Supporting information for

The rare *cis*-configured trisubstituted lactam products obtained by the Castagnoli-Cushman reaction in *N,N*-dimethylformamide

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1. General Information

All commercial reagents and solvents were used without further purification, unless otherwise noted. DMF for the synthesis was distilled over CaH_2 and stored under nitrogen over freshly activated molecular sieves 4Å. 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.

Analytical HPLC was carried out on Shimadzu LC-20AD chromatograph, equipped with spectrophotometric detector. Column: YMC Triart-C18-S, 3μm, 2×150 mm. Gradient : 0.1% TFA in water – 0.1% TFA in acetonitrile, from 5% to 95% acetonitrile for 15 min.
Preparative HPLC was carried out on Shimadzu LC-20AP chromatograph, equipped with spectrophotometric detector. Column: YMC-Actus Triart Prep C18-S, 15 μm, 12 nm, 50×250 mm. Eluent: A) water, B) ethanol. Gradient: method A – 5% B (0 –10 min), 5–45% B (10 – 50min); method B – 10% B (0 –10 min), 10–50% B (10–50 min); method C – 20% B (0 –10min), 20–70% B (10–60 min). Flow rate 50 ml/min, temperature ambient, detection UV at 214 and 254 nm. Injection 1000μl.

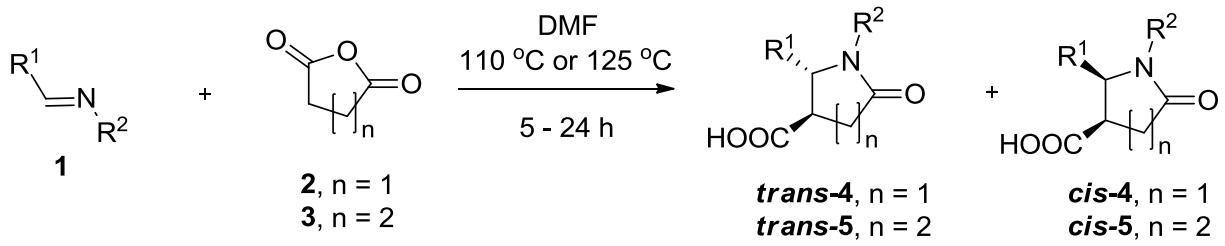
2. Experimental procedures and analytical data

Preparation of imines 1.

General procedure 1. A solution of corresponding amine (1 equiv.) and aldehyde (1 equiv.) in dichloromethane (~ 100 mL per mol) was kept over freshly calcinated $MgSO_4$ (~ 25 g per mol) at room temperature for 1–7 days. The progress of reaction was monitored by ^1H NMR. After completion of the reaction the insoluble material was filtered and the filtrate was concentrated *in vacuo* to give pure imines **3** (air-sensitive; store cold).

***N*-(4-Methoxybenzylidene)-2-methylpropan-2-amine** was synthesized according to general procedure **1** except for using 1.5 equiv. of *tert*-butylamine and molecular sieves 4Å instead of $MgSO_4$.

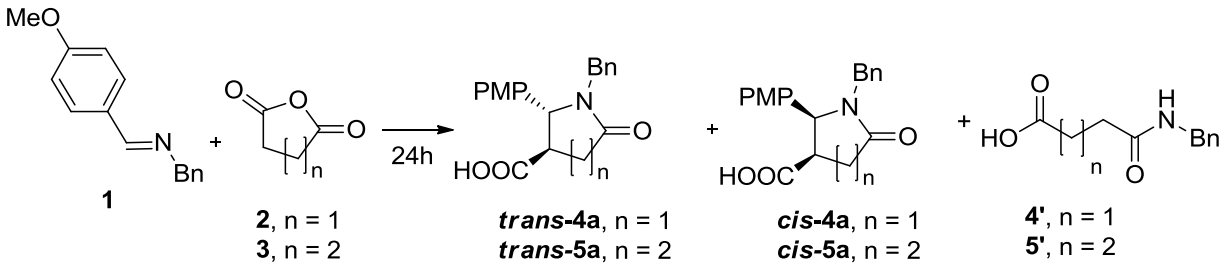
Preparation of diastereomeric mixtures of Castagnoli-Cushman lactams (*cis/trans*-4 and *cis/trans*-5).



General procedure 2 (scale – 1 or 2 mmol)**.** The corresponding cyclic anhydride (**2** or **3**, 1 mmol) and imine (1 mmol) were mixed with dry DMF (~0.5 mL) in a glass test tube with a screw cap, placed in a pre-heated oil bath (110 °C for *N*-alkyl or 125 °C for *N*-arylimines) and stirred at this temperature for indicated period of time. Mixture was concentrated under reduced pressure, dichloromethane (10 mL) and sat. aqueous $NaHCO_3$ (15 mL) were added to the oily residue followed by vigorous shaking for 30–50 min. The organic layer was separated and discarded. Aqueous layer 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.

In case of lactams **4h**, **4j** and **5l** no precipitate was formed after acidification. Aqueous solution was evaporated to dryness and product was extracted with hot acetonitrile (2×20 mL).

Table S1. Solvent screening for the reaction of anhydrides 2 and 3 with imine 1.[a]



№	Solvent	Temperature	Yield (isolated) n=2	*dr* (*cis/trans*) n=2	Yield (isolated) n=1	*dr* (*cis/trans*) n=1
1	DMSO	110 °C	80mg, 24%	1:2	186mg, 57%	1:1.5
2	HMPA	110 °C	NP	-	NP	-
3	CCl_4	reflux	117 mg, 34%[b]	1:9	NP	-
4	THF	reflux	NR	-	NR	-
5	MeCN	reflux	155 mg, 46%[c]	1:4.5	190mg, 58%[c]	1:6
6	DCE	reflux	181 mg, 53%[c]	1:10	201 mg, 62%[c]	1:4
7	$PhCF_3$	reflux	272 mg, 80%	1:9	225mg, 69%	1:5

[a]Reaction was carried out according to General Procedure 2 (1 mmol scale); [b] 0.5 equiv. of **5'**; [c] 0.1–0.15 equiv. of **4'/5'**; NP – no target product; NR – no reaction.

Table S2. Temperature screening for the reaction of anhydrides 2 and 3 with imine 1 in DMF. [a]

№	Temperature	Time	Yield (n = 2)	*dr* (n = 2)	Yield (n = 1)	*dr* (n = 1)
1	r. t.	80 h	NR	-	NR	-
2	40 °C	130 h	NR	-	Traces	-
3	60 °C	90 h	Traces	-	18%	1:2
4	80 °C	22 h	36%	1:2.5	65%	1:2.5
5	110 °C	24 h	44%	1:2.5	66%	1:3

[a]The data represent NMR yield of the product (*cis* + *trans*); *dr* - (*cis : trans*); NR – no reaction.

Sample preparation for Table S2: Anhydride **2** or **3** (20 mg) and *N*-(*p*-methoxybenzylidene)benzylamine (1 equiv.) were reacted in 100 mg of DMF according to general procedure 2. The reaction mixture was diluted with $CDCl_3$ and transferred into NMR test-tube. *n*-Tetradecane was added as internal standard (0.4–0.7 equiv.). The intensity of one of α-CH proton of **4a** or **5a** 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 **4a** or **5a** was calculated from equation:

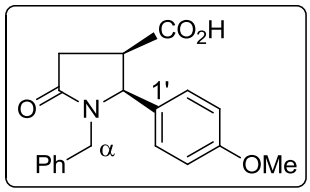
$$NMR\ yield = \frac{I \times n(st)}{0.1136 \times 0.88} \times 100\%$$

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

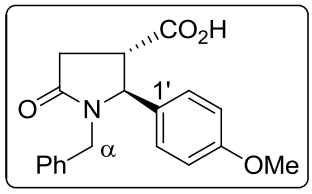
The factor of 0.88 was determined from ^{1}H NMR integration experiments of solutions containing known concentrations of **4a** or **5a** and *n*-tetradecane to reflect the difference in relaxation times of α-CH protons in **4a** or **5a** and the protons of terminal methyl groups in *n*-tetradecane.

***cis/trans*-1-Benzyl-2-(4-methoxyphenyl)-5-oxopyrrolidine-3-carboxylic acid (*cis/trans*-4a).** Prepared according to General Procedure 2; reaction time – 5 h; isolated yield 74% (*dr* 1:3.5); 256 mg of the mixture was submitted for HPLC separation (Method C); ***cis*-4a** – R_t 39 min; ***trans*-4a** – R_t 40–41 min.

***cis*-1-Benzyl-2-(4-methoxyphenyl)-5-oxopyrrolidine-3-carboxylic acid (*cis*-4a):** All attempts to separate individual *cis*-isomer for this compound failed; 88 mg of 2:1 mixture of this compounds with *trans*-isomer was obtained and spectral characteristics for *cis*-**4a** were thus obtained; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.42 (br.s, 1H, COOH), 7.35 – 7.24 (m, 3H, *m*-Ph and *p*-Ph), 7.12 (d, *J* = 6.9 Hz, 2H, *o*-Ph), 6.99 (d, *J* = 8.7 Hz, 2H, 2',6'-H), 6.87 (d, *J* = 8.7 Hz, 2H, 3',5'-H), 4.85 (d, *J* = 15.2 Hz, 1H, α-H), 4.64 (d, *J* = 9.0 Hz, 1H, 2-H), 3.74 (s, 3H, OCH_3), 3.54 (dt, *J* = 10.3, 9.1 Hz, 1H, 3-H), 3.40 (d, *J* = 15.2 Hz, 2H, α-H), 2.85 (dd, *J* = 16.9, 10.3 Hz, 1H, 4-H), 2.42 (dd, *J* = 16.9, 9.1 Hz, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.4, 172.0, 159.4, 137.0, 129.4, 129.0, 128.8, 128.0, 127.7, 114.2, 61.9, 55.5, 44.1, 43.8, 32.4.

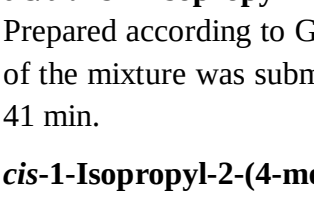


***trans*-1-Benzyl-2-(4-methoxyphenyl)-5-oxopyrrolidine-3-carboxylic acid (*trans*-4a):** 74 mg isolated; White solid; Mp 159−160 °C (lit[1] Mp 160−161 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.69 (br.s, 1H, COOH), 7.38 – 7.22 (m, 3H, *m*-Ph and *p*-Ph), 7.13 (d, *J* = 8.7 Hz, 2H, 2',6'-H), 7.02 (d, *J* = 6.9 Hz, 2H, *o*-Ph), 6.95 (d, *J* = 8.7 Hz, 2H, 3',5'-H), 4.80 (d, *J* = 15.1 Hz, 1H, α-H), 4.50 (d, *J* = 5.8 Hz, 1H, 2-H), 3.77 (s, 3H, OCH_3), 3.44 (d, *J* = 15.1 Hz, 1H, α-H), 3.06 (ddd, *J* = 9.7, 7.1, 5.8 Hz, 1H, 3-H), 2.83 (dd, *J* = 16.9, 9.7 Hz, 1H, 4-H), 2.63 (dd, *J* = 16.9, 7.1 Hz, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.3, 172.7, 159.6, 136.7, 131.6, 128.94, 128.90, 128.1, 127.7, 114.7, 63.5, 55.6, 45.9, 43.9, 33.6. $C_{19}H_{19}NO_4$ $[M–H]^-$ 324.1241, found 324.1241.

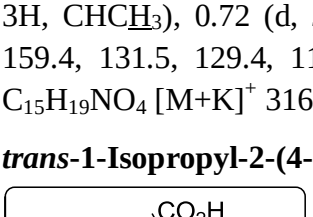


***cis/trans*-1-Isopropyl-2-(4-methoxyphenyl)-5-oxopyrrolidine-3-carboxylic acid (*cis/trans*-4b).** Prepared according to General Procedure 2; reaction time – 5 h; isolated yield 75% (*dr* 1:1.8); 402 mg of the mixture was submitted for HPLC separation (Method B); ***cis*-4b** – R_t 36 min; ***trans*-4b** – R_t 38–41 min.

***cis*-1-Isopropyl-2-(4-methoxyphenyl)-5-oxopyrrolidine-3-carboxylic acid (*cis*-4b):** 92 mg isolated; White solid; Mp 173−174 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.22 (br.s, 1H, COOH), 7.14 (d, *J* = 8.7 Hz, 1H, 2',6'-H), 6.87 (d, *J* = 8.7 Hz, 1H, 3',5'-H), 4.97 (d, *J* = 9.1 Hz, 1H, 2-H), 3.94 (hept, *J* = 6.8 Hz, 1H, C<u>H</u>$(CH_3)_2$), 3.73 (s, 3H, OCH_3), 3.61 (dt, *J* = 11.3, 9.1 Hz, 1H, 3-H), 2.87 (dd, *J* = 16.7, 11.3 Hz, 1H, 4-H), 2.30 (dd, *J* = 16.7, 9.1 Hz, 1H, 4-H), 1.12 (d, *J* = 6.8 Hz, 3H, CHC<u>H</u>$_3$), 0.72 (d, *J* = 6.8 Hz, 3H, CHC<u>H</u>$_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.4, 171.7, 159.4, 131.5, 129.4, 113.9, 60.6, 55.5, 44.5, 44.3, 32.6, 21.2, 20.1. HRMS (ESI), *m/z* calcd for $C_{15}H_{19}NO_4$ $[M+K]^+$ 316.0946, found 316.0939.



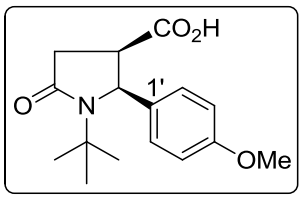
***trans*-1-Isopropyl-2-(4-methoxyphenyl)-5-oxopyrrolidine-3-carboxylic acid (*trans*-4b):** 226 mg isolated; White solid; Mp 207−208 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.71 (br.s, 1H, COOH), 7.27 (d, *J* = 8.8 Hz, 1H, 2',6'-H), 6.94 (d, *J* = 8.8 Hz, 1H, 3',5'-H), 4.79 (d, *J* = 4.4 Hz, 1H, 2-H), 3.77 (hept, *J* = 6.9 Hz, 1H, C<u>H</u>$(CH_3)_2$), 3.76 (s, 3H, OCH_3), 2.89 (ddd, *J* = 9.6, 5.3, 4.4 Hz, 1H, 3-H), 2.78 (dd, *J* = 16.7, 9.6 Hz, 1H, 4-H), 2.43 (dd, *J* = 16.7, 5.3 Hz, 1H, 4-H),



1.11 (d, *J* = 6.9 Hz, 3H, CHC<u>H</u>$_3$), 0.81 (d, *J* = 6.9 Hz, 3H, CHC<u>H</u>$_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.5, 172.4, 159.4, 134.4, 128.6, 114.5, 63.0, 55.6, 46.5, 44.8, 34.0, 20.7, 19.9. HRMS (ESI), *m/z* calcd for $C_{15}H_{19}NO_4$ $[M+H]^+$ 278.1387, found 278.1386.

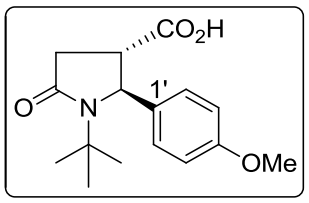
***cis/trans*-1-(*tert*-Butyl)-2-(4-methoxyphenyl)-5-oxopirrolidine-3-carboxylic acid (*cis/trans*-4c).** Prepared according to General Procedure 2; reaction time – 5 h; isolated yield 69% (*dr* 1:1.7); 385 mg of the mixture was submitted for HPLC separation (Method C); ***cis*-4c** – R_t 31 min; ***trans*-4c** – R_t 33–35 min.

***cis*-1-(*tert*-Butyl)-2-(4-methoxyphenyl)-5-oxopirrolidine-3-carboxylic acid (*cis*-4c):** 96 mg isolated;



White solid; Mp 197−198 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.21 (br.s, 1H, COOH), 7.12 (d, *J* = 8.7 Hz, 2H, 2',6'-H), 6.89 (d, *J* = 8.7 Hz, 2H, 3',5'-H), 5.13 (d, *J* = 8.6 Hz, 1H, 2-H), 3.74 (s, 3H, OCH_3), 3.53 (dt, *J* = 12.0, 8.6 Hz, 1H, 3-H), 2.82 (dd, *J* = 16.7, 12.0 Hz, 1H, 4-H), 2.25 (dd, *J* = 16.7, 8.6 Hz, 1H, 4-H), 1.23 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.2, 171.5, 159.2, 131.6, 129.1, 113.9, 62.3, 55.5, 54.8, 44.4, 33.2, 28.1. HRMS (ESI), *m/z* calcd for $C_{16}H_{21}NO_4$ $[M+Na]^+$ 314.1363, found 314.1367.

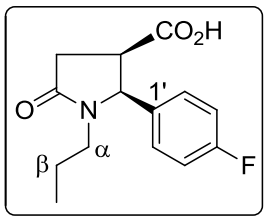
***trans*-1-(*tert*-Butyl)-2-(4-methoxyphenyl)-5-oxopirrolidine-3-carboxylic acid (*trans*-4c):** 132 mg



isolated; White solid; Mp 195−196 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.74 (br.s, 1H, COOH), 7.20 (d, *J* = 8.7 Hz, 2H, 2',6'-H), 6.96 (d, *J* = 8.7 Hz, 2H, 3',5'-H), 5.09 (d, *J* = 1.0 Hz, 1H, 2-H), 3.76 (s, 3H, OCH_3), 2.77 (dd, *J* = 16.8, 9.1 Hz, 1H, 4-H), 2.62 (ddd, *J* = 9.1, 1.5, 1.0 Hz, 1H, 3-H), 2.34 (dd, *J* = 16.8, 1.5 Hz, 1H, 4-H), 1.23 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.7, 173.4, 159.1, 135.8, 127.1, 114.7, 63.8, 55.5, 54.6, 46.4, 33.9, 28.1. HRMS (ESI), *m/z* calcd for $C_{16}H_{21}NO_4$ $[M+Na]^+$ 314.1363, found 314.1369.

***cis/trans*-2-(4-Fluorophenyl)-5-oxo-1-(*n*-propyl)pirrolidine-3-carboxylic acid (*cis/trans*-4d).** Prepared according to General Procedure 2; reaction time – 5 h; isolated yield 46% (*dr* 1:2.5); 220 mg of the mixture was submitted for HPLC separation (Method C); ***cis*-4d** – R_t 30 min; ***trans*-4d** – R_t 32–35 min.

***cis*-2-(4-Fluorophenyl)-5-oxo-1-(*n*-propyl)pirrolidine-3-carboxylic acid (*cis*-4d):** 21 mg isolated;



White solid; Mp 163−164 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.32 (br.s, 1H, COOH), 7.24 – 7.13 (m, 4H, ArH), 5.00 (d, *J* = 9.2 Hz, 1H, 2-H), 3.66 (dt, *J* = 10.2, 9.2 Hz, 1H, 3-H), 3.43 (dt, *J* = 13.7, 7.9 Hz, 1H, α-H), 2.79 (dd, *J* = 16.9, 10.2 Hz, 1H, 4-H), 2.41 (dd, *J* = 16.9, 9.2 Hz, 1H, 4-H), 2.45 – 2.39 (m, 1H, α-H), 1.46 – 1.26 (m, 2H, β-CH_2), 0.76 (t, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.0, 171.9, 162.3 (d, *J* = 243.9 Hz), 133.9 (d, *J* = 3.0 Hz), 130.1 (d, *J* = 8.4 Hz), 115.6 (d, *J* = 21.5 Hz), 61.8, 43.2, 42.4, 32.1, 20.3, 11.6. HRMS (ESI), *m/z* calcd for $C_{14}H_{16}FNO_3$ $[M+H]^+$ 266.1187, found 266.1198.

***trans*-2-(4-Fluorophenyl)-5-oxo-1-(*n*-propyl)pirrolidine-3-carboxylic acid (*trans*-4d):** 75 mg isolated; White solid; Mp 149−150 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.75 (br.s, 1H, COOH), 7.42 – 7.33 (m, 1H, 2',6'-H), 7.23 (t, *J* = 8.8 Hz, 1H, 3',5'-H), 4.81 (d, *J* = 5.6 Hz, 1H, 2-H), 3.39 (dt, *J* = 13.5, 7.8 Hz, 1H, α-H), 3.02 (ddd, *J* = 9.7, 6.9, 5.6 Hz, 1H, 3-H), 2.75 (dd, *J* = 17.0, 9.7 Hz, 1H, 4-H), 2.55 (dd, *J* = 17.0, 6.9 Hz, 1H, 4-H), 2.42 (ddd, *J* = 13.5, 7.8, 5.1 Hz, 1H, α-H), 1.43 – 1.19 (m, 2H, β-CH_2), 0.72 (t, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.2, 172.5, 162.3 (d, *J* = 244.1 Hz), 136.7 (d, *J* = 3.0 Hz), 129.7 (d, *J* = 8.4 Hz), 116.1 (d, *J* = 21.5 Hz), 63.3, 45.8, 42.0, 33.6, 20.0, 11.5. HRMS (ESI), *m/z* calcd for $C_{14}H_{16}FNO_3$ $[M+H]^+$ 266.1187, found 266.1199.

***cis/trans*-1-Ethyl-5-oxo-2-*p*-tolylpyrrolidine-3-carboxylic acid (*cis/trans*-4e).** Prepared according to General Procedure 2; reaction time – 5 h; isolated yield 70% (*dr* 1:2); 325 mg of the mixture was submitted for HPLC separation (Method B); ***cis*-4e** – R_t 36 min; ***trans*-4e** – R_t 38–41 min.

***cis*-1-Ethyl-5-oxo-2-*p*-tolylpyrrolidine-3-carboxylic acid (*cis*-4e):** 61 mg isolated; White solid; Mp 233−234 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.33 (br.s, 1H, COOH), 7.13 (d, *J* = 8.0 Hz, 1H, ArH), 7.03 (d, *J* = 8.0 Hz, 1H, ArH), 4.99 (d, *J* = 9.3 Hz, 1H, 2-H), 3.63 (dt, *J* = 10.4, 9.3 Hz, 1H, 3-H), 3.48 (dq, *J* = 14.6, 7.2 Hz, 1H, α-H), 2.77 (dd, *J* = 16.8, 10.4 Hz, 1H, 4-H), 2.48 (dq, *J* = 14.6, 7.2 Hz, 1H, α-H), 2.37 (dd, *J* = 16.8, 9.3 Hz, 1H, 4-H), 2.27 (s, 3H, 4'-CH_3), 0.90 (t, *J* = 7.2 Hz, 3H, $CH_2C\underline{H}_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.7, 171.9, 137.7, 134.7, 129.3, 128.1, 62.0, 43.4, 35.6, 32.4, 21.1, 12.8. HRMS (ESI), *m/z* calcd for $C_{14}H_{17}NO_3$ $[M+H]^+$ 248.1281, found 248.1282.

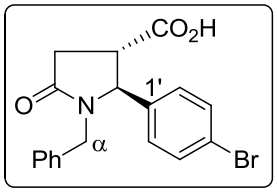
***trans*-1-Ethyl-5-oxo-2-*p*-tolylpyrrolidine-3-carboxylic acid (*trans*-4e):** 208 mg isolated; White solid; Mp 127−128 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.72 (br.s, 1H, COOH), 7.20 (s, 4H, ArH), 4.76 (d, *J* = 5.9 Hz, 1H, 2-H), 3.44 (dq, *J* = 14.5, 7.2 Hz, 1H, α-H), 3.00 (ddd, *J* = 9.7, 7.2, 5.9 Hz, 1H, 3-H), 2.72 (dd, *J* = 16.8, 9.7 Hz, 1H, 4-H), 2.58 – 2.41 (m, 2H, α-H and 4-H), 2.31 (s, 3H, 4'-CH_3), 0.85 (t, *J* = 7.2 Hz, 3H, $CH_2C\underline{H}_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.3, 172.1, 137.9, 137.5, 129.9, 127.5, 63.5, 45.9, 35.2, 33.9, 21.2, 12.4. HRMS (ESI), *m/z* calcd for $C_{14}H_{17}NO_3$ $[M+H]^+$ 248.1281, found 248.1289.

***cis/trans*-1-Benzyl-2-(4-bromophenyl)-5-oxopyrrolidine-3-carboxylic acid (*cis/trans*-4f).** Prepared according to General Procedure 2; reaction time – 24 h; isolated yield 48% (*dr* 1:3); 332 mg of the mixture was submitted for HPLC separation (Method C); ***cis*-4f** – R_t 48 min; ***trans*-4f** – R_t 49–51 min.

***cis*-1-Benzyl-2-(4-bromophenyl)-5-oxopyrrolidine-3-carboxylic acid (*cis*-4f):** 11 mg isolated; White solid; Mp 187−188 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.21 (br.s, 1H, COOH), 7.52 (d, *J* = 8.4 Hz, 2H, 3',5'-H), 7.35 – 7.25 (m, 3H, *m*-Ph and *p*-Ph), 7.16 – 7.10 (m, 2H, *o*-Ph), 7.05 (d, *J* = 8.4 Hz, 2H, 2',6'-H), 4.84 (d, *J* = 15.2 Hz, 1H, α-H), 4.72 (d, *J* = 9.3 Hz, 1H, 2-H), 3.66 (dt, *J* = 10.3, 9.3 Hz, 1H, 3-H), 3.49 (d, *J* = 15.2 Hz, 1H, α-H), 2.85 (dd, *J* = 16.8, 10.3 Hz, 1H, 4-H), 2.49 (dd, *J* = 16.8, 9.3 Hz, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.3, 171.8, 136.7, 136.6, 131.8,

130.4, 129.0, 128.1, 127.8, 61.8, 44.4, 43.3, 32.1. HRMS (ESI), *m/z* calcd for $C_{18}H_{16}BrNO_3Na$ $[M+Na]^+$ 396.0206, found 396.0206.

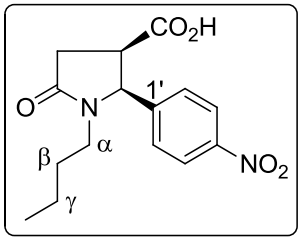
***trans*-1-Benzyl-2-(4-bromophenyl)-5-oxopyrrolidine-3-carboxylic acid (*trans*-4f):** 104 mg isolated;



White solid; Mp 194−196 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (br.s, 1H, COOH), 7.58 (d, *J* = 8.3 Hz, 2H, 3',5'-H), 7.34 – 7.22 (m, 3H, *m*-Ph and *p*-Ph), 7.17 (d, *J* = 8.3 Hz, 2H, 2',6'-H), 7.03 – 7.00 (m, 2H, *o*-Ph), 4.80 (d, *J* = 15.2 Hz, 1H, α-H), 4.55 (d, *J* = 5.5 Hz, 1H, 2-H), 3.51 (d, *J* = 15.2 Hz, 1H, α-H), 3.07 (ddd, *J* = 9.7, 6.9, 5.5 Hz, 1H, 3-H), 2.83 (dd, *J* = 17.0, 9.7 Hz, 1H, 4-H), 2.64 (dd, *J* = 17.0, 6.9 Hz, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.00, 172.9, 139.4, 136.5, 132.3, 129.9, 128.9, 128.1, 127.8, 121.8, 63.3, 45.6, 44.2, 33.4. HRMS (ESI), *m/z* calcd for $C_{18}H_{16}BrNO_3Na$ $[M+Na]^+$ 396.0206, found 396.0208.

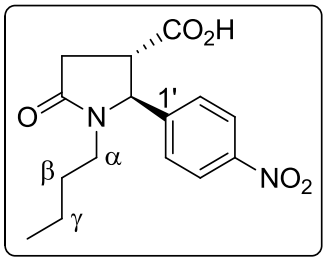
***cis/trans*-1-*n*-Butyl-2-(4-nitrophenyl)-5-oxopyrrolidine-3-carboxylic acid (*cis/trans*-4g).** Prepared according to General Procedure 2; reaction time – 24 h; isolated yield 28% (*dr* 1:4.5); 170 mg of the mixture was submitted for HPLC separation (Method C); ***cis*-4g** – R_t 38 min; ***trans*-4g** – R_t 39–41 min.

***cis*-1-*n*-Butyl-2-(4-nitrophenyl)-5-oxopyrrolidine-3-carboxylic acid (*cis*-4g):** 9 mg isolated; White



solid; Mp 161−163 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.58 (br.s, 1H, COOH), 8.21 (d, *J* = 8.8 Hz, 2H, 3',5'-H), 7.47 (d, *J* = 8.8 Hz, 2H, 2',6'-H), 5.17 (d, *J* = 9.2 Hz, 1H, 2-H), 3.72 (dt, *J* = 10.3, 9.2 Hz, 1H, 3-H), 3.54 (dt, *J* = 13.8, 7.7 Hz, 1H, α-H), 2.81 (dd, *J* = 17.0, 10.3 Hz, 1H, 4-H), 2.50 – 2.38 (m, 2H, α-H and 4-H), 1.41 – 1.28 (m, 2H, β-CH_2), 1.27 – 1.08 (m, 2H, γ-CH_2), 0.82 (t, *J* = 7.3 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.2, 171.8, 147.8, 145.9, 129.6, 123.9, 61.7, 43.3, 32.2, 29.0, 19.8, 14.0. HRMS (ESI), *m/z* calcd for $C_{15}H_{18}N_2O_5$ $[M+Na]^+$ 329.1108, found 329.1108.

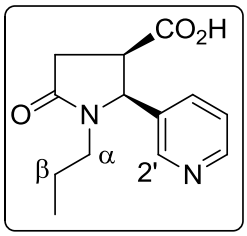
***trans*-1-*n*-Butyl-2-(4-nitrophenyl)-5-oxopyrrolidine-3-carboxylic acid (*trans*-4g)[2]:** 106 mg



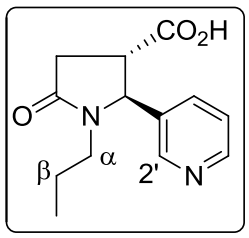
isolated; White solid; Mp 172−173 °C (lit[2] Mp 175 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.85 (br.s, 1H, COOH), 8.27 (d, *J* = 8.9 Hz, 2H, 3',5'-H), 7.63 (d, *J* = 8.9 Hz, 2H, 2',6'-H), 4.99 (d, *J* = 5.4 Hz, 1H, 2-H), 3.52 (dt, *J* = 13.7, 7.9 Hz, 1H, α-H), 3.06 (ddd, *J* = 9.7, 6.6, 5.4 Hz, 1H, 3-H), 2.75 (ddd, *J* = 16.9, 9.7, 0.7 Hz, 1H, 4-H), 2.58 (dd, *J* = 16.9, 6.6 Hz, 1H, 4-H), 2.44 (ddd, *J* = 13.6, 7.8, 5.6 Hz, 1H, α-H), 1.35 – 1.24 (m, 2H, β-CH_2), 1.23 – 1.06 (m, 2H, γ-CH_2), 0.80 (t, *J* = 7.3 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.9, 172.7, 148.3, 147.8, 129.0, 124.5, 63.1, 45.4, 33.3, 28.7, 19.7, 13.9. **HRMS** (ESI), *m/z* calcd for $C_{15}H_{18}N_2O_5$ $[M+Na]^+$ 329.1108, found 329.1108.

***cis/trans*-6-Oxo-1-(*n*-propyl)-2-(pyridine-3-yl)pyrrolidine-3-carboxylic acid (*cis/trans*-4h).** Prepared according to General Procedure 2; reaction time – 6 h; isolated yield 62% (*dr* 1:2); 302 mg of the mixture was submitted for HPLC separation (Method A); ***cis*-4h** – R_t 15 min; ***trans*-4h** – R_t 12–14 min.

***cis*-6-Oxo-1-(*n*-propyl)-2-(pyridine-3-yl)pyrrolidine-3-carboxylic acid (*cis*-4h):** 62 mg isolated; Yellow oil; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.43 (br.s, 1H, COOH), 8.51 (dd, *J* = 4.8, 1.8 Hz, 1H, 6'-H), 8.43 (d, *J* = 2.1 Hz, 1H, 2'-H), 7.55 (dt, *J* = 7.9, 2.1 Hz, 1H, 4'-H), 7.38 (dd, *J* = 7.9, 4.8 Hz, 1H, 5'-H), 5.06 (d, *J* = 9.3 Hz, 1H, 2-H), 3.73 (dt, *J* = 10.2, 9.3 Hz, 1H, 3-H), 3.43 (dt, *J* = 13.7, 7.9 Hz, 1H, α-H), 2.83 (dd, *J* = 16.9, 10.4 Hz, 1H, 4-H), 2.49 – 2.36 (m, 2H, α-H and-4-H), 1.47 – 1.22 (m, 2H, β-CH_2), 0.76 (t, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.1, 171.9, 149.9, 149.7, 135.5, 133.4, 124.0, 60.2, 43.1, 42.5, 32.1, 20.4, 11.6. HRMS (ESI), *m/z* calcd for $C_{13}H_{16}N_2O_3$ $[M+H]^+$ 249.1234, found 249.1239.

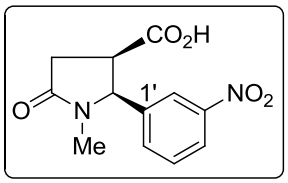


***trans*-6-Oxo-1-(*n*-propyl)-2-(pyridine-3-yl)pyrrolidine-3-carboxylic acid (*trans*-4h):** 122 mg isolated; Beige solid; Mp 124−125 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.83 (br.s, 1H, COOH), 8.62 – 8.50 (m, 2H, 2'-H and 6'-H), 7.77 (dt, *J* = 8.0, 1.8 Hz, 1H, 4'-H), 7.44 (dd, *J* = 7.8, 4.8 Hz, 1H, 5'-H), 4.85 (d, *J* = 5.7 Hz, 1H, 2-H), 3.39 (dt, *J* = 14.1, 7.9 Hz, 1H, α-H), 3.11 (ddd, *J* = 9.7, 7.0, 5.7 Hz, 1H, 3-H), 2.78 (dd, *J* = 16.9, 9.7 Hz, 1H, 4-H), 2.58 (dd, *J* = 16.9, 7.0 Hz, 1H, 4-H), 2.49 – 2.33 (m, 1H, α-H), 1.43 – 1.16 (m, 2H, β-CH_2), 0.72 (t, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.0, 172.7, 150.0, 149.4, 136.0, 135.3, 124.4, 61.7, 45.5, 42.1, 33.6, 20.1, 11.5. HRMS (ESI), *m/z* calcd for $C_{13}H_{16}N_2O_3$ $[M+H]^+$ 249.1234, found 249.1242.

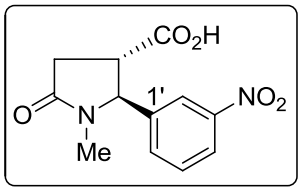


***cis/trans*-2-(3-Nitrophenyl)-1-methyl-5-oxopyrrolidine-3-carboxylic acid (*cis/trans*-4i).** Prepared according to General Procedure 2; reaction time – 6 h; isolated yield 48% (*dr* 1:1.8); 290 mg of the mixture was submitted for HPLC separation (Method B); ***cis*-4i** – R_t 28 min; ***trans*-4i** – R_t 30–32 min.

***cis*-2-(3-Nitrophenyl)-1-methyl-5-oxopyrrolidine-3-carboxylic acid (*cis*-4i):** 61 mg isolated; White solid; Mp 213−214 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.56 (br.s, 1H, COOH), 8.19 (ddd, *J* = 8.0, 2.3, 1.1 Hz, 1H, 4'-H), 7.99 (t, *J* = 2.0 Hz, 1H, 2'-H), 7.68 (t, *J* = 7.9 Hz, 1H, 5'-H), 7.60 (dt, *J* = 7.8, 1.3 Hz, 1H, 6'-H), 5.13 (d, *J* = 9.3 Hz, 1H, 2-H), 3.71 (dt, *J* = 10.0, 9.4 Hz, 1H, 3-H), 2.77 (dd, *J* = 17.0, 10.0 Hz, 1H, 4-H), 2.58 (s, 3H, CH_3), 2.45 (dd, *J* = 17.0, 9.4 Hz, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.3, 172.1, 148.1, 140.0, 134.5, 130.6, 123.6, 122.9, 63.8, 43.1, 32.1, 28.4. HRMS (ESI), *m/z* calcd for $C_{12}H_{12}N_2O_5$ $[M+K]^+$ 303.0378, found 303.0368.

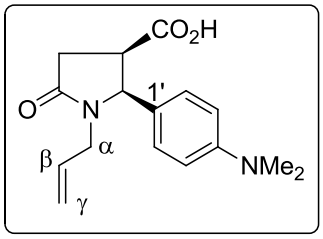


***trans*-2-(3-Nitrophenyl)-1-methyl-5-oxopyrrolidine-3-carboxylic acid (*trans*-4i):** 143 mg isolated; White solid; Mp 246−247 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.83 (br.s, 1H, COOH), 8.22 (ddd, *J* = 8.0, 2.3, 1.3 Hz, 1H, 4'-H), 8.15 (t, *J* = 1.9 Hz, 1H, 2'-H), 7.79 (dt, *J* = 7.8, 1.3 Hz, 1H, 6'-H), 7.73 (t, *J* = 7.8 Hz, 1H, 5'-H), 4.94 (d, *J* = 6.2 Hz, 1H, 2-H), 3.11 (ddd, *J* = 9.9, 7.3, 6.2 Hz, 1H, 3-H), 2.76 (dd, *J* = 16.9, 9.9 Hz, 1H, 4-H), 2.57 (dd, *J* = 16.9, 7.3 Hz, 1H, 4-H), 2.52 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.8, 172.8, 148.6, 143.0, 134.3, 131.0, 123.6, 122.4, 65.2, 45.4, 33.4, 28.2. HRMS (ESI), *m/z* calcd for $C_{12}H_{12}N_2O_5$ $[M+K]^+$ 303.0378, found 303.0386.



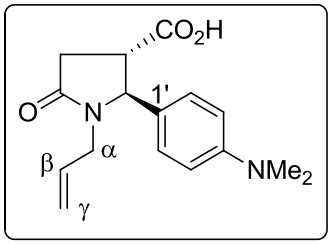
***cis/trans*-1-Allyl-2-(4-(dimethylamino)phenyl)-5-oxopyrrolidine-3-carboxylic acid (*cis/trans*-4j).** Prepared according to General Procedure 2; reaction time – 6 h; isolated yield 84% (*dr* 1:2); 432 mg of the mixture was submitted for HPLC separation (Method A); ***cis*-4j** – R_t 19 min; ***trans*-4j** – R_t 16–18 min.

***cis*-1-Allyl-2-(4-(dimethylamino)phenyl)-5-oxopyrrolidine-3-carboxylic acid (*cis*-4j):** 101 mg



isolated; Beige solid; Mp 188−189 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.23 (br.s, 1H, COOH), 6.92 (d, *J* = 8.9 Hz, 2H, 2',6'-H), 6.67 (d, *J* = 8.9 Hz, 2H, 3',5'-H), 5.66 (dddd, *J* = 17.1, 10.2, 6.8, 4.5 Hz, 1H, β-H), 5.10 (dq, *J* = 10.3, 1.6 Hz, 1H, γ-H), 5.03 (dq, *J* = 17.1, 1.6 Hz, 1H, γ-H), 4.77 (d, *J* = 9.0 Hz, 1H, 2-H), 4.19 (ddt, *J* = 15.7, 4.3, 1.8 Hz, 1H, α-H), 3.64 (dt, *J* = 10.3, 9.2 Hz, 1H, 3-H), 2.94 (ddd, *J* = 15.7, 6.8, 1.0 Hz, 1H, α-H), 2.88 (s, 6H, $N(CH_3)_2$), 2.81 (ddd, *J* = 16.8, 10.2, 0.8 Hz, 1H, 4-H), 2.41 (dd, *J* = 16.9, 9.2 Hz, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.7, 171.9, 150.6, 133.2, 128.8, 123.9, 117.5, 112.5, 62.0, 43.3, 42.9, 32.2. HRMS (ESI), *m/z* calcd for $C_{16}H_{20}N_2O_3$ $[M+Na]^+$ 311.1366, found 311.1376.

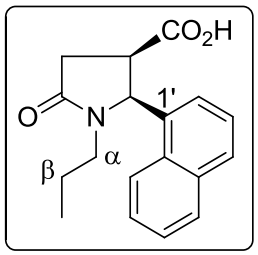
***trans*-1-Allyl-2-(4-(dimethylamino)phenyl)-5-oxopyrrolidine-3-carboxylic acid (*trans*-4j):** 168 mg



isolated; Beige solid; Mp 187−188 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.69 (br.s, 1H, COOH), 7.06 (d, *J* = 8.9 Hz, 2H, 2',6'-H), 6.72 (d, *J* = 8.9 Hz, 2H, 3',5'-H), 5.58 (dddd, *J* = 17.1, 10.3, 6.8, 4.4 Hz, 1H, β-H), 5.08 (dtd, *J* = 10.3, 1.6, 1.2 Hz, 1H, γ-H), 4.96 (dq, *J* = 17.1, 1.6 Hz, 1H, γ-H), 4.62 (d, *J* = 5.7 Hz, 1H, 2-H), 4.10 (ddt, *J* = 15.7, 4.3, 1.9 Hz, 1H, α-H), 3.01 (ddd, *J* = 9.7, 7.0, 5.7 Hz, 1H, 3-H), 2.94 (ddd, *J* = 15.7, 6.8, 0.9 Hz, 1H, α-H), 2.90 (s, 6H, $N(CH_3)_2$), 2.76 (ddd, *J* = 16.9, 9.7, 0.9 Hz, 1H, 4-H), 2.55 (dd, *J* = 16.9, 7.0 Hz, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.5, 172.1, 150.7, 132.8, 128.3, 126.9, 117.5, 112.9, 63.7, 45.9, 42.6, 33.8. HRMS (ESI), *m/z* calcd for $C_{16}H_{20}N_2O_3$ $[M+H]^+$ 289.1547, found 289.1548.

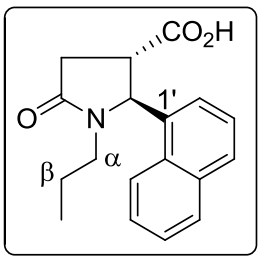
***cis/trans*-2-(Naphthalen-1-yl)-5-oxo-1-propylpyrrolidine-3-carboxylic acid (*cis/trans*-4k).** Prepared according to General Procedure 2; reaction time – 6 h; isolated yield 59% (*dr* 1:2.1); 225 mg of the mixture was submitted for HPLC separation (Method C); ***cis*-4k** – R_t 41 min; ***trans*-4k** – R_t 42–44 min.

***cis*-2-(Naphthalen-1-yl)-5-oxo-1-propylpyrrolidine-3-carboxylic acid (*cis*-4k):** 56 mg isolated;



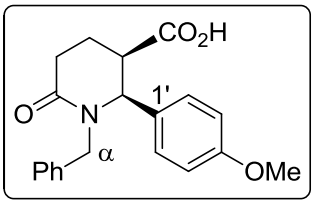
White solid; Mp 220−221 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.94 (br.s, 1H, COOH), 8.34 (d, *J* = 8.3 Hz, 1H, 8'-H), 7.94 (d, *J* = 7.8 Hz, 1H, 5'-H), 7.87 (d, *J* = 8.1 Hz, 1H, 4'-H), 7.63 – 7.46 (m, 3H, 3'-H, 6'-H and 7'-H), 7.17 (d, *J* = 7.2 Hz, 1H, 2'-H), 6.04 (d, *J* = 9.0 Hz, 1H, 2-H), 3.82 (q, *J* = 9.1 Hz, 1H, 3-H), 3.50 (dt, *J* = 13.5, 8.0 Hz, 1H, α-H), 2.85 (dd, *J* = 16.8, 9.1 Hz, 1H, 4-H), 2.56 (dd, *J* = 16.8, 9.2 Hz, 1H, 4-H), 2.41 (ddd, *J* = 13.5, 7.9, 5.3 Hz, 1H, α-H), 1.43 – 1.23 (m, 2H, β-CH_2), 0.74 (t, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.6, 172.3, 133.9, 133.4, 132.1, 128.9, 128.7, 126.6, 126.2, 125.8, 124.6, 124.0, 57.1, 43.0, 42.6, 33.0, 20.4, 11.7. HRMS (ESI), *m/z* calcd for $C_{18}H_{19}NO_3$ $[M+Na]^+$ 320.1257, found 320.1258.

***trans*-2-(Naphthalen-1-yl)-5-oxo-1-propylpyrrolidine-3-carboxylic acid (*trans*-4k):** 116 mg isolated; White solid; Mp 147−148 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.07 (br.s, 1H, COOH), 8.23 (d, *J* = 8.5 Hz, 1H, 8'-H), 8.02 (d, *J* = 8.5 Hz, 1H, 5'-H), 7.93 (d, *J* = 8.2 Hz, 1H, 4'-H), 7.67 – 7.52 (m, 3H, 3'-H, 6'-H, 7'-H), 7.16 (d, *J* = 7.0 Hz, 1H, 2'-H), 5.78 (br.s, 1H, 2-H), 3.64 (dt, *J* = 13.2, 7.8 Hz, 1H, α-H), 3.05 – 2.91 (m, 1H, 3-H), 2.59 – 1.24 (m, 3H, α-H and 4-CH_2), 1.52 – 1.24 (m, 2H, β-CH_2), 0.78 (t, *J* = 7.3 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.7, 173.4, 135.5, 134.3, 130.7, 129.4, 128.7, 127.2, 126.5, 126.0, 123.0, 122.6, 59.9, 45.3, 42.5, 32.8, 20.6, 11.5. **HRMS** (ESI), *m/z* calcd for $C_{18}H_{19}NO_3$ $[M–H]^-$ 296.1292, found 296.1291.

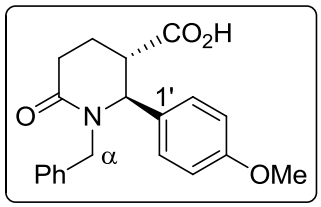


***cis/trans*-1-Benzyl-2-(4-methoxyphenyl)-6-oxopiperidine-3-carboxylic acid (*cis/trans*-5a).** Prepared according to General Procedure 2; reaction time – 24 h; isolated yield 66% (*dr* 1:2); 502 mg of the mixture was submitted for HPLC separation (Method C); ***cis*-5a** – R_t 38 min; ***trans*-5a** – R_t 40–42 min.

***cis*-1-Benzyl-2-(4-methoxyphenyl)-6-oxopiperidine-3-carboxylic acid (*cis*-5a):** 74 mg isolated; White solid; Mp 91−93 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.56 (br.s, 1H, COOH), 7.34 (t, *J* = 7.3 Hz, 2H, *m*-Ph), 7.28 (t, *J* = 7.2 Hz, 1H, *p*-Ph), 7.18 (d, *J* = 7.3 Hz, 2H, *o*-Ph), 7.06 (d, *J* = 8.8 Hz, 1H, 2',6'-H), 6.93 (d, *J* = 8.8 Hz, 1H, 3',5'-H), 5.25 (d, *J* = 15.2 Hz, 1H, α-H), 4.71 (d, *J* = 5.0 Hz, 1H, 2-H), 3.76 (s, 3H, OCH_3), 3.30 (d, *J* = 15.3 Hz, 1H, α-H), 3.11 (ddd, *J* = 12.7, 5.0, 3.6 Hz, 1H, 3-H), 2.63 – 2.53 (m, 2H, 5-CH_2), 1.91 – 1.68 (m, 2H, 4-CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.4, 169.3, 159.5, 137.7, 129.5, 129.2, 129.0, 127.9, 127.6, 114.2, 60.2, 55.6, 47.8, 44.8, 30.7, 18.1. HRMS (ESI), *m/z* calcd for $C_{20}H_{21}NO_4$ $[M–H]^-$ 338.1398, found 338.1406.

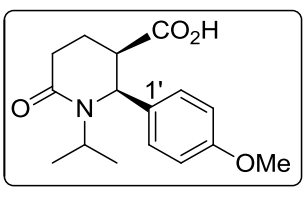


***trans*-1-Benzyl-2-(4-methoxyphenyl)-6-oxopiperidine-3-carboxylic acid (*trans*-5a):** 82 mg isolated. White solid; Mp 141−143 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.57 (br.s, 1H, COOH), 7.32 – 7.18 (m, 3H, *m*-Ph and *p*-Ph), 7.09 (m, 4H, *o*-Ph and 2',6'-H), 6.93 (d, *J* = 8.7 Hz, 2H, 3',5'-H), 5.16 (d, *J* = 15.2 Hz, 1H, α-H), 4.70 (d, *J* = 5.6 Hz, 1H, 2-H), 3.76 (s, 3H, OCH_3), 3.37 (d, *J* = 15.2 Hz, 1H, α-H), 2.82 – 2.75 (m, 1H, 3-H), 2.63 – 2.43 (m, 2H, 5-CH_2), 1.92 – 1.84 (m, 2H, 4-CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.9, 169.5, 159.2, 137.6, 132.5, 128.69, 128.66, 128.0, 127.3, 114.6, 61.5, 55.6, 47.4, 47.1, 30.4, 20.9. HRMS (ESI), *m/z* calcd for $C_{20}H_{21}NO_4$ $[M–H]^-$ 338.1398, found 338.1398.



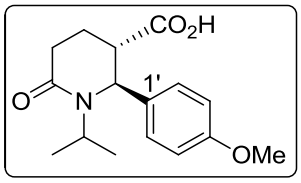
***cis/trans*-1-Isopropyl-2-(4-methoxyphenyl)-6-oxopiperidine-3-carboxylic acid (*cis/trans*-5b).** Prepared according to General Procedure 2; reaction time – 6 h; isolated yield 64% (*dr* 1:1.8); 270 mg of the mixture was submitted for HPLC separation (Method C); ***cis*-5b** – R_t 34 min; ***trans*-5b** – R_t 36–38 min.

***cis*-1-Isopropyl-2-(4-methoxyphenyl)-6-oxopiperidine-3-carboxylic acid (*cis*-5b)**: 49 mg isolated; White solid; Mp 206−207 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.61 (br.s, 1H, COOH), 7.09 (d, *J* = 8.7 Hz, 2H, 2',6'-H), 6.94 – 6.84 (m, 2H, 3',5'-H), 4.93 (d, *J* = 4.6 Hz, 1H, 2-H), 4.29 (hept, *J* = 6.9 Hz, 1H, C<u>H</u>$(CH_3)_2$), 3.74 (s, 3H, OCH_3), 3.00 (dt, *J* = 11.9, 4.6 Hz, 1H, 3-H), 2.57 – 2.47 (m, 1H, 5-H), 2.45 – 2.34 (m, 1H, 5-H), 1.79 – 1.63 (m, 2H, 4-CH_2), 1.12 (d, *J* = 6.9 Hz,



3H, CHC<u>H</u>$_3$), 0.77 (d, *J* = 6.9 Hz, 3H, CHC<u>H</u>$_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.6, 168.5, 159.1, 131.5, 129.4, 113.8, 57.6, 55.5, 47.6, 45.5, 30.9, 20.6, 20.1, 17.5. HRMS (ESI), *m/z* calcd for $C_{16}H_{21}NO_4$ $[M+Na]^+$ 314.1363, found 314.1364.

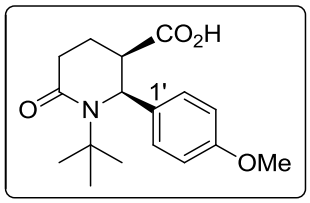
***trans*-1-Isopropyl-2-(4-methoxyphenyl)-6-oxopiperidine-3-carboxylic acid (*trans*-5b):** 135 mg



isolated; White solid; Mp 191−192 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.71 (br.s, 1H, COOH), 7.19 (d, *J* = 8.7 Hz, 2H, 2',6'-H), 6.94 (d, *J* = 8.7 Hz, 2H, 3',5'-H), 4.98 (d, *J* = 2.8 Hz, 1H, 2-H), 4.22 (hept, *J* = 6.9 Hz, 1H, C<u>H</u>(CH$_3$)$_2$), 3.75 (s, 3H, OCH$_3$), 2.75 – 2.68 (m, 1H, 3-H), 2.44 – 2.28 (m, 2H, 5-CH$_2$), 1.90 – 1.77 (m, 1H, 4-H), 1.72 – 1.59 (m, 1H, 4-H), 1.09 (d, *J* = 6.9 Hz, 3H, CHC<u>H</u>$_3$), 0.84 (d, *J* = 6.9 Hz, 3H, CHC<u>H</u>$_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.8, 168.7, 158.8, 134.6, 128.2, 114.3, 58.3, 55.5, 47.5, 46.3, 29.7, 20.2, 20.1, 18.0. HRMS (ESI), *m/z* calcd for $C_{16}H_{21}NO_4$ $[M+Na]^+$ 314.1363, found 314.1350.

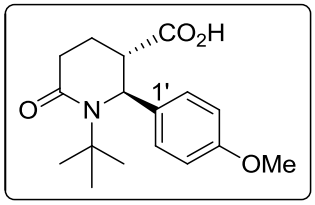
***cis/trans*-1-(*tert*-Butyl)-2-(4-methoxyphenyl)-6-oxopiperidine-3-carboxylic acid (*cis/trans*-5c).** Prepared according to General Procedure 2; reaction time – 6 h; isolated yield 59% (*dr* 1:1.4); 285 mg of the mixture was submitted for HPLC separation (Method C); ***cis*-5c** – R_t 44 min; ***trans*-5c** – R_t 46–48 min.

***cis*-1-(*tert*-Butyl)-2-(4-methoxyphenyl)-6-oxopiperidine-3-carboxylic acid (*cis*-5c):** 32 mg isolated;



White solid; Mp 232−233 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.64 (br.s, 1H, COOH), 7.03 (d, *J* = 8.8 Hz, 2H, 2',6'-H), 6.91 (d, *J* = 8.8 Hz, 2H, 3',5'-H), 5.22 (d, *J* = 4.1 Hz, 1H, 2-H), 3.75 (s, 3H, OCH$_3$), 3.01 (dt, *J* = 12.5, 4.1 Hz, 1H, 3-H), 2.55 – 2.40 (m, 2H, 5-CH$_2$), 1.70 – 1.52 (m, 2H, 4-CH$_2$), 1.28 (s, 9H, C(CH$_3$)$_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.7, 169.8, 159.0, 131.8, 129.3, 113.9, 58.56, 58.53, 55.5, 46.3, 32.7, 28.6, 17.9. HRMS (ESI), *m/z* calcd for $C_{17}H_{23}NO_4$ $[M+Na]^+$ 328.1519, found 328.1510.

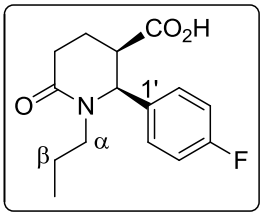
***trans*-1-(*tert*-Butyl)-2-(4-methoxyphenyl)-6-oxopiperidine-3-carboxylic acid (*trans*-5c):** 57 mg



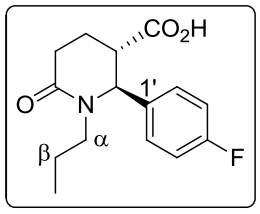
isolated; White solid; Mp 218−219 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.71 (br.s, 1H, COOH), 7.16 (d, *J* = 8.7 Hz, 2H, 2',6'-H), 6.96 (d, *J* = 8.7 Hz, 2H, 3',5'-H), 5.38 (d, *J* = 2.1 Hz, 1H, 2-H), 3.76 (s, 3H, OCH$_3$), 2.79 (dt, *J* = 5.3, 2.8 Hz, 1H, 3-H), 2.40 – 2.28 (m, 2H, 5-CH$_2$), 1.87 – 1.81 (m, 1H, 4-H), 1.54 – 1.45 (m, 1H, 4-H), 1.30 (s, 9H, C(CH$_3$)$_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.9, 169.7, 158.7, 134.9, 127.9, 114.4, 58.5, 58.1, 55.5, 46.5, 31.1, 28.4, 17.6. HRMS (ESI), *m/z* calcd for $C_{17}H_{23}NO_4$ $[M+Na]^+$ 328.1519, found 328.1506.

***cis/trans*-2-(4-Fluorophenyl)-6-oxo-1-(*n*-propyl)piperidine-3-carboxylic acid (*cis/trans*-5d).** Prepared according to General Procedure 2; reaction time – 6 h; isolated yield 51% (*dr* 1:2); 220 mg of the mixture was submitted for HPLC separation (Method C); ***cis*-5d** – R_t 36 min; ***trans*-5d** – R_t 38–41 min.

***cis*-2-(4-Fluorophenyl)-6-oxo-1-(*n*-propyl)piperidine-3-carboxylic acid (*cis*-5d):** 45 mg isolated; White solid; Mp 164−165 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.58 (br.s, 1H, COOH), 7.22 – 7.17 (m, 4H, Ar), 4.95 (d, *J* = 5.1 Hz, 1H, 2-H), 3.64 – 3.55 (m, 1H, α-H), 3.22 – 3.13 (m, 1H, 3-H), 2.49 – 2.33 (m, 3H, α-H and 5-CH_2), 1.78 – 1.65 (m, 2H, 4-CH_2), 1.56 – 1.43 (m, 1H, β-H), 1.42 – 1.29 (m, 1H, β-H), 0.77 (t, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.5, 168.9, 162.2 (d, *J* = 244.1 Hz), 134.4 (d, *J* = 3.0 Hz), 130.3 (d, *J* = 8.3 Hz), 115.5 (d, *J* = 21.4 Hz), 60.9, 47.8, 44.7, 30.7, 20.6, 17.9, 11.7. HRMS (ESI), *m/z* calcd for $C_{15}H_{18}FNO_3$ $[M+H]^+$ 280.1343, found 280.1347.



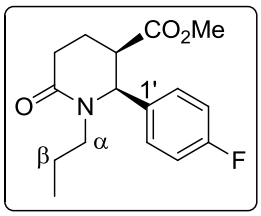
***trans*-2-(4-Fluorophenyl)-6-oxo-1-(*n*-propyl)piperidine-3-carboxylic acid (*trans*-5d):** 86 mg isolated; White solid; Mp 153−154 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.71 (br.s, 1H, COOH), 7.32 – 7.26 (m, 2H, 2',6'-H), 7.22 (t, *J* = 8.8 Hz, 2H, 3',5'-H), 4.97 (d, *J* = 4.1 Hz, 1H, 2-H), 3.71 (ddd, *J* = 13.3, 9.1, 6.7 Hz, 1H, α-H), 2.82 (dt, *J* = 5.7, 4.2 Hz, 1H, 3-H), 2.47 – 2.25 (m, 3H, α-H and 5-CH_2), 1.92 – 1.83 (m, 1H, 4-H), 1.79 – 1.68 (m, 1H, 4-H), 1.53 – 1.41 (m, 1H, β-H), 1.41 – 1.28 (m, 1H, β-H), 0.74 (t, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.8, 168.8, 161.9 (d, *J* = 243.5 Hz), 137.4 (d, *J* = 2.9 Hz), 129.3 (d, *J* = 8.3 Hz), 115.9 (d, *J* = 21.5 Hz), 61.1, 47.0, 46.2, 29.7, 20.2, 19.8, 11.6. HRMS (ESI), *m/z* calcd for $C_{15}H_{18}FNO_3$ $[M+H]^+$ 280.1343, found 280.1347.



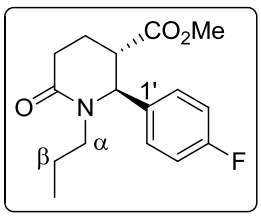
Preparation of *cis*- and *trans*-methyl 2-(4-fluorophenyl)-6-oxo-1-propylpiperidine-3-carboxylate (*cis*-6d and *trans*-6d).

Reaction was run according **General Procedure 2** (scale 2 mmol). After concentration of reaction mixture in *vacuo* the residue was dissolve in acetone (20 mL), methyl iodide (426 mg, 3 mmol) and K_2CO_3 (455 mg, 3.3 mmol) were added followed by stirring at ambient temperature overnight. Solvent was removed in vacuo, DCM (40 mL) and water (20 mL) were added. Organic layer was separated, washed with water (2×20 mL) and brine, dried over $MgSO_4$ and evaporated. Residue was subjected to column chromatography on SiO_2 (*n*-hexane–acetone–DCM, from 10:1:1 to 5:1:1).

***cis*-Methyl 2-(4-fluorophenyl)-6-oxo-1-propylpiperidine-3-carboxylate (*cis*-6d):** 105 mg (18%); White solid; Mp 110−111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 – 6.99 (m, 4H, ArH), 4.98 (d, *J* = 5.2 Hz, 1H, 2-H), 3.86 (ddd, *J* = 13.5, 8.6, 7.0 Hz, 1H, α-H), 3.62 (s, 3H, $COOCH_3$), 3.16 (dt, *J* = 12.4, 5.0 Hz, 1H), 2.70 (ddd, *J* = 18.3, 6.1, 1.9 Hz, 1H, 5-H), 2.53 (ddd, *J* = 18.3, 11.7, 8.2 Hz, 1H, 5-H), 2.42 (ddd, *J* = 13.6, 8.6, 6.3 Hz, 1H, α-H), 2.04 – 1.86 (m, 2H, 4-CH_2), 1.64 – 1.49 (m, 2H, β-CH_2), 0.88 (t, *J* = 7.4 Hz, 1H, $CH_2C\underline{H}_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 169.2, 162.7 (d, *J* = 247.8 Hz), 132.7 (d, *J* = 3.3 Hz), 129.3 (d, *J* = 8.2 Hz), 115.5 (d, *J* = 21.6 Hz), 61.0, 51.8, 48.0, 45.4, 30.7, 20.6, 17.6, 11.4. HRMS (ESI), *m/z* calcd for $C_{16}H_{20}FNO_3Na$ $[M+Na]^+$ 316.1319, found 316.1310.



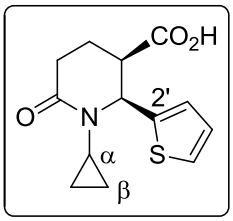
***trans*-Methyl 2-(4-fluorophenyl)-6-oxo-1-propylpiperidine-3-carboxylate (*trans*-6d):** 193 mg (33%); Viscous colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (dd, *J* = 8.8, 5.2 Hz, 2H, 2',6'-H), 7.08 (t, *J* = 8.6 Hz, 1H, 3',5'-H), 5.07 (d, *J* = 4.0 Hz, 1H, 2-H), 3.98 (ddd, *J* = 13.5, 8.8, 7.3 Hz, 1H, α-H), 3.75 (s, 3H, $COOCH_3$), 2.82 (dt, *J* = 5.7, 4.0 Hz, 1H, 3-H), 2.63 – 2.49 (m, 2H, 5-CH_2), 2.37 (ddd, *J* = 13.5, 8.5, 6.1 Hz, 1H, α-H), 2.10 – 2.02 (m, 1H, 4-H), 1.93 – 1.5 (m, 1H, 4-H), 1.64 –



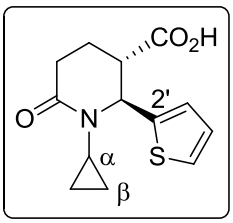
1.48 (m, 2H, β-CH_2), 0.85 (t, *J* = 7.4 Hz, 3H, $CH_2C\underline{H}_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 169.4, 162.3 (d, *J* = 247.1 Hz), 136.0 (d, *J* = 3.2 Hz), 128.2 (d, *J* = 8.1 Hz), 115.9 (d, *J* = 21.7 Hz), 61.0, 52.3, 47.4, 46.7, 29.5, 20.1, 19.4, 11.3. HRMS (ESI), *m/z* calcd for $C_{16}H_{20}FNO_3Na$ $[M+Na]^+$ 316.1319, found 316.1304.

***cis/trans*-1-Cyclopropyl-6-oxo-2-(thiophen-2-yl)piperidine-3-carboxylic acid (*cis/trans*-5e).** Prepared according to General Procedure 2; reaction time – 7 days; isolated yield 35% (*dr* 1:2.3); 167 mg of the mixture was submitted for HPLC separation (Method B); ***cis*-5e** – R_t 29 min; ***trans*-5e** – R_t 30–33 min.

***cis*-1-Cyclopropyl-6-oxo-2-(thiophen-2-yl)piperidine-3-carboxylic acid (*cis*-5e):** 27 mg isolated; White solid; Mp 202−203 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.79 (br.s, 1H, COOH), 7.49 (dd, *J* = 5.1, 1.2 Hz, 1H, 5'-H), 7.02 (dd, *J* = 5.1, 3.5 Hz, 1H, 4'-H), 6.86 (ddd, *J* = 3.5, 1.2, 0.7 Hz, 1H, 3'-H), 5.17 (d, *J* = 4.7 Hz, 1H, 2-H), 3.19 – 3.07 (m, 1H, 3-H), 2.44 – 2.30 (m, 3H, α-H and 5-CH_2), 1.88 – 1.74 (m, 2H, 4-CH_2), 0.83 – 0.72 (m, 1H, β-H), 0.64 – 0.44 (m, 3H, 3β-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.4, 170.7, 142.3, 127.4, 126.7, 126.3, 58.8, 45.1, 31.3, 30.0, 18.6, 9.0, 5.7. HRMS (ESI), *m/z* calcd for $C_{13}H_{15}NO_3SNa$ $[M+Na]^+$ 288.0665, found 288.0672.

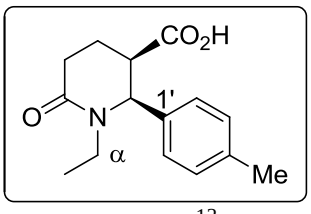


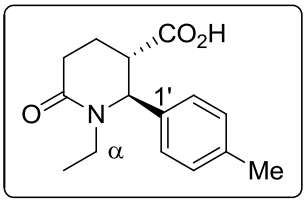
***trans*-1-Cyclopropyl-6-oxo-2-(thiophen-2-yl)piperidine-3-carboxylic acid (*trans*-5e):** 100 mg isolated; White solid; Mp 182−183 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.83 (br.s, 1H, COOH), 7.48 (dd, *J* = 5.0, 1.1 Hz, 1H, 5'-H), 7.02 (dd, *J* = 5.0, 3.4 Hz, 1H, 4'-H), 7.00 – 6.97 (m, 1H, 3'-H), 5.19 (d, *J* = 3.6 Hz, 1H, 2-H), 2.97 – 2.92 (m, 1H, 3-H), 2.49 – 2.41 (m, 1H, α-H), 2.38 – 2.21 (m, 2H, 5-CH_2), 1.98 – 1.88 (m, 1H, 4-H), 1.87 – 1.75 (m, 1H, 4-H), 0.86 – 0.73 (m, 1H, β-H), 0.65 – 0.39 (m, 3H, 3β-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.4, 170.4, 145.9, 127.8, 125.7, 125.5, 58.7, 46.6, 30.1, 29.7, 19.6, 9.2, 6.0. HRMS (ESI), *m/z* calcd for $C_{13}H_{15}NO_3S$ $[M+H]^+$ 266.0845, found 266.0843.



***cis/trans*-1-Ethyl-6-oxo-2-(*p*-tolyl)piperidine-3-carboxylic acid (*cis/trans*-5f).** Prepared according to General Procedure 2; reaction time – 6 h; isolated yield 53% (*dr* 1:2.2); 240 mg of the mixture was submitted for HPLC separation (Method C); ***cis*-5f** – R_t 35 min; ***trans*-5f** – R_t 37–39 min.

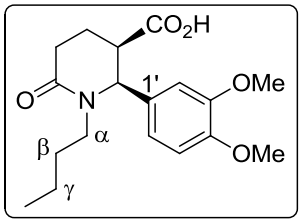
***cis*-1-Ethyl-6-oxo-2-(*p*-tolyl)piperidine-3-carboxylic acid (*cis*-5f):** 25 mg isolated; White solid; Mp 219−220 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.58 (br.s, 1H, COOH), 7.15 (d, *J* = 7.8 Hz, 2H, 2',6'-H), 7.03 (d, *J* = 7.8 Hz, 2H, 3',5'-H), 4.91 (d, *J* = 4.5 Hz, 1H, 2-H), 3.62 (dq, *J* = 14.2, 7.1 Hz, 1H, α-H), 3.16 – 3.08 (m, 1H, 3-H), 2.58 – 2.48 (dq, *J* = 14.2, 7.1 Hz, 1H, α-H), 2.47 – 2.32 (m, 2H, 5-CH_2), 2.29 (s, 3H, 4'-CH_3), 1.83 – 1.62 (m, 2H, 4- CH_2), 0.95 (t, *J* = 7.1 Hz, 3H, $CH_2C\underline{H}_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.5, 168.6, 137.6, 135.3, 129.2, 128.3, 60.9, 45.0, 41.1, 30.8, 21.1, 18.1, 13.1. HRMS (ESI), *m/z* calcd for $C_{15}H_{19}NO_3$ $[M+H]^+$ 262.1438, found 262.1450.



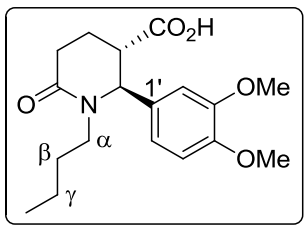
***trans*-1-Ethyl-6-oxo-2-(*p*-tolyl)piperidine-3-carboxylic acid (*trans*-5f):** 72 mg isolated; White solid; 

Mp 174−175 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.67 (br.s, 1H, COOH), 7.19 (d, *J* = 8.0 Hz, 2H, 2',6'-H), 7.12 (d, *J* = 8.0 Hz, 2H, 3',5'-H), 4.90 (d, *J* = 4.2 Hz, 1H, 2-H), 3.72 (dq, *J* = 14.2, 7.1 Hz, 1H, α-H), 2.79 (dt, *J* = 5.8, 4.2 Hz, 1H, 3-H), 2.42 (dq, *J* = 14.2, 7.1 Hz, 1H, α-H), 2.43 – 2.35 (m, 1H, 5-H), 2.29 (s, 3H, 4'-CH_3), 2.33 – 2.22 (m, 1H, 5-H), 1.89 – 1.81 (m, 1H, 4-H), 1.78 – 1.70 (m, 1H, 4-H), 0.93 (t, *J* = 7.1 Hz, 3H, $CH_2C\underline{H}_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.9, 168.5, 138.3, 137.2, 129.7, 127.2, 61.2, 46.4, 40.3, 29.8, 21.1, 19.9, 12.5. HRMS (ESI), *m/z* calcd for $C_{15}H_{19}NO_3$ $[M+Na]^+$ 284.1257, found 284.1270.

***cis/trans*-1-*n*-Butyl-2-(3,4-dimethoxyphenyl)-6-oxopiperidine-3-carboxylic acid (*cis/trans*-5g).** Prepared according to General Procedure 2; reaction time – 6 h; isolated yield 62% (*dr* 1:2); 335 mg of the mixture was submitted for HPLC separation (Method B); ***cis*-5g** – R_t 44 min; ***trans*-5g** – R_t 46–48 min.

***cis*-1−*n*-Butyl-2-(3,4-dimethoxyphenyl)-6-oxopiperidine-3-carboxylic acid (*cis*-5g):** 12 mg 

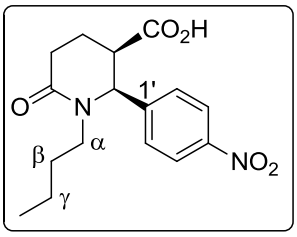
isolated; White solid; Mp 80−81 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.33 (br.s, 1H, COOH), 6.93 (d, *J* = 8.0 Hz, 1H, 5'-H), 6.72 (s, 1H, 2'-H), 6.65 (d, *J* = 8.0 Hz, 1H, 2'-H), 4.88 (d, *J* = 4.6 Hz, 1H, 2-H), 3.76 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.78 – 3.65 (m, 1H, α-H), 3.15 – 3.05 (m, 1H, 3-H), 2.50 – 2.32 (m, 3H, α-H and 5-CH_2), 1.82 – 1.66 (m, 2H, 4-CH_2), 1.51 – 1.34 (m, 2H, β-CH_2), 1.28 – 1.16 (m, 2H, γ-CH_2), 0.85 (t, *J* = 7.3 Hz, 3H, $CH_2C\underline{H}_3$); the signals are broadened and poorly resolved. ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.7, 168.8, 148.9, 148.7, 130.3, 120.1, 112.1, 111.8, 61.2, 55.9, 55.8, 45.8, 45.0, 30.8, 29.6, 20.1, 18.2, 14.2. HRMS (ESI), *m/z* calcd for $C_{18}H_{25}NO_5$ $[M+H]^+$ 336.1805, found 336.1818.

***trans*-1-*n*-Butyl-2-(3,4-dimethoxyphenyl)-6-oxopiperidine-3-carboxylic acid (*trans*-5g):** 114 mg 

isolated; White solid; Mp 103−104 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.67 (br.s, 1H, COOH), 6.94 (d, *J* = 8.3 Hz, 1H, 5'-H), 6.84 (d, *J* = 2.1 Hz, 1H, 2'-H), 6.67 (dd, *J* = 8.3, 2.1 Hz, 1H, 6'-H), 4.89 (d, *J* = 4.1 Hz, 1H, 2-H), 3.76 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.83 – 3.70 (m, 1H, α-H), 2.85 (dt, *J* = 5.5, 4.1 Hz, 1H, 3-H), 2.45 – 2.25 (m, 3H, α-H and 5-CH_2), 1.82 – 1.91 (m, 1H, 4-H), 1.80 – 1.70 (m, 1H, 4-H), 1.50 – 1.31 (m, 2H, β-CH_2), 1.25 – 1.10 (m, 2H, γ-CH_2), 0.82 (t, *J* = 7.3 Hz, 3H, $CH_2C\underline{H}_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.9, 168.8, 149.4, 148.6, 133.5, 119.0, 112.1, 110.9, 61.4, 55.98, 55.97, 46.2, 45.0, 29.7, 29.1, 20.0, 19.8, 14.2. HRMS (ESI), *m/z* calcd for $C_{18}H_{25}NO_5$ $[M+H]^+$ 336.1805, found 336.1816.

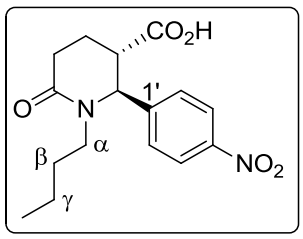
***cis/trans*-1-*n*-Butyl-2-(4-nitrophenyl)-6-oxopiperidine-3-carboxylic acid (*cis/trans*-5h).** Prepared according to General Procedure 2; reaction time – 24 h; isolated yield 16% (*dr* 1:2.2); 76 mg of the mixture was submitted for HPLC separation (Method C); ***cis*-5h** – R_t 38 min; ***trans*-5h** – R_t 39–42 min.

***cis*-1-*n*-Butyl-2-(4-nitrophenyl)-6-oxopiperidine-3-carboxylic acid (*cis*-5h):** 8 mg isolated;



Colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.98 (br.s, 1H, COOH), 8.18 (d, *J* = 8.8 Hz, 2H, 3',5'-H), 7.45 (d, *J* = 8.7 Hz, 2H, 2',6'-H), 5.18 (d, *J* = 5.2 Hz, 1H, 2-H), 3.66 (ddd, *J* = 13.3, 9.1, 6.5 Hz, 1H, α-H), 3.22 – 3.09 (br.m, 1H, 3-H), 2.48 – 2.29 (m, 3H, α-H and 5-CH_2), 1.76 – 1.55 (br.m, 2H, 4-CH_2), 1.51 – 1.27 (m, 2H, β-CH_2), 1.20 – 1.09 (m, 2H, γ-CH_2), 0.79 (t, *J* = 7.3 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.9, 169.1, 147.6, 146.7, 129.9, 123.6, 61.2, 46.1, 45.5, 30.9, 29.5, 20.0, 18.5, 14.2. HRMS (ESI), *m/z* calcd for $C_{16}H_{20}N_2O_5$ $[M–H]^-$ 319.1299, found 319.1299.

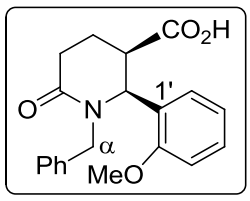
***trans*-1-*n*-Butyl-2-(4-nitrophenyl)-6-oxopiperidine-3-carboxylic acid (*trans*-5h):** 37 mg isolated;



White solid; Mp 172−173 °C (lit[3] Mp 173 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.97 (br.s, 1H, COOH), 8.23 (d, *J* = 8.7 Hz, 2H, 3',5'-H), 7.55 (d, *J* = 8.7 Hz, 2H, 2',6'-H), 5.15 (d, *J* = 3.7 Hz, 1H, 2-H), 3.78 (ddd, *J* = 13.5, 9.0, 6.8 Hz, 1H, α-H), 2.91 – 2.85 (m, 1H, 3-H), 2.42 – 2.21 (m, 3H, α-H and 5-CH_2), 1.93– 1.83 (m, 1H, 4-H), 1.72– 1.60 (m, 1H, 4-H), 1.50 – 1.27 (m, 2H, β-CH_2), 1.22 – 1.08 (m, 2H, γ-CH_2), 0.79 (t, *J* = 7.3 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.4, 168.9, 149.3, 147.4, 128.8, 124.2, 61.3, 45.9, 45.3, 29.6, 28.9, 19.9, 19.7, 14.2. HRMS (ESI), *m/z* calcd for $C_{16}H_{20}N_2O_5$ $[M–H]^-$ 319.1299, found 319.1312.

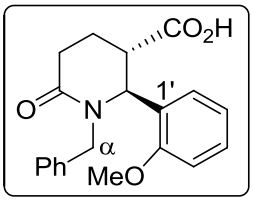
***cis/trans*-1-Benzyl-2-(2-methoxyphenyl)-6-oxopiperidine-3-carboxylic acid (*cis/trans*-5i).** Prepared according to General Procedure 2; reaction time – 24 h; isolated yield 52% (*dr* 1:1.7); 304 mg of the mixture was submitted for HPLC separation (Method C); ***cis*-5i** – R_t 39 min; ***trans*-5i** – R_t 41–43 min.

***cis*-1-Benzyl-2-(2-methoxyphenyl)-6-oxopiperidine-3-carboxylic acid (*cis*-5i):** 9 mg isolated; White



solid; Mp 96−97 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.21 (br.s, 1H, COOH), 7.36 – 7.25 (m, 4H, ArH), 7.18 – 7.14 (m, 2H, ArH), 7.05 – 6.93 (m, 3H, ArH), 5.22 (d, *J* = 15.3 Hz, 1H, α-H), 5.10 (d, *J* = 4.9 Hz, 1H, 2-H), 3.65 (s, 3H), 3.26 (d, *J* = 15.3 Hz, 1H, α-H), 3.04 (ddd, *J* = 13.0, 4.9, 3.1 Hz, 1H, 3-H), 2.60 – 2.53 (m, 2H, 5-CH_2), 1.96 – 1.83 (m, 1H, 4-H), 1.71 – 1.61 (m, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.8, 169.6, 158.2, 137.8, 129.7, 129.0, 128.9, 127.8, 127.6, 125.3, 120.6, 111.7, 55.7, 55.4, 48.0, 44.7, 30.8, 19.6. HRMS (ESI), *m/z* calcd for $C_{20}H_{21}NO_4$ $[M+H]^+$ 340.1543, found 340.1543.

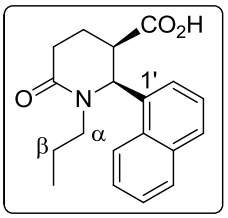
***trans*-1-Benzyl-2-(2-methoxyphenyl)-6-oxopiperidine-3-carboxylic acid (*trans*-5i):** 37 mg isolated;



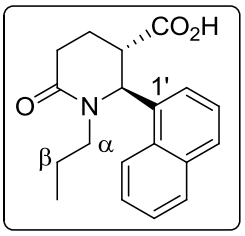
White solid; Mp 168−169 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.65 (s, 1H, COOH), 7.35 – 7.29 (m, 1H, ArH), 7.29 – 7.18 (m, 3H, ArH), 7.15 – 7.10 (m, 2H, ArH), 7.05 (d, *J* = 8.2 Hz, 1H, 3'-H), 7.01 – 6.97 (m, 2H, ArH), 5.17 (d, *J* = 4.0 Hz, 1H, 2-H), 5.14 (d, *J* = 15.3 Hz, 1H, α-H), 3.76 (s, 3H, OCH_3), 3.41 (d, *J* = 15.3 Hz, 1H, α-H), 2.81 (dt, *J* = 5.2, 4.0 Hz, 1H, 3-H), 2.49 – 2.43 (m, 2H, 5-CH_2), 1.95 – 1.86 (m, 1H, 4-H), 1.82 – 1.71 (m, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.0, 169.8, 156.9, 137.6, 129.5, 128.5, 128.0, 127.9, 127.6, 127.2, 120.8, 112.0, 57.3, 56.0, 48.4, 43.3, 29.6, 19.9. HRMS (ESI), *m/z* calcd for $C_{20}H_{21}NO_4$ $[M+Na]^+$ 362.1363, found 362.1361.

***cis/trans*-2-(Naphthalen-1-yl)-6-oxo-1-propylpiperidine-3-carboxylic acid (*cis/trans*-5j).** Prepared according to General Procedure 2; reaction time – 24 h; isolated yield 58% (*dr* 1:3.6); 182 mg of the mixture was submitted for HPLC separation (Method C); ***cis*-5j** – R_t 43 min; ***trans*-5j** – R_t 45–47 min.

***cis*-2-(Naphthalen-1-yl)-6-oxo-1-propylpiperidine-3-carboxylic acid (*cis*-5j):** 21 mg isolated; White solid; Mp 202−203 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.33 (br.s, 1H, COOH), 8.30 (dd, *J* = 7.5, 2.2 Hz, 1H, 8'-H), 7.95 (dd, *J* = 6.8, 2.5 Hz, 1H, 5'-H), 7.90 (d, *J* = 8.1 Hz, 1H, 4'H), 7.60 – 7.46 (m, 3H, 3'-H, 6'-H and 7'-H), 7.30 (d, *J* = 6.7 Hz, 1H, 2'-H), 5.91 (d, *J* = 5.4 Hz, 1H, 2-H), 3.58 (ddd, *J* = 13.4, 9.0, 6.3 Hz, 1H, α-H), 3.36 – 3.29 (m, 1H, 3-H), 2.64 – 2.45 (m, 2H, 5-CH_2), 2.33 – 2.21 (m, 1H, α-H), 2.14 – 2.02 (m, 1H, 4-H), 1.81 – 1.65 (m, 1H, 4-H), 1.58 – 1.43 (m, 1H, β-H), 1.43 – 1.27 (m, 1H, β-H), 0.73 (t, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.6, 168.9, 134.3, 133.7, 132.1, 129.0, 128.9, 126.6, 126.2, 126.1, 125.5, 123.6, 55.8, 47.9, 44.5, 30.7, 20.7, 19.0, 11.8. HRMS (ESI), *m/z* calcd for $C_{19}H_{21}NO_3$ $[M+Na]^+$ 334.1414, found 334.1429.

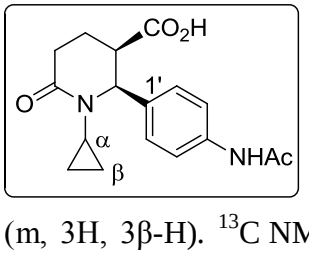


***trans*-2-(Naphthalen-1-yl)-6-oxo-1-propylpiperidine-3-carboxylic acid (*trans*-5j):** 116 mg isolated; Beige solid; Mp 248−250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.06 (br.s, 1H, COOH), 8.05 (d, *J* = 8.4 Hz, 1H, 8'-H), 8.02 (dd, *J* = 8.1, 1.1 Hz, 1H, 5'-H), 7.92 (d, *J* = 8.2 Hz, 1H, 4'-H), 7.66 (ddd, *J* = 8.4, 7.1, 1.4 Hz, 1H, 7'-H), 7.59 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H, 6'-H), 7.56 (dd, *J* = 8.2, 7.1 Hz, 1H, 3'-H), 7.22 (d, *J* = 7.1 Hz, 1H, 2'-H), 5.85 (br.s, 1H, 2-H), 3.85 (ddd, *J* = 13.3, 8.9, 6.8 Hz, 1H, α-H), 2.98 (dt, *J* = 4.1, 2.3 Hz, 1H, 3-H), 2.49 – 2.37 (m, 2H, 5-CH_2), 2.30 – 2.22 (m, 1H, α-H), 1.96 – 1.86 (m, 1H, 4-H), 1.70 – 1.58 (m, 1H, 4-H), 1.57 – 1.38 (m, 2H, β-CH_2), 0.76 (t, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.8, 169.3, 135.9, 134.2, 130.4, 129.6, 128.7, 127.4, 126.5, 125.8, 124.3 (br.s), 122.5, 58.8 (br.s), 47.6, 43.6, 28.9, 20.5, 18.8 (br.s), 11.6. HRMS (ESI), *m/z* calcd for $C_{19}H_{21}NO_3$ $[M+Na]^+$ 334.1414, found 334.1411.

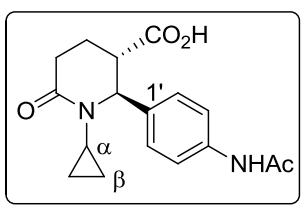


***cis/trans*-2-(4-Acetamidophenyl)-1-cyclopropyl-6-oxopiperidine-3-carboxylic acid (*cis/trans*-5k).** Prepared according to General Procedure 2; reaction time – 48 h; isolated yield 54% (*dr* 1:2.3); 323 mg of the mixture was submitted for HPLC separation (Method A); ***cis*-5k** – R_t 18 min; ***trans*-5k** – R_t 15–17 min.

***cis*-2-(4-Acetamidophenyl)-1-cyclopropyl-6-oxopiperidine-3-carboxylic acid (*cis*-5k):** 51 mg isolated; White solid; Mp 258−259 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.63 (br.s, 1H, COOH), 9.97 (s, 1H, NH), 7.54 (d, *J* = 8.5 Hz, 2H, 2',6'-H), 7.02 (d, *J* = 8.5 Hz, 2H, 3',5'-H), 4.84 (d, *J* = 4.9 Hz, 1H, 2-H), 3.10 – 3.05 (m, 1H, 3-H), 2.48 – 2.31 (m, 2H, 5-CH_2), 2.29 – 2.21 (m, 1H, α-H), 2.03 (s, 3H, CH_3), 1.74 – 1.64 (m, 2H, 4-CH_2), 0.78 – 0.70 (m, 1H, β-H), 0.58 – 0.35 (m, 3H, 3β-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.6, 171.1, 168.7, 139.3, 132.9, 128.3, 119.3, 62.0, 45.1, 31.4, 29.9, 24.4, 18.0, 8.7, 5.4. HRMS (ESI), *m/z* calcd for $C_{17}H_{20}N_2O_4$ $[M+H]^+$ 317.1496, found 317.1505.



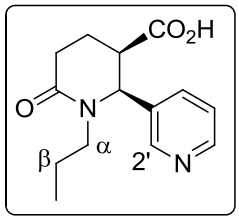
***trans*-2-(4-Acetamidophenyl)-1-cyclopropyl-6-oxopiperidine-3-carboxylic acid (*trans*-5k):** 122 mg isolated; White solid; Mp 251−252°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.68 (br.s, 1H, COOH), 9.96 (s, 1H, NH), 7.57 (d, *J* = 8.6 Hz, 2H, 2',6'-H), 7.13 (d, *J* = 8.6 Hz, 2H, 3',5'-H), 4.87 (d, *J* = 4.3 Hz, 1H, 2-H), 2.78 (dt, *J* =



5.6, 4.3 Hz, 1H, 3-H), 2.43 – 2.23 (m, 3H, α-H and 5-CH_2), 2.04 (s, 3H, CH_3), 1.89 – 1.80 (m, 1H, 4-H), 1.73 – 1.63 (m, 1H, 4-H), 0.79 – 0.73 (m, 1H, β-H), 0.58 – 0.39 (m, 3H, 3β-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.9, 170.8, 168.7, 138.9, 136.1, 127.3, 119.7, 62.1, 46.4, 30.4, 29.5, 24.4, 19.6, 9.1, 5.9. HRMS (ESI), *m/z* calcd for $C_{17}H_{20}N_2O_4$ $[M+Na]^+$ 339.1315, found 339.1313.

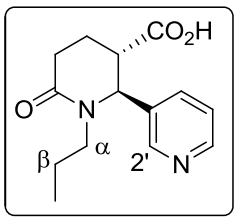
***cis/trans*-6-Oxo-1-(*n*-propyl)-2-(pyridine-3-yl)piperidine-3-carboxylic acid (*cis/trans*-5l).** Prepared according to General Procedure 2; reaction time – 24 h; isolated yield 61% (*dr* 1:2.5); 265 mg of the mixture was submitted for HPLC separation (Method A); ***cis*-5l** – R_t 15 min; ***trans*-5l** – R_t 11–13 min.

***cis*-6-Oxo-1-(*n*-propyl)-2-(pyridine-3-yl)piperidine-3-carboxylic acid (*cis*-5l):** 40 mg isolated;



Beige solid; Mp 179−180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.69 (br.s, 1H, COOH), 8.64 (d, *J* = 1.8 Hz, 1H, 2'-H), 8.47 (d, *J* = 5.1 Hz, 1H, 6'-H), 7.64 (dt, *J* = 8.0, 1.8 Hz, 1H, 4'-H), 7.47 (dd, *J* = 8.0, 5.0 Hz, 1H, 5'-H), 5.20 (d, *J* = 5.2 Hz, 1H, 2-H), 3.95 (ddd, *J* = 13.5, 8.7, 7.0 Hz, 1H, α-H), 3.26 (ddd, *J* = 13.4, 5.2, 3.2 Hz, 1H, 3-H), 2.72 (dd, *J* = 18.3, 6.1 Hz, 1H, 5-H), 2.63 – 2.54 (m, 1H, 5-H), 2.46 – 2.38 (m, 1H, α-H), 2.02 – 1.95 (m, 1H, 4-H), 1.81 – 1.70 (m, 1H, 4-H), 1.68 – 1.54 (m, 2H, β-CH_2), 0.91 (t, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 169.7, 147.2, 146.8, 136.8, 134.9, 124.3, 59.5, 48.2, 45.7, 30.7, 20.6, 17.6, 11.3. HRMS (ESI), *m/z* calcd for $C_{14}H_{18}N_2O_3$ $[M+H]^+$ 263.1390, found 263.1394.

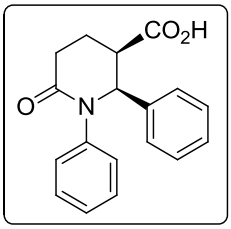
***trans*-6-Oxo-1-(*n*-propyl)-2-(pyridine-3-yl)piperidine-3-carboxylic acid (*trans*-5l):** 92 mg isolated;



Amorphous yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.80 (br.s, 1H, COOH), 8.53 (dd, *J* = 4.8, 1.2 Hz, 1H, 6'-H), 8.50 (d, *J* = 2.0 Hz, 1H, 2'-H), 7.67 (dt, *J* = 7.8, 2.0 Hz, 1H, 4'-H), 7.42 (dd, *J* = 7.8, 4.8 Hz, 1H, 5'-H), 5.04 (d, *J* = 4.2 Hz, 1H, 2-H), 3.69 (ddd, *J* = 13.4, 9.2, 6.7 Hz, 1H, α-H), 2.89 (dt, *J* = 5.9, 4.2 Hz, 1H, 3-H), 2.45 (dt, *J* = 17.7, 5.9 Hz, 1H, 5-H), 2.39 – 2.26 (m, 2H, α-H and 5-H), 1.95 – 1.86 (m, 1H, 4-H), 1.80 – 1.70 (m, 1H, 4-H), 1.54 – 1.42 (m, 1H, β-H), 1.41 – 1.28 (m, 1H, β-H), 0.74 (t, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.7, 168.9, 149.3, 149.0, 136.8, 135.1, 124.1, 59.7, 47.1, 46.0, 29.8, 20.2, 19.9, 11.6. HRMS (ESI), *m/z* calcd for $C_{14}H_{18}N_2O_3$ $[M+H]^+$ 263.1390, found 263.1399.

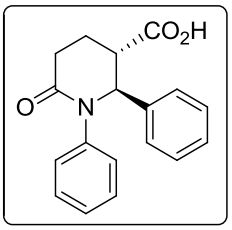
***cis/trans*-6-Oxo-1,2-diphenylpiperidine-3-carboxylic acid (*cis/trans*-5m).** Prepared according to General Procedure 2; reaction time – 22 h; isolated yield 39% (*dr* 1:5); 263 mg of the mixture was submitted for HPLC separation performed (Method C); ***cis*-5m** – R_t 33 min; ***trans*-5m** – R_t 35–37 min.

***cis*-6-Oxo-1,2-diphenylpiperidine-3-carboxylic acid (*cis*-5m):** 17 mg isolated; White solid; Mp



238−239 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.48 (br.s, 1H, COOH), 7.35 – 7.20 (m, 7H, ArH), 7.17 – 7.11 (m, 3H, ArH), 5.29 (d, *J* = 5.0 Hz, 1H, 2-H), 3.49 (ddd, *J* = 12.6, 5.0, 3.6 Hz, 1H, 3-H), 2.71 (m, 1H, 5-H), 2.65 – 2.53 (m, 1H, 5-H), 1.98 – 1.76 (m, 2H, 4-CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.5, 169.2, 143.1, 137.9, 129.1, 128.6, 128.5, 128.3, 128.0, 126.9, 65.6, 45.3, 31.2, 18.2. HRMS (ESI), *m/z* calcd for $C_{18}H_{17}NO_3Na$ $[M+Na]^+$ 318.1101, found 318.1097.

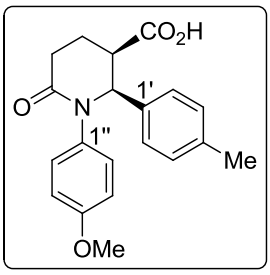
***trans*-6-Oxo-1,2-diphenylpiperidine-3-carboxylic acid (*trans*-5m):** 145 mg isolated; Beige solid;



Mp 265−266 °C (lit[4] Mp 200 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 (br.s, 1H, COOH), 7.35 – 7.11 (m, 10H, ArH), 5.39 (d, *J* = 4.2 Hz, 1H, 2-H), 2.98 (dt, *J* = 5.7, 4.2 Hz, 1H, 3-H), 2.67 (ddd, *J* = 18.0, 6.8, 4.8 Hz, 1H, 5-H), 2.49 – 2.40 (m, 1H, 5-H), 2.13 – 2.01 (m, 1H, 4-H), 1.93 (dddd, *J* = 11.2, 9.2, 6.8, 4.2 Hz, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.0, 169.1, 142.9, 140.8, 128.9, 128.9, 128.0, 127.9, 127.6, 126.8, 65.6, 46.6, 30.2, 20.0. HRMS (ESI), *m/z* calcd for $C_{18}H_{17}NO_3Na$ $[M+Na]^+$ 318.1101, found 318.1095.

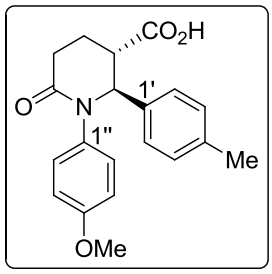
***cis/trans*-1-(4-Methoxyphenyl)-6-oxo-2-(*p*-tolyl)piperidine-3-carboxylic acid (*cis/trans*-5n).** Prepared according to General Procedure 2; reaction time – 22 h; isolated yield 47% (*dr* 1:4.2); 310 mg of the mixture was submitted for HPLC separation (Method C); ***cis*-5n** – R_t 45 min; ***trans*-5n** – R_t 47–49 min.

***cis*-1-(4-Methoxyphenyl)-6-oxo-2-(*p*-tolyl)piperidine-3-carboxylic acid (*cis*-5n):** 43 mg isolated;



White solid; Mp 206−207 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.66 (br.s, 1H, COOH), 7.16 – 7.06 (m, 4H, *p*-tolyl), 7.01 (d, *J* = 8.9 Hz, 2H, 2",6"-H), 6.80 (d, *J* = 8.9 Hz, 2H, 3",5"-H), 5.17 (d, *J* = 4.9 Hz, 1H, 2-H), 3.68 (s, 3H, OCH_3), 3.45 (ddd, *J* = 12.5, 4.9, 3.8 Hz, 1H, 3-H), 2.66 (dd, *J* = 18.2, 6.4 Hz, 1H, 5-H), 2.60 – 2.51 (m, 1H, 5-H), 2.26 (s, 3H, 4'-CH_3), 1.99 – 1.72 (m, 2H, 4-CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.4, 169.2, 157.9, 137.4 135.9, 134.9, 129.2, 129.1, 128.4, 114.2, 65.5, 55.6, 45.2, 31.1, 21.1, 18.2. HRMS (ESI), *m/z* calcd for $C_{20}H_{21}NO_4$ $[M+H]^+$ 340.1543, found 340.1543.

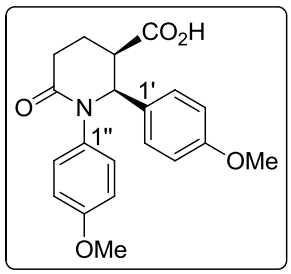
***trans*-1-(4-Methoxyphenyl)-6-oxo-2-(*p*-tolyl)piperidine-3-carboxylic acid (*trans*-5n):** 121 mg



isolated; White solid; Mp 213−214 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.84 (br.s, 1H, COOH), 7.19 (d, *J* = 8.2 Hz, 2H, 2',6'-H), 7.12 (d, *J* = 8.2 Hz, 2H, 3',5'-H), 7.05 (d, *J* = 9.0 Hz, 2H, 2",6"-H), 6.81 (d, *J* = 9.0 Hz, 2H, 3",5"-H), 5.26 (d, *J* = 4.2 Hz, 1H, 2-H), 3.68 (s, 3H, OCH_3), 2.91 (dt, *J* = 5.5, 4.2 Hz, 1H, 3-H), 2.63 (ddd, *J* = 17.9, 6.8, 4.9 Hz, 1H, 5-H), 2.42 (ddd, *J* = 17.9, 9.2, 6.9 Hz, 1H, 5-H), 2.25 (s, 3H, 4'-CH_3), 2.11 – 1.99 (m, 1H, 4-H), 1.97 – 1.87 (m, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.0, 169.1, 157.8, 137.9, 136.9, 135.7, 129.4, 129.0, 127.5, 114.2, 65.7, 55.6, 46.7, 30.2, 21.0, 20.0. HRMS (ESI), *m/z* calcd for $C_{20}H_{21}NO_4$ $[M+Na]^+$ 362.1363, found 362.1367.

***cis/trans*-1,2-bis(4-Methoxyphenyl)-6-oxopiperidine-3-carboxylic acid (*cis/trans*-5o):** Prepared according to General Procedure 2; reaction time – 24 h; isolated yield 53% (*dr* 1:4.1); 354 mg of the mixture was submitted for HPLC separation (Method C); ***cis*-5o** – R_t 31 min; ***trans*-5o** – R_t 33–35 min.

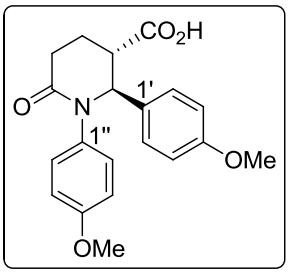
***cis*-1,2-bis(4-Methoxyphenyl)-6-oxopiperidine-3-carboxylic acid (*cis*-5o):** 27 mg isolated; White



solid; Mp 237−238 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.59 (br.s, 1H, COOH), 7.13 (d, *J* = 8.8 Hz, 2H, 2',6'-H), 7.01 (d, *J* = 9.0 Hz, 2H, 2",6"-H), 6.86 (d, *J* = 8.8 Hz, 2H, 3',5'-H), 6.80 (d, *J* = 9.0 Hz, 2H, 3",5"-H), 5.16 (d, *J* = 5.1 Hz, 1H, 2-H), 3.72 (s, 3H, 4'-OCH_3), 3.68 (s, 3H, 4"-OCH_3), 3.44 (ddd, *J* = 13.0, 5.1, 3.5 Hz, 1H, 3-H), 2.66 (ddd, *J* = 17.9, 6.6, 1.3 Hz, 1H, 5-H), 2.60

– 2.50 (m, 1H), 1.97 – 1.86 (m, 1H), 1.86 – 1.77 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.5, 169.1, 159.2, 157.9, 135.9, 129.70, 129.67, 129.1, 114.2, 113.9, 65.2, 55.6, 55.4, 45.2, 31.1, 18.1. HRMS (ESI), *m/z* calcd for $C_{20}H_{21}NO_5$ $[M+H]^+$ 356.1492, found 356.1500.

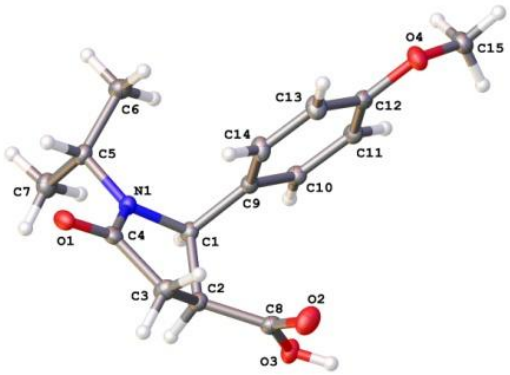
***trans*-1,2-bis(4-Methoxyphenyl)-6-oxopiperidine-3-carboxylic acid (*trans*-5o):** 192 mg isolated;



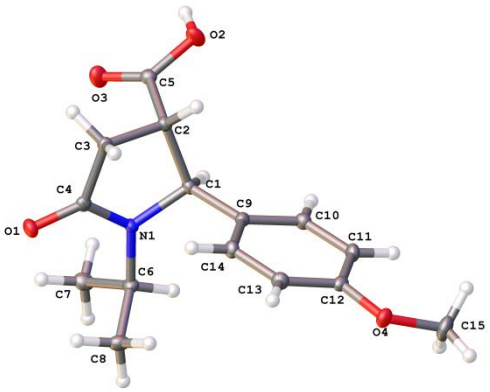
White solid; Mp 103−104 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.79 (br.s, 1H, COOH), 7.21 (d, *J* = 8.7 Hz, 2H, 2',6'-H), 7.04 (d, *J* = 9.0 Hz, 2H, 2",6"-H), 6.86 (d, *J* = 8.8 Hz, 2H, 3',5'-H), 6.81 (d, *J* = 9.1 Hz, 2H, 3",5"-H), 5.23 (d, *J* = 4.5 Hz, 1H, 2-H), 3.71 (s, 3H, 4'-OCH_3), 3.68 (s, 3H, 4"-OCH_3), 2.91 (dt, *J* = 6.0, 4.5 Hz, 1H, 3-H), 2.63 (ddd, *J* = 18.0, 6.5, 5.4 Hz, 1H, 5-H), 2.42 (ddd, *J* = 18.0, 8.8, 6.8 Hz, 1H, 5-H), 2.10 – 2.01 (m, 1H, 4-H), 1.99 – 1.90 (m, 1H, 4-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.1, 169.1, 158.9, 157.8, 135.6, 132.6, 129.1, 128.8, 114.2, 114.1, 65.4, 55.6, 55.5, 46.8, 30.3, 20.2. HRMS (ESI), *m/z* calcd for $C_{20}H_{21}NO_5$ $[M+H]^+$ 356.1492, found 356.1508.

4. Crystallographic data for compounds 4b-e and 5b,c,f,n.

X-ray Single Crystal analyses were performed on Agilent Technologies Xcalibur Eos and Bruker APEX-II CCD diffractometers. Using Olex2 [5], structures were solved with the Superflip [6] structure solution program using Charge Flipping and refined with the ShelXL [7] refinement package using Least Squares minimisation. CCDC 1438073, 1442379, 1442947, 1447518, 1447521, 1437633, 1442993, 1442357, 1442376, 1452491 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.



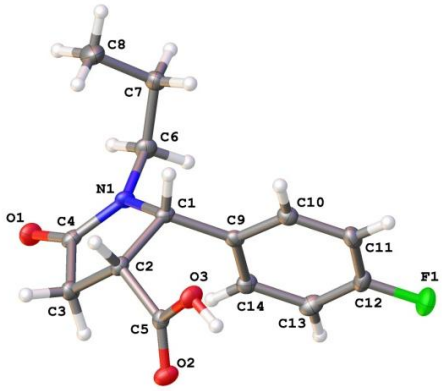
Cis-**4b**



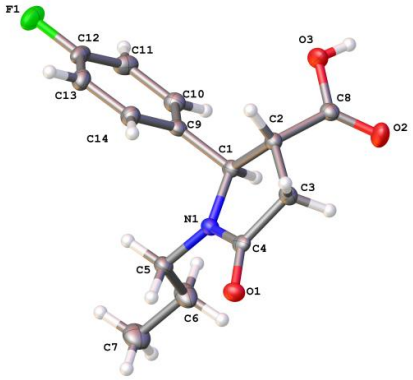
Trans-**4b**

Table S2 Crystal data and structure refinement for 4b	
Empirical formula	$C_{16}H_{19}FN_2O_3$
Formula weight	306.33
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	10.6754(4)
b/Å	8.1698(2)
c/Å	17.8582(6)
α/°	90
β/°	90.365(3)
γ/°	90
Volume/Å^3	1557.49(9)
Z	4
ρ_{calc}g/cm^3	1.306
μ/mm^{-1}	0.099
F(000)	648
Crystal size/mm^3	0.2 × 0.18 × 0.1
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.484 to 54.994
Index ranges	-13 ≤ h ≤ 13, -10 ≤ k ≤ 10, -16 ≤ l ≤ 23
Reflections collected	9759
Independent reflections	3491 [R_{int} = 0.0340, R_{sigma} = 0.0482]
Data/restraints/parameters	3491/0/202
Goodness-of-fit on F^2	1.03
Final R indexes [I>=2σ (I)]	R_1 = 0.0453, wR_2 = 0.0814
Final R indexes [all data]	R_1 = 0.0712, wR_2 = 0.0907
Largest diff. peak/hole / e Å^{-3}	0.28/-0.23
CCDC	**1447518**

Table S3 Crystal data and structure refinement for 4b	
Empirical formula	$C_{14}H_{16}FNO_3$
Formula weight	265.28
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	9.9465(16)
b/Å	15.9223(18)
c/Å	8.4185(7)
α/°	90
β/°	92.142(11)
γ/°	90
Volume/Å^3	1332.3(3)
Z	4
ρ_{calc}g/cm^3	1.323
μ/mm^{-1}	0.102
F(000)	560
Crystal size/mm^3	0.22 × 0.17 × 0.15
Radiation	Mo Kα (λ = 0.7107)
2Θ range for data collection/°	6.56 to 55
Index ranges	-12 ≤ h ≤ 12, -20 ≤ k ≤ 18, -10 ≤ l ≤ 6
Reflections collected	6163
Independent reflections	3007 [R_{int} = 0.0261, R_{sigma} = 0.0411]
Data/restraints/parameters	3007/0/174
Goodness-of-fit on F^2	1.039
Final R indexes [I>=2σ (I)]	R_1 = 0.0418, wR_2 = 0.0947
Final R indexes [all data]	R_1 = 0.0597, wR_2 = 0.1077
Largest diff. peak/hole / e Å^{-3}	0.30/-0.19
CCDC	**1442379**



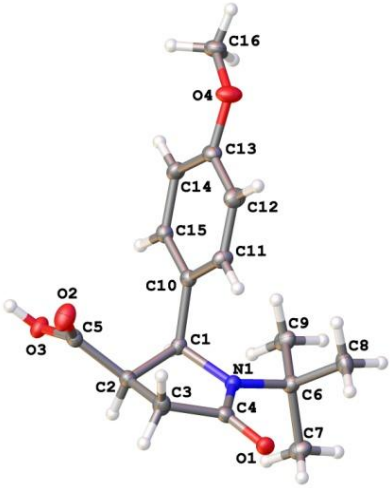
Cis-**4d**



Trans-**4d**

Table S4 Crystal data and structure refinement for 4d	
Empirical formula	$C_{16}H_{19}FN_2O_3$
Formula weight	306.33
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	10.6754(4)
b/Å	8.1698(2)
c/Å	17.8582(6)
α/°	90
β/°	90.365(3)
γ/°	90
Volume/Å^3	1557.49(9)
Z	4
ρ_{calc}g/cm^3	1.306
μ/mm^{-1}	0.099
F(000)	648
Crystal size/mm^3	0.2 × 0.18 × 0.1
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.484 to 54.994
Index ranges	-13 ≤ h ≤ 13, -10 ≤ k ≤ 10, -16 ≤ l ≤ 23
Reflections collected	9759
Independent reflections	3491 [R_{int} = 0.0340, R_{sigma} = 0.0482]
Data/restraints/parameters	3491/0/202
Goodness-of-fit on F^2	1.03
Final R indexes [I>=2σ (I)]	R_1 = 0.0453, wR_2 = 0.0814
Final R indexes [all data]	R_1 = 0.0712, wR_2 = 0.0907
Largest diff. peak/hole / e Å^{-3}	0.28/-0.23
CCDC	**1438073**

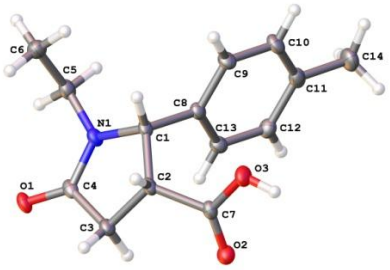
Table S5 Crystal data and structure refinement for 4d	
Empirical formula	$C_{14}H_{16}FNO_3$
Formula weight	265.28
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	9.9465(16)
b/Å	15.9223(18)
c/Å	8.4185(7)
α/°	90
β/°	92.142(11)
γ/°	90
Volume/Å^3	1332.3(3)
Z	4
ρ_{calc}g/cm^3	1.323
μ/mm^{-1}	0.102
F(000)	560
Crystal size/mm^3	0.22 × 0.17 × 0.15
Radiation	Mo Kα (λ = 0.7107)
2Θ range for data collection/°	6.56 to 55
Index ranges	-12 ≤ h ≤ 12, -20 ≤ k ≤ 18, -10 ≤ l ≤ 6
Reflections collected	6163
Independent reflections	3007 [R_{int} = 0.0261, R_{sigma} = 0.0411]
Data/restraints/parameters	3007/0/174
Goodness-of-fit on F^2	1.039
Final R indexes [I>=2σ (I)]	R_1 = 0.0418, wR_2 = 0.0947
Final R indexes [all data]	R_1 = 0.0597, wR_2 = 0.1077
Largest diff. peak/hole / e Å^{-3}	0.30/-0.19
CCDC	**1452491**



Crystal structure determination of *cis*-4c

Crystal Data for $C_{16}H_{21}NO_4$ (*M* =291.34 g/mol): monoclinic, space group $P2_1/c$ (no. 14), *a* = 23.216(3) Å, *b* = 11.7924(16) Å, *c* = 23.055(3) Å, *β* = 103.933(2)°, *V* = 6126.1(15) Å^3, *Z* = 16, *T* = 100(2) K, μ(MoKα) = 0.091 mm^{-1}, *Dcalc* = 1.264 g/cm^3, 73928 reflections measured (3.64° ≤ 2Θ ≤ 52.222°), 12171 unique (R_{int} = 0.0438, R_{sigma} = 0.0254) which were used in all calculations. The final R_1 was 0.0366 (I > 2σ(I)) and wR_2 was 0.0948 (all data).

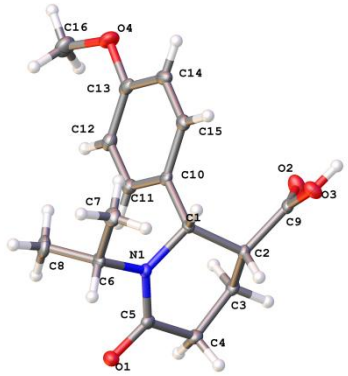
CCDC 1442947



Crystal structure determination of *cis*-4e

Crystal Data for $C_{14}H_{17}NO_3$ (M =247.28 g/mol): monoclinic, space group Pc (no. 7), a = 5.9545(5) Å, b = 10.6290(8) Å, c = 10.1521(6) Å, β = 98.878(7)°, V = 634.84(8) Å^3, Z = 2, T = 99.99(10) K, μ(MoKα) = 0.091 mm^{-1}, *Dcalc* = 1.294 g/cm^3, 5642 reflections measured (5.584° ≤ 2Θ ≤ 54.994°), 2768 unique (R_{int} = 0.0341, R_{sigma} = 0.0506) which were used in all calculations. The final R_1 was 0.0442 (I > 2σ(I)) and wR_2 was 0.1147 (all data).

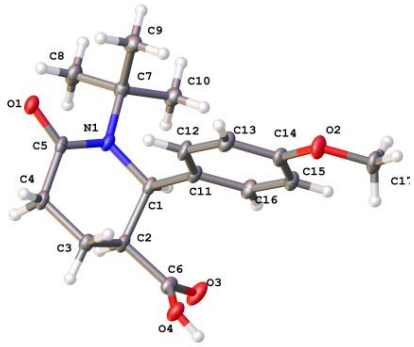
CCDC 1447521



Crystal structure determination of *cis*-5b

Crystal Data for $C_{16}H_{21}NO_4$ (M =291.34 g/mol): monoclinic, space group $P2_1/c$ (no. 14), a = 6.4049(2) Å, b = 21.3010(6) Å, c = 10.8631(3) Å, β = 100.374(3)°, V = 1457.85(8) Å^3, Z = 4, T = 100(2) K, μ(Mo Kα) = 0.095 mm^{-1}, *Dcalc* = 1.327 g/cm^3, 23949 reflections measured (5.4° ≤ 2Θ ≤ 55°), 3349 unique (R_{int} = 0.0527, R_{sigma} = 0.0240) which were used in all calculations. The final R_1 was 0.0464 (>2sigma(I)) and wR_2 was 0.1302 (all data).

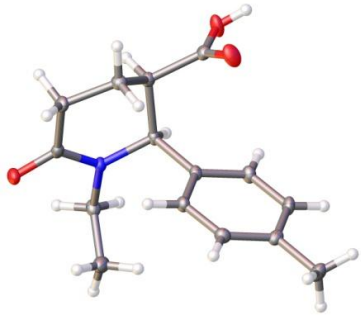
CCDC 144235



Crystal structure determination of *cis*-5c

Crystal Data for $C_{17}H_{23}NO_4$ (M =305.36 g/mol): monoclinic, space group $P2_1/c$ (no. 14), a = 6.5824(9) Å, b = 21.392(2) Å, c = 11.5002(13) Å, β = 105.054(12)°, V = 1563.8(3) Å^3, Z = 4, T = 100.00(10) K, μ(Mo Kα) = 0.092 mm^{-1}, *Dcalc* = 1.297 g/cm^3, 7643 reflections measured (6.4° ≤ 2Θ ≤ 55°), 3480 unique (R_{int} = 0.0359, R_{sigma} = 0.0535) which were used in all calculations. The final R_1 was 0.0767 (>2sigma(I)) and wR_2 was 0.1980 (all data).

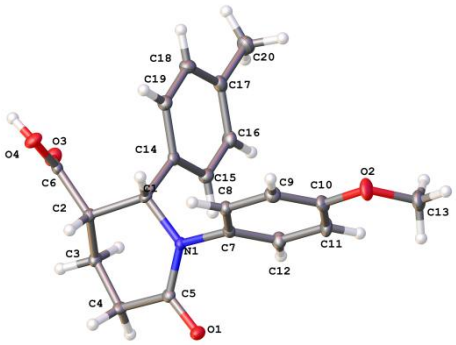
CCDC 1442993



Crystal structure determination of *cis*-5f

Crystal Data for $C_{15}H_{19}NO_3$ (M =261.31 g/mol): monoclinic, space group $P2_1/c$ (no. 14), a = 12.6016(4) Å, b = 19.0377(7) Å, c = 11.3636(4) Å, β = 100.352(3)°, V = 2681.80(16) Å^3, Z = 8, T = 100(2) K, μ(MoKα) = 0.090 mm^{-1}, *Dcalc* = 1.294 g/cm^3, 11740 reflections measured (5.396° ≤ 2Θ ≤ 54.992°), 6113 unique (R_{int} = 0.0219, R_{sigma} = 0.0390) which were used in all calculations. The final R_1 was 0.0479 (I > 2σ(I)) and wR_2 was 0.1268 (all data).

CCDC 1437633



Crystal structure determination of *cis*-5n

Crystal Data for $C_{20}H_{21}NO_4$ (M =339.38 g/mol): monoclinic, space group $P2_1/c$ (no. 14), a = 6.3469(6) Å, b = 27.815(3) Å, c = 10.8960(10) Å, β = 99.887(11)°, V = 1895.0(3) Å^3, Z = 4, T = 100(2) K, μ(Mo Kα) = 0.083 mm^{-1}, $Dcalc$ = 1.190 g/cm^3, 4297 reflections measured (5.8° ≤ 2Θ ≤ 55°), 4297 unique (R_{int} = 0.0000, R_{sigma} = 0.0555) which were used in all calculations. The final R_1 was 0.0549 (>2sigma(I)) and wR_2 was 0.1652 (all data).

CCDC 1442376

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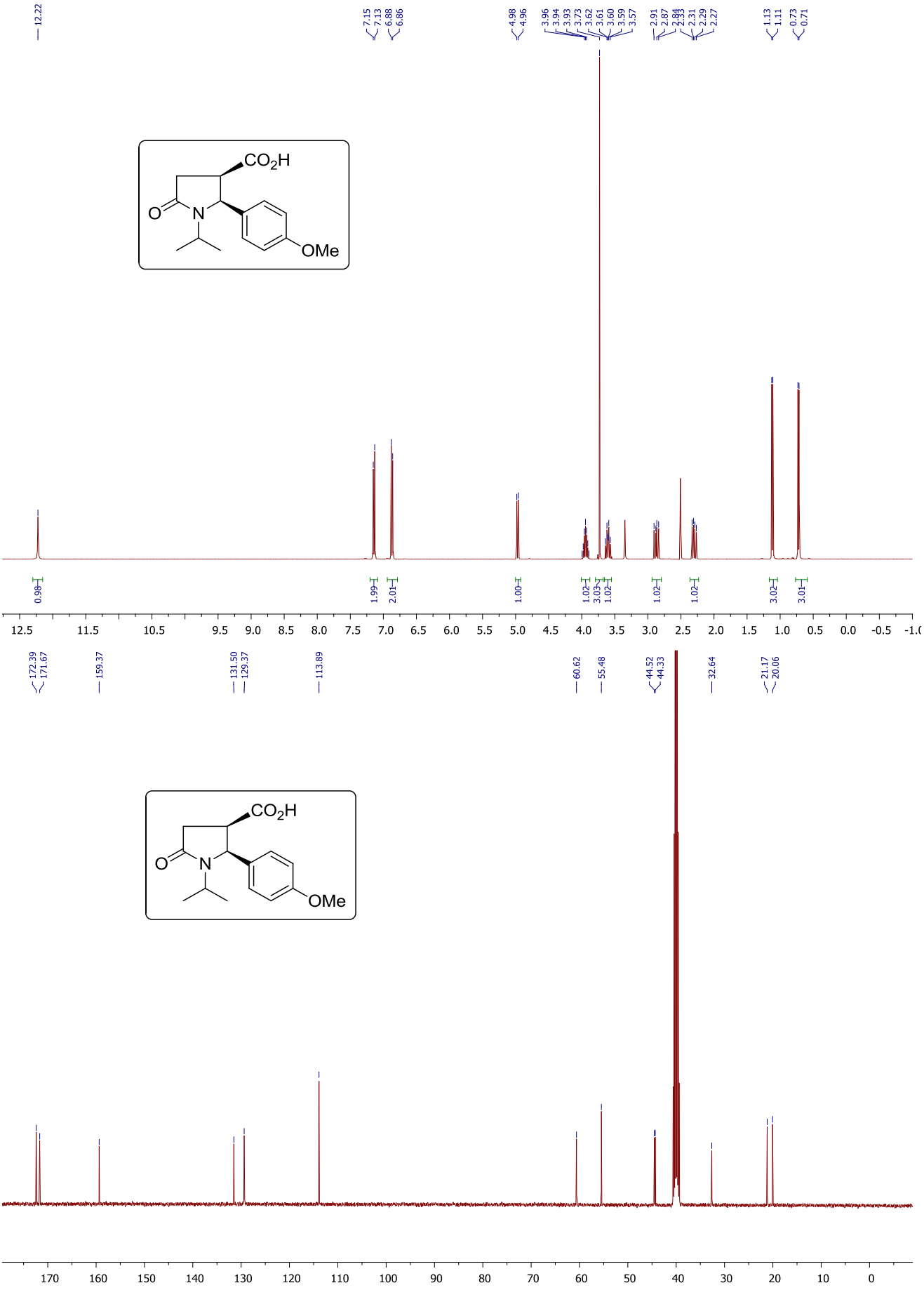
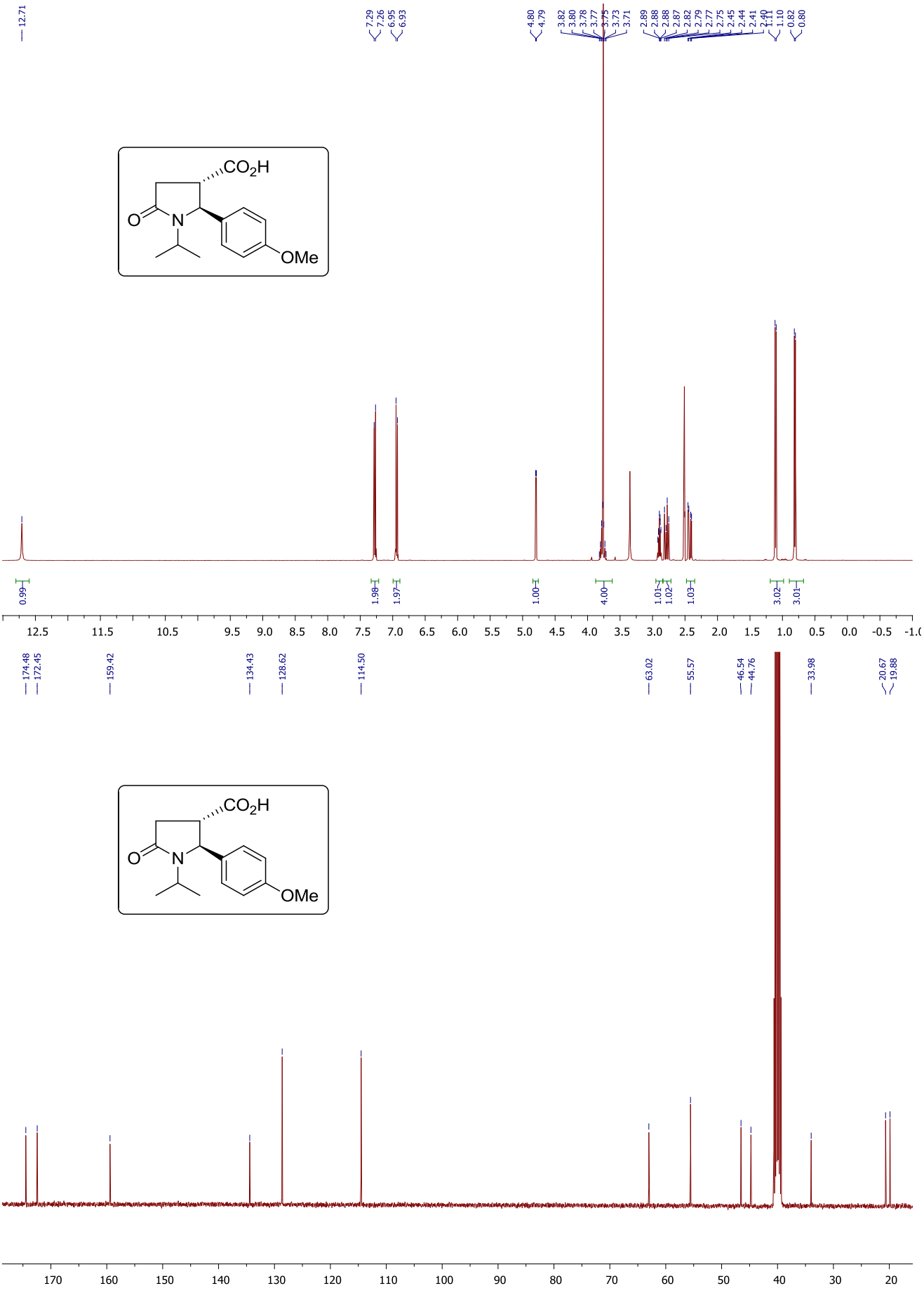
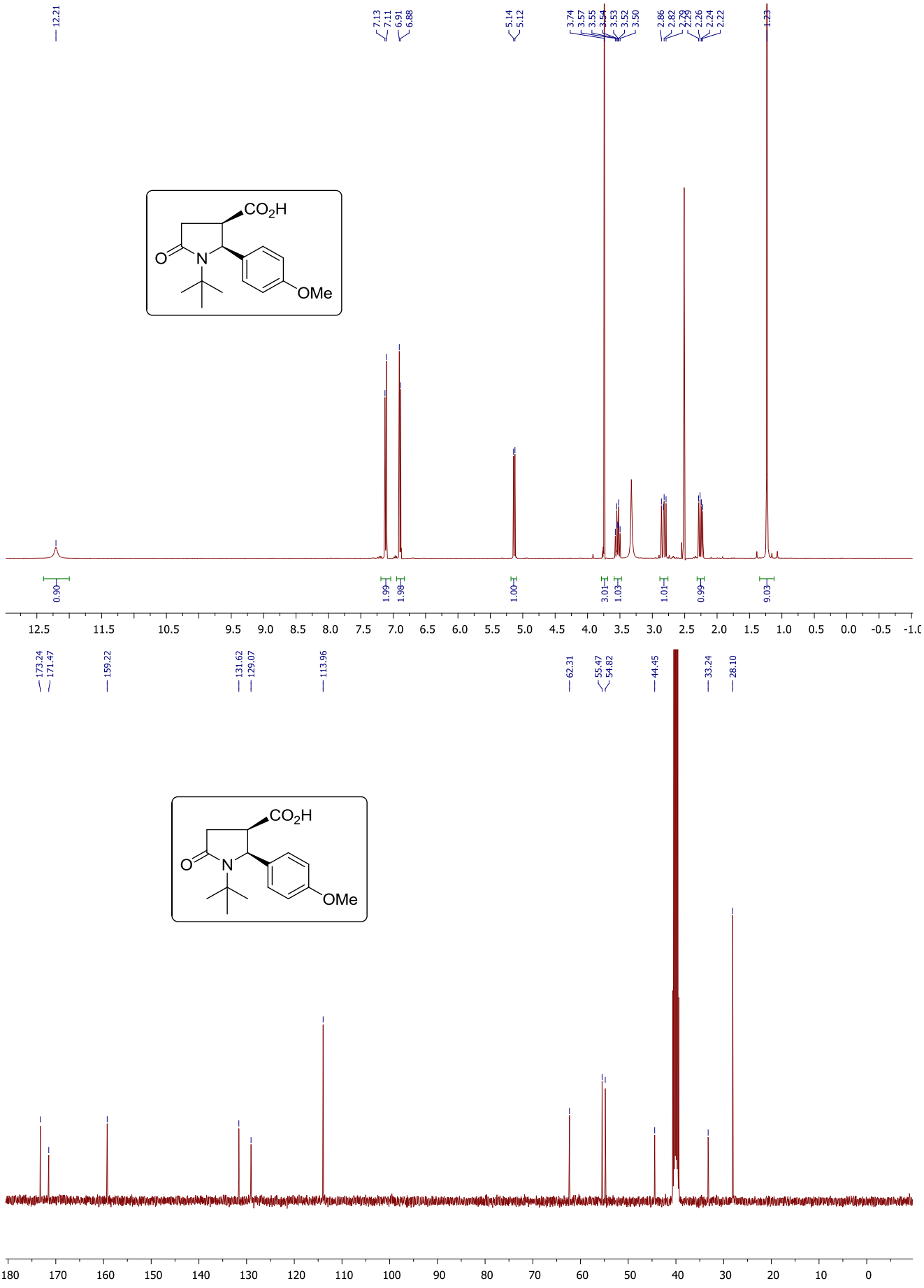
^{1}H and ^{13}C NMR spectra of ***cis*-4b**



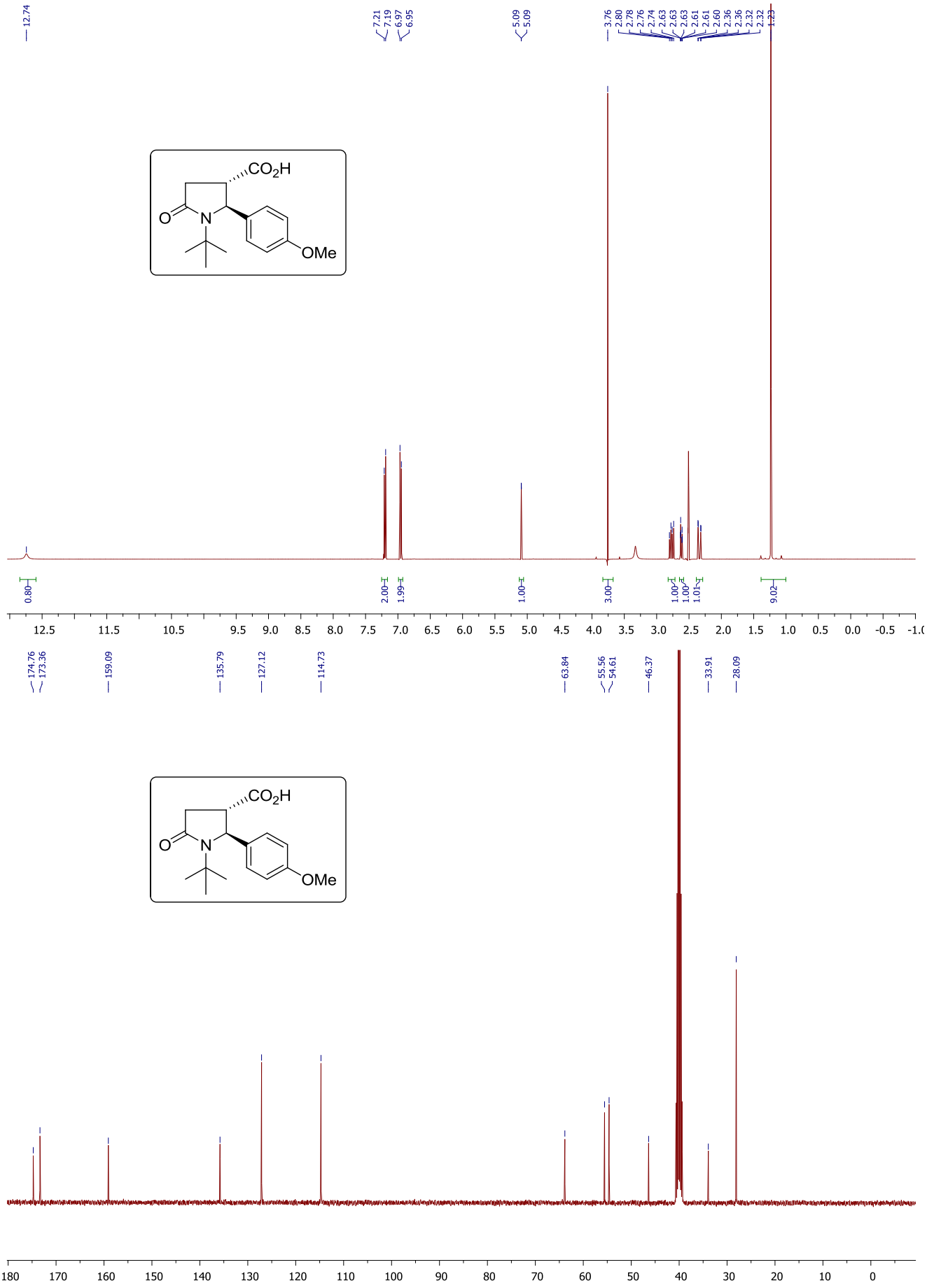
^{1}H and ^{13}C NMR spectra of ***trans*-4b**



^{1}H and ^{13}C NMR spectra of ***cis*-4c**



^{1}H and ^{13}C NMR spectra of ***trans*-4c**



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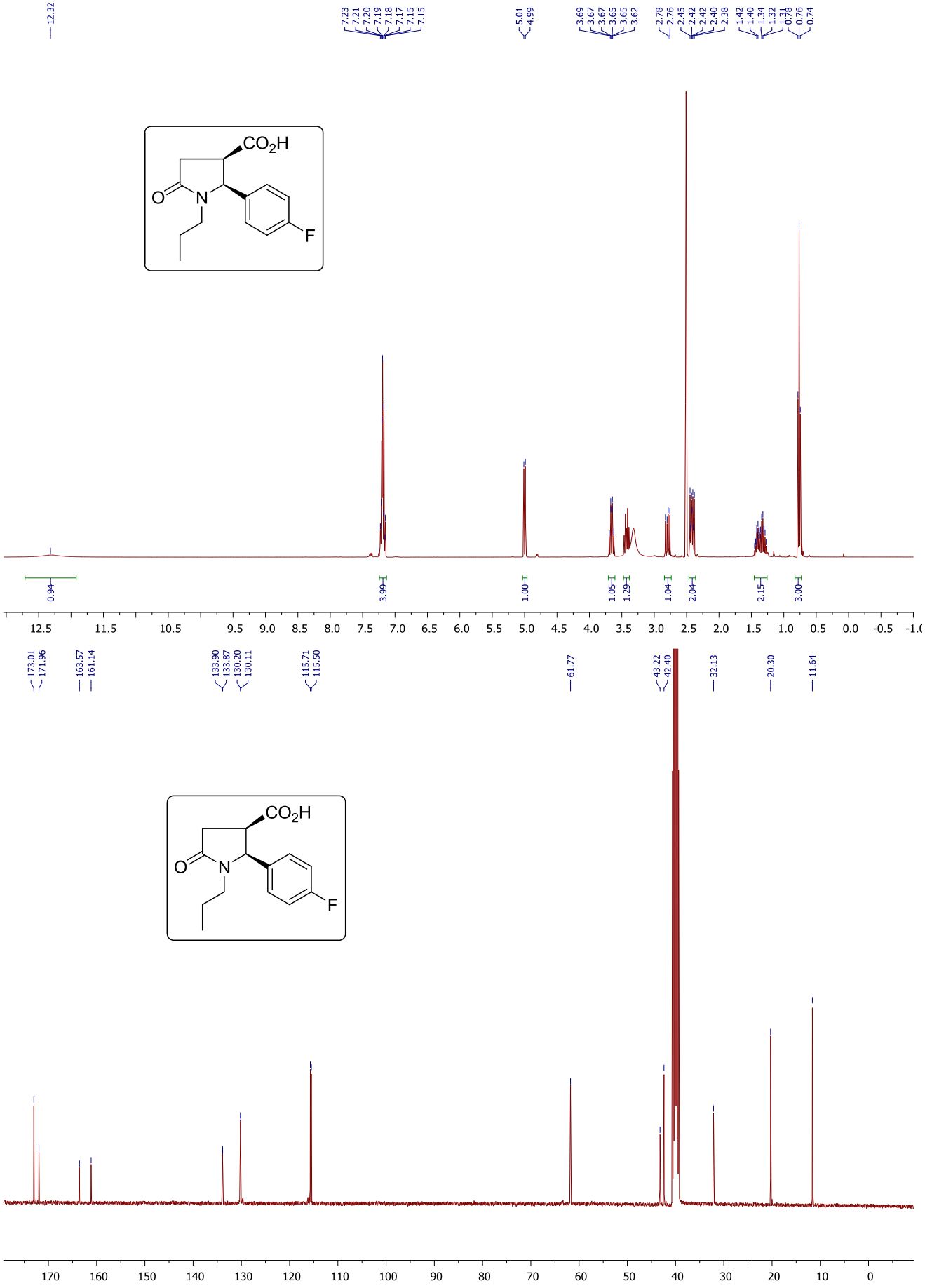

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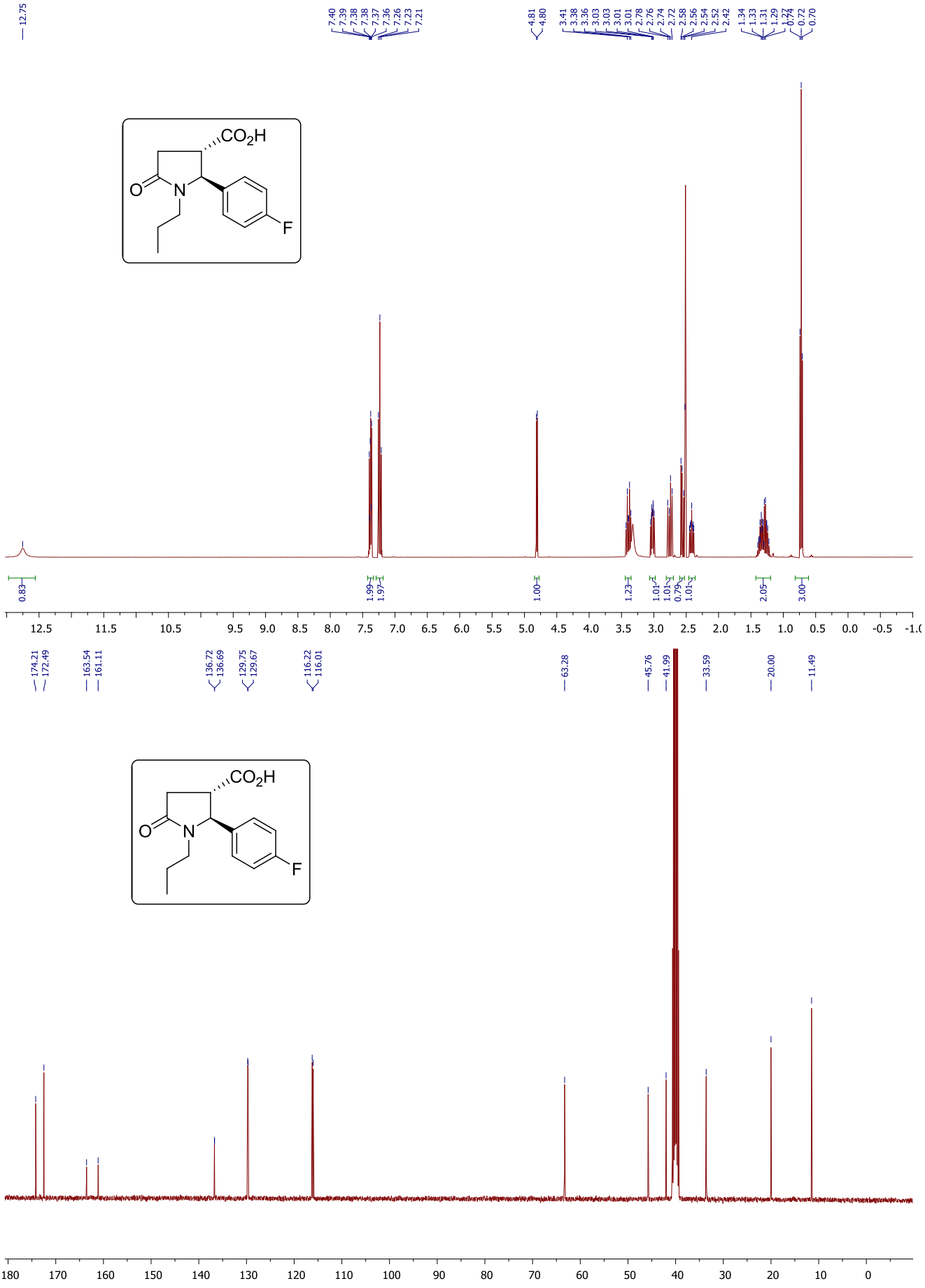
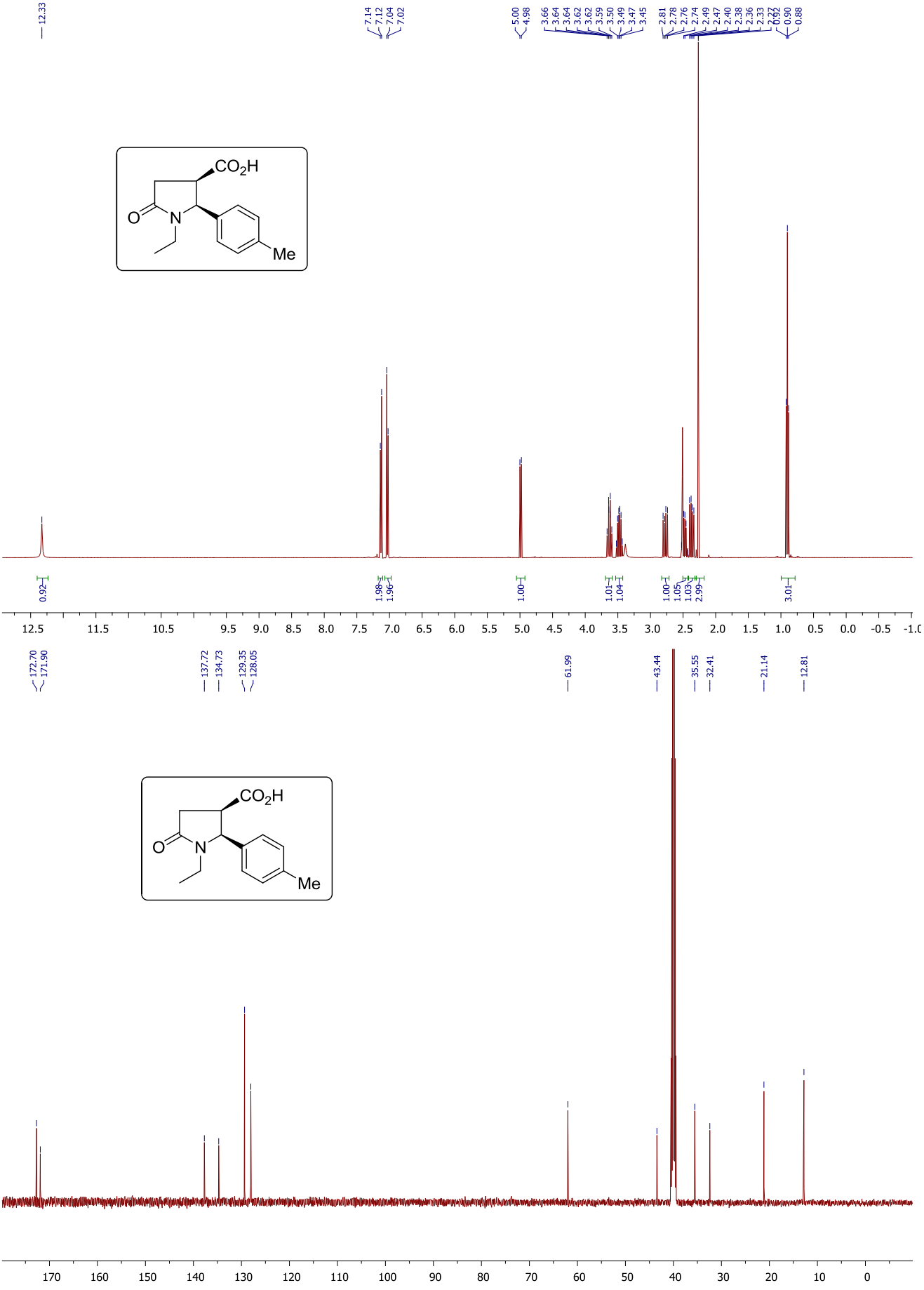


^{1}H and ^{13}C NMR spectra of ***cis*-4e**



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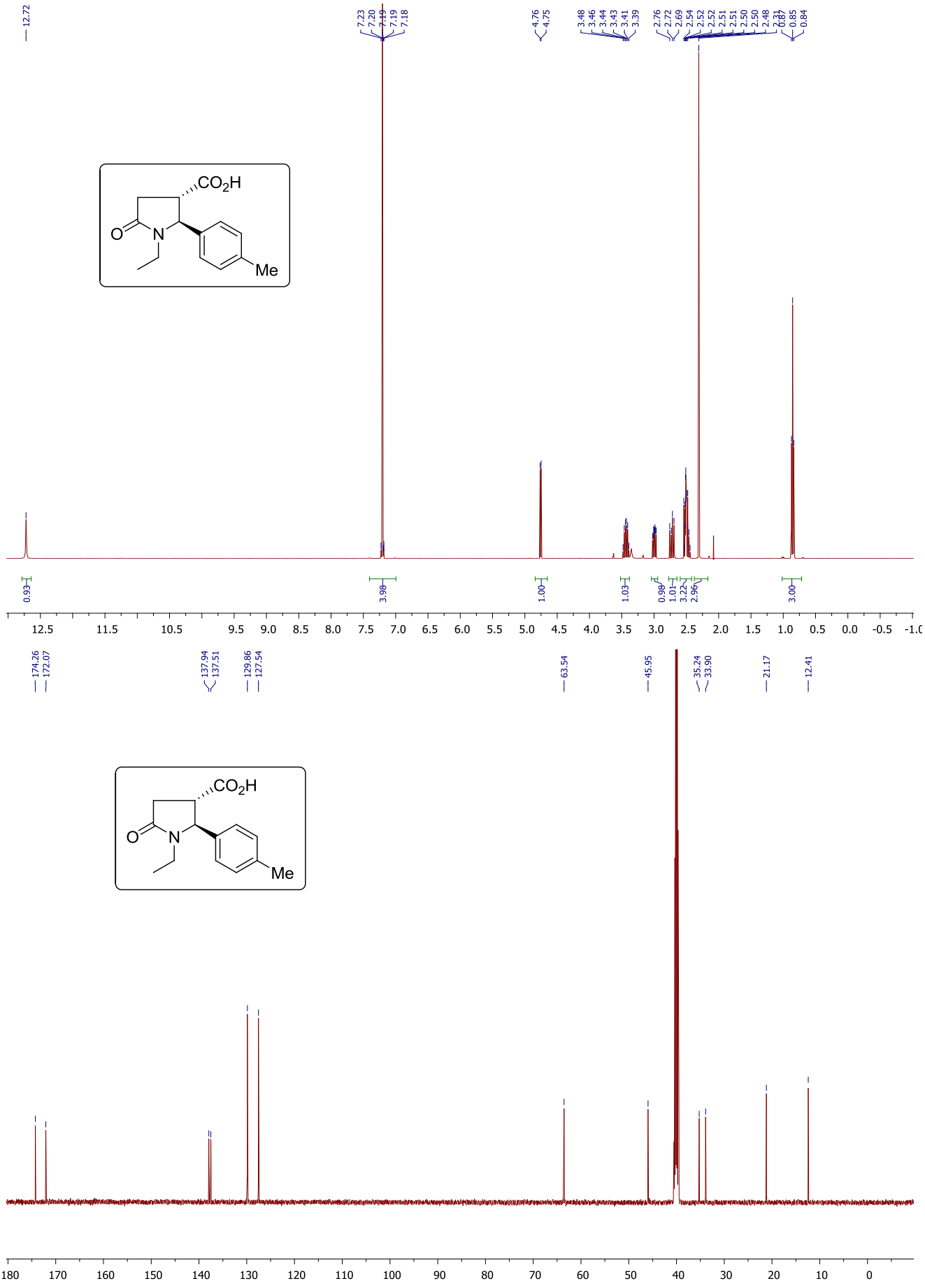

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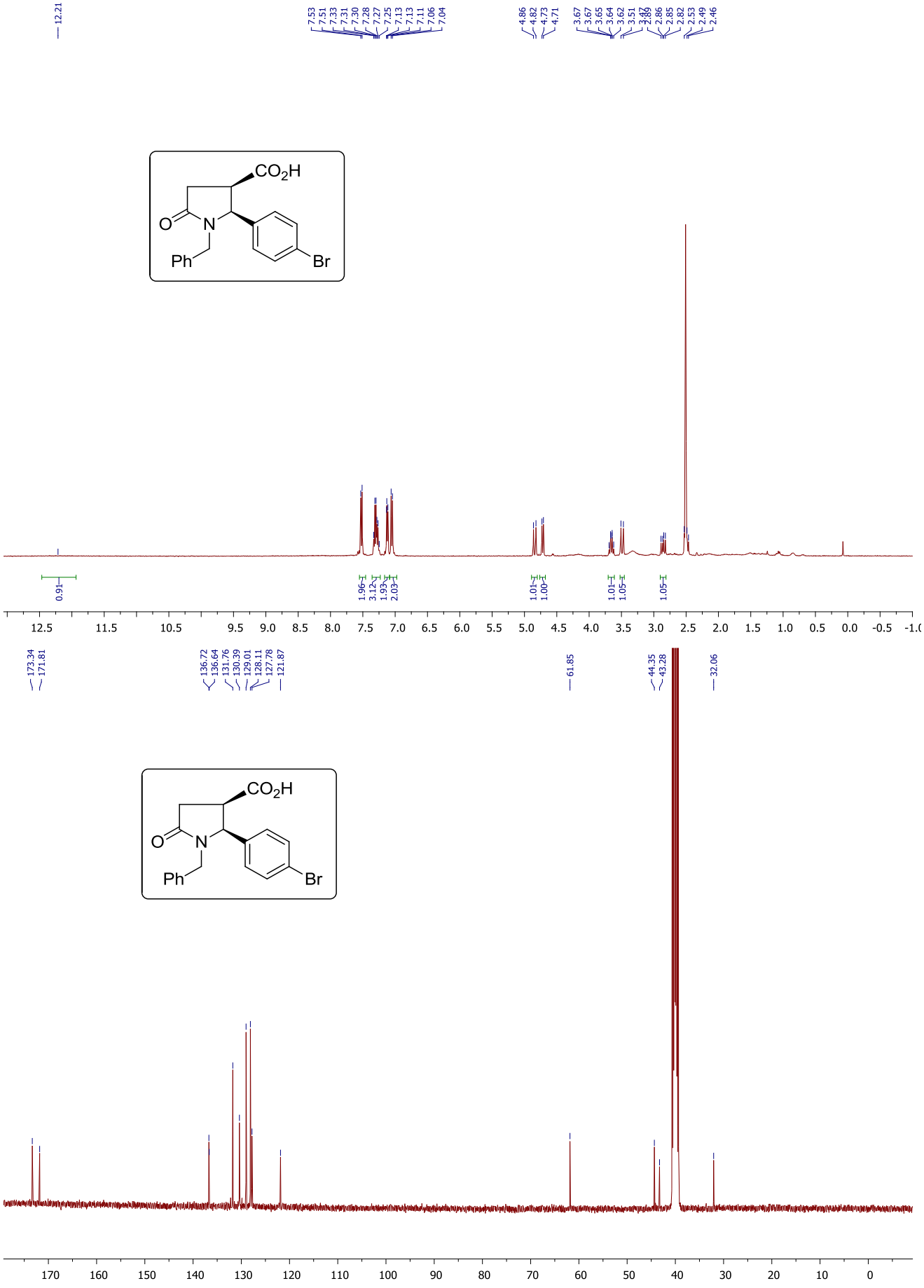

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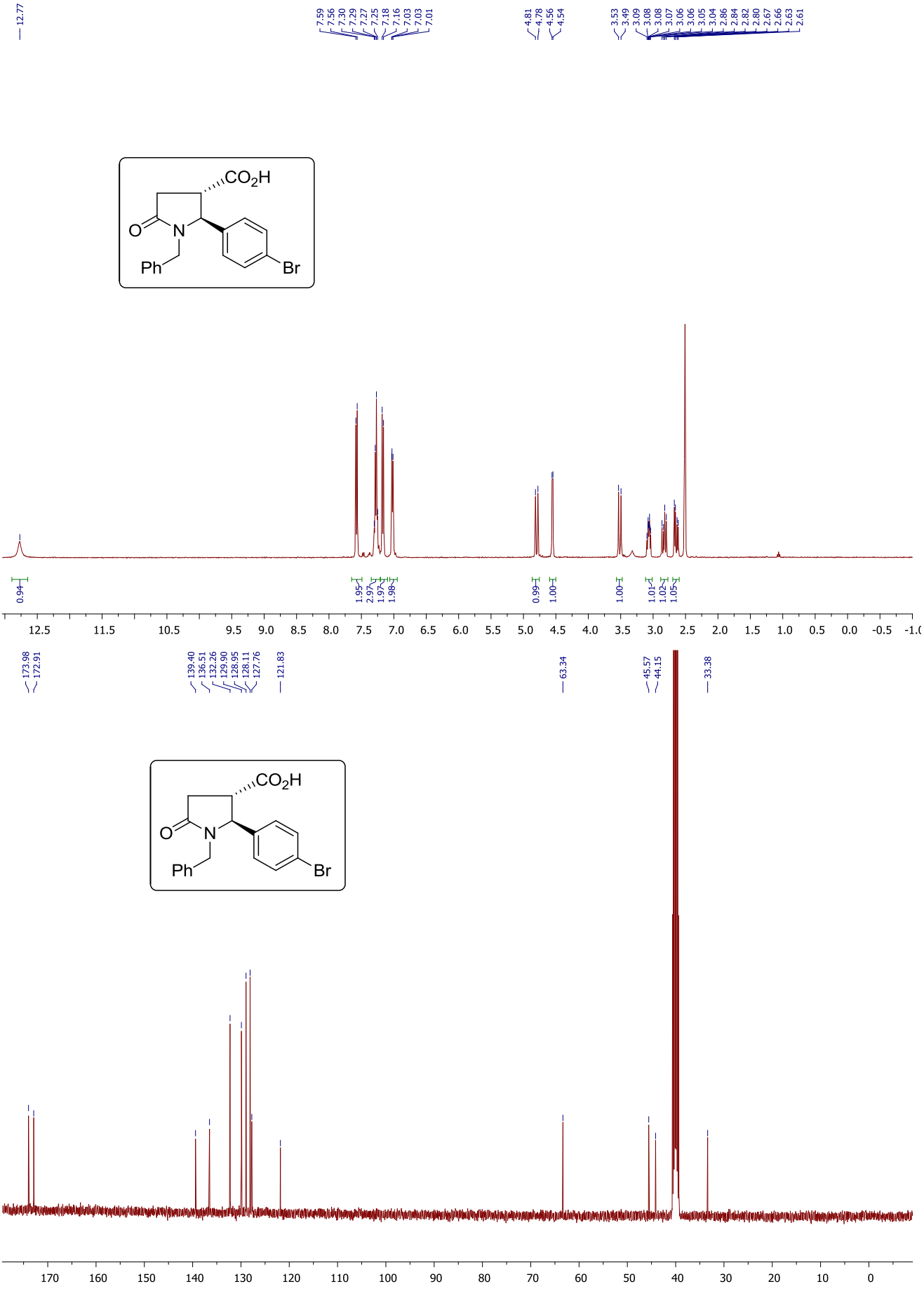
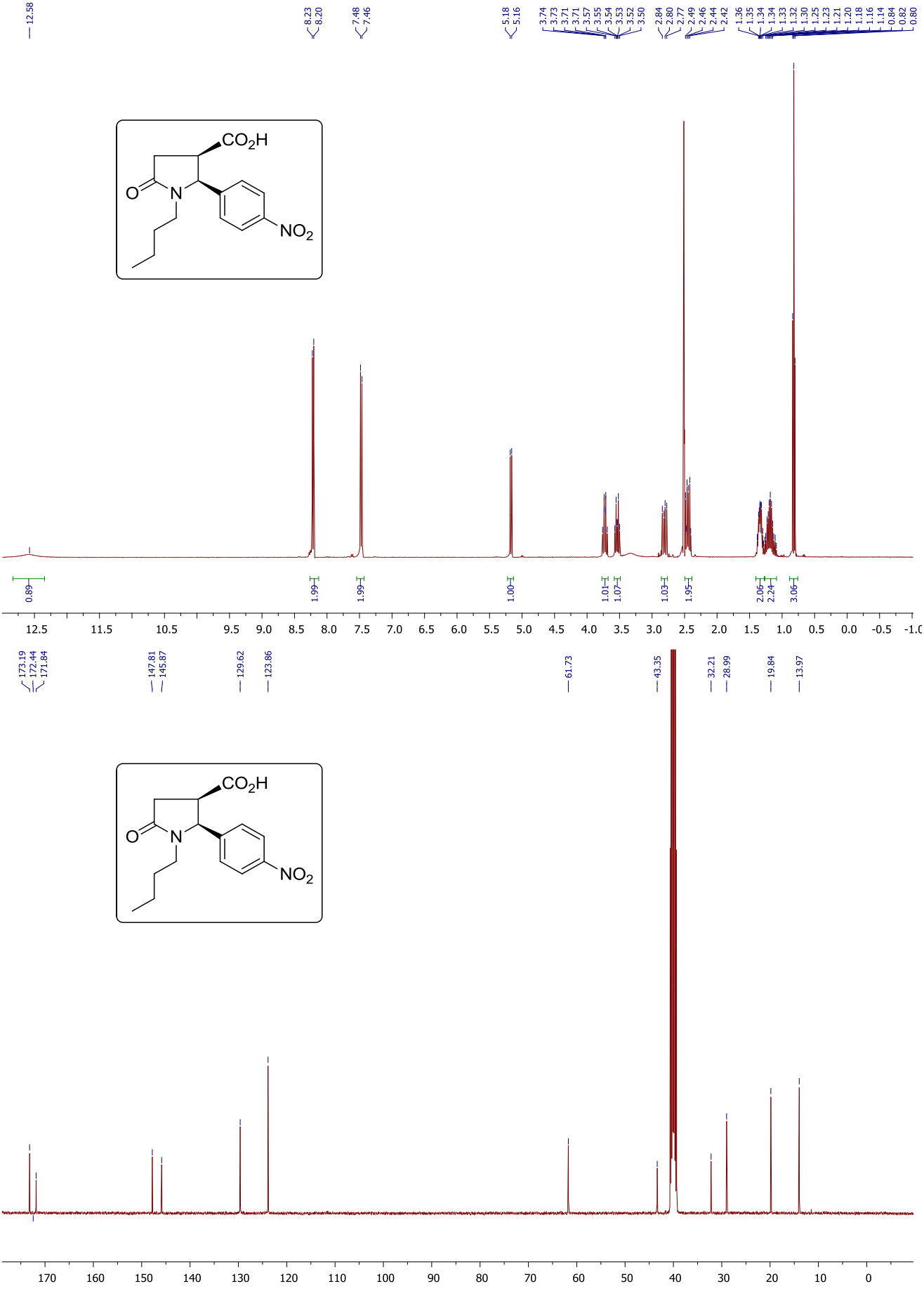
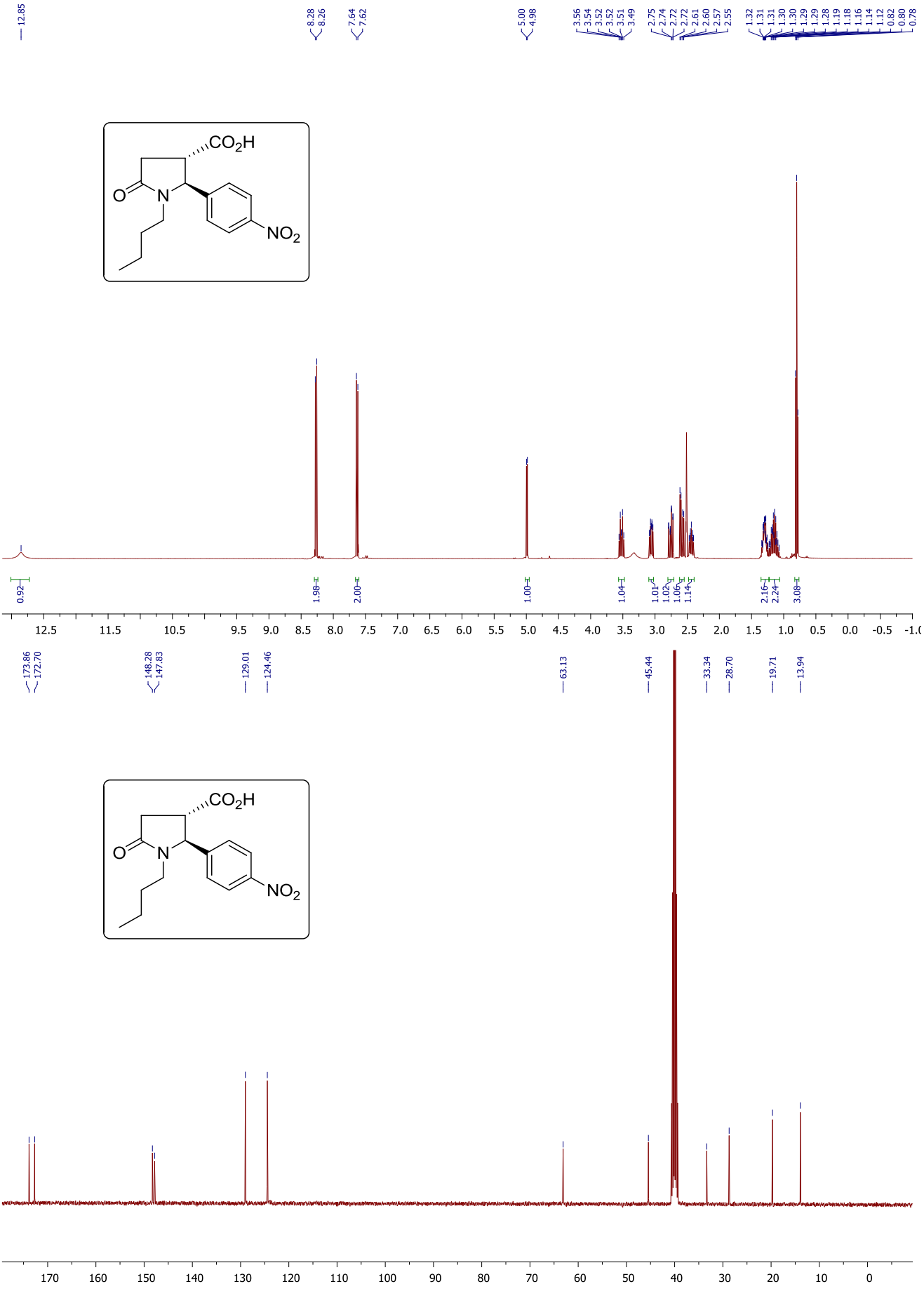


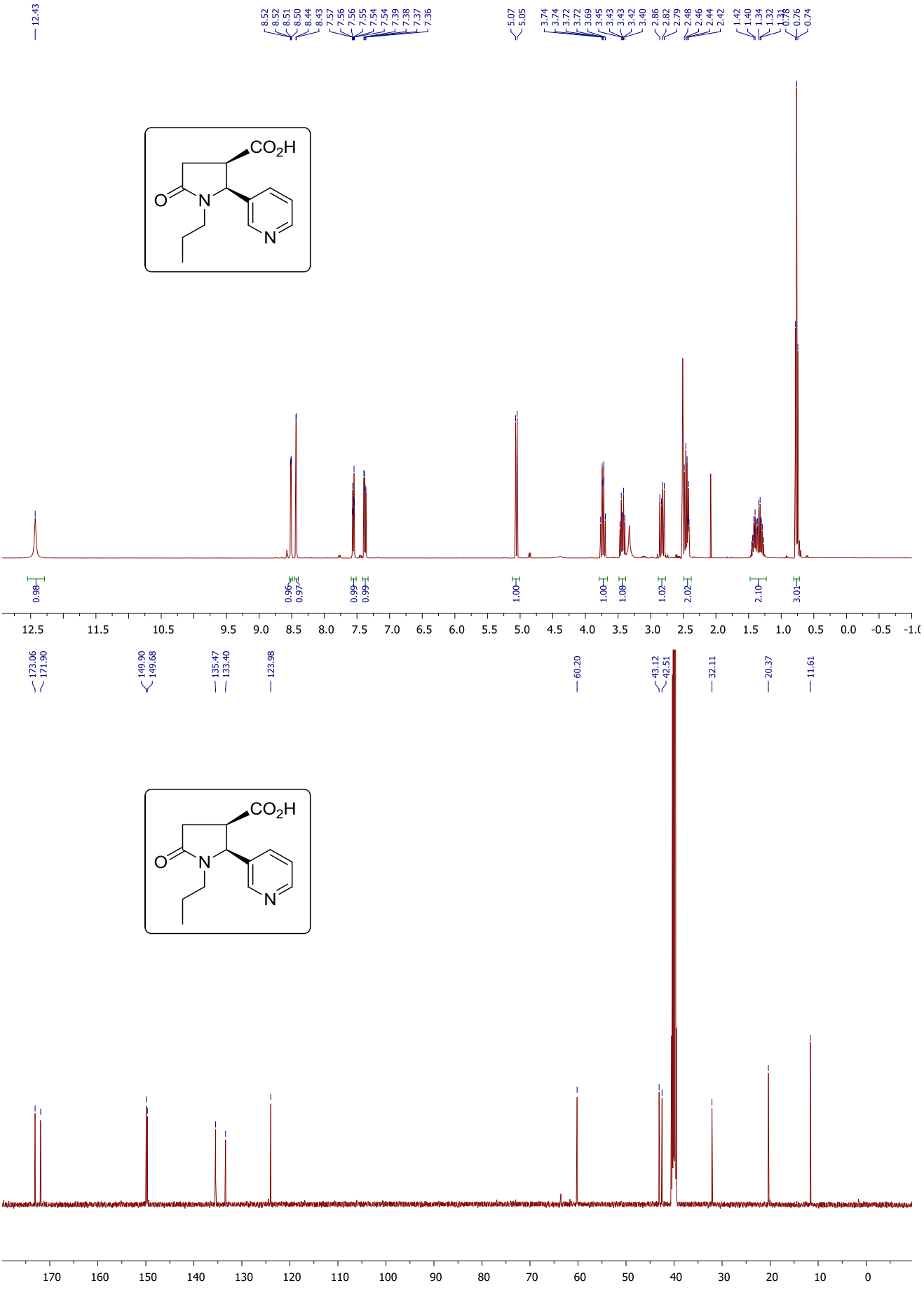
^{1}H and ^{13}C NMR spectra of ***cis*-4g**



^{1}H and ^{13}C NMR spectra of ***trans*-4g**



^{1}H and ^{13}C NMR spectra of ***cis*-4h**



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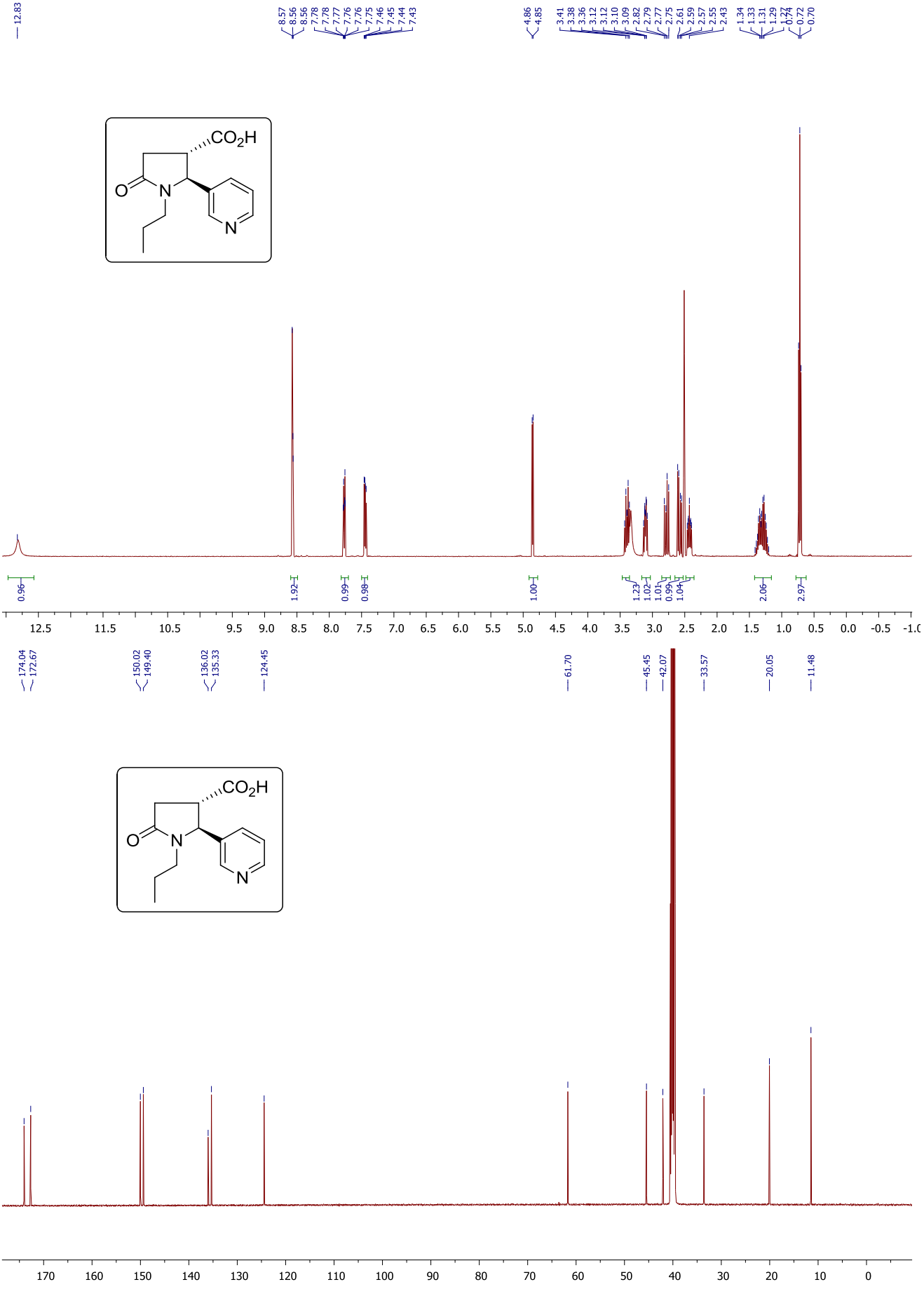

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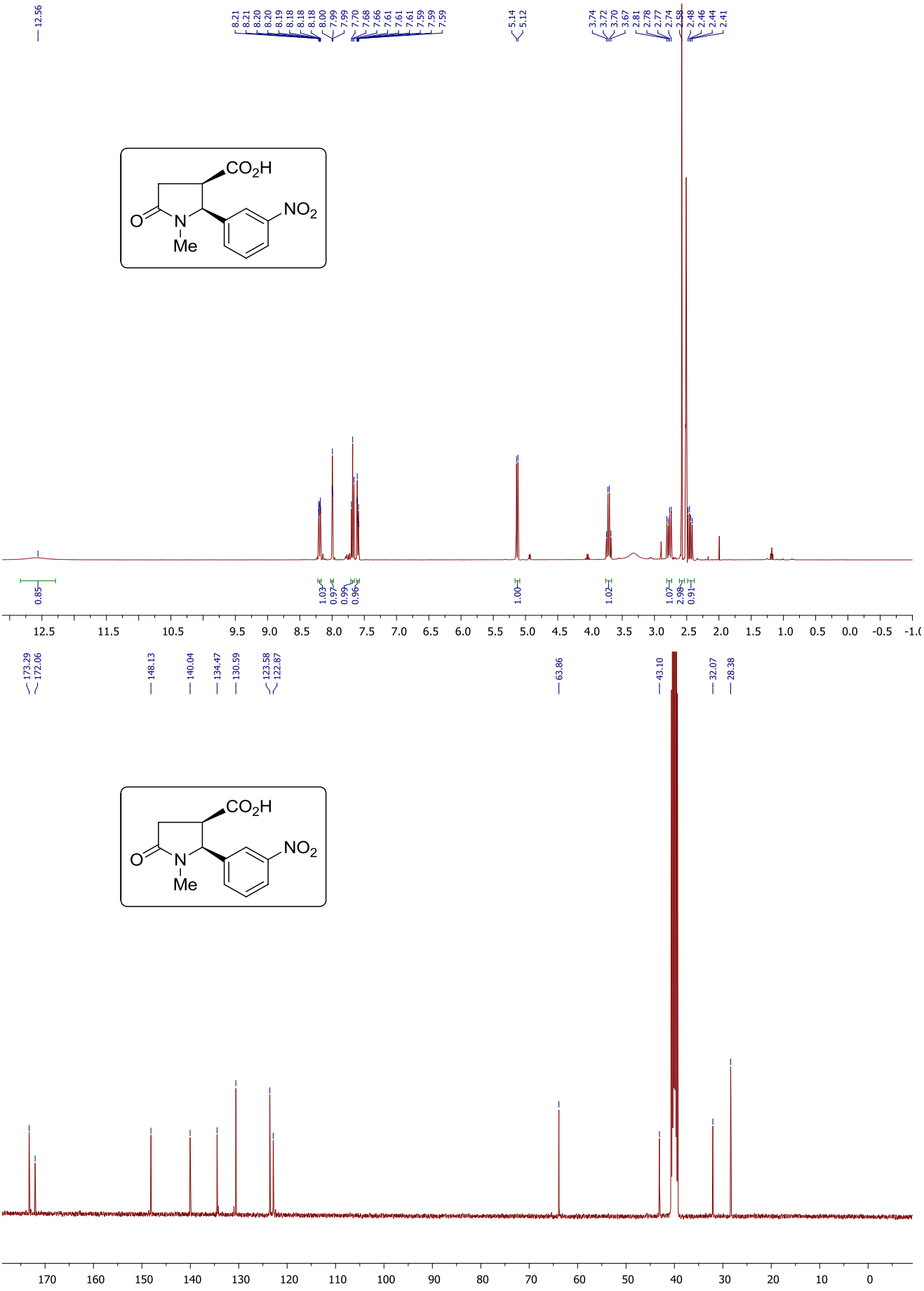

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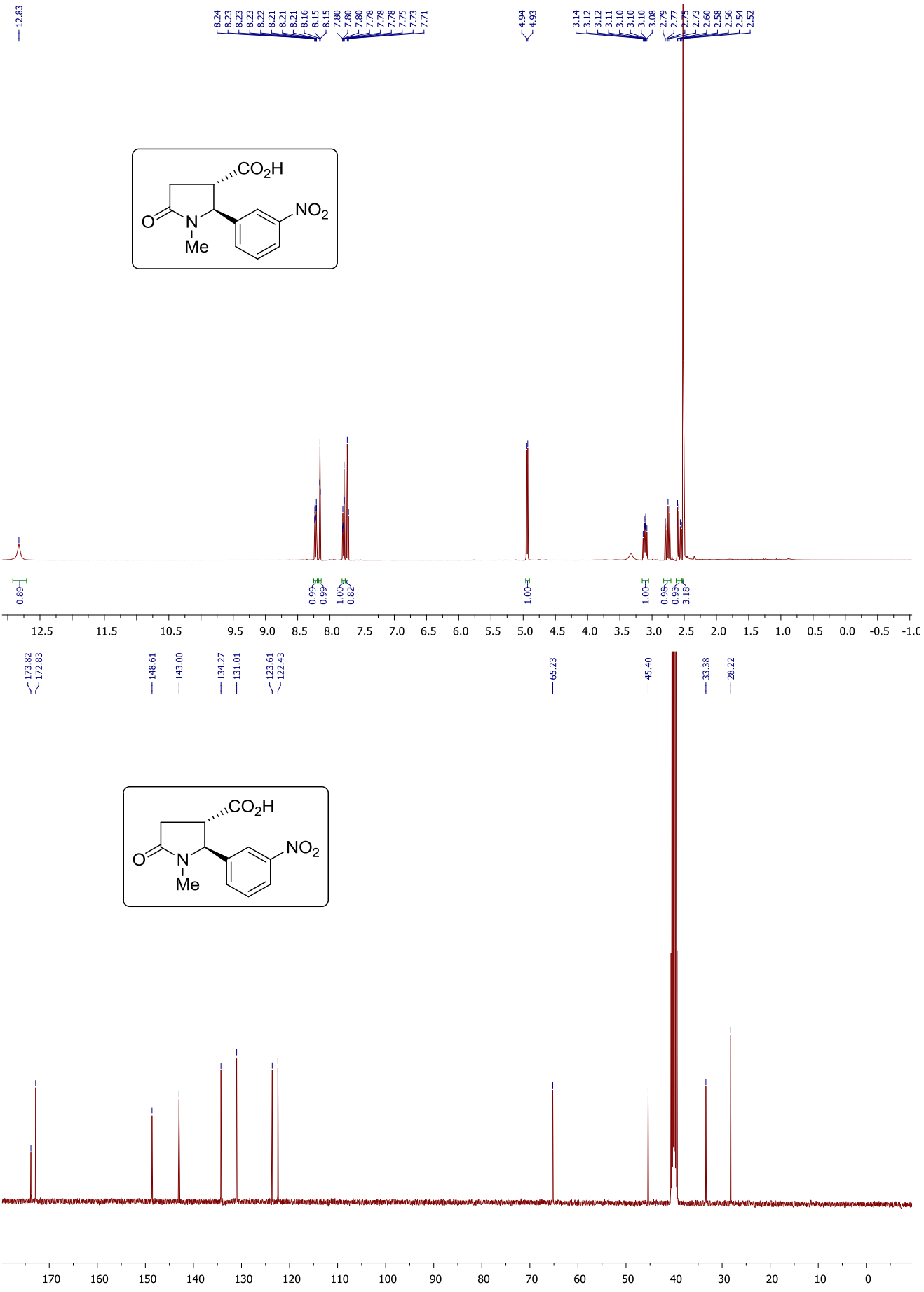
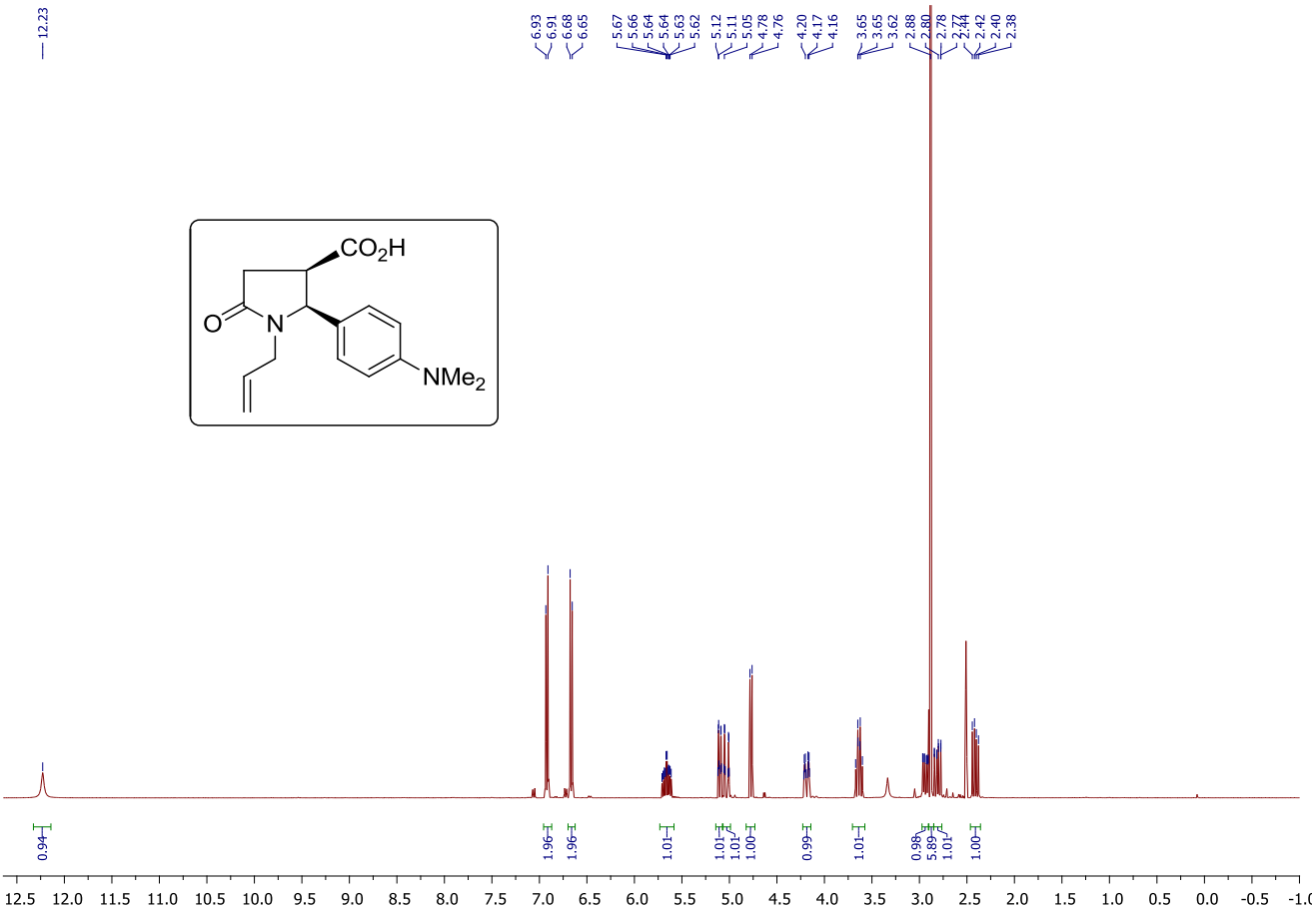
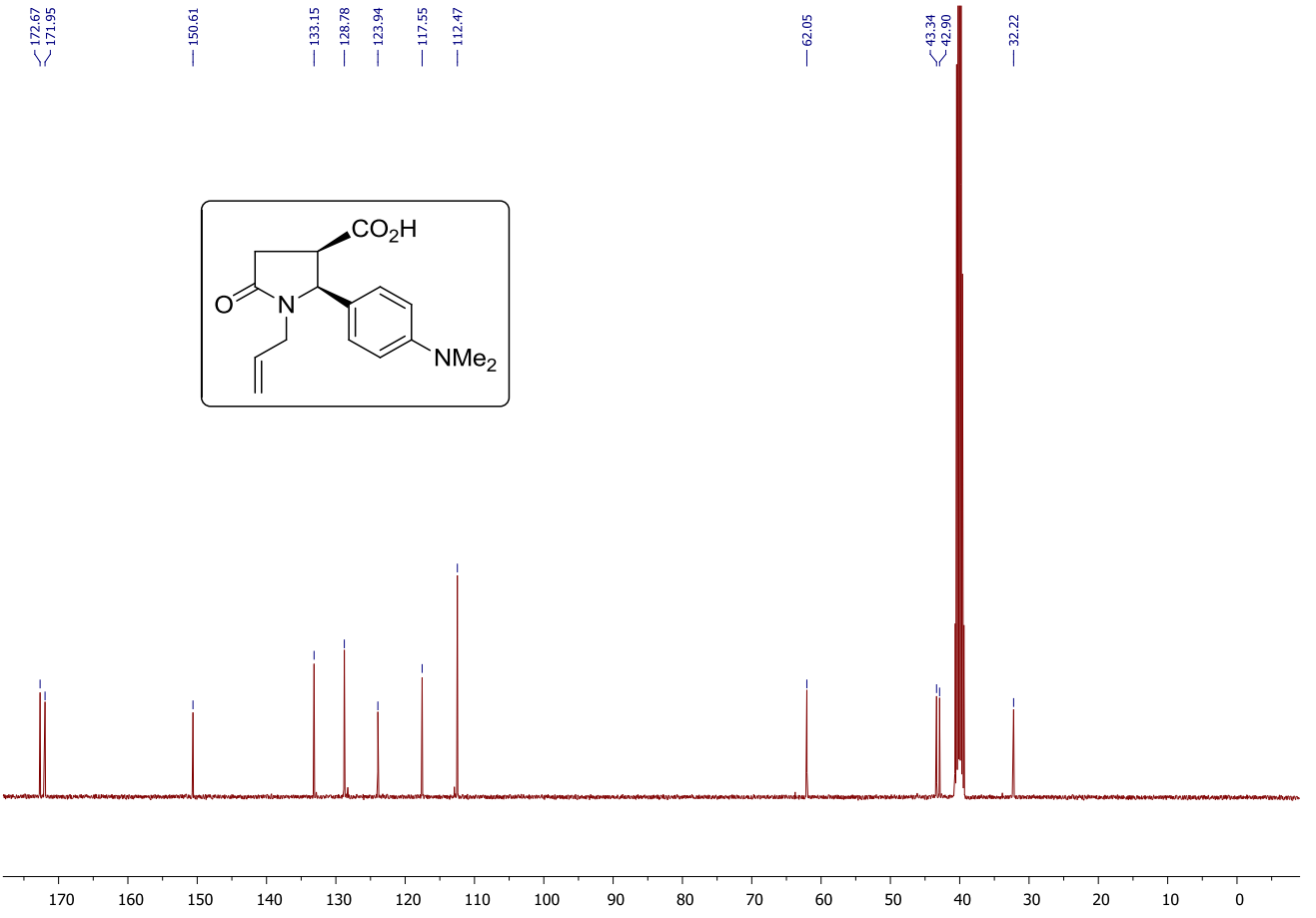


^{1}H and ^{13}C NMR spectra of ***cis*-4j**





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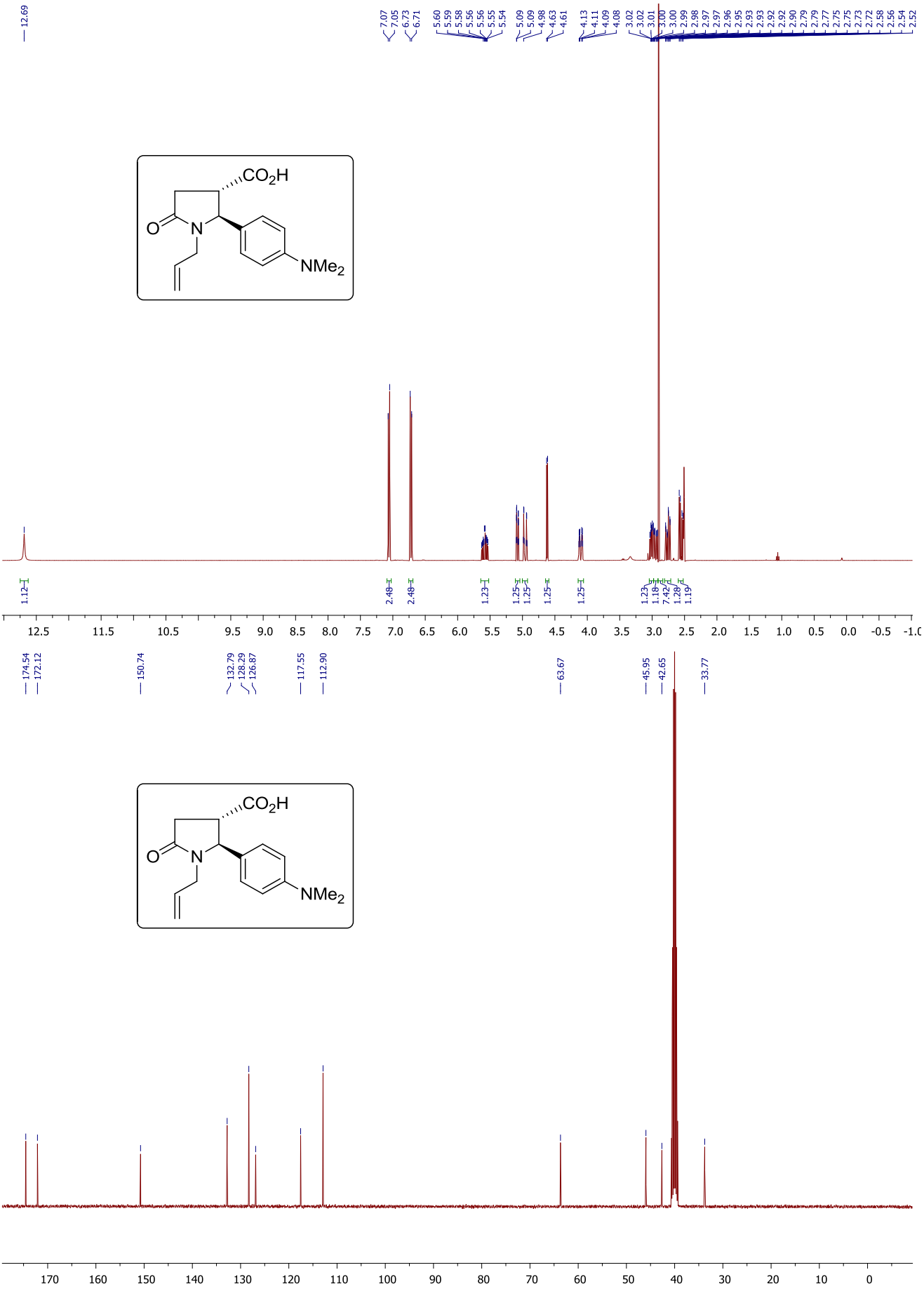

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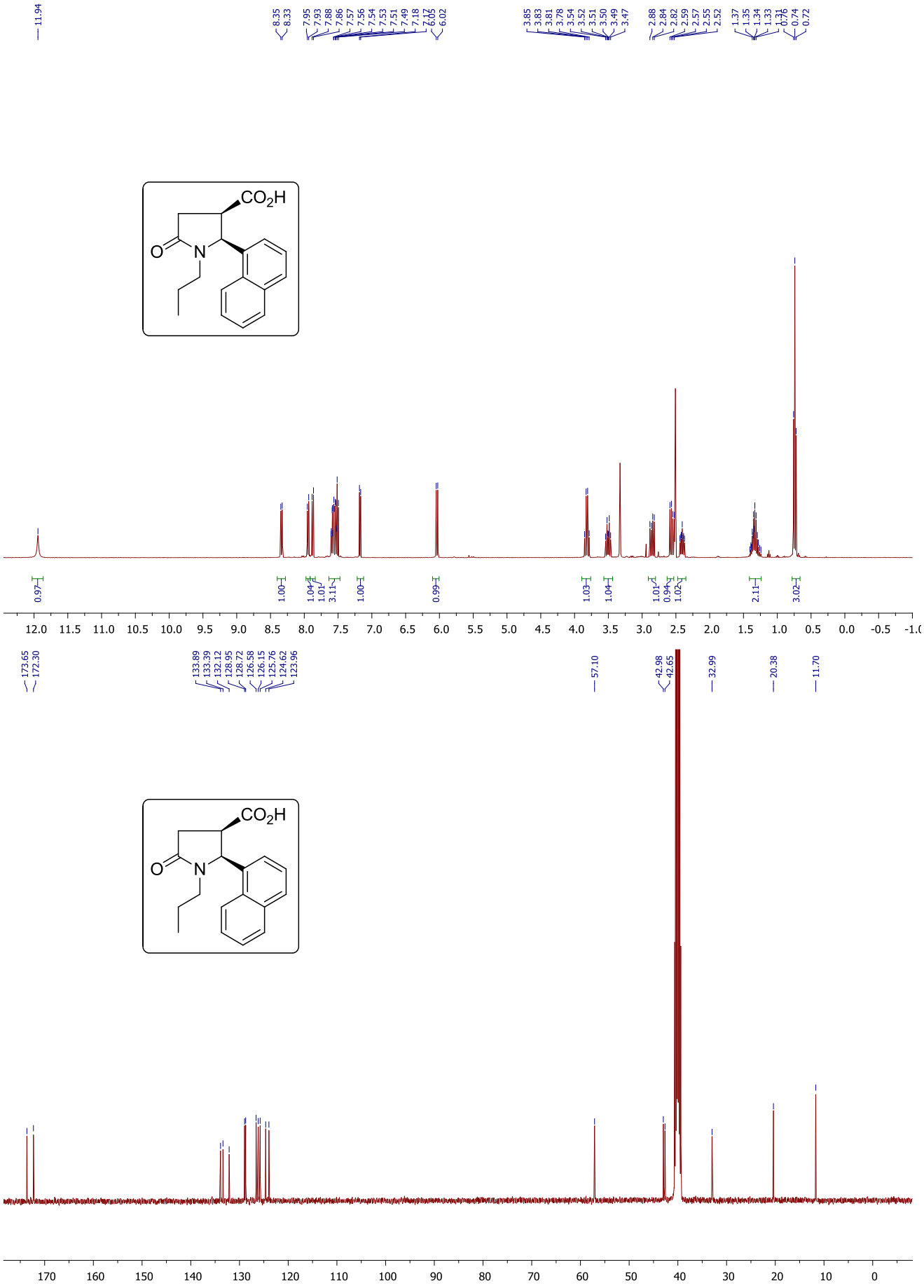

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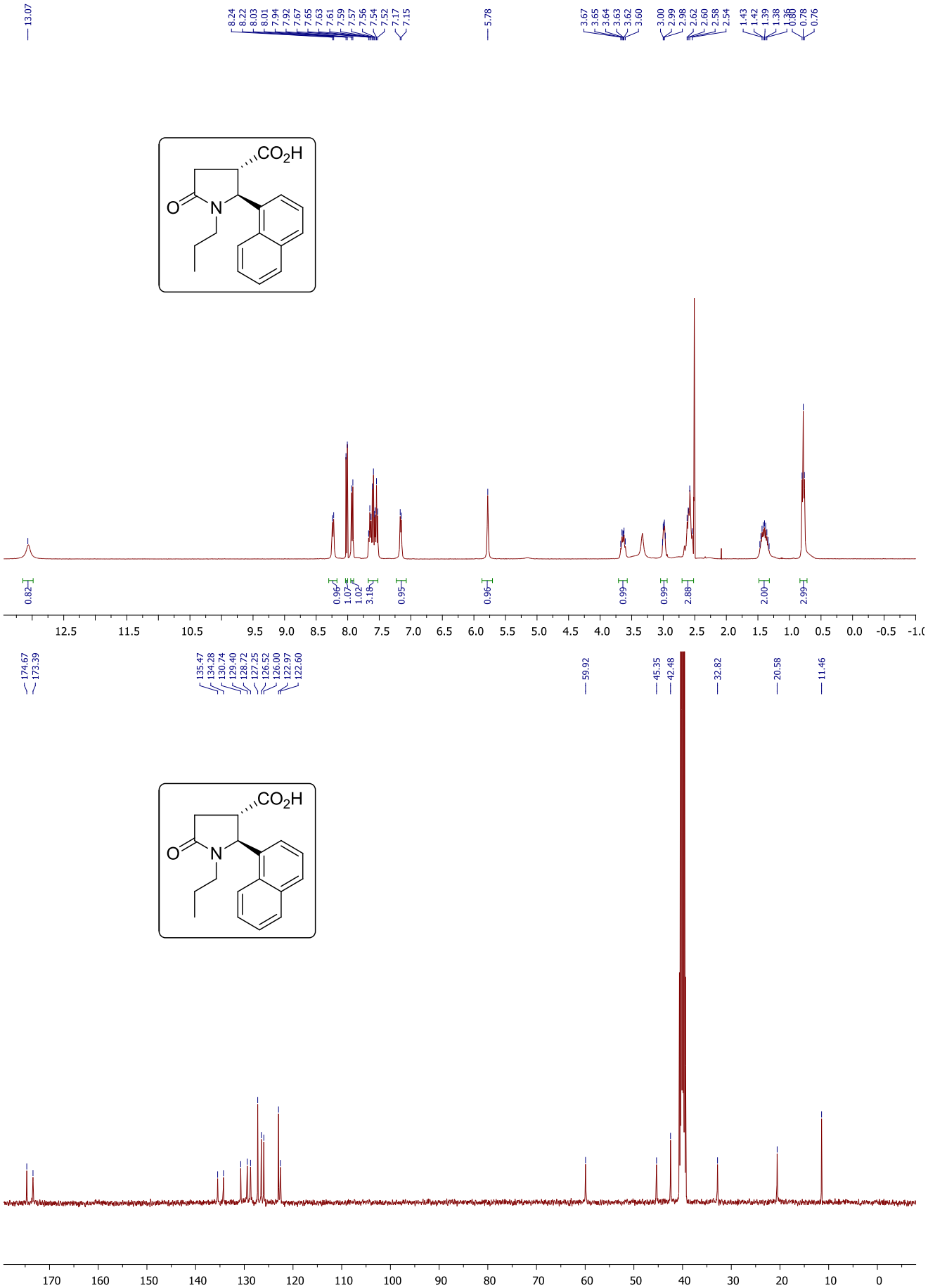
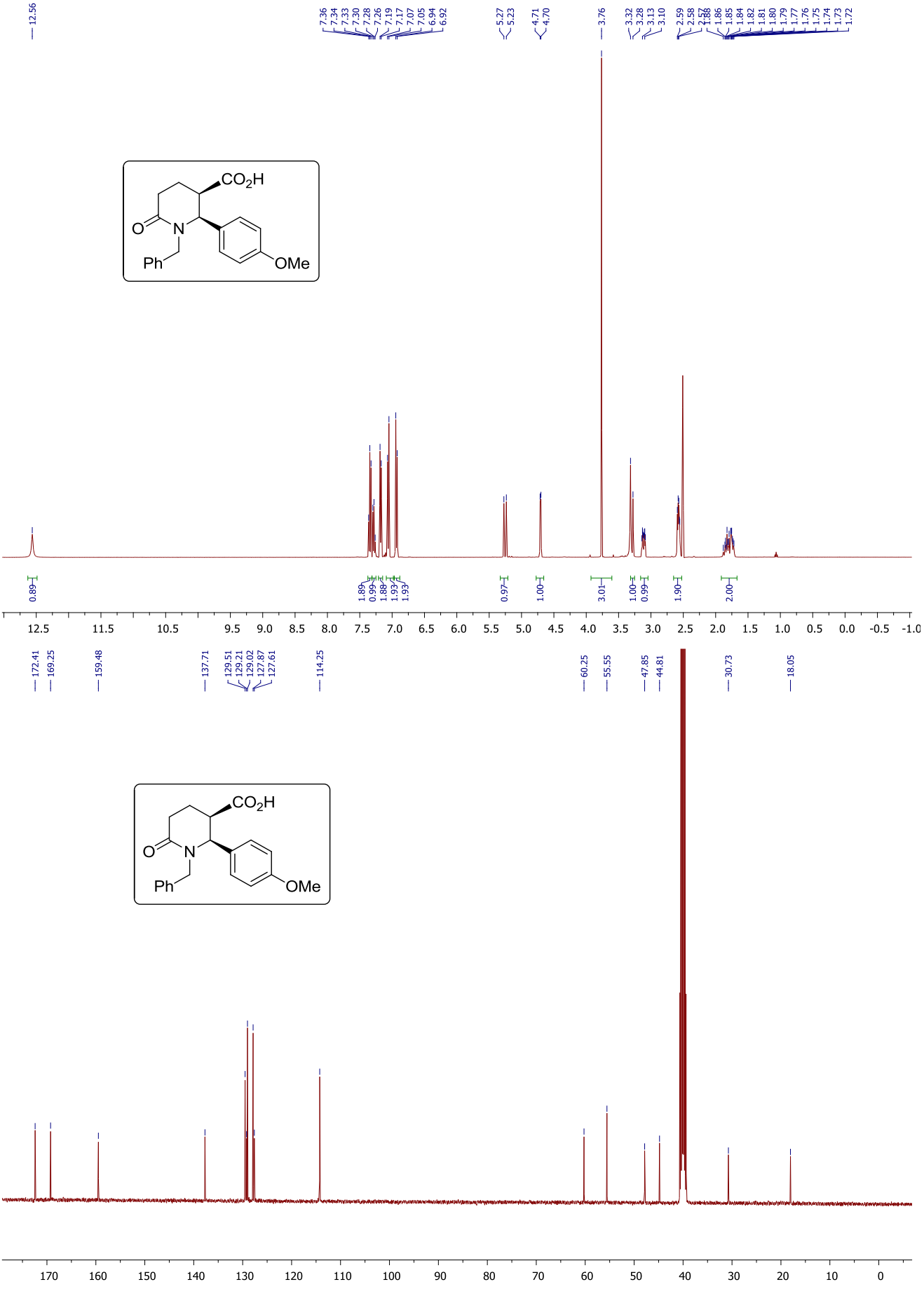


^{1}H and ^{13}C NMR spectra of ***cis*-5a**



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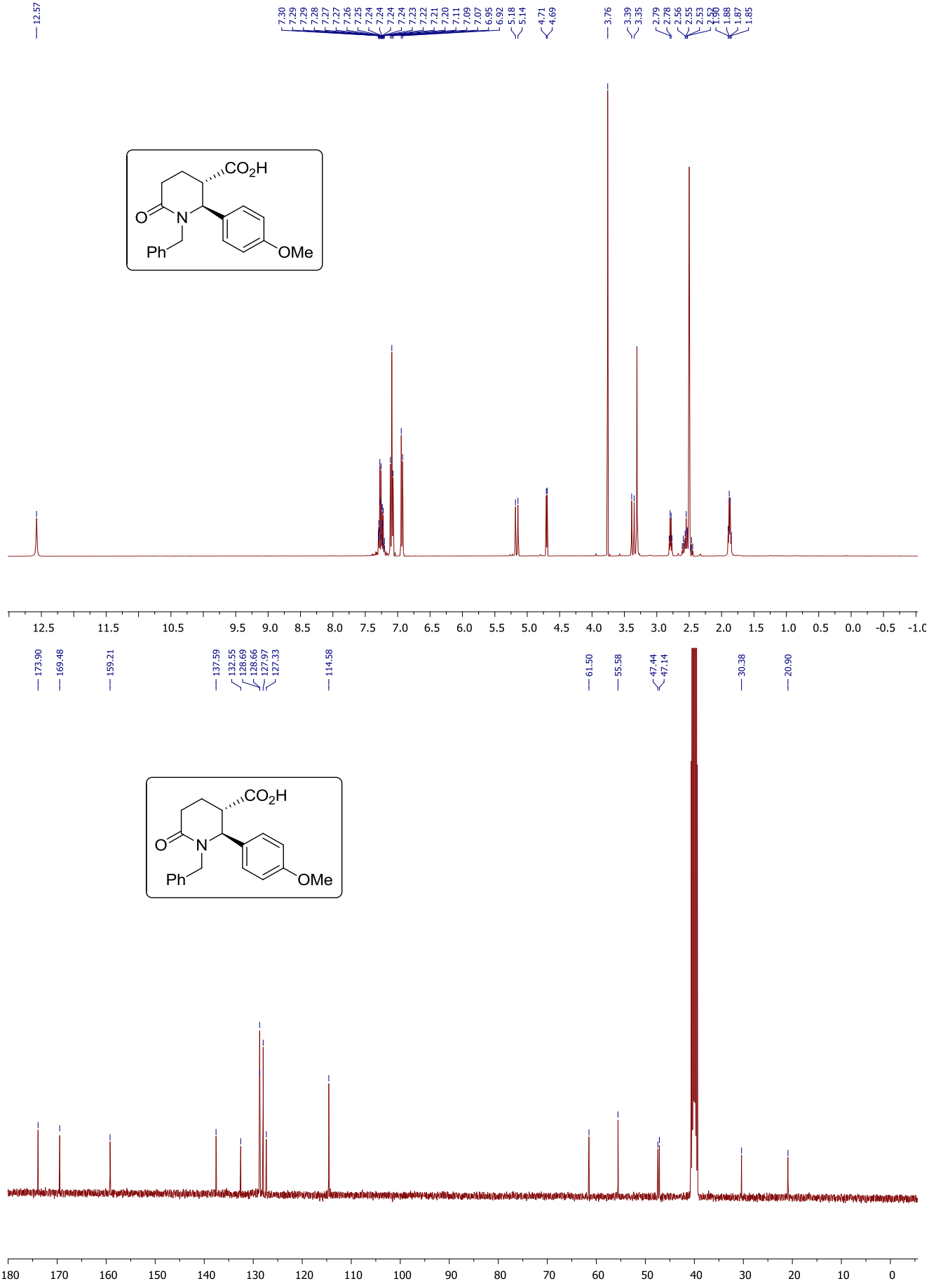
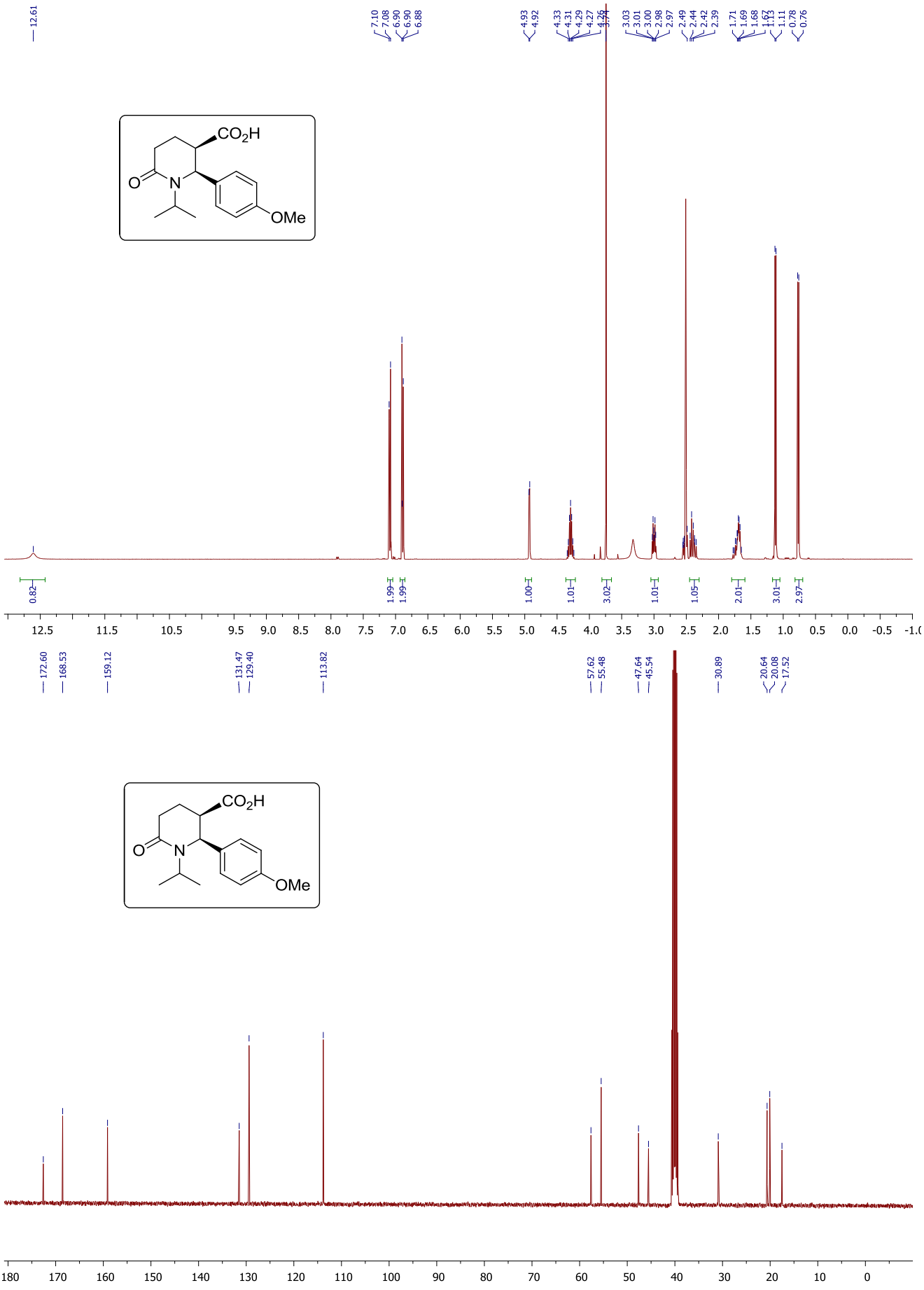
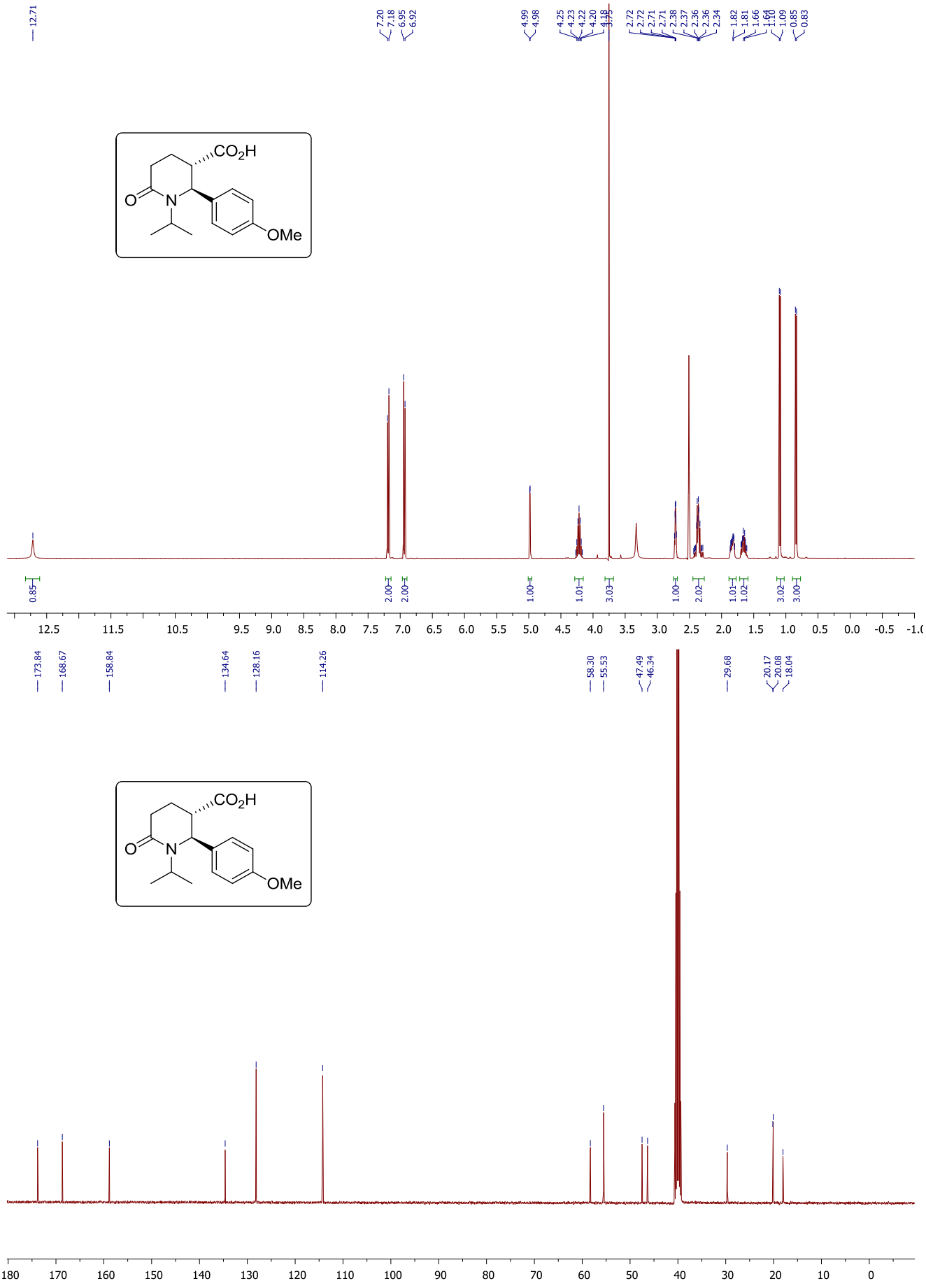


^{1}H and ^{13}C NMR spectra of ***cis*-5b**



^{1}H and ^{13}C NMR spectra of ***trans*-5b**



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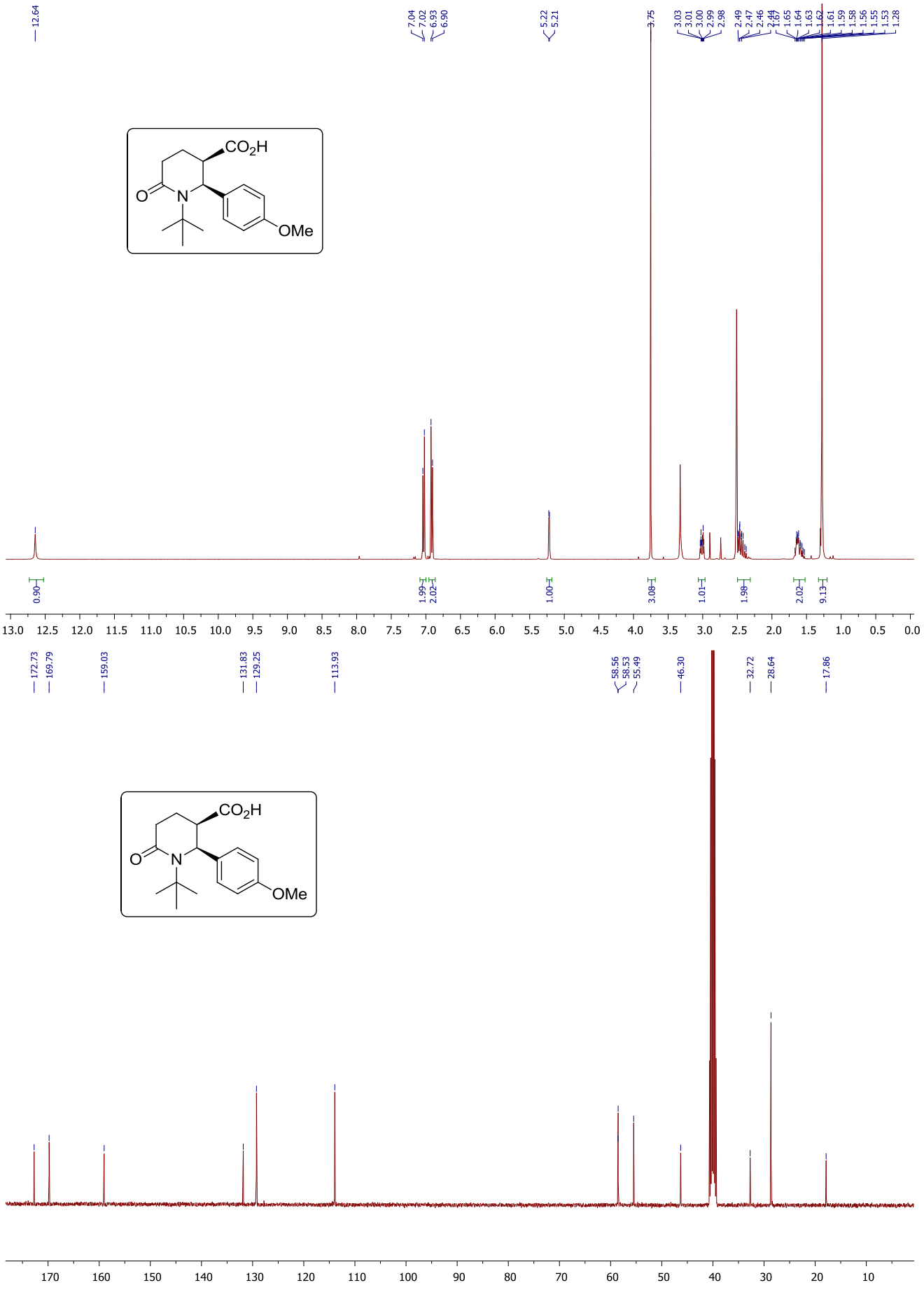

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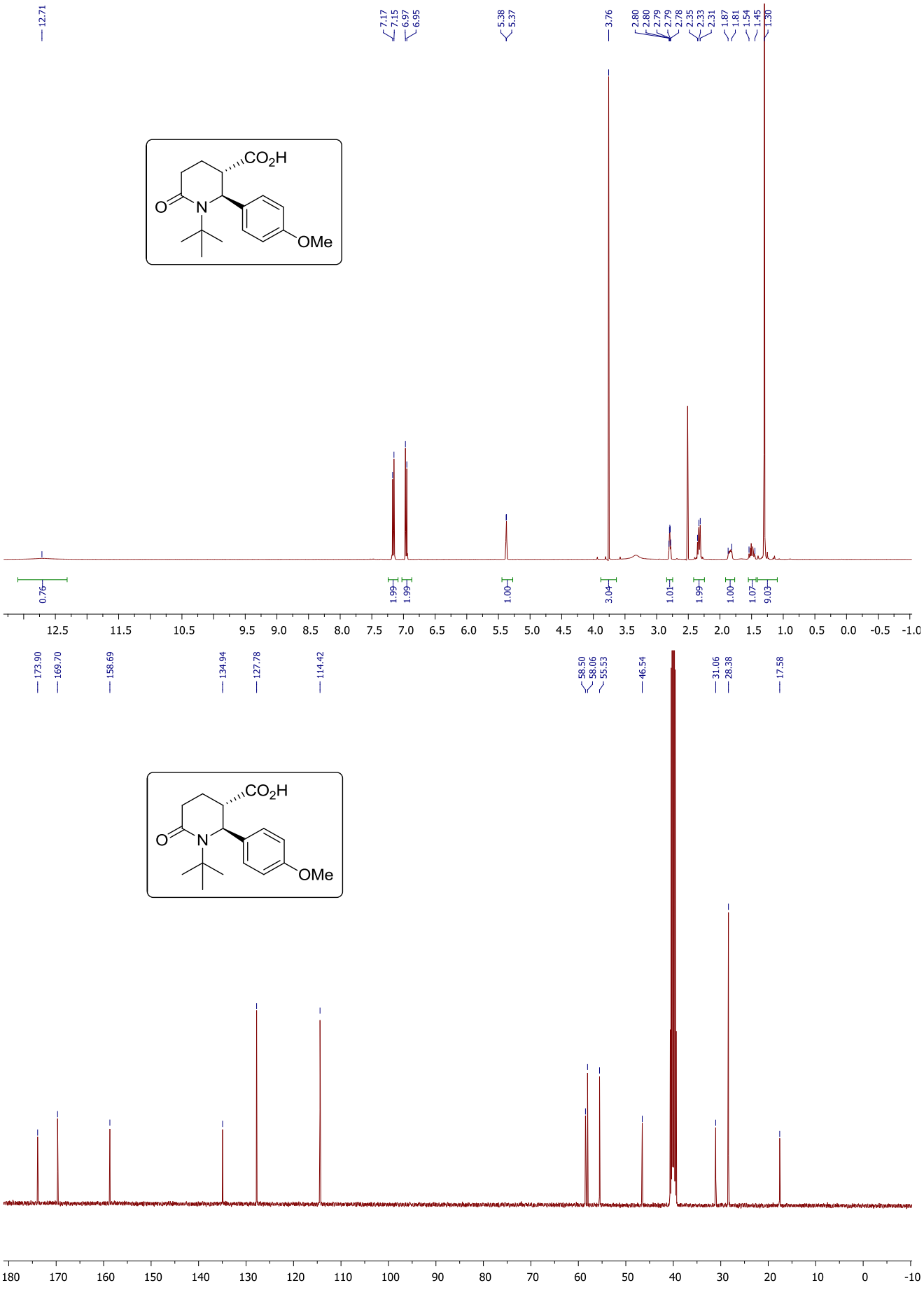

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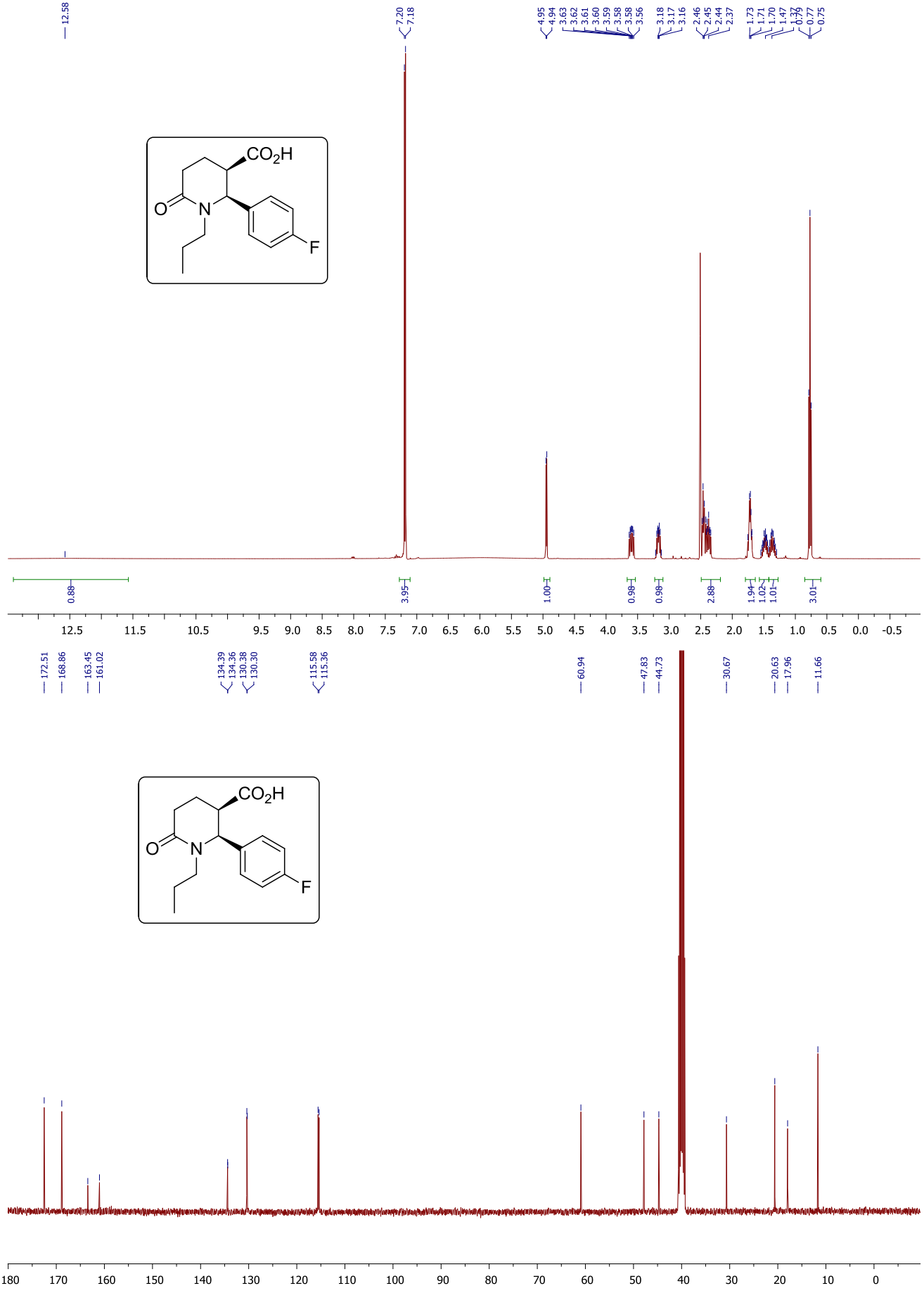

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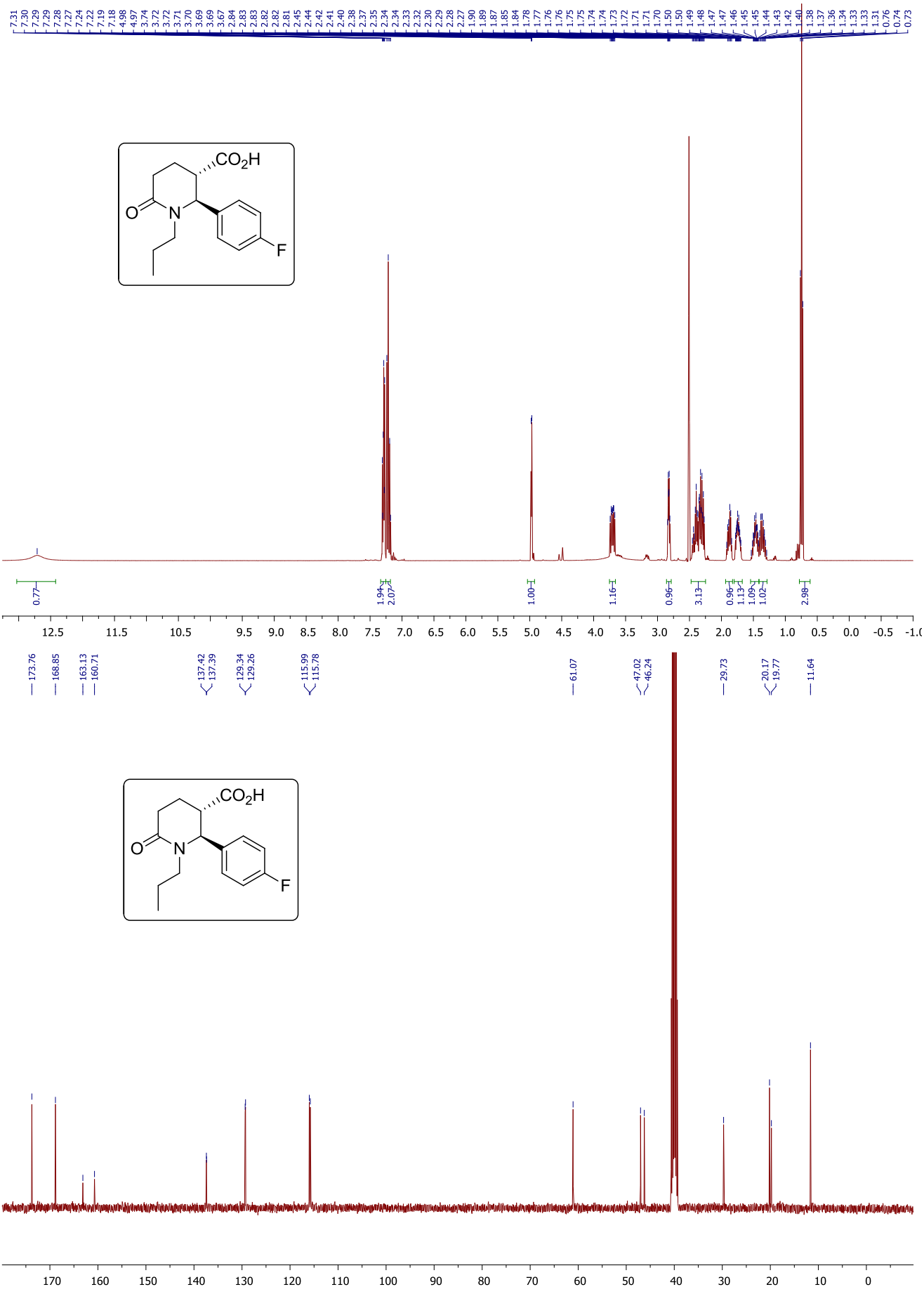
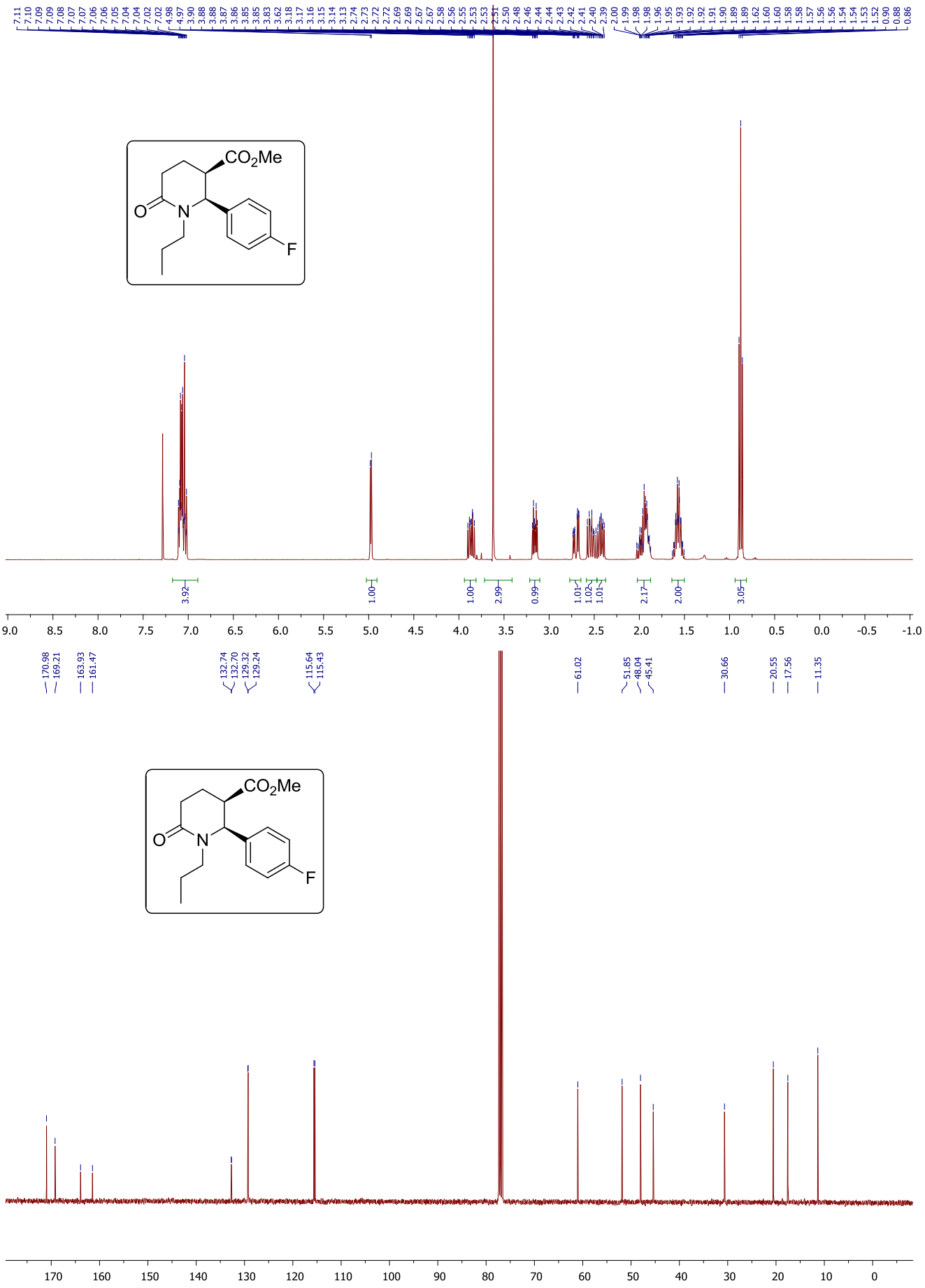
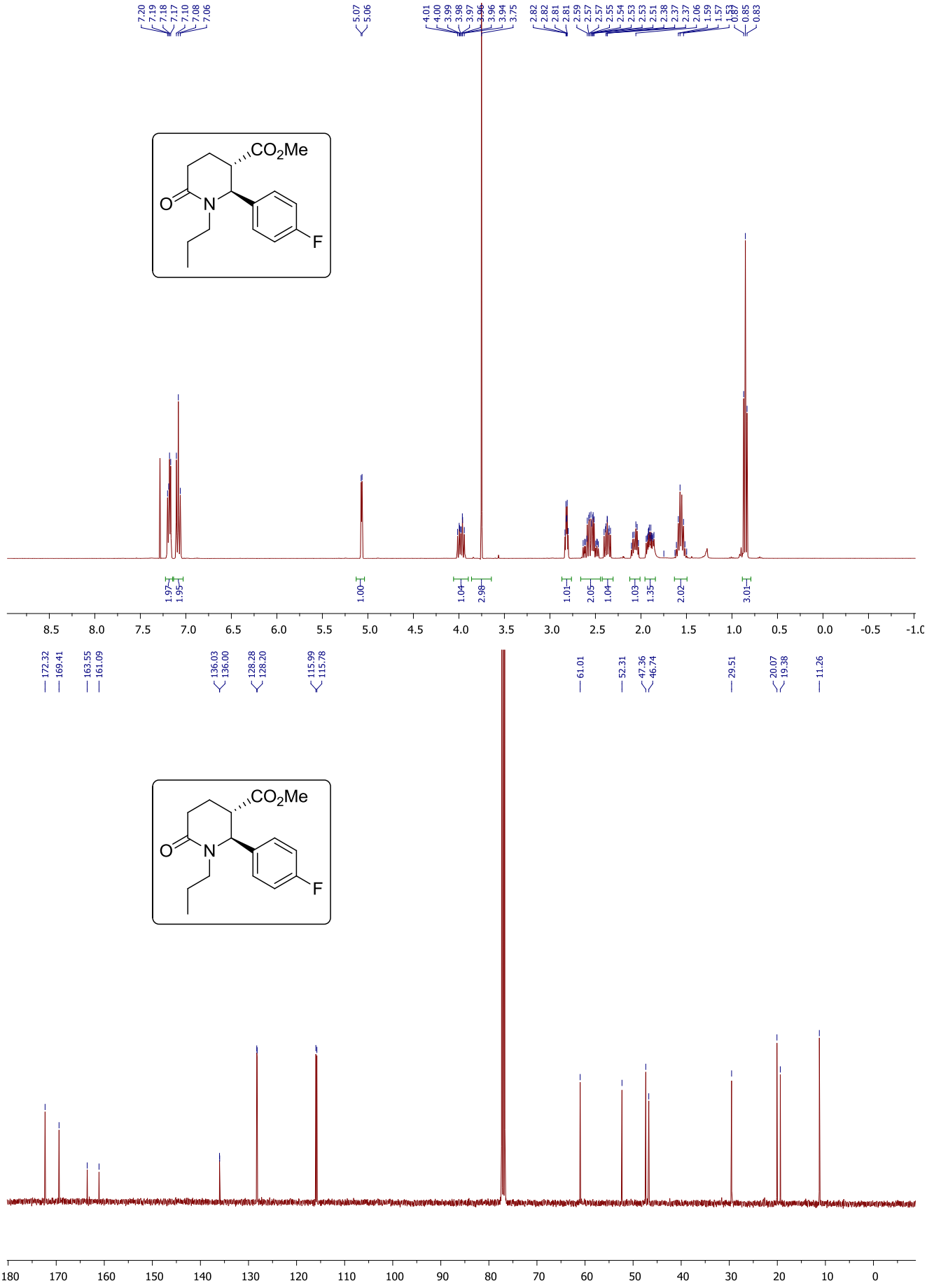


^{1}H and ^{13}C NMR spectra of ***cis*-6d**



^{1}H and ^{13}C NMR spectra of ***trans*-6d**



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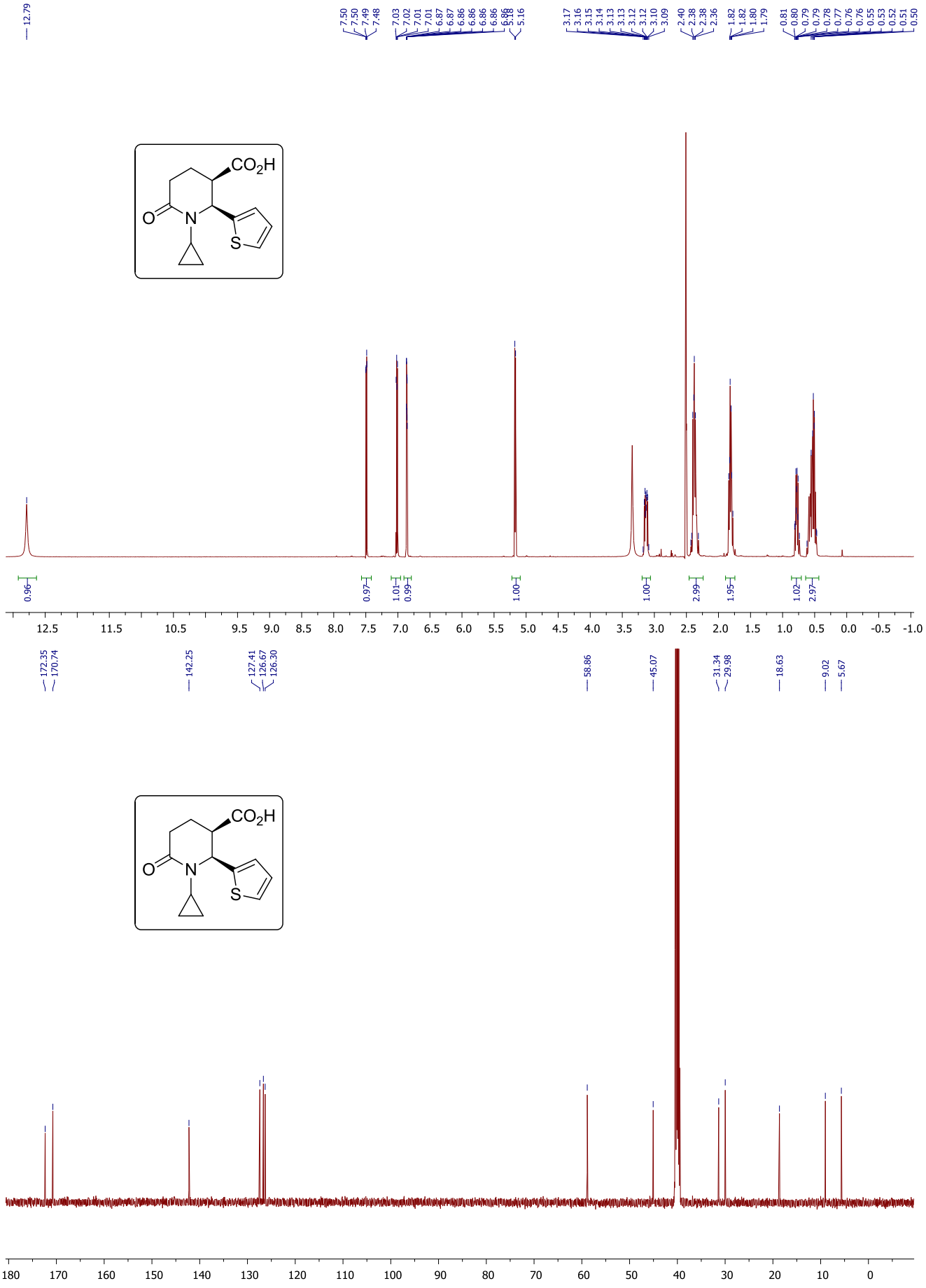

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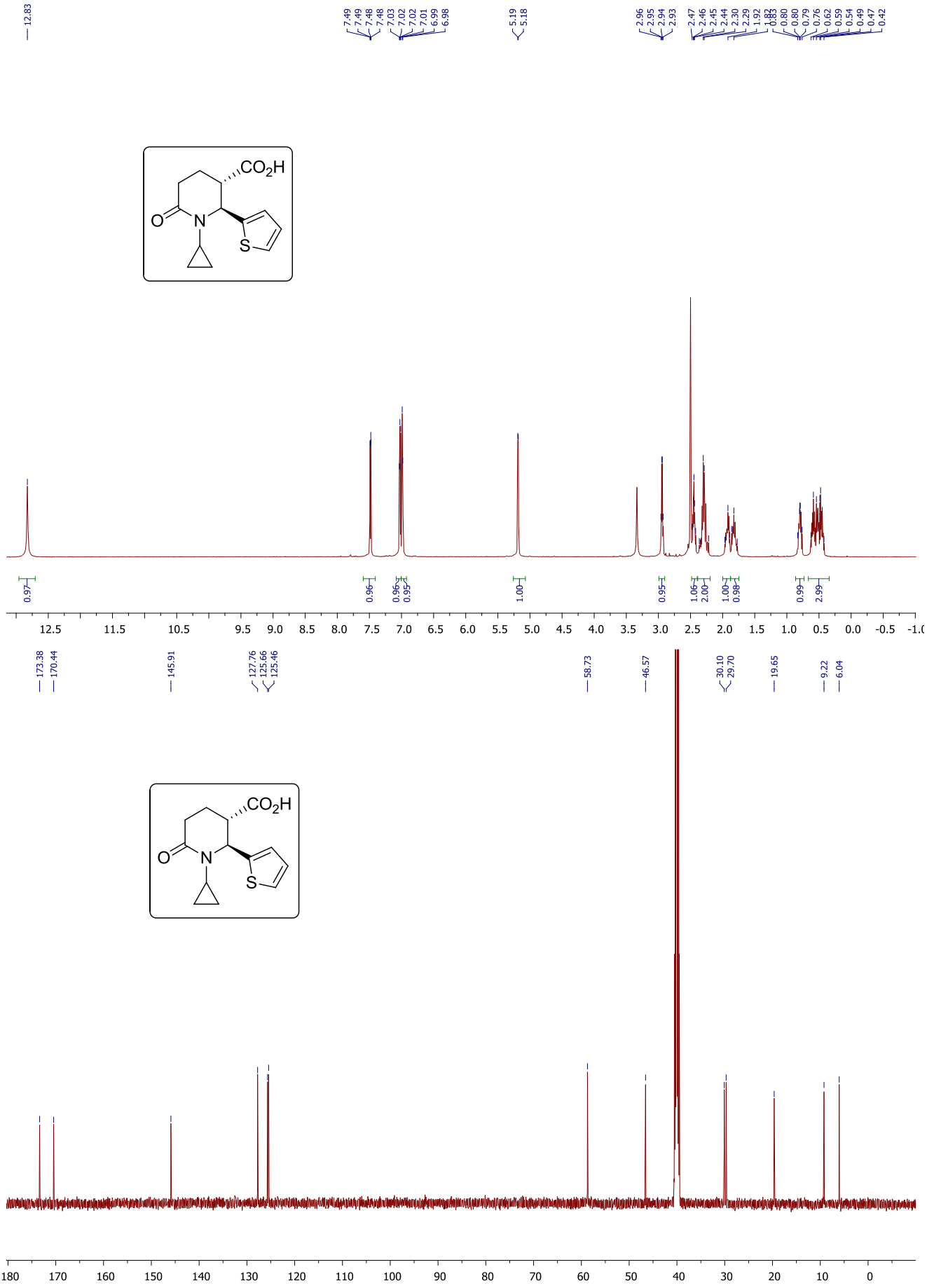

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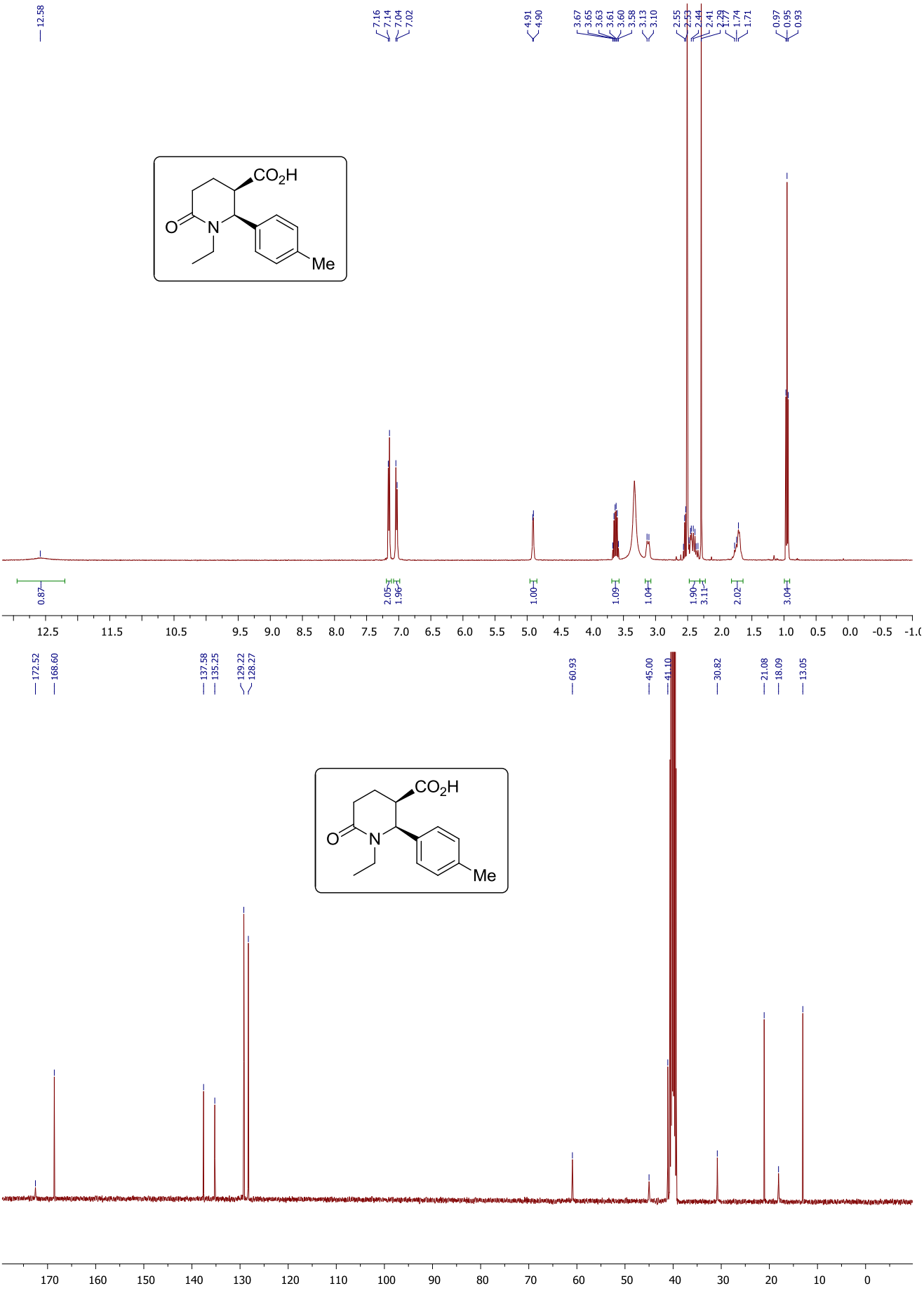

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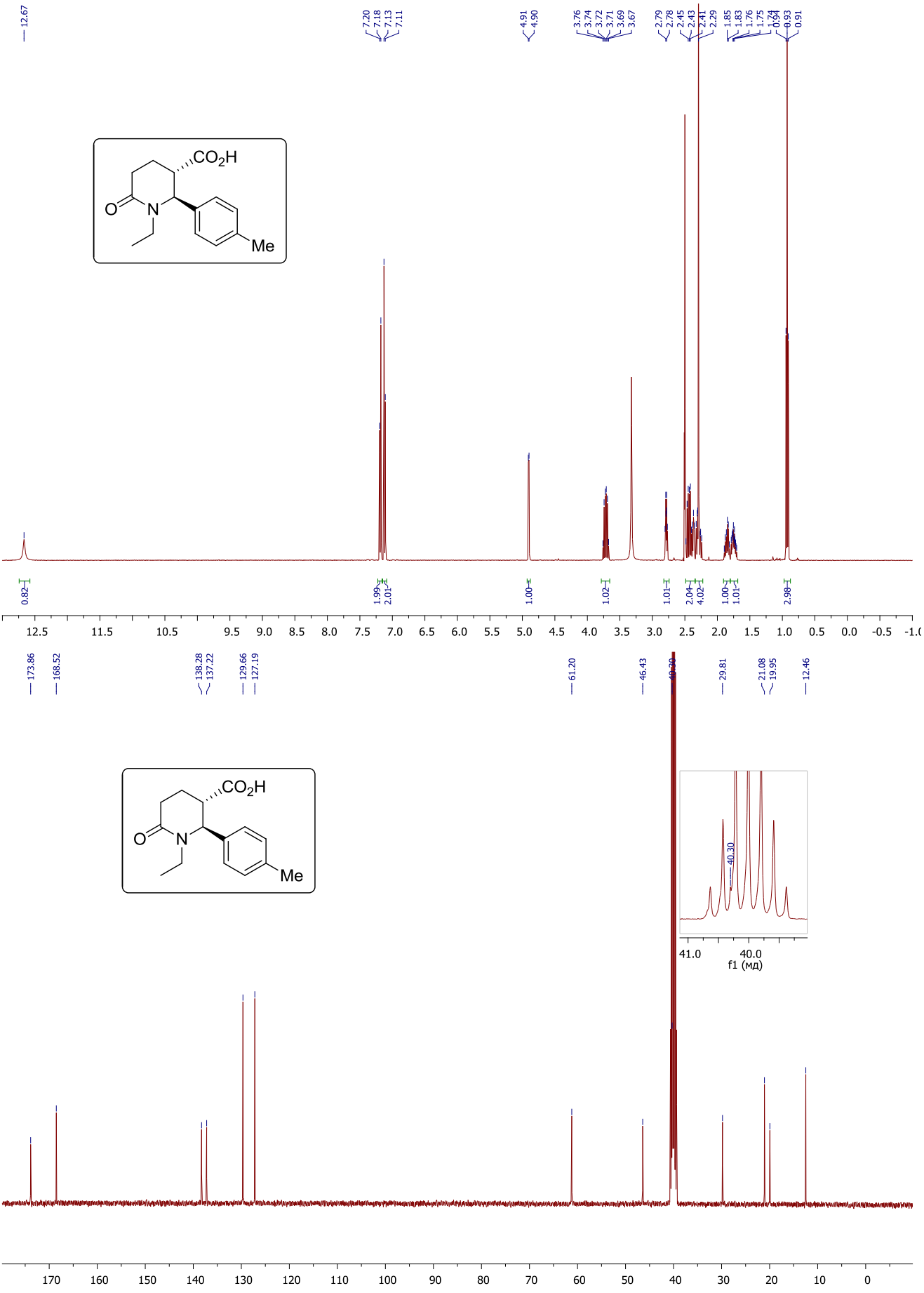
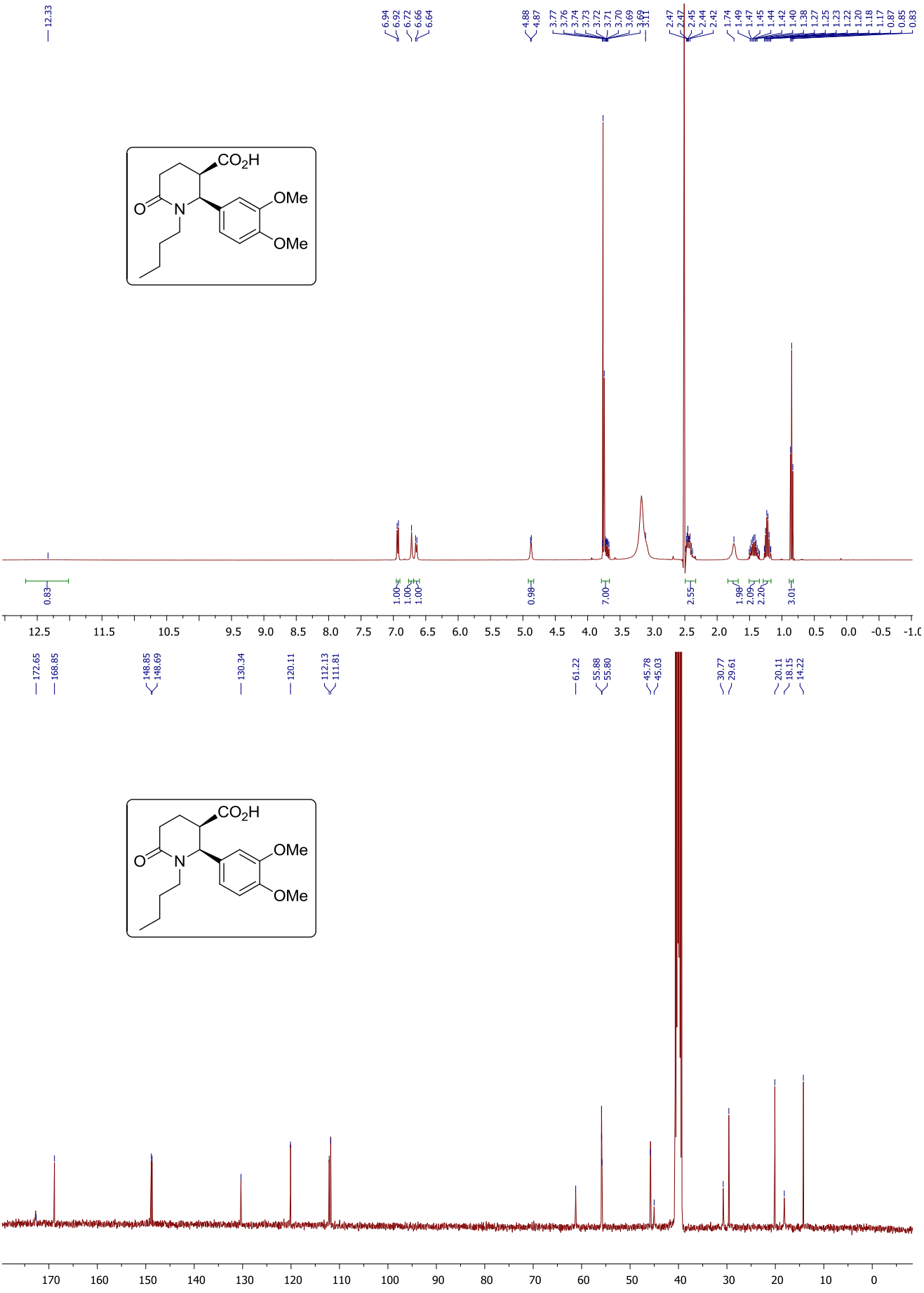


^{1}H and ^{13}C NMR spectra of ***cis*-5g**



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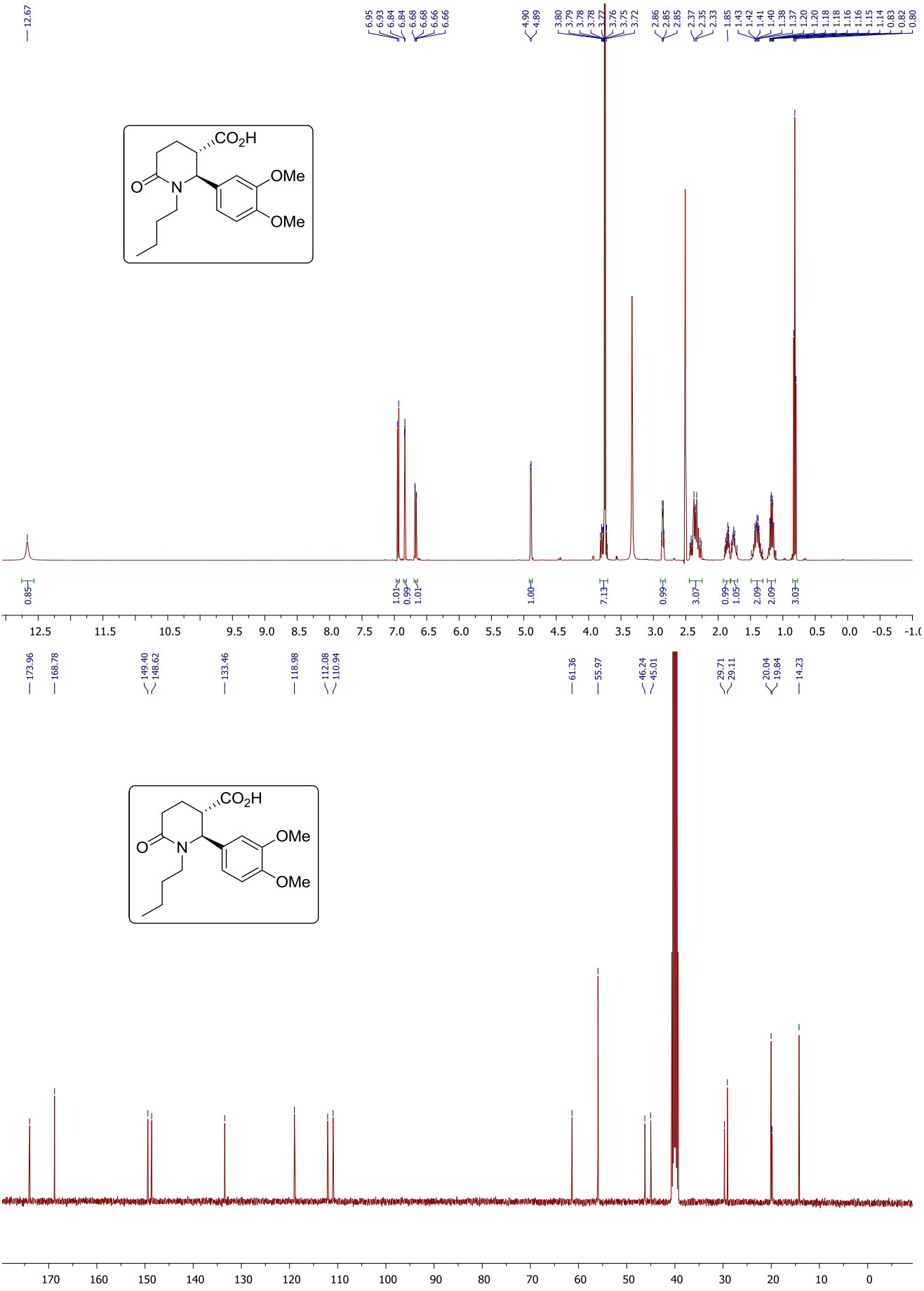
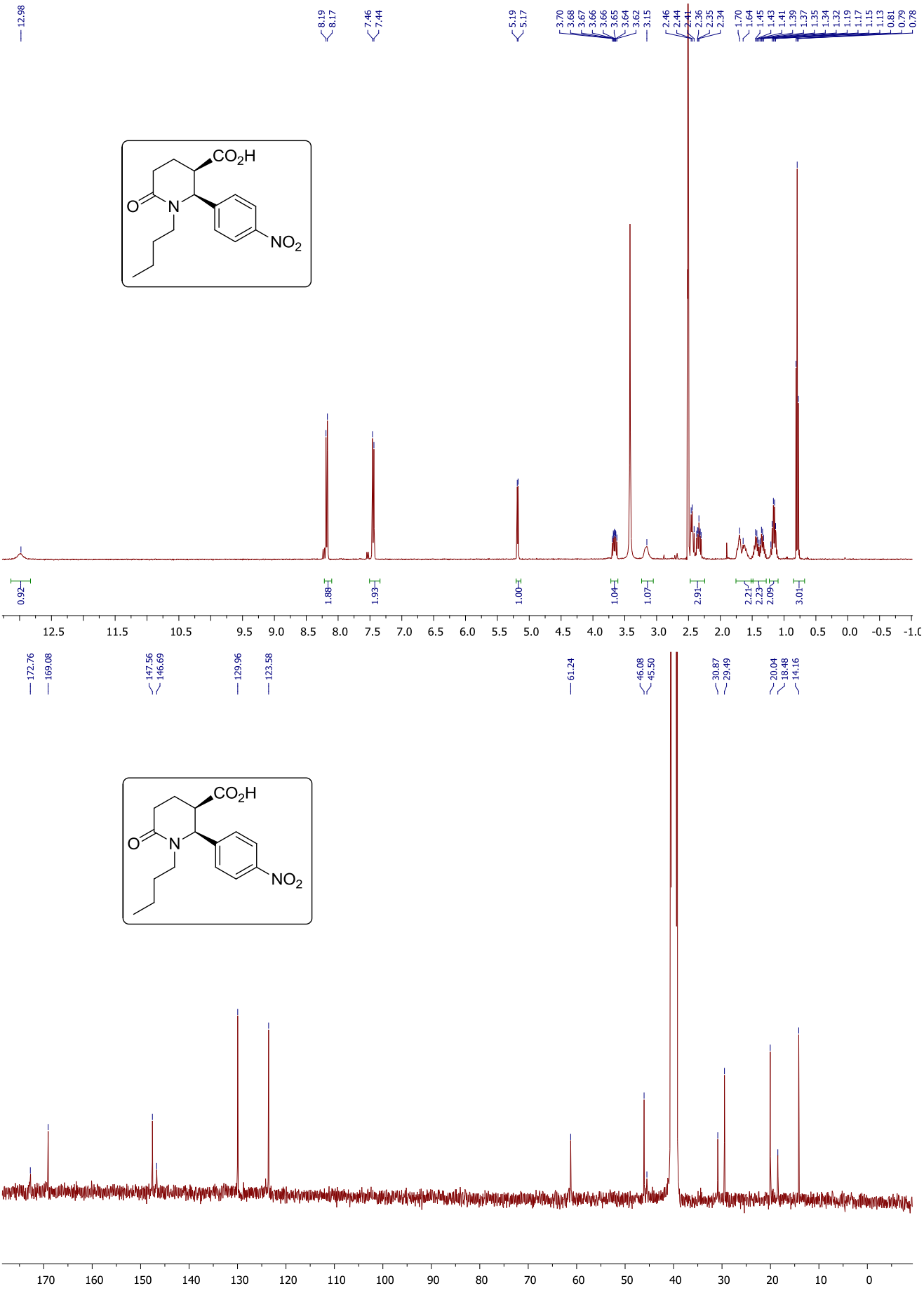


^{1}H and ^{13}C NMR spectra of ***cis*-5h**



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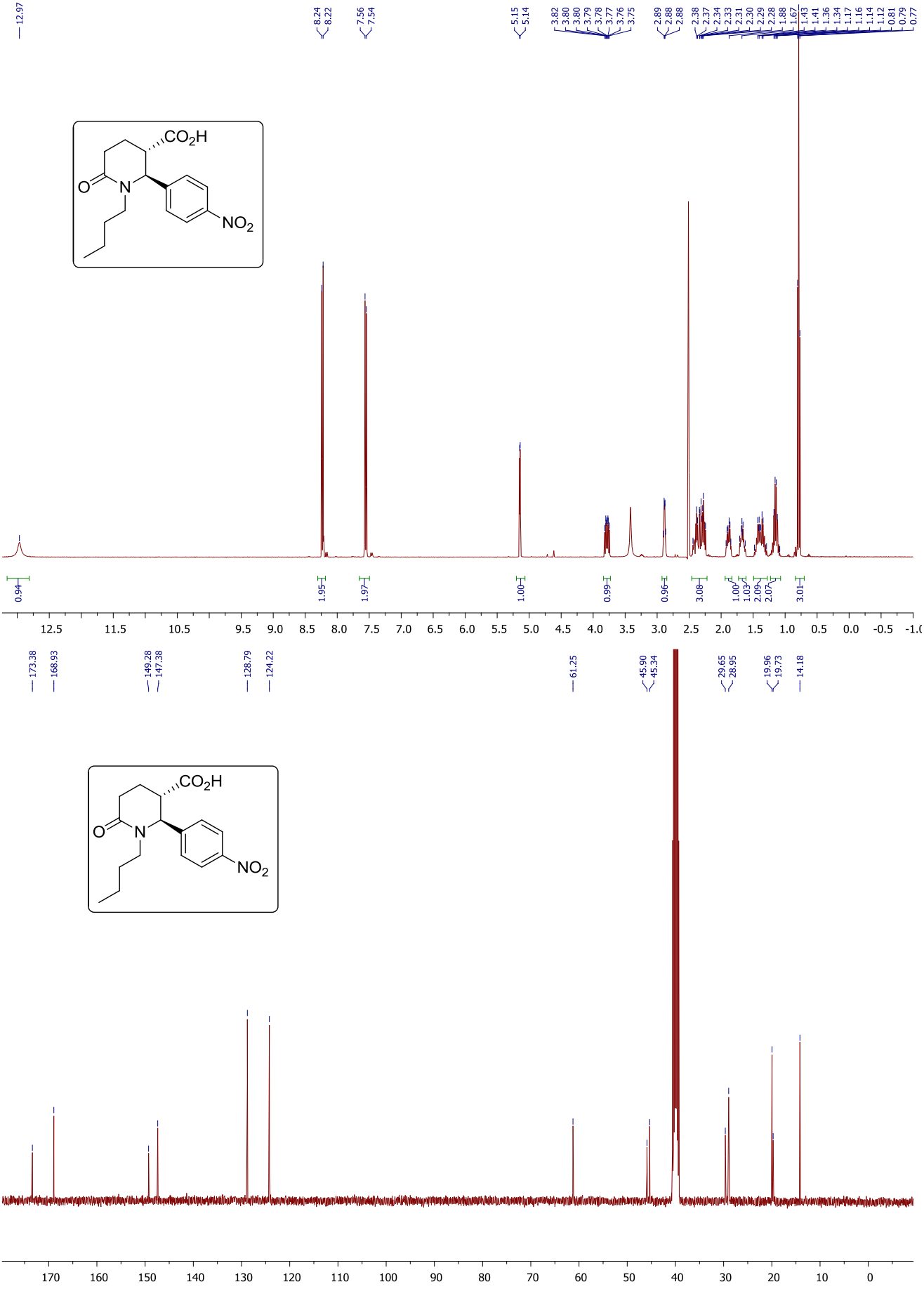
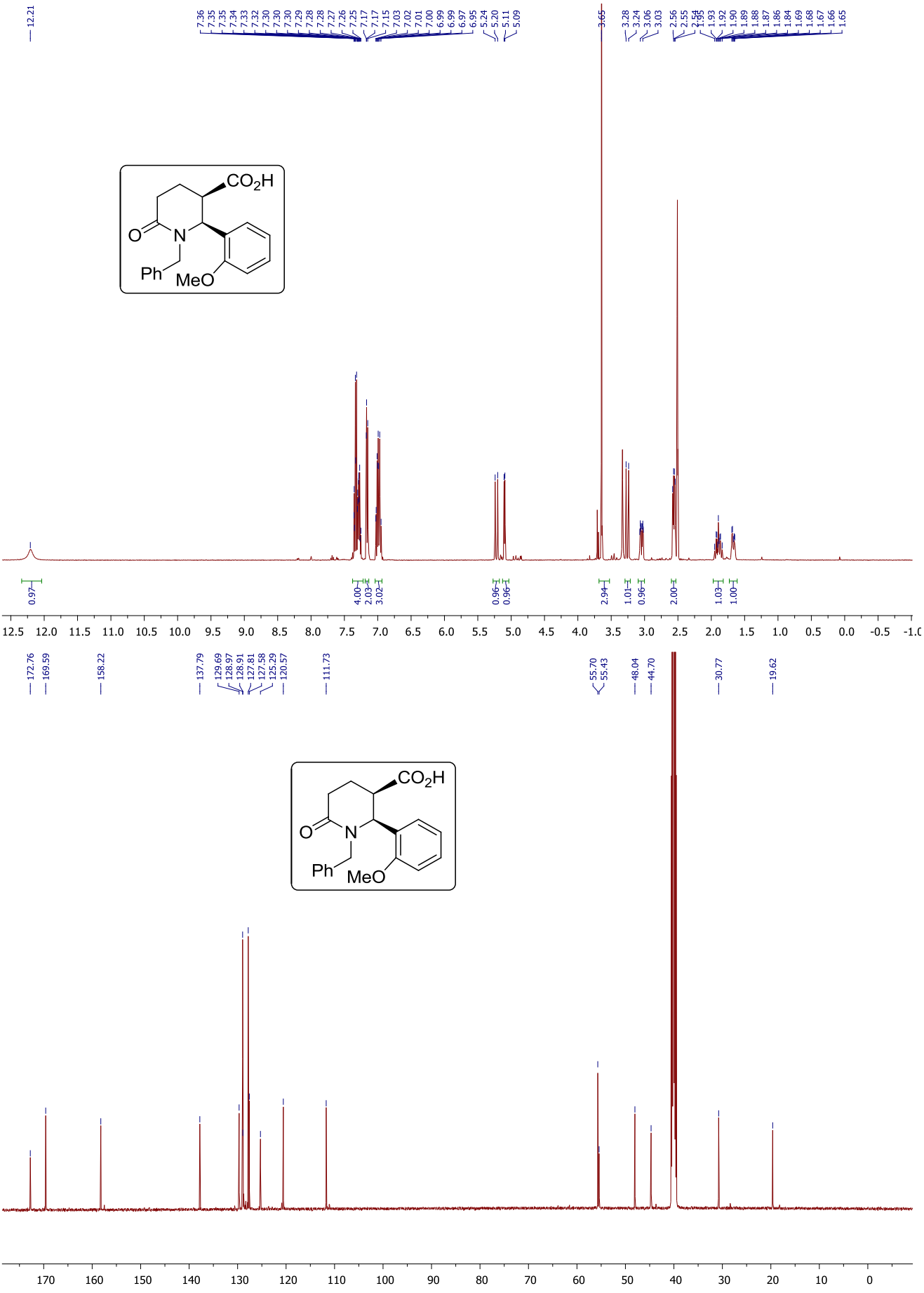
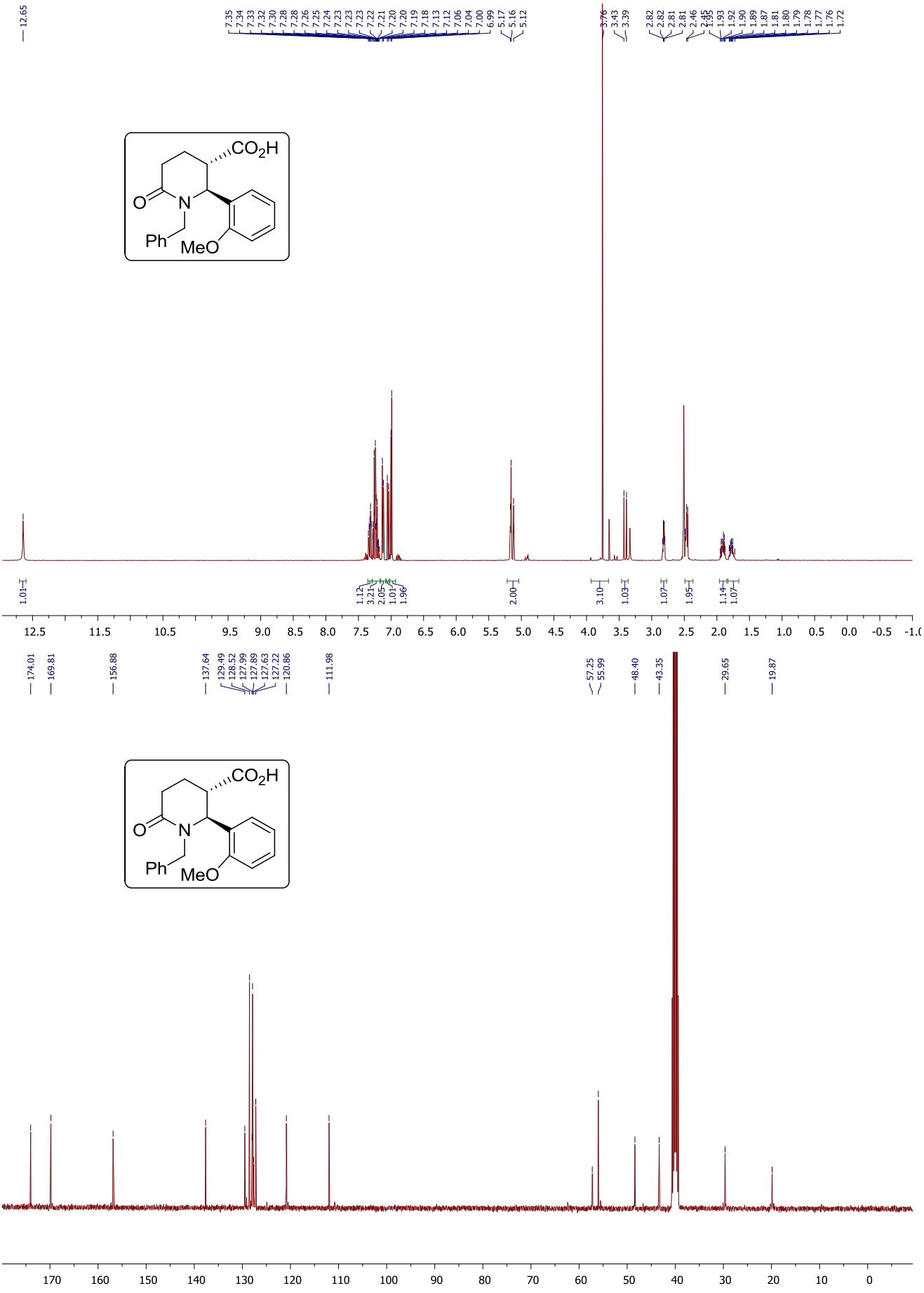


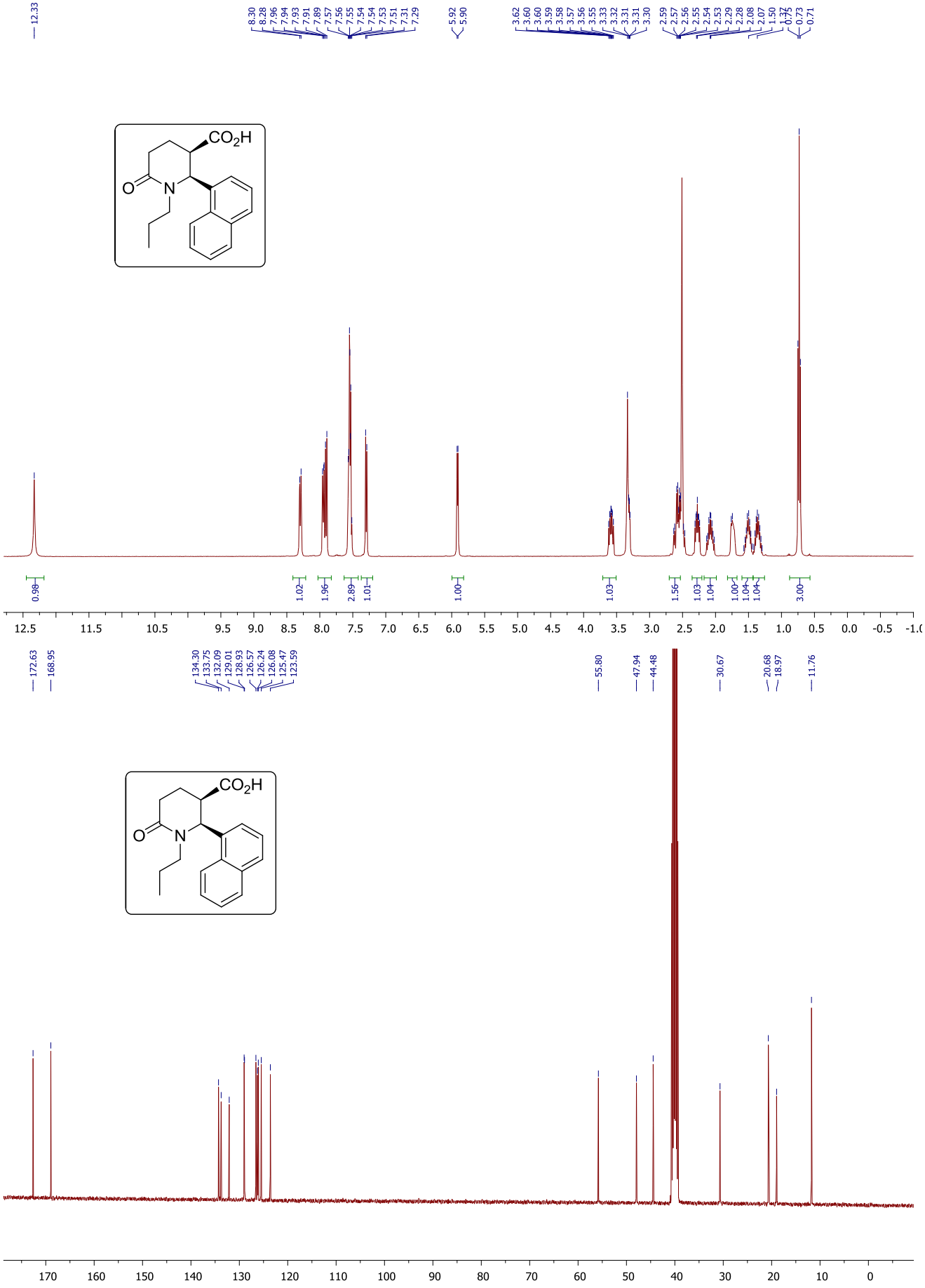
^{1}H and ^{13}C NMR spectra of ***cis*-5i**



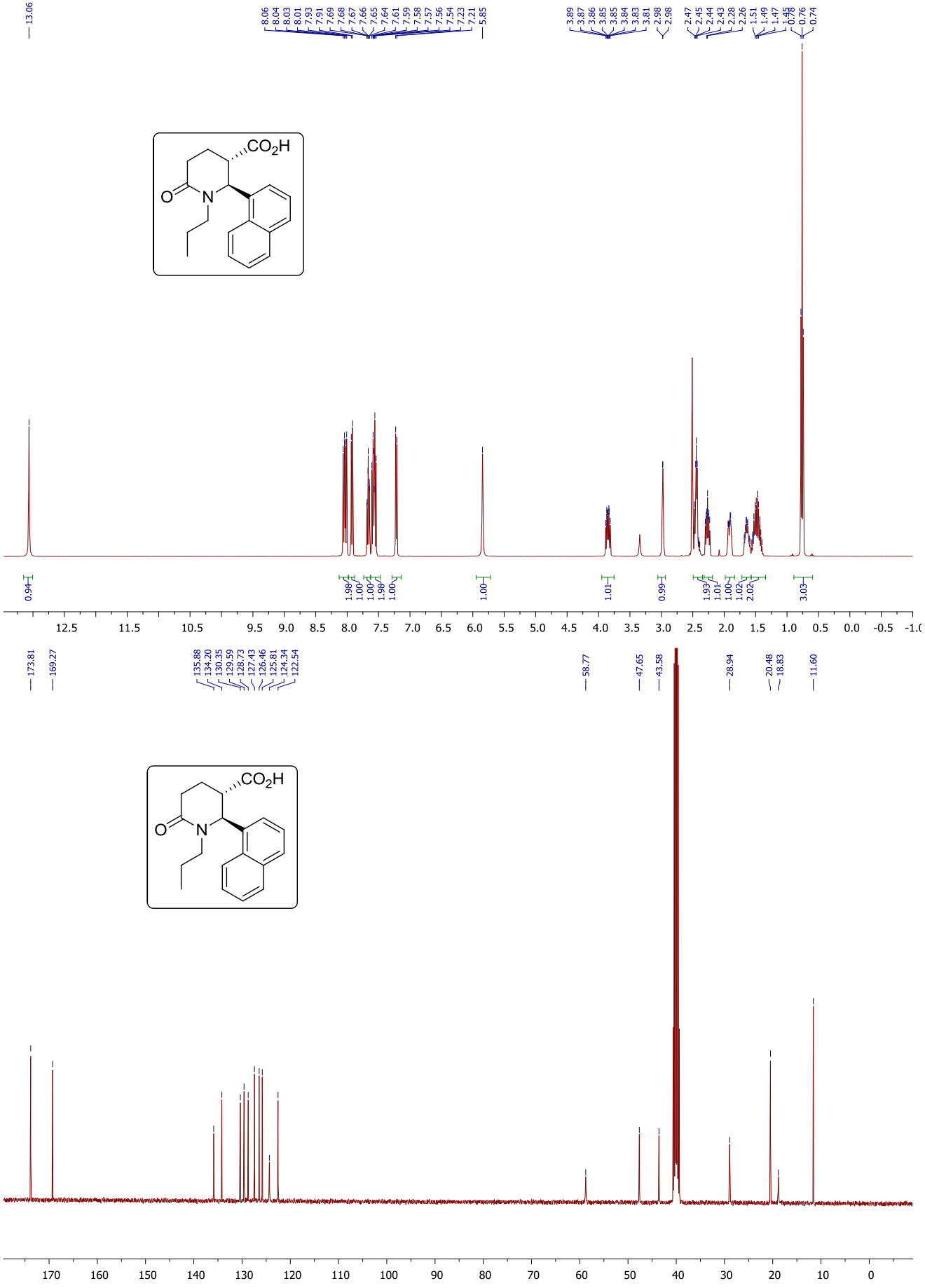
^{1}H and ^{13}C NMR spectra of ***trans*-5i**



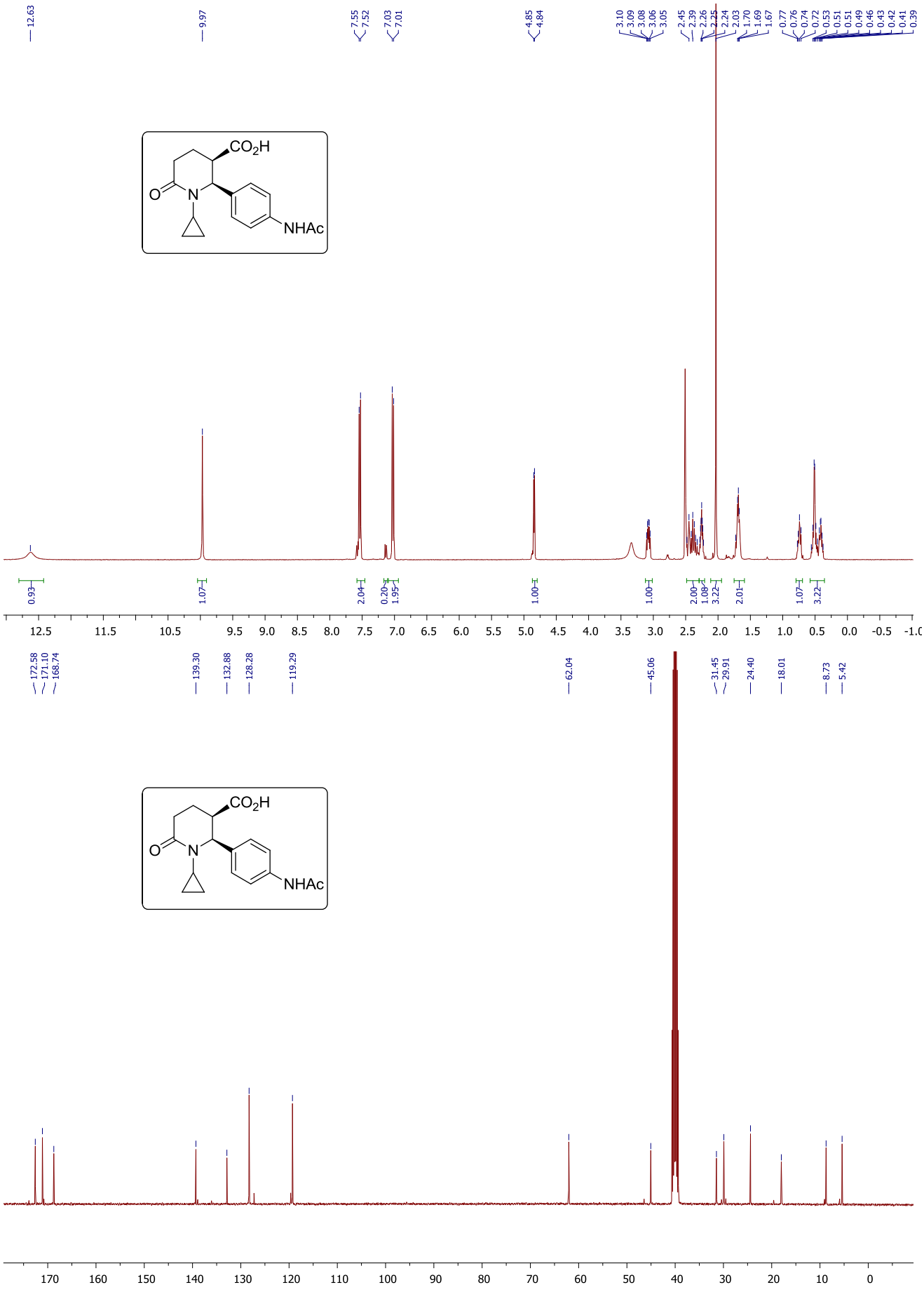
^{1}H and ^{13}C NMR spectra of ***cis*-5j**



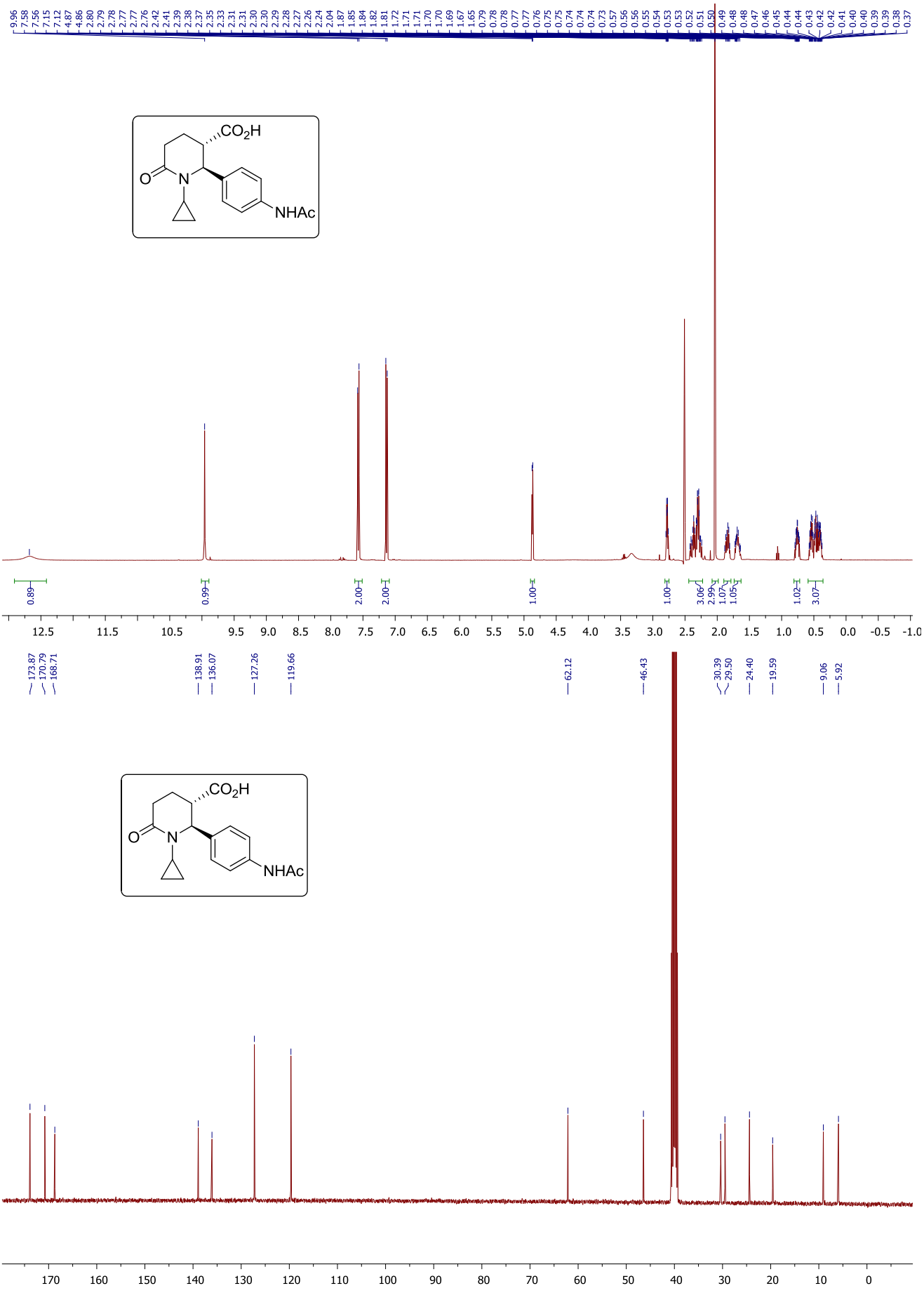
^{1}H and ^{13}C NMR spectra of ***trans*-5j**



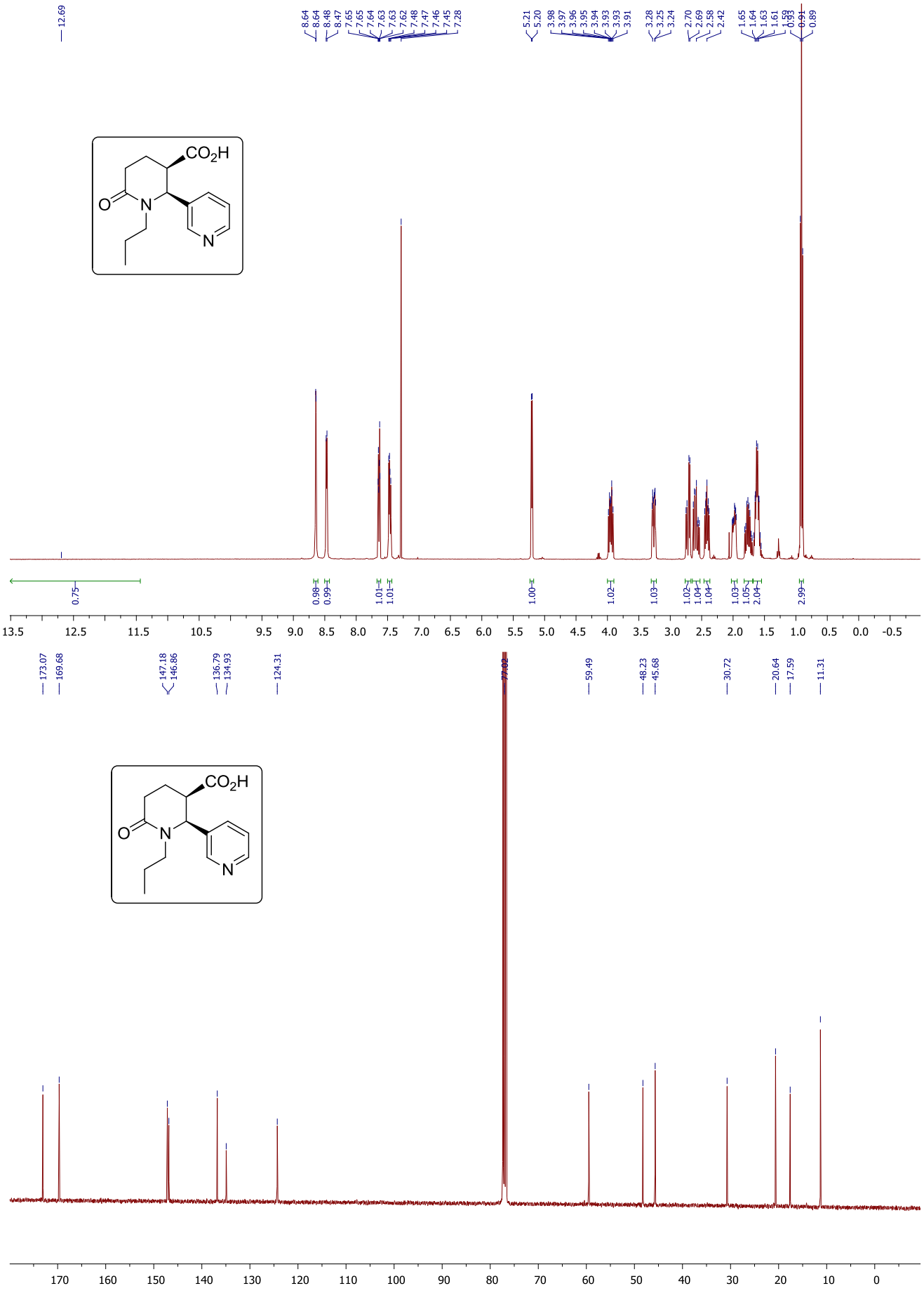
^{1}H and ^{13}C NMR spectra of ***cis*-5k**



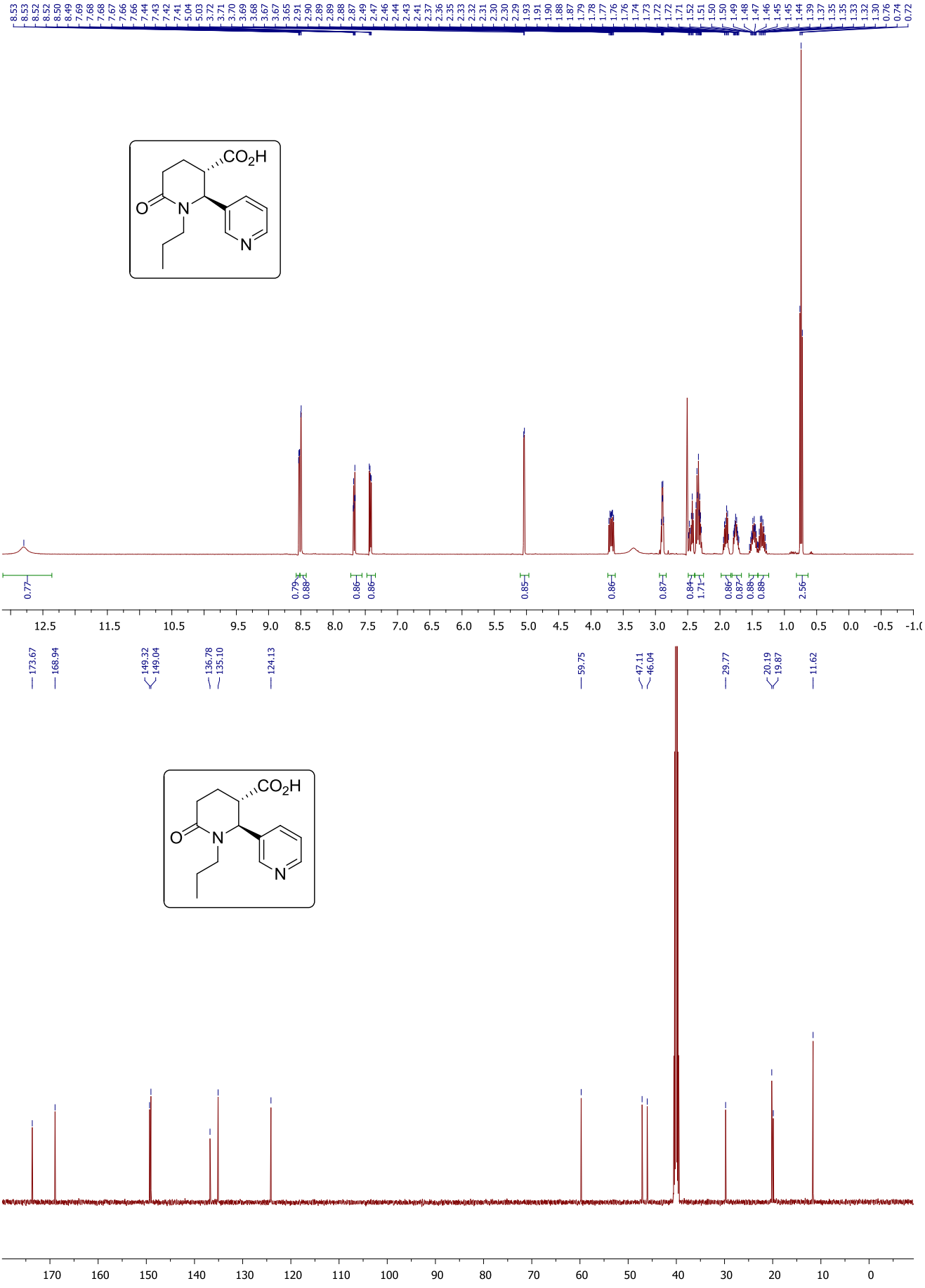
^{1}H and ^{13}C NMR spectra of ***trans*-5k**



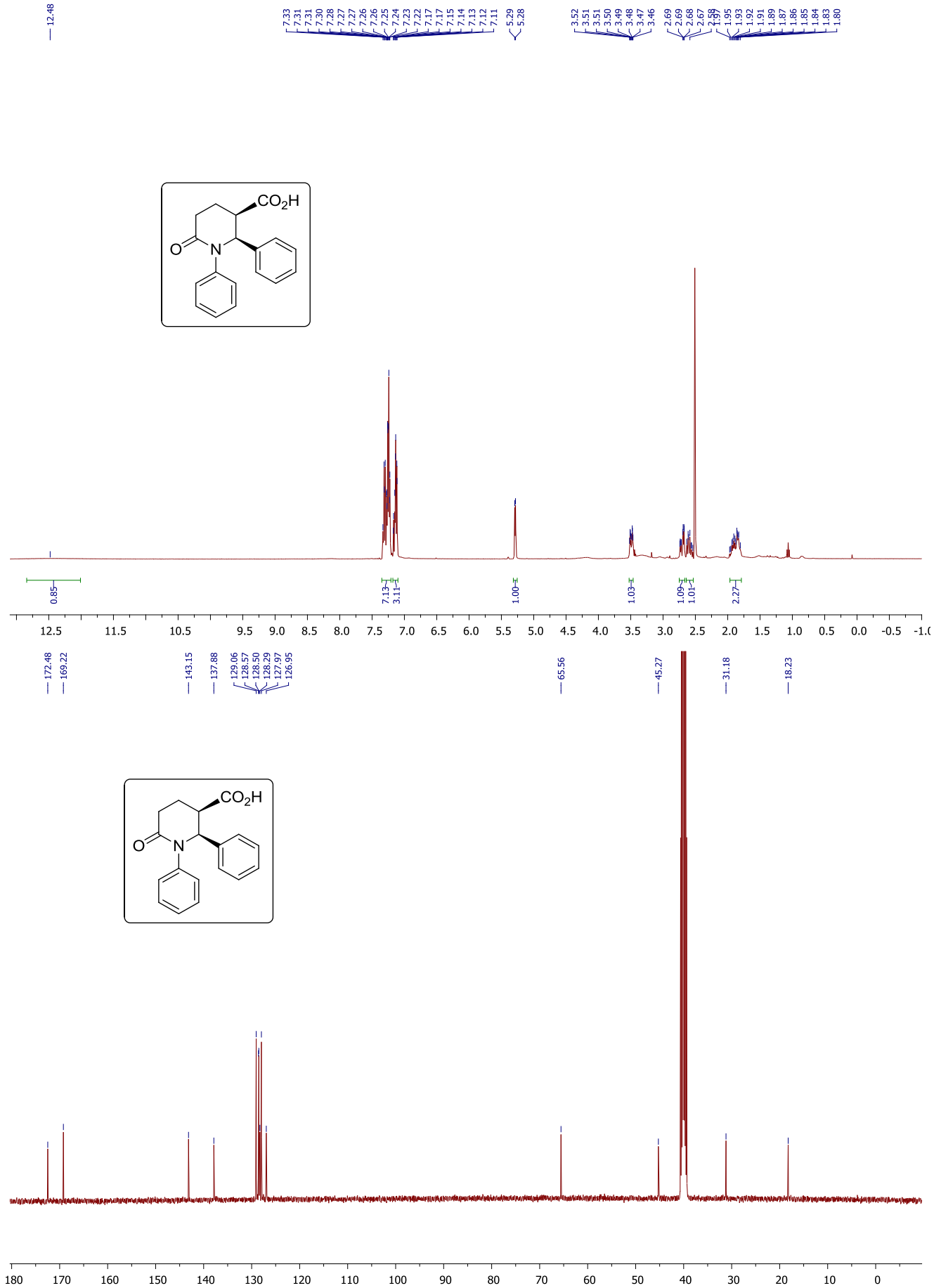
^{1}H and ^{13}C NMR spectra of ***cis*-5l**



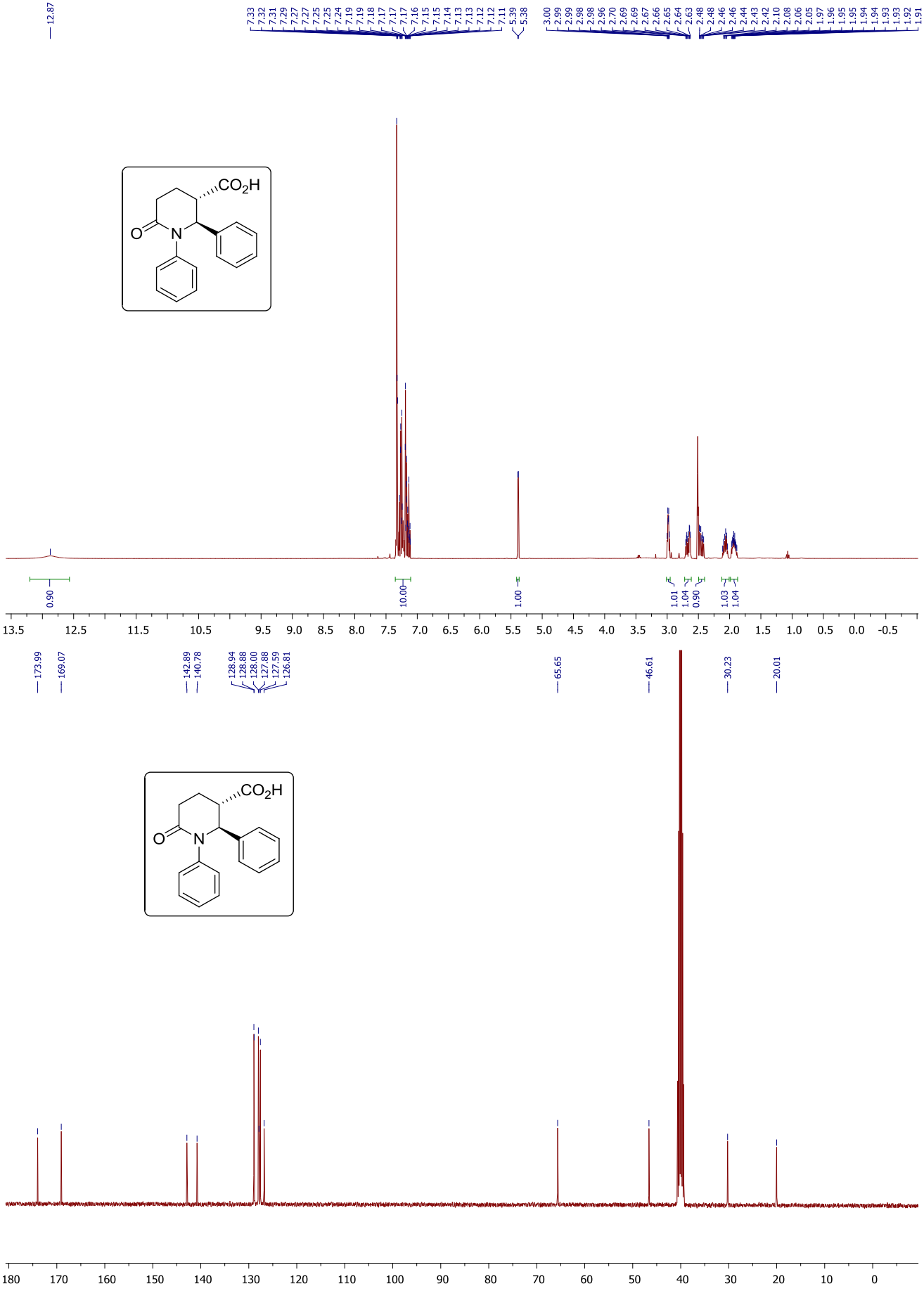
^{1}H and ^{13}C NMR spectra of ***trans*-5l**



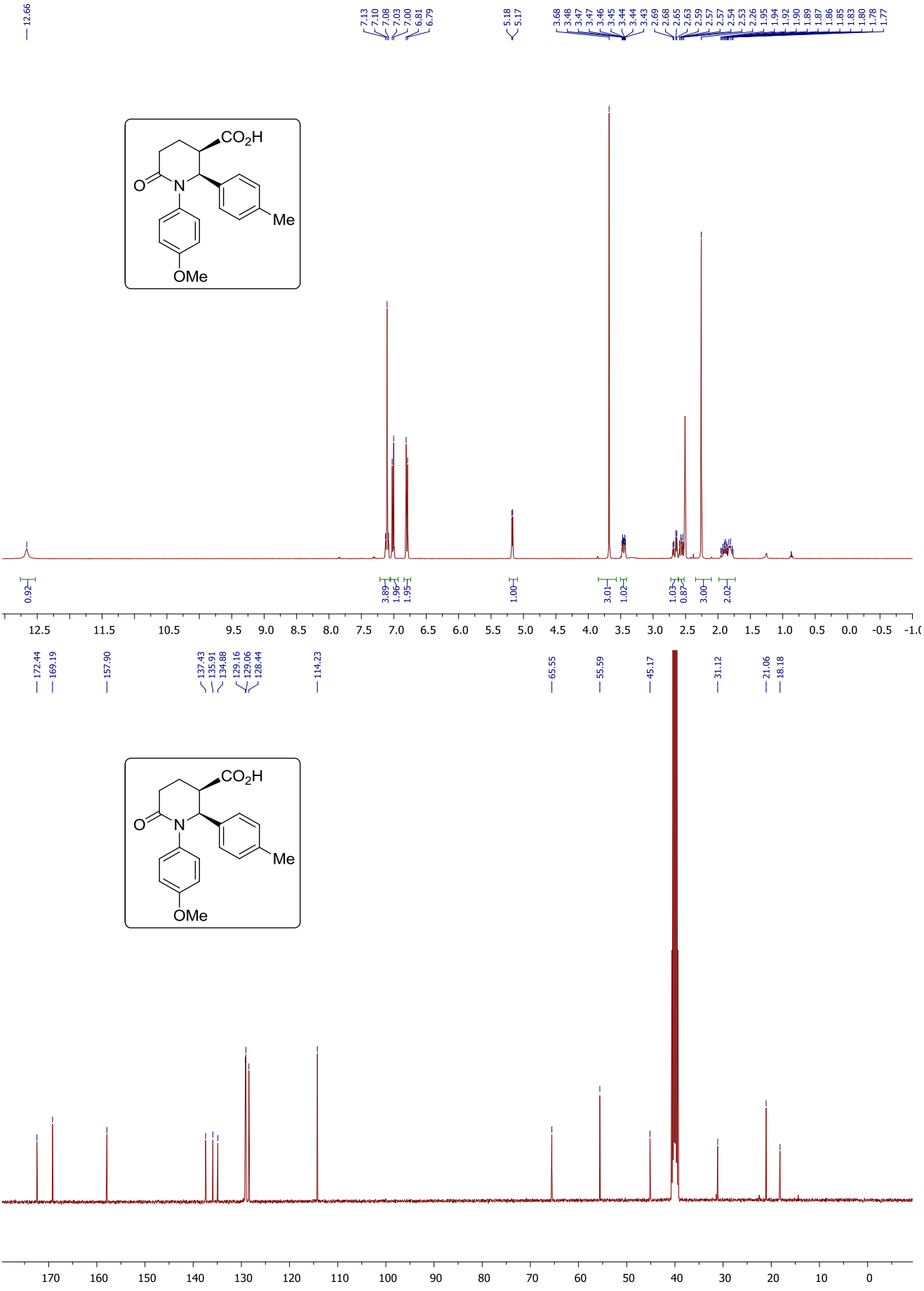
^{1}H and ^{13}C NMR spectra of ***cis*-5m**



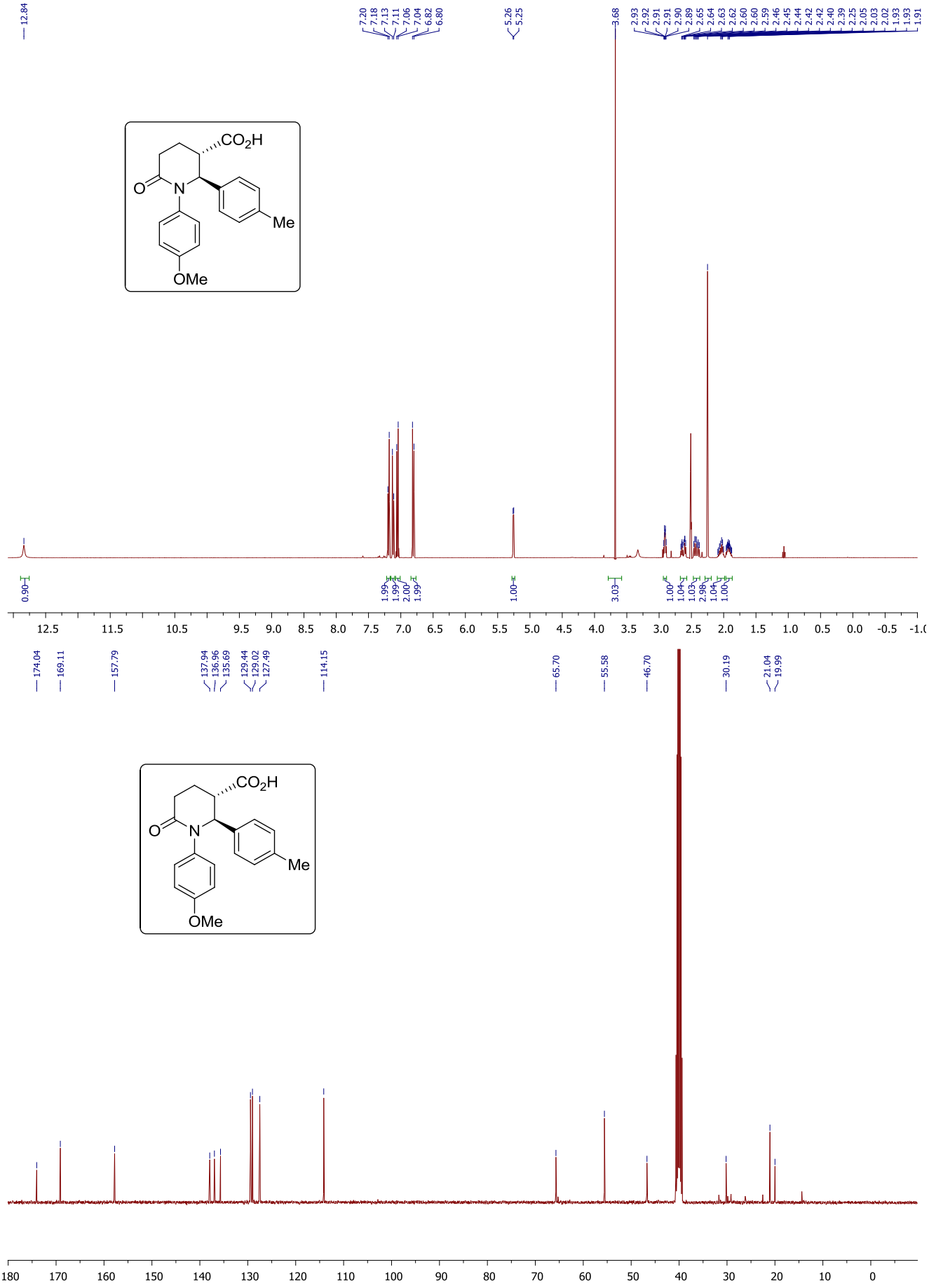
^{1}H and ^{13}C NMR spectra of ***trans*-5m**



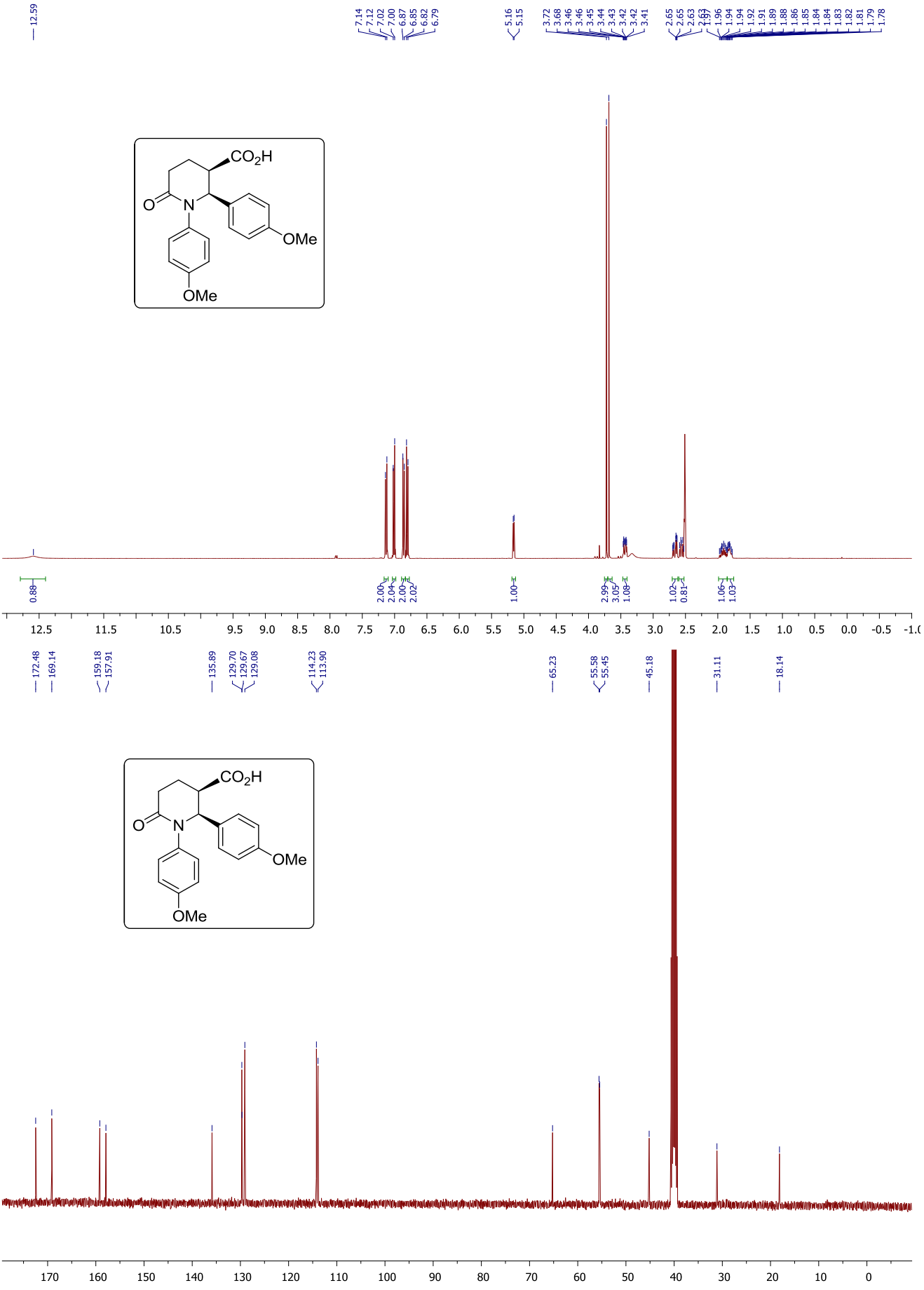
^{1}H and ^{13}C NMR spectra of ***cis*-5n**



^{1}H and ^{13}C NMR spectra of ***trans*-5n**



^{1}H and ^{13}C NMR spectra of ***cis*-5o**



^{1}H and ^{13}C NMR spectra of ***trans*-5o**