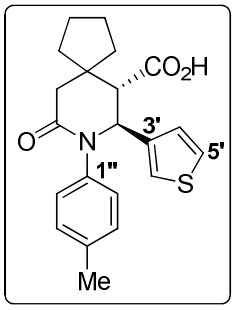
219 mg (63%), *dr* 4:1; pure *trans*-isomer was obtained after crystallization from aqueous ethanol; Colorless solid; Mp >300 °C (EtOH-H_2O); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.45 (br.s, 1H, COOH), 7.08 (d, *J* = 8.0 Hz, 2H, 2',6'-H), 6.99 (d, *J* = 8.0 Hz, 2H, 3',5'-H), 6.87 (d, *J* = 8.9 Hz, 2H, 2",6"-H), 6.71 (d, *J* = 8.9 Hz, 2H, 3",5"-H), 4.96 (d, *J* = 10.8 Hz, 1H, 7-H), 3.65 (s, 3H, OCH_3), 3.11 (d, *J* = 10.8 Hz, 1H, 6-H), 2.74 (d, *J* = 16.5 Hz, 1H, 10-H), 2.40 (d, *J* = 16.5 Hz, 1H, 10-H), 2.34 – 2.25 (m, 1H), 2.19 (s, 3H, 4'-CH_3), 1.81 – 1.60 (m, 4H), 1.59 – 1.38 (m, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.9, 169.2, 157.6, 137.4, 137.0, 134.0, 129.7, 129.2, 128.5, 114.0, 65.4, 57.0, 55.5, 46.3, 43.8, 37.4, 30.1, 24.9, 24.7, 21.1. HRMS (ESI), *m/z* calcd for $C_{24}H_{27}NO_4$ $[M+K]^+$ 432.1572, found 432.1579.

***trans/cis*-7-(2-Chlorophenyl)-9-oxo-8-(*p*-tolyl)-8-azaspiro[4.5]decane-6-carboxylic acid (9b).** Yield



238 mg (60%) *dr* 3:1; Colorless solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ for *trans*-isomer: 12.07 (br.s, 1H, COOH), 7.47 – 7.37 (m, 1H, 6'-H), 7.29 – 7.15 (m, 3H, ArH'), 6.99 (d, *J* = 8.3 Hz, 2H, 2",6"-H), 6.89 (d, *J* = 8.3 Hz, 2H, 3",5"-H), 5.52 (d, *J* = 10.0 Hz, 1H, 7-H), 3.34 (d, *J* = 10.0 Hz, 1H, 6-H), 2.69 (d, *J* = 16.5 Hz, 1H, 10-H), 2.48 (d, *J* = 16.5 Hz, 1H, 10-H), 2.42 – 2.31 (m, 1H), 2.20 (s, 3H, 4"-CH_3), 1.85 – 1.46 (m, 7H); signals of *cis*-isomer: 5.85 (d, *J* = 5.8 Hz, 1H, 7-H), 3.20 (d, *J* = 17.0 Hz, 1H, 10-H), 3.04 (dd, *J* = 5.8, 1.9 Hz, 1H, 6-H), 2.18 (s, 3H, 4"-CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ for *trans*-isomer: 172.4, 169.0, 138.7, 137.3, 136.2, 131.5, 130.3, 129.8, 129.2, 129.1, 128.0, 127.52, 127.48, 55.2, 46.6, 44.4, 37.9, 31.1, 25.0, 24.6, 20.8. HRMS (ESI), *m/z* calcd for $C_{23}H_{24}ClNO_3$ $[M+H]^+$ 398.1517, found 398.1522.

***trans/cis*-9-Oxo-7-(thiophen-3-yl)-8-(*p*-tolyl)-8-azaspiro[4.5]decane-6-carboxylic acid (9c).** Yield

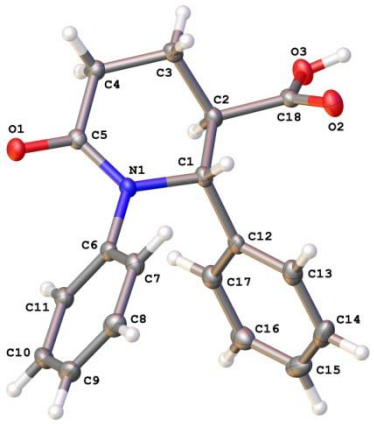


110 mg (30%) *dr* 2:1; Colorless solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ for *trans*-isomer: 12.17 (br.s, 1H, COOH), 7.32 (dd, *J* = 5.0, 2.9 Hz, 1H, 4'-H), 7.10 (dd, *J* = 2.9, 1.0 Hz, 1H, 2'-H), 7.04 – 6.95 (m, 3H, 5'-H and 2",6"-H), 6.85 (d, *J* = 8.2 Hz, 2H, 3",5"-H), 5.17 (d, *J* = 10.3 Hz, 1H, 7-H), 3.20 (d, *J* = 10.3 Hz, 1H, 6-H), 2.67 (d, *J* = 16.5 Hz, 1H, 10-H), 2.42 (d, *J* = 16.5 Hz, 1H, 10-H), 2.31 – 2.22 (m, 1H), 2.22 (s, 3H, 4"-CH_3), 1.85 – 1.44 (m, 7H); signals of *cis*-isomer: 5.54 (d, *J* = 5.6 Hz, 1H, 7-H), 3.01 (d, *J* = 17.0 Hz, 1H, 10-H), 2.90 (dd, *J* = 5.8, 1.6 Hz, 1H, 6-H), 2.19 (s, 3H, 4"-CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ for *trans*-isomer: 172.8, 168.7, 141.7, 139.0, 135.9, 129.2, 128.3, 127.4, 126.4, 124.3, 61.1, 56.5, 46.6, 44.0, 37.7, 30.6, 25.0, 24.6, 20.9; signals of *cis*-isomer: 173.1, 169.9, 140.0, 139.2, 135.3, 128.9, 128.5, 128.1, 125.1, 124.4, 59.0, 55.4, 43.3, 41.4, 38.0, 37.5, 23.9, 23.8, 20.9. HRMS (ESI), *m/z* calcd for $C_{21}H_{23}NO_3S$ $[M+Na]^+$ 392.1291, found 392.1294.

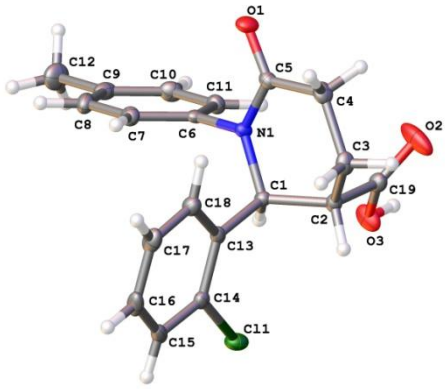
***trans/cis*-9-Oxo-7,8-diphenyl-8-azaspiro[4.5]decane-6-carboxylic acid (9d).** Yield 286 mg (82%), *dr* 5:1; Colorless solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ for *trans*-isomer: 12.20 (br.s, 1H, COOH), 7.24 – 7.09 (m, 7H, ArH), 7.06 (t, *J* = 7.5 Hz, 1H, *p*-Ph), 6.99 (d, *J* = 7.5 Hz, 2H, *o*-Ph), 5.12 (d, *J* = 10.5 Hz, 1H, 7-H), 3.18 (d, *J* = 10.5 Hz, 1H, 6-H), 2.76 (d, *J* = 16.5 Hz, 1H, 10-H), 2.47 (d, *J* = 16.5 Hz, 1H, 10-H), 2.40 – 2.29 (m, 1H), 1.87 – 1.45 (m, 7H); signals of *cis*-isomer: 5.49 (d, *J* = 5.7 Hz, 1H, 7-H), 3.13 (d, *J* = 17.0 Hz, 1H, 10-H), 2.94 (dd, *J* = 5.7, 1.5 Hz, 1H, 6-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ for *trans*-isomer: 172.7, 169.0, 141.6, 140.4, 128.7, 128.66, 128.65, 128. 6, 127.9, 126.6, 65.7, 57.2, 46.7, 44.1, 37.7, 30.5, 25.0, 24.6; signals of *cis*-isomer: 172.8, 170.4, 141.8, 138.6, 128.9, 128.3, 128.3, 127.9, 127.4, 126.0, 63.0, 55.9, 43.5, 41.2, 38.1, 37.4), 24.0, 23.8. HRMS (ESI), *m/z* calcd for $C_{22}H_{23}NO_3$ $[M+Na]^+$ 372.1570, found 372.1564.

3. Crystallographic data for compounds 7a, 7i and 8a

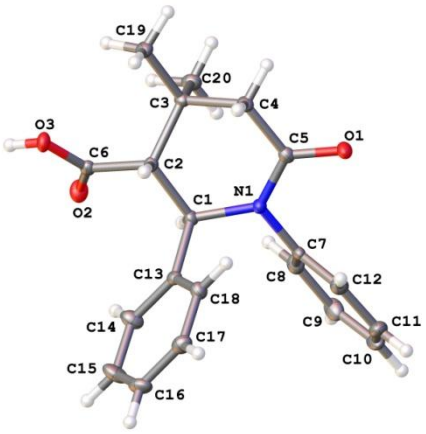
X-ray Single Crystal analyses were performed on Agilent Technologies Xcalibur Eos and Agilent Technologies (Oxford Diffraction) «Supernova» diffractometers. Using Olex2 [2], structures were solved with the Superflip [3] structure solution program using Charge Flipping and refined with the ShelXL [4] refinement package using Least Squares minimisation. CCDC 1470615, 1470616, 1470618 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk.



7a



7i



8a

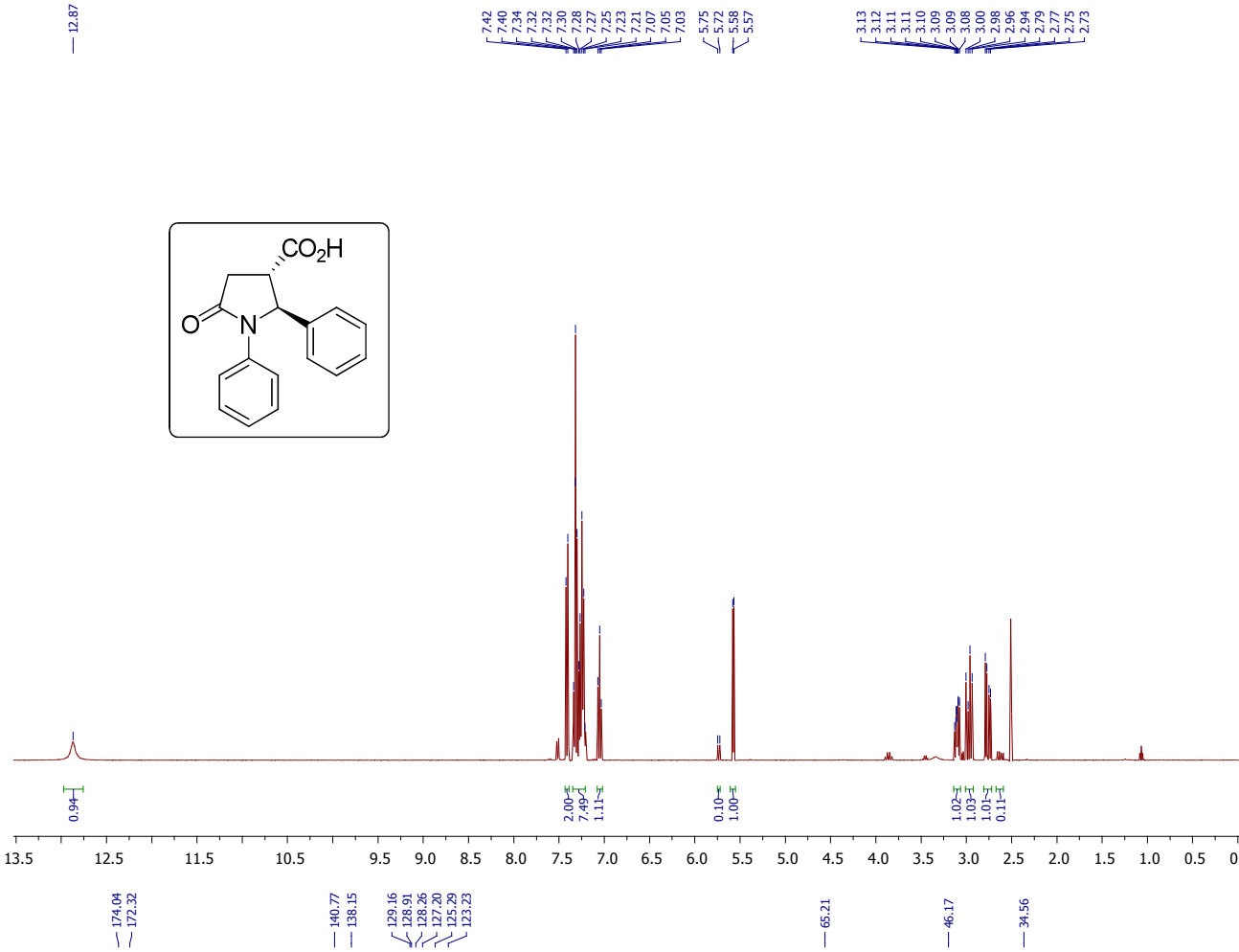
Table S2. Crystal data and structure refinement for 7a, 7i and 8a

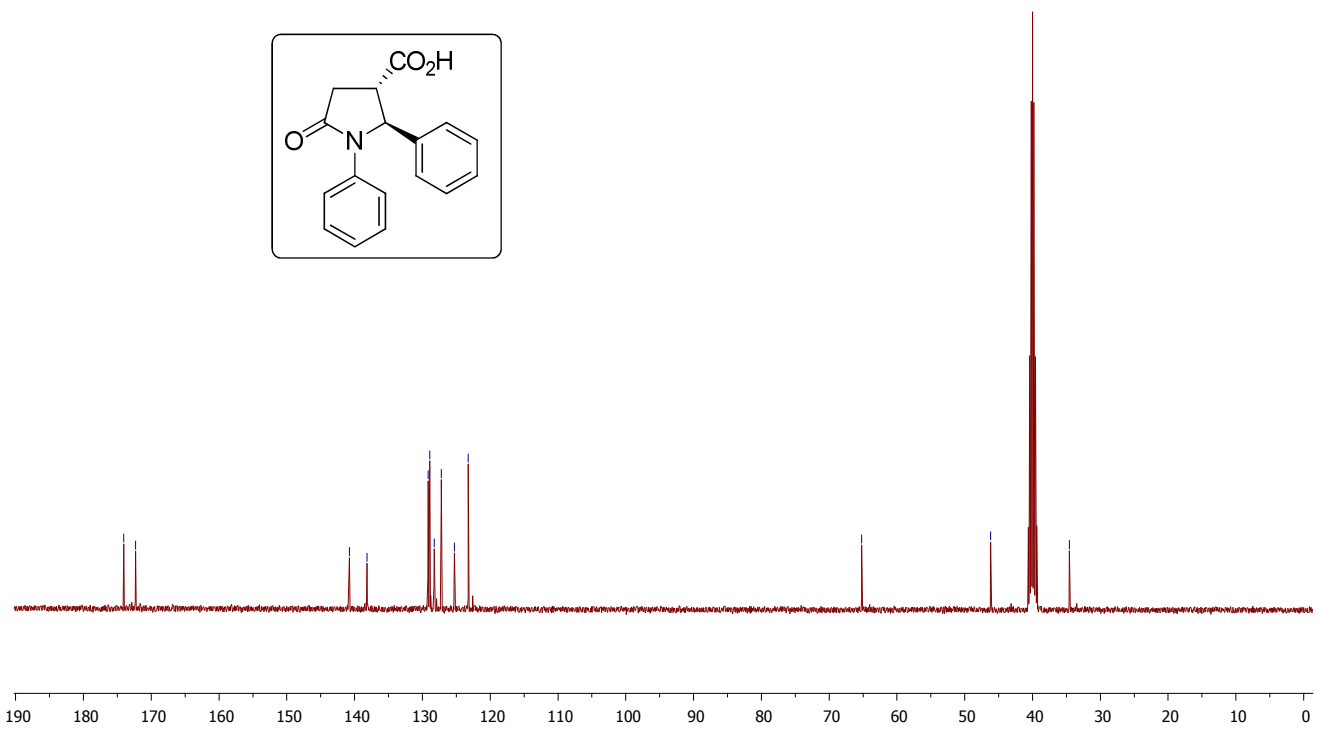
Identification code	**7a**	**7i**	**8a**
Empirical formula	$C_{18}H_{17}NO_3$	$C_{19}H_{18}ClNO_3$	$C_{20}H_{21}NO_3$
Formula weight	295.32	343.79	323.38
Temperature/K	100(2)	100(2)	100(2)
Crystal system	monoclinic	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$
a/Å	9.2973(3)	10.15491(19)	6.1741(3)
b/Å	9.6961(3)	11.7971(2)	22.3708(7)
c/Å	17.2808(6)	14.1333(3)	12.6253(4)
β/°	110.402(3)	97.8247(17)	103.267(4)
Volume/Å^3	1460.10(9)	1677.37(5)	1697.25(11)
Z	4	4	4
ρ_{calc}g/cm^3	1.343	1.361	1.266
μ/mm^{-1}	0.744	0.244	0.085
F(000)	624.0	720.0	688.0
Crystal size/mm^3	0.1 × 0.1 × 0.1	0.3 × 0.3 × 0.25	0.25 × 0.25 × 0.15
Radiation	CuKα (λ = 1.54184)	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)
2Θ range for data collection/°	10.15 to 149.95	5.322 to 55	6.392 to 54.998
Index ranges	-11 ≤ h ≤ 11, -11 ≤ k ≤ 12, -20 ≤ l ≤ 21	-13 ≤ h ≤ 13, -15 ≤ k ≤ 15, -18 ≤ l ≤ 18	-3 ≤ h ≤ 8, -26 ≤ k ≤ 29, -16 ≤ l ≤ 13
Reflections collected	9351	28349	7371
Independent reflections	2995 [R_{int} = 0.0406, R_{sigma} = 0.0362]	3845 [R_{int} = 0.0327, R_{sigma} = 0.0168]	3881 [R_{int} = 0.0197, R_{sigma} = 0.0362]
Data/restraints/parameters	2995/0/199	3845/0/219	3881/0/219
Goodness-of-fit on F^2	1.034	1.028	1.031
Final R indexes [I>=2σ (I)]	R_1 = 0.0431, wR_2 = 0.1103	R_1 = 0.0322, wR_2 = 0.0811	R_1 = 0.0436, wR_2 = 0.0941
Final R indexes [all data]	R_1 = 0.0511, wR_2 = 0.1185	R_1 = 0.0361, wR_2 = 0.0840	R_1 = 0.0583, wR_2 = 0.1009
Largest diff. peak/hole / e Å^{-3}	0.55/-0.25	0.38/-0.31	0.34/-0.20
CCDC	**1470616**	**1470618**	**1470615**

4. References:

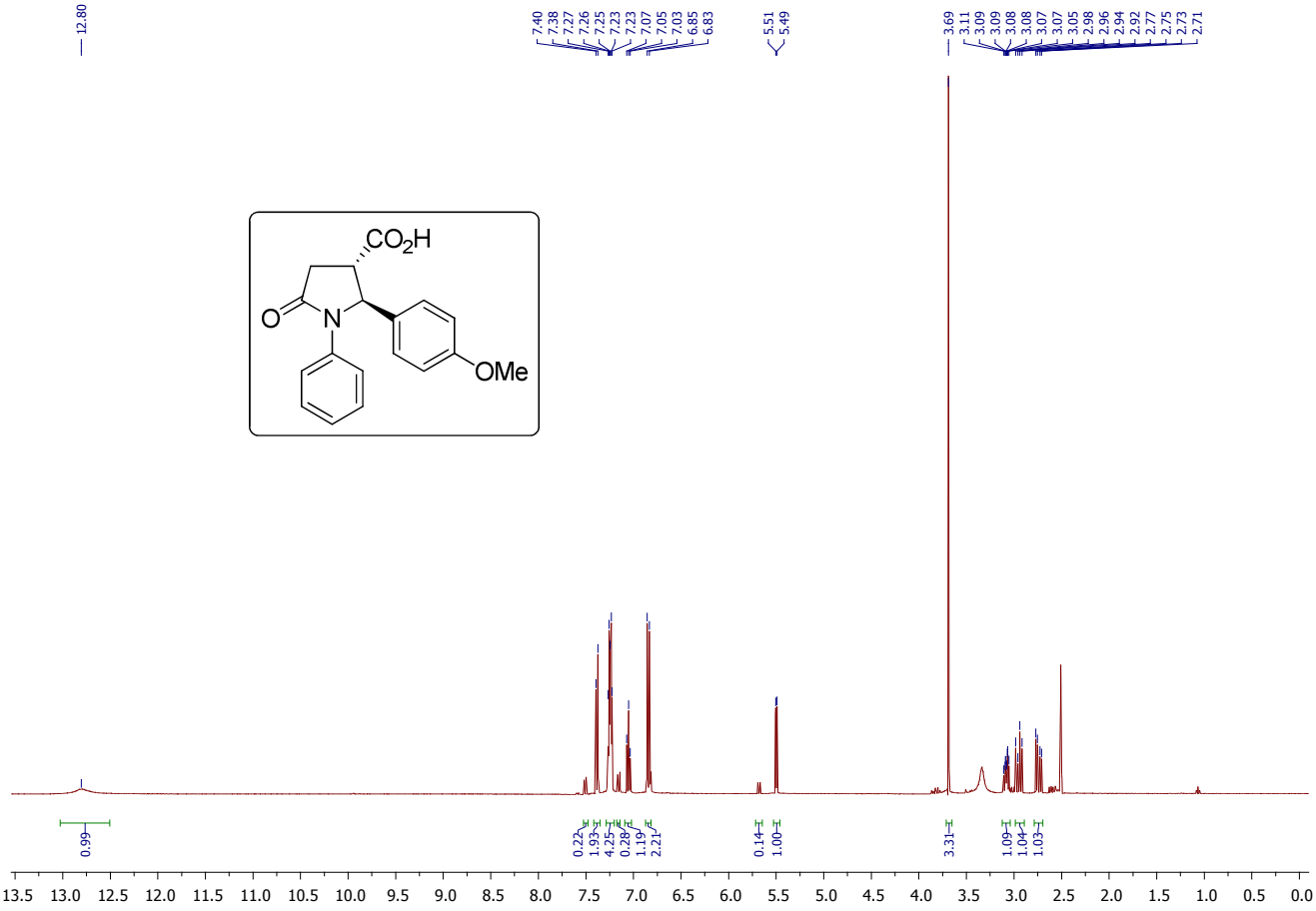
1. Tabcheh, M.; Baroudi, M.; Elomar, F.; Elzant, A.; Elkhatib, M.; Rolland, V. *Asian J. Chem.*, 2006, *18*(3), 1771–1782.
2. Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H. *J. Appl. Cryst.*, 2009*, 42*, 339–341.
3. Palatinus, L.; Chapuis, G. *J. Appl. Cryst.*, 2007, *40*, 786–790; Palatinus, L.; van der Lee, A. *J. Appl. Cryst.*, 2008, *41*, 975–984; Palatinus, L.; Prathapa, S. J.; van Smaalen, S. *J. Appl. Cryst.*, 2012, *45*, 575–580.
4. Sheldrick, G.M. *Acta Cryst.*, 2015, *C71*, 3–8.

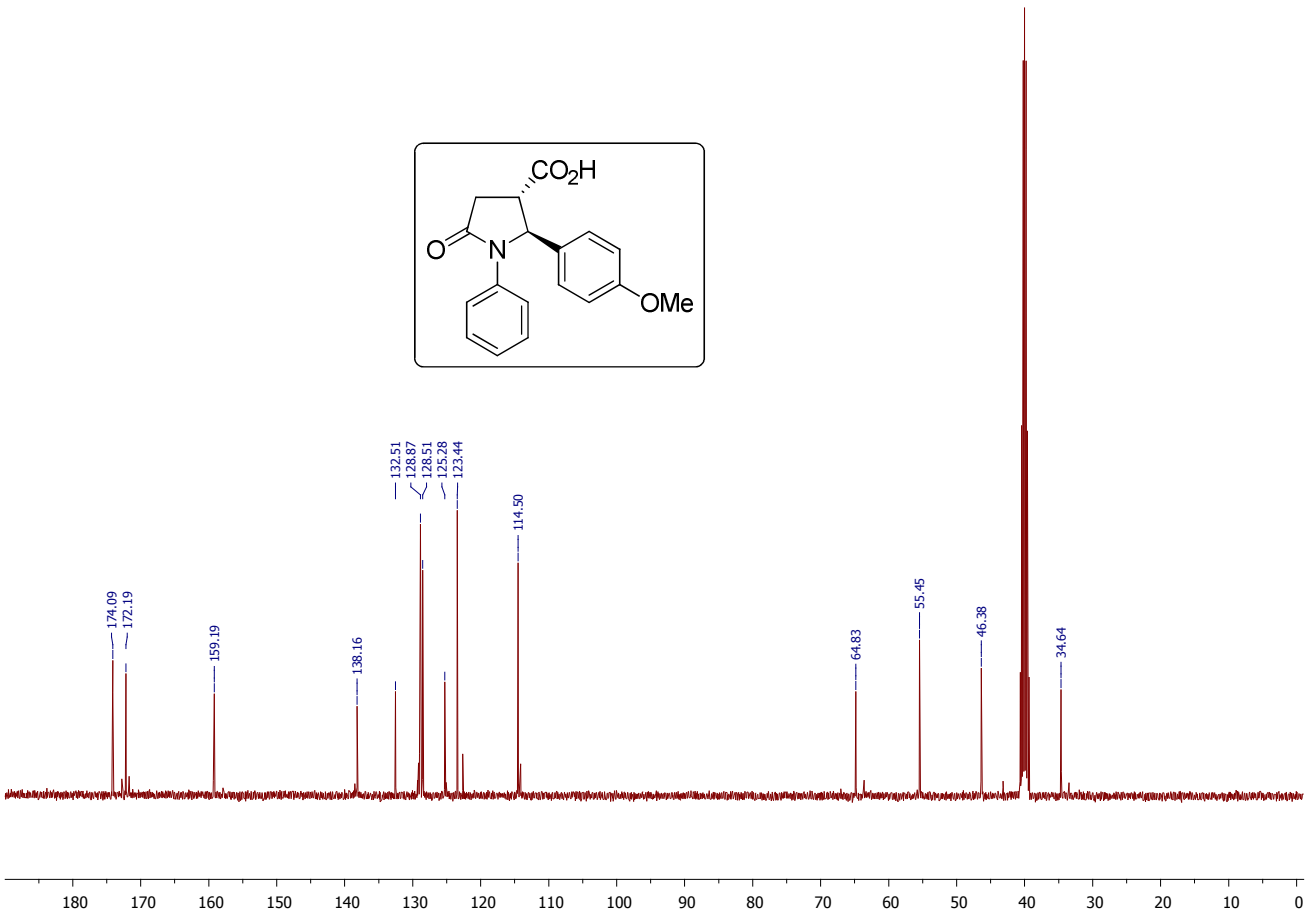
^{1}H and ^{13}C NMR spectra of compound 6a



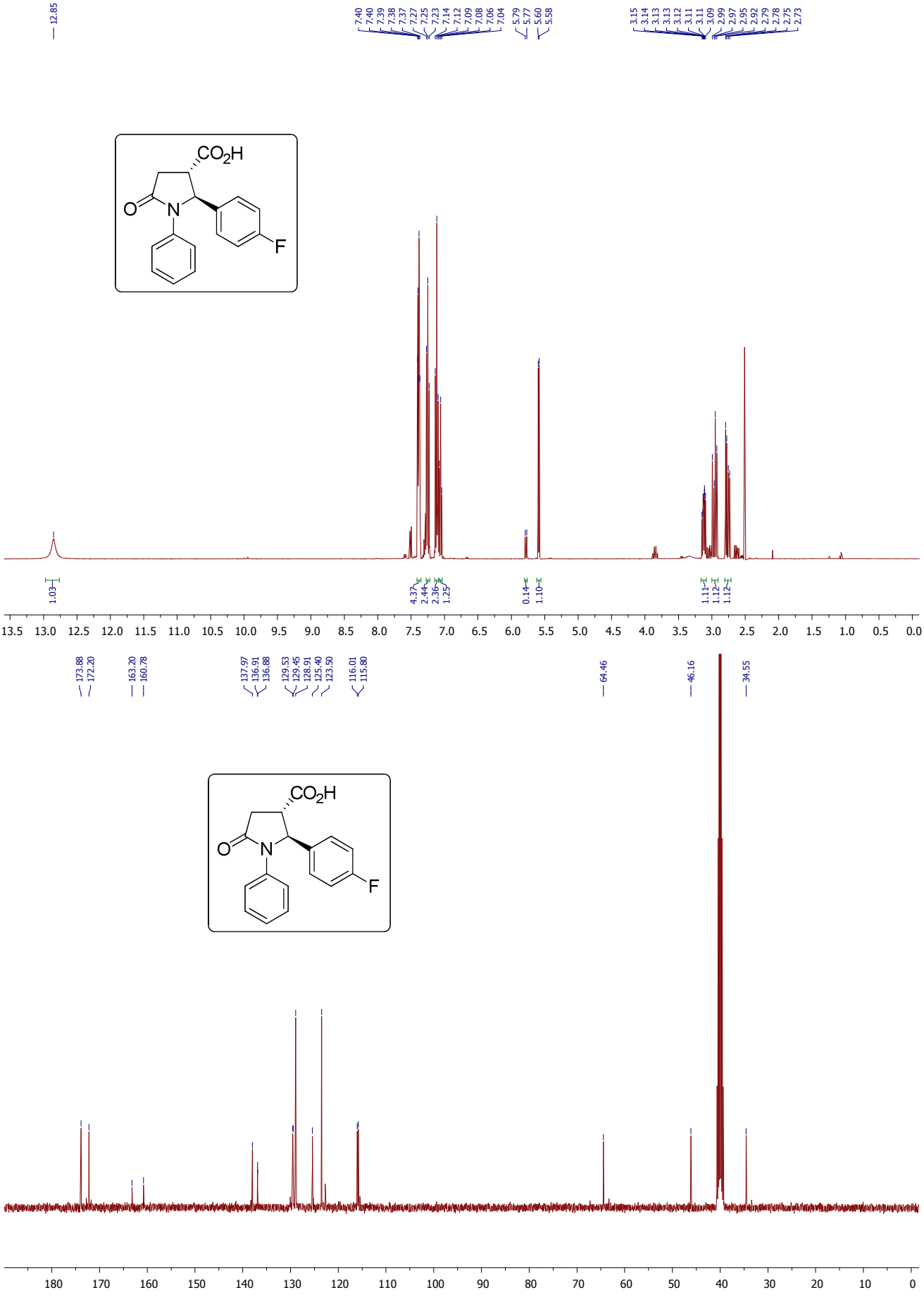


^{1}H and ^{13}C NMR spectra of compound 6b

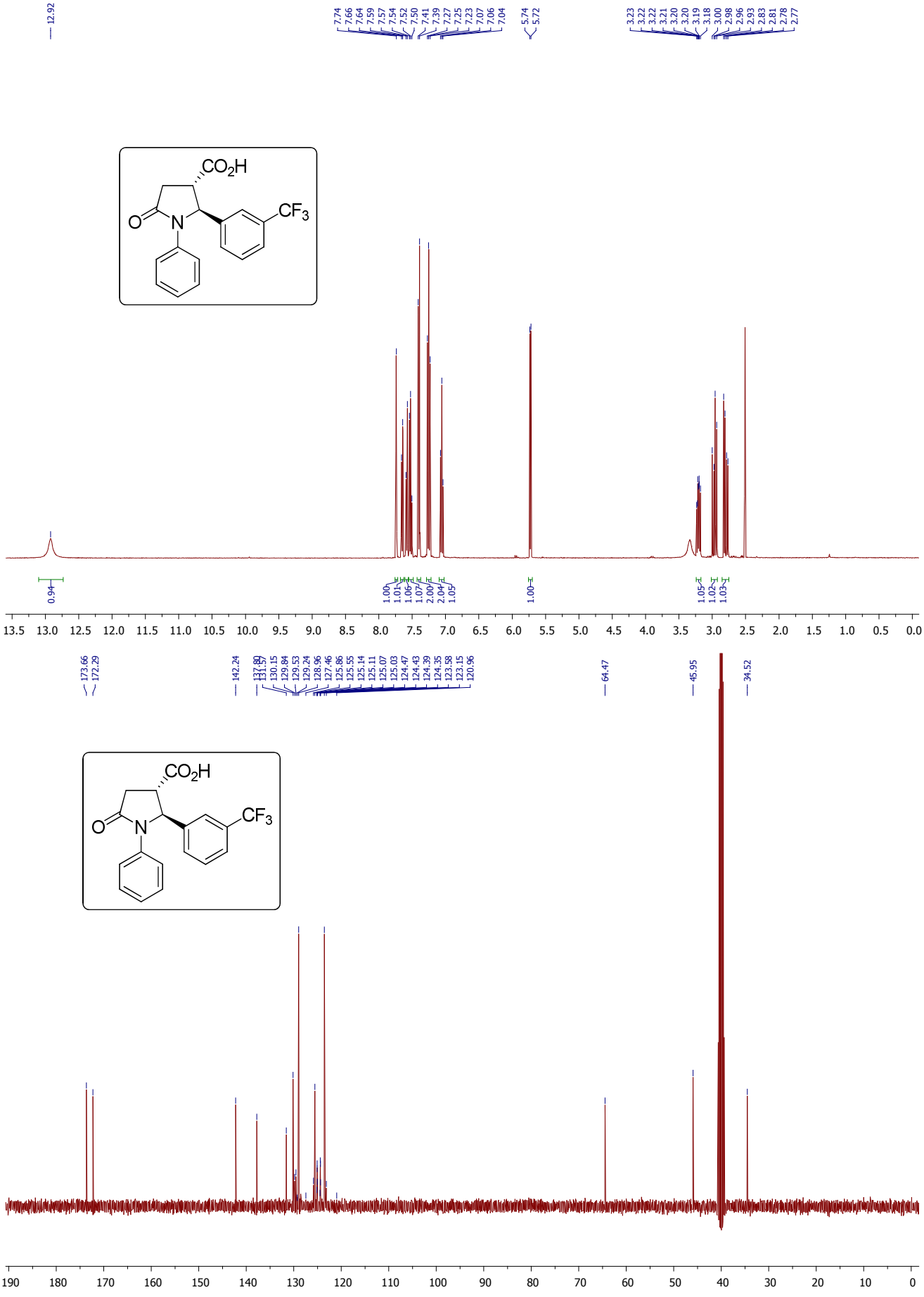




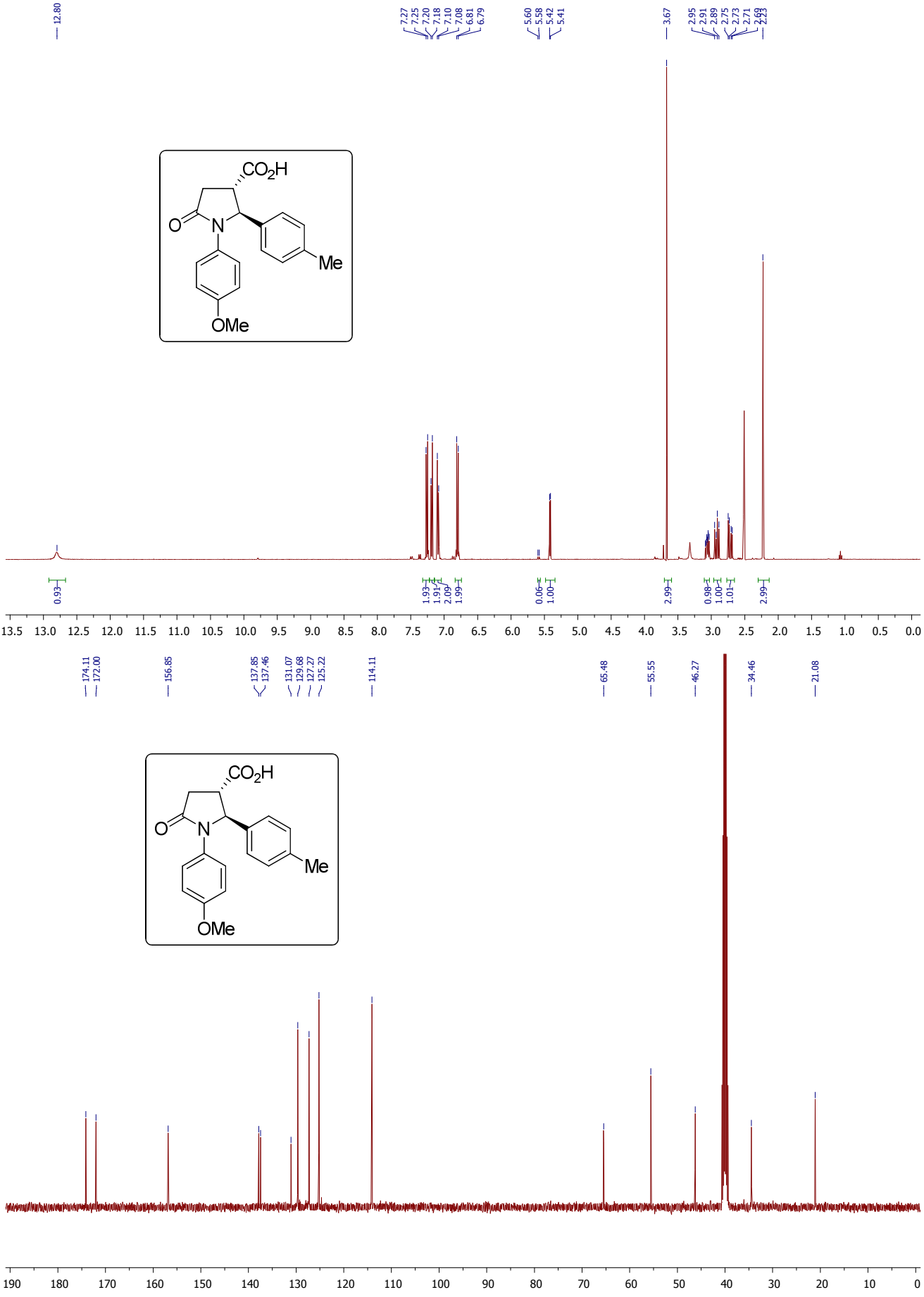
^{1}H and ^{13}C NMR spectra of compound 6c



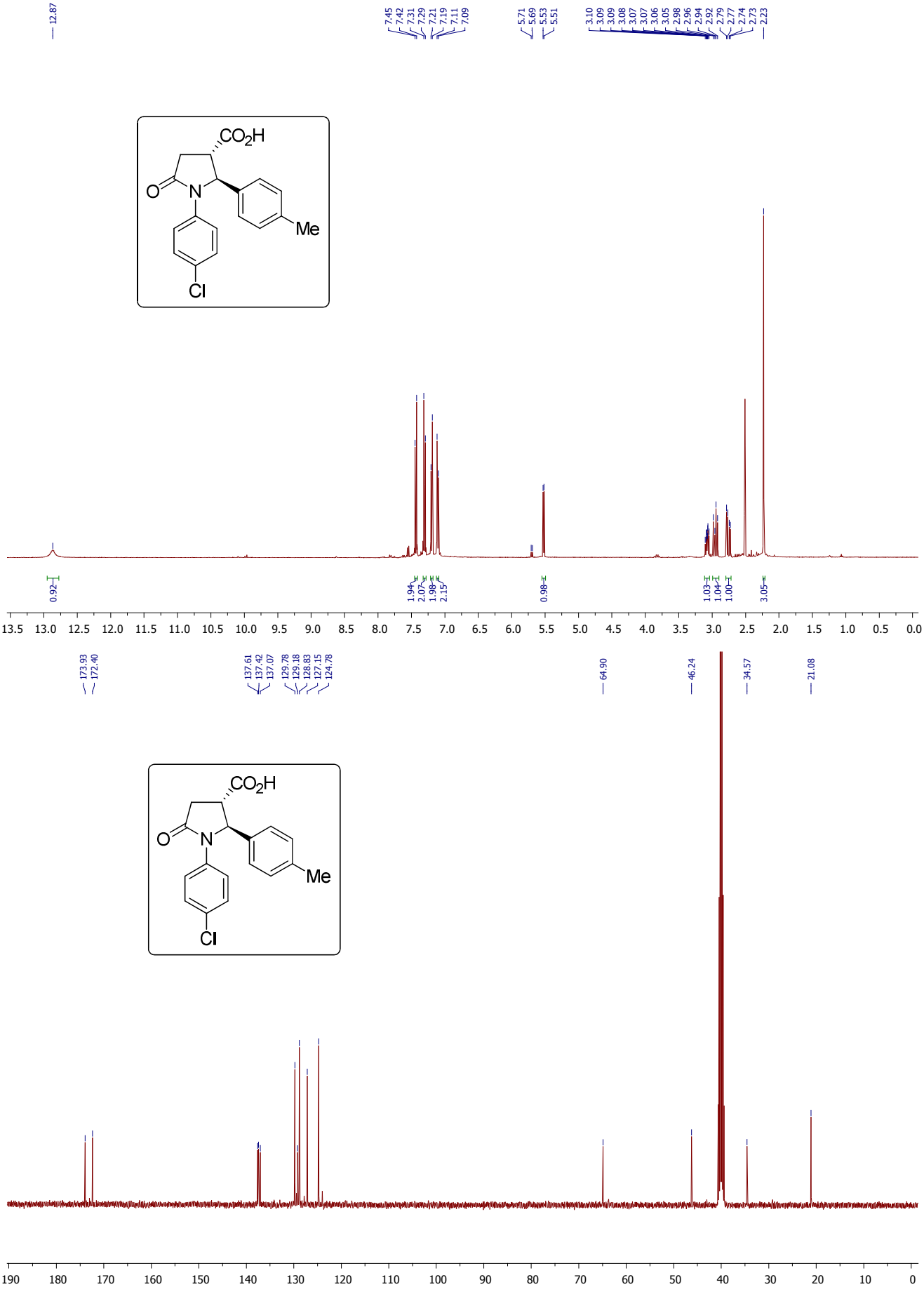
^{1}H and ^{13}C NMR spectra of compound 6d



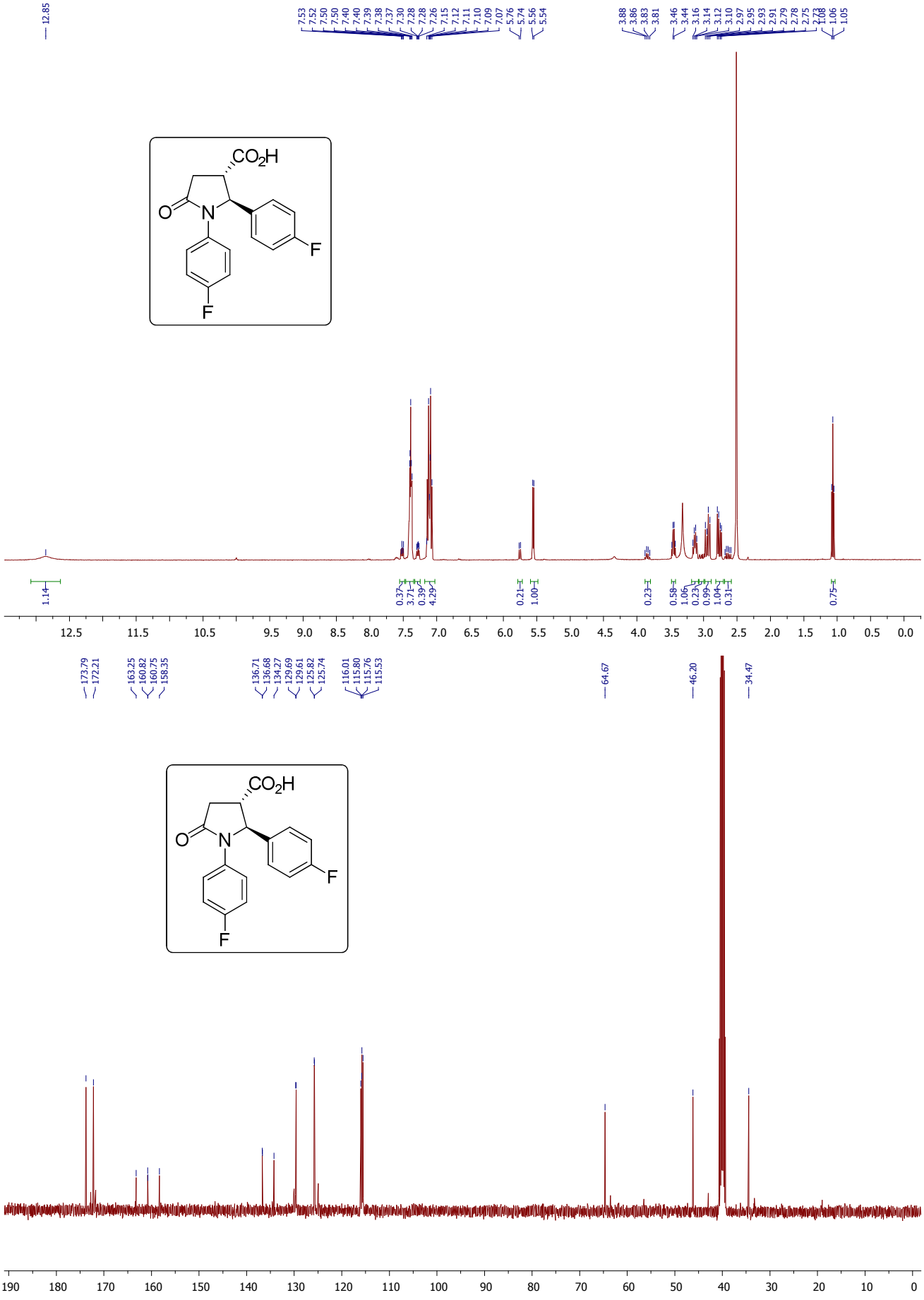
^{1}H and ^{13}C NMR spectra of compound 6e



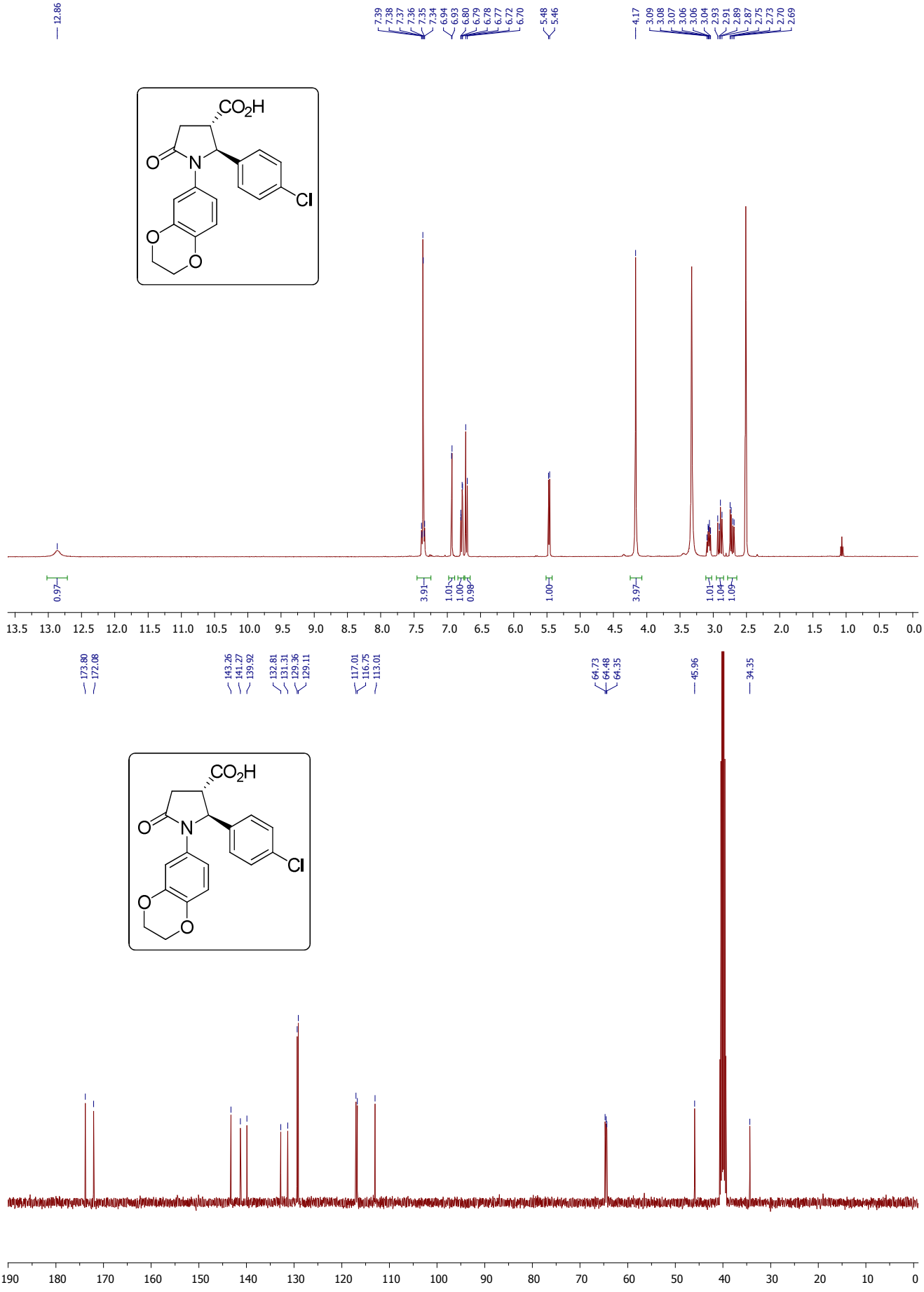
^{1}H and ^{13}C NMR spectra of compound 6f



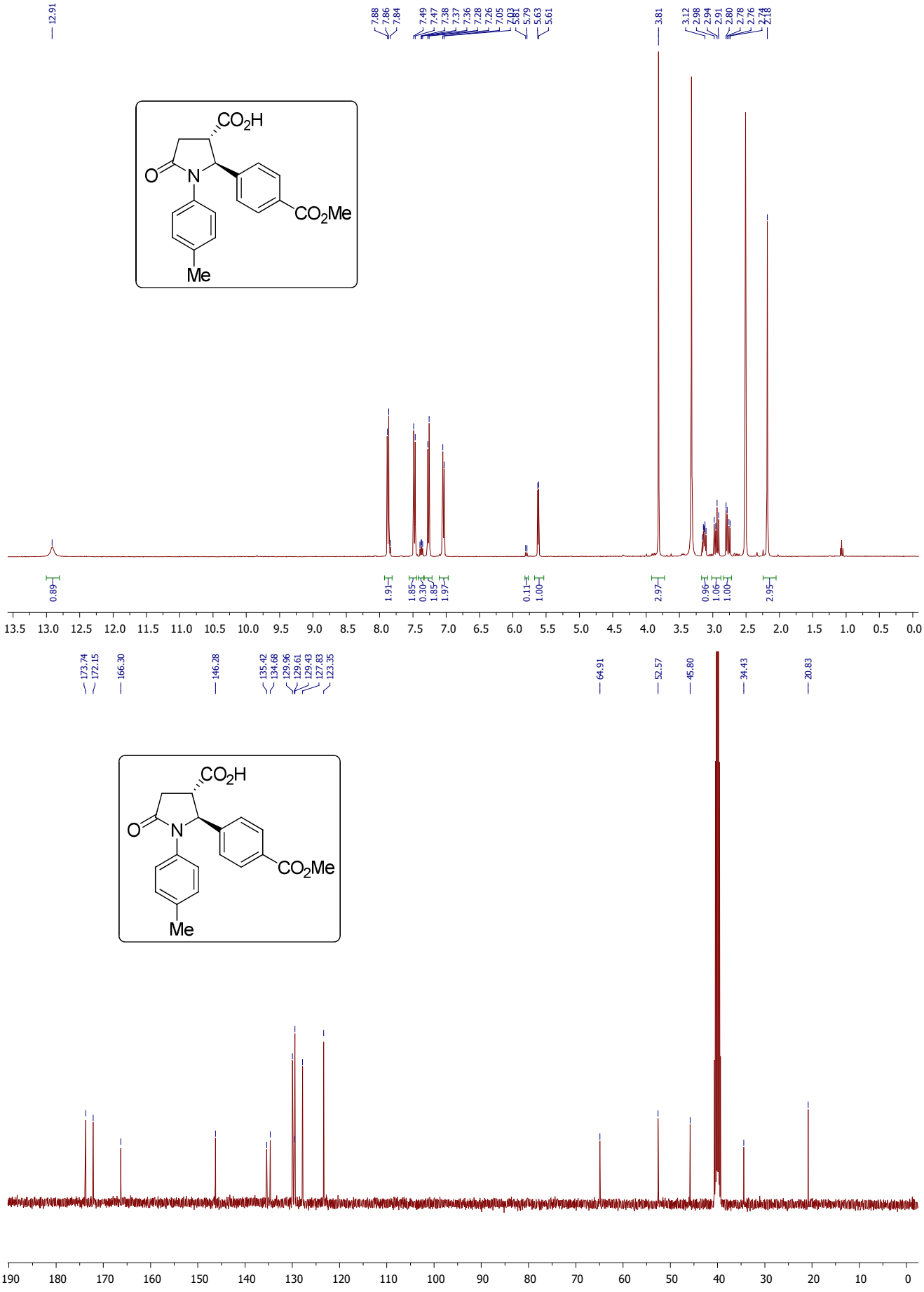
^{1}H and ^{13}C NMR spectra of compound 6g



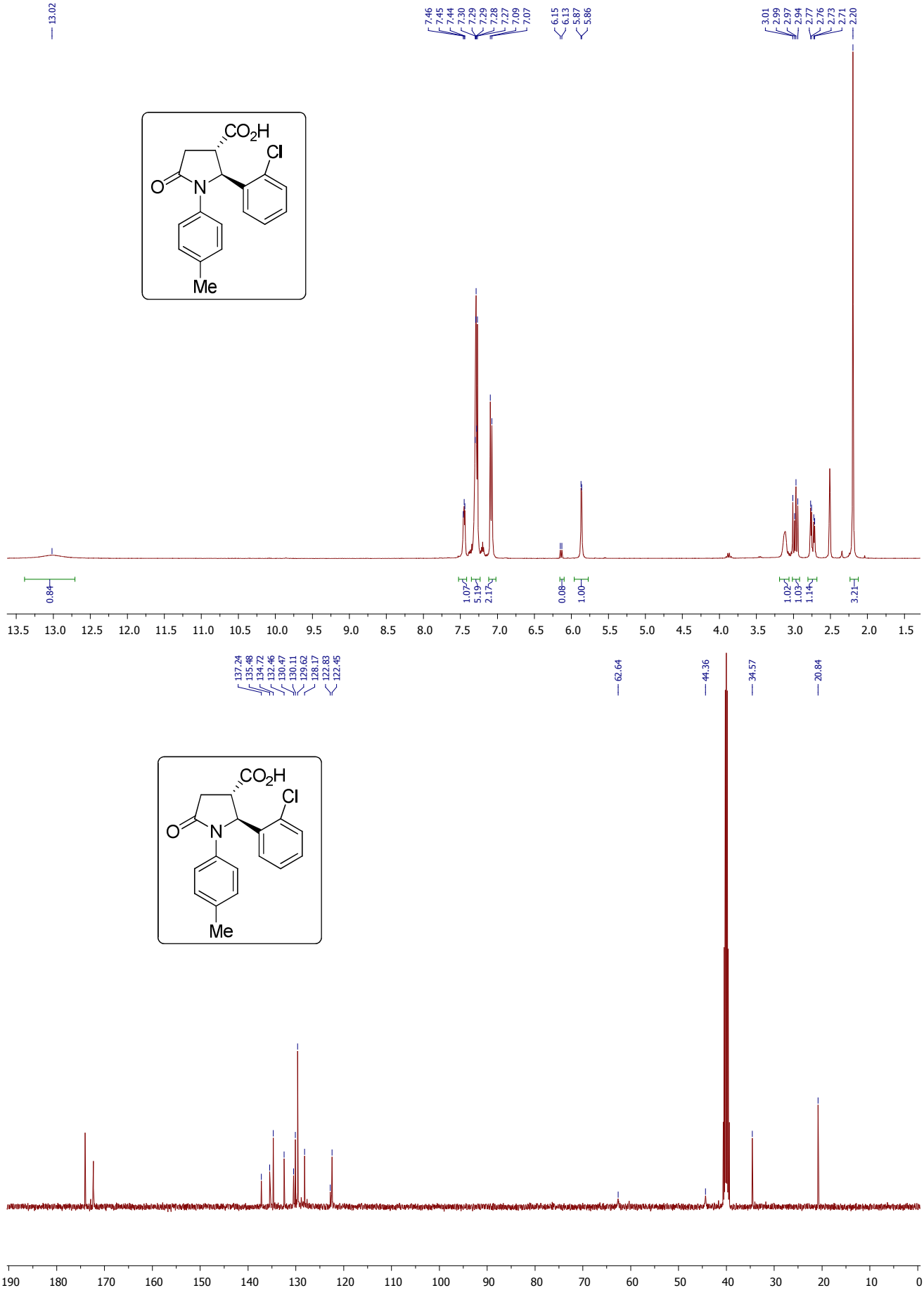
^{1}H and ^{13}C NMR spectra of compound 6h



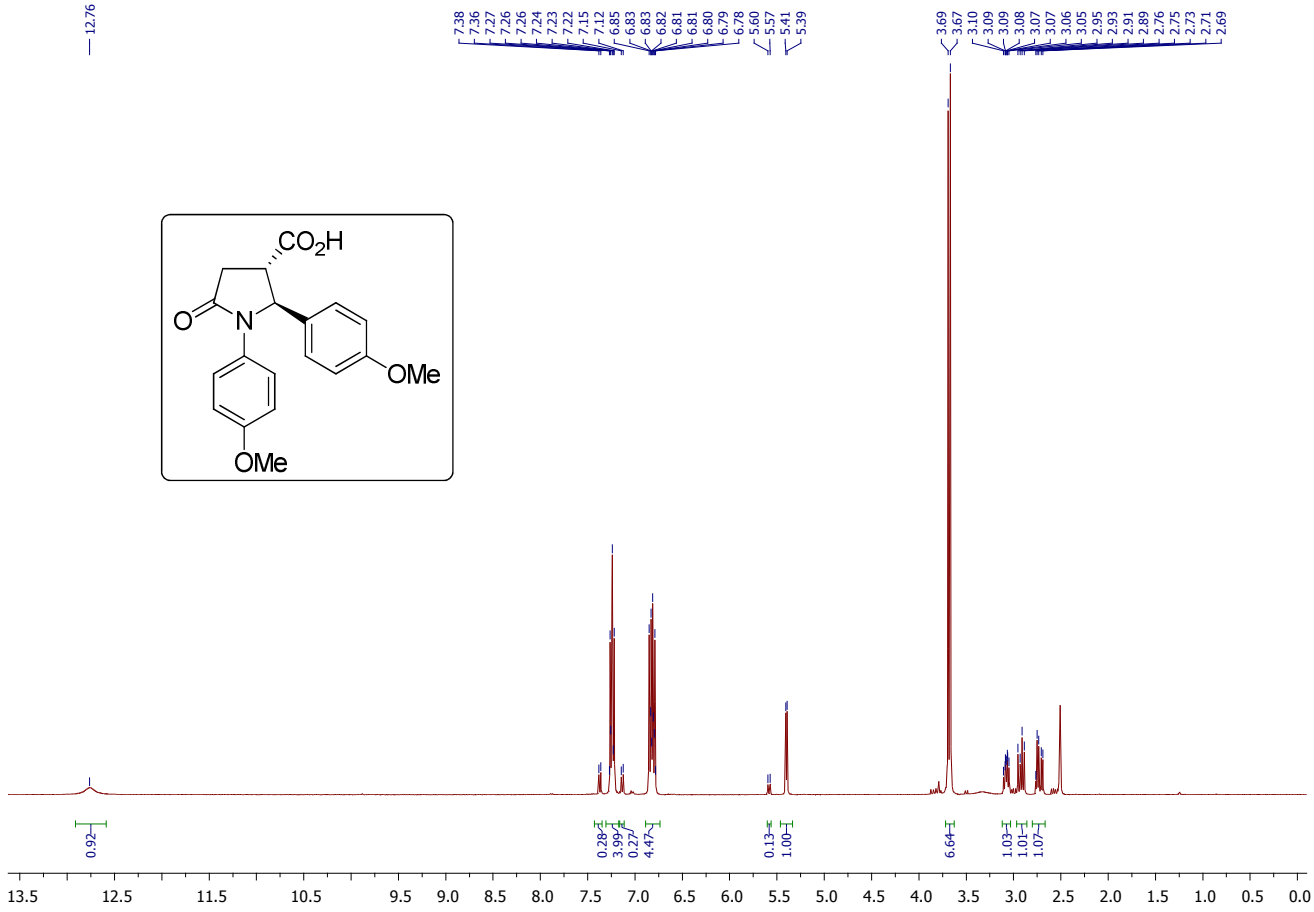
^{1}H and ^{13}C NMR spectra of compound 6i

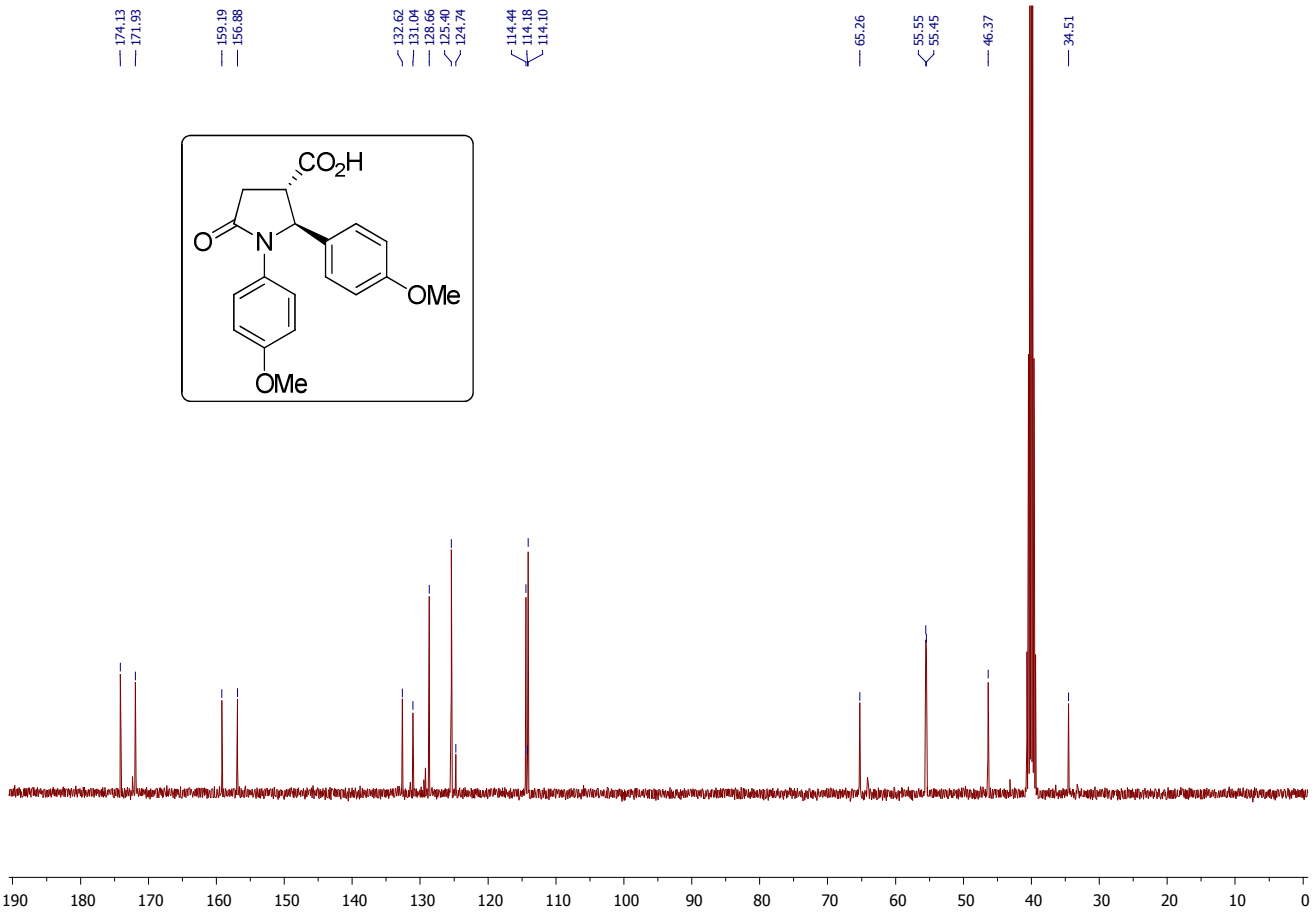


^{1}H and ^{13}C NMR spectra of compound 6j

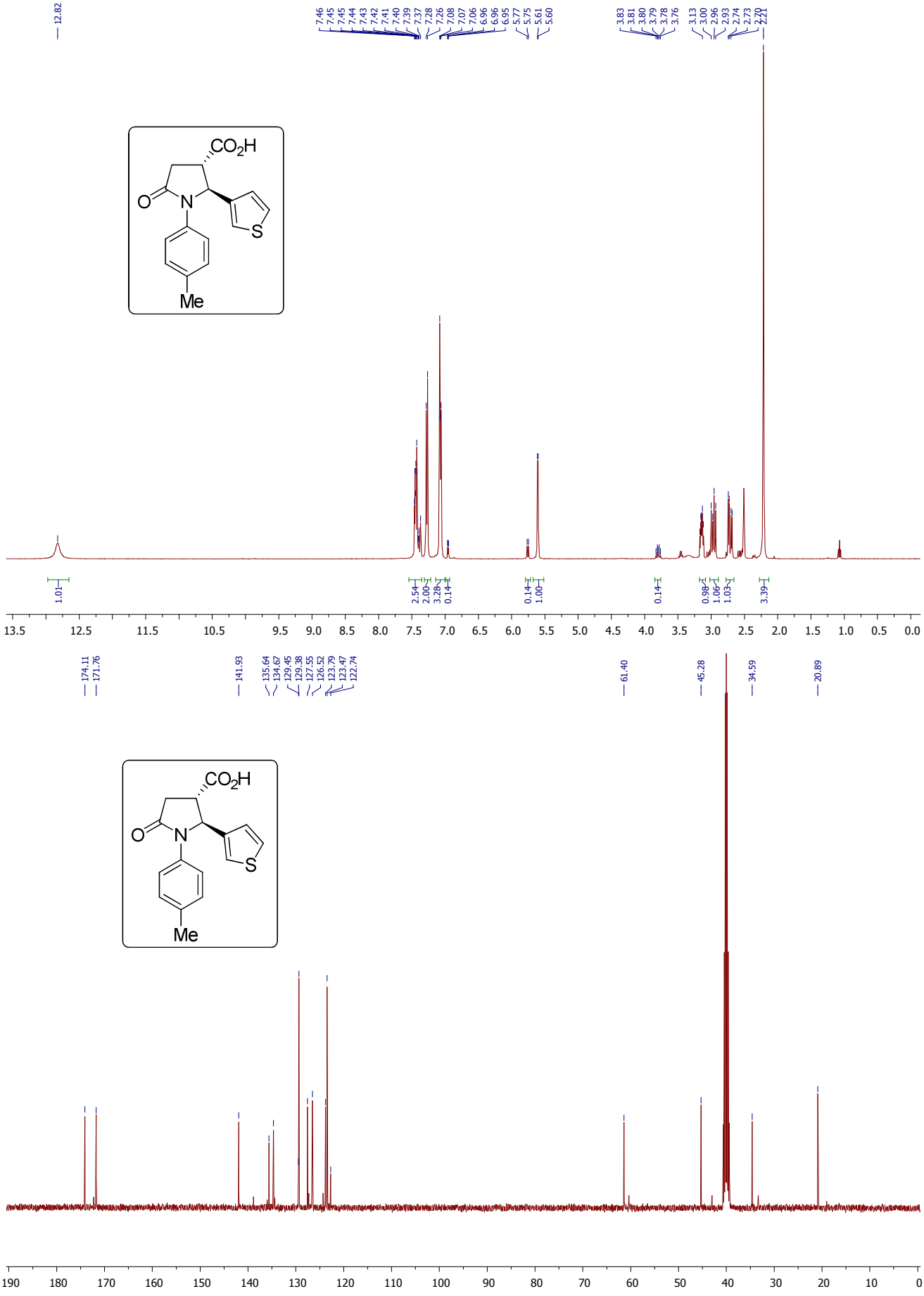


^{1}H and ^{13}C NMR spectra of compound 6k

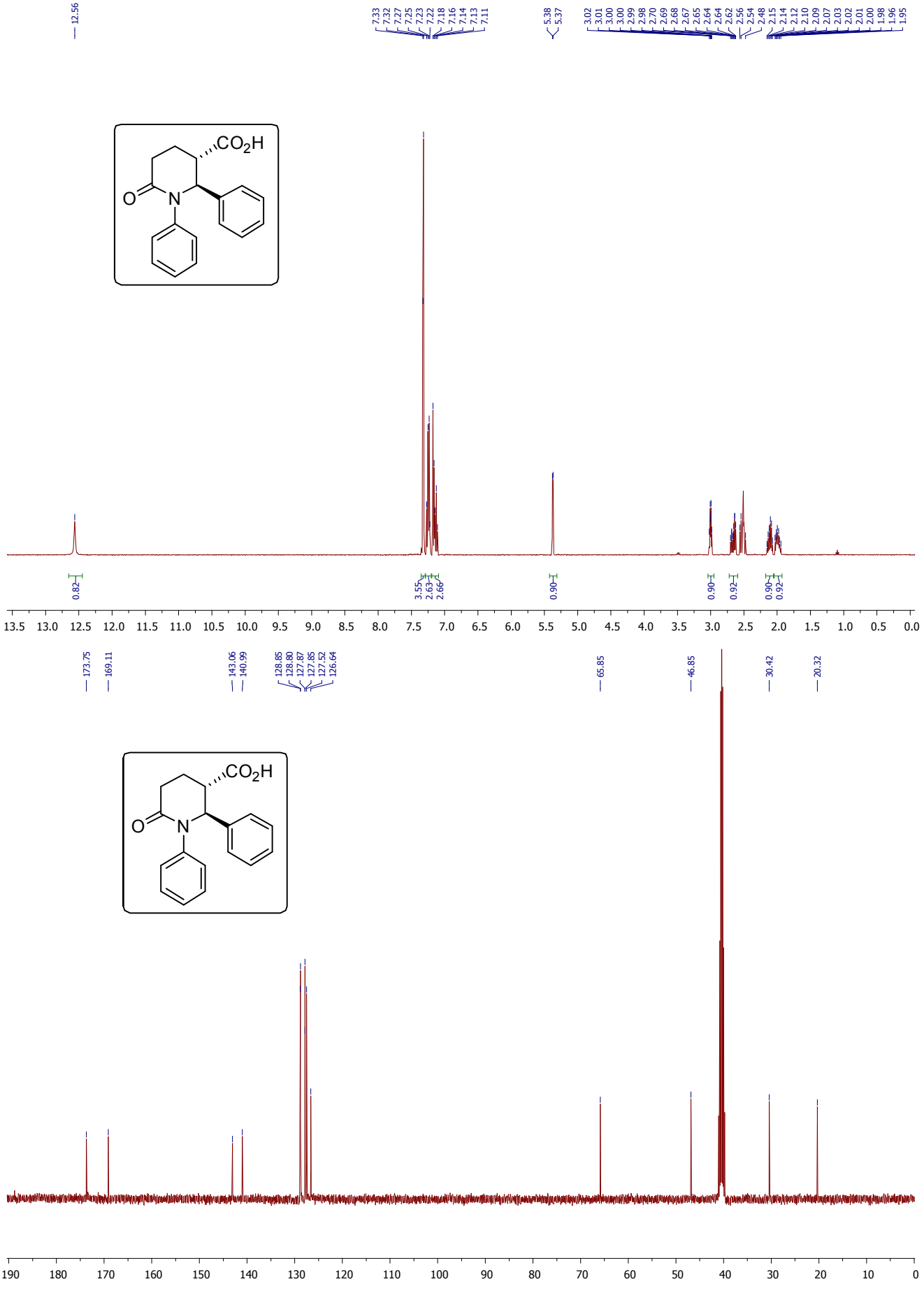




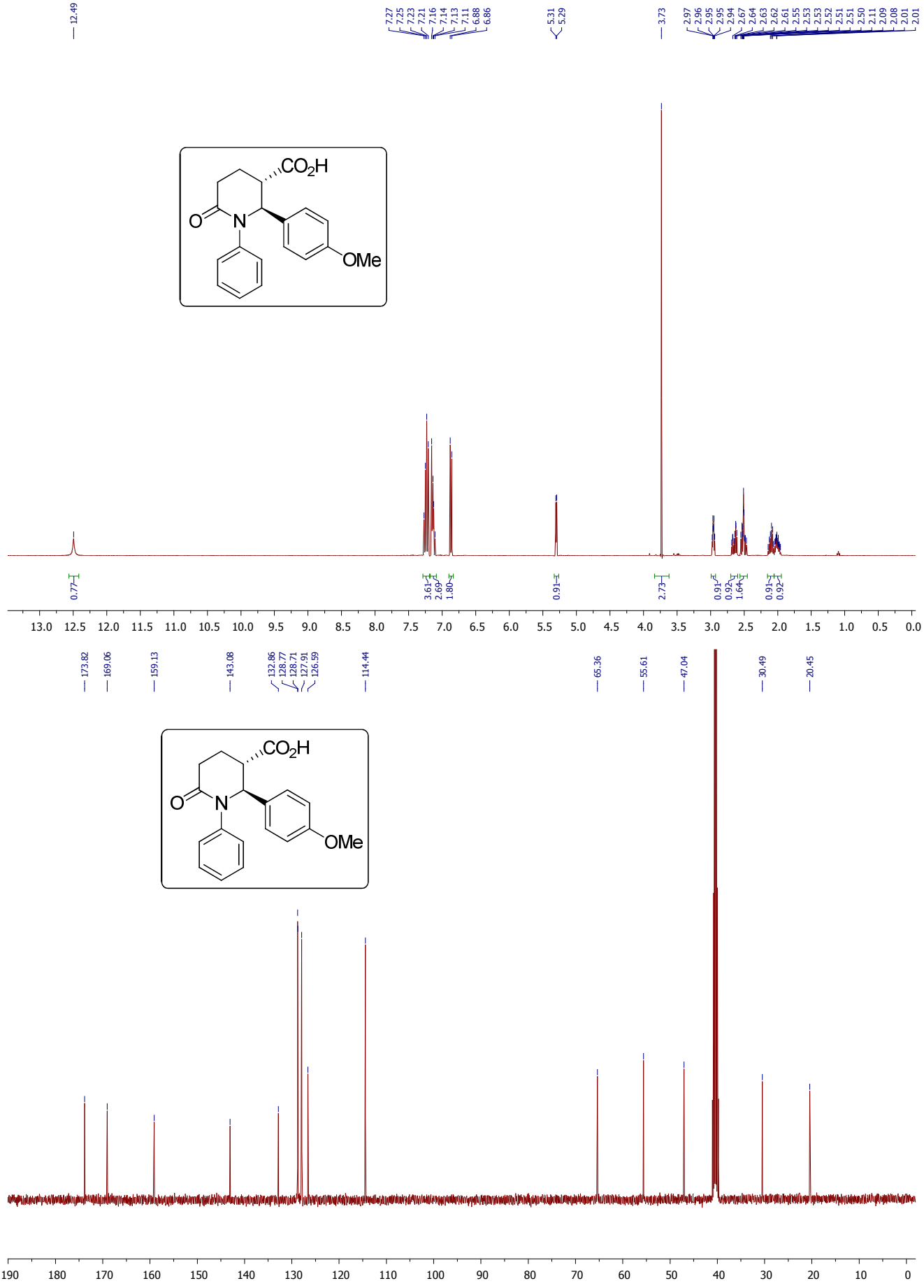
^{1}H and ^{13}C NMR spectra of compound 6l



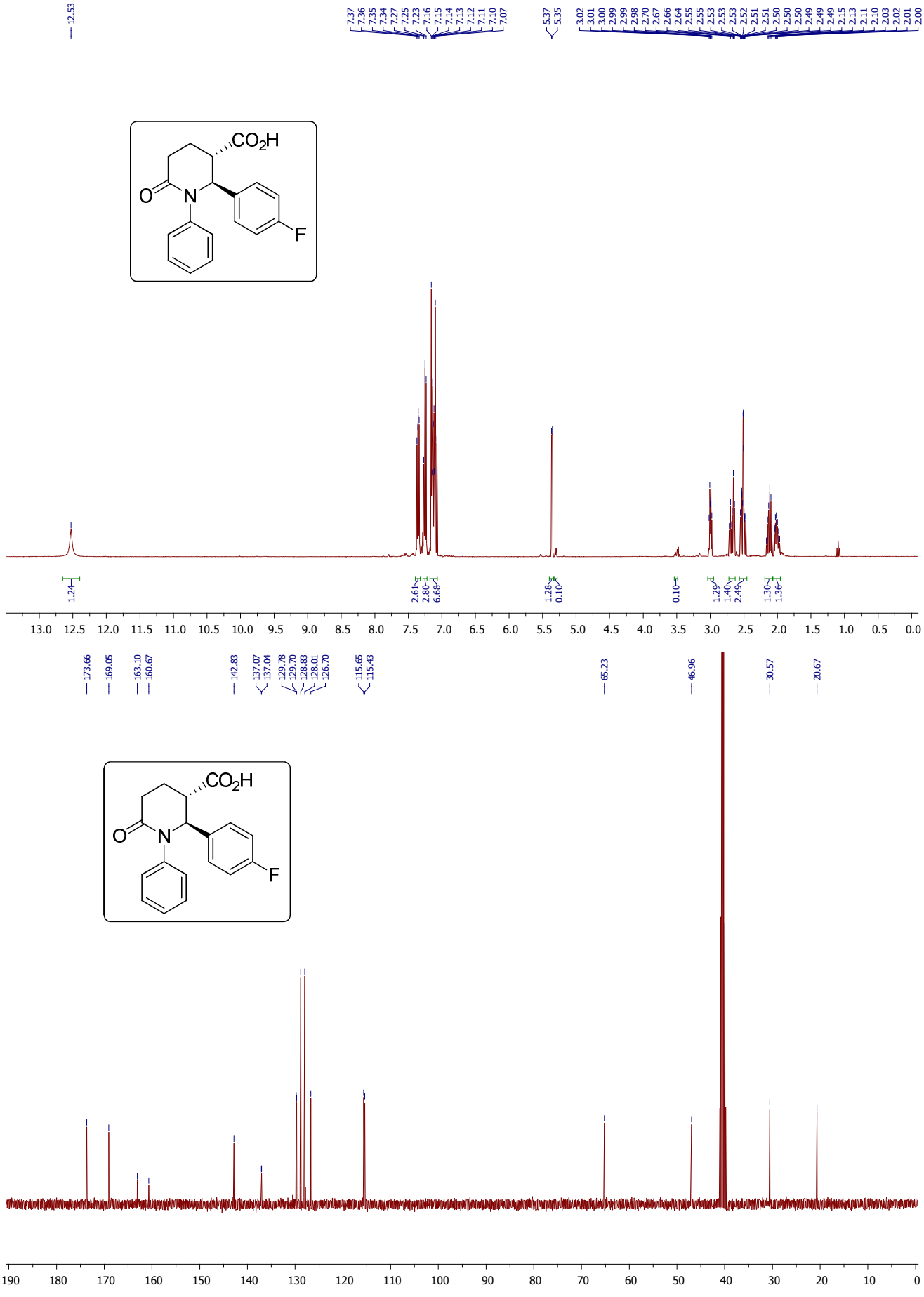
^{1}H and ^{13}C NMR spectra of compound 7a



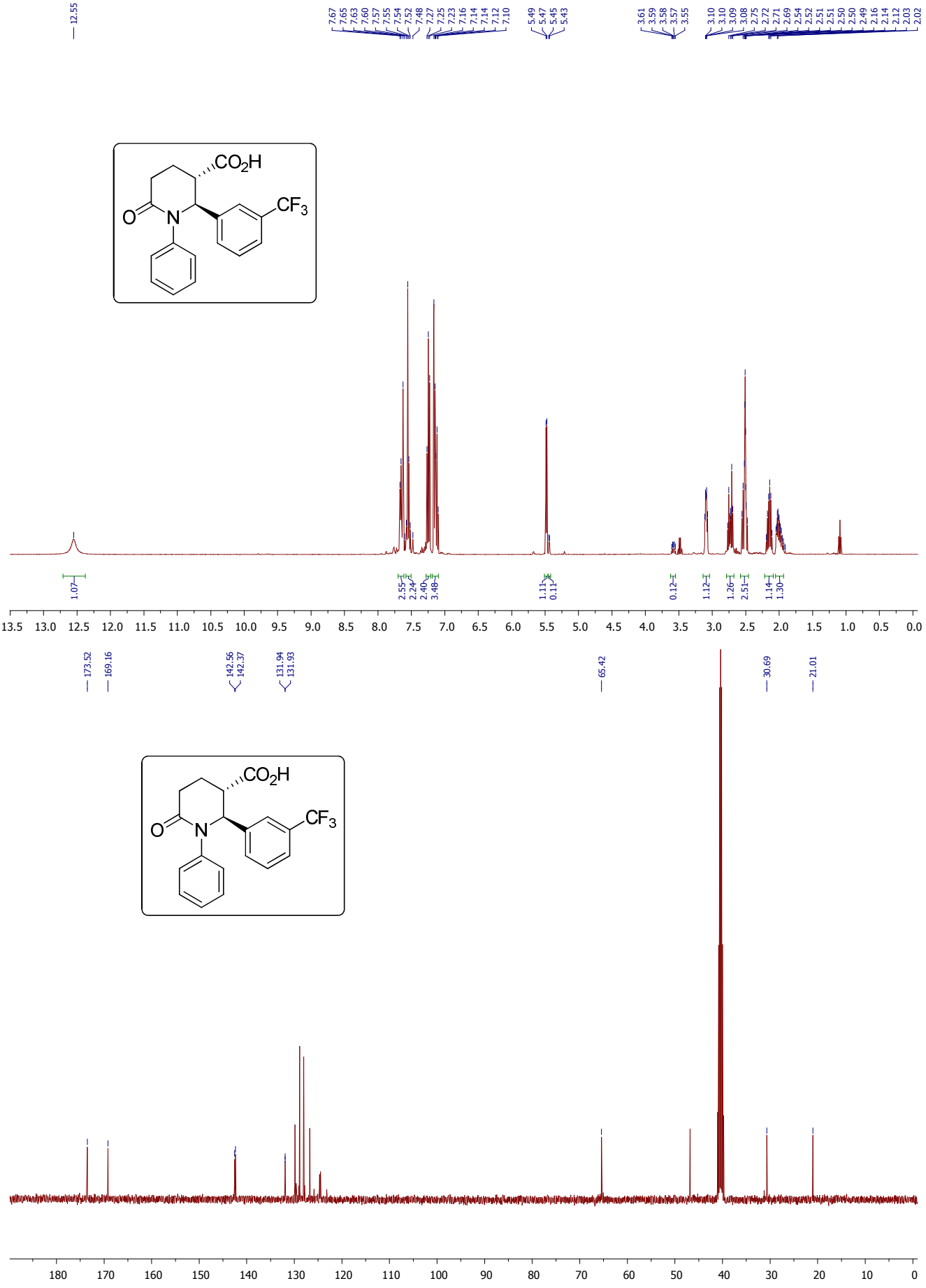
^{1}H and ^{13}C NMR spectra of compound 7b



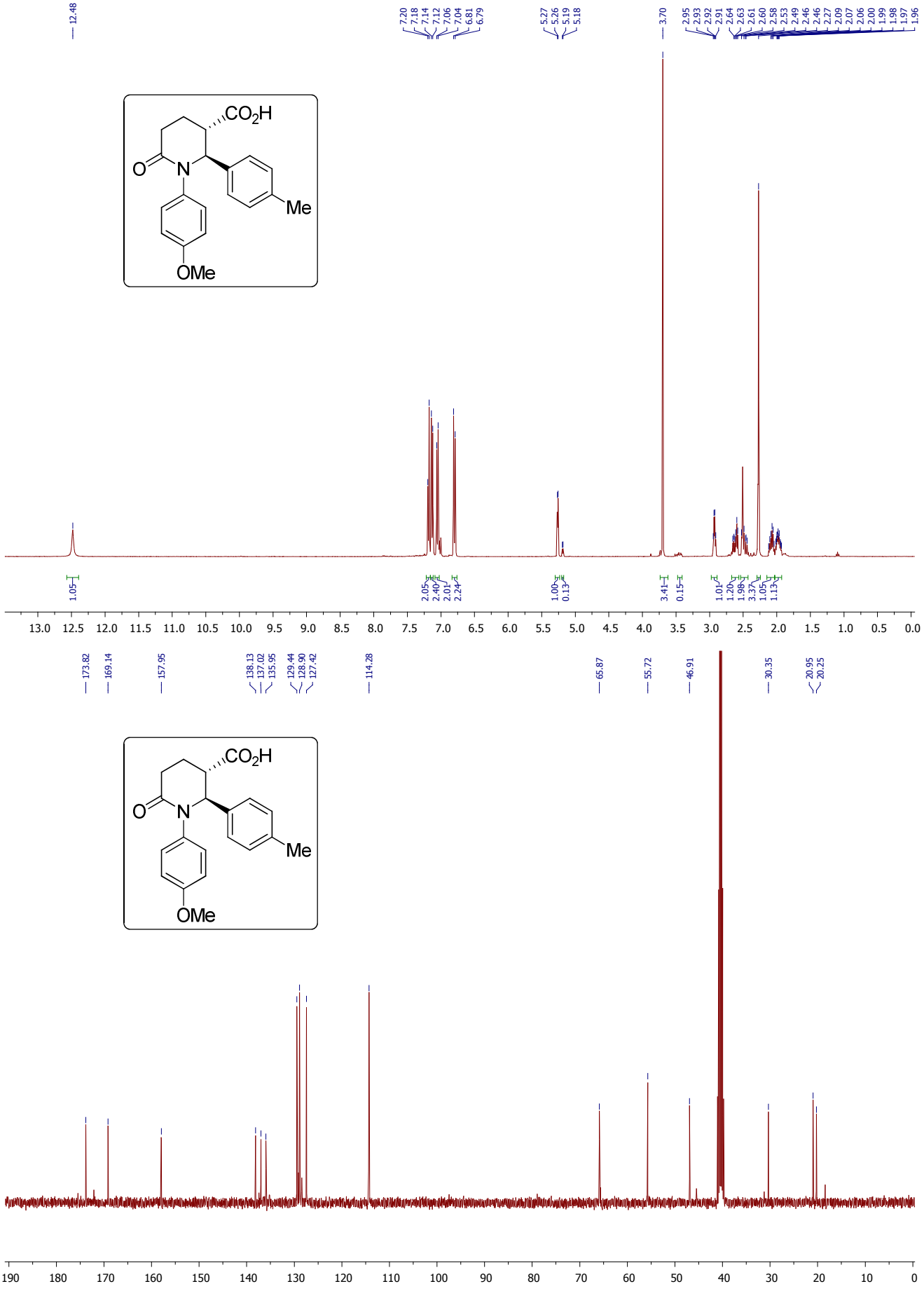
^{1}H and ^{13}C NMR spectra of compound 7c



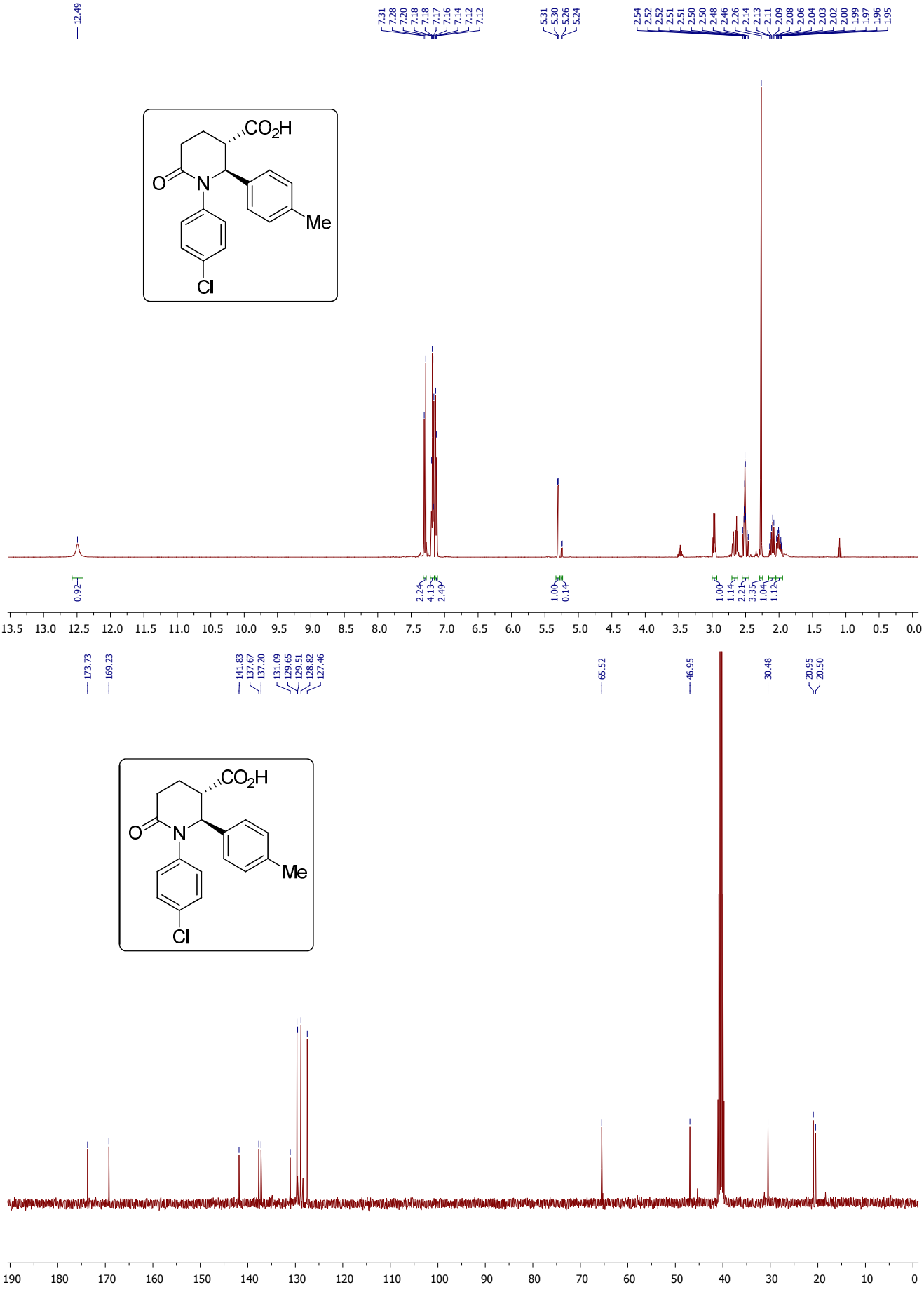
^{1}H and ^{13}C NMR spectra of compound 7d



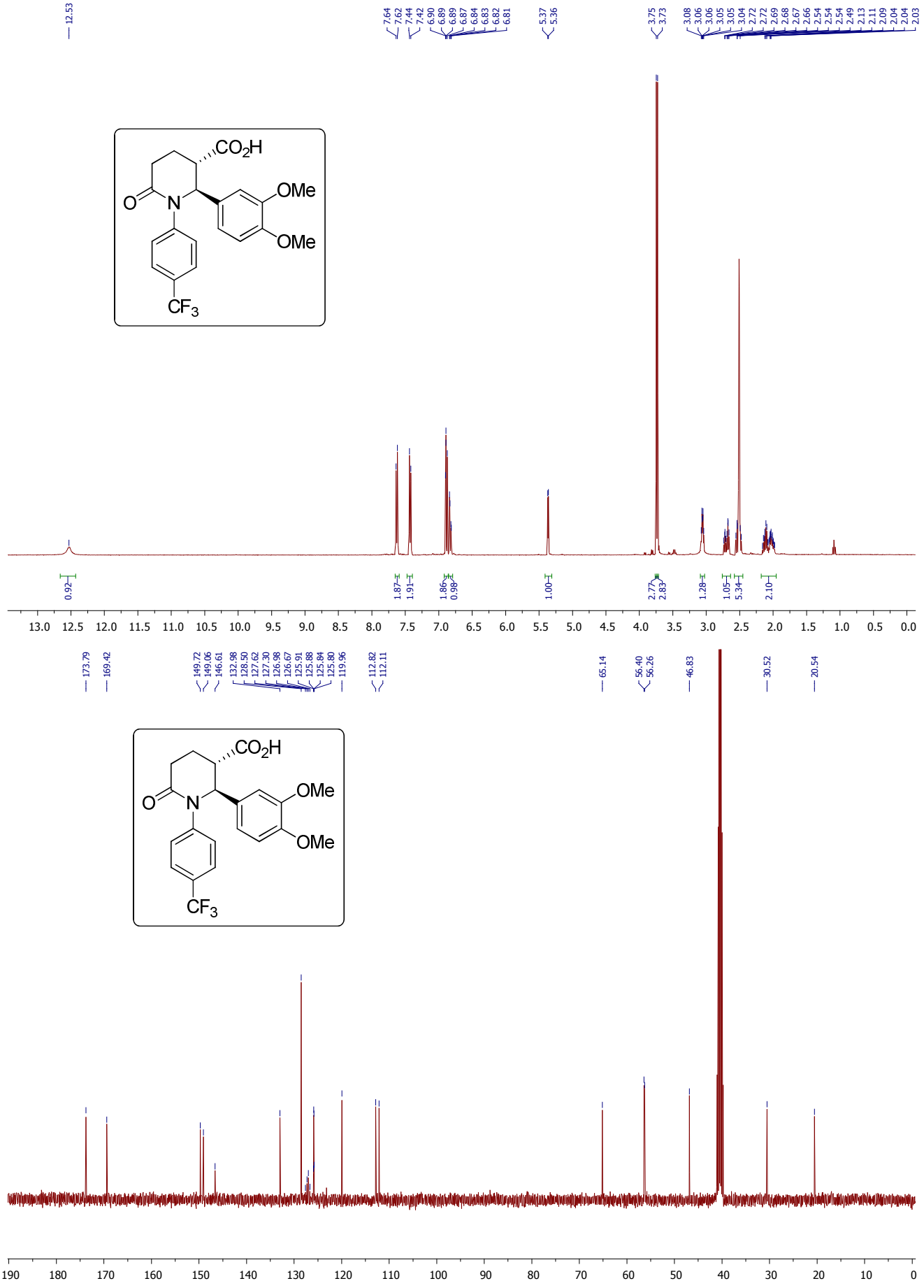
^{1}H and ^{13}C NMR spectra of compound 7e



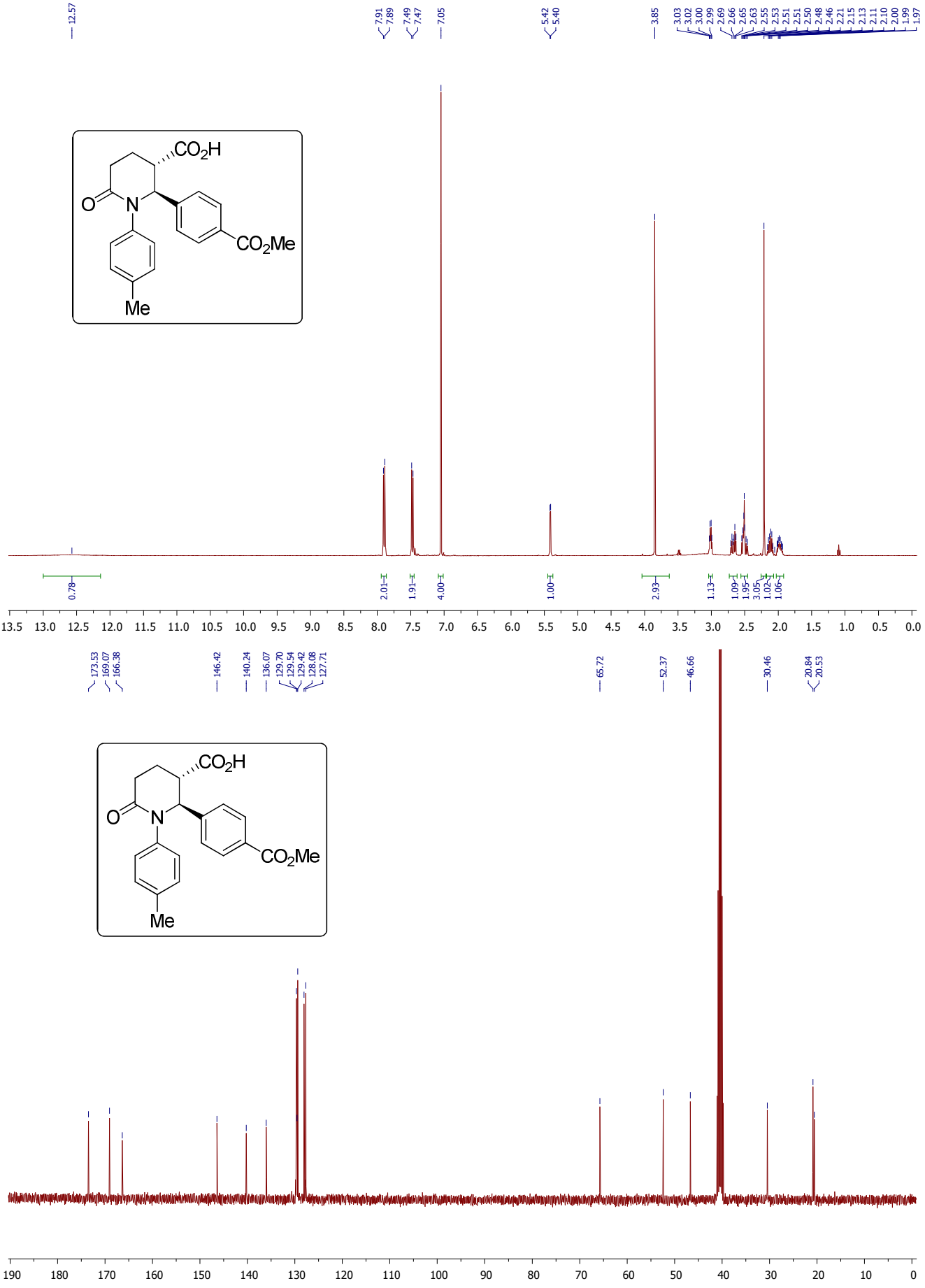
^{1}H and ^{13}C NMR spectra of compound 7f



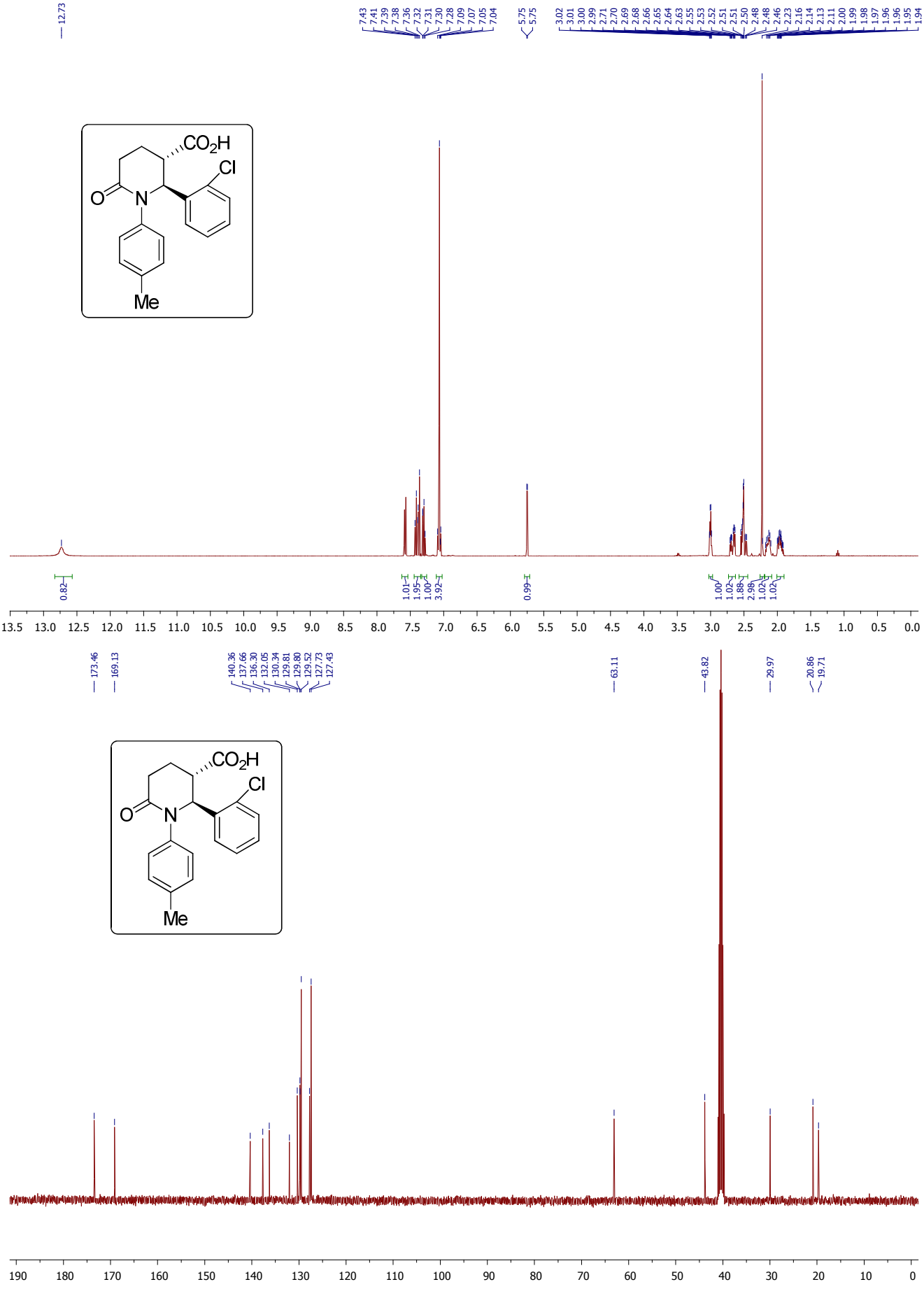
^{1}H and ^{13}C NMR spectra of compound 7g



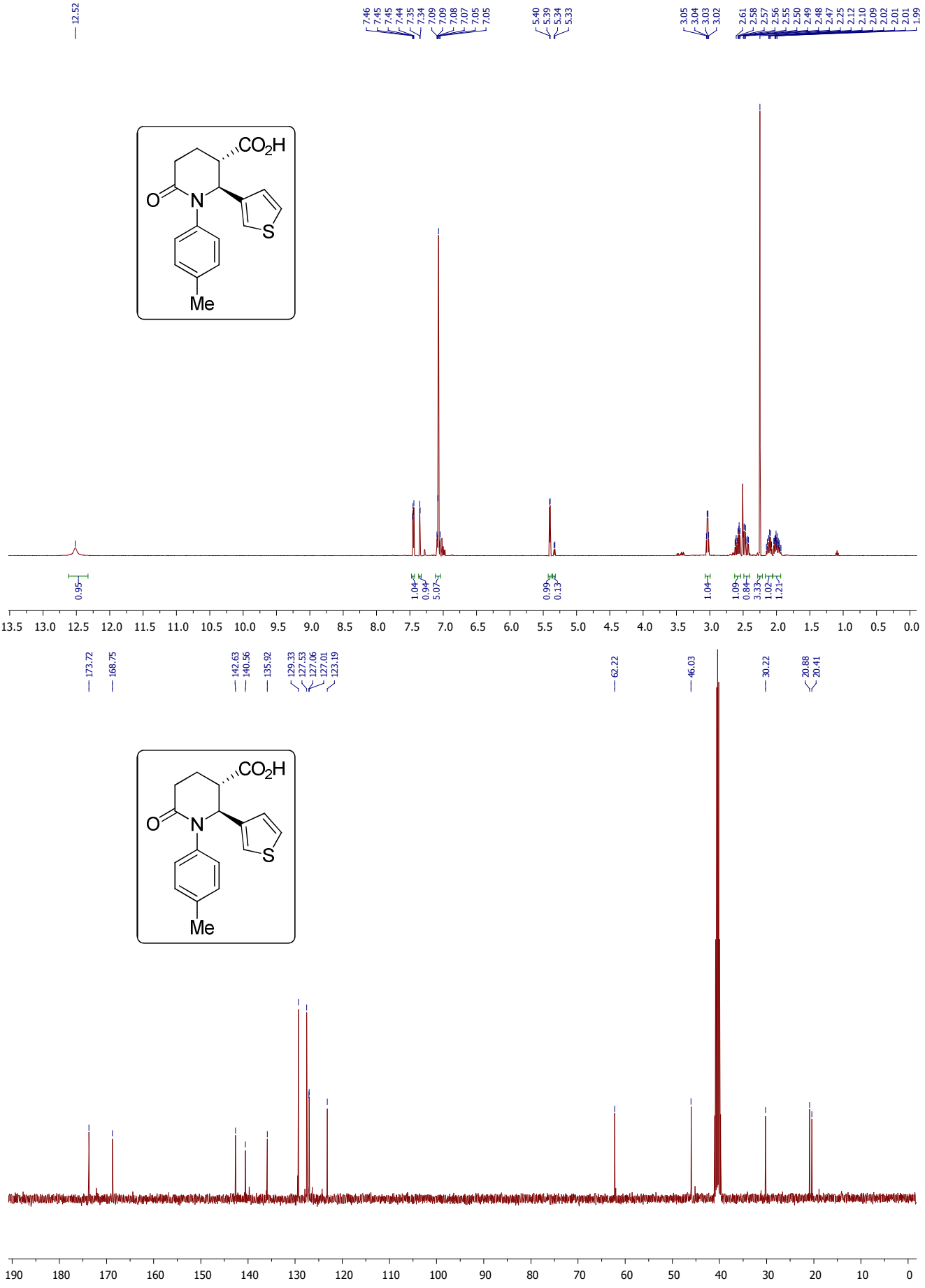
^{1}H and ^{13}C NMR spectra of compound 7h



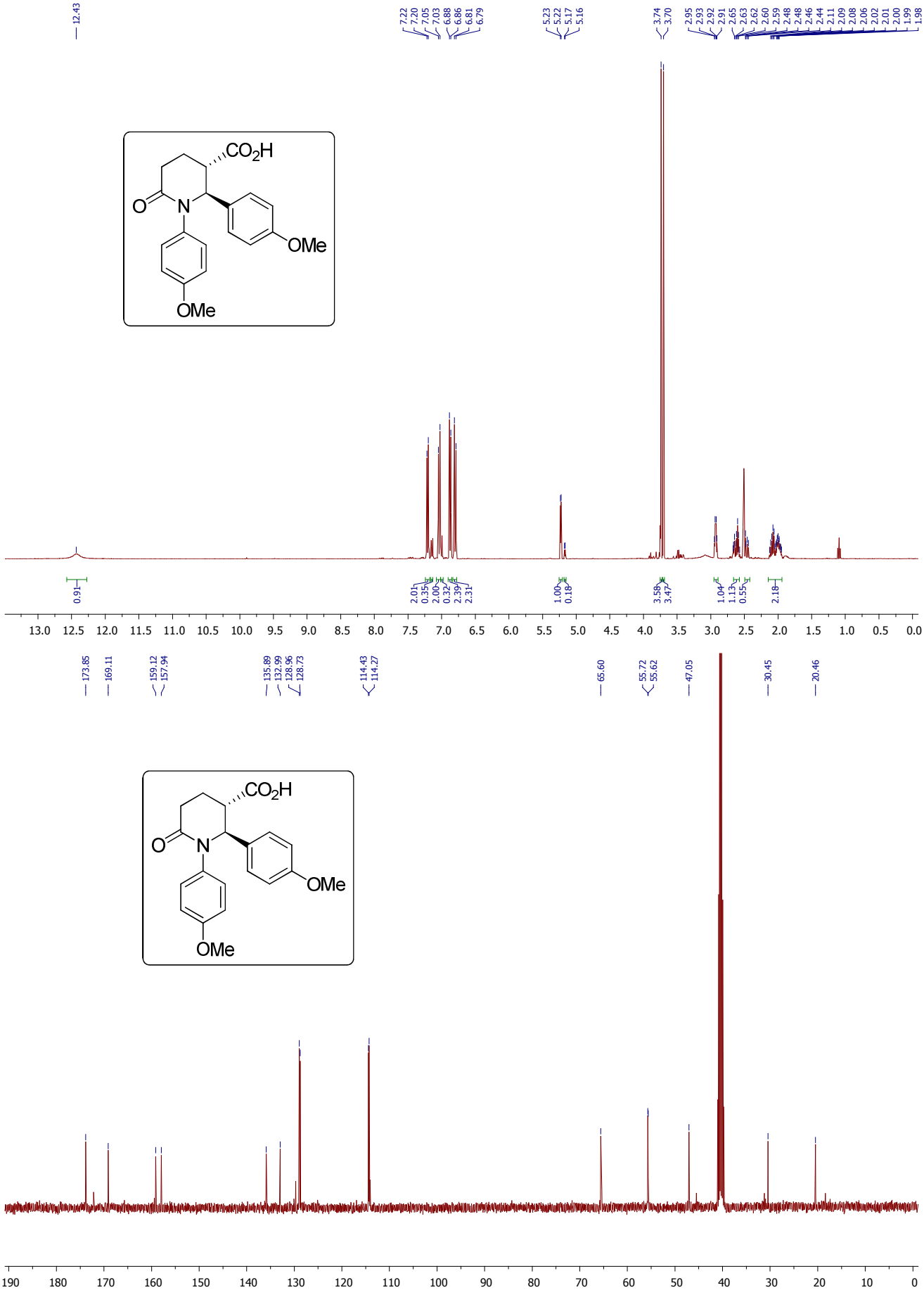
^{1}H and ^{13}C NMR spectra of compound 7i



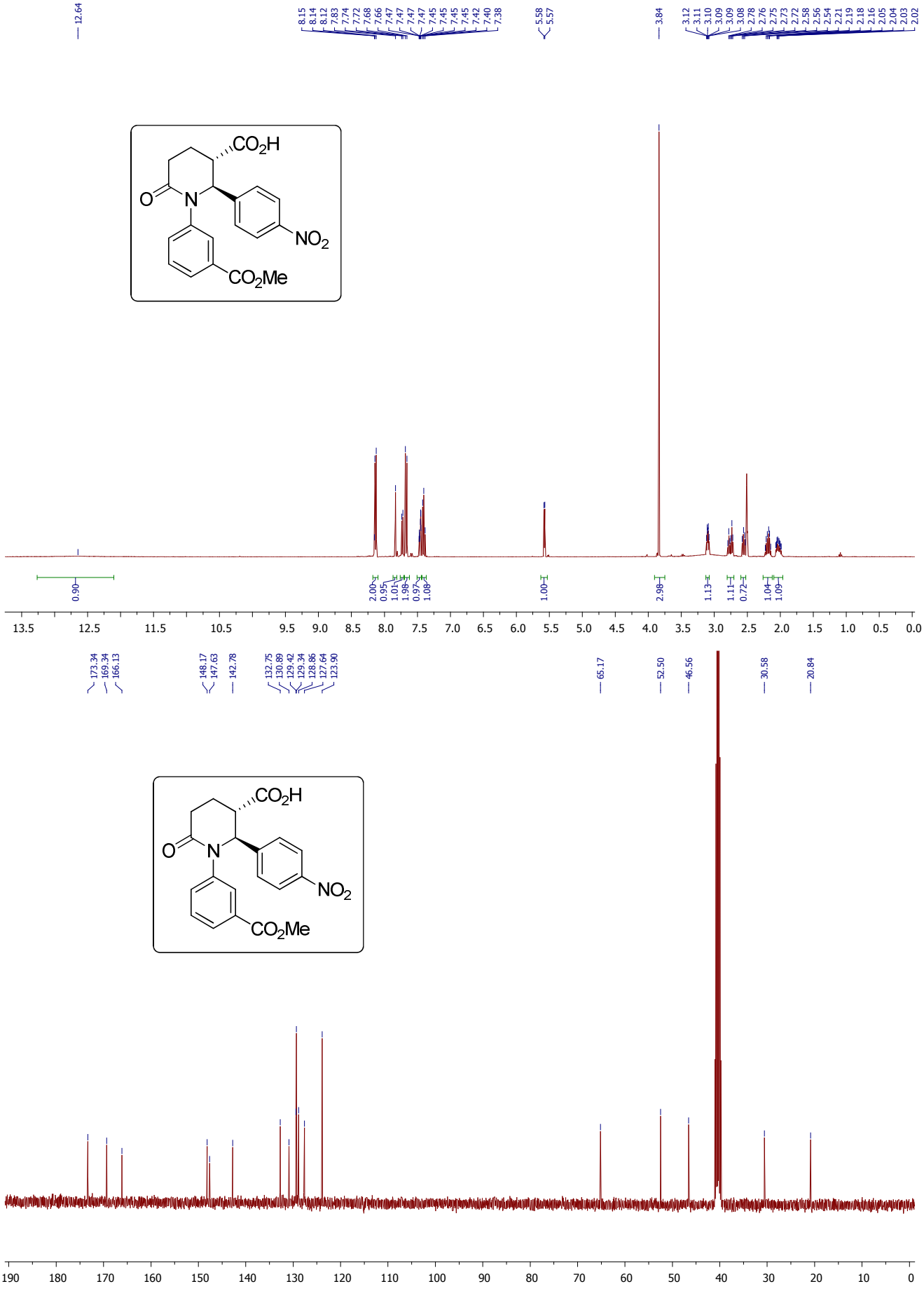
^{1}H and ^{13}C NMR spectra of compound 7j



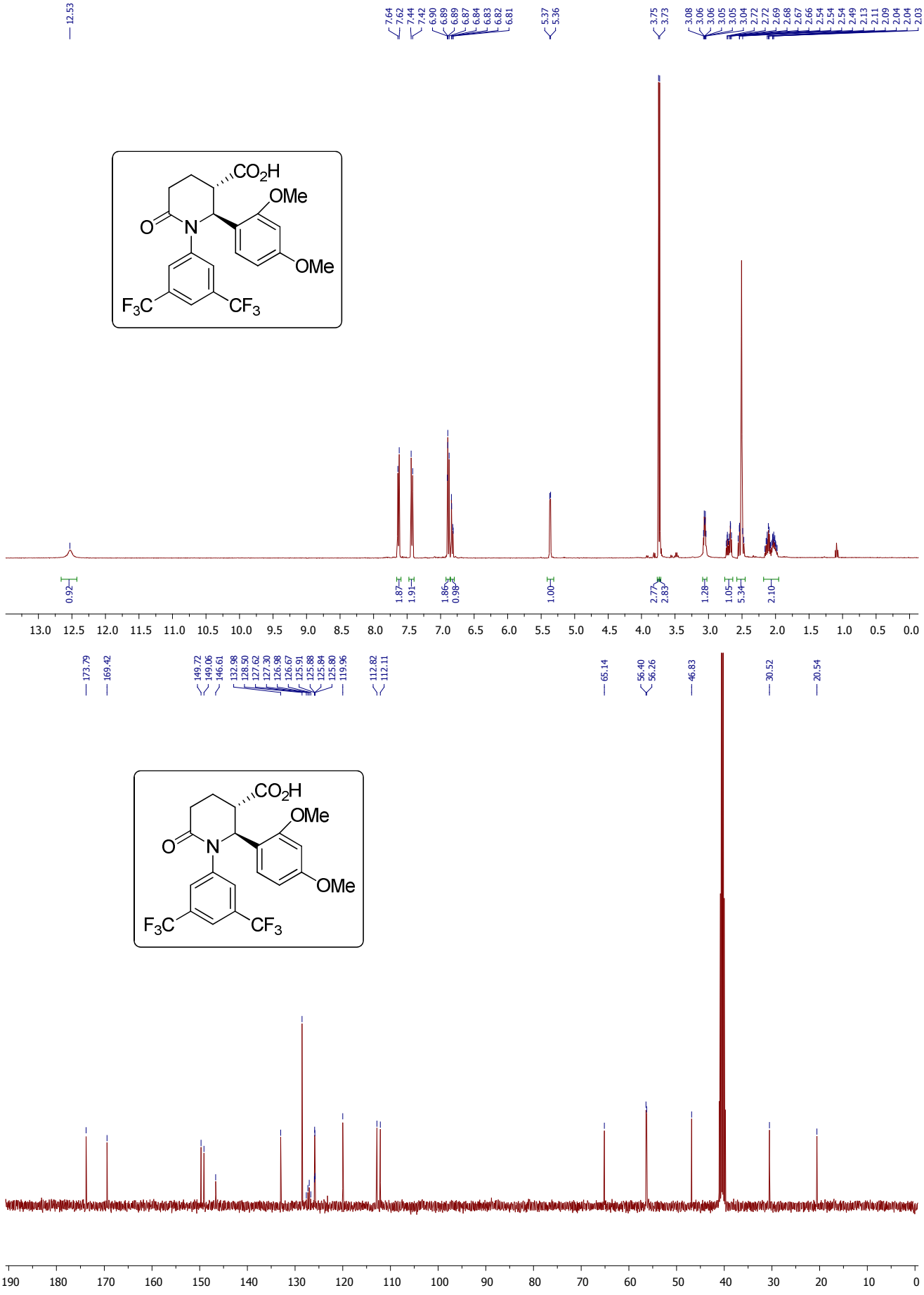
^{1}H and ^{13}C NMR spectra of compound 7k



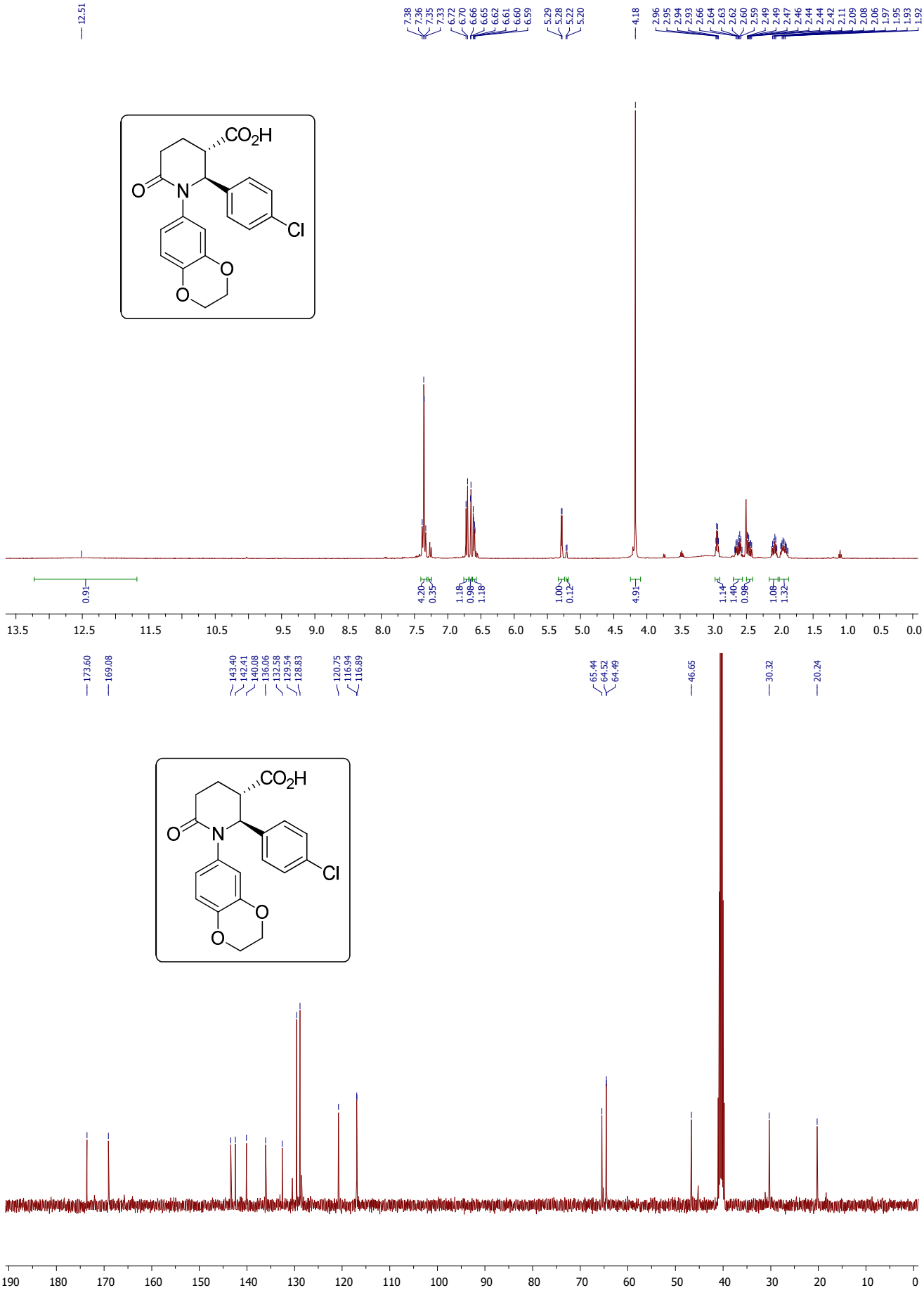
^{1}H and ^{13}C NMR spectra of compound 7l



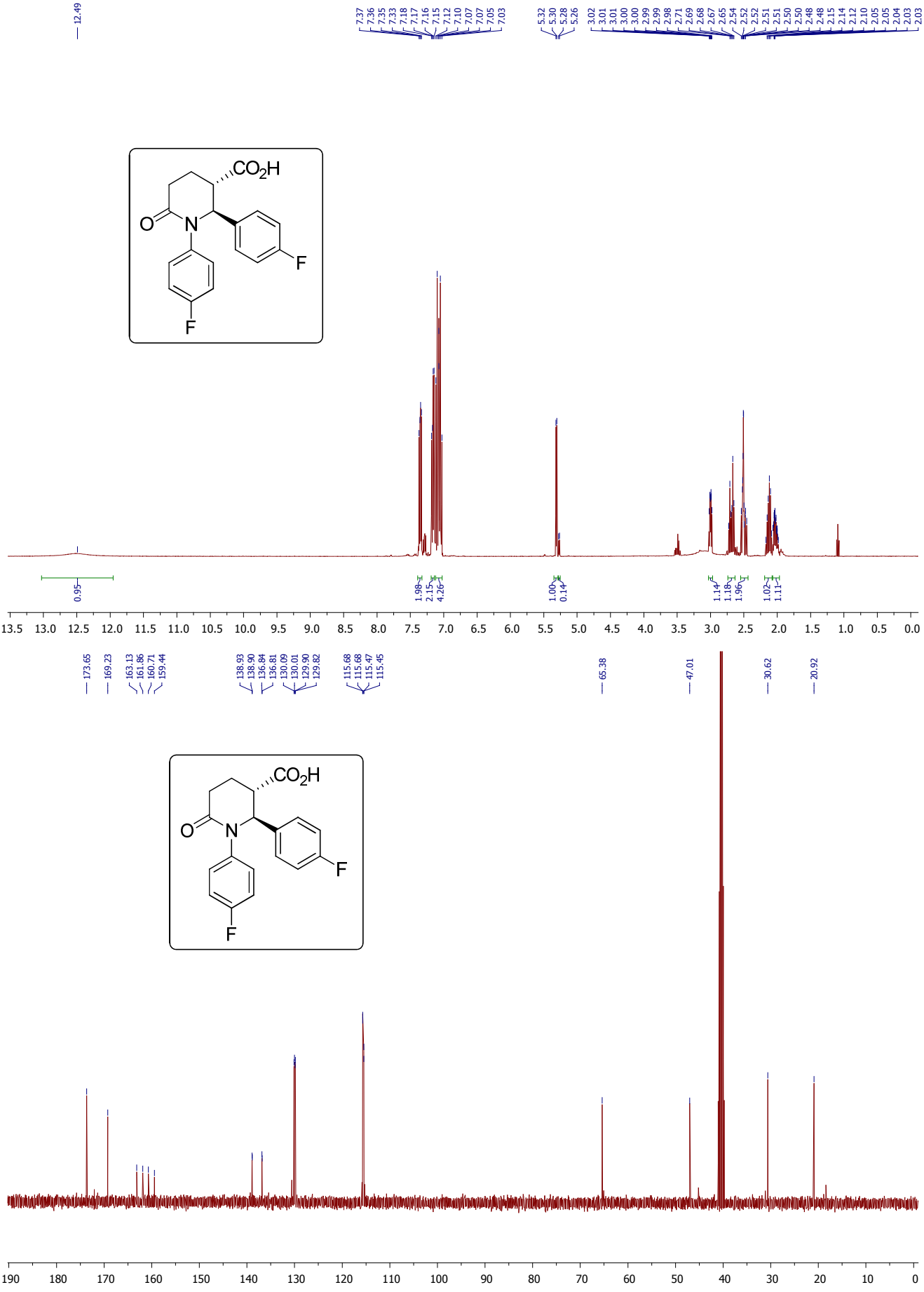
^{1}H and ^{13}C NMR spectra of compound 7m



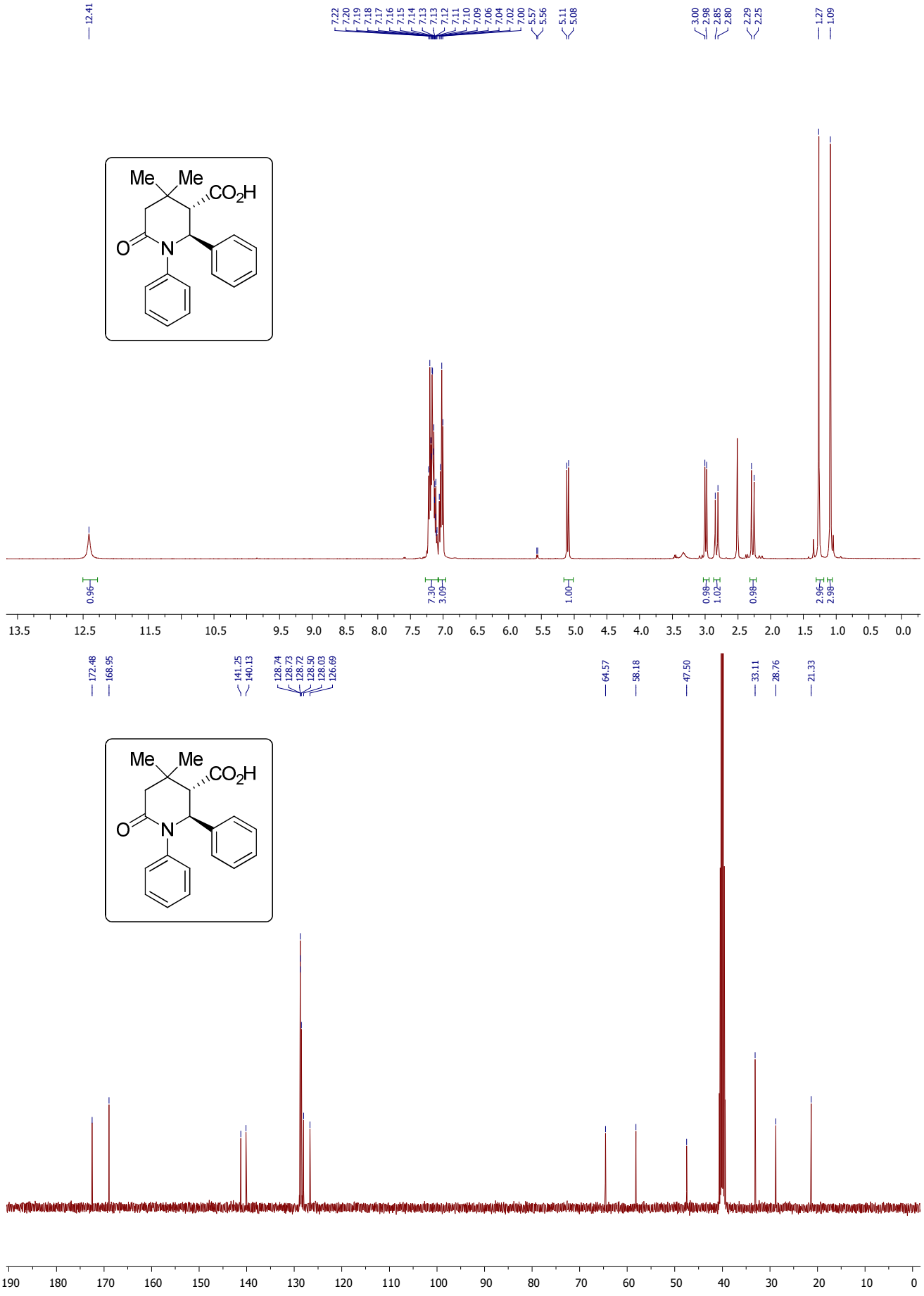
^{1}H and ^{13}C NMR spectra of compound 7n



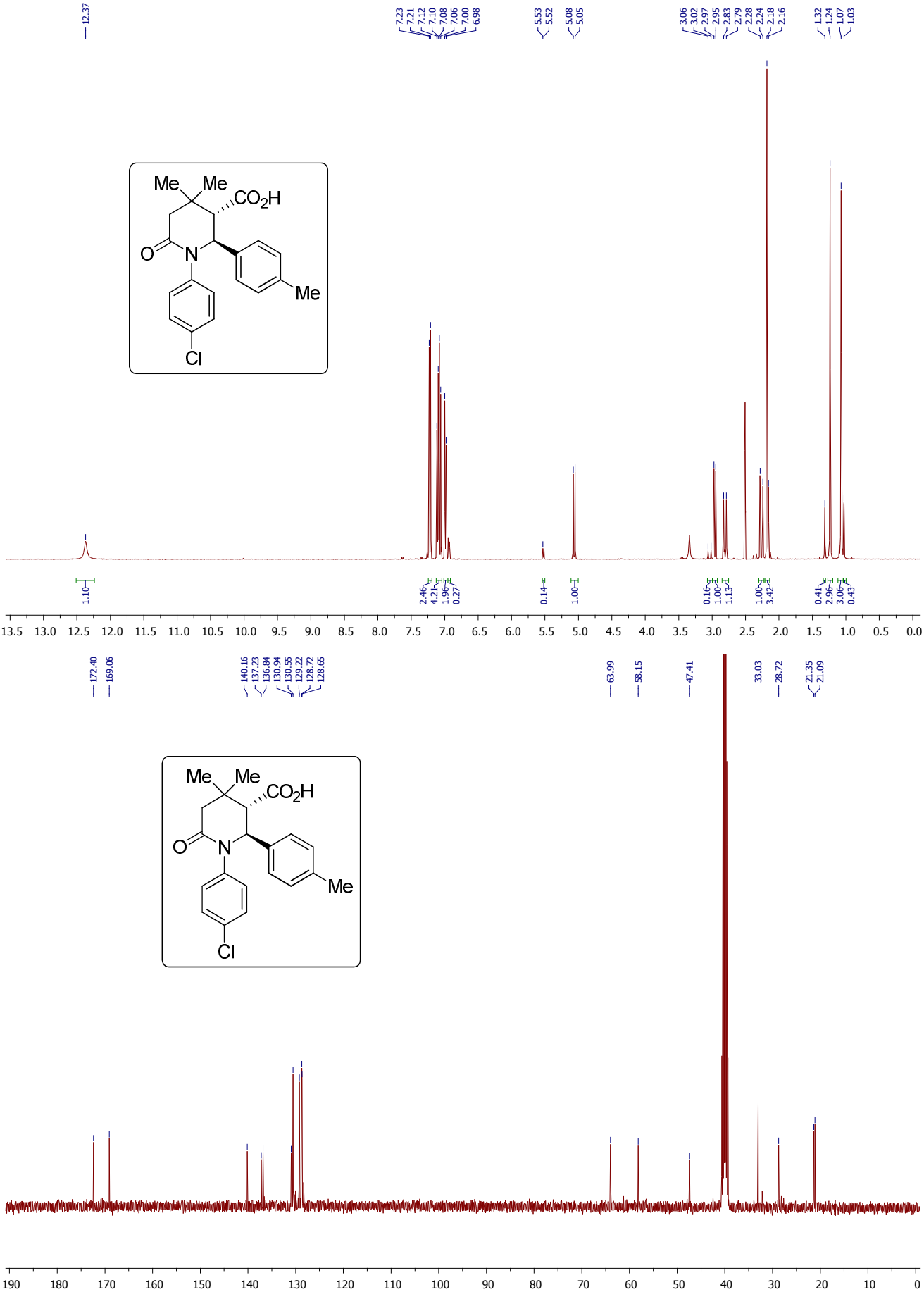
^{1}H and ^{13}C NMR spectra of compound 7o



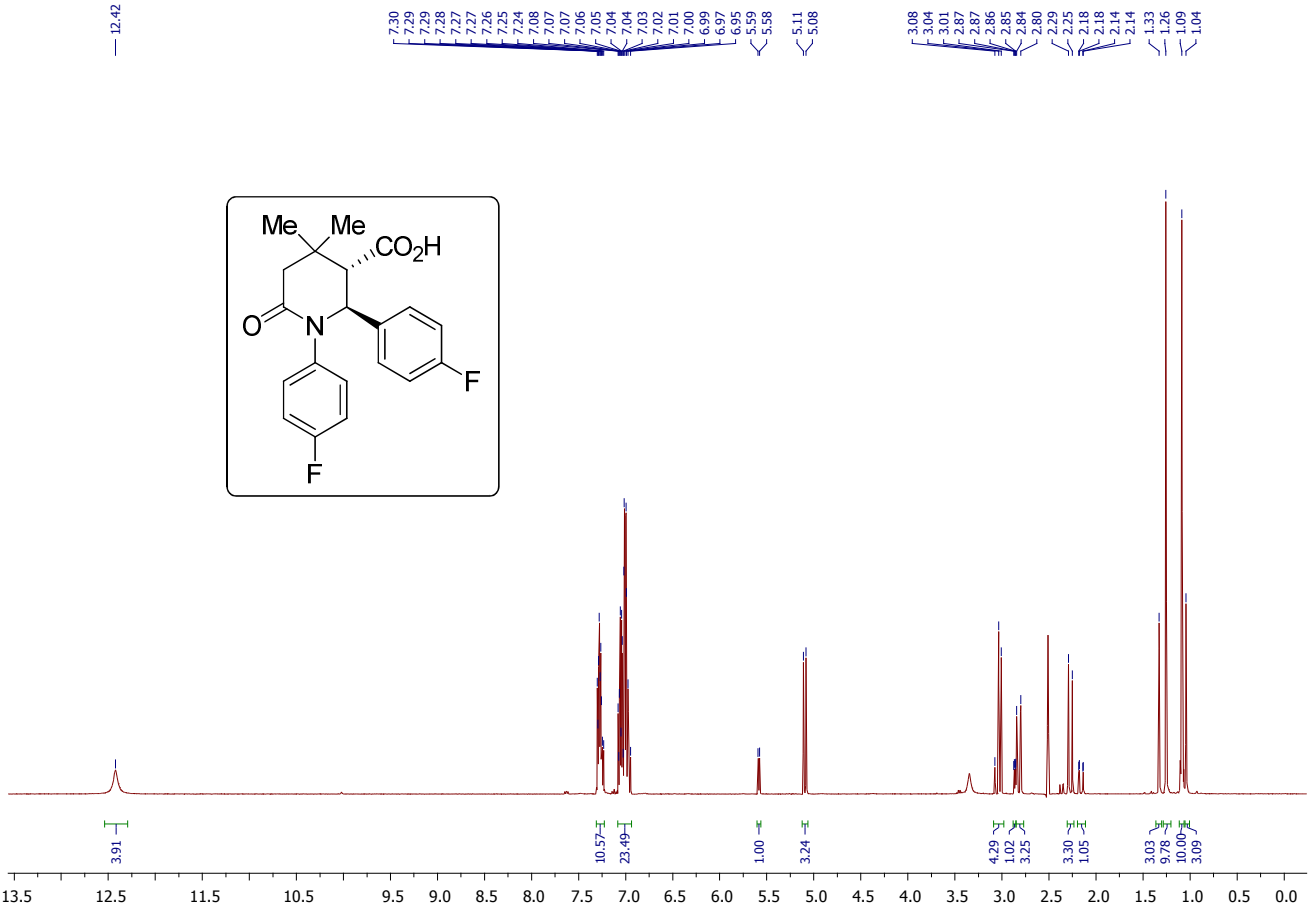
^{1}H and ^{13}C NMR spectra of compound 8a

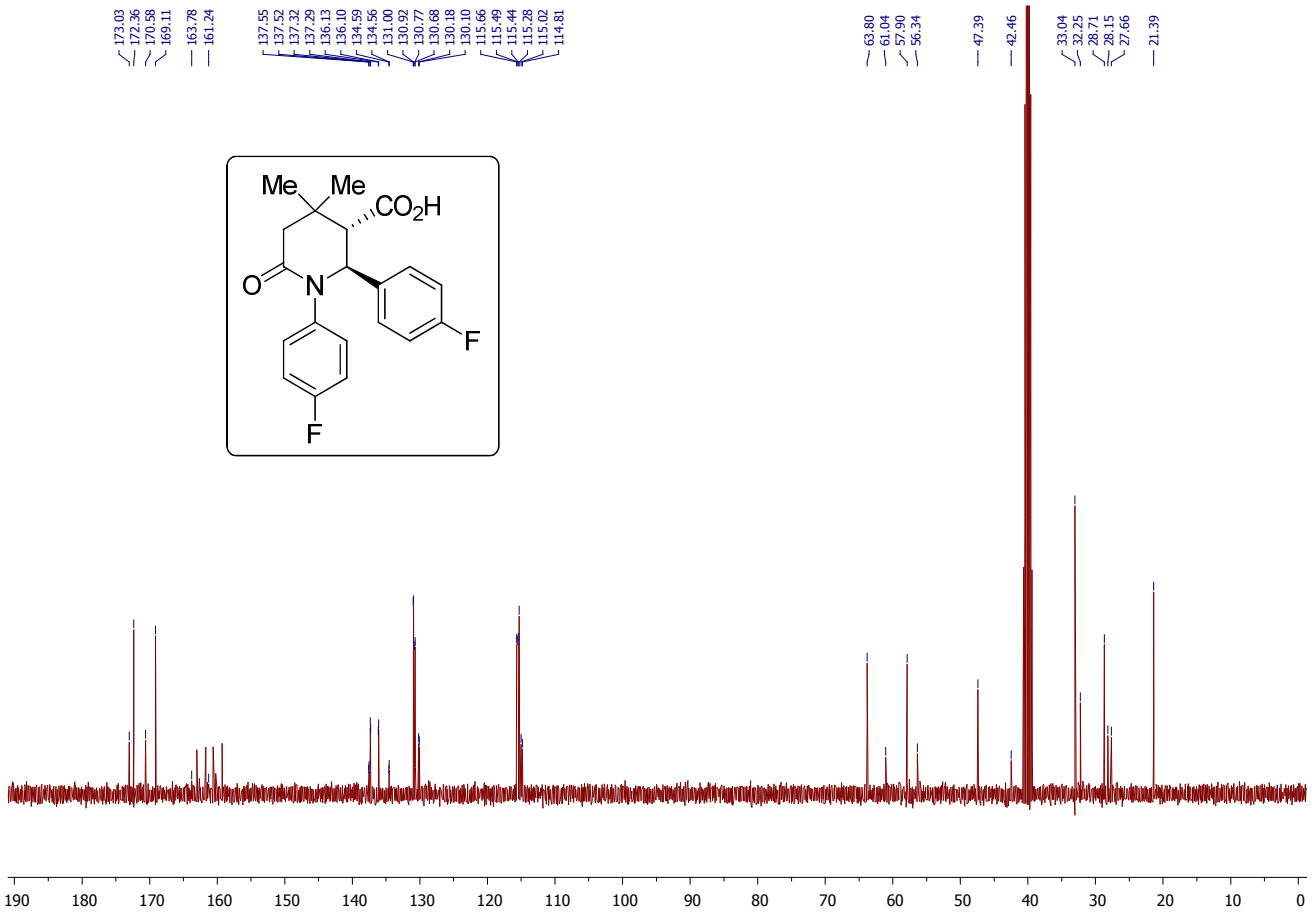


^{1}H and ^{13}C NMR spectra of compound 8b

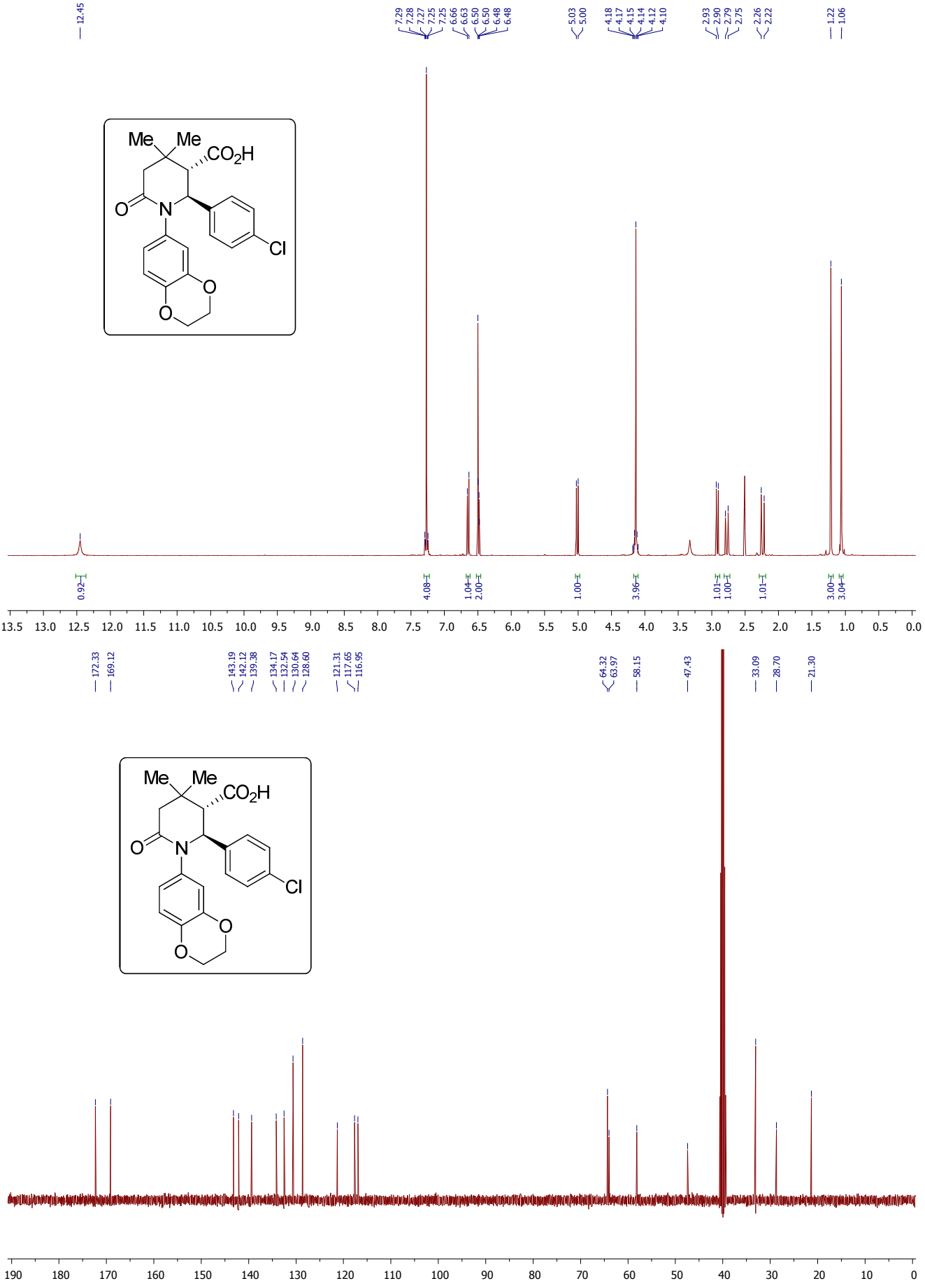


^{1}H and ^{13}C NMR spectra of compound 8c

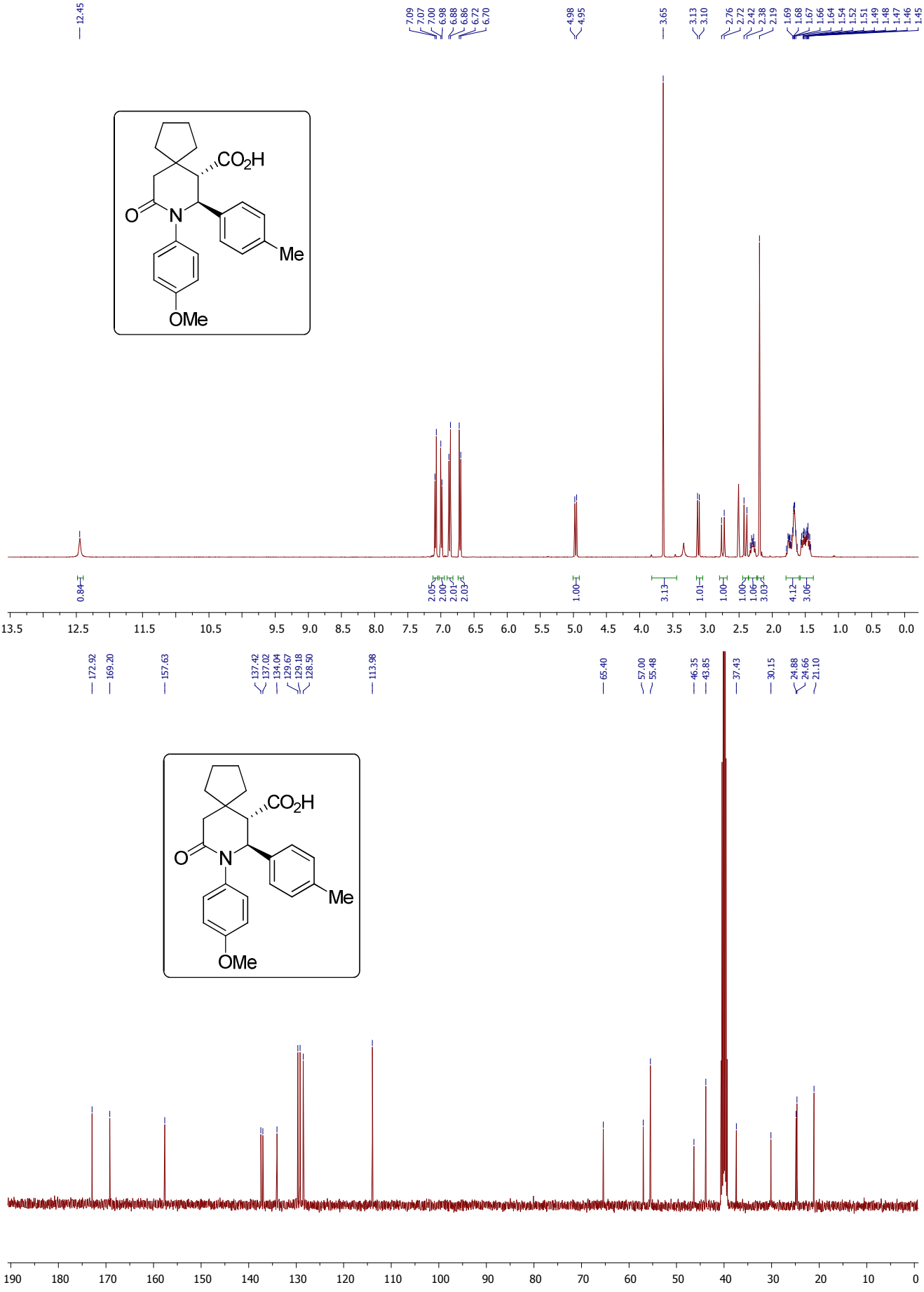




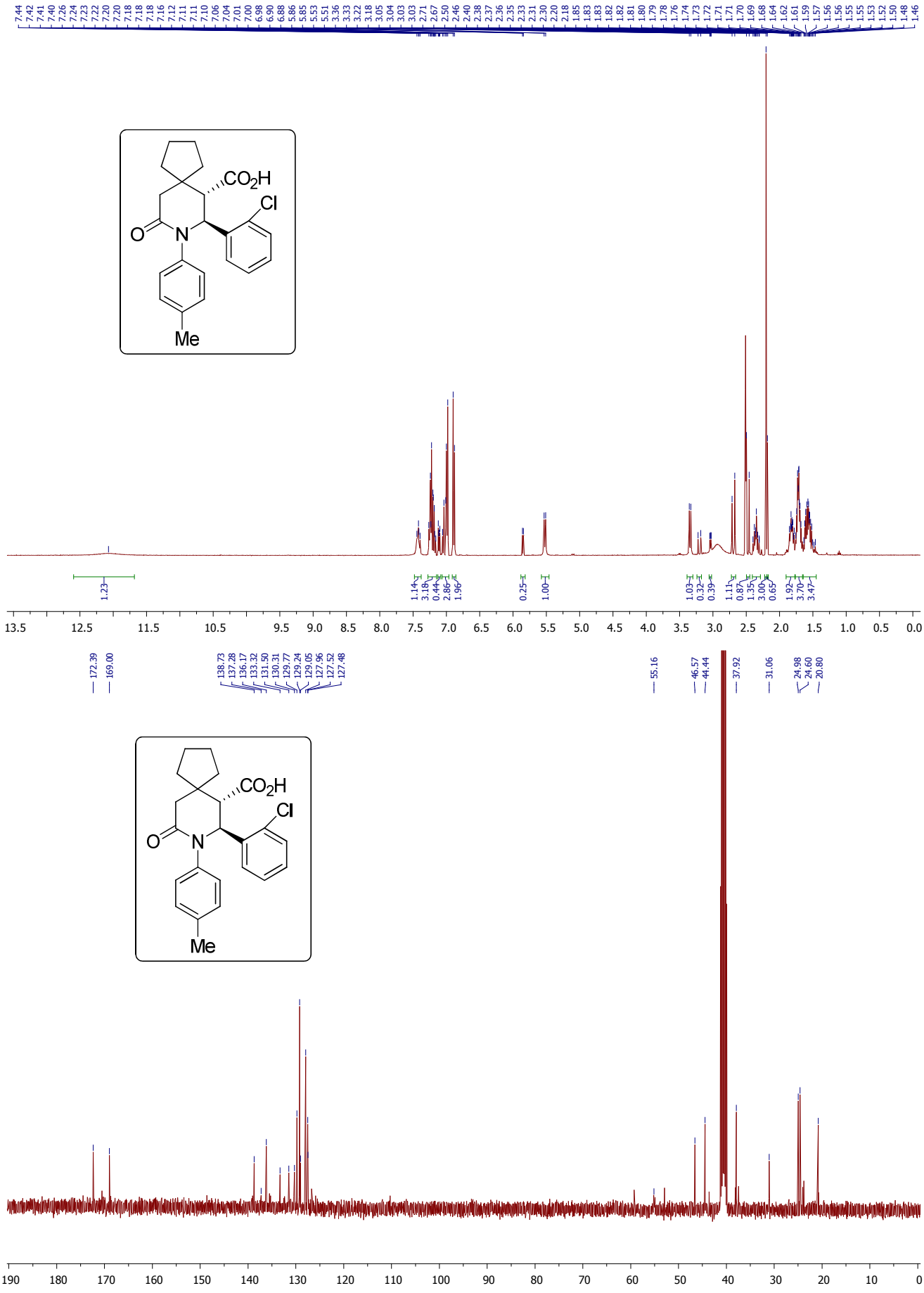
^{1}H and ^{13}C NMR spectra of compound 8d



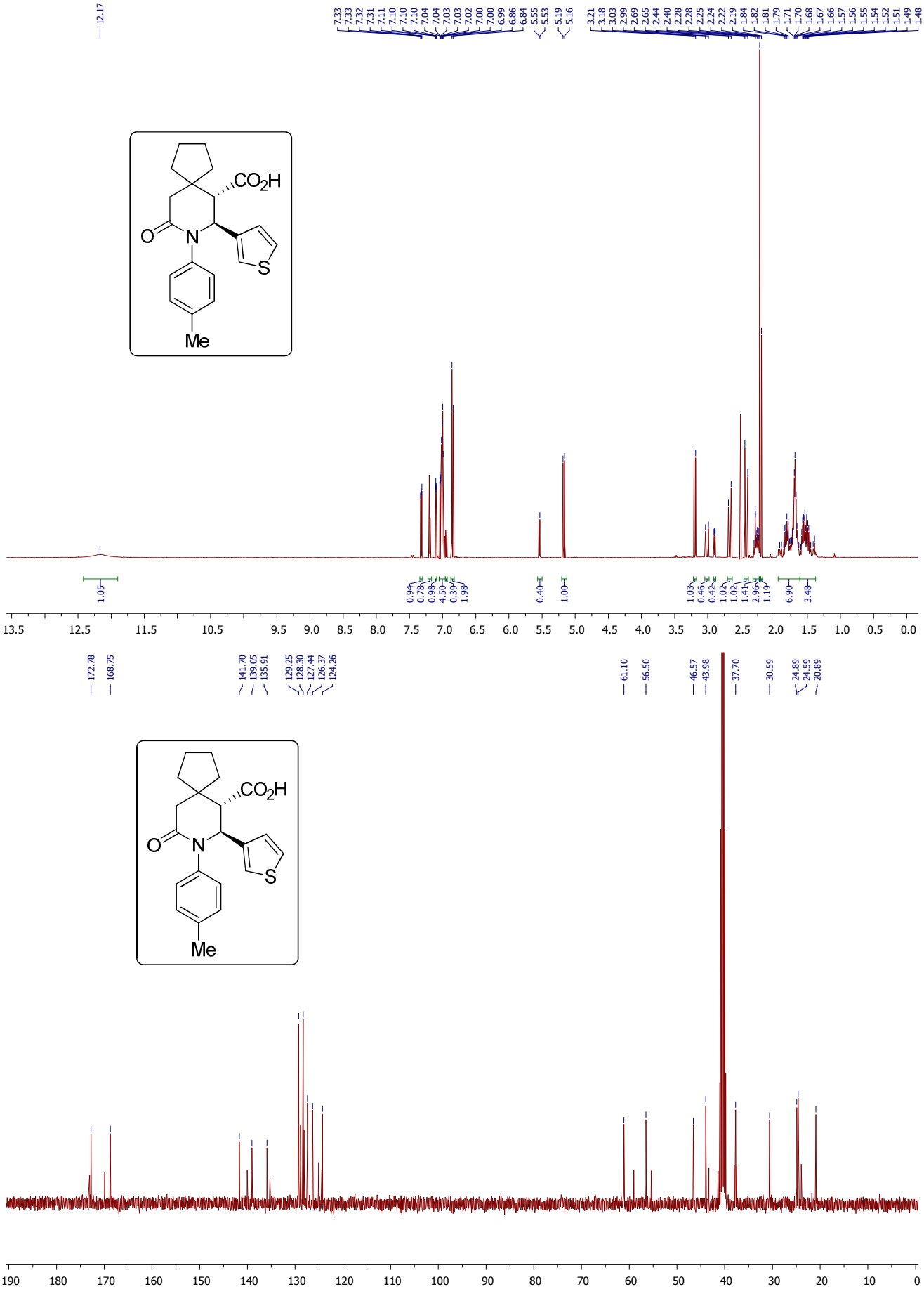
^{1}H and ^{13}C NMR spectra of compound 9a



^{1}H and ^{13}C NMR spectra of compound 9b



^{1}H and ^{13}C NMR spectra of compound 9c



^{1}H and ^{13}C NMR spectra of compound 9d